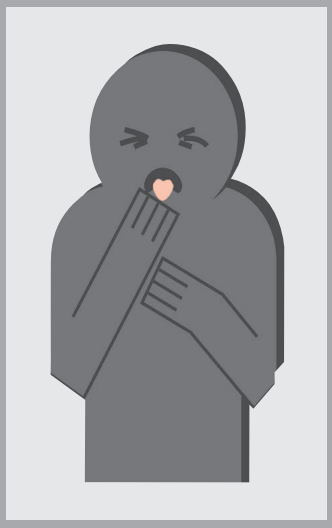

Tuberculosis and Public Health

Policy and Principles in Tuberculosis Control

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Preface

While criticism of verticality in disease control may be justified to a certain extent, the objective of focusing on a single subject is necessary. Paradoxically, studying a single health problem can facilitate an integrated approach.

This publication is one of a series of publications focusing on tuberculosis. Previous monographs in the series describe the epidemiologic basis of tuberculosis control[1] and interventions for tuberculosis control and elimination.[2] The present report deals with policy and operational strategies for intervention, the identification of the type of services and staff required, the logistics involved, and the design and implementation of quality assessment and monitoring. It aspires to provide an objective basis for the study of tuberculosis programs. The primary target group for this report is the participants in courses organized by the International Union Against Tuberculosis and Lung Disease (The Union).

Monographs on epidemiology and interventions often are seen as belonging to a secluded, scientific world. When entering the world of disease control practice, however, one is forced to face real-world complexities. For example, the identification and treatment of infectious patients is implemented within a health services environment where myriad problems, programs, and people —each having its own agenda and priorities—must coexist. Tuberculosis control officials need to coordinate with and encourage others to advance the work. Failing to do so will cause the intervention program to suffer sooner or later.

The tuberculosis program is above all a public health intervention. Although public health activities may change with changing technology and social values, the overall goals remain the same: The programs, services, and institutions involved emphasize the health needs of a population as a whole. Thus, epidemiology is the basic science of public health. There is more to public health than science, however. Public health as a social institution, a discipline, and a practice combines science, skills, and beliefs.

Recently tuberculosis control has been thoroughly analyzed and discussed in numerous publications in both the tuberculosis and the public health literature. This monograph highlights the scientific background for the national tuberculosis program. In practice, however, cultural and social values occupy a

central position in any public health policy or intervention. Partiality, the result of such values, is ubiquitous in public health campaigns. Partiality influences what is studied and how it is studied; what is reported and how it is reported; and what is said and how it is said. Conversely, it influences what is not said, not reported, and not studied. This publication reflects the background, values, and experiences of its author.

Whereas public health has its roots in the field of communicable disease control, in recent times the so-called "new public health" has been defined and debated with regard to whether or to what extent it should include the health care sector. The tendency is to examine how the health sector contributes to the health of communities in a wider sense rather than to look at issues such as medical treatment of individuals. Recent developments such as the emergence and spread of drug resistance seem to challenge this view in part. Drug resistance, one of the byproducts of the health services, affects the health of current and future communities. The health care sector and its overall organization and management for the treatment of individuals clearly plays an important role in public health, in communicable disease control in general, and in tuberculosis control in particular.

Tuberculosis has been referred to as the perfect expression of an imperfect civilization.[3] Can tuberculosis be managed in an unfavorable environment of poverty, marginalization, HIV/AIDS, and multidrug resistance? The fundamental approach to the prevention of tuberculosis should include improvement of the physical and social environment to enhance the standards of living of populations and individuals, and doing so requires economic development, higher levels of education, adequate housing, and world peace.[4] In the absence of an ideal society, strategies for tuberculosis control at the very least correct some of the worst outcomes of existing societies and thus strengthen the ability of men and women to move ahead with the wider agenda.[4]

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Introduction

"The world of ideas and the world of action are not separate . . . but inseparable parts of each other . . . The man and woman of action have no less responsibility to know and understand the world than does the scholar."[1]

This monograph is written primarily for the man and woman of action. It was inspired by the policy model developed in national programs collaborating with The Union as well as by countless debates with lay people and health professionals both within and outside tuberculosis programs. The aim in publishing it is to share experiences and thoughts that concern tuberculosis work in high-prevalence countries.

The overall objective is to present the tuberculosis program as part of the general framework within which it operates. The specific goals are to describe the model and review its historical background and scientific basis, as well as to consider the context within which it is implemented, that is, the health systems and services in countries with a high prevalence of tuberculosis. This monograph attempts to address the debates taking place not only within the tuberculosis community but also in the wider context of communicable disease control and health services organization in general. Although the internal debates are interesting, the external ones are no less important.

It is not immediately obvious how the policy model should be referred to. Whose model is it? Various researchers were involved in establishing its scientific base. Karel Styblo assembled the evidence into a kind of prototype for a national tuberculosis program. The model was tested in several locations, primarily in Africa, but also in Central America. Countless people, indigenous and expatriate, participated in its implementation and worked in the programs. Many governments and nongovernmental organizations, in poor and rich countries, supported the programs. Although Karel Styblo and Annik Rouillon, at the time The Union's Scientific Director and Executive Director, are the undisputed leaders of the collaboration, The Union as such was not directly involved in the policy model. Yet, because many if not most of those who

contributed to the work were in some way connected to The Union—as individual members, organizational members, constituent members, or as participants in the collaborative programs—it is reasonable to refer to the model as the Union model.

In the 1980s, several voluntary and nongovernmental organizations, confronted with problems in the field, expressed the need for a concise explanation of how to recognize and manage tuberculosis. In response, the *Tuberculosis Guide for High Prevalence Countries* was published in 1986.[2] This guide, often referred to as the Misereor Guide or the Orange Guide, came to represent the model and—in subsequent updated editions—record its development.

The Union model's policy prioritizes the control of tuberculosis based on an identification of patients with the disease, giving precedence to the detection of sputum smear-positive cases and treatment with multidrug therapy. The justification for this opinion is the topic of previous monographs in the series.[3,4] The first part of the present publication is devoted to transforming the Union policy statement into operational strategies with their own justification and evidence base. The second part describes the systems supporting policy implementation. This monograph does not deal specifically with financing, advocacy, or the political commitment that is essential for the success of any public health intervention.

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PART I

Tuberculosis Control

1

Background and context of the policy model

The public health aim of tuberculosis treatment programs is prevention: prevention of infection and prevention of death and disability.

Tuberculosis control can be seen as a public health intervention or, in a narrower sense, as communicable disease control. This opening chapter examines the disciplines of public health, disease control, and communicable disease control, and how they are related. It briefly reviews the forces that drive the course of tuberculosis in communities, the options for intervention, and the historical background and public health goals of tuberculosis programs. It describes how The Union became concerned with tuberculosis in low-income countries and what has been its contribution in the field of tuberculosis control. The chapter introduces the policy model developed under the leadership of Karel Styblo and Annik Rouillon, and explores some of the contextual factors contributing to its successful implementation. Finally, its links with the DOTS strategy (subsequently the Stop TB strategy) of the World Health Organization are explained.

Public health, communicable disease control, and tuberculosis

Public health

Organized efforts to promote health and prevent illness date back to ancient civilizations such as the Babylonians, Egyptians, and the Incas.[1] In Europe and the United States, the modern concept of public health originated some two hundred years ago when fear of morbidity and mortality from infectious diseases prompted scientists, social workers, statisticians, religious leaders, philanthropists, and governments to search for ways to protect the public's health.[2] Even if the roots of public health are planted in the field of communicable disease control, public health is the broader concept and term. Prevention of morbidity and mortality is always a public health intervention, regardless of whether or not it concerns an infectious disease or disease control is achieved.

Definition of public health

Public health is a social institution, a science, and a discipline, and it has been described as a combination of science, skills, and beliefs directed to the maintenance and improvement of the health of all people through collective action.[3] In 1920, Winslow defined public health as—

> the science and art of preventing disease, prolonging life and promoting physical health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing services for the early diagnosis and preventive treatment of disease, and the development of social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health.[4]

Griffith and Hunter claim that such a broad description of public health runs the risk of being a confusing and diffuse collection of ideas that is unable to deliver a concrete product.* According to Baggott, public health can be seen as a philosophy of intervention aimed at protecting and promoting the health of a population.[1] He points out that the interpretation of public health is essentially a political process in which different interests seek to advance their own interpretations, and the interplay of such interests establishes the meaning of the term. Thus, he argues, the orthodox medical model focuses on the prevention of specific diseases through immunization, health screening and surveillance, and the treatment of the early stages of disease. In contrast, other models emphasize health education and the provision of information on healthy lifestyles; still others stress the role of government in regulating economic, social, and environmental factors linked to ill health.[1] The tuberculosis program described here by and large maintains an orthodox medical focus that can be explained by its background and period of development, but also by the aim to describe a clearly defined intervention with measurable results.

Role and functions of public health

Another issue worth exploring when considering public health is the role and functions of public health versus primary health care. Primary health care has been defined in different ways, the underlying philosophy of which—in the broadest sense—is an emphasis on moving health services out of large institutions to community-based settings.[1] Baggott described the tension between general practitioners (primary health care) and public health practitioners (medical health officials) in the United Kingdom in the first half of the twentieth century. This struggle resulted in a fracturing of traditional medical soli-

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*Quoted in Baggott,[1] p. 1.

darities, which primarily revolved around turf and status.[1] Over time, the primary health care profession also clashed with specialized medical practitioners. Similar battles have been and are still being waged in different countries around the globe. The position regarding tuberculosis that is set forth here deems all medical and social professions important and to a large extent complementary in role. Their roles need to be defined in any given setting. Whereas hospitals, health centers, and private practitioners are considered providers of health services, public health professionals will be regarded here as independent but accountable actors possessing a range of skills and experiences whose practical role involves the coordination and integration of programs that cut across professions, institutions, and sectors. While primary health care practitioners might claim this as their role, it can be argued that, traditionally, their training has not equipped them for such a task. Some would go as far as to say that despite good intentions, the primary health care movement failed in taking on this role.[1,5] It can also be argued that a strong central authority is needed in key areas of public health and communicable disease control over and above what can be organized at the primary care level or by local governments. At the same time, a central authority must not suppress local initiatives generated by communities and professionals.

Scientific foundation and evidence base

Reminiscent of Gowman and Coote's observation that whereas public health may be an art and a science, it shouldn't be an act of faith,* a third issue to explore is the scientific basis of public health. While the public health concept originally emerged out of a multitude of disciplines (such as environmental and social sciences, epidemiology, statistics, nutrition, hygiene, medicine, and law) recent analyses emphasize that with time public health lost much of its multidisciplinary aspect and became increasingly medicalized, a development brought about primarily by advances in medical knowledge, particularly epidemiology and bacteriology, and the subsequently growing influence of the medical profession.[1] Discovery of the bacteriological causes of infectious diseases established a scientific basis for preventive medicine. It can be said that the laboratory, rather than society, consequently became the workshop for public health, and scientific evidence and quantitative studies were favored over circumstantial evidence and qualitative studies.[1] Likewise, medical rather than social interventions eventually dominated public health.[1]

Whereas epidemiology is commonly thought of as the basic science of public health,[7] the scientific basis is wider. When scientific knowledge is used to guide policy and practice, evidence is commonly ranked according to the relative merits of different data. There are various ways of doing this.

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*Quoted in Harrison,[6] p. 245.

A simple way of classifying evidence is to differentiate between good (well-designed randomized controlled trials), fair (retrospective analyses of observational data, with supporting clinical consensus or opinion), and little research-based evidence (principally clinical consensus or opinion).[8]

In another model, evidence from at least one good systematic review—which includes, at a minimum, one randomized controlled trial—is put at the top of the hierarchy and referred to as type I evidence. Type II evidence requires at least one randomized controlled trial; type III, at least one intervention study; type IV, at least one observational study; and, finally, expert opinion is placed at the bottom of the hierarchy.[6] Expert opinion carries little weight because experts are thought of as stakeholders with vested interests.

Systematic reviews aim to reduce large quantities of information to usable dimensions. Some claim that doing so is an efficient scientific technique, one that is less time consuming and more reliable than conducting new studies. Moreover, they contend that the diverse circumstances in which individual studies are carried out permit a review's results to be generalized across different contexts and become more significant than individual studies (that statistical power increases as a result of aggregation of data).[6] While it is clearly less time consuming to conduct a systematic review than to undertake original studies, the scientific merit and reliability is debatable. One argument is that different contexts call for comparison rather than aggregation. It is important to consider why an intervention works, reflect on the circumstances and conditions, and think about how the process of implementation can affect outcomes.[6] On the other hand, it can be argued that systematic reviews are useful in that they identify weaknesses and gaps in the evidence base and encourage clarity of procedures and methodology, which then allows comparison where needed and justified.

In recent times, economic analyses have played a prominent role in health and development research. Cost-effectiveness analyses compare different alternatives in a specific setting, one outcome at a time.[9] The results are context-specific and may be influenced by factors such as prevalence of disease, quality of service delivery, the presence of other diseases (such as HIV/AIDS in the case of tuberculosis), and other external factors.[9] Although this fact is seldom appreciated, economic analyses are heavily influenced by assumptions and values. Sensitivity analysis aims to make up for this. In today's search for "global solutions," international agencies spearheaded by the World Bank increasingly demand standardization of methodologies in cost-effectiveness analyses that yield results with little relevance for local settings.[10] At best, such analyses provide a framework to consider the policy options. In policy making, values must come from local communities, and the final policy choice is a local political process involving a range of stakeholders.[10] Thus, cost and cost-effectiveness analyses can only form part of the decision-making process.[11]

Finally, when it comes to using evidence in policy formulation, it is impor-

tant to acknowledge that conflicting research findings on health issues are common, that there is no simple formula for bringing science into policy decisions, and that advisors can seldom, if ever, limit themselves to purely scientific issues.[1] Likewise, clinical guidelines are rarely based solely on research evidence; in most cases, they also incorporate the views of experts.[12] Even when evidence from large and well-conducted studies is available, it is not always clear how the results might be applied to particular patients or settings.[13] Value judgments concerning underlying goals, interpretation of the literature, and a subjective assessment of the quality of the evidence and its relevance for particular patients and settings also come into play.[12]

Public health programs

In 1990, Bash pointed out the irony that while international health authorities gathered at a ceremony in Kenya in October of 1979 to congratulate themselves on the eradication of smallpox, an unknown virus was spreading quietly, the virus today known as the human immunodeficiency virus (HIV).[14] Not only did this virus cause a whole new pandemic that needed to be dealt with, it also seriously undermined ongoing efforts to control an old disease: tuberculosis. This is a useful reminder of the futility of emphasizing eradication or elimination programs at the expense of expanding appropriate and sustainable health services within which disease control can be addressed, not to mention reinforcing the wider public health agenda of worldwide social and economic progress. Nevertheless, it is important to formulate appropriate policies, strategies, and programs for diseases of public health importance in order to guide and coordinate the work of the health services. "Vertical" public health programs can and should cut across sectors (such as civil, prison, industry, public, and private). Such programs facilitate "integrated" approaches.

Many public health programs can be regarded as screening programs. There are two approaches to population screening programs. One is to restrict screening to members of identifiable "high-risk" groups in a population (selective screening), and the other is to attempt to include everyone, regardless of the degree of risk (mass screening).[15] As a rule, the latter is only indicated if groups at high risk cannot be defined in such a manner that the sensitivity and specificity of the program is satisfactory.[15] Whereas mass screening for tuberculosis was attempted in former days, modern tuberculosis programs—whether they offer treatment of overt tuberculosis or preventive chemotherapy—can be seen as selective screening programs targeting persons known to be at high risk of having or developing infectious tuberculosis.*

*When considering the orthodox definition of "screening," however, it can be argued that the modern tuberculosis program is not a screening program and sputum microscopy is not a screening test unless when it is used in surveys; that is, not when applied to patients, where it is better referred to as a diagnostic test.

Box 1.1 summarizes some key criteria to assess when justifying screening programs.[15] For the first two criteria, it is necessary to know the natural history of the disease in order to identify the point where screening should be introduced as well as to clarify the expected impact of the program. Results of clinical trials show whether prognosis is improved with early detection and treatment of disease. To be credible, such trials need to be performed on a group that is similar to the one proposed to be screened. Screening is preferably done early in the process of a disease, and ideally there is a long latent period before overt disease occurs. Tests used in screening should be rapid, easy to perform, and not too costly, so that many people can be screened within a short time frame and at reasonable cost.

Selective screening programs consist of at least two steps, the first being identification of persons at risk. Ideally, programs use a test with high sensitivity for screening and a test with high specificity for confirmation. In tuberculosis control, this could be a symptom screening as a first step (prolonged cough, for example) and a sputum examination (acid-fast microscopy) for confirmation. Chest radiography could be an additional step before or after sputum examination.

The operating characteristics of tests that are used in programs are important. "False-negative" results diminish the community benefits of a program, and "false-positive" ones exaggerate those benefits. The latter also result in a waste of resources.[15] The consequences for individual participants also need to be considered: unnecessary and potentially harmful treatment on the one hand and, on the other hand, false security if a person feels assured by the results of the program and does not seek care when the disease appears or progresses.[15] This consideration can be influenced by the quality of communication between programs and participants. The positive predictive value of a test is also important. This depends on the prevalence of disease among those tested and therefore improves with pre-test selection criteria. Because prevalence of non-disease is usually high in screening programs, the negative predictive value is, as a rule, little affected by prevalence of disease.

Box 1.1 Criteria to consider in relation to screening programs

1. How important is the disease in terms of seriousness and/or consequences?
2. Does an effective and acceptable intervention exist that affects mortality and/or morbidity?
3. Is it possible and acceptable to identify risk groups?
4. What is the sensitivity, specificity, and acceptability of any test(s) to be used?
5. What are the costs involved?
6. What are the participation rates?

Box 1.2 Terminology: efficacy, effectiveness, and efficiency

Efficacy refers to scientific research and ideal conditions (that is, randomized, controlled clinical trials). Efficacy can be defined as the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions.[3]

Effectiveness refers to application under routine conditions. In standard usage (made standard by epidemiologists), effectiveness is a measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specific population.[3]

Efficiency also refers to routine conditions, but focuses on resource expenditure. Efficiency is defined as the effects or end results achieved in relation to the effort expended in terms of money, resources, and time or, more precisely, the extent to which the resources used to provide a specific intervention, procedure, regimen, or service of known efficacy and effectiveness are minimized; in other words, it is a measure of economy.[3]

Efficacy, effectiveness, and efficiency are terms that recur in discussions on interventions and programs. Definitions for these terms are presented in Box 1.2.

Finally, it is often argued that public health programs must be amenable to the setting of objectives and targets and methods of monitoring.[1]

Goals and targets

The emphasis on goals and targets dates back to the 1975 concept of "Health for All by the Year 2000," promoted by the World Health Organization (WHO) and officially adopted as its policy in 1981.[15] Objectives and targets are considered by some to be essential for interpreting the data presented by information systems. Targets, expressed in quantitative terms, provide a yardstick against which progress can be monitored. Health targets have been defined as explicitly stated outcomes or as measurable improvements in health status within a given time frame.[3,16] It is generally accepted that assessment of epidemiological impact requires looking at incidence, prevalence, and deaths.

Targets can be divided into three subsets: outcome targets for improvements in health (for example, reducing infant mortality or mortality from any given disease), process targets for activities needed to make these improvements (such as steps in implementation of screening programs), and structural targets designed to improve health services management and organization, quality of care, and staff training, for example.[15] Baggott talks of symbolic targets that articulate long-term goals and values and are intended to motivate and inspire (one can argue, for instance, that "Health for All" was a symbolic target); risk factor targets (targets related to smoking, for example); health outcome targets (as above); and targets set for specific (risk) groups or areas (children or deprived

populations, for instance).[1] According to Baggott, symbolic goals and targets are of little practical use and can even demotivate if they are unattainable. Despite the fact that Health for All by the Year 2000 represents an unmet goal, goals and targets are nevertheless widely used today, and since the turn of this century the United Nations' Millennium Development Goals have taken center stage in the international health arena, replacing the Health for All goals.

Henderson, when discussing experiences from the smallpox eradication campaign (see below), recalls that the smallpox programs tended to drift until surveillance and quality control measures were established.[17] According to Henderson, goals were important, but he warned against using too many of them. He noted that when their number exceeded four or five, the staff became so involved in submitting and compiling data that they failed to use the data for its intended purpose, that is, monitoring the strengths and weaknesses in program implementation. Henderson emphasized that goals should feature the following qualities to be SMART: Specific (quantitative), Measurable (without unreasonable efforts), Adaptable (regularly reviewed for relevance and changed in order to address unforeseeable circumstances), Reasonable (achievable within reason), and Time limited (because goals are meaningless when they lack a reference point in time). Ideally, programs and staff should set their own context-specific goals locally rather than use goals that are set at a national or supra-national level.

Specific targets are sometimes criticized as unrealistic and unachievable or, at the other extreme, politically convenient, that is, too easy to accomplish or too close to being achieved when they are set, making subsequent evaluation inevitably favorable. It can be argued that targets are primarily useful in situations where things are not working well and problems and solutions have been identified. If targets are realistic, then they should be reached eventually. When they have been achieved, the focus of the targets is shifted to maintain or sustain success or new targets are set. As far as disease control is concerned, it is a serious limitation that success tends to erode political commitment for sustained control measures, which sometimes results in the eventual reversal of a favorable trend. Reichman refers to this phenomenon as the U-shaped curve of concern.[18] Unlike the changeable will of policy makers, though, the tuberculosis bacillus is steady in its proliferation into the future.

Communicable disease control

According to Canetti,* eradication of tuberculosis is synonymous with the total suppression of the disease, which implies the extinction of existing cases and the definite halting of the emergence of new ones—a condition that can-

*Quoted in Styblo,[19] p. 58.

not be achieved in the foreseeable future. This prompted suggestions of definitions of "close to" or "virtually identical with" eradication,[19] demonstrating perhaps more than anything the yearning of those devoted to the eradication of tuberculosis for some sort of closure—a major milestone, the turning of a page, the end of an era.

Eradication, elimination, containment, and control

The term *eradication* refers to extinguishing a disease, causing it to disappear absolutely from the world[14] or, more specifically, terminating all transmission by extermination of the infectious agent through surveillance and containment.[3] In 1992, the WHO defined disease eradication as a status achieved whereby no further cases of disease occur anywhere and continued control measures are not necessary.[3] The only example of a human disease being made extinct is smallpox, which was eradicated in the 1970s (see Box 1.3). Before the smallpox campaigns succeeded, four other global campaigns had failed: those against hookworm, yellow fever, yaws, and malaria.[17] Malaria may be the most notable example of an unsuccessful attempt at eradication. In spite of extensive worldwide efforts dating as far back as a decade before the establishment of the smallpox eradication program,[14] malaria remains an enormous health problem. On the other hand, a campaign to eradicate poliomyelitis has found notable success, efforts are underway for the eradication of Guinea worm infection, and there has been an impressive downward surge of leprosy.

The word *elimination* refers to reduction of case transmission to a predetermined low level.[3] This term also can signify the disappearance of transmission from a defined area, with a country or continent becoming free from infection but retaining the possibility of importation or reintroduction.[14] In 1959, an Expert Committee on Tuberculosis convened by the WHO decided that a point in tuberculosis control where there was less than 1% prevalence of natural reactors to tuberculin among 14-year-olds indicated that tuberculosis was no longer "a public health problem."[20] In 1991, elimination of tuberculosis as a public health problem was defined by the WHO as reduction of prevalence to

Box 1.3 Smallpox eradication

The WHO adopted the general goal of smallpox eradication in 1958 and established an intensified global smallpox eradication program in 1967.[14]

Surveys revealed that in 1967 alone, ten to fifteen million smallpox cases occurred, and the death toll was two million.[17] The last documented case of smallpox was diagnosed in a remote area in Somalia in 1977.[14]

In 1980, the WHO proclaimed that vaccination everywhere could cease.[17]

a level below one case per million population.[3] Henderson, however, has suggested using the phrase "effective disease control" rather than focusing on eliminating a disease or reducing it to something less than a public health problem (a level which is difficult to define).[17]

Tuberculosis elimination has been on the agenda of many a devoted visionary. Apart from the intrinsic qualities of tuberculosis, the human factors that have impeded tuberculosis elimination in defined areas involve migration and urban poverty coupled with inadequate health services and programs, as well as the HIV pandemic.[21]

The term *containment* conveys the concept of regional eradication of a communicable disease, first proposed by Soper in 1949 for the elimination of smallpox.[3] It is acknowledged that containment of a worldwide communicable disease demands a globally coordinated effort to prevent reintroduction of infection into countries that have achieved an interruption of transmission.[3] Thus, containment may well be the ideal term to use when discussing tuberculosis in modern times.

The word *control* is applied to communicable (and sometimes to noncommunicable) conditions when referring to ongoing operations or programs aimed at reducing the incidence or prevalence or eliminating the condition.[3] The term has been defined as the progressive decline in the incidence and prevalence of a disease in a population, ultimately leading to its elimination.[22]

To some, even the control of tuberculosis may seem an insurmountable task, but Enarson et al. point out that smallpox eradication began with implementing what was available.[23] They justify selecting elimination of tuberculosis as a target because it is likely to engage commitment, identify challenges, and stimulate critical evaluation of current strategies.

Disease prevention versus curative care

One of the most frequently used clichés in public health proclaims that "prevention is better than cure." When discussing tuberculosis, though, the two approaches are intimately related and concurrent. Disease prevention is defined as an activity or action to prevent the occurrence of disease (risk factor reduction), to arrest progress of disease, or to reduce the consequences of disease.[24] Treatment of tuberculosis addresses all of these concerns. Not only does treatment arrest the progress of tuberculosis and reduce its consequences for the individual undergoing treatment, it also prevents further spread of *Mycobacterium tuberculosis* and thus the occurrence of disease in the community.

Prevention is sometimes divided into primary, secondary, and tertiary prevention. Primary prevention aims to prevent initial occurrence of the disease, whereas secondary and tertiary prevention seek to arrest and retard existing disease and its effects through early detection and appropriate treatment, as well as to reduce the occurrence of relapse and chronic conditions. Screening

programs backed by effective interventions are classically listed as the most important examples of secondary prevention.[15] In communicable disease control, as clearly demonstrated in the example of tuberculosis, early detection and treatment is an important primary prevention activity. Secondary and tertiary prevention activities at the level of the individual result in primary prevention at the community level, as treatment of the disease reduces the period of infectiousness, thereby slowing the force of transmission. To date, the main primary prevention policy in tuberculosis programs in high-prevalence countries is indeed implementation of secondary and tertiary prevention.

Acute, chronic, and social diseases

A chronic condition is commonly defined as one having a duration of three months or more,[3,25] but more complex definitions exist.* Interestingly, the definition usually does not explicitly take into account whether or not the condition is curable. While it may be problematic to use the term "curable" to describe chronic conditions in which individuals suffer relapses or carry, for example, lifelong viruses, the term logically applies to tuberculosis. In modern times, tuberculosis is generally curable, and thus it arguably should not be classified with chronic conditions. Even if the duration of disease exceeds three months—anti-tuberculosis treatment lasts, as a minimum, six months—it is eventually cured within a relatively short time frame. Usually, the patient is well on the way to being cured within three months of onset of efficacious treatment. Therefore, an important difference exists between tuberculosis and HIV infection, or tuberculosis and diabetes mellitus, for example.

The term "chronic" seems to have stuck with tuberculosis even after the development of chemotherapy, and today it is still occasionally referred to as a chronic disease. However, even in the era of chemotherapy, infectious diseases can lead to truly chronic conditions if not promptly and correctly managed. In the case of tuberculosis, this could be pulmonary insufficiency (not to mention incurable drug-resistant tuberculosis); and in leprosy, physical and neurological disabilities. The risk in characterizing tuberculosis as a chronic disease is that it may negatively influence the attitudes of the community and health personnel, the pace of response, and even expectations regarding outcome. Health workers confronted with tuberculosis patients must maintain positive outlooks and expect rapid recovery and permanent cure to motivate patients accordingly. It can be argued that tuberculosis programs call for an attitude that is different from those appropriate for confronting truly chronic conditions.

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*An example of a more complicated definition is, "diseases which have one or more of the following characteristics: they are permanent, leave residual disability, are caused by non-reversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care."[26]

Tuberculosis is frequently referred to as a social disease. Surely social, economic, and environmental factors are involved in the persistence of tuberculosis. Depending upon the setting, various external forces (such as poverty, economic inequality, political violence, and racism)[27] shape individual risks and behaviors among populations. While it is crucial to take note of this in the design and implementation of tuberculosis programs locally (that is, to tailor the program to the characteristics and needs of those who have the disease), for success in tuberculosis control in the long term, large-scale social and economic forces need to be convincingly addressed in and by the wider community, locally and internationally. This is primarily a question of political will.

Communicable disease programs

Because there are no absolute or universally agreed upon eligibility criteria for categorizing or ranking communicable diseases for eradication or elimination,* an examination of the only human disease ever eradicated by human effort promises to shed light on the debate. The comparison presented in Table 1.1 is adapted from one presented in Bash's *Textbook on International Health*.[14]

The epidemiology of smallpox and tuberculosis is radically different. While transmission efficiency was much higher in smallpox than in tuberculosis,† that fact does not necessarily favor tuberculosis control, as high transmission efficiency may just as well constitute vulnerability to intervention. The basic mechanisms for the control of smallpox and tuberculosis are also radically different. Vaccination was the main strategy to control smallpox; in contrast, case finding and treatment are the key tactics to control tuberculosis. The strategy of smallpox eradication defined an attack phase with universal immunization, followed by aggressive surveillance and isolation of cases and contacts in the final stages of the campaign. Similarly, an attack phase in tuberculosis would involve case finding and cure of infectious patients, followed by a consolidation and maintenance phase with aggressive contact investigation and preventive chemotherapy. HIV control is somewhat more complex because it includes behavioral change; malaria control is more complex still, including vector control, behavioral change, and treatment.

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*Criteria that have been considered refer to scientific feasibility (epidemiological vulnerability, effectiveness and practicality of available intervention, and demonstrated feasibility) and political will (perceived disease burden, expected cost, and necessity for eradication rather than control).[17]

†Transmission efficiency is calculated by multiplying the probabilities of passing from one step to the next in the epidemiological model: exposure-infection-disease-death. The inefficiency in tuberculosis transmission stems from the relatively low (compared to smallpox, for example) probability of infection given exposure and in passing from the state of infection to the state of disease. Tuberculosis transmission efficiency is enhanced in a setting with a high prevalence of HIV infection, primarily by the increase in probability of passing from infection to disease.

Table 1.1 Comparison among smallpox, malaria, tuberculosis, and AIDS

	Smallpox	*Malaria*	*Tuberculosis*	*HIV/AIDS*
Agent	Orthopox (Variola) virus	Sporozoan parasites, 4 species of plasmodium: *vivax*, *malariae*, *falciparum*, and *ovale*	*Mycobacterium tuberculosis* complex (*typus humanum*)	Retrovirus: HIV or variant
Transmission	Direct, by contact with case	Vector-born (anopheles mosquitoes), blood transfusion	Airborne	Sexually transmitted, by blood or congenitally
Incubation period	8–17 days	7–14 days (up to 30 days for *P. ovale* and rarely up to 8–10 months for *P. vivax*)	2–10 weeks (infection usually goes unnoticed; latent infection may persist for a lifetime)	1–3 months to detection of virus in blood, 1–15 years to development of symptoms
Visibility of infection/disease	Pox are usually obvious, and cases thus easily recognizable	Not evident from appearance	Infectious patients are usually symptomatic, with bacilli visible on microscopy of sputum	Not evident from appearance
Infectious period	About 3 weeks from appearance of skin lesions, highest in the first week	May be prolonged; weeks to years	Theoretically, as long as viable bacilli are being discharged in the sputum	Unknown, presumed to be lifelong from the onset of infection
Immunity after natural infection	Usually solid and lifelong	Partial and temporary	Uncertain	Probably none
Seasonality	Usually pronounced	Often pronounced, sometimes none	Not well defined	None
Non-human reservoir	No	Probably unimportant	Primarily human reservoir, rarely primates; in some areas, diseased cattle and other mammals are infected	None known
Prevention and control	Safe and effective vaccine	Environmental modification, insecticides (impregnated bed nets), prophylactic drugs (treatment of cases)	Detection and treatment of infectious cases, preventive chemotherapy for contacts, variable protection from immunization depending on the setting	Control of blood products and intravenous drug paraphernalia, elimination of sexual exposure, prevention of pregnancy in HIV-positive women or specific treatment in pregnancy
Specific treatment	None	Effective chemotherapy; drug resistance complicates the situation and may decrease treatment efficacy	Effective multidrug treatment; drug resistance complicates the situation and may decrease treatment efficacy	ART suppresses viral load and prolongs life, problems with drug resistance

Adapted from Basch.[14] AIDS = acquired immune-deficiency syndrome; HIV = human immunodeficiency virus; ART = antiretroviral treatment.

Table 1.2 Smallpox eradication compared to tuberculosis control

Factors favorable for smallpox eradication	*Tuberculosis*
Absence of non-human reservoir	Practically true for tuberculosis as well
Acute, severe and easily recognized clinical presentation	Only partially true for tuberculosis
Transmitters easily identified	Only partially true for tuberculosis (laboratory support required)
Short time from infection to infectiousness	Not so in tuberculosis and therefore difficult to link cases and contacts
Period of infectiousness limited, short and well defined	Not so in tuberculosis
No subclinical cases	Latent infection is a problem in tuberculosis
Effective vaccine providing lifelong immunity	Not so in tuberculosis
Possible to vaccinate contacts	Not so in tuberculosis and difficult to identify contacts in the first place

Henderson discussed the factors that, in his view, may have facilitated smallpox eradication.[17] In Table 1.2, the characteristics of smallpox that favored its eradication are listed and compared with those of tuberculosis. Smallpox was a severe illness with abrupt onset and an easily recognizable skin rash. Diagnosis was not a problem; anyone could make it, based on clinical signs. Laboratory tests were not required. There were no subclinical cases. It was easy to trace the chain of transmission, and contacts of cases could be vaccinated with a single injection of an inexpensive, field-stable, easily administered, and virtually 100%-effective vaccine.

Despite the fundamental differences between smallpox and tuberculosis, lessons from the smallpox program might apply to tuberculosis control. Henderson noted that three successful eradication programs featured surveillance as key components: smallpox, Guinea worm, and polio.[17] These programs modified and changed their strategies and tactics over time. Whereas surveillance in the smallpox program was aimed at the typical skin lesions (pox), in tuberculosis programs, surveillance is aimed at cough and the presence of acid-fast bacilli in sputum, as will be discussed later. Generally speaking, the aim of surveillance should be to follow trends nationally, by geographic area, and by risk groups. Henderson also identified continuous research as an important component of the smallpox campaign. In his view, without a better understanding of smallpox epidemiology its eradication might not have been accomplished.

Competition for funding in disease control

Recently, advocates of the Integrated Management of Childhood Illness (IMCI) strategy lamented that their cause did not receive sufficient funds even though many more children die of various treatable conditions than the number of adults who die of tuberculosis and AIDS.[28,29] Meanwhile, the HIV lobby positions its cause with the following case: Why invest in tuberculosis treatment only to have the patients then die of AIDS? The tuberculosis lobby stakes its counterclaim with this challenge: What is the point in investing in antiretroviral (ARV) treatment programs if patients die a few weeks later of extensively drug-resistant tuberculosis?* Each claim is valid, and yet together they characterize the current political, economic, and social environment within which public health organizations compete for government, corporate, and private foundation funding.

It seems that the jockeying for public health funding may have been exacerbated by the economic approaches to priority setting in public health and the methodologies used in cost-effectiveness analyses: the focus on comparing quantitative aspects (disease burden, mortality, and morbidity). In reality, health problems tend to be interrelated. With regard to serious childhood diseases, it is necessary to address all of them during at least the first five years of a child's life; if not, only the causes of illness and death are changed. Furthermore, when parents die, the children are at a higher risk of dying of childhood diseases. Thus, saving the lives of parents can be seen as part of a child survival strategy. Regarding the parents, at one time it was argued that tuberculosis usually occurred only once in an individual's life, and if you took away the disease, patients likely would survive, resume production, and be able to provide for their families. Whereas this changed with the HIV pandemic, it may change again with implementation of ARV treatment programs. Ignoring the essential interrelatedness of diseases is shortsighted and therefore, it seems, cost-effectiveness analyses are of limited use when setting priorities.

Communicable disease control programs should not compete amongst themselves. Such competition is counterproductive and undermines the public good. What is needed is a comprehensive health service that tackles all the health problems of children and adults, men and women, in urban and in rural areas. Public health professionals should not settle for less. This, however, requires appropriate strategies and attention to costs, including opportunity costs. Thus, while it can be argued that international leadership has failed to coordinate the public health funding needs into a cooperative effort, it is also the responsibility of the different expert groups to think of the public good.

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*Quote from "Expert: Killer TB strain, found in 28 South African hospitals, must have crossed borders," *International Herald Tribune*, Paris, France, September 7, 2006.

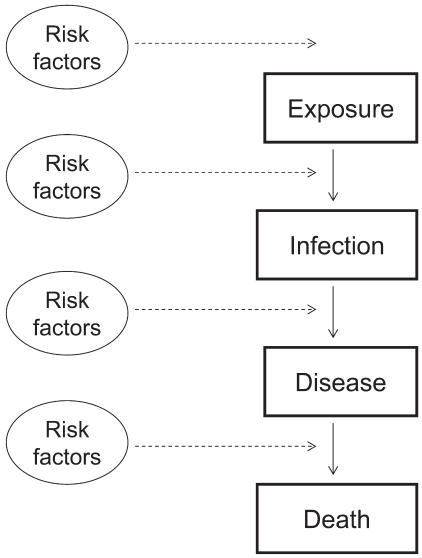
Tuberculosis epidemiology and options for intervention

Epidemiology

The progress of tuberculosis in a community,* in contrast to that of many other infectious diseases like smallpox, cholera, or Ebola, can be likened to low-intensity warfare. The tuberculosis bacillus digs in deep, preparing for a long fight. Although most people never develop active tuberculosis, one third of the world's population is infected, and the potential for disease is always there. Thus, the bacillus defies the changeable political commitment to public health of its human hosts.

The classical epidemiological model for tuberculosis is composed of exposure, infection, disease, and death (Figure 1.1). The determinants or risk factors for progression from one stage to the next in the pathogenesis of tuberculosis are discussed in detail in Rieder's *Epidemiologic Basis of Tuberculosis Control*.[30] A thorough understanding of these factors is essential to comprehend the dynamics of tuberculosis, to appreciate the forces that drive its progress in a community, and to hypothesize on the impact of interventions.

Figure 1.1 The epidemiological model for tuberculosis



The main factors that determine the risk of being exposed to tubercle bacilli include the number of infectious cases in the community, the duration of infectiousness, and social mixing patterns ("who mixes with whom").[30] Although exposure is a prerequisite for tuberculosis infection, infection does not always follow exposure. The main risk factors for infection are density and duration of exposure.[30] While an important aim of tuberculosis programs is to reduce exposure in the community, all the steps in the epidemiological model involve socioeconomic and environmental factors and thus the wider public health. Although research has identified a number of factors that can increase the risk of disease in persons infected with *M. tuberculosis*, in most cases (unless there is recent infection, which is a risk factor in itself) it is impossible to determine why a particular individual does or does not develop tuberculosis after infection.[30] The

*At least in communities where the bacillus is well established.

exception is in settings with a high prevalence of co-infection with HIV, where the latter is the obvious culprit.

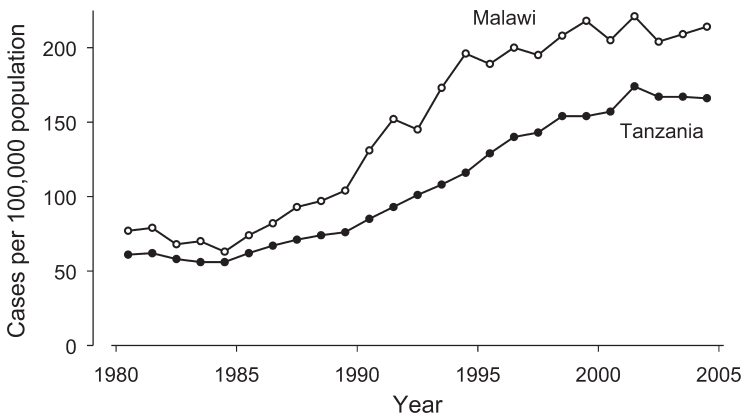
HIV infection is by far the strongest risk factor ever known for the development of disease, given that infection with *M. tuberculosis* and an HIV epidemic will upset the epidemiological equilibrium existing in settings with a high prevalence of tuberculosis infection among young adults. Provided that a surveillance system is in place, an increase in the number of tuberculosis cases, arising to a large extent from the pool of individuals infected with *M. tuberculosis*, is clearly demonstrated when HIV epidemics hit, as seen in the surveillance data from Malawi and Tanzania presented in Figure 1.2.[31]

Anti-tuberculosis treatment is the most important risk modifier regarding case fatality, and treatment is a powerful weapon in tuberculosis control. It shortens the duration of infectiousness and ill health and increases survival of patients. Therefore, it addresses all three public health objectives: reducing transmission, morbidity, and mortality. This is, as discussed in Chapter 2, provided that treatment programs are well organized so that cases are detected early in the course of disease and are rendered permanently cured with treatment. If, on the other hand, treatment programs perform badly, transmission can actually increase.

Interventions

The various options for intervention in tuberculosis are discussed in Rieder's *Interventions for Tuberculosis Control and Elimination*.[32] They are the following: prophylactic treatment, vaccination with bacille Calmette-Guérin (BCG), preventive

Figure 1.2 Notification rates of tuberculosis in Malawi and Tanzania, 1980–2004



Source: World Health Organization, 2006.[31]

chemotherapy, and treatment of tuberculosis patients. The first strategy seeks to prevent infection; the second, to prime the immune system to reduce the risk of progress from infection to disease in case infection occurs; the third, to prevent progress from infection to disease once infection has occurred; and the fourth, to reduce the risk of death from tuberculosis, restore health, and cure patients.[32] Little evidence of the efficacy of the first method to prevent infection exists, and BCG vaccination is not expected to have much epidemiological impact.[32] As a public health strategy, preventive chemotherapy is less efficient and more operationally difficult than treatment of tuberculosis. The target groups for the various intervention strategies differ. To be effective, a preventive chemotherapy program must target groups that can be easily identified and are likely to contribute a large fraction of future cases.[32] Recruiting recent converters (contacts of smear-positive cases, for instance) will yield greater efficacy than when there is remote infection. Tuberculosis case finding and treatment programs target infectious patients with the aim to render them noninfectious.

Whereas all the intervention strategies strive to reduce morbidity, mortality, and transmission of *M. tuberculosis* eventually in the community, the mechanisms, efficiency, and speed of effect differ, and they may perform differently in different epidemiological settings. Blower et al. put it like this: Tuberculosis epidemics may be viewed as a series of linked, time-lagged subepidemics. Different control strategies may be necessary for controlling each subepidemic, and different strategies may need to be employed as a particular epidemic ages.[33] Rieder uses the term "tuberculosis control" when referring to case detection and treatment, whereas he refers to preventive chemotherapy as part of a strategy for tuberculosis elimination. Furthermore, he argues that tuberculosis control is the first priority, followed by an elimination strategy only when control has been achieved and maintained over a period of time.[32] The policy model discussed here is primarily concerned with tuberculosis control.

As discussed above, the characterization of tuberculosis as a chronic disease can be counterproductive. One can argue that instances in which tuberculosis was administratively within the department of chronic—rather than communicable—disease control may have contributed to a slowing down of efforts to control the disease. The term "communicable disease control" carries the connotation of something rapid and effective, as opposed to the term "chronic," which suggests something slow and permanent that calls for adaptation rather than a solution. Indeed, an important element of care for those who suffer from chronic conditions is help with living and coping with a given condition. The introduction of anti-tuberculosis treatment in the 1950s, and later of short-course treatment, transformed tuberculosis from a truly chronic condition to a curable one, with profound consequences for the epidemiology of the disease and the organization of care for its patients. In short, the development of anti-tuberculosis treatment had a fundamental impact on tubercu-

losis programs. Many professionals, for various reasons, found it hard to adjust to the strategic changes brought on by the advent of chemotherapy. It can be difficult to change firmly established practices, and more difficult still when institutions and professionals see it in their interest to defend the status quo. Nevertheless, in industrialized countries, improved socioeconomic conditions and implementation of anti-tuberculosis treatment within generously funded health services effected rapid improvement in the tuberculosis situation, to the extent that the disease was no longer considered a problem. As tuberculosis was removed from the health agenda in these countries, it somehow fell off the international agenda as well. There was a failure to look at the wider picture—the situation in the rest of the world.

Historical background of tuberculosis control

Two twentieth-century occurrences fundamentally changed the management and course of tuberculosis in the community. The first was the development of chemotherapy, which radically reduced the risk of death from tuberculosis and exposure to infection in the community. The second was the HIV pandemic, which both altered the underlying forces that drive the course of tuberculosis in the community and undermined the efforts of treatment programs. Even in situations where the HIV pandemic did not decrease the effectiveness of tuberculosis programs as such, it did call the appropriateness of the control policy—case finding and treatment—into question. This is because the policy does not address progress from tuberculosis infection to disease, which is where HIV primarily exerts its force.

A further important development that surfaced toward the end of the twentieth century and that does affect the effectiveness of treatment programs is multidrug-resistant tuberculosis. Even if multidrug resistance is encountered in virtually every country, it is not at this stage a universal problem but rather primarily a consequence of bad local control programs. Multidrug-resistant tuberculosis does, however, have the potential to spread. Some experts choose to regard it as a separate epidemic.

Finally, despite the obvious advantages of a coordinated national policy, demonstrable public health gains, and recognized cost-effectiveness, in the late 1990s tuberculosis programs in high-prevalence countries had to fight for their existence in a hostile institutional environment to a large extent brought about by the structural adjustment programs imposed by international institutions such as the International Monetary Fund and the World Bank,[34] aided by external donors who did not always follow in their own countries the policies they advocated overseas (Box 1.4). In 1999, a case study in Shandong Province in China (a "World Bank province") suggested that financial decentralization, and the subsequent public funding shortfall in the poorer regions, may have

Box 1.4 Different agendas at home and abroad

In the late 1980s, following what was described as high-profile failures of the public health and communicable disease control function in the United Kingdom, there was concern that community medicine as a profession was in crisis, and it was considered important to reinforce public health functions and communicable disease control efforts.* At the same time, however, even if communicable diseases were a much greater concern in low-income countries than in rich countries, external donors called for "integration" that resulted in uncritical attempts to do away with communicable disease control structures in poor countries, structures that were conceived as "vertical."[40] This can be viewed as an inconsistency between advisors on national health as opposed to those on international health. In 2004, an article from Colombia characterized the effects of health reform as negative, citing a loss of focus, deterioration in surveillance, and weakening of public health functions with adverse consequences primarily affecting the poor.[41]

In the United States, progress toward controlling tuberculosis slowly ground to a halt after 1970, at the same time as targeted funding for tuberculosis control was phased out and replaced with general block grants to the states for public health services.[42] In early 1985, the incidence of tuberculosis, for various and complex reasons (for example, HIV, substance abuse, homelessness, and increased immigration), had begun to rise again.[43,44] By then, a disabled program infrastructure was ill prepared to meet the challenge. Targeted funding was eventually restored in 1991.[42] At the same time, international donors were encouraged to pool their funds in low-income countries, an approach referred to as basket funding, which discouraged earmarking of funds for particular activities or programs.[45] In the case of Mozambique—a country heavily dependent on external aid—donors complied, pooled their funds, and encouraged integration and coordination in what was referred to as the sector wide approach.[46] The result, from the point of view of tuberculosis control, was described in 2004 as the program becoming a victim of integration, with shortage of funds for supervision, evaluation, and training.[46]

*From the Acheson Report, quoted in Baggott,[1] pp. 85–86.

negatively affected tuberculosis control, contributing to an increase in the number of cases seen over the past decade in that nation's poorer areas.[35] Whereas some reports (a report from Kenya, for example[36]) have focused on the opportunities introduced by health sector reform, others have described the potential threats and real adverse consequences of reforms, as evidenced in Brazil,[37] Zambia,[38] and Thailand.[39]

The pre-chemotherapy era

Before the development of chemotherapy, sputum smear-positive pulmonary tuberculosis, referred to at the time as "open" tuberculosis, resulted in death in

30–40% of patients within a year of the onset of illness and in 50–70% within five to seven years.[30] The outcome was more favorable in so-called "closed" cases, suggesting that there might be distinct forms of pulmonary disease rather than a single course of events, with "closed" cases gradually developing into "open" ones. In this period, intervention was characterized by segregation of tuberculosis patients, nutrition and fresh-air regimes, and various types of surgical intervention. In the 1940s and 1950s, mass radiography for active case finding was a prominent component of control activities in many industrialized countries.[47]

Chemotherapy and its implications for tuberculosis control

The first-ever publication reporting the results of a randomized clinical drug trial concerned streptomycin treatment in tuberculosis and appeared in the *British Medical Journal* in 1948.[48,49] That same year, an article describing streptomycin resistance was published.[50] For the individual patient, the discovery of curative treatment meant survival; for the community, it meant reduced transmission. This discovery, along with the later application of preventive chemotherapy for those infected but not ill, raised hopes that the disease could be controlled and eventually eliminated.

From the point of view of tuberculosis treatment, the individual antituberculosis drugs were discovered in the 1940s and 1950s, and ethambutol and rifampicin were not introduced until the 1960s.[32,51] The early clinical trials with streptomycin demonstrated that treatment of tuberculosis with a single drug leads to the emergence of drug-resistant strains of *M. tuberculosis*, and subsequent trials of multidrug therapy concentrated on methods to prevent drug resistance from treatment.[32] By 1962, the role of treatment in the control of tuberculosis in industrialized countries had been firmly established, as Crofton observed: "If all patients could be treated, and their sputum converted to negative, new infections would cease. For a time new cases would continue to arise from previous infections, but this source should gradually decrease. Immigrants to the community would require to be carefully watched and treated when necessary."[52]

In Scotland, where tuberculosis mortality was rising at the time antituberculosis treatment was introduced, tuberculosis mortality declined immediately, and a few years later the number of notifications of tuberculosis cases declined as well.[53] However, the impact of treatment on the morbidity and mortality of tuberculosis in industrialized countries where both parameters were declining by the time chemotherapy was introduced has been disputed. Even so, it would be erroneous to conclude that chemotherapy cannot reduce tuberculosis mortality and morbidity in a different epidemiological situation or that tuberculosis control cannot be achieved in the absence of a favorable

socioeconomic situation. Cuba, which had a reported rate of tuberculosis of 4.8 per 100,000 population in 1991, is an example where tuberculosis was controlled in spite of economic depression and absolute poverty.[54] It is in fact somewhat ironic that Cuba might even be among the first nations to eliminate tuberculosis as a public health problem, because its precarious economic situation makes it an unlikely destination for migrants from high-prevalence countries.

In the early 1950s, treatment duration was commonly 12 to 18 months, or even longer in the case of extensive disease.[53] In the 1960s, treatment regimens of 12 months in duration became the norm, and a regimen consisting of isoniazid and thioacetazone, with streptomycin added in the first two months of treatment, was widely referred to as "standard treatment" or "the standard regimen." Anything shorter than 12 months came to be referred to as "short-course treatment." In the 1970s, clinical trials established the efficacy of 9-month regimens.[55–57] Since 1982, when a 6-month short-course regimen was definitively established as the standard of treatment in industrialized countries and as the minimally required duration of treatment, no fundamentally new regimen has been identified.[58]

In the early days of tuberculosis chemotherapy, the tendency of tuberculosis to relapse led to a recommendation of anywhere from five years to lifelong follow-up of persons with "inactive" tuberculosis. At the time, this high-risk group yielded an appreciable proportion of all reported "active" cases, even as much as 20%, in spite of the fact that those at highest risk were least likely to return for follow-up appointments.[59] When it became clear that reactivation among those who received good chemotherapy was very low—whereas among those who received poor and inadequate chemotherapy the rate was much higher—it was concluded that resources were better spent on ensuring adequate treatment to prevent relapse rather than on post-treatment follow-up care.[59]

Even after the development of short-course treatment, 12-month treatment continued to be used in low-income countries, primarily because rifampicin and pyrazinamide were considered expensive. When in the 1990s, as a result of decreasing drug prices and modifications in treatment recommendations, short-course regimens eventually became less costly than the 12-month regimen recommended in areas with high prevalence of HIV infection, the scenario changed and 12-month regimens became, to a large extent, obsolete.[60] This added to the urgency of improving tuberculosis programs in low-income countries, as the widespread use of the increasingly affordable rifampicin threatened accelerated the development of serious drug resistance.[60] With the increasing pressure on tuberculosis programs to use 6-month regimens with rifampicin administered throughout treatment (see Chapter 3), this demand became even more critical.

Tuberculosis programs

Apparently, the first public health act to prevent tuberculosis was the Decree of Lucca, in Italy in 1699, which required physicians to notify the General Sanitary Council of the names of patients with phthisis and to destroy their belongings after death.[61] While the former mandate is still one of the cornerstones of tuberculosis control, public health has come a long way since Lucca.

A tuberculosis program can be defined as a methodical approach, within a national health program, designed to progressively reduce the tuberculosis problem in the community.[62] The selection of technical policies in a program is made on the basis of priorities that may change with time and from place to place.[62] As discussed above, the discovery of curative treatment for tuberculosis had major implications for tuberculosis programs. Eventually, it meant that patients could be registered, treated, cured, and then discharged from care without the need for the prolonged follow-up that had been practiced before. This radically simplified case management as well as program management, and increased the feasibility of implementing tuberculosis treatment programs in developing countries.

What characterized tuberculosis programs early on was an emphasis on case finding and segregation of patients from the rest of the community. This emphasis lingered on even after the discovery and application of curative treatment. Only later was there wide acknowledgement of the importance of case holding and of the implications of drug resistance. The early programs emphasized a highly complicated, if not obsessive, surveillance register to keep track of high-risk groups, active and inactive cases, suspects and contacts. Such programs even attempted to follow all former patients for life.[63]

In 1957, Wherrett, the executive secretary of the Canadian Tuberculosis Association and a former member of the Council of The Union, noted that health problems are international and need to be attacked on a global scale.[64] At this time, he already felt that the world was getting smaller and he clearly expressed the importance of an international perspective. In an article published in the *Indian Journal of Tuberculosis*, he described the essentials of a tuberculosis program: adequate diagnostic services, treatment and supervision of known patients, and follow-up of contacts. He discussed training and motivation of health personnel, health education, and legislation. He pointed out the significance of primary care providers and a coordinated network of services, and he emphasized the importance of keeping good records. He discussed the different options for treatment administration, home-based and hospital-based, and recognized that the former presupposes a home in which treatment is possible.

In 1959, the prototype for tuberculosis services as the public health program seen today was put forward in the recommendations of the Arden House

Conference on tuberculosis, which emphasized government responsibility for control activities, ambulatory chemotherapy, standardized multidrug regimens under the supervision of a specialist, case detection based on an examination of individuals attending the general health services and having symptoms compatible with tuberculosis, bacteriological monitoring of the course and outcome of treatment, and periodic evaluation of the activities.[65,66]

Early development in low-income countries

By 1980, technically advanced countries had achieved good results in tuberculosis control.[67] At the same time, the tuberculosis problem had increased in developing countries. Bosman recalls how, in the 1950s, Western powers introduced programs for the control of tuberculosis in their colonies.[38] At independence, most of the emerging countries had national tuberculosis programs organized following concepts of control developed in industrialized countries, and relying primarily on surveys and radiology for case finding and treatment with isoniazid and streptomycin. Often, as in the example of Mozambique, these programs were predominantly urban.[46] A survey undertaken in Tanzania by the East African and British Medical Research Council, referring to patients enrolled on 12-month treatment in the period from 1969 to 1970, found that only 35% completed treatment (85% received at least three months, 67% at least six months, and 54% at least nine months).[68] Although a failure to complete treatment was not the only problem, the development of shorter treatment regimens was considered important for developing countries. In the 1960s and 1970s, massive research programs were conducted introducing rifampicin and pyrazinamide into tuberculosis treatment. Many of the clinical trials involved were carried out in developing countries. The result of these efforts was what is today referred to as short-course treatment.

As early as 1964, at a meeting of an Expert Committee convened by the WHO, the Director General noted that whereas tuberculosis remained a major public health problem in almost all countries, from a global epidemiological viewpoint, the increasing gap in tuberculosis prevalence between rich and poor countries was disturbing.[20] This development was seen as largely the consequence of an inadequate application of existing knowledge in developing countries (that is, insufficient intervention). The task of the Expert Committee was to advise on how the technology available at the time could best be applied under varying socioeconomic conditions and how the WHO could assist programs in developing countries. The Expert Committee identified four basic requirements for national tuberculosis programs to satisfy: efforts should be country-wide and permanent, adapted to the felt needs of the population, integrated into primary health care services, and appropriate given the available resources.[20] They emphasized the need for the WHO to strengthen its role as coordinator of a global tuberculosis program and advised that international

cooperation, coordination, and assistance were mandatory if tuberculosis was ever to be eliminated as a global threat to public health.

In the decade that followed, the implementation of tuberculosis control encountered many problems, from the shortage and poor distribution of financial, material, physical, and human resources to the inability to apply control measures and the lack of managerial skills and leadership.[62] An Expert Committee convened in 1974 refined the recommendations of the former committee. By this time there had been technological advances with the development of short-course treatment and evidence of the effectiveness of ambulatory treatment. Whereas this progress was partly a result of research conducted in developing countries, the main benefactors were the rich countries that were able to adapt their programs and apply the new knowledge. By the end of the 1970s, tuberculosis was no longer considered an important public health problem in industrialized countries and, in spite of the situation in developing countries and voices of concern, it gradually ceased to be considered a priority on the international health agenda.[38]

Divided opinions and mixed experiences

In 1979, an article published in the *New England Journal of Medicine** claimed that "leprosy and tuberculosis require years of drug therapy and even longer follow-up periods to ensure cure" and suggested that tuberculosis might be better addressed with an investment in research aimed at finding cheaper and more efficacious means of prevention and therapy rather than implementing immediate large-scale treatment programs.[69] The authors recommended that, in areas where resources were limited, "selective primary health care services" should be provided by fixed units or mobile teams visiting once every four to six months. Treatment of tuberculosis was not included.

At about the same time, The Union collaborated with the governments of Tanzania and several other developing countries to expand tuberculosis services country-wide and within the context of national tuberculosis programs, in accordance with the recommendations of the 1974 Expert Committee. Tanzania offered several advantages favorable for the implementation of a national program. The nation had participated in the clinical trials network, maintained a well-functioning reference laboratory, and was committed to improving access to integrated health services nationwide. There were, however, enormous obstacles as well: a rapidly expanding and widespread rural population, a high prevalence of tuberculosis, and a great shortage of qualified medical staff.[70]

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*This was presented at the meeting on Health and Population in Developing Countries held in the Bellagio Center in Italy and cosponsored by the Ford Foundation, the International Development Research Center, and the Rockefeller Foundation.

In 1980, responding to a request of the World Health Assembly, the WHO and The Union convened a joint study group to review the obstacles to implementing the recommended strategies to control tuberculosis in developing countries.[71] In an article in *Tubercle* in 1982, Bignall observed that the challenge for the study group was not so much to identify the causes of failure to control tuberculosis in developing countries, many of which were well known, but to report them effectively using the diplomatic phraseology necessary for the sponsoring bodies, namely the WHO and The Union.[71] The study group concluded that the difficulties involved in putting into practice the principles put forward by the 1974 Expert Committee had been greatly underestimated.[67] In their report, they identified numerous reasons for the malfunction in tuberculosis control, including a lack of specialized technical support for the general health services (that is, supervision), misunderstood integration, and reluctance of the primary health services to take responsibility for tuberculosis control, as well as deficient coordination of public and private service providers. Other reasons listed were the meager primary health care infrastructure in many countries, limited involvement of the community, inadequate financial resources and materials for diagnosis and treatment, insufficient staff training, and other human resource issues such as scarce opportunities for career development and frequent turnover of staff at the peripheral level of the health system. Finally, they pointed out the absence of evaluation of activities at all levels and of applied research on the problem of program delivery in the different settings of the diverse countries. They predicted that the effect of tuberculosis control would depend mostly on the quality and rate of development of primary health care and the degree of integration, and emphasized the importance of studying the program modifications implied by this as well as the value of maintaining expertise in the new scenario, that is, after decentralizing program activities. Many if not most of the issues involved had already been described by Fox in the 1960s.[72,73] The 1980 report concluded that it was not realistic to expect tuberculosis to be no more of a problem in developing countries than in technically advanced countries by the year 2000, a fact explained to a large extent by the disease's natural history. Perhaps it was partly this last observation that resulted in the international community finally turning its gaze away from tuberculosis.

The World Bank studies

Approximately ten years into The Union's collaborative programs referred to above, a report of a Commission on Health Research for Development identified tuberculosis as a neglected disease.[74] It came as a surprise to many when the World Bank, having included the national tuberculosis program in Tanzania in a study on the cost-effectiveness of various health interventions, con-

cluded that tuberculosis control was among the most cost-effective interventions in the health sector in low-income countries.[10,75,76] The main program issues addressed in these studies were cost-effectiveness of treating smear-positive patients with 12-month versus short-course treatment, hospitalization versus ambulatory treatment, and the issue of HIV-positive patients. Whereas diagnosis and treatment of tuberculosis were free of charge in the programs collaborating with The Union, various other costs borne by patients (such as transport and lost income) were not included in the World Bank analyses. The studies only included three of the African countries collaborating with The Union: Tanzania, Malawi, and Mozambique. These were all countries with universal health systems, and it was not obvious that the findings could be generalized to pluralistic health systems. Finally, the studies did not compare tuberculosis programs in countries collaborating with The Union to tuberculosis programs in other countries. The reason programs collaborating with The Union were chosen had much to do with the fact that they were well defined and organized, which could not be said of all tuberculosis programs in Africa or in other high-prevalence settings at the time. The programs collaborating with The Union were not the only examples available, however; for example, a program based on similar principles had been successfully implemented in Beijing, China, in 1978, but this program was not country-wide.[77,78]

While Kim et al. claim that many health policy makers, including tuberculosis experts, look to cost-effectiveness analyses to help them recommend the most favorable interventions within a context of limited or shrinking resources,[79] it may be more prudent to say that tuberculosis experts simply seized the opportunity created by the World Bank studies—which they had not commissioned—to promote tuberculosis control. What primarily made the World Bank studies credible was the fact that they were conducted by experts who had nothing to do with the programs they were studying and thus were not stakeholders. This cannot be said about all cost-effectiveness analyses subsequently undertaken in various tuberculosis projects. In the World Bank studies, tuberculosis control, as implemented in the programs collaborating with The Union, was compared with a number of interventions in other health fields such as immunization against measles and oral rehydration therapy.[76] Thus, the World Bank studies did not help the tuberculosis community find cheap solutions but rather changed the ranking of tuberculosis in relation to other health problems in low-income countries for the purposes of setting priorities. Kim et al. may, however, be right in that tuberculosis experts subsequently may have used the results of cost-effectiveness analyses differently.

Generally speaking, cost-effectiveness analyses have been criticized as technocratic, disease focused, and efficiency driven. Further, such analyses have been charged with not taking into account major issues such as context,

coverage, and infrastructure.[10] The World Bank analyses, however, coupled with the effect of the HIV pandemic and the recurrence of tuberculosis in Western cities, helped put tuberculosis back on the international health agenda. The Union model was there at a convenient moment. As pointed out by Ogden et al., if it had not been for the circumstances at the time, the model might never have made it onto the international policy agenda.[80] Although the initiative did not come from the WHO, the organization did not fail to respond once the problem had been exposed.

The return of tuberculosis to the international health agenda

The reemergence of tuberculosis as a priority led the WHO's Tuberculosis Program to reassess its control strategy and activities in the early 1990s and to put forward a new framework for tuberculosis control.[81] In April of 1993, the WHO declared tuberculosis a global emergency.[81] Because tuberculosis for so long had been neglected and labeled a "chronic" or "social" disease, such a declaration was a clever move. It was important to emphasize the fact that tuberculosis is a communicable disease that can and should be treated and cured, and that there were no excuses for not achieving that goal. This was a long overdue wake-up call for national governments, health professionals, academicians, and the international community, who had become dormant or indifferent to tuberculosis. It also strongly motivated those who worked on the front line. Suddenly, their efforts seemed important; they felt the expectation to deliver and anticipated recognition if they did.

By the time the WHO declared tuberculosis a global emergency, the incidence of tuberculosis in sub-Saharan Africa had increased dramatically, especially since the pandemic of HIV in the second half of the 1980s. Drug-resistant tuberculosis was emerging in several countries as a result of badly organized tuberculosis services. The Union's collaborative programs were identified as a suitable model for a new tuberculosis control policy to be endorsed by the WHO. Although the policy put forth by the WHO and known as the "DOTS strategy" has since been successfully introduced in many countries,[65] it is increasingly debated whether this model is adequate in areas with a high prevalence of HIV infection and in programs where high levels of poly- and multidrug resistance exist.

The Union, in advising tuberculosis programs in low-income countries, adhered to a set of basic principles. Its model otherwise remained dynamic and flexible, and adaptation to local circumstances characterized its implementation in the various collaborative programs. Today it can be said that the model is surprisingly "modern" when compared even to communicable disease programs and health services in many industrialized countries. This observation is made not in terms of technology but rather in terms of its operational and

managerial focus: the comprehensive and integrated approach used, its simplicity and coherence, the patient-focused approach emphasizing active follow-up and support on an individual basis, the way information is handled and used, and the emphasis on quality assurance and outcome assessment. These characteristics of the model are an important source of motivation for those involved in its implementation.

Tuberculosis control as a public health program

Keeping in mind the prerequisites for public health programs discussed above, the justification for tuberculosis control is straightforward. First, tuberculosis is a communicable disease and ranks among the priority health problems in low-income countries. Even if the absolute disease rate fails to impress, the relatively young age of tuberculosis patients in poor countries and the prolonged duration of illness and high mortality when the disease is left untreated should underscore the fact that the disease burden is greater than suggested by the mere number of cases. Furthermore, inadequate treatment brings the risk of drug resistance, which worsens matters. Finally, tuberculosis is commonly a disease of the poor and disadvantaged; addressing it, therefore, is a question of equity.

Second, criteria and standards in tuberculosis control are relatively well defined. An effective and acceptable intervention exists to affect mortality, morbidity, and transmission. Risk groups can be defined and assessed. The cost, participation rate, effectiveness, and efficiency depend primarily on the health infrastructure and local policy adaptation.

Third, the natural history of tuberculosis was thoroughly studied before the development of chemotherapy and provides the background against which the impact of interventions is evaluated. Information sources exist in programs successfully implementing tuberculosis registers, treatment cards, and reports. The overall policy is fairly well researched, and the operational strategies and processes are clearly described.

Local tuberculosis control policies, strategies, and programs should not be static.* They need to adapt to changing epidemiological, operational, and social scenarios and incorporate technological advances. Styblo suggested that as tuberculosis declines it is desirable to replace the tuberculosis program with what he referred to as a surveillance system for the disease.[19] Thus, in low-prevalence countries (elimination phase), a surveillance and containment strategy similar to that utilized in the final stages of the smallpox eradication campaign replaces or is added to the tuberculosis control strategy (case finding and

*Referring to a program as "the new national program" or "the revised national program" can be seen as going against the notion of dynamism and policy development.

Box 1.5 The Orange Guide* on the aim of the fight against tuberculosis

According to the Guide, the aims of the fight against tuberculosis are

—*for individual patients*, to cure their disease, to quickly restore their capacity for activities of daily living, and to preserve their position in their family and community; and

—*for a community*, to decrease the spread of infection and, by this means, to hasten the disappearance of the disease from the society.[82]

*This guide was first published in 1986, and is frequently referred to as the Misereor Guide, or the Orange Guide.

treatment). This is the focus of tuberculosis control in many rich countries today, where the main emphasis is on surveillance and outbreak investigation.

The public health goals of tuberculosis programs

The policy model primarily deals with case finding and treatment of tuberculosis. Reducing tuberculosis morbidity and mortality is always a public health intervention even if tuberculosis control is not achieved. The first publication containing comprehensive recommendations based on the policy model developed in The Union's collaborative programs summarized the aim of the fight against tuberculosis, as presented in Box 1.5.

The stated objective of the tuberculosis program in the early 1990s, with the launch of the new control strategy of the WHO, was to reduce tuberculosis mortality and the prevalence and incidence of the disease.[83]

Styblo's policy model

The Union

The International Union Against Tuberculosis, an international nongovernmental organization, was formally incorporated in 1920 with the goal of forming a federation of national associations dedicated to fighting global tuberculosis and promoting scientific collaboration, as well as coordinating the findings of tuberculosis studies.[84] In its early years, the organization arranged international meetings and conferences and launched a publication as early as 1924. During the Second World War, all activities of the organization came to a standstill. With the creation of the WHO in the post-war period it was uncertain if this new body would take over the activities of The Union.[84] Instead, in 1948, The Union became affiliated with the WHO, and efforts were made to define the respective functions of the two organizations. It seemed that by vir-

tue of its independent nature, The Union was particularly suited as a forum for discussing the scientific and medico-social problems that needed to be solved in order to facilitate action planning in the fight against tuberculosis.[84] The role of the WHO, on the other hand, a government-sponsored organization possessing administrative and financial resources, would be to help develop anti-tuberculosis campaigns targeted at less-developed countries and carried out on a scientifically determined plan of action.[84]

In 1948, an Expert Committee on Tuberculosis put forward a frame of reference for the activities of the WHO.[85] The report identified five fields of activities and a list of techniques to be employed. The fields were the following: prevention, case finding, isolation and medical care, rehabilitation and aftercare, and social and economic protection of afflicted families. The techniques included: determination of the extent of the problem (that is, disease burden or needs assessment), including consideration of a surveillance or information system; recruitment and training of professional personnel; provision of physical facilities, supplies, and equipment; health education; establishment of field services for demonstration purposes (to be taken over by nationals); financial support to member countries; research for the purpose of developing and recommending uniform procedures; clarification of the role and nature of bovine tuberculosis; issues of law and regulations; preparations for reviews; and evaluation.

In accordance with its mission, The Union conducted research of public health issues under the auspices of scientific committees set up in 1953, including cooperative studies on chemotherapy, preventive treatment, radiology, and standardization of bacteriological procedures.[84] The Union was also involved in developing epidemiological surveillance. Then there was the Mutual Assistance Program.

After the Second World War, The Union paid particular attention to the so-called underdeveloped countries.[84] A first technical meeting concerned with tuberculosis control in Africa was held in 1955.[84] By this time, in order to extend its influence to countries far from its headquarters (in Paris), The Union had set up Regional Committees. In 1959, the Union secretariat, acting on an initiative from the U.S. National Association for the Study and Prevention of Tuberculosis, placed a resolution before the Executive Council of the WHO, who in turn forwarded it to the World Health Assembly held in Geneva in 1960, that the WHO make the worldwide elimination of tuberculosis a top-priority public health problem.[84]

The term "Mutual Assistance Program" was proposed by Eddie O'Brien of the Canadian Tuberculosis Association and adopted at the international conference of Toronto in 1961.[86] Supported with a Canadian government grant, it sought to provide technical and material assistance to national tuberculosis associations in developing countries to enable them to fulfill their roles as

partners to their governments in the fight against tuberculosis. This represented an innovative approach to promote solidarity between governments and voluntary organizations and between rich and poor countries.[86] According to Rouillon, the direction that the Program eventually took, however, was to assist in formulating a model for national programs in poor countries with a high prevalence of tuberculosis and to back its launching and evaluation.[86] This course of events was spurred by a request to The Union and other international experts from the Government of the Republic of Tanzania, in 1977, to advise it in integrating the health services of numerous charitable bodies into a national framework to control tuberculosis and leprosy. Styblo applied the results of his own research as well as that of many others to weave the essential elements into a comprehensive policy that realistically could be implemented in developing countries.

The Mutual Assistance Program and the policy model

Rouillon divides the Mutual Assistance Program into two phases.[86] According to her, its main activities from 1961 to 1976 involved support to national tuberculosis associations; organization and sponsoring of meetings, conferences, and courses; financing the publication and distribution of printed material; and field activities in specific countries. During a session held by the African Region of The Union in November of 1976, several key issues were raised, including the necessity of having a modern national tuberculosis program in every country, training of health personnel, and obtaining reduced drug prices for the region, as well as the criterion that any support provided to countries should be in response to felt and expressed needs of the countries concerned.[70]

Following the international consultation called for by Tanzania in 1977, The Union entered into extensive direct collaboration with several national tuberculosis programs with the aim of assisting country-wide implementation of tuberculosis control measures in developing nations (Box 1.6). The main reasons for this change in direction, according to Rouillon, were disappointment with the results of the Mutual Assistance Program up to that point, as well as the belief that it would be more rewarding to work with governments directly, given that several governments were showing real interest in tackling the problem of tuberculosis at the same time as national tuberculosis associations and international agencies were losing interest.[86] The policy model was based on the principles laid out in the Arden Conference and reflected in the report of the Expert Committee of 1974. The initial approach was subsequently modified to take into account local circumstances and lessons learned along the way.[86] As an example, at the request of the Minister of Health of Tanzania, the policy of hospitalizing tuberculosis patients was reintroduced because ambulatory treatment was problematic in some cases. As discussed later, the results with 12-month treatment turned out to be disappointing; therefore,

Box 1.6 The Union partnerships and development of the policy model

A survey undertaken in Tanzania by the East African and British Medical Research Councils and published in 1977 revealed inadequate results of 12-month treatment, with only 35% of patients completing treatment, a finding similar to the one reported earlier for Kenya.[68] Of note, however, was the finding that districts where no specialized tuberculosis services had been organized achieved a substantial level of success when compared to districts with specialized services. Thus, it was concluded that treatment could well be conducted within the framework of the general health services and following instructions laid down by the Ministry of Health. This was considered an observation of great importance and very relevant to the policies of the WHO at the time: decentralization and primary health care.

In 1977, the Government of Tanzania requested that The Union coordinate support of international donors to their national tuberculosis program.* With input from numerous experts, a national program was approved on May 4, 1977, by the Minister of Health of Tanzania.[70] The Union undertook to give further technical guidance for training activities and for evaluating progress. The aim of the national program was to progressively reduce the tuberculosis problem in the country. For this purpose, the program was regarded as permanent—that is, continued for at least a generation—in order to make a marked impact.[70]

In the years that followed, The Union entered into collaboration with several other developing countries, among them Benin, Malawi, Mozambique, and Nicaragua.[87–93] In each country, the collaboration involved a government (the Ministry of Health and the National Tuberculosis Program), a donor (a government or nongovernmental organization; sometimes more than one donor and more than one country was involved), and an expert from The Union as technical advisor and monitor. Government commitment was considered an important precondition and thus the initiative for collaboration came from the recipient government.

Together with its collaborators, The Union pioneered country-wide expansion of short-course treatment in poor countries in the early 1980s.[70,86,94,95] A new information system was introduced: in Tanzania in 1979 (fully operational in all districts in 1984),[96] in Mozambique in 1984,[91] in Malawi in 1984,[97] and in Nicaragua in 1988.[98] Short-course treatment was also introduced: in Tanzania in 1982 (in five years it covered 85% of new cases treated), in Nicaragua in 1984 (with almost 80% coverage of new smear-positive cases enrolled in treatment five years later),[98] in Malawi in 1985 (with expansion to all districts in three years), and in Mozambique in 1985.[46] In Mozambique, however, expansion was held back by the civil war, and satisfactory coverage was achieved only in 2000, four years after the end of the war, in 1996.[46]

(*continued*)

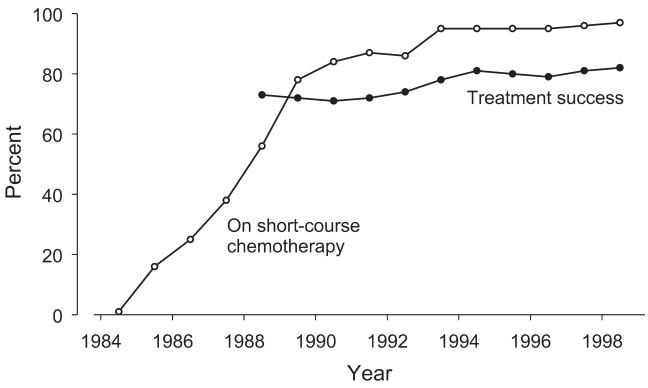
*The Tanzania project was a joint undertaking of the Government of Tanzania, the Anti-Tuberculosis Association of Tanzania, and The Union, in collaboration with the WHO, Misereor, the Swiss Association Against Tuberculosis and Respiratory Disease, the Swiss Technical Co-Operation Department, the Government of Japan, and a number of other organizations,[70] including leprosy organizations.

Box 1.6 *Continued*

It is important to acknowledge that the Union collaborations concerned implementation of tuberculosis control within the general health services of these countries rather than a vertical structure in the classical sense. The programs differed depending on the characteristics of the local health services. Following training of health personnel and implementation of a comprehensive management system, short-course treatment was introduced first in pilot areas and then progressively expanded until it was in use country-wide. Although in the long run the initiative can be regarded as health services and policy research with wide and, to some extent, universal relevance, local ownership and responsibility as well as sustainability were always stressed. From the outset, The Union emphasized continuity for at least a generation and sustained commitment of external input. These collaborations arguably surpassed in valuable assistance any politically driven donor initiative.

The extent of external funding to each national program differed, but invariably covered only a proportion of the total cost of the program, no more than 15% to 25%.[86] The external assistance was nonetheless essential in that it subsidized drugs and laboratory equipment and materials, which generally required foreign currency, as well as training and evaluation. The majority of the cost—for infrastructure, salaries, and transportation, for example—was borne by the countries themselves.[86] The guiding plan directed countries to progressively finance more of the consumables as their economic situation improved and the tuberculosis problem came under control.[86]

Figure 1.3 Phased introduction of short-course treatment in Nicaragua



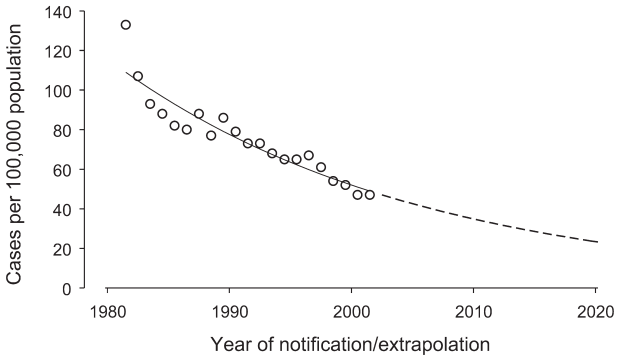
Data from annual reports of the Nicaraguan tuberculosis program.

Box 1.6 *Continued*

In retrospect, reaching the aforementioned goals may have been a battle lost from the start. Just as the initiative took off, so too did the HIV pandemic, and by the mid-1980s its devastating effects on the tuberculosis situation had begun to unfold. In 1983, the first cases of AIDS were reported in Tanzania.[96] As early as the period from 1986 to 1987, the tuberculosis program reported an increasing number of unexplained deaths.[86] An epidemiological study referring to 1991 to 1993 estimated that two thirds of the increase in smear-positive tuberculosis cases were directly due to HIV infection.[96] In spite of the increase in the number of cases treated in Tanzania, though, treatment outcome in smear-positive cases remained good and drug resistance low.[96]

Nicaragua eventually became an early partner that was little affected by the HIV pandemic and the setting where the intended effect of the policy was most clearly realized (Figures 1.3 and 1.4); namely, that with a 4% to 5% annual reduction in risk of infection, the tuberculosis problem would decrease by 50% in 15 years,[19] tuberculosis would cease to be a major health problem within 20 to 30 years,[99] and the program would be financially sustainable.[86] For comparison, in Malawi—a country hard hit by the HIV pandemic—the reported number of tuberculosis cases increased dramatically. The national program all but collapsed, and the cure rate dropped as the country struggled to cope with the increasing case load.[100] Longitudinal epidemiological studies in Karonga District in Northern Malawi suggest, however, that the control program is working reasonably well, with the estimated rate of smear-positive tuberculosis in the absence of HIV decreasing from 78 in the years from 1988 to 1990 to 45 per 100,000 population in the period from 2000 to 2001.[101]

Figure 1.4 Trend in observed and expected tuberculosis case rates, Nicaragua



Data from annual reports of the Nicaraguan tuberculosis program.

a short-course regimen was introduced for the treatment of smear-positive cases. With this came the necessity to develop the laboratory services further, to increase treatment supervision, and to devise an appropriate retreatment regimen.

The model was not developed for global tuberculosis control, as is sometimes stated.[102] It was developed in a specific context and with the participation of local professionals. Styblo had against him the forces of the "primary health care" movement, the "selective primary health care" movement, the "integration" movement, and the "tuberculosis community" who did not approve of short-course treatment for developing countries and were against hospitalization of patients for tuberculosis treatment.

The Union's collaborative programs were not research projects in the strict sense of the word; for example, elements of comparison were missing. They were carefully designed and executed, though, and above all continuously evaluated. It can be argued that the situation was ideal for policy development. The countries were relatively small (in population), with uniform and well defined, if to some extent poorly developed, health systems. In such a scenario, practically all patients that are detected are included and featured in the evaluation. Isolated urban or rural programs would not have been fully representative. A pluralistic health system would have raised the issue of patients being under someone else's care, receiving inferior care, or being excluded from care altogether. Without local initiative, commitment, and ownership, the intervention might not have succeeded. Whereas some commentators regard the model as being prepared, branded, and marketed by the WHO and "transferred" to low- and middle-income countries,[80] the model was in fact a product of collaboration between rich and poor countries and governments and nongovernmental organizations, which then influenced tuberculosis control policies in both rich and poor countries alike via the WHO. Thus, one could even speak of "transfer" from low-income to middle- and high-income countries.

The preconditions

Government commitment

Government commitment is important for bringing about policy change. On the other hand, prevailing institutional arrangements can restrict access to the policy-making process and inhibit new ideas.[1] In this context, two things were important for the development of the policy model. First, the political environment in most of the countries collaborating with The Union was favorable for the purpose of tuberculosis control. As an example, while during the postcolonial period many sub-Saharan African countries attempted to build health systems that would better serve disadvantaged areas, the majority of government and international funding continued to go to curative, urban services.

Tanzania and Mozambique were the exception, both of them promoting a strategy emphasizing community-based health care.[34] A significant development was expansion of rural health centers staffed by auxiliary medical workers, which improved health services coverage. By the mid 1970s, however, these early efforts to reshape health care delivery and governance were severely undermined by economic recession, which resulted in dramatic shortages of resources to invest in health care, education, and social services.[34] A quarter of a century later, the situation in Malawi was described as featuring severe staff shortages in the health sector as well as poor salaries and conditions resulting in high turnover of health workers.[103]

Although some observers view tuberculosis as a problem put on the agenda by external experts and donors, an examination of The Union's early collaborating nations contradicts this interpretation. In all the countries, local health authorities identified tuberculosis control as a priority. Addressing health in general and tuberculosis in particular, in addition to collaboration, was a clear, local, and actively sought intention.[46,70,104] Because of broader political changes in the countries concerned, genuine will arose to bring about change and move forward. This provided an opportunity for critical thinking and formulation of sensible policies. The experience has been described by independent researchers as a bottom-up process, with a good deal of discussion and interaction taking place among policy communities of domestic, regional, and international actors.[46] The fact that the model was formulated largely outside of an institutional structure such as those of industrialized countries formed the other important element. Because no powerful local institutes existed in the countries collaborating with The Union at the time, and no such institutions in industrialized countries or international organizations showed much interest in tuberculosis, the model was developed without interference from powerful and influential stakeholders. This is a different scenario altogether than exists today.

The Union's collaborations were often cited as proof that effective case management of tuberculosis could be achieved in any situation,[105] but the similar contexts shared by the collaborating nations in question and the presence of universal health systems rendered this notion debatable. It was yet to be proven that the model could work in different settings and in pluralistic health systems.

Scientific context

In the scientific context, the model was conceived at a turning point. On the one hand, there was a radical shift in the approach to case finding, with clarification of the role of sputum microscopy vis-à-vis mass radiography. Secondly, there was the gradual realization that case-finding activities without proper organization of treatment services to ensure a favorable outcome (that is, the importance of what was referred to as "case holding") was futile.

The radical shift in the approach to case finding was brought about by the findings in the 1960s and 1970s of studies in Czechoslovakia's Kolin District that mass radiography surveys did not produce the expected result, namely the prevention of occurrence of infectious cases in the community.[106,107] Infectious cases continued to appear in spite of periodic mass surveys implemented for 12 years in the study areas. Most of the cases were detected when symptomatic patients contacted the health services in between surveys. Thus, it was clear that case finding could simply be organized within the health services.

Regarding case holding, the 1974 Expert Committee argued that whereas case finding was an essential component of tuberculosis control, case finding per se was not a control measure; rather, its objective was to identify the sources of transmission in a community in order to render them noninfectious.[62] Thus, the Expert Committee concluded that case finding and treatment must go together and the two activities should be regarded as a single functional entity. This was an important shift in focus: until this time, little attention had been paid to treatment outcomes in mass chemotherapy programs in developing countries, despite concerns that irregular and incomplete treatment would result in drug resistance. It was only after a joint WHO mission to India headed by Grzybowski and Styblo that, in analyzing the results of data from Bangalore, Grzybowski awoke to the well-known fact that case finding without treatment was a useless and unethical activity.[108,109] His insistence during meetings of the Tuberculosis Surveillance Research Unit (TSRU) in the early 1970s persuaded Styblo and others that the focus must shift to documenting treatment success.

Sustainability

In the context of development assistance, sustainability was already considered an important issue when the policy model was developed. Sustainability can be defined as a system's ability to produce benefits sufficiently valued by users and stakeholders to ensure the resources to continue activities.*

Sustainability demands that interventions take note of local settings in terms of both appropriate technology and competing priorities. A potential problem with regard to sustainability arises when international agencies or donors unduly influence local communities or governments on matters of policy and priority setting. (In the 1980s, for example, external aid became increasingly conditional on standardized economic and political restructuring that included the health sector.[110]) Further, donor inputs in the policy development process can reinforce the fragmented manner in which policy is formulated. Often, donor agendas are inconsistent. As an example, consider the promotion

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*UNICEF. *Health Policies and Strategies: Sustainability, Integration and National Capacity-Building*. Unpublished document E/ICEF/1992/L.2. New York, NY: UNICEF, 1992.

of vertical programs and projects out of a desire for short-term results, on the one hand, and broader health systems development initiatives, on the other, without the necessary dialogue between the two contrary approaches.[111] Another problem with regard to sustainability occurs if money flows regardless of local needs. Sustainability may be drowned by the massive mobilization of funds at the international or global level and their indiscrete disbursement. External funds may compromise long-term sustainability if a low-income country struggling to achieve the sustainability of its health programs on its own terms gives up the effort and, instead, accepts whatever the donors offer. It is not uncommon to find inconsistencies in high-level policy documents and discussions (for example, in tuberculosis[112]) where at one point policy makers argue that available funds make the implementation of one strategy or another advisable and then, at a later point (in the same document even), that increased resources are needed so that the proposed strategy can be implemented properly. Perhaps the most complicated problem in terms of sustainability in recent times, however, is the influence of external debt servicing on social and health policies in poor countries. This problem is of a different nature, and could not in any way be dealt with at the program level.

Operational flexibility is an advantage of the involvement of international nongovernmental organizations in low-income countries, as they may be able to increase funding allocations according to changing needs or requirements, which may reduce implementation delays.[103] This, however, can result in removing the priority setting from the hands of local governments and communities and, in the worst-case scenario, leaving them with all kinds of programs initiated by enthusiastic but sometimes naïve expatriates lacking thought or planning with regard to sustainability. In the long run, external funding tends to fade away. What then becomes of initiatives is often ignored. This question is relevant for those participating in new partnerships in the field of tuberculosis control today.

The product

The Union model used evidence from scientific and operational research and applied it in a specific context. Styblo did not initially present a final product but rather the pieces of an incomplete puzzle. The various pieces were obtained here and there; some were kept and others discarded. Policy was developed gradually as lessons were learned along the way, even after Styblo had left the scene. In 2004, an article from Mozambique describes how tuberculosis policies there evolved in the 1980s through a technical network of national and international experts, emphasizing that policy transfer was not a linear, top-down process but rather one that occurred in a series of policy loops over a long period.[46] Lessons learned in Mozambique and in the other countries then fed into the globally promoted policies of the 1990s.

Certain components of the resulting policy model are clearly universally applicable. These include the managerial strategy; that is, the comprehensive and the patient-centered approach, the coordination within the health services, the information system, and the materials management and supervision methodologies. Other components depend on the setting, such as specific treatment regimens and what is referred to as the treatment algorithm. These are constructed in a balanced fashion such that, if meddled with, the consequences must be carefully worked out all the way through. (This matter is discussed later.) Strictly speaking, there was only one element in need of standardization at the supra-national level: basic surveillance, because tuberculosis is without a doubt an infectious disease of international significance.

When considering the policy model, various aspects can be differentiated. First, there are the preconditions for tuberculosis control as discussed above, in particular government commitment. Second, there are basic principles—a general approach based on a scientific foundation and to a large extent universally relevant; this is the topic of the following chapter. Third, there are operational strategies. The term "operational strategy" as used here refers to technical details that depend on the setting to an important extent. The operational strategies are discussed in Chapters 3 to 5. Finally, there is operational support: services structure, logistics, and information and quality-assurance systems. These topics are addressed in Part II.

Summary and conclusions

Tuberculosis is a well-established disease in human populations. Its control constitutes a public health program. Treatment of tuberculosis is at the same time a policy of cure and prevention. The discovery of anti-tuberculosis chemotherapy in the twentieth century radically changed the epidemiology of tuberculosis and the approach to tuberculosis control. Whereas the broader public health and social agenda is important for the long-term containment of the disease, it would have been unethical to wait for the results of their implementation while there was a way to reduce tuberculosis morbidity and mortality with medical intervention at reasonable cost. Primary health care is the most important level of implementation of tuberculosis control, but coordination within the health system is essential and the place where public health professionals play a key role.

While influential players advised against investment in tuberculosis programs in the late 1970s, the technical staff of The Union, together with collaborators in rich and poor countries, went ahead and pioneered the national expansion of tuberculosis programs and short-course treatment within the general health services in developing countries. One way to look at this phe-

nomenon is as a technology transfer: a short-course regimen was introduced in Tanzania in 1982, at the same time as short-course therapy was definitively established as the standard of treatment in industrialized countries. A system for delivering short-course treatment in the circumstances of developing countries was needed, a strategy that would at the same time prevent the emergence of drug resistance. The resulting policy model should be examined with this in mind.

Independently of The Union, the World Bank identified the approach used in the collaborative programs as among the most cost-effective health interventions in low-income countries. When the WHO stepped up its commitment for tuberculosis control in response to a worsening global epidemiological situation, they used the policy model as the basis for their new strategy that was launched in the early 1990s.

The background and contextual factors contributing to successful implementation of the policy model have been discussed in this chapter. The following chapter describes the model itself, and examines its scientific foundation and the basic principles of tuberculosis control.

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2

Scientific foundation, policy, and principles

The making of policy is a continuous pursuit. Research findings enlighten the policy formulation process but cannot replace it.

The first priority of tuberculosis programs is detection and treatment of patients with the disease. This chapter examines the basic principles of tuberculosis control and their scientific foundation and describes the policy model arising from the tuberculosis programs developed in collaboration with The Union. But first some general aspects of policy formulation in public health will be considered.

Background

Policy, evidence, and public health

What is referred to as the evidence-based approach originates in clinical medicine. Some observers insist upon pausing before the evidence-based approach is transferred wholesale to policy making in general and public health policy in particular. Many policy questions present thorny issues concerned with complex and ever-changing situations in which many elements interact. Applying evidence to such problems is not simple. Kemm has pointed out that the assumption of comparable groups is rarely justified when the unit of intervention is a community.[1] Thus, randomized controlled trials—the gold standard in evidence-based medicine—are not always appropriate for the study of public health interventions. At least the results from such trials must be considered together with other evidence. The requirements of trial design may lead investigators to fit the intervention to the trial rather than the other way around, which can result in a weak intervention. With this in mind, it is not surprising that few public health programs have been shown to be effective by controlled clinical trials, even if specific components of programs may have been proven effective by such trials.

Further, according to Kemm, the notion of a "best solution" ignores the complexity of the decision-making process. For example, in tuberculosis

control several treatment regimens have been shown to be efficacious in randomized controlled clinical trials, but they may not all be equally appropriate in all situations. It is not a given that a treatment regimen shown to be superior in a clinical trial is indeed superior in each and every real-life setting where the community is the unit of intervention and when looking at a treatment program's long-term impact. In the process of transferring evidence from clinical trials to public health policy, different questions arise that are likely to require different study methods, and it seems irrational to regard any method as superior for all purposes.[1] Not everyone agrees with this view, however. To give an example, the Cochrane database contains analyses whose recommendations insist on randomized trials on various operational strategies to promote adherence to tuberculosis treatments.[2–4]

The term "pragmatic" or "practical trial" is used to designate clinical trials for which the hypothesis and study design are developed specifically to answer questions faced by decision makers.[5] Pragmatic trials measure effectiveness rather than efficacy.[6] They compare relevant alternatives, include a diverse population of study participants from heterogeneous practice settings, apply minimum exclusion criteria, and measure relevant outcomes. This improves external validity (which refers to generalizing the findings), but may result in lower internal validity (reliability) compared to traditional trials.

The evidence-based approach encourages a methodology where results from different randomized trials are selected by applying strict rules in systematic reviews. To borrow further from Kemm's analysis, a considerable volume of information may be lost in this process, as most published work is excluded —not to mention the "gray literature" of semi-published reports—leaving only a few studies to constitute the evidence on which conclusions and recommendations are based.[1] Kemm argues that the most dependable conclusions are likely to come from a combination of systematic reviews and expert opinion.* The latter is, however, considered largely irrelevant in systematic reviews. Meta-analysis, a procedure where data from several studies are pooled to produce a combined estimate of effect, is sometimes applied in systematic reviews. This method is only warranted if studies involve comparable interventions, use analogous outcomes, and take place in comparable settings. In public health and policy making, the need to tailor interventions to particular communities frequently renders meta-analysis inappropriate.

It is not easy to set up control groups in public health interventions or make clear predictions of what could happen in the absence of an intervention.[7] Such predictions depend on the ability to measure clearly defined outcomes, isolate interventions, and even to reduce interventions to single, simple

*This conclusion is similar to the one reached by others in the field of quality assurance (see Chapter 10).

actions in order to eliminate other causes of any observed changes. It is not always reasonable to generalize results, whether from randomized trials or other studies; moreover, the ability to replicate the effects of an intervention in different places and at different times may not be possible.[1,7] A criterion or assumption that the effect of an intervention should be independent of context is clearly a limitation insofar as many interventions are likely to be context-specific.[7] Finally, feasibility and an assessment of the risk of adverse outcomes from interventions are also important.[1]

Although several cost-effectiveness studies have focused on tuberculosis control, it has been argued that the methods used are not always robust and sufficient. Ideally, real outcome data should be used rather than historical statistics taken from the literature; the difficulties of introducing a theoretically cost-effective change into a health service should be considered; marginal rather than average costs should be used; and different viewpoints—such as those of the patient, provider, or population—should be considered.[8] Furthermore, the cost-effectiveness studies have thus far exclusively assessed services within the public sector. Finally, it can be costly to achieve effectiveness in the first place. When evaluating cost-effectiveness, it should be decided a priori what is meant by "effective" (that is, a value or a range should be defined) so as not to end up concluding that an ineffective program is cost-effective.[8]

In conclusion, it is debatable what constitutes the best evidence for the purpose of public health policy. Concern with validity and causal attribution should not be discarded altogether. In tuberculosis control, scientific research and technology assessment are valuable inputs into the policy formulation process. Broad policy frameworks, based on sound research principles and a degree of standardization, are equally important. Operational and logistic issues, however, depend to a large extent on the context, and adaptations need to be made locally. In global policy recommendations, it is important to focus on the main points rather than attempt to accommodate the universe of different settings. Otherwise the thrust of the recommendations is easily lost. Regarding local adaptations, clinical and operational research in tuberculosis control does not always assist the policy making process. A recent review from South Africa found that many studies are deficient as concerns the relevance of the studies and the methodologies used.[9]

Standardization: Why standardize? Why not?

Randomized controlled clinical trials originated within the field of tuberculosis. This initiative and the subsequent practices in tuberculosis programs paved the way for standardized treatment and standardization in clinical practice in general, and thus eventually for the development of clinical guidelines. Development of guidelines within well-defined health programs began in the late

1970s.[10] In the 1990s, driven by the movement for evidence-based medicine, the method changed, emphasizing instead systematic literature reviews and explicit linkage of recommendations to scientific evidence.[10] Nevertheless, factors other than scientific evidence affect decisions regarding issuing guidelines, and it is increasingly acknowledged that evidence is but one feature in the development of guidelines.[10]

The results of clinical trials identify the treatment that produces the best outcome for a group of patients. Therefore, it is indeed logical to use the evidence from clinical trials for standardization and policy making in health programs. Strictly speaking, without clinical trials, treatment cannot be standardized. The results of trials, however, do not necessarily isolate the treatment that will produce the best outcome for a particular patient unless such a consideration is built into the design. Apart from questions regarding whether the results can be generalized, the outcome of clinical trials may not accurately predict the impact of a population-based intervention. Here, other factors such as coverage and operational characteristics come into play.

A practitioner's choice of treatment and follow-up is influenced by training and experience. This is one of the justifications for using clinical guidelines in training as well as in clinical practice. The proper use of guidelines is a two-way process. On the one hand, guidelines aid practitioners in their work; on the other hand, policy formulation is enriched by clinical experience. This necessitates monitoring and evaluation of practice. Without it the process is incomplete.

In 1968, Fox pointed out that decisions in tuberculosis programs must be clear-cut, simple, and standardized as much as possible, since their implementation might rest with relatively unskilled staff.[11] But who is skilled when it comes to tuberculosis? In 1984, Horne pointed out the importance of applying strict policies and standardized regimens as tuberculosis became rare in low-prevalence countries.[12] Standardizing treatment in the peripheral health services in developing countries offers a number of advantages, including the following:[13] treatment guidelines promote the rational use of drugs and render drug requirements more predictable, providing a convenient basis for drug supply. Standardized treatment facilitates continuity of care within and between health units. Ideally, the guidelines are used in the undergraduate training of health professionals as well as for in-service training, supervision, and quality assessment. To be effective, treatment guidelines must be properly introduced, regularly updated, and available to all.

Some health professionals regard standardized treatment and guidelines as second-class practice or even as infringements on freedom in clinical practice.[13] Millenson[14] claimed that functionaries of the American Medical Association so valued autonomy that they could not use the word "guidelines" when coordinating guideline development, inventing instead the phrase "practice

Box 2.1 Standardization of anti-tuberculosis treatment in Algeria

In the period from 1965 to 1967, treatment of tuberculosis in Algeria was not standardized. In 1967, a national tuberculosis program was established and treatment was standardized. Until 1980, treatment of new cases involved a 12-month regimen including streptomycin, isoniazid, and PAS. Short-course treatment was introduced in 1980 (2SHRZ/4HR). Drug resistance in previously treated cases was particularly serious in the years of haphazard treatment and showed a marked downward trend when treatment was standardized. Primary drug resistance decreased from 15% in the period from 1965 to 1970, to 10% in 1971–1979, and to 6% in 1980–1985. The decrease was more pronounced for polydrug resistance.[16]

parameters." Little by little, however, the medical profession has acknowledged that quality does not simply "flow mysteriously from the presence of a physician who graduated from an accredited medical training program,"[14] and has increasingly accepted a degree of standardization. A systematic review of the effects of clinical guidelines on the medical practice included 59 published evaluations of clinical guidelines, including guidelines for specific clinical conditions, preventive care, and prescription or support services. The review found that all but four evaluations reported significant improvements in the process of care after the introduction of guidelines, and all but two of the eleven that assessed the outcome of care detected significant improvements.[15]

An early example of the effects of standardization in a tuberculosis program is presented in Box 2.1.

Pilot testing and phased implementation

"All at once" implementation can result in a weak intervention. By the time problems are recognized in such scenarios, they may be widespread and difficult to solve—this is the rationale for pilot testing and phased implementation of strategies and programs. A pilot phase is then succeeded by an expansion phase, and finally routine practice is established.

In the context of national programs, findings from pilot areas can be misleading if pilots are conducted only in accessible, well-organized areas; if they are conducted with greater technical and financial support than could be expected in national implementation; or if they result in systems suitable for the pilot area but less suitable for other parts of the country.[13] Preferably, pilot projects should include several implementation sites with disparate populations and conditions so that variations in cost and feasibility can be studied.[17] The cost of training and quality assurance as well as the difficulty in recruiting,

retaining, and motivating personnel invariably increases with expansion to remote areas having low population density.[17] Strategies may need to be adapted in order to succeed in such areas.

Once experience has been gained in pilot areas and policies, and strategies and plans have been adapted accordingly, expansion commences. Phased implementation can start at the central level and proceed level by level. This strategy constitutes gradual decentralization of activities.[13] Expansion can also occur by geographical areas, completing the implementation in one area (for example, a province) before moving to the next. This approach seems rational because it addresses the entire system in the pilot phase.[13] While it is important to standardize procedures and to plan expansion, a certain flexibility is called for when executing the plans. The main point is to adhere to important principles but at the same time allow for emergent strategies and to adjust the pace of expansion according to progress. Expansion should be slowed if necessary, as determined by quality criteria. Speeding up implementation, on the other hand, may prove difficult. Even if an accelerated schedule is judged feasible, the availability of resources may restrict the pace of expansion.

Ideally, the commencement and pace of expansion should be ambitious and not too slow. Recruitment of areas for expansion does not need to be fixed beforehand in a long-term plan. Expansion plans can be formulated in a general manner, and the exact order of recruitment of new areas adapted as expansion proceeds (for example, in annual planning). For maximum efficiency in expansion, it may be wise to recruit first those who actively seek recruitment, given that motivation is a significant factor in success. When motivated personnel exist at the service level, the administrative level must sustain support of expansion. Whereas it may be reasonable to slow down expansion if absorption capacity at the local level is reached or exceeded, or if other problems at the local level impede expansion, it is difficult to justify slow expansion when the bottleneck is located at central or intermediate levels. It is even more difficult to defend slow expansion when the bottleneck is at the international or donor level, whether or not such impediments have to do with the availability or disbursement of funds. It can be argued that if funds for expansion and capacity for evaluation are not guaranteed, the whole program should not have been started in the first place.

As early as 1964, an Expert Committee on Tuberculosis convened by the WHO advised that plans for tuberculosis programs first be implemented in "test areas" to assess whether they were suitable and that a demonstration site be established before expansion.[18] The Committee recommended that pilot areas be representative of overall socioeconomic conditions—especially with regard to the density of health services—and that the program be applied continuously for one to two years, at which time an assessment prior to national expansion would be made. The Expert Committee of 1974 advised that expan-

Box 2.2 Examples of piloting in tuberculosis programs in different settings

When the WHO introduced the DOTS strategy in the Caucasus in 1995, two criteria were used to select pilot districts: first, their relative proximity to the capital city to facilitate supervision from the national level and monitoring by the WHO; second, the availability, in the area, of laboratory services to allow sputum smear microscopy.[21] In the case of Mongolia, the pilot area in 1995 was selected because it had a well-run tuberculosis hospital, skilled staff, and an estimated tuberculosis prevalence three times higher than the national average.[22] In Bangladesh, where implementation of the DOTS strategy started in 1993, the program was first tested in rural areas.[23]

sion of case finding should not proceed ahead of the service's ability to deliver effective chemotherapy to patients and cure them.[19] By this time, it was clear from rising levels of drug resistance that the prior emphasis on case finding and coverage was inappropriate in situations where case holding was not guaranteed.

A central element in the launch of pilot programs of the Union partnerships was a commitment—including a financial one—to national expansion as well as a general plan of expansion even if all the details had not been worked out. The rationale is that isolated pilot sites and model centers of a project that addresses important health care needs but does not plan for reasonably rapid expansion will likely be overburdened with patients coming from other areas. This may lead to poor performance and bad results in otherwise well-organized services. According to Styblo, development of the programs usually proceeded by areas, starting in the best-performing districts of two to three regions (or provinces) having a favorable logistic situation.[20] He emphasized the importance of evaluating from the outset the feasibility and the actual "flow" of the program under field conditions.

Some examples from the introduction of the DOTS strategy in three countries are presented in Box 2.2, demonstrating that reality often is different from the ideal.

The scientific foundation of tuberculosis control

Before proceeding further, it is important to recall the scenario in the late 1970s when The Union began collaborating with national programs. In the 1950s, large parts of entire populations were surveyed in mass case-finding surveys undertaken in many countries. With the passing of time, remnants of these activities became institutionalized within ever more extensive and organized health services in industrialized countries. Attempts had been made to replicate these activities in developing countries without notable achievements.

The surveys or "campaigns," as these activities were often referred to, relied heavily on the use of mobile radiography equipment, but the tuberculin skin test, sputum smear microscopy, and symptom queries were also used. The surveys were huge undertakings out of the reach of the programs collaborating with The Union. Furthermore, such surveys were never proven to be essential for the control of tuberculosis. On the contrary, in the 1960s, attempts at case finding with mass surveys were shown to be irrational because, in spite of such activities, infectious cases continued to occur. Most infectious cases developed in between surveys and were identified within the routine health services. In any case, an alternative strategy had to be devised for developing countries. A radical change in the way of thinking about tuberculosis control was needed.

Radical thinking is more easily explored in an environment removed from firmly rooted institutional structures and practices. The collaborations entered into by The Union provided a valuable opportunity for testing innovative strategies. Whereas most of the actual research took place elsewhere (in India, Kenya, and Hong Kong), the national programs collaborating with The Union provided a platform whereby the evidence from various studies was pieced together to form a coherent policy that was tested on a small scale before national expansion. Over time, tuberculosis control was modernized in most countries, including industrialized countries, and active population surveillance and lifelong follow-up of tuberculosis patients were discontinued.

Case finding

The term "case finding" refers to detecting patients with tuberculosis. Definitions of cases may differ but invariably refer to disease. The objective of case finding is to treat and cure patients and thus to permanently arrest the spread of tuberculosis bacilli. Case-finding programs differ from preventive chemotherapy programs, which aim to recruit persons already infected with *M. tuberculosis* and prevent new cases from occurring by applying preventive chemotherapy.

Sources of transmission

The central questions in tuberculosis control are the following: Who transmits tuberculosis? Can the sources of transmission be defined?

Transmission of tuberculosis bacilli occurs through aerosolized particles rather than more voluminous particles.[24] Bacilli present on patients' clothing, objects, or bedding cannot be dispersed as aerosols, and thus do not play a significant part.[24] Numerous studies contribute evidence to support the conclusion that the principal sources of transmission are patients with respiratory symptoms whose sputum smear is positive by acid-fast microscopy. These findings have been shown to be universally relevant, even in the HIV era. This is the basis for the policy of case finding by sputum examination and priority

given to treatment of sputum smear-positive cases. The primary objective is communicable disease control—to slow down transmission. In addition, sputum smear-positive tuberculosis carries a high mortality without treatment and a risk of acquired drug resistance with inadequate treatment. Thus, the public health objective of reducing mortality is addressed as well as that of preventing adverse outcomes from the intervention (that is, drug resistance).

Acid-fast microscopy

In 1954, Shaw and Wynn-Williams reported the results of a survey including roughly a thousand source cases, 823 child contacts, and 1,431 adult contacts, where they related infectivity of pulmonary tuberculosis to sputum status of source cases.[25] They found a high tuberculin conversion rate* among children in close family contact with patients whose sputum was positive by acid-fast microscopy; in contrast, the study suggested that patients whose sputum was positive by culture only were, if anything, just slightly more infectious than patients whose sputum was negative altogether. The same was true for the development of secondary cases in adult and child contacts. They concluded that if this was true for close family contact, it could be assumed that it was also true for more casual contact, and that this had implications for isolation of patients as well as for employment. They also pointed out that it justified classifying sputum smear-positive cases separately from other cases.

In a study of 190 children diagnosed with tuberculosis in the Greater Vancouver area in Canada from 1990 to 2001, a source case was identified in 63%.[26] The majority of the source cases (83%) had a positive sputum smear. The study suggested that smear-negative cases were sources of transmission in no more than 10% of the children in the study. Findings of other recent studies suggesting that high-grade smear-positive cases and cases with cavities on chest radiography are more infectious than low-grade smear-positive cases lend further support to the evidence base for the aforementioned conclusion. In a U.S. study from 1996 to 1997, household contacts to highly smear-positive cases and cases with cavities on chest radiography were at increased risk of infection.[27] In a study in Santo Domingo, Dominican Republic (2000), transmission was associated with sputum smear grade in the index case, and HIV-positive index cases were less likely to transmit.[28] A study in Thailand (2002–2003) examined child contacts of smear-positive cases and found that the risk of being infected increased when there was exposure to female patients, when the patient was the parent of the child, and when the index case had cavities on chest radiography or was heavily positive (3+) on sputum smear.[29]

Thus, sputum smear-positive cases, as a group, are more infectious than other cases. Consequently, acid-fast microscopy detects the principal sources

*Tuberculosis infection is detected by conversion of the tuberculin skin test.

of transmission. The next question is the following: can those who are likely to be positive on sputum examination be identified?

Symptoms

In 1963, Banerji and Anderson reported the results of an epidemiological survey in India's Tumkur District that suggested 95% of those with smear-positive tuberculosis had symptoms, with cough being the cardinal symptom.[30] A study in Hong Kong, published in 1979, found that most (96%) of the patients presenting at government chest clinics and considered to have tuberculosis requiring treatment had coughs at the time they first sought medical care.[31] A study in Uganda (1993–1994) found that 98% of smear-positive patients included in the study (91% were HIV positive) had productive cough and that clinical symptoms did not differ between HIV-positive and HIV-negative patients.[32]

Generally speaking, survey findings can be expected to be different from what is found in routine practice. Some surveys detect smear-positive results among patients who appear to lack symptoms.[33] On the other hand, patients may not seek care even if they have symptoms. Data from a tuberculosis prevalence survey in the Philippines in 1997 suggested that action taken in response to symptoms was inadequate and slow.[34] The presence of bacillary disease was among the determinants for utilization of the primary health care services.

Thus, sputum smear-positive patients with respiratory symptoms are the main sources of transmission. Can they be detected before widespread transmission occurs? This is partly an operational issue and as such is discussed elsewhere, but here the issue of the infectious period will be reviewed briefly.

Infectious period

Epidemiological findings suggest that the majority of persons infected with *M. tuberculosis* are non-intimate or casual contacts.[35,36] Transmission, on the other hand, is frequently measured by looking at close contacts. If contacts are often already infected by the time "source cases" are diagnosed, one might wonder whether case finding is an effective strategy for reducing transmission. However, with a tenfold difference between an average duration of infectious period in the pre-chemotherapy era (20 to 30 months) versus one of two to three months where there is an effective treatment program, the potential clearly exists for a significant reduction in transmission. One might still wonder if this is so obvious. What if transmission primarily takes place early in the infectious period, and when the disease progresses and they become increasingly bedridden, patients are likely to reduce social activities and contact with the community? What if there is a threshold in delay to diagnosis beyond which there is less potential for transmission, as in the case of saturation?

A study from the pre-chemotherapy era found that more than 60% of the

children who became infected did so within three months of the onset of symptoms in the adult source case.[37] Likewise, in high-prevalence areas, household exposure contributed to primary infection until the age of 15 years, by which time most children were already infected.[37] In a Canadian study in the 1970s, approximately 60% of children under 10 years old remained uninfected at the time of contact investigation even in households where the source case was smear-positive.[35] In this study, smear-positive source cases did not have fewer contacts than other source cases, regardless of intimate or casual contacts; if anything, they had more contacts.* Furthermore, there are numerous accounts of highly infectious patients with extensive multi-cavitary disease going about their daily lives in the community for months on end—not without symptoms, but ambulatory nevertheless—and undetected in spite of contact with the health services. The following U.S. examples illustrate such a scenario: a 32-year-old man in Maine started treatment in 1989 after walking around symptomatic for eight months;[38] a 9-year-old child with bilateral cavities in a rural farming community in North Dakota was estimated to have been infectious for almost a year before treatment was started in 1998;[39] and noncompliant patients in the 1990s in San Francisco were smear-positive for many months.[40] Most of these cases represent missed opportunities in diagnosis; that is, they had been in contact with health facilities or public health services. Finally, a prospective study in the United States from 2000 to 2001 examined whether longer delays in diagnosis of tuberculosis were associated with increased transmission as measured by positive skin tests in close contacts (household and workplace contacts and close friends and relatives).[41] U.S.-born patients (57% were smear-positive) had longer delays to diagnosis compared to non-U.S. born. Among the former, the delay in diagnosis was associated with greater transmission to contacts. The association was stronger when the delay exceeded 90 days.

Clearly, prompt diagnosis and treatment has an important potential for reducing transmission if coughs and other symptoms of tuberculosis are taken seriously and patients properly assessed. Ensuring that such opportune, careful measures are taken is the essence of the tuberculosis control policy. The aim of case finding is to shorten the infectious period to reduce the transmission of tuberculosis bacilli. How well this is achieved can be measured reasonably accurately by studying the delay in care seeking, diagnosis, and treatment (see Chapter 7).

Thus, timely diagnosis of patients with smear-positive tuberculosis has a potential for decreasing transmission. Can sources of transmission be detected differently; that is, other than by sputum examination?

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*That, however, may be a bias if contact investigation was more aggressive in smear-positive cases.

Radiography

There is an association between cavities on chest radiography (such cases were traditionally referred to as "open" cases) and acid-fast bacilli on sputum smears.[42] Does this mean that sputum examination can be replaced by chest radiography in assessment of care seekers? Even if there is an association, the results yielded by the two methods do not always concur; but more important—especially in the context of developing nations—is the issue of access to different means of testing. Microscopy can be decentralized further than radiography, and it is more easily standardized. Radiography, wherever there is access to it, is commonly used for assessment of patients with long-standing respiratory symptoms, however. Where this is the case, other radiographic abnormalities apart from cavities need to be considered, and this poses a problem related to the accuracy of reading and interpreting chest radiographs.

In 1959, Garland found considerable intra- and inter-observer variation in readings.[43] The results of an international multi-center trial conducted in 1963 found suboptimal concordance among tuberculosis specialists.[44] Because of low specificity, the positive predictive value of radiography as an isolated test is low; therefore, it needs to be followed by sputum examination.[45]

Although the level of services is important (routine or referral), to this day the difficulty in guaranteeing quality in readings of chest radiographs in the diagnosis of tuberculosis is widely acknowledged.* In many African countries a sizeable increase in the notification of smear-negative cases occurred with the HIV pandemic. A study in routine hospital services in Malawi from 1996 to 1997 found that as much as a third of all chest radiographs in smear-negative tuberculosis suspects were incorrectly read (using as gold standard a panel of experts) and would have resulted in some patients failing to receive treatment when they should have, and vice versa.[48] A study in a referral center in Nairobi in Kenya (2005) concluded that the low specificity of chest radiography was a subject of concern. In this study, depending on whether chest radiography was performed on all tuberculosis suspects or on smear-negative suspects only, 22% to 45% of patients labeled as tuberculosis had a negative culture.[49] In contrast, Canadian investigators in a tertiary referral center found other results. They read films from adults suspected of active tuberculosis and found moderate to substantial reproducibility of readings (inter- and intra-observer variability) and reasonable validity (the gold standard being culture-confirmed tuberculosis).[50]

In conclusion, chest radiography cannot replace bacteriology. Radiography can, however, be used for pre-selection of cases for bacteriological examination. Radiography should always be followed by bacteriology in the event that abnormalities are found.

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*Reading of radiographs in prevalence surveys is another matter, which has recently been addressed.[46,47]

Organization of case finding

Active versus passive case finding

When used to characterize case-finding strategies, the terms "active" and "passive" refer to the point of view of the program. In the first case, action is initiated by the tuberculosis service (for example mass surveys, screening of high-risk population groups, information campaigns); in the latter, it is the patient who takes the initiative (that is, attends a health facility) and the services respond.[51]

Several questions arise when considering how to go about detecting patients. Do infectious patients contact the health services? How should the services respond? Can they organize a screening so that effective tuberculosis control is achieved? Numerous studies provide evidence that patients with persistent cough can be recognized with routine questioning by nonspecialist health personnel. Further, services do not always respond effectively when symptomatic patients attend health facilities. Finally, self-referred patients may be more likely to accept and adhere to treatment than patients recruited by community-based screening. This is the basis for the policy of passive rather than active case finding in tuberculosis programs. The original studies were conducted in developing countries, and the results are likely to have been affected by the coverage and quality of the health services in the study areas at the time. These factors need to be considered when generalizing the results. Coverage, where insufficient, can be improved, however.

The central piece of evidence aiding the formulation of a case-finding strategy in developing countries was the fact that patients with infectious tuberculosis had symptoms leading them to contact the health services. The results of the survey in Tumkur, India, in 1963 suggested that a great proportion of infectious cases were aware of symptoms (70% to 95%, depending on the level of probing); in roughly 50% of the cases, symptoms drove them to take action; and when they attended health facilities, a simple questionnaire could be used to detect these patients.[30] While the proportion of highly infectious cases with symptoms in this study was encouraging, the overall effectiveness when considering taking action was somewhat less so. It could be argued, however, that a potential to be harnessed existed.

The Expert Committee of 1964 pointed out that in developed and developing countries, the large majority of new tuberculosis cases were diagnosed by means that relied essentially on the initiative of individual patients.[18] The Committee argued that it should not be necessary to actively seek out new cases in the community. If services were equipped to react quickly when patients came forward with symptoms of tuberculosis, that preparedness might indeed be enough to slow down transmission in the community and tip the odds against the bacillus. Responsive or facility-based case finding is a better

term for describing this strategy than passive case finding, as it is traditionally called. Passive is indeed an unfortunate term, given that it implies a laid-back approach that is far from what was intended.

A study in Bangalore, India, in 1966 showed that the majority of care seekers at specialized tuberculosis clinics, and tuberculosis patients among them, attended the services within three months of developing symptoms. Rural residents did so only slightly later than urban ones.[52] This study did not include those who never attended, however. It seemed that women in rural areas experienced the most restricted access to these clinics.

Further support for the case-finding strategy came from a series of studies conducted in Kenya in the 1970s and early 1980s (Box 2.3).

In the late 1970s and early 1980s there was documented evidence that the health services were not sufficiently alert in diagnosing attending tuberculosis patients; that is, there were missed opportunities to identify those with tuberculosis and unnecessary delays in diagnosis once patients made contact. These were tangible shortcomings, ones that could be addressed relatively easily within the services. It was logical to start by improving this aspect of the recruitment process. Evidence also suggested that attempts at more active recruitment were either not feasible or not productive. The overall conclusion from the studies in Kenya was that outreach services were not practical, and it was recommended that the district hospital be the focal point in tuberculosis control, with peripheral health services charged with identifying "at risk" suspects and referring them to the district hospital for assessment. These recommendations are in line with what was implemented in the programs collaborating with The Union. However, the population per district in Kenya was commonly 300,000 to 500,000 at the time, and concerns arose about access to the district hospital for those living more than 15 km away. The Orange Guide recommended that a microscopy center for examination of sputum for acid-fast bacilli be established in hospitals or health centers serving populations of about 50,000 to 70,000[60] or as many as 150,000, according to the incidence of tuberculosis.[61] Decentralization of tuberculosis services is discussed further in Chapter 7.

Apart from passive case finding and decentralization, the main messages from the Kenyan studies for increasing case detection were to guarantee quality in the laboratory network (that is, reduce false-negative results); to increase training and supervision of the staff at district and peripheral health facilities, with the aim of further decentralization; and to facilitate communication between peripheral and referral units.

More recent findings in tuberculosis programs show that strengthening case finding within the health services is not an outdated policy issue. An audit of the case-finding process in a central hospital in Malawi in 1995 suggested substantial deficiencies in case detection. Of 135 tuberculosis suspects, perhaps

Box 2.3 The series of case-finding studies in Kenya

In 1968, Fox noted that the issue of whether or not to decentralize all the activities relating to diagnosis and treatment in a tuberculosis program as much as possible was open to operational research.[11] Starting in 1974, a series of studies was conducted in Kenya to examine the organization of case finding. The results were published from 1977 to 1987. The investigators started out by comparing various methods in active case finding, but the results led them in the direction of case finding within the general health services.

A community-based study conducted in Kenya's Machakos District in 1974–1975 looked at identification of "tuberculosis suspects" (the definition used in the studies is a person with a cough of longer than one month's duration) by interrogating "community leaders" (village elders) and "heads of households" in a random sample of households.[53] The former identified 19% and the latter 90% of tuberculosis suspects (the denominator was the number identified using both approaches). The corresponding proportions for smear-positive and culture-positive cases were 40% and 93%, and 31% and 96%, respectively. Community leaders tended to identify patients already known to the tuberculosis program. Thus, in this setting they were not useful in case finding whereas heads of households were. Interrogating the latter implied making house-to-house visits, an approach not operationally feasible as a routine. The most important finding of this study was the fact that roughly 80% of tuberculosis suspects had attended a health facility on at least one occasion prior to the study without being diagnosed. This was true for seven out of eight smear-positive cases and six out of seven cases positive on culture only. This indicated that case finding within health facilities (that is, identification and examination of persons attending the facilities with symptoms of tuberculosis) might indeed be an effective case-finding measure.

A second study carried out in the same district from 1975 to 1976 revisited the usefulness of eliciting data from community leaders and investigated the yield of examining sputum samples from all previously registered tuberculosis cases and their contacts.[54] This study confirmed the previous findings regarding the community leaders. Bacteriological examination of household contacts of known patients was not rewarding: the yield was three culture-positive cases (none of them smear-positive) out of 612 persons examined. Additionally, the investigators found that a high proportion of previously known patients had died (17%) and that isoniazid resistance was common (eight out of nine) among survivors with positive bacteriology. These findings indicated badly organized treatment services.

A third study undertaken from 1976 to 1978 compared five methods of case finding: quarterly interrogation of community leaders, interrogation of heads of households, identification of tuberculosis suspects among outpatients attending local health facilities (two health centers and three dispensaries covering a population of 24,500), examination of previously registered tuberculosis patients, and examination of their close contacts.[55] The findings were comparable to those in the previous studies in addition to the disappointing results of involving outpatient facilities. The staff at these facilities were expected to identify tuberculosis suspects. Health units were visited once a month by a supervisor who arranged a home visit and sputum examination of the tuberculosis suspects identified. Compared to the number of tuberculosis suspects who claimed they had visited health units, less than 10% were registered in the facility-based "chronic cough registers" implemented for the study. Thus, it seemed that it was no easy task to involve the peripheral health services; this would require substantial

(*continued*)

training, motivation, and supervision. However, 3% of the tuberculosis suspects identified at health facilities and subsequently examined were smear-positive, and 7% were culture-positive. Clearly potential existed there.

A fourth study further investigated the outpatient services of peripheral health facilities, again with disappointing results.[56] Out of 45 suspects registered in a full year (the population of the service area was 27,500), only four smear-positive cases were diagnosed (a low absolute yield but a high relative one). As in previous studies, interrogation of heads of households detected the highest proportion of cases (70% of smear-positive cases identified by all the active case-finding methods combined) but was labor intensive and inefficient (that is, had a relatively low yield, with only about 1% of suspects examined being positive). The failure of the peripheral services suggested it might be unwise to decentralize the efforts to such a degree; instead, it might be advisable to focus on district hospitals.

Accordingly, a fifth study was conducted in a district hospital and involved careful screening to identify tuberculosis suspects among those over six years of age attending the outpatient department.[57] Among 20,756 attendees questioned for symptoms, 601 (2.9%) were identified as tuberculosis suspects. Among tuberculosis suspects, 2.2% were found to have smear-positive tuberculosis, 1.2% were positive on culture only, and 2.2% had negative bacteriology but were diagnosed as having tuberculosis based on chest radiography. Overall, 39% of the cases detected were smear-positive cases. This case-finding method was more productive (a higher yield among examined tuberculosis suspects) than interrogation of heads of households. In addition, the method was realistic. Investigators concluded that the district hospital was the appropriate level of implementation of tuberculosis control in a context of poor primary health care services and infrastructure, with referral of tuberculosis suspects from peripheral facilities to the district hospital. From the results, it seemed that whereas such a strategy would be uniformly effective for the population residing within 15 km of the district hospital, it would be less effective for the population outside of that radius; that is, case detection would depend on health infrastructure and population density. More than three quarters of the tuberculosis suspects identified in this study had visited the district hospital on a previous occasion in the year before inclusion in the study, and the majority of them had attended peripheral health units as well. This was a confirmation of similar findings in the first study, underscoring the wisdom of starting by improving case finding within health facilities before considering active case finding.

A sixth study focused on finding a narrower definition of tuberculosis suspects in order to reduce the number of sputum smears to be examined at district hospitals.[58]

A final study examined the involvement of mother-and-child welfare clinics in tuberculosis case finding.[59] These clinics had a wide service network throughout the country (20,000 to 30,000 population per clinic) and were considered very popular. The women attending the clinics were asked about tuberculosis suspects in their household and instructed to deliver a letter to any such person. If the persons identified subsequently visited the district hospital, their sputum was examined in the hospital laboratory, and a further specimen was examined at a reference laboratory. If they didn't, the household was visited. The results were disappointing, with inefficient referral of suspects and discrepancies between local and reference laboratories, which highlighted the need to strengthen the laboratory services at the district hospital level.

only 59% actually underwent sputum examination.[62] A community-based survey carried out in South India's Tiruvallur District from 1999 to 2000 suggested that 80% of the smear-positive cases found had already consulted a health care provider.[63] Data from a nationwide survey in China in the year 2000 suggested that 40% of tuberculosis patients identified by the survey had sought care, mostly at the village and township levels, but had not been diagnosed.* A retrospective study in Burkina Faso referring to recruitment of cases in 2001 reported inefficiency in the process of case finding and referrals within the health services.[65] Studies in Peru and Bolivia from 2003 to 2005 found inefficiency in referral of tuberculosis suspects for sputum examination.[66] While other factors may have come into play simultaneously in Georgia and Armenia, the shift from an emphasis on active to passive case finding in 1995 coincided with an increase in the number of cases detected.[21] A cross-sectional study in India in 2001–2002 found that almost a third of the patients with cough—17% of all smear-positive cases—did not spontaneously mention their symptom, underlining the importance of actively questioning patients for cough.[67] Finally, almost one third of the patients detected by the survey in Tiruvallur either refused to start treatment altogether or did not complete treatment. This phenomenon was more pronounced among the smear-negative cases identified.[63]

In spite of the fact that many tuberculosis patients seek care in the health services without being identified or properly referred as tuberculosis suspects, the idea of active case finding by mass community surveys remains tempting. In 1998, Murray and Salomon, guided by mathematical modeling, proposed active case finding by mass miniature radiography to increase case detection,[68] and gave China as an example of a country where such a strategy might work.[69] In 1999, De Cock and Chaisson suggested exploring active case-finding methods to improve case detection in areas with high HIV prevalence.[70] A survey in rural South Africa (2001), using single interrogation of heads of households, found only a modest burden of undiagnosed tuberculosis in a community with high HIV prevalence.[71] Most of the previously unknown cases detected by the survey had attended health services at some point during their illness, once again supporting the call to strengthen passive case finding. The investigators concluded that it seemed unlikely, in the context of rural South Africa with its reasonably well-developed health infrastructure of primary care services, that active case finding would prove a cost-effective means to reduce the burden of tuberculosis.

Mobile services

The topic of mobile services versus fixed services partly overlaps with that of active case finding. Working within the fixed health services demands fewer

*Wang et al., quoted in Tang and Squire,[64] p. 99.

resources and is more efficient than surveying the community to find cases. Mobile activities are always added to a fixed health service but cannot replace it. Patients who present at health facilities with symptoms of tuberculosis need immediate attention, not someone who tells them that a health worker is out looking for them.

From 1979 to 1980, a study in Nepal compared active case finding by mobile teams in one district with self-referral of patients to existing services in neighboring districts.[72] The mobile campaign lasted for seven months and brought in 111 smear-positive patients compared to 159 patients diagnosed in a year within the fixed services, including patients less likely to present on their own initiative. Compared to the self-referred patients, those patients identified by active case finding were more likely to be older and female. On the down side, they were less likely to adhere to treatment irrespective of proximity to a health facility (71% had a period of absence compared to 33% of the self-referred patients). The treatment outcome was worse than in the self-referred group, and 10% refused treatment altogether. It was accepted that attempts to increase case finding were controversial unless the services succeeded at case holding. A later intervention study in a remote, hilly area in Nepal from 1990 to 1993 implemented mobile microscopy camps where patients were diagnosed and then referred for treatment within the fixed health services.[73] This strategy did not appreciably increase case finding.

Contact investigation

Whereas contact tracing worked well in smallpox eradication, in tuberculosis the matter is more complex. In the smallpox program the objective of contact tracing was vaccination to prevent disease in contacts. In tuberculosis, three objectives need consideration: case finding (identifying source cases and secondary cases among contacts), recruitment of infected contacts for preventive chemotherapy (prevention of secondary cases), and operational or epidemiological investigation to study transmission dynamics with the goal of improving future strategies.

Contact investigation became a part of tuberculosis control activities after the discovery of anti-tuberculosis chemotherapy in the 1950s, and is commonly thought of as a form of active case finding.[74] The yield of contact investigation as well as its role in tuberculosis control is, to a certain degree, context-specific. The risk of infection and disease is always higher in contacts than in "non-contacts," and thus the yield of contact tracing may appear impressive when compared to examining "non-contacts." On the other hand, the contribution of contact investigation to case finding is usually relatively modest, and as a rule the effectiveness in prevention of secondary cases fails to impress.

Studies in this field differ widely in many respects, such as the following: the methodological approach used (retrospective, cross-sectional, or prospec-

tive); definition and recruitment or selection of cases and secondary cases (adults, children, or both, and smear- or culture-positive, or all cases); definition of contacts (children, adults, or both, and intimate, close, or other); methods of contact recruitment (active, passive, or mixed); procedures in screening of contacts (skin test, radiography, sputum microscopy, sputum culture, HIV testing, clinical signs, and symptoms); indications for preventive treatment; and outcome measures (number of identified contacts per case, proportion of contacts screened, proportion of latent tuberculosis infection among contacts, secondary cases as a proportion of screened contacts, index cases or overall case finding, efficiency of preventive treatment, or number of cases prevented). Thus, direct comparisons are difficult.

A classical paper from the pre-chemotherapy era describes the study of families in Cattaraugus County in New York in the years from 1923 to 1930.[75] The incidence of active disease among family contacts of patients in rural areas was 11% within 10 years. Half of the cases occurred within the first two years. The risk for family contacts was 13 times the average risk in the community. This fact and the fact that family contacts are easily identified would justify preventive chemotherapy for close contacts. In the chemotherapy era, however, infection and secondary cases in family contacts are expected to be less common, and in routine practice contact investigation might be less efficient than in a research study. In 2001, a case-control study in Malawi found a rate of tuberculosis of 2% in 12 months in tuberculosis households as opposed to a rate of 0.27% in control households.[76] Thus, the Cattaraugus study measured approximately five times higher incidence in tuberculosis households than the study in Malawi, suggesting an impact of chemotherapy (although other factors may come into play as well) and twice as high a gradient in the comparison made. The difference in observation periods in the two studies is offset by the fact that in Malawi 75% of notified tuberculosis cases were HIV-positive. The households studied in Malawi were comparable except for the presence or absence of an index patient in the household at the time of the study; in contrast, the comparison made in Cattaraugus involved the community as a whole, which is a different scenario.

Looking at the matter from another angle, only 16% of the tuberculosis cases diagnosed in the Cattaraugus study cited a family history of tuberculosis, and it was difficult to obtain a history of tuberculosis in wider circles.[75] Similarly, of 163 consecutive new smear-positive patients attending a chest clinic in Addis Ababa in Ethiopia in the early 1990s, information on contact history was reported for 67, of whom 7 (10%) had a history of close contact with a proven case of tuberculosis, 5 (7%) had a history of contact with a person with chronic cough, and the remaining 55 had no known contact with either.[77] The low proportion of cases involving a history of close contact with tuberculosis patients suggests that the majority of cases are infected by means other than family

contact and that a strategy of preventive chemotherapy among household contacts is thus not likely to have a major epidemiological impact. Indeed, in absolute terms, fewer infected household contacts than other close contacts were found in a study in the Netherlands from 1963 to 1964,[78] and in a Canadian study from 1966 to 1971 the majority of tuberculin-positive contacts were casual as opposed to intimate contacts.[35] A case-control study of contacts in a Peruvian shantytown in 1995 suggested that children were often infected outside of the immediate household, or possibly within the household but not by the immediate family. The older the child, the more likely this effect was.[36] This suggests that for epidemiological impact, high coverage with a preventive chemotherapy program and extended contact tracing beyond the immediate family are necessary—and are two criteria that represent an operational challenge. The response or participation rate in the Peruvian study was rather low: roughly one out of three symptomatic contacts did not provide a sputum sample. Low participation rates have also been found in other studies in low-income countries[79,80] and even in some studies in industrialized ones.[81]

In developed countries in the past, contact examination commonly yielded about 10% of all notified tuberculosis cases.[82] A recent study in India that followed household contacts for 15 years found an adjusted hazard ratio of 3.4 for contacts of smear-positive and 1.7 for smear-negative cases compared to noncontacts, and suggested that 8.5% of cases in the area came from household contacts of tuberculosis cases.[83] A different contribution may be expected when looking at contribution to notification of smear-positive cases, depending on the characteristics of cases found in contact tracing. The contribution would also differ depending on the procedures followed in contact investigation. The findings of a pilot study in a shantytown in Lima, Peru, from 1996 to 1997 suggested a similar or lower contribution of contact tracing to case finding, approximately 5% to 7%, depending on whether index alone or also neighborhood households were visited.[84] Other studies have suggested a more modest contribution still: 4% to 5% in Hong Kong in 1996,[85] and 1% to 2% in a 1996–1998 study in Nepal.[79,80] Box 2.4 looks more closely at a few studies in high-prevalence countries.

Even if the yield of contact tracing decreases with declining incidence of tuberculosis, as most infectious cases can then be expected to occur as a result of endogenous exacerbation in the elderly, examination of contacts should be maintained until tuberculosis is eradicated.[82] The question of which procedures to use then remains. Various studies have suggested that as many as one third of the tuberculosis cases in U.S. urban areas result from recent transmission.[88] In the new scenario of tuberculosis in rich countries, there are subpopulations that resemble populations in poorer countries with regard to tuberculosis prevalence and transmission. A prospective study in Baltimore from 1994 to 1996 showed that intensive contact tracing and patient interviews established epidemiological links among only 24% of 84 clustered patients; that is, cases

Box 2.4 Studies in contact investigation in high-prevalence countries

In a retrospective cohort study in Eastern Nepal, the index cases were tuberculosis patients registered during the period from 1996 to 1998, and the study set out to find cases among their household contacts.[79] The procedures targeted adult contacts, applying acid-fast microscopy, as neither radiology nor tuberculin was widely available in the study setting. The number of cases registered in the study period was 1,340, of which 754 (56%) had positive smears. Information on contacts could be collected from 50% of the cases (668). The smear-positive case yield was 0.6%, and all but 1 of the 14 cases detected were contacts of smear-positive index cases. The yield corresponded to less than 1% of all tuberculosis cases in the study area and less than 2% of smear-positive cases registered in the period. The investigators concluded that, in this setting, sputum examination of household contacts of smear-negative and extra-pulmonary cases was not justified and that further research was needed to judge the utility and cost-effectiveness of testing contacts even of smear-positive patients. They suggested considering the possibility of further restricting contact tracing to households of patients with smear-positive tuberculosis having results of at least 2+ on acid-fast microscopy.

A prospective study in rural Haiti looked at contact investigation in households of children (younger than six years of age) diagnosed with tuberculosis from 1996 to 1998.[80] The contact investigation was aimed at finding potential source cases: adults with pulmonary tuberculosis. The 32 children included had 109 adult household contacts, 56 (51%) completed the evaluation, and of these 9 (16%) had pulmonary tuberculosis. The yield of smear-positive cases among contacts completing the assessment was 4%. Additional cases were found by radiography. Targeting only the contacts identified as possible cases through use of a simple questionnaire reduced the workload without reducing the absolute yield of contact tracing. Applying the questionnaire, it was found that the adult who accompanied the child proved to be a more accurate information source than the contacts themselves.

A study in a shantytown in Lima, Peru, looked at active versus passive contact investigation and the extent or range of contact investigation by studying the yield of examinations of household contacts only as opposed to including neighborhood contacts as well.[84] Among symptomatic household contacts who provided sputum samples, 10% were smear-positive. The yield was higher when source cases had a high positive grade on acid-fast microscopy. Absolute and relative yield of contact examination was lower in neighborhood contacts than in household contacts.

Of 76 secondary cases identified in a prospective cohort study in Kampala, Uganda, from 1995 to 1999, 51 were identified in the baseline evaluation (that is, co-prevalent) and 25 during follow-up.[86] Secondary cases often had minimal disease. The risk of secondary cases was greater among children and HIV-positive contacts. The protective effect of preventive chemotherapy was modest (25%) compared to what is reported in clinical trials (70% to 80%). Similarly, an evaluation in California, United States, in 1999–2000 estimated that only 35% of cases expected to occur within two years following contact investigation were prevented.[87]

A prospective study in the United States in 2000–2001 suggested that delay to diagnosis in U.S.-born index cases (particularly if this parameter exceeded 90 days) could be used independently of other patient factors to identify contacts at greater risk of infection.[41]

considered recently infected.[88] It is a different story when starting with childhood cases. In a study of 190 children diagnosed with tuberculosis in Canada's Greater Vancouver area from 1990 to 2001, a source case was identified in 63%.[26] Roughly half of the source cases identified (53%) were household contacts. Indeed, it is argued that in low-prevalence areas, household exposure remains an important contributor to primary infection throughout life; and all household contacts, irrespective of age, require screening.[37]

In conclusion, the contribution of contact tracing to case finding is variable but relatively small (1% to 10%). Factors such as the following will influence the catch and the cost: net size (household or wider), mesh measure (children or adults, smear-positive or all cases), and time frame (baseline only or follow-up as well). When the aim of contact tracing is further case detection, the yield is likely to be higher in household contacts of child cases because they as a group are more likely to be recently infected and to be infected by a close contact. Nevertheless, depending on the setting, a substantial proportion of adult cases may be recently infected. This proportion can be expected to be higher where there is a weak control program, high prevalence of HIV, or low prevalence of tuberculosis. In low-income countries, it seems appropriate to restrict contact tracing as suggested by some of the studies cited above: for example, to examine contacts of (heavily) smear-positive cases only and use primarily passive contact tracing, applying a simple questionnaire to identify potential source cases.[80] When the objective of contact tracing is recruitment of infected contacts for preventive chemotherapy, the thrust should seek to detect infected children and HIV-positive adults. The goal of this procedure is primarily individual protection rather than tuberculosis control. Finally, it is wise to build on local studies and experiences when formulating contact tracing policies.

Information campaigns

Publicity and information campaigns aimed at raising public awareness of tuberculosis symptoms and services and, ultimately, at prompting self-presentation to the medical services, are sometimes referred to as enhanced case finding.[89] Community health education or advocacy that attempts to increase the attendance at and demand for tuberculosis services must at least deliver what is promised.

In the 1970s, the Hong Kong Government Chest Service provided—throughout the country and without referrals—free consultation, investigation, and treatment. A study in 1979 showed that despite this service, the majority (53%) of patients presenting at government chest clinics with tuberculosis had consulted a private practitioner first; three out of four because they were unaware they had tuberculosis.[31] In response to the findings of the study, case-finding campaigns using television, radio, posters, and leaflets were carried out in Hong Kong in 1979 and 1981, encouraging people with a long-standing

cough to visit chest clinics for free advice and treatment if necessary.[90] The results were disappointing, with only a minor increase in the number of persons attending the clinics and no increase in the number of cases detected. The content of the information campaign either was flawed or did not target the right group. Such campaigns also may not succeed when they fail to capture their audience's attention. Finally, perhaps case detection was already as successful as possible in this setting.

In the early 1990s, a media-based health education campaign was organized in Cali, Colombia. The campaign lasted six weeks.[91] An immediate and sharp increase in the number of individuals examined and acid-fast smears performed in the laboratories was noted, as well as an increase in the number of smear-positive cases notified. The effect was short-lived, however, and may have been the result of a temporary reduction in diagnostic delay or a temporary shift from private to public providers. At any rate, it can be argued that a one-time event makes little or no difference in the long run.

A mass media (television, radio, newspapers) information campaign organized in Delhi, India, in 2000 was found to have less influence on the poor and disadvantaged populations of the city.[92] Given that such populations are disproportionately affected by tuberculosis, this is a serious limitation of the campaign.

In conclusion, the limited evidence available does not support the notion that publicity and information campaigns enhance case finding in tuberculosis programs.

Community-based surveys

Can infectious cases be prevented by periodic screening of the population to find cases early in the disease process? Studies performed in the 1960s and 1970s provided evidence to the contrary. At the time, it could be argued that surveys diverting funds from improving health services might harm case finding in the long run. This further supported the policy of passive case finding with a focus on strengthening and expanding the general health services rather than establishing or maintaining a vertical structure for community-based case-finding surveys.

Generally speaking, mass screening programs may selectively miss aggressive cases. In mass screening, it is common to distinguish between a prevalence screening (that is, the first round of screening) that will yield more cases than repeated screening (subsequent rounds).[93] Judging the most appropriate interval for periodic screening requires detailed research. When contemplating screening, two important forms of bias merit consideration.[93] The term "lead-time bias" signifies a lengthening of survival achieved by earlier diagnosis rather than by efficacious intervention. Thus, survival time, when used in isolation as a measure of a screening program's effectiveness, can be misleading.

Box 2.5 Early experience with mass screening of populations in Europe

As much as one quarter of the adult population in Denmark was examined (by tuberculin and chest radiography) annually from 1954 to 1956, mostly (88%) in routine checks.[94] These studies concluded that an enormous number of subjects must be investigated to identify a very small group at high risk of developing tuberculosis, and still two out of three of the cases arising in the tuberculin-positive group were not identified.[94]

In the Netherlands, one quarter to one third of the population was examined with mass miniature radiography from 1951 to 1957. Nevertheless, 50% to 60% of smear-positive patients in the period were detected as a result of symptoms.[51] Furthermore, the proportion of cases, according to bacteriological status, remained more or less constant throughout the period, suggesting that smear-positive cases were not prevented.

Interval screening is more likely to identify slowly progressing cases whose prognosis is significantly better than that of aggressive disease. This is referred to as "length bias." Consequently, cases identified by screening will appear to have a better prognosis than those who are identified following the appearance of symptoms.[93] The overall mortality in the population may be unaltered in spite of screening if the screening program selectively misses people with aggressive disease.[93]

Early experience in various European countries suggested that infectious tuberculosis was not prevented by mass screening programs. A survey interval of two to three years was common and based on practicality rather than scientific basis.[51] Two examples are presented in Box 2.5. Furthermore, early observations in the United States (1959) noted that tuberculosis mortality declined equally in states whether or not there were active survey programs.[43]

In the 1960s, Czechoslovakia collaborated with the WHO in a longitudinal epidemiological study of tuberculosis. In 1961 and 1963, mass radiography and tuberculin surveys, with 95% coverage, were conducted for all persons over 14 years of age in the Kolin District,* which had a population of roughly 100,000 in 1961.[95] Surveys were repeated in 1966, 1969, and 1972.[96] All persons with active tuberculosis received treatment, and all those registered with "active" or "inactive" tuberculosis or "fibrotic lesions" were followed throughout the study period. In 1967, Styblo et al. reported that while the prevalence of bacillary cases fell from 150 cases in 1960 to 91 cases in 1964, mainly owing

*The epidemiological, population and health services profiles in Kolin were different from those in the countries with a high prevalence of tuberculosis today. Most of the cases occurred in males in the group aged 55 to 64 years (it was thus a mature epidemic) and there was no HIV infection. The infrastructure was much more elaborate than in low-income countries.

to a decrease in the number of chronic cases, the incidence of bacillary tuberculosis detected by sputum smear microscopy remained stable.[95] The incidence eventually declined, but despite repeated mass surveys new smear-positive cases continued to occur in the community. They concluded that priority should be given to individuals who are consulting physicians as a result of symptoms and who require prompt diagnosis and adequate treatment if they are found to have active tuberculosis. To be clear, it should be noted that these surveys were case-finding surveys directed at detecting tuberculosis cases for treatment. Preventive chemotherapy for those infected, but not ill, was not applied. Preventive chemotherapy has been shown to be effective in preventing tuberculosis in clinical trials. Whether this is feasible and effective in practice and whether preventive chemotherapy can be applied successfully in low-income countries is another question. At the time the Union model was developed, most public health professionals assumed that preventive chemotherapy was beyond the capacity of the health services in the collaborating countries.

In conclusion, mass surveys are only expected to be useful as a component of a preventive chemotherapy program. To date, this has not been considered feasible in low-income countries, nor has it been evaluated for cost-effectiveness, primarily because it has not been implemented on a large scale.

Smear-negative pulmonary tuberculosis

So far, discussion has focused on smear-positive cases. But what is the difference between smear-negative and smear-positive tuberculosis? What are smear-negative cases, and can tuberculosis be controlled without considering them? What is the evidence regarding smear-negative cases, and is some evidence questionable or insufficient?

It has long been recognized that negative sputum smears do not rule out the presence of pulmonary tuberculosis.[97] There are, however, no explicit criteria for the diagnosis of pulmonary tuberculosis when acid-fast microscopy is negative and cultures unavailable, and the proportion of such cases among all cases who receive anti-tuberculosis treatment varies from one country to another.[98] For the purpose of tuberculosis control, whether or not bacilli are present in lesions is not the point. The point is whether the bacilli cause disease and can be transmitted. If they are not transmitted and the disease they cause is mild and self-healing, then strictly speaking treatment is not needed. The outcome of "smear-negative cases" is likely to differ by setting, partly because the diagnosis is not standardized.

The definition of a "smear-negative case" of tuberculosis is not easy. It can be said that tuberculosis constitutes a spectrum from infection to disease, and it may not always be clear where the dividing line should be drawn. This is a dilemma, particularly when examining chest radiographs of apparently healthy individuals or persons with minor or unclear symptoms. Diagnosis of

smear-negative pulmonary tuberculosis can be difficult, however, even in persons with suggestive symptoms. Abnormalities seen on chest radiographs are often nonspecific, and the results of culture are commonly late and possibly negative. Differential diagnosis is a challenge in any setting, let alone where there are limited possibilities to make a proper assessment. This matter is still the subject of intense debate, particularly in areas with a high prevalence of HIV infection.

"Smear-negative cases" and even culture-negative cases can transmit tuberculosis. This is not doubted. The most infectious patients, however, are easily found by properly performed sputum microscopy; and culture-positive cases with a negative smear, as a group, are less infectious and therefore less important epidemiologically.[99] Furthermore, the latter are less consistently positive; that is, they are more likely to excrete bacilli intermittently rather than continuously, and therefore many serial sputum specimens may be needed to detect such cases.[52] Finally, if persons with signs and symptoms of tuberculosis are subjected to properly performed sputum microscopy only, over-treatment is unlikely. These were the arguments that the control policy was originally based on, and they have largely held over the course of time. As discussed further on, in relation to operational strategies, it is considered important to reduce the number of sputum smears examined in the assessment of tuberculosis suspects, particularly in areas with high prevalence of HIV infection. Increasing the number of smears to be examined, as would be necessary in order to assist diagnosis of less consistently positive cases, is hardly an option.

Behr et al., studying the molecular epidemiology of tuberculosis in San Francisco (1991–1996), concluded that smear-negative, culture-positive tuberculosis was responsible for about 17% of transmission in the study area.[100] Similar findings have been reported from the Greater Vancouver region in Canada (1995–1999).[101] It is agreed that molecular epidemiological studies may overestimate transmission from smear-negative cases.[26,101] Thus, later studies applying new technology seem, if anything, to support the original policy. With pulmonary smear-positive tuberculosis cases responsible for 80% to 90% of transmission of *M. tuberculosis*, it is obvious why such cases would be targeted by a tuberculosis control policy. This, however, does not mean that tuberculosis programs neglect other patients.

Critics claim that inadequate attention is paid to smear-negative cases,[102] that such cases are not recognized by tuberculosis programs as public health issues,[103] and even that such cases are largely ignored.[104] These remarks seem unsupported when looking at what actually takes place in tuberculosis programs. Nonetheless, such criticism is perhaps aimed at the report of the 1974 Expert Committee, which may be understood to recommend treating only those cases that are confirmed with bacteriology.[19] In the programs collaborating with The Union, smear-negative and extra-pulmonary tuberculosis cases were never

denied free care and treatment, and as many as half of all new pulmonary cases in these programs were indeed reported as smear-negative. This reflects the wider public health aspect of the program; that is, considerations that go over and above communicable disease control. When looking at other programs, one can conclude that rarely has there been a policy of treating only smear-positive and severely ill smear-negative patients. The latter group, however, has sometimes been limited to a certain proportion compared to smear-positive cases. Such policies either have been justified by the reluctant prioritization resulting from severe resource restriction (smear-negative patients may then have to pay for treatment, as in the case of Vietnam, for example[105]), or as a strategy to halt extensive over-diagnosis and over-treatment of tuberculosis in settings where this was a problem. In its new framework for tuberculosis control in 1994, the WHO clearly stated that even if, to have the greatest impact on reducing mortality, morbidity, and transmission, priority should be given to detecting sputum smear-positive patients and seriously ill smear-negative patients, ideally all tuberculosis cases should receive short-course treatment.[106]

Diagnosis of smear-negative pulmonary tuberculosis

It is simplistic and misleading to claim that in low-income countries the acid-fast smear is the only test used, and smear-negative patients are generally not diagnosed and frequently not treated as a consequence.[100] One needs only to look at notifications of tuberculosis in low-income countries to see that this is not so.[107] Although it is true that culture of mycobacteria is not routinely performed in low-income countries, this does not mean that those who would test positive by culture are not detected. It is a fair assumption, however, that diagnosis of cases other than sputum smear-positive ones is less accurate than diagnosis of sputum smear-positive cases, to varying degrees depending on the setting.

Logistically and operationally, it is more difficult to diagnose smear-negative than smear-positive tuberculosis, and caution is needed to avoid misdiagnosis and over-treatment, which are detrimental to individual patients and costly for the health service. Furthermore, smear-negative cases as a group have a better prognosis without treatment than smear-positive cases. Thus, unless they are severely ill or have a serious concomitant disease or HIV infection, they can be expected to fare reasonably well even without treatment. How well depends, among other things, on the definition of a smear-negative case.

A longitudinal community-based survey in Bangalore District in India in the early 1960s (where there was no anti-tuberculosis treatment program at the time) suggested that fewer than 5% of persons with abnormal radiographs but negative bacteriology in the first survey progressed to become positive by bacteriology on re-examination at 12 months.[108,109] A prospective study in Bangalore City in the 1970s followed symptomatic care seekers where chest radiography suggested tuberculosis but bacteriology was negative (by a single negative

direct sputum smear).[110] Of 457 suspects identified by the clinic, 144 (32%) were found by the study procedures to have positive sputum (smear and/or culture), and 100 (22%) not to have radiographic findings compatible with tuberculosis. Thus, half of the patients identified by the clinic were not truly negative. The remaining 213 patients were randomized to receive either self-administered anti-tuberculosis treatment for one year (103 patients) or placebo (110 patients). In the placebo group, 21% progressed to positive bacteriology versus 11% in the treatment group. Of those who did progress, the majority (62% and 71%, respectively) did so within four months. This outcome led the investigators to recommend not treating cases who were negative on bacteriological examination, but rather to increase the number of sputum specimens examined per suspect and improve sputum examination and radiography so as to better identify truly smear-negative tuberculosis suspects. Such subjects would then be given nonspecific treatment and followed for three to four months to see how they fared. This was done primarily in order to emphasize a proper process in diagnosis of tuberculosis and to minimize the number of patients erroneously enrolled in treatment. This study undoubtedly influenced the Expert Committee in 1974. The observations of the investigators can be regarded as precursors to the diagnostic algorithm for smear-negative tuberculosis, which is discussed in Chapter 3.

The findings of the Indian study cannot be generalized universally (that is, in time and place), and they represent an example of where recommendations should take note of context. At the time, the situation in many developing countries might have resembled this particular setting in India, but this is no longer the case in places where good tuberculosis programs exist. Universal conclusions concerning diagnosis and management of smear-negative cases are hardly justified, as local conditions vary considerably and must be taken into account. Indeed, later studies with proper recruitment of subjects (symptomatic care seekers) and proper diagnostic work-up challenged the findings of the Indian study and argued that a significant proportion of smear-negative cases progress to smear-positive disease.[42]

In a controlled trial in Hong Kong, published in the 1980s, 53% of smear-negative suspects progressed to positive bacteriology within 30 months,[111] and 57% did so within five years.[112] The definition of smear-negative tuberculosis was very strict in this trial and was arrived at via five negative smears and good-quality radiology services. It was easy to justify treatment of smear-negative tuberculosis in this setting and it was possible to conclude that an appropriate algorithm could minimize over-treatment of smear-negative cases without excluding them altogether. This course of action was attempted in the programs collaborating with The Union. Increases in the prevalence of HIV infection, however, resulted in a disproportionate rise in the reported rate of smear-negative cases as compared to smear-positive cases in many settings.

Although the frequency of positive microscopy was similar in HIV-positive and HIV-negative tuberculosis patients in a Tanzanian central hospital that participated in a study published in the 1990s,[113] this was not the case in Zambia[114] and in several other countries in sub-Saharan Africa with variable HIV prevalence.[115] It was suggested that the deteriorating reliability of sputum smear microscopy—which occurred as local case loads soared and diagnostic services were overwhelmed—might partly explain the disproportionate increase in smear-negative cases seen.[98] In 1991, smear-negative pulmonary tuberculosis cases reported in Malawi were nearly double the number of smear-positive cases. Analysis of records from a large central hospital, which reported the country's largest number of tuberculosis cases, revealed that sputum smears were examined for only five percent of those patients with smear-negative tuberculosis.[116] Furthermore, in fragile and overworked laboratory networks, the question of technical quality and false-negative smears arises. Coinciding with clearer procedural instructions and improved adherence to guidelines, the proportion of smear-positive results among pulmonary cases in Malawi subsequently increased again, reaching almost 60%, according to a review of the period from 1997 to 1998.[116]

In conclusion, diagnosis of smear-negative tuberculosis is not easy. Studies in the 1960s and 1970s suggested that concrete procedures in the diagnosis of such cases were needed. This will be discussed with operational strategies in Chapter 3.

Early versus late diagnosis of tuberculosis

What is early diagnosis of tuberculosis or "early tuberculosis," for that matter? It is common to confuse this matter with the issue of smear-positive versus smear-negative disease. The fact that the difference between infection and disease is not always clear in people's minds might explain some of the confusion. Clearly, infection always precedes disease, but disease does not always follow infection. Subclinical infection is not "early disease," but some might refer to it as "early tuberculosis." It is important to clearly differentiate infection and disease when discussing tuberculosis epidemiology and intervention. For all practical purposes, when public health officials discuss the interval between onset of disease and diagnosis, and thus early versus late diagnosis, they refer to the duration from the onset of symptoms (or cough).

In tuberculosis, the extent of disease is not a simple function of duration of illness, and a cavity is not necessarily a late occurrence.[117] What is referred to as "advanced tuberculosis" is defined by the extent and nature of lesions within the lungs rather than the duration of disease. "Advanced tuberculosis" is not invariably a result of "late diagnosis." Though it commonly develops within six months, tuberculosis can have a fulminant course in which the clinical picture known as "advanced tuberculosis" develops rapidly.

If smear-positive pulmonary tuberculosis were invariably a late occurrence, one would expect to find longer average patient delay (delay referring to the patient seeking care) in smear-positive cases.* In a retrospective record review of 378 cases with positive cultures in New York City in April 1994, patient delay was not associated with acid-fast smear status or findings on chest radiography at diagnosis.[118] A study in Australia also found similar patient delay in smear-positive and smear-negative disease.[119] Extra-pulmonary cases may have blurred the picture in both of these studies, however. Very short patient delay was measured in a recent study in Thailand—10 and 15 days, respectively, for HIV-positive and HIV-negative patients diagnosed with smear-positive tuberculosis[120]—and an average delay of 20 days was reported in a study from South India.[121] Thus, clearly smear-positive pulmonary tuberculosis is not necessarily a "late" occurrence.

Investigators in South Africa argued that there was likely to be a relationship between the duration of clinical disease and the condition of the patients when they arrived at the hospital. They measured longer delays in accessing tuberculosis treatment among those who died in a rural hospital,[122] and a higher death rate among those who traveled very long distances to reach the hospital.[123] Numerous factors influence delays in diagnosis and treatment of tuberculosis. As this is often a structural issue, it is discussed further in Chapter 7.

Chemotherapy

Early in the chemotherapy era, randomized controlled clinical trials provided evidence that the high mortality in smear-positive tuberculosis could be greatly reduced and transmission permanently arrested with specific anti-tuberculosis treatment. With time, however, it became clear that the results of clinical trials were not necessarily indicative of what actually occurred when chemotherapy was introduced in routine practice. No less important than clinical trials are effectiveness studies, which need to be conducted in different settings where operational aspects, drug resistance, and drug tolerance may vary.

Acknowledgement of the need for treatment policies

When recounting the history of tuberculosis chemotherapy in 1977, Fox reminded his audience how, in the 1950s, the introduction of multidrug therapy, which included streptomycin, isoniazid, and para-aminosalicylic acid (PAS), was celebrated as the era of 100% successful therapy.[124] Nevertheless, treatment of tuberculosis was in no way regarded as a trivial quest at the time.[124] In addi-

*Note that the term "patient delay" in smear-positive cases is not synonymous with "infectious period."

tion to chemotherapy, a strict regimen of bed rest, nutrition, and fresh air was considered important. Smear, culture, and radiological examination were performed every month during treatment, and drug susceptibility testing was conducted when treatment began and on every positive culture thereafter. Treatment was adjusted to the findings. Finally, there was regular follow-up every three to six months for several years (or for life) after treatment completion. Gradually, treatment was shortened and simplified as new drugs were introduced and clinicians relaxed the rituals. Little by little, superfluous procedures were discontinued, often with considerable resistance from conservative institutions and specialists. Eventually, monitoring was trimmed down to taking a culture of a specimen obtained at five to six months (in a 12-month treatment regimen) for the purpose of confirming bacteriological conversion. Whereas drug resistance had been of considerable concern in the early chemotherapy era, routine susceptibility testing was eventually discontinued when it was demonstrated that patients with resistance did well on a 3-drug regimen (streptomycin, isoniazid, and PAS).[124] It was then considered most important to perform susceptibility tests in case of failure or relapse to guide the choice of drugs in retreatment cases.[124]

Disappointingly, the 100% successful therapy was demonstrated to be only about 50% successful in most developing countries, as the organization required seemed beyond the capacity of their health systems.[11,124] The duration of treatment in the early days was up to two years, and drugs were administered in two to four doses per day.[124] For purely operational reasons, it was of vital importance to developing countries that shorter and simpler treatment be developed. In retrospect, this would have provided a sound justification for the participation of East Africa in the clinical trials of short-course regimens; that is, provided such regimens were intended for introduction into Africa. The fact of the matter is, however, that experts in rich countries opposed the introduction into developing countries of short-course treatments that had been fully developed. Thus, it can be argued that the participation of developing countries in the clinical trials of short-course regimens is an example of exploitation, and that developing nations were used as laboratories to develop what was intended for use in the rich countries.

When rifampicin and pyrazinamide were introduced into the treatment regimens, the relapse rate was decreased. Further studies demonstrated that it was neither necessary to give rifampicin daily nor throughout treatment in order to reduce the relapse rate in short regimens. Eventually, numerous options for short-course treatment became available. The fact that drug susceptibility testing was not needed[125] represented an important change when moving from 2-drug regimens to 3-drug regimens and finally to short-course treatment with four to five drugs in the intensive phase: this signified increased safety in areas where it was not possible to perform drug susceptibility testing.

As early as 1962, Crofton, analyzing the situation in Edinburgh, Scotland, concluded that it was principally good treatment combined with reasonably good case finding and contact management that dramatically reversed, after 1954, the city's previously rising tuberculosis notification rate.[126] He warned that although tuberculosis morbidity in developing countries should quickly diminish as well, poorly organized treatment could result in treatment failures, and a residuum of sputum-positive patients with drug-resistant bacilli could accumulate. Such a problem would be costly in terms of human misery and economic resources. At the time, evidence of this chain of events was already noted in India.[127] Crofton encouraged effective treatment of the maximum number of patients and prevention of drug resistance via a controlled national treatment policy, restricting the provision of anti-tuberculosis drugs to doctors trained in their use.[126] This is one of the basic principles in tuberculosis control: standardized treatment and control of anti-tuberculosis drugs. Crofton also discussed the problem of insecure and inadequate drug supply that leads to drug resistance. This is another of the basic principles of tuberculosis control: secure supply of anti-tuberculosis drugs.

The looming threat of serious drug resistance was acutely realized when countries collaborating with The Union started expansion of short-course treatment in the early 1980s. It was considered crucial to protect the new drugs introduced with short-course treatment, particularly rifampicin. This was done with the following measures: prescribing four drugs in the intensive phase of treatment; using rifampicin only in a fixed-dose combination with isoniazid; having the patients take medications under direct observation of health personnel; observing a strict balance of regimens with a different regimen for previously treated cases (assuming they might harbor drug-resistant bacilli); and forbidding the sale of anti-tuberculosis drugs in the private market. While this protocol may sound overly restrictive, it was probably appropriate given the circumstances. If one safety mechanism faltered (which would surely, if unpredictably, occur), another one provided a safety net. In the course of time and with changing circumstances, it would seem appropriate to relax some of these procedures.

Drug resistance

The problem of acquired drug resistance was discovered soon after the introduction of anti-tuberculosis drugs. In a hospital-based study involving 96 patients in the 1950s, Dressler et al. observed that the majority (68%) of patients who had been treated with streptomycin prior to admission remained susceptible to the drug,[128] but patients with cavities and far-advanced disease (that is, with more numerous bacilli) were more likely to have streptomycin-resistant bacilli. The majority (76%) of patients who had been treated with isoniazid prior to admission excreted bacilli resistant to isoniazid.

Enarson has argued that isoniazid resistance and subsequent multidrug resistance stems from the decision to use isoniazid monotherapy in resource-poor countries.[129] A certain degree of controversy concerning the efficacy and safety of isoniazid monotherapy lingered in many circles in the early days of chemotherapy,[130] and even into the 1970s.[131] This had to do with the apparent improvement in individual cases on isoniazid therapy, many of them with minimal disease and smear-negative, and the belief that drug-resistant strains had reduced virulence and thus did not pose a public health threat.[132] To evoke the atmosphere prevailing at the time, the example of India is presented in Box 2.6.

Box 2.6 Treatment practices in India in the 1950s and 1960s

In the 1950s, isoniazid monotherapy, owing to its simplicity and low cost, was considered by many to be the best available chemotherapy for mass domiciliary treatment of tuberculosis patients in poor countries, and it was being used on an increasing scale in India. It was considered important to study the potential epidemiological consequences of this practice. In this context, a controlled comparison of the treatment of pulmonary tuberculosis with isoniazid monotherapy in different daily doses (high or low) and rhythm of administration (single daily dose or divided doses) and treatment with PAS and isoniazid (PAS-H) was undertaken in Madras.[132] Patients were recruited in 1957–1958 and the results published in 1960. The study concluded that the public health risks from isoniazid-resistant organisms was considerable in the isoniazid monotherapy series, with a high proportion of cases developing isoniazid resistance early in treatment (30% to 43% at three months compared to 2% in the PAS-H series), which continued for the rest of the 12 months. The proportion of cases with unfavorable response at 12 months was 27% to 56% in the different isoniazid monotherapy series as opposed to 9% in the PAS-H series. Only cases with negative smears gave evidence of satisfactory response to treatment with isoniazid monotherapy, and this could clearly not be used as justification for a treatment regimen in a mass chemotherapy program where a considerable proportion of patients were likely to be smear-positive.

In 1964, Fox condoned the practice of isoniazid monotherapy in resource-poor countries if physicians were faced with the choice of administering either monotherapy or no treatment at all. Nonetheless, he advised that, if possible, it was better not to give such therapy to patients whose sputum smear was heavily positive or who were previously treated.[133] The Expert Committee of 1964 endorsed as acceptable, in areas with scarce resources, the practice of using two or, if possible, three drugs in the intensive phase followed by isoniazid monotherapy in the continuation phase, which could be started upon demonstration of a negative sputum sample.[18] Thioacetazone was proposed, however, as an inexpensive accompanying drug for isoniazid in the continuation phase in areas where this drug was well tolerated. The standard practice in technically advanced countries at the time was three drugs in the intensive phase and two in the continuation phase.[18]

(*continued*)

Box 2.6 *Continued*

It became common practice in poor countries to use only streptomycin and isoniazid in the initial phase and then isoniazid monotherapy for what remained of a 12-month treatment course, or to use the two drugs throughout in a fully supervised, intermittent (twice weekly) regimen. Accounts taken from a publication in India in 1965 suggest that because it required injection, streptomycin was problematic for treatment in rural areas, and thus it was not recommended for use. It seems that it was decided that treatment in rural areas must be given on an ambulatory basis with self-administration, and that the view at the time—in spite of the study cited above—was that "The fear of increasing drug resistance in the community should not . . . hinder the development of tuberculosis programs in rural areas while continuing the efforts to define the epidemiological and clinical significances of the prevalence of drug resistance"[134] (p. 65).

A publication in 1971 discussed the findings of successive tuberculosis prevalence surveys conducted in Bangalore District in South India in the 1960s. The findings suggested that the large increase in the number of isoniazid-resistant cases between the second and third surveys was a result of haphazard and irregular treatment with isoniazid monotherapy in smear-positive patients after the second survey.[135,136] In a controlled drug trial in South India reported in 1997,[137] roughly one in five cases (21.6%) had drug-resistant sputum cultures.

Consequences of badly organized chemotherapy

Numerous operational data and laboratory studies have demonstrated that tuberculosis treatment programs have not always achieved the expected results. Failure of mass treatment programs in developing countries was common in the early days. Whereas it must have been tempting to conclude that the conditions in developing countries were simply inadequate for implementation of tuberculosis treatment in general and short-course treatment in particular, the programs collaborating with The Union demonstrated that under certain conditions good results could be achieved.

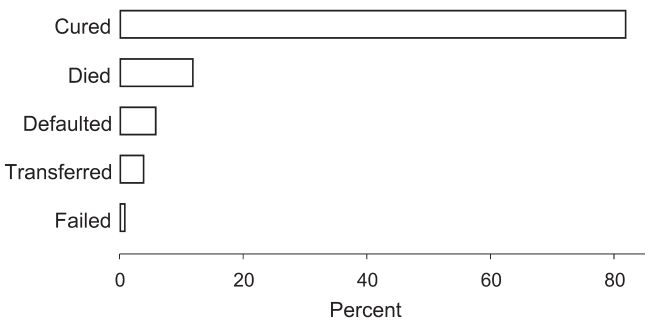
In 1970, Kent et al., using data from Kenya, compared the results in controlled clinical trials with those in routine application of chemotherapy, emphasizing the difference in case mix (a highly selective group recruited in the trials) and therapeutic effectiveness.[138] The principal problem was inadequate intake of treatment under routine conditions.

In an article published in 1978, Grzybowski and Enarson compared the outcomes of patients without chemotherapy to the results obtained in various programs that applied 12-month regimens.[139] In an example from India, referring to the period between 1961 and 1968 in an area where no treatment was available, about a quarter of the patients died after 18 months, one third had

converted to negative, and the rest (roughly 40%) were still excreting bacilli. At five years, half of the patients had died, one third were negative, and almost 20% were excreting bacilli. Examples from what was commonly referred to as "mass chemotherapy programs" in developing countries typically showed that roughly 60% of the patients were sputum-negative, only 10% to 15% died, but approximately 25% were excreting bacilli at the end of two years; that is, they were known as "chronic bacillary cases." This was in contrast to the excellent results obtained in countries with better organization and more resources, where typically 90% of the patients were rendered sputum-negative and a very small proportion of cases became chronic. Thus, the problem with the mass chemotherapy programs was the accumulation of chronic cases—a phenomenon that may result in increased transmission. Even if these programs saved lives, they failed in their role of reducing the number of sources of transmission in the community.[139] A further problem with chronic cases in these circumstances was that they frequently excreted drug-resistant bacilli, thereby compromising the potential of control programs to succeed later unless new drugs were introduced. This is a second reason why the development of short-course treatment was particularly important for resource-poor countries, but the introduction of the new drugs was controversial given the previous failures.

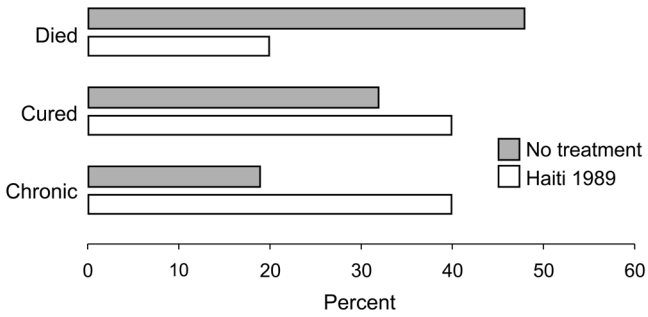
The National Tuberculosis Program in Tanzania demonstrated that, given appropriate organization, it was possible to achieve good treatment results with standardized short-course treatment in a low-income country. Figure 2.1 demonstrates the outcome of short-course treatment of new cases enrolled in the program in 1992. For comparison, the example from Haiti (1989) presented in Figure 2.2 clearly shows that short-course treatment, in and of itself, is insufficient.

Figure 2.1 Outcome of treatment in new smear-positive pulmonary tuberculosis in Tanzania in 1992



Data from the Tanzania National Tuberculosis Program.

Figure 2.2 Outcome of tuberculosis in Haiti (1989) compared to outcome without treatment (India, 1960s)



Data from a report on a technical mission to Haiti in 1990 (D Enarson, personal communication) and Grzybowski and Enarson, 1978.[139] The data from India refer to status at 5 years after diagnosis. At 18 months there were fewer deaths (25%) and more with positive bacteriology (43%).

As seen in Figure 2.2, badly organized treatment does reduce the number of deaths (compared to a situation where no treatment at all exists), but results in a growing number of chronic cases, thereby increasing the prevalence of tuberculosis. The result of badly organized treatment is demonstrated in the findings of a cross-sectional study in a district in India (referring to patients registered from 1986 to 1988) that found evidence of grossly irregular treatment, early default, and drug resistance in a program applying short-course treatment.[140]

In settings with low overall cure rates, tuberculosis surveys (and program statistics, if reliable) establish that a high proportion of active tuberculosis cases in the community (or recruited in the program, if reliable statistics are available) has a history of previous treatment. Furthermore, in this situation, resistance to anti-tuberculosis drugs is higher in previously treated cases than in cases not previously treated. Increased prevalence of drug resistance in the community will eventually lead to resistance in previously untreated cases due to transmission of resistant strains. This latter phenomenon is a matter of time; a concomitant HIV epidemic accelerates the process.

The role of poor treatment programs in the development of drug resistance is demonstrated in the case of Korea, where repeated surveys of representative samples of the population were carried out.[141,142] In 1965, the majority of infectious cases found in the survey were those who were previously known to the tuberculosis program but had not been cured. Although drug resistance was common, multidrug resistance was rare, allowing improved organization and the introduction of short-course treatment to improve the situation. A more recent example comes from Moldova in the late 1990s, although in this case the

figures are only suggestive, given that they are not taken from representative surveys but rather from routine susceptibility tests in clinical practice.[143] In the example of Moldova, the situation is all the more serious, as considerable multidrug resistance resulted from the use of short-course treatment in unfavorable circumstances. In Table 2.1, we see that the proportion of previously treated cases, among all cases with results of drug susceptibility testing, increases with time, and that the proportion of any drug resistance and multidrug resistance among all cases combined (new and previously treated) increases.

It is clear from the above that in tuberculosis programs a focus on outcome is essential. The aim is to render infectious patients permanently noninfectious and thus to prevent new infections in the community from known sources. Routine cohort analysis of treatment results is the easiest way to evaluate a program in this respect. Such an analysis provides a speedy assessment of outcome and can be done anywhere. A more advanced surveillance—but not one that is uniformly necessary or feasible—is the monitoring of trends in drug resistance. According to Chaulet et al. in 1995, the incidence of acquired drug resistance is not an epidemiological surveillance indicator for a national program, but rather an indicator of the effectiveness of the chemotherapy, and is used in specific situations, such as clinical trials, to compare the effectiveness of different chemotherapy regimens.[144] It has since been argued that the prevalence of drug resistance can be used in programs to assess or even monitor the appropriateness of the treatment strategy, although factors such as HIV infection and other causes of mortality can obscure the picture.[145,146] In 2001, Van Deun et al. in Bangladesh demonstrated that whereas a one-time study reveals little, repeated studies reveal trends that make it possible to evaluate programs based on drug resistance data—especially when looking at resistance in previously treated cases.[146] In 2005, the technical staff of the Tuberculosis Division of The Union stressed that under unfavorable conditions rapid increases in the

Table 2.1 Results of routine drug susceptibility testing in Moldova, 1995–1999

	1995 (*n* = 293) %	*1996* (*n* = 266) %	*1997* (*n* = 786) %	*1998* (*n* = 719) %	*1999* (*n* = 764) %
Previously treated	25	40	39	48	44
Any drug resistance	16.7	23.7	37.0	44.6	40.7
Multidrug resistance	1.4	4.9	7.9	12.5	11.9

Data from Crudu et al.[143]

levels of drug resistance may occur but will first be evident among strains isolated from retreatment cases, which should therefore be the primary target for surveillance of drug resistance.[147] This is in line with Styblo's original recommendations in the 1980s,[60] as discussed elsewhere.

Standardized treatment regimens

Randomized controlled clinical trials provided the evidence that treatment could be standardized as multidrug regimens with fixed content and duration of treatment were tested and compared. As multiple options became available for efficacious treatment, the question arose as to whether the choice of regimens should be left entirely up to individual practitioners or whether policy should oblige health professionals to prescribe certain regimens. To a certain extent, the answer to this question may depend on the context. Operational studies in various settings have shown that treatment choices made by individual practitioners may be haphazard and often inadequate. This is likely to jeopardize the treatment and control of tuberculosis at the community level to such a degree that individualized treatment regimens may eventually become necessary, at the point in time when drug resistance patterns—as a result of haphazard treatment practices—are no longer predictable.

In the setting of the Union collaborative programs, in order to make treatment accessible, it needed to be prescribed and managed by medical assistants or paramedics with less than optimal training. In this context, a standardized treatment strategy was obviously the safest policy. Styblo recommended that the national tuberculosis program categorize patients according to the priority for treatment and determine the regimens to be used in each category in the program.[20] If implementation of a program was successful in preventing drug resistance, in the long run the necessity of individualized treatment might never materialize (or at the most would be a rare occurrence). This was largely borne out in the Union collaborative programs, where drug resistance levels remained low and tuberculosis thus was a curable disease. Further advantages of standardized treatment regimens are continuity of care within and between health units and easier management of drug supply, both of which are likely to contribute to better overall results of treatment in the long run.

The overall approach

In 1937, Wade Hampton Frost pointed out that for the eventual eradication of tuberculosis it is not necessary that transmission be immediately and completely prevented.[148,149] How much reduction in transmission is enough? What impact can be expected when a tuberculosis control program is implemented? Which factors are likely to modify the impact, and how relevant is the control policy in different settings?

In the 1960s and 1970s, longitudinal epidemiological investigations in Kolin, Czechoslovakia, documented trends in incidence and prevalence of tuberculosis.[96] A rapid decline in prevalence was observed mainly as a result of a reduction in the number of chronic patients, to some extent on account of specific treatment for chronic cases but chiefly because the effective treatment of new cases and relapses prevented the development of new chronic cases. New cases and relapses were less responsible for the decline in prevalence. It was concluded that in an area where a large proportion of the population is infected, a decline in incidence—even with a good program—is delayed and gradual and cannot be speeded up considerably.

Mathematical modeling and estimation of impact

Early in the history of tuberculosis programs, all emphasis was placed on case finding. This may have been a remnant of hard-grown habits from the prechemotherapy era. If so, it was reinforced by the so-called "Piot-Waaler model" of the 1960s[150] and became the basis of practice in India, where mobile teams rushed around finding the cases but paying little attention to how they were managed. As later demonstrated by Grzyboski and Enarson, this model failed to account for the negative impact of poor chemotherapy.[139] Styblo, together with Bumgarner, eventually put forward a simple model to demonstrate the importance of case holding.[151] Their model assumes a baseline incidence of 100 cases per 100,000 population and a prevalence of 200 per 100,000, and predicts what occurs regarding tuberculosis prevalence as case finding and cure rates rise with implementation of a treatment program. The values presented in the cells in this model, which is presented in Table 2.2, refer to prevalence of tuberculosis per 100,000 population after intervention. If case detection is as low as 35% (referring to actual disease burden in the community), there is a reduction in prevalence, as shown in the shaded cell in Table 2.2, if the cure rate is 75% ($173 < 200$). On the other hand, if the cure rate is very low—for example, 35% to 50%—the prevalence actually increases to above 200 or, at the best, remains constant even with impressive case finding. Only when the cure rate approaches 75% is there measurable impact in terms of reducing the prevalence of tuberculosis in the community. Though the model as presented here is a simplification (that is, it is important to

Table 2.2 Styblo's mathematical model

Case detection	*Cure rate*			
	35%	*50%*	*75%*	*85%*
35%	215	197	173	161
50%	218	196	159	146
65%	223	193	145	125
70%	223	192	140	119

Source: Styblo and Bumgarner, 1991.[151] See text for details.

consider what actually becomes of patients who are not cured, and one would need to speculate and make assumptions as to that in a given setting*), its value lies primarily in demonstrating the importance of the cure rate as a first priority in a program and the fact that, from the point of view of tuberculosis control, it is futile and potentially harmful to increase case finding if the cure rate is low.[151]

Case detection refers to the activity of identifying infectious cases through sputum smear examination.[152] Case detection (rate) is the number (rate) of reported cases—or cases diagnosed and treated—divided by the estimated annual number (incidence rate) of tuberculosis in the community.[153] The real number of cases in a community (the denominator for case detection) is not known, so achievements in case finding are not easily measured but rather have to be estimated. The outcome of treatment, on the other hand, is easily measured and lends itself to target setting. A success rate refers to routine conditions (with all diagnosed cases as denominator[151]) and reflects the potential for impact provided that all cases are included. Thus, a target cure rate would have made sense in the Union collaborative programs where it was reasonable to assume that the information system captured the total effort in case finding and treatment. Yet definite targets were not set in this respect. Instead, the general direction was made clear to all: the intervention was controversial unless it achieved a reasonable success rate. Therefore, the focus was on curing individual patients and contemplating the fate of those patients who did not achieve cures, the reason why this occurred, and what could be done about it.

Styblo encouraged speculation on the impact of the program from the wider epidemiological perspective as well as from the point of view of the individual patient. The fuel for the tuberculosis epidemic is primarily the smear-positive form of the disease. With the program in place, how much of the total ongoing transmission in the community is due respectively to new cases, relapse, default, and treatment failure? This refers to health services structure and coverage and to program performance. It is a core issue and, if it can be elucidated in any given setting, has important implications for improving the operations of the program. Such speculations empower those responsible for the program to advance control measures. Each program, given its specific reality, ideally can set its own targets.

At the beginning of the Union collaborations, an important question was how to record and process data to facilitate such speculations, and whether it

*In the model, Styblo made assumptions concerning cases undiscovered in the community, patient and doctor delay in diagnosis and treatment in detected cases (average four months), relapses, and survival of failure cases (average three years) (source: Karel Styblo, Arusha course, April 1991).

was possible and useful to have routine outcome analysis in the programs. The programs subsequently demonstrated that this was possible even in a difficult setting and thus that it could be accomplished anywhere. Cohort analysis of treatment results can be implemented, given sufficient interest in doing so, and often it reveals unexpected findings that assist reflections on program direction and impact. The method is discussed in detail in Chapter 8.

In 1998, Dye et al. applied mathematical modeling to examine the potential effect of the DOTS strategy.[153] Their results supported Styblo's point. According to their model, 70% case detection allows an increase in tuberculosis incidence until the cure rate exceeds about 50%.* They described some of the characteristics of tuberculosis control by case finding and treatment, observing that the ratio between annual risk of infection and incidence of smear-positive cases decreases as tuberculosis declines because case detection and treatment shorten the duration of infectiousness, and the annual risk of infection falls faster than the incidence. In their model, case detection and cure reduced transmission, which first affected cases of tuberculosis arising from recent infection. Even when case detection and cure rates remained constant, a slowing of the decline in incidence of tuberculosis occurred. The fall in incidence was greater if a program was applied to a population of younger average age as compared to one of older average age (in younger populations, a high proportion of cases comes from recent infection) and if a program was implemented in an area where a previously ineffective program had achieved low cure rates. Finally, in a scenario where HIV incidence rates were high, a tuberculosis control program prevented cases merely by slowing down the rise that would otherwise occur in the incidence of tuberculosis as a result of an HIV epidemic.

Expected and observed impact

The policy model aims to reduce mortality, morbidity, and transmission. How effective is it in reducing mortality? The potential of chemotherapy in this respect is clear from pre-chemotherapy data, clinical trials, and outcome analysis in good programs. A study in Guinea-Bissau demonstrated how the duration of treatment before default (brought on by disruption of services due to war) affected the mortality rate for patients with tuberculosis, suggesting that each week of treatment reduced mortality by five percent.[154] It is difficult to accurately measure the impact on mortality on a country-wide scale if all cases do not come forward and are treated, if all tuberculosis deaths are not known to the program, and if the cause of death in patients with tuberculosis is primarily something other than tuberculosis, which is particularly the case in areas where HIV prevalence is high. In this context, as discussed in Chapter 6, it has been

*They assumed that all "failure," "default," and "transfer out" cases remain infectious.

suggested that it is necessary to invest in improving vital statistics.[155] It may be wise, though, to pause and consider that vital statistics are not perfect even in rich countries. Today, it is easy to become obsessed with information, but it is also difficult to justify how improved vital statistics could be an appropriate response to the dual epidemic. Information systems do not need to be perfect to be useful, as is discussed in Chapter 8.

How effective is the control policy in reducing morbidity? This is clear at the level of the individual patient as well as at the population level, considering that treatment substantially shortens the duration of illness and results in permanent cure in the majority of cases. Depending on efficiency in reducing transmission, a reduction in future population morbidity is expected as well. In areas with a high prevalence of tuberculosis infection, however, the program does not prevent an increase in the number of tuberculosis cases as a result of an HIV epidemic. This fact was clearly demonstrated in the Union collaborative programs. Another example is found in the case of Botswana, where in spite of a decade of implementation of a program using a more efficacious treatment regimen than the one used in the Union collaborative programs (see Chapter 3), the case rates increased by 120% from 1989 to 1996.[156]

How effective is the control policy in cutting transmission? It is sometimes argued that much of the transmission takes place before a patient makes contact with the health services. Research has shown that domestic contacts of tuberculosis patients frequently show signs of infection after two months of exposure.[157] The difference in the infectious period in the present-day period, as compared to the pre-chemotherapy era, is great enough to dispel doubt that a well-organized treatment program with reasonable population coverage decreases transmission in the community. The problem is that its main impact—that is, the effect of the current risk of infection on the prevalence of infection in future generations—is largely hidden from view. It is difficult to measure this impact directly, and little effort and resources have been spent on even trying. Styblo stressed the importance of demonstrating impact in this way and insisted on periodic surveys of the risk of infection in school children. In spite of his insistence, with the exception of Tanzania, the collaborative programs never convincingly accomplished this task. Rieder has since pointed out the numerous problems associated with conducting infection prevalence surveys using currently available technology (the tuberculin test) and with interpreting the results.[158] Enarson et al. have stressed the importance of improved technology in measuring the reduction in prevalence of infection.[159]

Whereas experts in epidemiology and public health have intensively debated and harshly criticized the model in terms of its ability to control tuberculosis in Africa—as judged by its failure to reduce morbidity in areas with high HIV prevalence—it is generally accepted that the strategy is effective in limiting development and spread of drug resistance if it is implemented in a

timely manner and/or adapted sensibly.[70] This issue is discussed further in Chapter 3.

Finally, to what extent do the HIV pandemic and multidrug-resistant strains of *M. tuberculosis* challenge the approach previously outlined? This question will be discussed in Chapter 6. The current chapter will conclude with an examination of the policy model for tuberculosis control programs as presented by The Union.

The policy model

The basic principles of, and the conditions for, achieving success in Union tuberculosis control programs have been summarized.[129] They include the following: commitment on the part of the government, a secure supply of drugs and materials, a network of microscopy centers with a system of quality control, proper recording and reporting of cases, adequate supervision of drug taking during the initial intensive phase, proper training and supervision of health workers, and proper pilot testing and a gradual introduction of policy change.

The prototype

The Union's policy model took note of available evidence and operational characteristics in the collaborating countries, as interpreted by the experts involved. The main policy points are summarized in Box 2.7.

Box 2.7 The main policy points in the Union model

Diagnosis by sputum microscopy
Case finding was primarily aimed at identifying the most infectious patients: those demonstrated to be positive on direct microscopy of sputum. Sputum examination was administered free of charge. The number and proportion of sputum smear-positive patients among all patients treated was used as a parameter in surveillance and quality assurance.

Standardized treatment regimens and fixed-dose combinations
The programs used standardized treatment regimens which were based on the results of clinical trials but also took into account operational feasibility. A sequence of regimens was used: a regimen for new cases, which would cure the bulk of the patients; and a second option (retreatment) for those not permanently cured with the first regimen. The regimen for new cases used rifampicin only in the intensive phase of treatment (first two months). Rifampicin was never used in single preparation but always in a fixed-dose combination with isoniazid. The effectiveness of each regimen and the overall treatment algorithm was monitored with a standardized recording and reporting system.

(*continued*)

Box 2.7 *Continued*

Directly observed treatment
To prevent adverse outcome of the intervention (serious drug resistance), treatment was directly observed by a health worker whenever it included rifampicin, which took place in the intensive phase of short-course treatment for previously untreated sputum smear-positive patients and throughout retreatment. The patient had the option to attend daily for ambulatory treatment at a hospital or health center, or to be hospitalized. Self-administered treatment without rifampicin was an option for those who, for whatever reason, could not accept either of these choices.

Dependable supply of medicines
It was recognized that the decentralized purchase of medicines was likely to have detrimental effects such as irregular supplies, acquisition of low-quality medicines, and high prices. Therefore, procurement of anti-tuberculosis drugs was centralized, and needs-based, reliable distribution to peripheral units was to be guaranteed. Anti-tuberculosis treatment was provided to patients free of charge.

Information and accountability
Quality was a key concern in the model, and emphasis was placed on accountability at all levels. A system for standardized collection of information for case management, surveillance, administration, supply management, and quality assessment was implemented.

Training and supervision
It was recognized that in the context of the general health services in low-income countries, training was usually a waste of resources if it was not followed by supervision of services. Therefore, it was considered important that training and supervision should go hand in hand. In particular, short-course treatment was not introduced until specific training had been conducted and subsequent supervision of services guaranteed.

Gradual introduction
Whereas the aim was national expansion, implementation did not occur all at once. A gradual, phased procedure was used both in terms of sequential implementation of the different activities (training, microscopy, surveillance, short-course treatment, etc.) and increase in geographical coverage. It was expected that units and areas would not all perform equally well, and that different strategies would likely be needed in different locations, both within and between countries. It was considered particularly important to prepare the ground before introducing short-course treatment. Such groundwork would include establishing a network for sputum microscopy, implementing reliable information and supply systems, and demonstrating capacity for case holding. Meanwhile, 12-month treatment was used. Finally, only when reasonable results had been demonstrated in short-course treatment should a health facility implement the retreatment regimen. Until such a point, patients were to be referred elsewhere for retreatment. Thus, there were certain conditions for implementation and subsequent advance of the program in a given location or unit. This tactic was primarily driven by concern for quality, but it can be said that it ideally encourages local commitment and responsibility and results in gradual and consistent capacity building.

When the Union collaboration took off, a 12-month regimen referred to as the "standard regimen" was considered the only safe and appropriate regimen for the setting. When discussing the experience in Tanzania, Styblo himself said that the results of the 12-month regimen, after four years of implementation (1978–1981) and logistics and training efforts, were not good enough to justify the effort and cost involved.[160] At that point, treatment success had increased from just over 30% to 56% and seemed to have stabilized at that level.[129] It was concluded that no substantial further improvement was likely with the 12-month regimen, despite improvement in drug supplies and patient supervision.* The problem with the 12-month regimen was that after the first two months almost half of the patients remained sputum-positive. If the patients then discontinued treatment or failed to take their drugs regularly, especially if this happened soon after they had completed the intensive phase, they often became chronic excretors of tubercle bacilli. Although they were not cured, their lives had been prolonged by the treatment and, as chronic cases, they increased the pool of sources of infection within the community and perpetuated transmission. Styblo argued that the short-term compliance of patients while they still felt ill, and their stay in hospital, should be exploited with the administration of an efficient treatment regimen that was able to kill most tubercle bacilli in a short time. Thus, short-course treatment was introduced in Tanzania in 1982.[160] In Styblo's view, the considerable improvement in the cure rate of smear-positive cases (both new and relapses) resulting from the introduction of short-course treatment was undoubtedly one of the most, if not *the* most, important success in the programs collaborating with The Union.[161] Kochi emphasized that the improved cure rate with shorter regimens was mainly due to the fact that it was easier to secure patient compliance with short-course regimens, the use of shorter regimens reduced the number of patients under treatment at any given time, and the regimen showed superior performance in preventing drug resistance.[162]

Several strategies were implemented more or less simultaneously in the programs collaborating with The Union. This approach has been criticized as unscientific. It can be argued, however, that an intervention conducted as a scientific experiment and reduced to single, simple actions tested against counterfactuals would have defeated the purpose of the program, and a comprehensive intervention might never have been realized. The response to complex problems is seldom simple. A recent example can be found in the response

*Note that whereas the results of universal 12-month treatment versus universal short-course treatment can be compared (which would be a "before-after comparison" and one would only need to consider eventual secular changes when interpreting the findings), it is not justified to compare simultaneous cohorts of the two regimens in a country if the group of patients receiving 12-month treatment is selected.

to the deteriorating tuberculosis situation in New York City in the 1990s, which was complicated by HIV and multidrug-resistant tuberculosis. The response was a combination of different strategies, which eventually could be evaluated only as the comprehensive approach that it was, rather than piece by piece. In retrospect, was it the policy of directly observed treatment, incentives, enablers, improved infection control, outcome analysis, drug susceptibility testing, or second-line drugs that did the trick? What was the relative contribution of each strategy? This is difficult to assess. The response to a public health crisis or emergency is just that. It is the response to a pressing need, not a scientific experiment.

Policy development

When good results have been achieved in a program, the program then should be advanced based on local characteristics, program performance, and changing circumstances. The treatment algorithm can be changed, for example, to a more efficacious treatment regimen with rifampicin used throughout to treat new cases, and/or the policy of directly observed treatment relaxed. How then should this be done? One can imagine a step-wise process: from treatment regimens without rifampicin in the continuation phase (the model), to regimens using rifampicin throughout in selected cases, and eventually to universal use of the rifampicin-throughout regimen. A similar scenario could be the following: from using directly observed treatment in all cases (the model), to using directly observed treatment in selected cases, and eventually abandoning directly observed treatment altogether. However, based on experience from wealthy nations, it is unlikely that such a stage will be reached, given that when tuberculosis prevalence decreases, the characteristics of patients who get the disease tend to change in such a way that they are in more need of active encouragement and support to adhere to treatment. Whatever changes are proposed along the way, small-scale trials should be undertaken before embarking on policy change on a national scale.

Expanding the model: can the results be generalized?

In this context, it is important to consider what factors are likely to have contributed to the successful implementation of the model in the programs collaborating with The Union, and how relevant the experience is as a basis for policy recommendations for different programs at different times. The main issues of interest in this respect are government commitment, health system characteristics, drug resistance (related to previous use of anti-tuberculosis drugs), and the prevalence of HIV infection.

The Union model was developed in a certain milieu. The governments in

the countries collaborating with The Union were, as a rule, committed to controlling tuberculosis in the context of overall improvement of the health of the populations. They recognized tuberculosis as a serious problem, a perspective demonstrated by their commitment of policy, personnel, and infrastructure for its control. In each of the countries, a program manager and support staff were appointed for planning, budgeting, and information and supply management. The ministries of health published manuals outlining the policy and procedures in the programs. Health personnel at all levels were trained, and their performance supported and supervised.

Further evidence of government commitment was reflected in the measures taken to introduce a system to record, report, and notify the national program of tuberculosis cases. In order to curtail drug resistance, attempts were made to address the free sale of anti-tuberculosis drugs, even if achievements in this respect were not equally impressive in all countries. Finally, the governments supported a policy aimed at preventing discrimination against patients with tuberculosis with regard to utilization of services. Tuberculosis patients were admitted to general hospitals (although in all countries at least one tuberculosis hospital remained) and treated within the routine services.

In addition to government commitment, the health systems in the collaborating countries were fairly uniform and the general context otherwise comparable in many respects. Indeed, all the governments were dedicated to equity regarding health and education, and made credible efforts to expand the general health services with this goal in mind, although success varied. Of the African countries, it is safe to say that accomplishments in this respect were commendable in Tanzania, but for various reasons, including external factors and interference, progress was eventually arrested and even reversed. In Mozambique, a civil war retarded progress. In Malawi, judging from published material, the decentralization of the program was not convincingly realized in the years of its collaboration with The Union. Accomplishments in expanding coverage of health services in Nicaragua were impressive, in spite of the detrimental effects of a civil war in which guerilla forces targeted the health infrastructure and personnel.

There was no private health sector to speak of in any of the countries collaborating with The Union; at least, it is safe to say that it did not play a significant role in tuberculosis treatment. The government sector was divided, as is common, into services for the general public (civil sector) and parallel services for the military, police, and penitentiary systems.* Thus, there was a need for coordination in this respect as well as between the different health facilities

*This is a common arrangement, albeit difficult to justify. The obvious explanation is that the military and police sectors have power and the penitentiary sector is often shrouded in mystery for various reasons, including security and politics.

within the civil sector (hospitals, health centers, health posts, and community health workers).[60] Achievements in the former aspect, coordination between the parallel systems, were not documented. Suffice it to say that for whatever reason this did not surface as an issue of major concern.

The success of the model is likely to depend, to an important extent, on the health system. Insufficient or inappropriate infrastructure is a serious limitation. Organization and management skills are very important. Personnel must be available if skills are to be created by training and supervision. Before implementation of the model within any given setting takes place, the infrastructure should be appraised to fully use what is available and identify gaps in infrastructure and services that need to be addressed in the long term.

Finally, whereas in the early days of Union partnerships HIV was not yet a problem, the African countries came to be hard hit by the HIV pandemic, which severely undermined their efforts to control tuberculosis and impeded an assessment of impact. What is clear, however, is that the policy did not prevent the explosive increase in incidence of tuberculosis in the wake of HIV.

Whereas the broad technical framework and managerial strategies in the Union model were still valid when the DOTS strategy was launched, the challenge for the WHO was to show how the policy model could be adapted to different settings, such as countries with different population sizes and cultures and, even more importantly, with different health systems and drug resistance profiles. Finally, there is the issue of the appropriateness of the model in the HIV era. This will be explored further in Chapter 6.

Summary and conclusions

The development of short-course chemotherapy was important for low-income countries for two reasons. First, it was easier to manage than the previous regimens, and second, it overcame the drug resistance that had been created, thereby making drug susceptibility testing in individual cases irrelevant. Introduction of short-course regimens in high-prevalence countries was controversial, however, unless organization of treatment was simultaneously improved.

Assuming that the great majority of patients with infectious tuberculosis had persistent cough, the policy model aimed to recruit patients as they attended health units for medical care. Health facilities and personnel were to respond to a demonstrated need for services. Rather than reaching out with case-finding surveys in the community, the aim was to expand and improve the health services and make them accessible to all so that patient recruitment would be effective. It was assumed that case detection would increase with expansion of the program and improved access to health services, and that eventually a high proportion of infectious cases in the community would be recruited reasonably early in the infectious period.

No attempt was made in the programs collaborating with The Union to set quantifiable targets concerning how many cases were to be recruited or what exactly early diagnosis meant. In the first place, there was no sound basis to set such targets in specific locations. Further, it was emphasized that the first priority of the tuberculosis program should be case holding; that is, to obtain good treatment results in order to prevent an adverse outcome of the intervention. This target was measurable and represented an important shift in focus from previous mass treatment programs, which had emphasized case finding but largely ignored case holding, with often disastrous consequences such as irregular and chaotic treatment and drug resistance. In time, most of the programs collaborating with The Union did indeed reach high levels of case detection without having set specific targets in this respect. It is tempting to conclude that where accessible health services and good tuberculosis programs exist, active case finding is not required and unlikely to yield much; whereas, in contrast, where such services and programs do not exist, active case finding is not the immediate priority.

This is the policy model and its scientific foundation and relevance; the next chapter turns to the various operational strategies that spell out detailed processes applied at the level where patients meet with the health services.

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3

Operational strategies in case finding and treatment

Strategies are only as good as their implementation.

The previous chapter laid out a general approach to tuberculosis control that can be applied to a very wide range of situations and settings. This chapter looks at operational strategies: specific processes that are implemented at the level where patients meet with the health service. Operational strategies are to an important degree context-specific, requiring local adaptation, and are thus likely to vary from one program to another. In the 1970s and 1980s, it was considered important to standardize practices to allow decentralization of program activities in developing countries. This chapter will examine the strategies recommended in the national programs collaborating with The Union: how they were formulated, what is their evidence base, how they compare with strategies elsewhere, and how they have kept up over time.

Strategies for the recruitment of cases will be discussed first, and then treatment regimens. Details pertaining to clinical medicine and bacteriology, such as the clinical presentation and forms of tuberculosis and the application of diagnostic tests in clinical practice, for example, are beyond the scope of this publication. Here, the focus remains on public health and communicable disease control.

Recruitment of cases

The recruitment process in tuberculosis control essentially revolves around identifying sputum smear-positive cases among patients with cough. The recruitment strategy in the Union model is described in Box 3.1.

Selecting patients to be assessed for tuberculosis

The prevalence of acute respiratory infections is high in any community. Microorganisms other than *M. tuberculosis* cause most respiratory infections. Diseases caused by these infections are usually resolved within two to three weeks of the

Box 3.1 The original recruitment strategy in the Union model

Case finding
Health professionals, wherever they are stationed, should be on the alert for symptoms of tuberculosis among persons visiting health facilities and should identify and refer tuberculosis suspects for assessment. Referral pathways are defined locally.

Tuberculosis suspects
Persons with cough of at least three weeks' duration, with or without other symptoms or signs of tuberculosis, are referred to as "tuberculosis suspects."*

Assessment by sputum microscopy
Three sputum samples are examined by acid-fast microscopy using Ziehl-Neelsen staining. The three samples should be collected within two days if assessment is to be done on an ambulatory basis: the first sample collected on the spot at the patient's first contact with the health service, the second the following morning, and the third on the spot when the patient hands in the second sample. One on-the-spot and two morning samples can be collected from hospitalized patients.

Smear-positive cases
Patients with sputum positive by acid-fast microscopy are classified as cases of smear-positive pulmonary tuberculosis.

Management of smear-negative tuberculosis suspects
In the event that acid-fast bacilli are not demonstrated in any of the three smears, a diagnostic algorithm for smear-negative tuberculosis should be followed.

*Note that "tuberculosis suspect" as defined here is not the same as "probable case" or "possible case," which are terms sometimes used in surveillance (see Chapter 8).

onset of illness, distinguishing them from tuberculosis. This is the basis for selection of patients with respiratory symptoms whose probability of excreting tubercle bacilli in sputum in numbers such that they are demonstrable by acid-fast microscopy is reasonably high, which is convenient for two reasons. First, it is not realistic to subject all patients with respiratory symptoms to sputum examination. Second, the higher the prevalence of disease in the group selected for sputum examination, the better the test performance of acid-fast microscopy.[1] Acid-fast microscopy is not a particularly good test for use in indiscriminate screening in a low-prevalence population.[2] The positive predictive value decreases with decreasing prevalence of tuberculosis in the group tested, even when there is good laboratory technique. Whereas it has been suggested that false-positive smears become important where the prevalence of tuberculosis is down to 10% to 20%, in a South African study where

the proportion positive among those tested fell within this range, this was not a problem.[3]

From the point of view of tuberculosis control, the question of interest is who, among patients with respiratory symptoms, should be referred for sputum examination. The nature and the duration of clinical symptoms determine the answer.

In 1967, Baily et al. reported the results of an operational study performed in a rural setting in India's Tumkur District.[4] They used as a recruitment criterion a cough of more than one week's duration and examined only one sputum specimen per patient, collected on the spot. Nearly 7% of the new outpatients were considered symptomatic in this study, and in 93%, a satisfactory spot specimen was obtained. For the remainder, a morning specimen was obtained. Of 724 symptomatic patients, 622 (86%) spontaneously complained of cough, and all but one of the remaining 102 only did so when actively questioned. Most of the smear-positive patients (44/45) spontaneously complained of cough, and 7% (44/622) of those who spontaneously reported cough were smear positive. The proportion who tested positive was higher (11%) among those who spontaneously reported a cough of at least two weeks' duration (43/381). The 43 constituted 96% of all cases diagnosed in the study. A total of 45 smear-positive cases were diagnosed (6% of the 724). More than one third of all the patients reported coughing for a period shorter than two weeks. Only one of them was smear-positive. Thus, examining sputum samples of persons with coughs of less than two weeks' duration yielded only a very small proportion of cases of pulmonary tuberculosis in this setting. To include those with coughs of two weeks' duration or more required examining 4% of adults attending the health facilities and exhibited 98% sensitivity for detecting smear-positive cases (43/44), whereas applying a criterion of three weeks' duration for cough exhibited 84% sensitivity (37/44). Those excluded by the latter criterion, however, may have had other symptoms leading a health worker to suspect the diagnosis of tuberculosis. This possibility was not investigated. The yield of tuberculosis cases increased with duration of cough up to a certain point only; the yield was poor in those reporting cough of more than six months' duration. Similarly, a study of outpatients in a tuberculosis clinic in India's Bangalore District during the 1960s showed that when symptoms had lasted for either less than four weeks or more than a year at the time of first contact with a specialized tuberculosis center, a nonspecific etiology was more likely.[5]

Consecutive case series in Kenyan district hospitals in the mid-1980s (part of the Kenyan case-finding studies discussed in the previous chapter) focused on defining a tuberculosis suspect in such a way as to minimize the number of sputum smears to be examined at district hospitals.[6] The investigators found that with a one-year upper limit to the duration of cough, the number of sputum smears examined could be reduced by 30%, and still 92% of smear-positive

cases would be detected. They recommended examining one or preferably two sputum smears from patients with coughs of durations of more than one month and less than 12 months.

In the Union model, patients with long-standing respiratory symptoms, regardless of where or why they sought help within the health system, were to undergo assessment for tuberculosis starting with sputum smear microscopy. In the program in Tanzania, it was originally recommended that patients complaining of respiratory symptoms, "notably persistent and productive cough, bloodstained sputum, and chest pain, especially if they have been present for more than four weeks," be examined.[7] The first edition of the Orange Guide recommended that "patients with relevant symptoms" be examined, and the first among the most common symptoms was given as: "persistent cough for three weeks or more, mostly with sputum, sometimes bloodstained."[8]

Local recruitment strategies may consider adjusting the threshold value of symptom duration according to the prevalence of tuberculosis, utilization of health services by the population, service performance, laboratory workload, and competing priorities. Ideally, acid-fast microscopy should be decentralized to provide good access to the service but maintain the positive predictive value of microscopy and laboratory proficiency within acceptable limits.

In some countries, the limit (referring to duration of symptoms) was set at 15 days or two weeks rather than three weeks. As a rule, access to health services in Latin America was easier than in Africa, and easier access makes patients more likely to seek care early. A study in Brazil suggested that relaxing the criterion for duration of symptoms might improve case detection.[9] A study conducted in India in 2001–2002[10] (a cross-sectional study in six districts, including a mix of urban and rural residences) suggested that the detection of smear-positive tuberculosis could be substantially improved (by as much as 46%) by actively eliciting a history of cough from all outpatients, and by changing the criterion for performing sputum microscopy among outpatients from three to two weeks for duration of cough.* They found that almost one third of the patients with cough (17% of all smear-positive cases) did not spontaneously mention their cough, underlining the importance of actively questioning every patient for cough regardless of the patient's complaints.

Some public health officials propose setting targets for the proportion of outpatients with respiratory symptoms to be assessed for tuberculosis. Whether this is justified is debatable. The prevalence of cough is likely to vary between sites as well as seasonally in any given area. Furthermore, the targets may increase the workload on the laboratory services without increasing the yield of cases. In turn, an increasing workload may adversely affect laboratory perfor-

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*The study did not clearly distinguish between the two interventions. Ideally, such a study would include comparison with sputum culture, which was not the case.

mance. Caution is needed so as not to overdo the standardization of policies and targets.

The percentage of positive reports on microscopy depends considerably on the method used for detecting tuberculosis.[11] When making comparisons, the method of recruitment and processing of specimens needs to be considered. It has been suggested that the definition of a tuberculosis suspect should include a feature other than the duration of cough, such as weight loss or a lack of response to antibiotics. Ideally, such an effort should be made on the basis of local studies. Generally speaking, in a high-prevalence country, such attempts may introduce delays in the diagnosis of tuberculosis. If the goal is to reduce the workload in the laboratory network, using a stricter criterion for duration of cough is a logical alternative, as is reducing the number of serial smears examined per suspect.

It is never sufficiently stressed that all health workers—not only those working in the tuberculosis program—should be on the alert regarding the identification of tuberculosis suspects. Even if it has been said that "cases find themselves,"[5] patients cannot be expected to attend any particular service. They may present anywhere within a health system. In cities and metropolitan areas where marginalized populations have an increased risk of tuberculosis, it is particularly important to involve general hospitals, especially hospital emergency departments, as these patients are more likely to present there than in outpatient departments or within the primary health care system.[12]

In conclusion, sputum microscopy should be performed on the basis of a sensible indication. It is important to define the nature and duration of symptoms to allow the screening of care seekers for the presence of smear-positive pulmonary tuberculosis.

Assessment by sputum examination

In the diagnosis of infectious diseases, a test that has high sensitivity and negative predictive value is important so that patients with true disease are treated and those with a low possibility of disease can be discharged safely without treatment.[13] But which point of reference should be used? A high sensitivity compared to what? With tuberculosis control, infectiousness rather than positive culture, or some other consideration, is key. Acid-fast microscopy of sputum identifies the principal sources of infection. The question is how many samples should be examined and when and how to collect them.

As a rule, the samples obtained in tuberculosis programs are spontaneously expectorated sputum. Sputum induction or advanced techniques such as bronchoscopy are rarely used. It can be argued that when you have to pursue the bacillus with invasive methods, the patient is substantially less likely to be infectious. A study performed from 1991 to 1993 in a central hospital in Dar es

Salaam, Tanzania, where the HIV seroprevalence rate among patients hospitalized for acute respiratory disease was high (54% in the study), concluded that bronchoalveolar lavage added little to the diagnosis and thus should not be a high-priority procedure in routine work-up.[14]

The yield of consecutive specimens in sputum microscopy varies depending on the setting. When three consecutive early morning specimens are examined in a high-quality laboratory service, 80% of those eventually positive (on smear) are detected on the first specimen, 15% on the second, and 5% on the third.[15] The yield of smear microscopy, as well as the yield of the first two smears, is higher for cases with high positive grade. Studies in Kenya (2000–2001)[16] and Bangladesh (2002)[17] confirm earlier findings from 1959,[18] suggesting that an early morning specimen is more likely to be positive than a spot specimen. Thus, the yield from a third spot specimen might be expected to be even lower than indicated above. The method of selection of subjects for sputum examination may influence the yield of the different specimens (spot and morning varieties). Box 3.2 presents some of the studies carried out in India in the 1960s that formed the basis of the original policy on sputum examination. Two issues are critical: the number and type of specimens examined, and the effectiveness of the procedure.

The Orange Guide originally recommended that three sputum specimens be collected and, whenever possible, examined within two days.[8] The first and third specimens could be spot specimens even if it was acknowledged that they might be inferior to early morning specimens. These recommendations were intended for public health programs, not hospital wards. When considering operational issues, the compromise in terms of yield was regarded as smaller than the gain. It was thought important that the patient receive immediate attention, and that a sputum specimen be collected without delay, on the spot, from all tuberculosis suspects in contact with the health services. At this time, the patient was to be logged into the laboratory register (name, sex, age, and address), so if the specimen turned out to be positive and the patient did not follow through with the procedure for some reason, the patient could be traced. This is a sound communicable disease control perspective.

This strategy is likely to have been most valuable in settings where access to health services was improved and sputum microscopy decentralized, for example in Nicaragua. Otherwise, the issue of sending the specimens to a laboratory and then awaiting results still posed a challenge. The considerable delay and inefficiency involved in such a system has been documented, for example, in Malawi. A study undertaken in 23 districts in Malawi in 1997 found that 27% of all the specimens from health centers took eight days or more to arrive at the laboratories at the district hospitals, not counting the delay for transmitting the results of microscopy back to the referring facility.[20] Such delays are not confined to low-income countries, however. Another example can be

Box 3.2 Early studies on sputum microscopy in India

In a study in the Tuberculosis Chemotherapy Center in Madras, reported in 1959, two "spot" and two overnight ("collection") specimens* were obtained from patients after a provisional diagnosis of tuberculosis.[18] All study subjects had radiographic appearances compatible with pulmonary tuberculosis: 71% had bilateral disease, and 75% appeared to have cavities. Overall, 20% of the 461 spot specimens were graded 3+ with acid-fast microscopy, whereas this proportion was 45% for the 237 collection specimens. Acid-fast microscopy of two spot and one collection specimen had 84% sensitivity (the reference was smear- and/or culture-positive on any of the four samples). For comparison, examination of one spot specimen had a sensitivity of 66%, and one spot and one collection specimen had a sensitivity of 81%. Because most of the patients included in the study had extensive disease (the research was carried out in a reference center), the findings were unlikely to represent those found in a routine service. Thus, results for cases with less extensive disease and without cavities were evaluated separately, concluding that a spot specimen was relatively less valuable in such cases. Even if the examination of one collection specimen detected essentially the same proportion of positive cases as examination of two spot specimens, the investigators recognized that a spot specimen was nevertheless valuable because it was frequently positive in patients with symptoms and at least moderately extensive disease, and it required only one attendance by the patient. The overall conclusion was that, in developing countries where only microscopy services were available, examination of at least two spot specimens and one collection specimen was deemed useful.

In a mass case-finding program in India's Tumkur District in 1962–1963, where two specimens (spot and overnight) were examined per patient, the yield of the two types of specimens differed, but not significantly.[19]

In a study in Bangalore in the 1960s where a spot specimen was obtained, 140 (7%) out of 1,985 attendees did not return to learn the results.[5] Among them were 12 cases of tuberculosis, and this initial or primary default constituted 10% of all cases. Thus, the importance of the spot specimen was revealed: those leaving a positive smear in the laboratory could be traced. This study also showed that patients referred for sputum examination due to symptoms were most likely to collect their results, followed by those with symptoms who sought care on their own initiative. Those who were asked to attend but had no symptoms (contacts, for example) were least likely to return for the results of sputum examination.

In an operational study in Tumkur in 1966, 95% of the patients waited for the results of a spot specimen in peripheral units where microscopy was performed (among them all of the 24 smear-positive patients), whereas in referring health units (sputum examination performed at referral centers) where patients were asked to give sputum and return for the result in 48 hours, 71% returned for the results (among them 15 of the 21 who were found to be smear positive).[4]

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*Intuitively, "collection" and "overnight" specimens are not the same as early morning specimens (the former constituting a larger volume of sputum, the latter produced with a single expectoration). Nevertheless, they are sometimes used synonymously.[8]

found in the tuberculosis clinics in New York in the early 1990s, where sputum induction was performed daily, sputum was then transported to the central laboratory, and the results of smear examination returned to the clinic charts 12 to 14 days later.[21] Sluggishness may be explained simply by staff's lack of awareness of the problem, insufficient appreciation of the importance of rapid action and speedy services, or bad habits. Occasionally, however, there are true logistical difficulties that may be hard to solve. Systems that are slow and cumbersome anyway may obscure the advantages of a spot specimen, but nevertheless they exist in case a single spot specimen tests positive and the patient does not return. Otherwise, there may be no trace of such a patient ever having attended the services.

In Bangladesh in 2002, Van Deun et al. challenged the strategy of collecting spot specimens. In their setting, very few persons (1.5%) failed to return with a second specimen, and thus they argued for examining two morning specimens.[17] This phenomenon may not occur in other settings, however. On the other hand, indirect support for the policy of collecting a spot specimen can be derived from recent experiences in another field. Several studies report that people do not reliably return for results of HIV testing, and that a lack of immediate results may seriously deter voluntary HIV counseling and testing programs.[22] The return rate is likely to depend to an important degree on effective communication between the health worker and the patient. This communication is often referred to as pre-test counseling. In some settings, pre-test counseling may not be routinely performed with sputum examination, and this may be one explanation why a considerable number of tuberculosis suspects do not complete the process of sputum examination.[23]

A further advantage of a system in which the first specimen is a spot specimen is that the health personnel can then observe specimen collection, even in an ambulatory setting, which should increase the probability of a good quality specimen. A proper specimen is important for a high yield in microscopy. If the first specimen collection is observed and a good quality specimen obtained, it can be argued that subsequent specimens are likely to be of good quality as well, even if collected without observation, since the patient by then should know the proper procedure.

The second specimen in the Union strategy was an early morning one and was thus as good a specimen as can be expected. By having the third specimen a spot specimen, three specimens could then be collected (as recommended by the Madras study[18]) in two days, requiring only one return visit by the patient if the assessment was made on an ambulatory basis. Ideally, the patient should also receive the final results of the assessment on the second day. Obviously, there is no need to examine any further specimens once tuberculosis has been confirmed.

Reducing the workload and increasing the yield in acid-fast microscopy

The justification for requiring the examination of three smears rather than two or even one has been debated. In 1985, Urbanczik pointed out the low increase in sensitivity with the third smear, noting that the third smear therefore could be sacrificed.[2] This issue was particularly hotly debated in sub-Saharan Africa where, as a result of the high prevalence of HIV, an alarming increase was seen in the number of tuberculosis suspects. In this situation, the workload required to examine three specimens per suspect threatened to collapse the laboratory services.[24] In such settings, a local decision to make two specimens suffice is easily justified because it makes little sense to insist on doing something that is not possible. The yield of sputum examination can even increase when the number of specimens examined per suspect is reduced, if a three specimen policy resulted in low quality sputum examination or no examination at all. In 2000, the Orange Guide took note of this scenario by endorsing the strategy of examining two samples per suspect.[15]

Examining three specimens per suspect may not be considered worthwhile, regardless of whether or not the laboratory services are overwhelmed. It all depends on how important the third specimen is considered in a particular context. In 2006, a retrospective study of a sample of laboratory registers in Mongolia (low HIV prevalence) and Zimbabwe (high HIV prevalence) found that the expected number of slides examined to detect one additional case on the third of serial smears was roughly 1,150 in Mongolia and 130 in Zimbabwe.[25] Prior to the study, the critical numbers of 100 and 75 were regarded as reasonable (that is, not to be exceeded) in the two settings, respectively. The proportion positive for the first time on the third smear was 0.7% in Mongolia, and 4.5% in Zimbabwe. The investigators concluded that the policy of routinely examining three serial smears in the assessment of tuberculosis suspects should be reconsidered. A similar conclusion was reached in retrospective studies in Uganda and Moldova, where the average number of smears examined to detect one additional case on a third smear was 175 and 273, respectively.[26] This workload amounted to seven and 11 days' work, respectively, for a small gain in case finding.

A systematic review in 2007 concluded that the yield of examining a third specimen ranged between 2% and 5%.[27] The review looked at the incremental yield, assuming that a single positive specimen was required for diagnosis of smear-positive tuberculosis, whereas in the Orange Guide, two positive specimens were required (see below). This distinction might change the results when calculating the yield of serial smears in the direction of increasing the "yield" of a third smear. Limited data on the yield of examining early morning specimens versus spot specimens suggested that a single morning specimen

had approximately 12% higher yield than a single spot specimen. The authors concluded that reducing the required number of smears from three to two (particularly if the two specimens were examined on the same day) could increase case detection by improving quality in laboratory work as a result of decreased workload and by facilitating patient compliance to follow through with the process of sputum examination. For the majority of studies identified by the review, information on sputum characteristics, timing and manner of sputum collection, mycobacterial culture methods, or quality assurance for microscopy was not provided, making interpretation difficult.

The yield of sputum microscopy is different in different settings and depends to an important degree on methodology and operational characteristics. Methods other than varying the number of specimens exist to increase the yield of sputum microscopy where the yield is low, such as improving sputum collection (the quality of samples) or improving acid-fast microscopy (reducing false-negative results). Such strategies also need to be considered. A randomized trial in an urban clinic in Indonesia (2005) suggested that pre-test counseling could improve case finding by as much as 15%.[28] A randomized trial in Pakistan (2007) found higher positive rates in female tuberculosis suspects after enhancing pre-test counseling.[29] The instructions given to those in the intervention group concerned increasing the quality and volume of sputum samples and the likelihood of the subjects to follow through with the process (that is, to return with a second sample). The observed effect on the quality of the sample was greater for spot specimens than for morning ones. A study in Cameroon (2007) suggested that more careful microscopy—increasing the examination time per smear—substantially reduced false-negative error and thus increased the yield of microscopy.[30]

Finally, the sensitivity of sputum microscopy can possibly be increased by changing the technique, such as by treatment and concentration of the sputum prior to microscopy, a procedure referred to as "bleach technique."[31] This issue has recently been disputed and needs to be resolved. Because details on laboratory techniques are beyond the scope of this publication, other sources should be consulted for more information on this subject, as well as the issue of fluorescence versus light-microscopy and new diagnostic tests, which—it is hoped—will be introduced into tuberculosis programs in the near future.

In conclusion, the procedure referred to as the "spot-morning-spot" strategy is, as noted above, all the more relevant where accessible health services and decentralized acid-fast microscopy exist. The establishment of such services was originally envisioned. The tuberculosis program was a public health program, and its strategies were focused on communicable disease control. The program was meant to operate within the primary health care services and, as much as possible, on an ambulatory basis. The extent to which this was then achieved in the different programs collaborating with The Union varied. On the

whole, it can be said that the little progress made in expanding good quality primary health care services with laboratory facilities was disappointing; yet, on the other hand, a built-in resistance within some of the programs to a public health focus and decentralization may also have affected results.

Confirmation of a case of tuberculosis

Tuberculosis may ideally be confirmed by culture of *M. tuberculosis*, but in many low-income countries such cultures are not (and were not, historically) routinely performed. Instead, tuberculosis was considered "confirmed" by acid-fast microscopy. In fact, since the positive predictive value of acid-fast sputum microscopy is higher in high-prevalence countries and particularly if used with good indication—that is, with prior symptom screening among persons attending the health services—it can be argued that culture confirmation is less important in this setting than in low-prevalence countries or in mass screening programs. In the Union model, two positive smears were required before a case could be classified as smear-positive tuberculosis. Apparently, the risk of administrative (clerical or procedural) and technical errors (cross-contamination between specimens, for instance) in the laboratories supplied the rationale for confirming a positive smear result. This requirement has been debated.

Transcription errors were in fact detected in well-organized central laboratories, for example in Nairobi in the 1970s.[32] The issue of clerical errors in labeling sputum specimens was raised in reports of investigations conducted in Kenyan district hospitals as part of the case-finding studies.[6,32,33] A certain degree of chaos was expected in routine microscopy work within the various health facilities in tuberculosis programs.* It can be assumed that the precaution of requiring two positive smears was primarily aimed at preventing errors resulting from mixing up specimens or results in busy laboratories, such as when sputum containers from different patients are incorrectly identified, slides are mislabeled, or results of specimens are improperly recorded. It is unlikely that such random errors would be repeated consistently, thus requiring a second positive smear to confirm a diagnosis of smear-positive tuberculosis. An additional precaution was to label specimen containers on their sides rather than on their lids, which could become disassociated from their containers. In programs where administrative errors in laboratories are unlikely to occur, these precautions may be considered superfluous.

In cases where information from another source (for example, chest radiographs) is on hand, it is less important to have confirmation by a second positive smear. The Union policy was formulated primarily for programs where

*It should be noted, however, that administrative and technical errors do not exclusively occur in laboratories in low-income countries.[34]

such additional information was seldom available. In many settings, however, even if the program does not request chest radiographs, they are often taken anyway, are of low quality, and are paid for by the patient.

In practice, the policy of a second positive smear in high-prevalence countries was not considered a nuisance until recently. It was assumed that an infectious tuberculosis patient was, as a rule, consistently positive on smear. A 2000–2001 study in a high-volume central laboratory in Nairobi, Kenya, found that a considerable proportion of smear-positive cases with three sputum smears examined had only a single positive smear.[16] Such findings may have a logical explanation or be related to low laboratory quality and/or high workload, which should lead to a consideration of changes in structure (centralization versus decentralization) and/or operational policy (requesting fewer specimens per tuberculosis suspect). A recent study looking at laboratory data in four countries —Moldova, Mongolia, Uganda, and Zimbabwe—found that positive results from sputum microscopy were easily confirmed if serial smears were examined but that such a step, to a different extent in each setting, was not always done.[35]

The "scanty-positive" phenomenon

In 1991, the Orange Guide recommended reporting the results of acid-fast microscopy in the following manner: negative (if no acid-fast bacilli are seen in 100 immersion fields), 1–9 bacilli (if the exact number of bacilli after examining 100 immersion fields falls within this range), and different grades of positive results (+/++/+++), referring to the quantity of bacilli per area examined.[36] The result of 1–9 bacilli was referred to as "scanty."[15] The WHO, on the other hand, defined 1–3 bacilli per 100 high-power fields (HPF) as "scanty-negative" and 4–9 as "scanty-positive."[37] Various studies have used different definitions and cut-off points, making it difficult to make sense of the results.

The criteria for labeling a smear as positive have been debated. The term "scanty-positive," commonly used when more than 3 bacilli were seen,[8] was not considered a conclusive positive result.[37] Since 1994, the Orange Guide has recommended that the laboratory report the exact number of bacilli if few bacilli were found (1–9),[38] considering that the clinician had the final say on how to interpret such results. This advice was based on the understanding that clinicians have access to additional patient information such as clinical signs and symptoms and clinical history (for example, a history of contact with an infectious case or previous treatment elsewhere). In case of doubt, a clinician might decide to perform chest radiography or to send further specimens to the laboratory. Thus, in this case it was not considered appropriate to standardize practices.

Ideally, general conclusions on the relevance of scanty-positive smears in the assessment of tuberculosis suspects would take note of the results of culture as well as of the clinical relevance (that is, progress of disease and fate of the patient with treatment versus without). In the surveys in Bangalore, India, in

the 1960s, Narain et al. claimed that the finding of a few bacilli in a smear (fewer than 4 bacilli) was most probably due to artifacts and should not be the basis for a diagnosis of tuberculosis.[39] According to these researchers, such "cases" had negative sputum cultures and did not progress when followed in time, such as between surveys (no treatment was provided). Because almost none of the individuals with such smears had sought treatment, it could be argued that as a rule they ought not to be seen in tuberculosis programs. Finally, scanty-positive smears were mostly isolated findings in the surveys; that is, in a series of four smears, only a single smear had a few bacilli and the rest were negative. Thus, a practice of considering smears having fewer than 4 bacilli as negative arose.

In a prospective, hospital-based study in South Africa in 1986, the positive predictive value of scanty-positive smears (fewer than 5 bacilli in a smear examined for five minutes) was high (93%), with culture representing the gold standard. The investigators reckoned that patients with repeated scanty-positive results on sputum microscopy should be diagnosed as tuberculosis and treated.[3]

In 2004, retrospective analysis of laboratory registers in Bangladesh found that scanty bacilli (fewer than 10) were reported in 10% of the smears in tuberculosis-suspect series, but unconfirmed scanty results were rare (only 10% of scanty results were not confirmed by another scanty result).[37] Thus, in a number equivalent to 1% of the smear-positive cases, there was a single scanty smear. The investigators concluded that scanty results are not rare in the assessment of tuberculosis suspects and should not be ignored. Their interpretation was that considering such results as positive by adopting a lower cut-off for a positive smear (as low as 1 bacillus in a single smear) added 1.5% false positives, but the gain in confirmed positive cases was as much as 10%. A recent study in Nigeria supported the findings of the Bangladesh study.[40] It can, however, be argued that requiring a confirmation of a scanty-positive result, which according to the data from Bangladesh is easy, might get rid of the false positives without compromising the gain in confirmation of cases.

In 2005, the technical staff of the Tuberculosis Division of The Union proposed the following lowered threshold for declaring a case smear-positive: a single positive smear and a cut-off lower than the previously accepted one for positive smear (10 bacilli/100 immersion fields).[41]

An alternative approach using chest radiography

An alternative recruitment procedure is a three-step strategy using two tests. First, a tuberculosis suspect is identified based on symptoms, then chest radiography is performed and, if radiographic abnormalities suggest tuberculosis, the patient is referred for sputum examination. In a high-quality, well-organized and equipped health service, this may well be the preferred method.

In a study of 529 consecutive adult patients attending a chest clinic for respiratory symptoms in Algiers in 1969, 71 cases of tuberculosis were confirmed by bacteriology, of whom 45 (63%) were smear-positive. All 45 would have been detected had the first test been a chest radiograph followed by sputum examination only when indicated by radiographic findings.[42] The workload in the laboratory was only 20% compared to what would have been the case had patients been referred to sputum examination based on the presence of cough, in which case 43 of the 45 would have been detected. However, this was a chest clinic, and thus some pre-selection of subjects likely occurred. Indeed, 45% of the 529 patients had suffered a cough for more than two weeks, and roughly 40% had a history of hemoptysis at the time of attendance. Furthermore, the clinic was well-equipped and featured experienced radiologists and chest physicians, unlike in primary health care clinics.

As a rule, there were no radiology services in peripheral health facilities in low-income countries. Out of 724 patients with symptoms participating in an operational study in India's Tumkur District, in the 1960s,[4] 490 (68%) were willing to attend for chest radiography at the district tuberculosis center, which was on average 55 km away from the peripheral facilities. However, only 76 (16% of those willing, and 11% overall) actually attended, and only 55 (8% overall) then returned to the peripheral health facility for the result (that is, being "willing" and being able to attend are not the same). These proportions were higher for smear-positive patients: roughly 85% were willing to travel for chest radiography, and almost 25% did. The most common reason given for not attending involved financial difficulties, regardless of the distance to be traveled. It was concluded that radiology could play only a modest role in case finding in this setting.

In the mid-1980s, data from one of the Kenyan case-finding studies found that radiography prior to sputum examination would reduce the number of smear examinations dramatically.[6] If only the 12% who had abnormal radiographs in this study had been referred for sputum examination, all the smear-positive cases would have been detected. However, logistics (supplies and maintenance of equipment and materials), technical issues (quality and standardization in the reading of chest radiographs), and cost made pre-screening by radiography unrealistic in much of the country.

The World Bank-assisted DOTS project introduced in China in 1991 is an example of a program using an alternative recruitment strategy. Patients presenting at tuberculosis dispensaries and meeting symptom criteria were examined by chest fluoroscopy. Those whose results showed suspicious findings on fluoroscopy (46%) then submitted three sputum samples for smear examination; approximately 35% to 40% of them were smear-positive.[43] Chest radiography was performed if indicated, for example, in the case of a smear-negative tuberculosis suspect. As discussed elsewhere, however, this project covered

only a fraction of the population, as is common when interventions are implemented within vertical structures.

In conclusion, in central and urban hospitals and chest clinics, chest radiography is commonly used in the assessment of patients with long-standing respiratory symptoms and other symptoms suggestive of tuberculosis. Radiography cannot replace sputum microscopy, however. In peripheral and rural facilities in low-income countries, access to radiography is frequently limited, and referral only justified in cases with negative smears.

Smear-negative tuberculosis

Followed by acute respiratory infections and community-acquired pneumonia, tuberculosis tops the list of differential diagnoses among people in sub-Saharan Africa, infected with HIV or not, who present to the health care system with chronic cough and other pulmonary symptoms.[44] It can be difficult to diagnose smear-negative tuberculosis in any setting. In a study in San Francisco referring to the period from 1993 to 1998, 40% of smear-negative, culture-positive cases were not started on any anti-tuberculosis treatment during their hospitalization or at the time of hospital discharge.[13] In the context of high-prevalence countries, algorithms and scoring systems have been suggested for predicting smear-negative tuberculosis in the clinical setting. The question is how to distinguish smear-negative pulmonary tuberculosis from other respiratory diseases.

In 1968, Fox noted that too frequently in developing countries—even in long-established tuberculosis clinics—a high proportion (as many as half) of the patients under treatment for pulmonary tuberculosis exhibited either no evidence at all of the disease or clearly inactive lesions on the radiographs and a negative sputum at the time of diagnosis, if sputum had been examined at all.[45] Fox argued that the reading of radiographs should be centralized. The degree of centralization was a matter of debate. According to Fox, in countries with 5,000 to 10,000 tuberculosis cases per year, a single central facility was sufficient; otherwise, facilities at the state or provincial level should exist. Fox assumed that these facilities would confirm diagnosis; that is, treatment could be started on the basis of a local decision and then continued if confirmed centrally or stopped if not confirmed. This approach is not considered appropriate today.

The Orange Guide published in 1986 referred to smear-negative tuberculosis as "bacteriologically unconfirmed cases," taking as examples the cases of children in contact with smear-positive index cases, and cases of persons with suspected tuberculosis based on clinical and radiography appearances, which the Guide proposed should be notified separately from confirmed cases (that is, smear- and/or culture-positive cases).[8] The Guide stressed that the interpretation of chest films for the purposes of differential diagnosis was difficult and a matter for experts.

Revised international definitions published in *The International Journal of Tuberculosis and Lung Disease* in 2001 stressed that, in keeping with good clinical and public health practices, the diagnostic criteria in sputum smear-negative tuberculosis should include at least three sputum specimens negative for acid-fast bacilli, radiographic abnormalities consistent with active pulmonary tuberculosis, a lack of response to a course of broad spectrum antibiotics, and a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.[46]

Diagnostic algorithms

As mentioned in Chapter 2, a precursor to a diagnostic algorithm is found in the report of a prospective study conducted in Bangalore City, India, in the 1970s. The investigators recommended improving sputum examination and radiography to allow proper identification of smear-negative tuberculosis suspects, who would then be given nonspecific treatment and followed to evaluate their progress. The study findings suggested that if the disease progressed, it did so within three to four months.

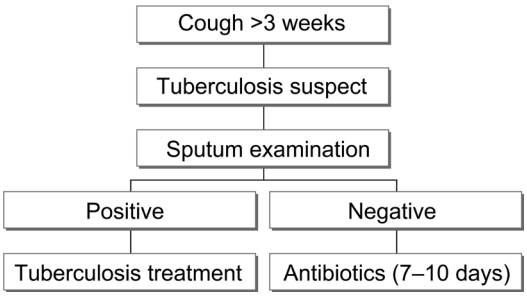
In the programs collaborating with The Union, a diagnostic algorithm was recommended to assist health workers with decision-making when confronted with smear-negative tuberculosis suspects in peripheral health facilities. Apparently, the algorithm was based on the findings in Bangalore but was not formally assessed. The original recommendations from 1986 that placed antibiotics before chest radiography,[8] and those from 1996 that placed antibiotics after radiography,[47] are presented in Box 3.3. In 1997, the WHO included in their technical guidelines for national programs an algorithm placing radiography after

Box 3.3 The Orange Guide on smear-negative tuberculosis suspects

According to the original Orange Guide, published in 1986, while awaiting laboratory smear results (initial series of three smears), patients were to receive symptomatic treatment or, if indicated, a course of antibiotics (but not streptomycin or rifampicin).[8] Those not responding to antibiotic treatment were to be subjected to repeated sputum examination (two smears) and referred for further investigation (clinical and radiological).

In the 1996 version of the Guide, the algorithm is presented as follows.[47] In the case of a smear-negative tuberculosis suspect, chest radiography is performed (if available). If radiography demonstrates shadows in the lung fields consistent with a pulmonary infection, a course of antibiotics is given. If the patient continues to show symptoms after completing the antibiotics, sputum examination is repeated (three smears), and if still negative, the clinician might consider starting anti-tuberculosis treatment for smear-negative pulmonary tuberculosis.

Figure 3.1 Management of tuberculosis suspects on first attendance

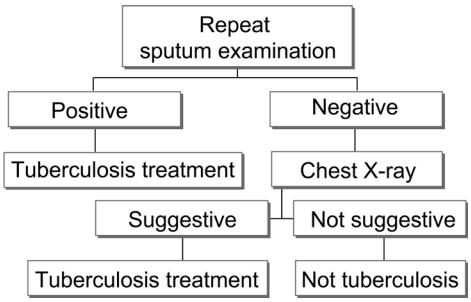


a course of antibiotics.[48] Which algorithm is appropriate depends on the setting, such as the level of the health unit (referral health units often see patients who have already had a course of antibiotics, and inaccessible facilities see patients who cannot easily be referred) and the tools available for assessment (microscopy only, radiography, or culture).

A simple algorithm, which would be appropriate in facilities where chest radiography is not easily available, is presented in Figures 3.1 and 3.2: a smear-negative tuberculosis suspect receives a course of antibiotics, and if symptoms do not improve, then the patient is referred for chest radiography.

When an algorithm is implemented, the local antibiotic resistance pattern in community-acquired pneumonia is an important element. Benzylpenicillin, ampicillin, and amoxicillin have been widely used within diagnostic algorithms and seem to have retained their potency in vivo.[44] It has been argued that, apart from rifampicin and streptomycin, fluoroquinolones should not be used in the algorithm because their use has been associated with delays in the initiation of appropriate anti-tuberculosis therapy and drug resistance in *M. tuberculosis*.[49–53] Other broad-spectrum antibiotics may, however, also cause delay in the diagnosis of tuberculosis, either because of partial treatment of the tuberculosis or treatment of bacterial co-infections that mask the underlying tuberculosis

Figure 3.2 Reassessment of sputum smear-negative tuberculosis suspects



disease.[53–55] Thus, whereas non-response to antibiotics may support a diagnosis of smear-negative tuberculosis, apparent symptomatic or clinical response does not exclude it.[56] To further complicate matters, a time lag arises, introduced by the algorithm while waiting for response to nonspecific therapy. This time lag is sometimes called an "algorithm delay."[55]

All the algorithms referred to above share in common the recommendation that smear examination be repeated before treatment for smear-negative tuberculosis is started, that is, after the time lag introduced by the algorithm. A prospective cohort study in Malawi (1997–1998) found that of 352 patients about to start treatment as "smear-negative" tuberculosis—most of them after being assessed with the aid of a diagnostic algorithm—78 (57%) of 137 culture-positive cases were smear-positive when acid-fast microscopy was repeated.[57] A similar phenomenon was observed in a study conducted in Guinea from 1997 to 1999.[58] Such patients may have been incorrectly assessed in the first attempt (procedural error or laboratory error), may have excreted bacilli intermittently, or their disease may simply have progressed to become smear-positive.

In a review of diagnosis of smear-negative pulmonary tuberculosis in low-income countries published in 2003, Siddiqi et al. pointed out the lack of specific radiographic or clinical signs in the diagnostic decision tree.[59] Whether such detail would be useful depends partly on by whom and where the algorithm is to be used. Although originally considered important for assisting health workers in primary care facilities, algorithms have primarily been studied in hospitals and often in the inpatient setting. Siddiqi et al. drew attention to the fact that the algorithms had not been validated within local contexts, a concern echoed by Lambert et al. in Ethiopia in 2003, who emphasized that no magic bullet could solve the difficult problem of smear-negative pulmonary tuberculosis in deprived settings.[60] Studies that have been conducted vary regarding the selection of study subjects, process and tools applied, reference (gold standard), and period of follow-up.

How well diagnostic algorithms perform in practice is likely to differ from one setting to another. For a rough idea, one can look at figures of the proportion of smear-negative among all cases of new pulmonary tuberculosis, as was done in the programs collaborating with The Union, or the results of operational research that specifically assesses diagnostic algorithms. A few studies pertaining to the issue of diagnosis of smear-negative tuberculosis are presented in Box 3.4.

Clinical symptoms

A hospital-based study in Tanzania and Burundi, published in 1997, found that simple clinical symptoms alone were helpful in differential diagnosis of respiratory disease in smear-negative tuberculosis suspects.[24] The reference in Tanzania was positive culture, but in Burundi it was radiographic and clinical

Box 3.4 Studies related to diagnosis of smear-negative tuberculosis

In a nested case-control study in Maryland (U.S.) referring to the period from 2000 to 2001, Golub et al. found that 85 of 158 (54%) patients with confirmed pulmonary tuberculosis had received empiric antibiotics prior to receiving anti-tuberculosis therapy, and 67% had undergone chest radiography at their first health care visit.[55] Patients with coughs of more than three weeks' duration were less likely to receive antibiotics, as were patients who had had chest radiography at their first health care visit. The delay to anti-tuberculosis therapy was greater among those who had received antibiotics (median 39 days, range 2–519) than those who had not (median 15, range 0–191). The antibiotic delay did not depend on the antibiotic class used. The median delay for those who had chest radiography at the first visit was 15 days as opposed to 69 days for those who had not. Even if the delay was shorter for those who had chest radiography at the first visit, an antibiotic trial was still administered in some of those cases where the chest radiograph suggested tuberculosis.

A study in Kenya evaluated the routine process in diagnosing pulmonary tuberculosis in a high-volume referral chest clinic in Nairobi in 2000–2001.[61] Because they were attending a referral clinic, many of the patients may already have been treated with antibiotics before presenting at the clinic. Acid-fast microcopy was performed in patients with productive cough of at least three weeks' duration, and if smears were negative, then chest radiography was performed. The process detected 509 (92%) culture-positive tuberculosis cases: 332 (60%) with sputum microscopy and 177 (32%) by chest radiography. The sensitivity of the overall process was 92%, specificity 66%, positive predictive value (PPV) 77%, and negative predictive value (NPV) 86%. Almost 45% of the cases diagnosed by radiography were culture-negative.

A publication in 2006 reported the results of a study performed in an outpatient dispensary in Conakry (Guinea).[62] A scoring system was derived from demographic, clinical, and radiographic features to help distinguish pulmonary tuberculosis from other types of lung disease in patients with long-standing respiratory symptoms. The application of the scoring system was compared with that of administration of a 10-day course of amoxicillin in differentiating between tuberculosis suspects. Results from amoxicillin treatment were superior to the scoring system, with 92% sensitivity, 93% specificity, PPV 91%, and NPV 94%. The study enrolled 396 self-referred consecutive adults (over 15 years of age) at a free public sector health care facility dedicated to pulmonary diseases. All had suffered coughs for at least 21 days and had three negative smears. Participation was restricted to residents of Conakry who gave consent for HIV testing (14.5% were HIV positive). Of 396 patients, 204 (52%) entered the study. Of the 204, 87 (43%) responded to treatment with amoxicillin (it was not stated whether or not these patients were followed after they were considered to have responded). Of the 117 suspects who did not respond clinically and radiographically and remained smear-negative, 110 (94%) had pulmonary tuberculosis, confirmed either by positive culture (73 patients) or response to anti-tuberculosis treatment (37 patients). This study supports the use of a simple algorithm, placing antibiotic treatment before chest radiography in an area with a moderately high prevalence of HIV co-infection.

The results of a cohort study in northwest Vietnam, published in 2006, suggested deficient management of smear-negative tuberculosis suspects, resulting in progress of disease and death in some cases.[63] The investigators pointed out the need for a follow-up strategy aimed at identifying and treating smear-negative tuberculosis within the national program.

improvement on therapy. Excluding patients with chronic lung disorders, the study identified four clinical criteria for diagnosis of smear-negative tuberculosis (comparison was with non-tuberculosis respiratory disease): presence of cough for more than 21 days, chest pain for more than 15 days, absence of expectoration, and absence of shortness of breath. Diagnosis by any two (three) of the four criteria had 85% (49%) sensitivity, 67% (86%) specificity, a PPV of 43% (50%), and a NPV of 94% (86%).

Trial of anti-tuberculosis treatment

A trial of anti-tuberculosis treatment is generally not recommended.[59] If it works, the patient may still not have tuberculosis (if whatever the patient has responds to anti-tuberculosis treatment or improves in spite of such treatment). If it does not work, the patient may still have tuberculosis (the result of drug resistance or some other cause). Fourie and Weyer have pointed out that building a trial of anti-tuberculosis treatment into a national tuberculosis control policy, as has been suggested in Malawi,[64] is to confuse clinical application with public health interests and should be discouraged.[65] According to them, trial treatment is likely to be limited to hospitalized patients anyway and to require special management structures. Finally, there is little evidence that trial of anti-tuberculosis treatment leads to improved diagnosis.[65]

Defining cases of smear-negative pulmonary tuberculosis

As discussed in Chapter 2, it is difficult to define a case of smear-negative pulmonary tuberculosis. Nevertheless, a definition is needed in tuberculosis programs to assist clinical case management and, perhaps primarily, for monitoring and surveillance purposes. It is interesting to review the evolution of definitions for smear-negative pulmonary tuberculosis (Box 3.5). The Orange Guide and revised international definitions published in 2001 use a simple and straightforward definition.

The proportion of children among notified tuberculosis patients is highly variable,* and childhood tuberculosis is as a rule smear-negative. To improve surveillance in this respect and to facilitate comparisons, in 1996 it was decided to recommend distinguishing between adult (15+ years of age) and childhood cases (<15 years of age) of smear-negative pulmonary tuberculosis on the reports on case finding.[47] However, operational deficiencies can still influence to an important degree the proportion of smear-negative cases among reported cases, as will be discussed later.

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*To give an example, a record review in 95 health centers in Nicaragua found that 30% of new pulmonary tuberculosis patients enrolled in treatment were registered as "smear-negative"; 43% were children.[67] A record review in a central facility in Laos found that 46% of new cases were reported as "smear-negative" cases.[68] There were no children among them.

Box 3.5 Evolution of the definition of smear-negative pulmonary tuberculosis

In the first edition of the Orange Guide, published in 1986, the definition of a smear-negative case on the quarterly report of case finding was the following: "patients with pulmonary tuberculosis, having a negative sputum . . . in whom the diagnosis of tuberculosis was made by means other than sputum microscopy."[8]

The third edition, in 1994, defined a smear-negative case as "patients with pulmonary tuberculosis, started on treatment, in whom sputum smears were negative," further specifying that the reporting of a sputum smear-negative case required three sputum examinations.[38] The fourth edition, in 1996, distinguished between child (<15 years of age) and adult (15+ years of age) smear-negative cases.[47]

In 1993, the WHO's Guidelines for National Programmes defined a case of smear-negative pulmonary tuberculosis as "a patient with at least two sputum specimens negative for acid-fast bacilli by microscopy, radiographic abnormalities consistent with active pulmonary tuberculosis, and decision by a physician to treat with a full curative course of anti-tuberculosis chemotherapy; OR a patient with at least one sputum specimen negative for acid-fast bacilli, which is culture-positive for *M. tuberculosis.*"[66]

In the second edition, published in 1997,[48] the definition was "EITHER: a patient who fulfills all the following criteria: two sets (taken at least two weeks apart) of at least two sputum specimens negative for acid-fast bacilli on microscopy; radiographic abnormalities consistent with pulmonary TB and a lack of clinical response despite a week of a broad-spectrum antibiotic; a decision by a physician to treat with a full curative course of anti-TB chemotherapy; OR: a patient who fulfills all the following criteria: severely ill; at least two sputum specimens negative for acid-fast bacilli by microscopy; radiographic abnormalities consistent with extensive pulmonary TB (interstitial or miliary); a decision by a physician to treat with a full curative course of anti-TB chemotherapy; OR: a patient whose initial sputum smears were negative, who had sputum sent for culture initially, and whose subsequent sputum culture result is positive." Thus, in the absence of culture, chest radiography was necessary to document cases of smear-negative tuberculosis. It was specified that fluoroscopy examination results were not acceptable as documented evidence of pulmonary tuberculosis.

Revised international definitions published in 2001 define a sputum smear-positive case of pulmonary tuberculosis as a patient with two or more initial sputum smears positive for acid-fast bacilli, or with a single positive smear plus at least either radiographic abnormalities consistent with active pulmonary tuberculosis as determined by a clinician or sputum culture-positive for *M. tuberculosis*, and sputum smear-negative pulmonary tuberculosis cases as cases of pulmonary tuberculosis that do not fit the definition for smear-positive cases.[46]

Quality of diagnostic procedures in tuberculosis programs

The proportion of smear-positive cases among new pulmonary cases is frequently mentioned as a performance indicator in tuberculosis programs, but it is difficult to set a precise target range as far as this is concerned. In the programs collaborating with The Union, it was accepted that the proportion of

sputum smear-negative cases among all new pulmonary tuberculosis cases should not be high. It is debatable, however, how high it should be. Some argue that this indicator, except when very low or very high, depends on too many factors to be a good proxy for the quality of diagnosis.[60] This is valid criticism. The proportion of smear-negative cases among pulmonary tuberculosis cases may depend on the prevalence of HIV infection, the age distribution of the population covered by the services and/or covered by the surveillance system, and the methods and tools used in case finding. It may also depend on the prevalence of tuberculosis in the community. All this makes direct comparisons between sites difficult. Nevertheless, there are studies that indicate what can be considered reasonable in different settings. Arbitrarily, a retrospective hospital-based study in Virginia in the late 1970s found that one quarter of 977 culture-positive pulmonary cases were repeatedly smear-negative prior to treatment, a finding similar to that found in studies in other locations in the United States at the time.[69] A retrospective study in a Danish hospital, referring to the period from 1983 to 1993, found that out of 548 cases of pulmonary tuberculosis, 71% were positive by direct smear and 95% by culture.[70] In a study in a referral center in Nairobi (Kenya) in 2000–2001, 60% of 554 culture-positive cases were smear-positive, which is a common finding in an African setting with high HIV prevalence.[61] In a 2000–2001 prospective cohort study of 300 routinely diagnosed pulmonary tuberculosis patients in a provincial hospital in Zimbabwe, 80% could be bacteriologically confirmed: 161 were positive by direct microscopy, 51 by microscopy of a concentrated specimen, and 30 by culture only.[71] These examples provide a background for comparison with performance in routine settings where culture is not available.

Strictly speaking, the rate of bacteriological confirmation of pulmonary cases (by acid-fast microscopy) in tuberculosis programs is comparable only if the methods of obtaining and processing sputum samples are comparable. The classical studies on sources of transmission and the original policy recommendations referred to spontaneously expectorated, nonconcentrated sputum samples. Samples obtained by sputum induction and bronchoalveolar lavage are not strictly comparable, nor are concentrated sputum samples. Sputum induction and gastric lavage have been proposed as techniques to improve the confirmation rate of pulmonary tuberculosis. A study in a central referral hospital in Malawi reported an increase of almost 20% in cases positive on acid-fast microscopy after implementation of sputum induction when patients could not produce a sputum sample spontaneously.[72] Some of this increase could be a study effect, though. Sputum induction is a cumbersome procedure and is not without risks. It may not be a practical strategy in busy clinics. Care must be taken where sputum induction is practiced so as not to cause nosocomial spread of infection.

Box 3.6 Sputum "smear-negative" pulmonary tuberculosis

Data from 40 hospitals in Malawi suggested that the proportion of adult patients with "smear-negative" tuberculosis who actually had sputum smear examinations increased from 76% in the first semester of 1997, to 85% in the second semester, and 89% in the first semester of 1998, probably to a large extent because of implementation of structured supervision.[76]

In Gaborone and Francistown, Botswana, in 1997, of 374 patients with pre-treatment smear results missing—according to reporting to an electronic surveillance system (39% of all pulmonary tuberculosis cases)—224 (60%) actually had a record locally.[73] Most missing results had not been transcribed from the laboratory record to the treatment card. Correcting this, 16% of patients had no pre-treatment smear.

A 1997–1998 study in a chest clinic in Nairobi, Kenya, found that of 163 smear-negative adults enrolled in a laboratory study (55% HIV positive), 100 (61%) had two smears assessed before recruitment and two further specimens examined in the research laboratory.[75] The second examination revealed that 26 (26%) were actually smear-positive. The investigators concluded that under-reading (false-negative error) resulting from excessive workload in laboratories likely explained the problem.

Operational deficiencies

The HIV pandemic created and may well have unmasked existing operational weaknesses in the diagnosis and reporting of tuberculosis. To be classified as smear-negative, a patient has to undergo sputum examination. This policy is not always adhered to.[60,73,74] A number of diverse reasons may explain this failure: for example, patients may claim they are unable to produce sputum, clinicians may not insist on sputum examination, ruptures in the supply chain for laboratory consumables may arise, and various types of procedural failures and errors at the different levels within the health services may occur. If a case is to be classified correctly, the sputum examination must be of good quality. This is not always the case either.[75] Sometimes patients are wrongly reported as "smear-negative" even if they have a record of a positive sputum examination.[73] Box 3.6 presents some examples from operational evaluations of "smear-negative" tuberculosis.

In conclusion, the policy for diagnosis of smear-negative tuberculosis will vary from country to country depending on the epidemiological situation (of both tuberculosis and HIV), drug resistance (in tuberculosis and community-acquired pneumonia), health service characteristics, and financial resources. Response to a trial of antibiotics should not be part of the definition of a tuberculosis suspect. Diagnostic algorithms are necessary and useful in management of tuberculosis suspects with negative sputum smears. Chest radiography should be performed early in the process of assessment of smear-negative tuberculosis

suspects if possible. Antibiotic trials can be administered anywhere (provided antibiotics are available), can assist differential diagnosis in smear-negative tuberculosis suspects, and will reduce the number of referrals where radiography is not easily accessible.

Contact investigation

A Canadian study carried out from 1966 to 1971 concluded that examining contacts—especially younger intimate contacts of smear-positive source cases—was a worthwhile activity.[77] Nonetheless, the 1980 report of a joint study group of The Union and the WHO concluded that preventive treatment in child contacts had virtually no role in tuberculosis programs in developing countries, due primarily to resource constraints and the fact that this was a second priority, the first priority being the treatment of active cases.[78] Members of the study group affirmed that until the first priority was adequately addressed, it was premature to organize contact tracing other than what could be easily achieved by advising that symptomatic contacts come forward for sputum examination.

Thus, it is unsurprising that contact investigation was not prioritized in developing countries. Procedures in contact investigation were not subject to strict standardization, nor were these activities routinely evaluated. Interestingly, though, the same seems to be true for some rich countries, even if contact tracing was and is considered an important part of their tuberculosis program strategies.[79] An audit of contact procedures that looked at several outcome measures (proportion of contacts screened, follow-up attendance rates, number of secondary cases detected, and quality of record keeping) was performed in South Glamorgan, U.K., referring to the period between 1987 and 1989.[80] The audit identified various operational deficiencies. Investigators concluded that inadequate data, nonadherence to guidelines, and failure to distinguish highly infectious cases from other index cases resulted in the unnecessary screening of many contacts. There seemed to be insufficient coordination between the clinical and laboratory services on the one hand and contact investigation teams on the other hand, resulting in unfocused contact investigation and low yield. An evaluation in the United States in 2003 found that nearly one quarter of the tuberculosis cases had no contacts identified,* one third of identified contacts did not complete the screening process, and more than one half of those enrolled did not complete a full course of preventive chemotherapy.[79]

As discussed in the previous chapter, the following features of context are important when contemplating contact procedures in tuberculosis programs:

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*It is frequently found that a significant proportion of the homeless in large urban centers in rich countries have few or no contacts identified. Either they are without friends as well as a home, or little effort is made in contact investigation as far as the homeless are concerned.

the epidemiological situation and thus the expected contribution of contact tracing to tuberculosis control, available technology, feasibility of the proposed strategy, and cost. It is important to define the objective of contact tracing and priority vis-à-vis other components of the program. Confidentiality is another issue to be considered. Where stigma or discrimination is a threat, conducting contact investigations carefully prevents harming the patients and jeopardizing control measures.

Several questions need to be addressed when devising an operational strategy for contact tracing: what event(s) should trigger contact investigation; who should carry it out; what procedures should be followed; within what time frame; whether or not there should be an element of follow-up (for example, 18 to 24 months after diagnosis of an index case); and how it will be monitored.

The ring principle* in contact investigation stems from the findings of a study in the Netherlands in 1963–1964.[82] This study found 18 times more infected household members of smear-positive index cases than of smear-negative index cases. Furthermore, only a very small proportion of less intimate contacts of the smear-positive index cases in the study were infected. A policy for contact examination based on the ring principle distinguishes different scenarios: if the index case is smear-positive, other household members† are examined as well as close relatives, friends, co-workers, or other contact groups defined by the lifestyle and socialization patterns of the patient. Only if examination of persons other than household contacts yields results is the examination extended further. If, on the other hand, the index case is not smear-positive (as commonly occurs in the case of childhood tuberculosis), only members of the household are examined. In this scenario, the contact examination is extended to less intimate contacts only if doing so is justified by the yield. Thus, contact examination is focused and takes note of the findings as it proceeds. As a result, the extent of contact tracing and the number of nonhousehold contacts examined per case is likely to be highly variable. This policy aims for high efficiency.

Contact investigation was certainly not thoroughly pursued in the programs collaborating with The Union. Where it was, protecting young children among contacts of smear-positive cases[8] was the main objective because, at the time, children with household exposure to a sputum smear-positive source case experienced the greatest risk of becoming infected and developing disease and dying following primary infection.[83]

In Nicaragua, contact investigation had two objectives.[84] One objective was to find source cases. This was the main objective when children were diagnosed with tuberculosis; the younger the child, the greater the chance that infection

*The "ring principle" is also referred to as the "stone in the pond principle" and refers to contact circles.[81]

†A creative definition of "household" may be needed in case the patient is "homeless."

had occurred recently and that a source case might be identified. The second objective was to seek infected contacts in order to administer preventive chemotherapy. Here, the primary emphasis was on examining young children living in households of smear-positive patients, particularly children under five years of age. Other contacts were examined if they were reported to be symptomatic. As a general rule, contact investigation was more convincingly addressed where progress in case finding and treatment was good and the staff not overwhelmed with these key activities (for example, in areas where program performance was better than average and/or where there were practicing pediatricians). In a study of 223 consecutive smear-positive patients in one such setting in Nicaragua in the 1980s, contact investigation yielded 24 smear-positive cases and 43 smear-negative cases.[85] A record review corresponding to patients registered in 95 health centers in Nicaragua in 1994 found that a large proportion of unconfirmed pulmonary tuberculosis cases (that is, reported as "smear-negative") were children (43%).[67]

A survey in 44 hospitals in Malawi, in 2001, reviewed the examination of child contacts of 659 hospitalized adult patients with smear-positive tuberculosis and found that, in total, 33 children had been examined, 23 received preventive chemotherapy, 6 received anti-tuberculosis treatment, and in 4, no action was taken.[86] A retrospective review conducted in a central hospital in Blantyre from 2003 to 2005 found that attendance for contact investigation corresponded to less than 10% of smear-positive tuberculosis patients.[87] The investigators concluded that implementation of child contact management in Malawi was a challenge.

In conclusion, how much emphasis is placed on contact investigation in national programs depends on how much capacity there is and how important this activity is considered in the overall picture of tuberculosis control. Some might argue that if it is not a priority, it should not be part of the policy. However, performance and capacity vary within as well as between countries, and thus a range of policy issues needs to be addressed in any given country. Whether contact investigation is prioritized may also reflect a focus on communicable disease control, which is sometimes lacking in centralized and hospital-based programs.

Periodic screening of high-risk population groups

The chance of detecting tuberculosis by the routine health services is to some extent an individual characteristic. Criminals, for example, as a group might have a relatively low chance of having tuberculosis detected if special case-finding efforts were not applied to them.[88] This scenario holds true if they are not likely to use the general health services. The argument can be used to justify assessment for tuberculosis upon entry to the penitentiary system not only

for the good of the individual but also because it is controversial to incarcerate persons with infectious tuberculosis, exposing those who are imprisoned with them to a high risk of tuberculosis infection. Mine workers in high-prevalence settings represent another population group where screening is warranted and can be organized, provided the will to do so exists. Screening programs for miners have been developed, for example, for South African gold miners.[89,90] The primary aim of such campaigns is occupational safety, that is, to protect the workers by decreasing the risk of tuberculosis infection in the mines. It is more difficult to design screening programs to reach other high-risk population groups such as those who are infected with HIV, drug addicts, and the homeless. Participation in such programs is often poor.[91]

Periodic screening for tuberculosis among prison inmates is more difficult to justify than screening on entry. As periodic surveys do not prevent smear-positive cases from occurring, relying entirely on routine screening might delay detection of smear-positive tuberculosis. If entry screening is to be effective in preventing smear-positive tuberculosis in prisoners, inmates with tuberculosis infection need to be enrolled in a program of preventive chemotherapy. The cases that still occur should then be detected as they arise, and contact investigation should be performed without delay once a case is diagnosed. This aspect of prison tuberculosis programs is thus largely comparable to those out in the community.

In conclusion, screening by chest radiography (or other means) is often used in penitentiary systems. Screening upon entry to the system is justified. It is important that prisoners not enter the prison population until they are confirmed clear of infectious tuberculosis. In this context, a single chest radiograph is highly effective in ruling in, or out, potentially infectious tuberculosis.[92] An objection to the periodic screening of inmates is that it may delay diagnosis if no other strategy is in place for continuous case finding among prisoners. If another strategy is implemented and effective, the need for periodic screening of inmates should be greatly reduced.

Effectiveness in recruitment

What errors can arise in the process of identifying sources of transmission? There are numerous steps in the process of recruiting tuberculosis patients for treatment, and something can go wrong in almost every one of them. The overall effectiveness of case finding is a product of the effectiveness in each step: access to and utilization of health services; alertness of the health personnel in identifying suspects and referring them for sputum examination; the quality of sputum collection and acid-fast microscopy; and the coordination between the laboratory and the treatment services that will determine whether a patient diagnosed with smear-positive tuberculosis is registered for

anti-tuberculosis treatment. Some of these issues have been discussed above and some (such as access, utilization, coordination, and referral) are discussed in Chapter 7.

Even if laboratory issues—including quality control—are not the topic of this publication, the discussion of patient recruitment can not be completed without mentioning the false-negative error in acid-fast microscopy and its potential to affect case detection. For example, if 5% of tuberculosis suspects are sputum smear-positive according to the laboratory, and 1.5% of tuberculosis suspects have false-negative results (using tuberculosis suspects rather than smears, for the sake of simplicity),this would make a considerable difference in case finding, since the microscopy network may then miss as many as 20% of the smear-positive cases. Depending on the setting, some or even many of them may actually be registered as smear-negative cases in the program, which means they do receive treatment yet are wrongly reported as smear-negative. This, as discussed further on, is an argument for treatment regimens for smear-negative patients that are appropriate for smear-positive tuberculosis as well.

In conclusion, effectiveness in recruitment of patients should not be taken for granted, and efficiency should be periodically assessed as part of quality assurance in tuberculosis programs. This is the topic of Chapter 10.

Treatment strategies

The major recommendation emerging from the Arden House Conference strategies in 1959 was that anti-tuberculosis chemotherapy be employed as a public health measure, much the same as had been done in a nationwide campaign against syphilis in the United States.[93] Whereas the notion of a public health program based on treatment of individuals was met with skepticism by some at the time, others realized that implementation of such programs was an urgent issue given that, with time, drug resistance would unavoidably result and the development of new drugs was not guaranteed to keep pace with resistance.[93]

Many issues need to be considered when formulating treatment policies in public health programs. First, of course, are the results of clinical trials. Then, there is the question of safety and operational feasibility: how well are different regimens likely to perform under routine field conditions? How good are they if there is prior drug resistance? What is known about the prevalence and patterns of drug resistance in the setting where the policy is to be implemented? How well are the treatment regimens likely to be tolerated? Can adverse effects be managed? Finally, there is the issue of affordability and availability of the various drugs. In 1979, Fox and Nunn pointed out the importance of looking at the cost and therapeutic effectiveness of a treatment regimen rather than simply the cost of individual drugs.[94] Operational cost—supervision of treatment,

for example—needs to be considered as well, and the cost of retreatment in case first-line treatment fails.[94]

Numerous anti-tuberculosis treatment regimens have been tested in clinical trials. For a newcomer to the field, the plethora of different regimens may be a deterrent.[95] However, no program uses all available regimens simultaneously. National programs choose among the plethora, usually two or three regimens that are explained in clinical guidelines. Recommendations in any given program may change over time, which may or may not alter the results of treatment at the program level. To give an example, although recommendations changed in Cuba during the period from 1962 to 1997, treatment results remained stable.[96]

Advocates of 6-month regimens often state that longer regimens have lower adherence and completion rates, contributing to the accumulation of partially treated patients with drug-resistant tuberculosis.[95] Treatment default, however, often occurs early in treatment, and the difference between short and long regimens is not only the duration of treatment. Partly treated patients in settings where treatment is badly organized may differ from those who default from well-organized, directly observed treatment programs in terms of nature and prevalence of drug resistance. Unless structural and operational issues are improved, short regimens per se are unlikely to fix a bad situation. Indeed, much of the multidrug resistance seen today may be the result of the use of 6-month regimens under inappropriate conditions.

Clinical trials and routine practice: efficacy versus effectiveness

Results of clinical trials are reported as cure, failure, and relapse rates among subjects available for analysis. The trials study culture conversion rather than smear conversion, whereas in clinical practice and under routine conditions in tuberculosis programs, treatment is monitored with sputum microscopy. Criteria commonly applied in efficacy trials are: at least 85% culture conversion at two months, and no more than 5% relapses. Until recently, it was impossible to distinguish between reactivation and reinfection among relapses. A subanalysis usually looks at the impact of drug resistance on outcome.

Comparisons of different treatment regimens within a randomized controlled trial are always valid provided randomization is successful. However, for randomization to ensure comparability, the number of recruited subjects must be very large, a situation rarely achieved in clinical trials of tuberculosis treatment. Whereas recruitment criteria in anti-tuberculosis treatment trials were probably fairly uniform, there may be some differences between trials—for example, in the proportion of smear- and culture-positive cases. Other than that, clinical trials subjects as a rule were the following: adults, cooperative, not previously treated (or not treated for more than some determined duration),

without concomitant diseases, and not critically ill at the time treatment was begun. This means that the population studied is never the same as the target population. For example, there has never been a clinical trial of tuberculosis treatment that included pregnant women, even though pregnant women are frequent among tuberculosis cases in high-prevalence countries. Even with careful recruitment criteria, occasional patients are inevitably lost from sight in clinical trials. This may result in overestimation of treatment efficacy and underestimation of acquired drug resistance, as the group of defaulters is excluded from the main analysis. As a rule, in cases of doubt, the bias was directed in favor of reporting failure and relapse rather than ignoring or concealing them.[97]

A paper from India, published in 1982, describes how only 25% of the patients registered in the tuberculosis program in Madras and Bangalore in 1978 were entered in the clinical trials conducted there.[98] A study of 300 consecutive cases recruited in the trials found that in spite of the selective recruitment, one third of the patients required home visits during the course of treatment, some of them repeatedly, to maintain treatment adherence. It was pointed out that this was not realistic under routine program conditions and that it was important to devise alternative methods for promoting adherence as well as to select regimens having maximum potential for being given on a self-administered basis.[98]

The original treatment algorithm in the Union model

The 1974 Expert Committee recommended using 12-month chemotherapy in resource-poor countries.[99] When tolerated well, thioacetazone was an economical option in combination with isoniazid. It also had good storage properties even in tropical conditions and, being small in bulk, was convenient both to dispense and for the patients to take. Owing to irregular treatment and high absconder rates in programs in developing countries, regimens without rifampicin were considered safer. In 1981, treatment with streptomycin and isoniazid with or without thioacetazone* still remained the basic regimen in many developing countries.

At the time The Union started its collaboration with national programs, the introduction of short-course treatment was quite a challenge and was regarded as controversial. Protecting the two drugs that are key to short-course treatment—rifampicin and pyrazinamide—from drug resistance that would jeopardize subsequent efforts to control tuberculosis was essential. Thus, rifampicin was not used in a single preparation but always in a fixed-dose combination with isoniazid and was not handed out to patients for self-administration.

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*Thioacetazone was used in Anglophone countries and ethionamide in Francophone countries.

Box 3.7 The original treatment regimens in the Union model

Category of case	*Treatment regimen*
New smear-positive pulmonary cases	2S[HR]Z/6[HT] or 2S[HT]/10[HT]
Previously treated cases	2S[HR]ZE/1[HR]ZE/5[HR]E
Smear-negative cases	2S[HT]/10[HT] or 12[HT]

E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; T, thioacetazone. Fixed-dose combinations are indicated by square brackets.

Drugs were always purchased from the main international pharmaceutical firms, even though their price was substantially higher, to ensure the highest level of quality.* All treatment within the collaborative programs was standardized, but there was more than one treatment regimen. The term "treatment algorithm" will be used for recommendations in a program. The objective of the algorithm is to ensure coherence in tuberculosis treatment.

The original treatment regimens in the Union model are presented in Box 3.7.[8] The short-course regimen for new smear-positive pulmonary cases consisted of an intensive phase with four drugs (two months of streptomycin, isoniazid, rifampicin, and pyrazinamide) and a continuation phase with two drugs (six months of isoniazid and thioacetazone). The treatment regimen for previously treated smear-positive cases relied on an intensive phase of three months' duration, which was identical to that of the regimen for new cases except for the addition of ethambutol. The continuation phase, five months, was conducted using three drugs (isoniazid, rifampicin, and ethambutol). Finally, there was a regimen that did not use rifampicin: 12 months of isoniazid and thioacetazone, with the addition of streptomycin in the first two months whenever possible (in 1994, "as a minimum if the patient was sputum smear-positive" was added to the recommendations).[38] If streptomycin injections could not be administered, ethambutol was substituted. All treatment was administered on

*Styblo, at the outset, argued that he would not pay attention to the cost of the drugs so as to obtain the cheapest versions, as he feared being criticized for using poor-quality drugs, especially fixed-dose combinations for which there was a great deal of pressure to use only drugs from "reputable" firms—an official position of The Union prepared by a working group that included active participation of drug firm employees. The costs were eventually reduced primarily in the period following Styblo's retirement, when the strategy was administered by the WHO, whereupon The Union pursued competitive pricing through the use of generics. To defend their position, The Union argued that the case was already demonstrated and the risk was very small. The main suppliers promptly slashed their prices to less than one third of their original prices.

a daily basis, with the exception of the continuation phase of the regimen for previously treated cases, where treatment was intermittent with drugs administered three times a week. According to the original recommendations, the choice of drugs in the continuation phase for treating previously treated cases was to be guided by the results of drug susceptibility testing on a sample taken before starting treatment, whenever possible. Thus, if the patient demonstrated sensitivity to isoniazid, then daily isoniazid and thioacetazone were prescribed; otherwise, isoniazid, rifampicin, and ethambutol were given three times a week.[8] Major attempts at decentralizing drug susceptibility testing were undertaken in Tanzania, Nicaragua, and, to some extent, Mozambique, but it was never feasible to put this into practice, and the approach was finally abandoned after a decade of trying. Therefore, the latter continuation phase became the norm, without susceptibility testing.

In the model program, the following different options could be presented to new patients with smear-positive tuberculosis: hospitalization (two months) for short-course treatment, short-course treatment on ambulatory basis with daily attendance for directly observed treatment for the first two months, or self-administered 12-month treatment. The outcome of treatment in new smear-positive cases was monitored on a routine basis, so the overall results in all new smear-positive cases were always known. At the outset, the results in 12-month treatment, which were worse, affected the overall treatment results in the program, but as time went by, fewer and fewer patients were enrolled on this regimen. The outcome of treatment of previously treated smear-positive cases was also monitored on a routine basis. In the event that a patient failed to be cured on this regimen, no further treatment was available.

Why short-course chemotherapy?

Although the 12-month regimen performed well, judging by the end result in clinical trials (eventual culture conversion rate was around 90%), in routine application of the same regimen, sputum conversion was often considerably lower. One example comes from a study in India, where conversion was 60% among patients on isoniazid and thioacetazone, and 68% among patients on streptomycin and isoniazid, examined at 12 months.[100]

One of the advantages of short-course regimens over 12-month ones was that culture conversion occurred earlier in treatment. In 1954, Dressler et al. studied sputum culture conversion in 96 patients treated with streptomycin and isoniazid. Only 51% of all patients and 67% of those who eventually converted had culture conversion by two months.[101] Conversely, in a British short-course chemotherapy trial reported in 1981,* there was culture conversion in 77%

*The trial recruited 511 patients with cultures susceptible to isoniazid. Treatment was with four drugs in the intensive phase: SHRZ or EHRZ.

by two months (in 70% of smear-positive cases) and 98% by three months.[102] A trial in Singapore* reported negative culture in 98% of those examined at two months,[103] and trials in Hong Kong† reported 90% to 94%, depending on whether treatment was intermittent or daily.[104] In the Hong Kong trials, resistance to isoniazid or streptomycin did not affect the culture conversion rate significantly.[105] In a multi-center trial (published in 2004) recruiting 1,175 sputum smear- and culture-positive cases,‡ there was significantly higher culture conversion at two months (85%) when treatment was administered daily, than when the same drugs were given as intermittent treatment three times a week (77%).[106] Smear conversion at two months in this trial was 78% in both groups.

The late conversion to negative bacteriology in 12-month treatment programs called for close supervision of treatment for at least the first five months when this regimen was used, a level of supervision that was not feasible in rural areas in many developing countries.[107] This was one of the arguments for introducing short-course treatment: with earlier bacteriological conversion, treatment supervision could be relaxed. Another was that patient compliance was best early in treatment while the patient felt sick, and it was argued that this short-term compliance, lasting often only a few weeks, must be fully exploited by giving all patients an efficacious combination of drugs under close supervision to kill almost all bacilli as quickly as possible.[107] It was argued that a higher proportion of defaulters would be permanently "cured" when using a short-course regimen because even if the patient had converted by the time of default, reversion to infectiousness after short treatment (for example, two to five months) was greater for the 12-month regimen.

The results with the 12-month regimen in routine practice in Tanzania were disappointing even after organization in the program had been improved. It seemed illogical to use a 12-month regimen with a relatively weak intensive phase when most patients were hospitalized or attended the ambulatory services daily for injections, and knowing that the short-term results of the four-drug intensive phase of short-course regimens was superior. When it was decided that the 12-month regimen did not perform satisfactorily in Tanzania, a short-course regimen was piloted with promising results compared to the 12-month regimen. It was therefore decided to expand short-course treatment.

Why an 8-month short-course regimen?

Rifampicin was introduced into tuberculosis treatment in many Western European countries and the United States in the period from 1968 to 1970, initially

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*Singapore 1981 (SHRZ): 330 patients with fully susceptible organisms (61% had cavitary disease).

†Hong Kong 1982 (SHRZ or EHRZ): patients with fully susceptible organisms.

‡Intensive phase was with EHRZ. Of 880 with drug susceptibility results, 9% were resistant to isoniazid alone and 2% were multidrug-resistant.

in 9-month regimens without pyrazinamide. Today, the level of isoniazid resistance in these countries is commonly 5% to 10%. At the time the treatment algorithm for the Union collaborative programs was devised, a 6-month regimen with four drugs in the intensive phase (SHRZ or EHRZ) and rifampicin throughout (HR) in the continuation phase had been proven highly efficacious in fully supervised treatment in Singapore and with self-administered treatment in the continuation phase in the United Kingdom. This was regarded as the option of choice in countries having an uninterrupted drug supply, a high degree of patient cooperation, and adequate outpatient supervision.[103,108] Even cases resistant to isoniazid and/or streptomycin fared well on this 6-month regimen in African trials where at the time about 10% of the cases were drug-resistant.[109] A large international multi-center trial reported in 2004 concluded that the greater benefits of the 6-month regimen in patients having organisms initially resistant to isoniazid alone—the most common form of initial drug resistance—contributes substantially to its greater overall efficacy when compared to the 8-month regimen using ethambutol and isoniazid in the continuation phase.[106]

The backbone of the treatment algorithm in the Union model was a short-course regimen of 8-months' duration using isoniazid and thioacetazone in the continuation phase. Because it was decided that rifampicin would not be handed out to patients for self-administration, the continuation phase of a 6-month regimen would have required administration under direct observation —a step that was not considered feasible. The continuation phase of the 8-month regimen, on the other hand, could be based on self-administration.[107] The 8-month regimen had been tested in clinical trials in East Africa: Kenya, Tanzania, Uganda, and Zambia. There was no relapse among the 81 smear-positive cases with fully susceptible organisms who were enrolled on this regimen in a trial in 1974–1975 and hospitalized for six months.[110] Of ten patients with resistance to isoniazid and/or streptomycin, one had an adverse outcome, and one relapsed.[110] The findings from the trials at this time concluded that in an area with 10% prevalence of initial resistance to isoniazid, a failure rate of 2% could be expected in treatment of new smear-positive cases with the 8-month regimen.[110]

Public health officials were primarily concerned that treatment with self-administered rifampicin and isoniazid in the continuation phase of the 6-month regimen might give rise to resistance to rifampicin in a setting where isoniazid resistance is already prevalent (that is, functional monotherapy*). It may seem that such a concern is not warranted, given that the number of bacilli should be low when the continuation phase of treatment is started and the risk of

*Monotherapy is the administration of a single drug, and functional monotherapy is when there is resistance to all but one of the drugs administered.

selection of resistant mutants consequently low as well. Indeed, the 6-month regimen had been shown to adequately cover isoniazid-resistant cases in clinical trials in the United Kingdom. It was expected, however, that program quality would be weak in many locations in the early days of the collaborative programs, resulting in highly irregular and sporadic treatment. Consequently, it was feared that the observations from clinical trials might not hold, which urged public health workers to proceed with extra caution. Information suggested that when rifampicin was given for at least four months in clinical trials, the risk of acquired resistance in failures increased: of 23 failures, additional resistance to rifampicin developed in 74%.[105] Even if many of these cases received 4-month regimens (which were too short), it did raise concerns regarding the safety of regimens using rifampicin throughout in treatment programs with high defaulter rates (and thus a shorter than prescribed treatment course). There was less acquired resistance (and almost no resistance to rifampicin) in regimens using rifampicin for one to two months only;[105] thus, such regimens seemed to offer safer options in settings where organization was suboptimal.

Whereas the 8-month regimen was not the most efficacious according to the results of the clinical trials, it was regarded as superior in the setting of the Union collaborative programs for two reasons: sustainability (considering the high price of rifampicin at the time*) and operational feasibility (minimizing the need for directly observed treatment). An operational strategy was devised in order to strengthen the 8-month regimen in selected cases that were considered at risk for adverse outcome. In case of a positive smear at two months, the directly observed intensive phase with four drugs was prolonged (see Chapter 4). Furthermore, although the 8-month regimen contained rifampicin only in the intensive phase, any cases not permanently cured with this regimen received an enforced 8-month regimen with rifampicin, and consequently directly observed treatment, throughout. Directly observed treatment thus targeted those most likely to benefit from it.

Some refer to the algorithm presented in the Orange Guide as a two-step policy. The argument of a two-step policy extends back to Fox in the 1960s who discussed regimens with differing efficacies: "Even if relapse would be entirely prevented by a second year of chemotherapy, it would be undesirable to give a second year of chemotherapy to 100 patients in order to prevent a maximum of 20 relapsing, unless every newly diagnosed patient with active disease could also be brought under effective chemotherapy."[112] In the results of a study in Hong Kong in the 1970s, researchers argued for a two-step policy from a different angle: standardized treatment versus individualized treatment. The

*The price of the treatment regimen chosen in the Union collaborative programs was US$ 45 per patient in 1983 if purchased through The Union, and US$ 40 in 1986.[8,111] The price for a 6-month regimen would have been almost double this price.

study did not report better outcomes in a group of patients where the results of pre-treatment drug susceptibility results were used to modify treatment as compared to a group where the results were ignored. Thus, the study recommended treating all patients with a standardized regimen and then treating any failures that emerged with another good combination of drugs.[113]

Treatment of new versus previously treated cases

The principle of using a different regimen for previously treated cases predates the Union model and was based on early observations in various settings that previously treated cases were more likely to be drug-resistant. When a 12-month treatment was used in new cases (isoniazid and thioacetazone with or without streptomycin), the recommendation for treatment in previously treated cases was to administer streptomycin, pyrazinamide, and PAS. If this did not work, then an array of ethionamide, pyrazinamide, and cycloserine were used, which was more expensive and more toxic.[99] Eventually, where resources permitted, rifampicin and ethambutol were used.[99] Implementing such retreatment regimens was considered justified only in programs that demonstrated satisfactory results in the treatment of new cases.[99]

In the context of the Union collaborative programs, it was known that previously treated cases could be expected to harbor bacilli resistant to streptomycin and/or isoniazid.[107] A regimen relying on isoniazid and thioacetazone in the continuation phase was not a good choice in such cases. Although it could be argued, based on clinical trials, that a 6-month regimen should be relatively effective in curing this group of patients, it was considered safer to add ethambutol as a fifth drug in the intensive phase and as a third drug throughout the continuation phase for a total duration of eight months in the treatment of previously treated cases.

In the beginning, the regimen for previously treated cases was prescribed for those patients whose prior treatment dated back to before the introduction of short-course treatment. No significant problem with resistance to rifampicin was expected among these cases, since the drug had practically not been used in the collaborating programs (except in Nicaragua, where it was introduced in 1978). Over time, patients enrolled on the regimen for previously treated cases included increasing numbers of relapses and returning defaulters formerly administered the short-course regimen for new cases and thus previously treated with rifampicin. Because of the precautions taken to protect rifampicin and the strict policy of directly observed treatment, it was assumed that these cases were unlikely to experience rifampicin resistance and what later came to be known as multidrug resistance (that is, resistance to both rifampicin and isoniazid).

Using the regimen for previously treated cases when patients had failed short-course treatment as new cases in the program might have been contro-

Table 3.1 Results of treatment in previously treated cases, Nicaragua, 1996–1997

Category of case	*n*	*Success* %	*Failure* %	*Died* %	*Default* %	*Transfer out* %
Relapse	355	83	3	5	8	3
Return after default	148	67	1	6	24	2
Treatment after failure	74	73	14	3	5	5
Total	577	77	2	5	12	3

versial. This possibility was recognized, and all such cases were to be subject to drug susceptibility testing.[8] Figures from Tanzania published in 1989 showed that among 139 cases who failed treatment for new cases,* there was resistance to isoniazid and/or streptomycin in roughly half (as compared to 11% in new cases) and to RHS in almost 4% (as compared to no such resistance in new cases).[114] Of 284 cases failing the retreatment regimen (including not only cases who had failed treatment as new cases but also relapses and returning defaulters), these proportions were 60% and 12%.[114] For comparison, routine cohort analysis of treatment results in the program showed 3% failure rate in treatment of new cases and 4% failure rate in treatment of previously treated cases.[115] Routine outcome assessment may not accurately reflect drug resistance, however, partly due to irregular treatment, defaulting (10% in new cases, and 14% in previously treated cases in Tanzania at the time[115]), and death (6% in both cohorts[115]).

Whereas the recommendation to perform drug susceptibility testing upon failure in short-course chemotherapy was, at least partly, heeded in Tanzania—enough to reassure Styblo that the treatment algorithm was justified—it was never convincingly accomplished in any of the other countries. Even to this day, as documented in Malawi, it has been difficult to implement a policy of drug susceptibility testing upon enrollment of patients on the regimen for previously treated cases; sputum specimens are not always sent for susceptibility testing, and often cultures are negative.[116,117] Previously treated cases seemed to fare well on this regimen in general, however, suggesting that they were, as a rule, not multidrug-resistant (see Table 3.1 for treatment outcome in previously treated cases in Nicaragua in 1996–1997). The explanation for this is twofold: first, failure may have been primarily due to irregular treatment or (as expected) the weak drug combination used in the continuation phase of the regimen for new cases; and second, the protection of rifampicin actually worked to the extent that the programs did not produce multidrug resistance.

*After excluding atypical mycobacteria.

Treatment outcome was carefully monitored, and as time went by, the assumptions were shown to be reasonable. Thus, whereas there were occasional multidrug-resistant cases in the early days of the programs due to prior chaotic treatment practices and early operational weaknesses, this did not seem to pose a problem in the long run: there were, as a rule, no signs of increasing prevalence of multidrug resistance. Multidrug resistance remained barely measurable after 15 years of rifampicin-based regimens in Tanzania, despite an HIV epidemic that caused the number of tuberculosis cases registered in the program to quadruple over the period.[118] In a survey conducted from 1991 to 1993, multidrug resistance was measured at 0.4% in new cases, and any other isoniazid resistance was 4.1%, and these proportions in relapses were 2.7% and 16.4%, respectively.[119] Drug resistance was not associated with HIV status. Similarly, the prevalence of isoniazid monoresistance and multidrug resistance in previously untreated cases in Benin (another collaborative program) was reported as 5.4% and 0.3%, respectively, in a survey from 1995 to 1997.[120,121] In Nicaragua, where rifampicin was introduced five years before the implementation of the Union treatment algorithm and where treatment was largely on an ambulatory basis, these resistance rates were reported as 9.4% and 1.2%, respectively, in a survey carried out from 1997 to 1998.[122] Thus, multidrug resistance was not absent but rare. Nevertheless, continued vigilance is crucial.

A retrospective record review looking at cases registered in Nicaragua in the years from 1988 to 1996 suggested that the number of cases failing on the regimen for previously treated cases was small compared to the number of cases treated in the program (0.7%, compared to the number of new cases and relapses, and 0.4% to 0.5%, compared to all cases registered in the program), but that a high proportion of cases who did fail, and where results of drug susceptibility testing were available, were multidrug-resistant (89%).[123] The output of such cases decreased over time, and the mean age of patients failing on the retreatment regimen rose.

In Bangladesh, where the same treatment algorithm was introduced in 1995, Van Deun et al. estimated the degree of drug resistance created by the tuberculosis program.[124] They compared resistance rates in 2EHRZ/6HT failure and relapse cases to a baseline measured at the start of the program, and also compared resistance profiles of repeat isolates. They found virtually no evidence of acquired drug resistance during the study period (1995–1999) and specifically no "amplification" toward multidrug resistance. The study's findings pointed to an accumulation of primary drug resistance as the main mechanism explaining resistance levels; that is, drug resistance in previously treated cases seemed to consist of passed-on primary resistance rather than acquired resistance. The investigators concluded that the application of the treatment algorithm was safe in this setting even if directly observed treatment was not strictly applied. Conversely, it can be argued that in and of itself, directly ob-

served treatment is not enough to prevent drug resistance when treatment policies are flawed.

In conclusion, the assumption that in Union collaborative programs those who failed on the 12-month or 8-month regimens for new cases were likely to be resistant to isoniazid and/or streptomycin but not to rifampicin was reasonable. Likewise, the prerequisite of treatment with at least three drugs (REZ) to which there was susceptibility was fulfilled when looking at the regimen for previously treated cases in the context of the algorithm.[125] When devising the algorithm, Styblo did what has recently been discussed in the context of DOTS-Plus programs:[126] He looked at the overall resistance pattern in treatment failures (or in previously treated cases) and designed a retreatment regimen with it in mind. The interpretation of the treatment algorithm as adding a single drug to a failing regimen is a misinterpretation when examining it from this angle. (It can also be argued that it is a misinterpretation at the level of the individual patient when considering that the patient is on isoniazid and thioacetazone at the point of classification as a failure qualifying for retreatment). Finally, the few cases failing the regimen for previously treated cases, even if multidrug-resistant, would be expected to be fully susceptible to second-line drugs, as these drugs were not used in the algorithm.

Treatment of smear-negative pulmonary tuberculosis

Styblo consistently argued that symptomatic adult patients with smear-negative pulmonary tuberculosis should receive treatment, given that a proportion of these cases would become smear-positive if not treated.[107] In line with this notion, in 1986, the first edition of the Orange Guide stressed that smear-negative patients must be enrolled in treatment if the presence of active pulmonary or extra-pulmonary tuberculosis was suspected.[8] The programs set about to strengthen the process of diagnosis by expanding a network of acid-fast microscopy and using an algorithm for management of smear-negative tuberculosis suspects in order to tease out those most likely to have tuberculosis and thus to benefit from treatment. It was assumed that proper diagnostic procedures would result in lower patient numbers, which could well be managed by the programs. Whereas paramedics could start treatment in smear-positive cases, the decision to treat a smear-negative patient was to be made by a medical officer, a decision justified by the difficulty in diagnosing smear-negative tuberculosis.

In Tanzania all patients were originally treated with a 12-month regimen. With the introduction of short-course treatment in 1982, the new regimen was reserved for smear-positive cases (the most infectious) and serious forms of smear-negative and extra-pulmonary tuberculosis (such as miliary tuberculosis). Thus, a different treatment regimen came to be prescribed in sputum smear-negative cases as opposed to smear-positive ones. This was an issue of

cost. The short-course regimen was expensive at the time,* which on the one hand was an immediate matter for the donors funding the drug supply, but on the other hand an issue of sustainability in the longer term. It was also considered important to emphasize sputum microscopy in the assessment process to counteract over-diagnosis. It was argued that if all cases received the same regimen, health workers might not insist on performing sputum microscopy, a cumbersome process. This was not least important in places featuring access to radiology, as many physicians were known to prefer radiology to microscopy for diagnosing tuberculosis, with consequent over-diagnosis.

When a program matures, smear microscopy ideally becomes firmly established in the assessment of tuberculosis suspects, and it then seems less important to have a different regimen for smear-negative cases. Furthermore, over the course of time, the cost of short-course treatment decreased, and eventually expense became irrelevant,[128] particularly as a modified 12-month regimen with ethambutol throughout was equally or even more costly than a short-course regimen (see Table 3.2). Finally, the HIV pandemic made it increasingly controversial to use the 12-month regimen at all in settings with high HIV prevalence, as it was demonstrated to be inferior to short-course chemotherapy in treatment of HIV-infected tuberculosis patients.[130] Under routine program conditions, HIV status of patients is often unknown and thus, strictly speaking, in countries with a high prevalence of HIV infection, all treatment regimens must cover HIV-infected patients.

Before discussing the evolution of the treatment algorithm, it will be useful to summarize briefly the conclusions of the World Bank studies published in 1991.

Cost-effectiveness

The World Bank studies concerned treatment with the regimens recommended in the Orange Guide (the 8-month and 12-month regimens) in the context of three tuberculosis programs in Africa (Tanzania, Malawi, and Mozambique). The main conclusions of the studies can be summarized as follows.[125] Chemotherapy for smear-positive tuberculosis was cheaper than other cost-effective health interventions such as immunization against measles and oral rehydration therapy. In terms of deaths averted and cost per year of life saved, chemotherapy for tuberculosis was the cheapest health intervention available in developing countries. The greatest benefit of chemotherapy was reduction in transmission, and treating HIV-infected smear-positive tuberculosis patients

*In 1996, the hard-currency cost to The Union of the 8-month regimen was equivalent to US$ 18, whereas that of 12-month treatment was US$ 8;[127] earlier, this cost difference was even greater.

Table 3.2 Cost of treatment regimens

Treatment regimen	*1992 UNICEF US$*	*1996 UNICEF US$*	*1994 WHO US$*	*2000 KNCV US$*	*DOT doses*
2SHRZ/6HT	46	34.6	22.28		60
2SHRZ/4HR	75	48.0	36.06		180
2SHT/10HT	22		10.3	7.1	NA
2EHRZ/6HT	31	21.3	18.56	13.3	60
2EHRZ/6HE	40	30.5		18.5	60
2EHRZ/4HR	60	34.7	32.34	22.2	180
2SHE/10HE		40.4	23.9	17.4	NA
2EHRZ/4H3R3	42	25.9			110
2E3H3R3Z3/4H3R3		16.1		11.0	77
Retreatment*	109	73.6	56.4		240
Retreatment†	85	61.0	46.2		154

Sources: UNICEF data from World Health Organization,[48,66] WHO data from Chaulet,[129] and KNCV data from van Gorkom et al.[128] UNICEF estimates include handling charges. WHO and KNCV estimates refer to free-on-board prices.

*Daily.

†Daily intensive phase and intermittent (thrice weekly) continuation phase.

UNICEF, United Nations International Childrens' Fund; WHO, World Health Organization; DOT, directly observed treatment; S, streptomycin; H, isoniazid; R, rifampicin; Z, pyrazinamide; T, thioacetazone; NA, not applicable; E, ethambutol.

was only slightly less cost-effective than treating HIV-negative patients, assuming that they were equally infectious. Short-course chemotherapy was cheaper than 12-month chemotherapy per death averted and per year of life saved, and preferable to 12-month chemotherapy because of a higher cure rate and higher efficacy in drug-resistant cases. Where feasible, ambulatory chemotherapy was much cheaper than hospital-based chemotherapy, but at what point was the extra cost justified in order to increase the cure rate? Treating smear-negative cases who otherwise would go on to become smear-positive was less cost-effective than treating those who were smear-positive, but still compared favorably with many other health interventions. Apart from cost-effectiveness, treating smear-negative and HIV-infected patients was considered important for the credibility of the program.

Earlier cost-effectiveness studies had supported shorter treatment using rifampicin (6-, 8-, and 9-month regimens) compared to longer treatment without rifampicin (12-month regimens). Sensitivity analyses in cost-effectiveness studies in Botswana (1986)[131] and Indonesia (1989)[132] suggested that the degree to which cases dropped out of treatment was much more influential in determining the cost-effectiveness of a program than the efficacy of the regimen.[133]

Evolution of the treatment algorithm

Injections

With the HIV pandemic, it was important to limit the use of injections, and thus streptomycin, in the tuberculosis program. In 1994, the treatment policy was modified by replacing streptomycin with ethambutol in the intensive phase of the 8-month regimen for new cases.[38] This was not a controversial change because it did not obviously weaken the treatment algorithm. Indeed, in addition to doing away with the need for injections, with this change the 8-month regimen became less costly and logistically easier to implement: no syringes, needles, or sterile water. Streptomycin injections were, however, still part of the 12-month regimen (but could be substituted with ethambutol) and the 8-month regimen for previously treated cases (where there was no alternative available).

Thioacetazone

Historically, thioacetazone had a reputation as a dangerous drug causing serious adverse effects. Although adverse reactions to thioacetazone were common (34%) when a dose of 200 mg was used, fewer reactions occurred (6%) when the dose was lowered to 150 mg.[134] Thioacetazone then became an appealing component of multidrug regimens because of its very low price. In 1971, the results of a large, international study comparing adverse reactions in three regimens—two of them involving thioacetazone—reported that severe rashes occurred in 3.5% of the patients on a regimen using streptomycin, isoniazid, and thioacetazone; and 3.2% on a regimen using isoniazid and thioacetazone compared to 0.4% on the control regimen (streptomycin and isoniazid). However, out of 2,561 patients treated with thioacetazone (1,396 on the SHT-regimen, and 1,165 on the HT-regimen), serious cutaneous reactions occurred in only 0.3% of cases (exfoliative dermatitis in seven, and Steven Johnson syndrome in one, of whom two were known to have died).[135] Serious reactions occurred only in patients in Singapore and India, and thioacetazone was well tolerated in African countries,[136] where it came to be widely used.

In March 1991, in the wake of anecdotal reports, an article by Nunn et al. in Kenya reported increased risk of cutaneous hypersensitivity reactions to thioacetazone in HIV-infected patients treated for tuberculosis at a chest clinic in Nairobi: 22/111 (20%) of HIV-positive patients in their material had experienced such reactions, as opposed to 2/176 (1%) of HIV-negative patients.[137] Three HIV-positive patients with toxic epidermal necrolysis died. This report was followed by similar observations from elsewhere.[138] In spite of initial hesitation resulting from the financial and operational implications for programs in low-income countries,[139] the use of thioacetazone eventually came to be reconsidered.[140]

A strategy of patient counseling and early detection and management of cutaneous adverse effects was devised and tested in Tanzania. The results at program level were published in 1995, reporting a frequency of fatal outcome of 0.3% from any cutaneous reaction and 19% from toxic epidermal necrolysis.[138] In 1996, van Gorkom and Kibuga, in Kenya, argued for a conservative strategy until the level of HIV prevalence among tuberculosis patients approached 50%, whereupon a strategy of routine HIV testing should be adopted to allow selective use of an alternative regimen,* and universal replacement of thioacetazone only when the prevalence approached 75%.[139] The issue was hotly debated,[127,143] but as HIV prevalence rose, thioacetazone use was gradually regarded as increasingly controversial until eventually discontinuing its use altogether was unavoidable in countries with a very high prevalence of HIV infection. By then, many programs in Africa were grappling with too many problems to justify insisting on implementation of a conservative strategy, and thereby risking operational failure.

The implications

The increased substitution of ethambutol for thioacetazone in the continuation phase of treatment of new cases threatened to weaken the regimen for previously treated cases and thus the treatment algorithm itself. With routine use of ethambutol in the continuation phase in the regimen for new cases, failures could be expected to be resistant to ethambutol and isoniazid. Accordingly, there was a risk of functional rifampicin monotherapy in the continuation phase of the regimen for previously treated cases. The only option available to strengthen the continuation phase in the regimen for previously treated cases was pyrazinamide. Some evidence suggested potential value of pyrazinamide in this context, such as in preventing the growth of scanty resistant organisms that might have survived the initial intensive phase of chemotherapy.[105,144] Many researchers were not convinced, however. In cases of resistance to ethambutol and isoniazid, was rifampicin sufficient in the continuation phase? Using the argument of demonstrated efficacy of the 6-month regimen in new cases with isoniazid resistance, some public health officials believed such a regimen would be effective unless treatment was highly irregular. Strict supervision throughout treatment in previously treated cases was now even more important than before.

Some warned against prescribing an 8-month regimen with ethambutol and isoniazid in the continuation phase in areas with significant isoniazid

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* As an example, in the Mbeya Region in South Tanzania, the HIV prevalence of smear-positive tuberculosis patients was 52% in 1991.[141] In a country-wide survey from 1991 to 1993, the overall HIV prevalence in new cases and relapses in Tanzania was 32%[119] and 44% in 1998.[142]

resistance.[145] By this time, considerations of cost lent support to the 6-month regimen in treatment of new cases: the price of rifampicin and pyrazinamide had decreased, and the expense of the 6-month regimen could be reduced even further through intermittent treatment, apart from the fact that the alternative 8-month regimen, with ethambutol replacing thioacetazone in the continuation phase, was expensive (see Table 3.2). As a consequence, the odds were progressing in favor of the 6-month regimen. Issues of operational feasibility and safety remained, however: was it necessary and possible for health facilities to provide directly observed treatment throughout, and in all cases, if the 6-month regimen was adopted? Doing so, some argued, would be made easier by intermittent treatment. Or, were the programs now robust enough to allow the use of self-administered rifampicin in the continuation phase? Finally, there was the matter of a regimen for failure cases; if a 6-month regimen was administered to new cases, failures would increasingly be resistant to both rifampicin and isoniazid.

Adapting the recommendations

In 1991, the Orange Guide warned of increased risk of adverse reactions to thioacetazone in HIV-infected patients. The Guide urged discontinuing use of the drug with patients who had demonstrated such reactions and suggested substituting it with ethambutol.[36] It also encouraged medical practitioners to consider using the 8-month regimen for all seriously ill HIV-infected patients, regardless of sputum status. In 1996, a clause was introduced recommending that treatment of HIV-infected tuberculosis patients be modified to avoid the risk of serious adverse reactions to thioacetazone among those with HIV.[47] In 2000, the wording was intensified: thioacetazone should never be given to patients known or suspected of having HIV infection.[15]

In 1996, the Orange Guide cautioned that if ethambutol was used routinely in the continuation phase in treatment of new cases, pyrazinamide should be used throughout treatment in the regimen for previously treated cases.[47] Hence, with pressure mounting in the mid-1990s to end the use of thioacetazone, The Union found itself forced by circumstances to adapt the treatment algorithm without satisfactory alternatives. Although some programs might at least partly (that is, in selected settings) be ready to use the 6-month regimen, it was considered necessary to have an alternative short-course regimen with rifampicin in the intensive phase only and thus ethambutol, replacing thioacetazone, as a drug to accompany isoniazid in the continuation phase. At the same time, The Union had established a multi-center, randomized clinical trials network where current and future alternatives could be tested. Such a network had clearly become essential to aid future policy development.

In 1997, the results of a randomized clinical trial undertaken by the Tuberculosis Research Center in Chennai, India, found that of 305 fully susceptible cases

treated with 2EHRZ/6HE, 3.6% had an unfavorable outcome (failure or death), and 15/290 (5%) relapsed after completing treatment.[146,147] Of 94 isoniazid-resistant cases, 16 (17%) had an unfavorable response and 6/73 (8%) relapsed. Overall, in a group with 24% isoniazid resistance, 6.8% had an adverse outcome and 5.8% relapsed. This trial, however, did not include a gold standard regimen as control but rather a fully intermittent 6-month regimen with treatment administered twice a week. In The Union's clinical trials network, a multi-center, randomized trial recruiting previously untreated smear-positive patients from 1998 to 2001 compared 2EHRZ/6HE with daily therapy versus intermittent therapy (three times a week) in the intensive phase to a gold standard 6-month regimen (2EHRZ/4HR). Treatment was directly observed in the intensive phase and self-administered in the continuation phase. The results, published in 2004, showed the latter to be superior (5% adverse outcome*) to the 8-month regimens (10% adverse outcome in the daily and 14% in the intermittent regimen).[106]

In conclusion, the implications of the HIV pandemic for the treatment algorithm were primarily twofold. First, the introduction of ethambutol in the intensive phase of the 8-month regimen for new cases (2EHRZ/6HT), and even more so in the continuation phase (2EHRZ/6HE), compromised the regimen for previously treated cases. Second, the weakening of the original algorithm called for a more radical change, namely the introduction of the 6-month regimen in treatment of new cases. The argument against adopting the 6-month course under these conditions is that whereas a good program can safely use a 6-month regimen, a weak program might still need to rely upon an 8-month regimen and evaluate outcomes before making a decision to adopt the 6-month regimen. Not all experts agree here, which is not surprising since the problem is complex.

Policy development

8-month versus 6-month regimens

Some countries provoke concern over their use of a 6-month regimen with rifampicin throughout. The classic example cited is Ivory Coast, but other examples can be found as well. Rifampicin was introduced in the Ivory Coast in 1985, the same year as the national program was established.[121] The prevalence of any drug resistance in previously untreated cases in the Ivory Coast was reported to be 13.4%, and that of multidrug resistance was 5.3%, according to a survey conducted in 1995–1996.[148] Drug resistance in previously treated cases was not measured in the survey. A retrospective study in Chiang Rai, Thailand,

*Adverse outcome defined as failure or relapse in the study.

which looked at patients registered on at least two occasions from 1996 to 2000, suggested that on a 6-month regimen, seven out of eight cases resistant to either isoniazid or rifampicin acquired multidrug resistance.[149] How high this proportion is in different settings is likely to depend on the quality of the program, and how much of a problem it represents at the program level would depend on the prevalence of resistance in previously untreated cases. The above study concluded that an isoniazid drug resistance level of 6% among new cases—which was the level reported in northern Thailand—was not a problem. A study carried out from 1998 to 2000 of a random sample of patients in an inner city area within Ho Chi Minh City, Vietnam, where there were high levels of both isoniazid resistance in new cases (25%) and of combined resistance to isoniazid and streptomycin, reported an increased risk of multidrug resistance in previously treated cases in districts using a 6-month as opposed to an 8-month regimen.[150] Doubts have been raised recently (2006) in Bujumbura, Burundi, as well, urging that longitudinal studies be undertaken to document the effectiveness of programs using a 6-month regimen in new cases.[151]

Examples of seemingly successful programs using 6-month regimens exist as well. One such example is Botswana, a small country with well-developed health care and one that is relatively rich compared to most African nations. A national tuberculosis program was established in Botswana in 1975, and rifampicin was introduced in 1986.[152] In spite of a sharp increase in tuberculosis cases following the HIV pandemic, a national survey from 1995 to 1996 found low levels of drug resistance. The prevalence of any drug resistance in new and retreatment cases was 3.6% and 14.9%, respectively, and that of multidrug resistance was 0.2% and 5.8%.[152] Although drug resistance levels remained low in repeated surveys in 2000[153] and 2002,[154] drug resistance of any kind in new cases increased significantly (increase in multidrug resistance in new and retreatment cases was not significant).*

For programs still using an 8-month treatment regimen, it is interesting to contemplate why, when, and how to change to the 6-month regimen. The obvious advantage of 6-month regimens is the lower failure and relapse rates in clinical trials. Some, however, claim that such a change is likely to improve treatment results in settings with high defaulter rates. This is debatable. One could in fact argue that only when treatment results are good with an 8-month regimen is it safe to introduce the 6-month regimen, either in selected areas or countrywide. Only then would the benefits of the 6-month regimen over and above those of the 8-month regimen—lower failure and relapse rates—actually be realized without the potential drug resistance risks of the 6-month regimen.

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*Of the 145 retreatment cases in the drug resistance survey in Botswana in 2000, 90 (62%) were relapses, 19 (13%) treatment after failure, 35 (24%) returning defaulters, and one chronic.[153]

As always when contemplating changes in the treatment algorithm, a logical first step is to carefully consider, in light of the local circumstances, the pros and cons of changes.

Previously treated cases

When a good treatment program has been implemented for some time, the assumption that previously treated cases have a high prevalence of drug resistance may not hold true equally for all categories of previously treated cases in all settings. In a well-organized treatment program, for example, relapses after 8-month treatment for new cases may have different drug susceptibility rates than failure cases. Patients returning to treatment after default constitute a variable proportion in programs, depending on the frequency and timing of default, and drug resistance in these cases is likely to vary according to the operational characteristics of programs. In most settings, the prevalence and pattern of drug resistance in this group is not well known. In some settings, a high proportion of these cases are patients who have been partially treated in the private sector. To give an example, a study of 165 cases registered as returning after default in five districts in Rajasthan, northern India, in 2003, found that 85% had been treated in the private sector.[155] In the programs collaborating with The Union, it was not feasible—and probably not important—at the outset to try to tease out which previously treated cases should be assumed drug-resistant. In the early phase of the programs, unreliable subclassification of previously treated cases might result from staff inexperience and the previously chaotic organization of treatment, thereby leading to misclassified patients. For that reason, all previously treated patients were enrolled on the same treatment regimen. If anything, this probably resulted in over-treatment in a number of cases. It should be expected that, at some point in a program's maturation, it becomes feasible to subclassify previously treated cases and to study drug resistance patterns in the different groups to guide policy development.

Previously treated patients who return might not be drug-resistant if they participated in programs that are organized well, feature regular treatment, and particularly programs that use directly observed treatment, as in the model. Table 3.1 (above) shows the results in previously treated cases in Nicaragua by category of case. Relapses have treatment outcomes similar to new cases, suggesting they have benign drug resistance and are curable with the retreatment regimen. Returning defaulters are likely to default again and primarily need more support for adherence; additionally, drug susceptibility should be studied in this group of patients at the program level. Finally, those who failed treatment as new cases have, as a group, a higher failure rate than the other categories, indicating more serious drug resistance (albeit not a high prevalence). Those who fail on the regimen for previously treated cases would be candidates for treatment with second-line drugs, were such a strategy adopted.

HIV-positive patients

In 2001, Harries et al., in Malawi, argued that it was important to assess the optimal duration and type of tuberculosis treatment for the first episode of tuberculosis in areas with high HIV prevalence.[156] There was substantial pressure on program administrators to adopt a 6-month regimen with rifampicin throughout. Although functional monotherapy in the continuation phase has not been considered a serious problem (when following a potent intensive phase), this consideration may need to be re-evaluated in HIV-positive cohorts. In this context, it has been argued that the utilization of isoniazid and rifampicin in the continuation phase (particularly if intermittent) should be discouraged in settings where second-line drugs are not routinely available for treatment after failure, particularly if HIV infection is prevalent in the patient population and there is considerable resistance to isoniazid.[157]

Summary and conclusions

Contentious issues appear at every turn regarding operational strategies in tuberculosis programs. Agreed strategies for case finding within the health services dictate that patients with coughs of at least two to three weeks' duration submit at least two sputum specimens for acid-fast microscopy. In the absence of other evidence, a positive smear needs to be confirmed according to the policy model. The importance of this step has been debated. The significance of a single scanty-positive sputum smear in the process of assessment of a patient with cough is another source of dispute. In patients with negative sputum examination, algorithms assist the diagnosis of smear-negative tuberculosis. Strategies for active case finding other than contact investigation, although frequently recommended, have not been proven feasible or useful in routine settings in high-prevalence countries. In pluralistic health systems, coordination between different care providers is likely to yield more in terms of increasing case detection or notification than community-based case-finding surveys. This is discussed in Chapter 7.

The treatment algorithm used in the programs collaborating with The Union is an illustration of how evidence is used by policy makers. In the context of the collaborative programs, they opted for an inferior treatment regimen as judged by technology assessment. This was over concerns that the more efficacious regimen was inappropriate and potentially dangerous in settings where the programs were implemented; that is, it might paradoxically result in lower quality intervention. At the time, cost was also a consideration: the more efficacious 6-month regimen was considerably more expensive than the 8-month regimen. A more important matter, however, was operational feasibility—it was deemed impossible to administer directly observed treatment

for six months, and unsafe to prescribe rifampicin for self-administration. In the 8-month regimen, rifampicin was used only during the intensive phase of treatment, and thus treatment could be self-administered in the continuation phase. However, the 8-month regimen was modified in cases considered to be at risk of adverse outcome, as discussed in Chapter 4. Furthermore, there was a highly efficacious regimen for those not permanently cured in the first attempt.

The treatment algorithm was carefully and meticulously thought through. It was a wise policy given the time, place, and overall context. It was designed for developing nations with a high prevalence of tuberculosis before the onset of the HIV pandemic. Rifampicin was expensive and had not been used widely in the collaborating countries, and there was no multidrug resistance to speak of. The health services were not uniformly well developed, and the skills of peripheral health workers often limited. In a different time and location—such as one with a high prevalence of HIV infection and/or multidrug resistance—the original treatment algorithm is no longer justifiable. However, there is nothing to suggest that in comparable settings the original algorithm should not be employed.

Some public health professionals contend that the policy model is too demanding and complicated for tuberculosis programs in high-prevalence countries. Reasonable simplifications have been proposed, such as reducing the number of smears in the process of sputum examination and using a single treatment regimen for all except treatment failure cases.[158] For the former, there is already sufficient evidence. The latter would require prior studies of prevalence of drug resistance in all categories of previously treated cases in the local setting.

In the countries collaborating with The Union, rifampicin and, to a lesser extent, pyrazinamide, were probably used prior to the implementation of the policy model, but this was on a very limited scale and resistance to these drugs was not a problem. In this respect, the context was different from that of many of the settings where the WHO later introduced the DOTS strategy, and the DOTS strategy also introduced changes in the treatment algorithm. In recent years, drug resistance has increased in numerous countries, significantly complicating tuberculosis treatment in those areas hit worst. Basic research and clinical trials have not kept up with the need for new drugs and alternative drug regimens. Furthermore, the prevalence and patterns of drug resistance are not always known in problematic areas. The enthusiastic expansion of the DOTS strategy may have led to inadequate responses in policy development and program evaluation as regards drug resistance. This issue will be discussed further in Chapter 6. First, however, the next chapter will look at what happens after the recruitment of cases and review operational strategies for case management and accountability.

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4

Case management and accountability

Questions surrounding tuberculosis reveal much about societies as well as health systems and services: Who suffers from the disease? How do they fare? The answers offer a wealth of information.

The previous chapter examined operational strategies for recruitment of cases and the treatment algorithm in the policy model. This chapter explores case management strategies and accountability. As before, the focus remains on public health and communicable disease control.

Case management

The term "case management" is used to describe the process that follows the diagnosis of tuberculosis and aims to cure without relapse. This process can be divided into classification of cases using case definitions, registration and assignment of treatment regimens, administration of treatment, monitoring response to treatment, and discharge from care.

Case definitions

To facilitate surveillance, case management, and evaluation, it is convenient to standardize case definitions and outcome analysis at the national and even international level. Case definitions, though, depend on diagnostic tests and procedures that may differ among countries. As an example, a smear-positive case of pulmonary tuberculosis in a setting where concentration of sputum samples is routinely performed is not exactly the same as one where this is not practiced, since the procedure changes the sensitivity of the microscopy examination. Similarly, case definitions are likely to change when new diagnostic tests are introduced. If case definitions are linked to treatment, this matter may be even more complex.

As discussed in Chapter 8, definitions of tuberculosis cases in the policy model take into account localization of disease (pulmonary and extra-pulmonary),

smear status (smear-positive and smear-negative), and previous treatment history (new and previously treated). The public health implications of smear-positive pulmonary tuberculosis have it override any other case definition as far as priority for notification and case management are concerned.* (The justification for differentiating smear-positive and smear-negative pulmonary tuberculosis is discussed in Chapter 3.)

Early studies found that patients with a history of previous treatment were more likely to have drug-resistant disease,[1] and that such patients fared less well on treatment.[2,3] Clinical studies suggested that drug resistance usually appeared only after the first month of treatment in patients with initially sensitive organisms.[4] In a study in Madras in the 1950s, resistance appeared within the first two months of treatment in only one of the 27 cases who eventually developed resistance to isoniazid on a regimen with PAS and isoniazid.[2] Further studies supported the notion that rarely did drug resistance appear in the first month of treatment.[5] In studies of the early bactericidal activity of drugs and drug combinations in Nairobi in the 1970s, only one out of 120 patients developed resistance to isoniazid within the study period of 14 days.[4] These observations influenced early case management and treatment practices.

In the policy model, a new case was defined as a patient who has never been treated for tuberculosis before or who has received treatment with antituberculosis drugs for less than one month.[6,7] At the time, drug resistance was usually to a single drug only, most commonly isoniazid, but resistance to streptomycin was also seen. With the implementation of more potent treatment regimens, such as short-course treatment with four drugs in the intensive phase, drug resistance was much less of a problem than before, particularly if a 6-month regimen using rifampicin throughout was used. It can be argued that in the Union model, the definition of a new case and the policy of a different treatment regimen for previously treated cases were primarily explained by the relatively weak first-line regimen applied in the programs (see Chapter 3). Thus, it seems that the case management strategy, if not the case definitions, ought to be revisited if a different treatment regimen is chosen. Furthermore, the prevalence and patterns of drug resistance have changed over time, rendering the definitions and treatment recommendations controversial in the worst-hit settings.

As discussed further on, three categories of previously treated cases were distinguished in the Union model: relapse, treatment failure, and return after default. Finally, while previously the term "chronic excretor of tubercle bacilli," and later simply "chronic cases," was vaguely defined,[6] since 1991 the term has

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*Only disease involving the lung is classified as pulmonary tuberculosis. This excludes pleurisy and tuberculosis of hilar lymph nodes, unless there is concomitant involvement of the lung.

been used for those who are smear-positive after having completed the regimen for previously treated cases.[8]

Assignment of treatment regimens

Although in the Union model the short-course regimen for new cases was intended primarily for smear-positive cases, it was used for severe forms of smear-negative and extra-pulmonary tuberculosis as well. Similarly, the 12-month regimen, primarily intended for smear-negative (unconfirmed) tuberculosis, was also used for new smear-positive cases in areas that had not yet implemented short-course treatment (that is, those still in the expansion phase) and for patients who for some reason could not abide by directly observed treatment.

The regimen for previously treated cases was reserved for smear-positive patients. Styblo's position was that although smear-negative pulmonary or extra-pulmonary cases might also be failure, relapse, or chronic cases, such instances were likely to be rare, and only with proven evidence of active tuberculosis were they to be addressed with the regimen for previously treated cases.[9] It can also be argued that in cases of smear-negative or extra-pulmonary tuberculosis that apparently fail or relapse, the original diagnosis may have been wrong. Great care should be taken in differential diagnosis before initiating retreatment for tuberculosis in such cases. This is an example of an issue in which standardization is not justified. Accordingly, such cases should be referred to a specialist for differential diagnosis and/or confirmation of tuberculosis lest, for example, a patient with Hodgkin's lymphoma be enrolled in retreatment as extra-pulmonary tuberculosis. Finally, post-tuberculosis sequelae following extensive smear-positive pulmonary tuberculosis are frequently confused with smear-negative relapse, and constitute an example of a case that merits careful diagnostic work-up before retreatment for tuberculosis is initiated.[10] In tuberculosis programs, it is important to decide when case management can be standardized and treatment initiated by paramedics, and when not.

Drug dosage

In the early studies, in India, drug dosages were calculated according to pre-treatment body weight and adjusted upward in the event of weight gain but not downward for weight loss.[2,11] In the Union model, drug dosages were based on pre-treatment body weight but were not changed in case of weight gain.[6]

Hospitalization and isolation of patients

In the 1950s, tuberculosis patients in industrialized countries were hospitalized. During this period, it was estimated that there were 2.5 million cases in

India for the 23,000 sanatorium beds in the country, and it was clearly not realistic to hospitalize patients for treatment of pulmonary tuberculosis.[2] At the same time, there was concern that domiciliary treatment might be inadequate. Three issues can be identified in this context: immediate infection control and protection of family contacts, the best interest of the patient, and the long-term prospects regarding disease control, the primary concern being acquired drug resistance.

Immediate infection control

In 1960, Andrews et al. reported the results of a randomized trial of tuberculosis treatment in a sanatorium versus treatment at home, comparing the attack rate in contacts.[12] The trial was undertaken in Madras City, India, in the late 1950s. The attack rate was similar in both groups of contacts, and most of the cases among contacts arose in the first three months, half of them in subjects already tuberculin-positive and therefore infected before the index case was enrolled in treatment. In keeping with these findings, Crofton observed in 1962 that for preventive purposes it was not essential to admit patients to hospital until sputum conversion to negative was achieved.[13] In 1966, Kamat et al. reported a follow-up of the Madras trial, concluding that the incidence of active tuberculosis and of tuberculosis infection was no greater in close family contacts* of tuberculosis patients treated at home than in the contacts of patients treated in a sanatorium, either in the first year or in the subsequent four years.[14] This was before short-course treatment was introduced and among poor living conditions where the majority of homes were overcrowded and nutritional status was low. Among those originally tuberculin-negative, 10.5% of the contacts of home patients and 11.5% of the sanatorium patients developed active tuberculosis within the study period (five years). Of contacts who were initially tuberculin-negative in both series, 40% to 50% converted to positive. It seemed that contacts not infected at diagnosis of the index case rarely became infected by the index case later on, but rather became infected from other sources of infection in the community. Finally, a further study in Madras (1970) concluded that, in domiciliary treatment programs, the attack rate of tuberculosis in contacts did not appear to be influenced by the duration of positive smear status in the index case during treatment or resistance to isoniazid.[15]

In 1974, Riley and Moodie reported the results of a study in inner city homes in Baltimore, Maryland (U.S.), where they compared infectivity of pulmonary tuberculosis patients for their household contacts before and after initiation of treatment.[16] Of the 65 index cases identified, 8 (12.3%) had no household contact, and 12 (18.5%) had no tuberculin-negative household contact at diagnosis:

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*In this study, close family contact was defined as related by blood or marriage, cooking and feeding in the same hut or house as the index case for at least the three months immediately prior to the start of treatment of the index case.[14]

they thus either never had a potential for infecting household contacts, or at least they did not by the time they were diagnosed. In 5 cases, the contacts refused to participate in the study, and 13 index cases were disqualified. Consequently, 27 households with 70 non-reactive contacts were included in the analysis. The study suggested rapid loss of infectivity after treatment—which did not include rifampicin—was started. None of the non-reactive contacts converted.

Studies of early bactericidal activity of anti-tuberculosis drugs, conducted in the 1980s, supported this view. Such surveys found that the number of tubercle bacilli in sputum, as demonstrated by growth in culture, decreased impressively in the first two days: tubercle bacilli dropped by as much as 25 times with a four-drug regimen including pyrazinamide, and by 99% in the first two weeks of treatment.[4] It was also documented that cough diminishes rapidly on treatment, resulting in reduced infectivity.[17,18] Thus, evidence from different settings and different studies suggested that most contacts were infected before diagnosis and treatment of the index case.[19] This conclusion had implications concerning discrimination against tuberculosis patients—for treatment of tuberculosis in general hospitals, for advice concerning interpretation of bacteriological examination for the discharge of patients from hospitals, and for their return to work. It has been argued, however, that these findings also resulted in a dogmatic protocol, namely that treatment should be administered on an ambulatory basis, and that tuberculosis patients should not be hospitalized, which was not the intended message.

Whereas the findings concerning the infectivity of patients on treatment have been widely used to reduce the duration of hospital respiratory isolation and to support ambulatory treatment of tuberculosis, they also might suggest that the need for directly observed treatment to prevent drug resistance is diminished early in the intensive phase of treatment (after two to four weeks). However, the rapid fall in the number of bacilli is not irreversible and may be followed by a rise in bacterial count if treatment is stopped or becomes irregular, a possibility that supports the need for more prolonged supervision of treatment.

The issue of infection control strategies and respiratory isolation in hospitals later resurfaced in situations where many hospital patients were HIV-positive and multidrug-resistant tuberculosis was a problem. These scenarios, it was argued, required a reconsideration of the issue of hospital infection control strategies. The traditional view that two weeks of treatment are adequate to render a patient noncontagious was disputed.[20] Skeptics pointed out that, in the setting of the Madras study, infection risk and community transmission was very high and may have obscured the picture,* and that if family contacts

*Cases of tuberculosis arising in family contacts can be attributed to infection from one of four sources: the index case before diagnosis, the index case during treatment, or other sources, common or different.[15] Other environmental sources are likely to be more important when the risk of infection in the community is high, as in the case of India at the time of the study.

are HIV-positive they may become infected even if a tuberculosis patient is less infectious after two weeks of treatment.[20] In 1996, researchers conducting a small bacteriological study of ten elderly South African patients with cavitary tuberculosis argued that negative sputum smears are a delayed but reliable indicator of disease control, and that patients with cavitary tuberculosis, until their smears and cultures are negative, should not be allowed in an environment where there might be immunocompromised individuals.[21] Others point out that the number of viable bacilli in sputum is not the only concern when assessing infectivity: factors such as symptoms (cough), hygienic measures (covering the nose and mouth when coughing), and environmental factors (ventilation) are also important, and a decision regarding the infectiousness of any given tuberculosis patient must be individualized for that patient.[22] Nevertheless, the U.S. Centers for Disease Control and Prevention currently recommends that, in hospital settings, isolation of smear-positive tuberculosis patients be lifted only when the patient is on treatment and improving clinically, and three consecutive sputum smears collected on different days are negative.[23]

The best interest of the patient

The Madras studies of the 1950s also compared the outcomes of domiciliary treatment with sanatorium treatment, concluding that despite the apparent advantages of sanatorium care (rest, adequate diet, nursing, and supervised medicine-taking), the results of domiciliary treatment were comparable. Provided adequate services were established, it was therefore reasoned to be appropriate to treat the majority of tuberculosis patients at home.[2] Although policy makers at the national and international level jumped to embrace these findings, they largely ignored the stipulation that adequate services be available for at-home care.

Almost 200 patients were recruited in Madras. Of these, 96 received at-home treatment, and 97 received sanatorium treatment. The patients were selected according to strict criteria in a one-year period (from 1956 to 1957) from those attending at local chest clinics in what was deemed an adverse urban environment. The treatment program was quite generously funded, having 100 staff members, eight cars, and a fund for financial assistance to patients and their families.[2] Treatment included PAS and isoniazid in two daily doses for 12 months. The majority of the patients who received home treatment attended the clinic every week throughout the 12 months. In addition, a health visitor (or, less regularly, a doctor or a public health nurse) usually paid a weekly visit to the patient's home during the first month, with less frequent visits in later months. The all-cause adverse events were more frequent in the domiciliary group. Culture conversion tended to occur later in those treated at home than in those treated in a sanatorium (50% versus 68%), and acquired drug resistance was seen more often, but not significantly so, statistically speaking.

Treatment at home was less regular but this seemed not to influence outcome of treatment.[2,24] The investigators, however, commented that a level of irregularity below which outcomes would be affected must exist. The study did not look at post-treatment relapse rate in the two groups, an important limitation. On the other hand, treatment at home carried certain advantages: it was easier to persuade the domiciliary patients to complete the 12 months of treatment (there was serious disruption or default in 12/97, or 12%, of sanatorium patients but only 1/96 in those treated at home), and domiciliary treatment was less disruptive for the families.[2] There was optimism that with earlier diagnosis and a more potent treatment regimen, the results in home treatment would be better than was the case in the study.

Future disease control

Whereas the findings of the Madras studies are frequently quoted to provide support for ambulatory treatment, the investigators warned that certain minimal requirements needed to be met when organizing mass chemotherapy programs based on this concept. These prerequisites included an adequate supply of medicines, an alternative treatment regimen for patients not responding satisfactorily, sufficient staff to supervise the patients (including social workers and public health nurses), efficient appointment and tracing systems, adequate transport, a small number of hospital beds for gravely ill patients or complications during treatment, a good quality laboratory for sputum examination, and a welfare fund for patients in particular need.[2] From their report, it can be understood that successful domiciliary treatment was unlikely if these requirements were not met. A mass treatment program with insufficient resources and organization could do more harm than good, namely to create a problem of acquired drug resistance.

Policy making

In policy making, one needs to consider the many different circumstances surrounding tuberculosis as a public health concern. Rather than issuing a uniform recommendation of "all ambulatory" or "all hospitalized" care, the organization of treatment administration ought to be a local decision, taking note of local conditions in both urban and rural areas. Although, generally speaking, the evidence showed that uniform hospitalization was necessary for neither infection control strategies nor cure, this was not to say that there was no need for hospital beds in the treatment of tuberculosis.

In 1967, Moodie claimed that "comprehensive orthodox tuberculosis control programs" were obviously impossible in developing countries due to high disease burden and scarce resources.[25] Thus, in Hong Kong it was decided to establish a clinic-based program for implementation of partly or fully supervised ambulatory treatment, which employed paramedical personnel to make up for

the shortage of fully qualified staff, and used the few available hospital beds in a supportive role only.[25] This was truly a mass treatment program—12,000 patient visits per week were registered in the clinic. Clinic opening hours were adapted to the needs of the patients rather than the personnel, waiting time was kept to a minimum, and a designated doctor followed each patient throughout treatment. One physician followed up to 1,500 patients under treatment as well as carrying out diagnostic functions, and supervised paramedical personnel. Treatment was administered by nurses almost as if on a production line; the treatment cards were kept by the patients themselves.[25] According to district caseloads, centers that were used only for the administration of treatment were set up in various parts of the city, using already established clinics and other available health facilities whenever possible. A tracing system was put in place and set in action whenever a patient missed three successive days of treatment. Later, fully supervised, intermittent short-course regimens were developed, tested, and implemented in Hong Kong.

How, then, were the hospital beds used in Hong Kong? One hospital bed dedicated for every ten patients enrolled in treatment fully met the program's needs. Patients giving a definite history of prolonged previous treatment of doubtful quality (presumptive drug-resistant cases), patients whose sputum remained positive after 24 weeks in treatment, and patients who showed a poor attendance record on ambulatory treatment or who lived far from a treatment center were all hospitalized.[25]

When short-course treatment was implemented in the early 1980s in the programs collaborating with The Union, it was not considered safe to treat each and every patient on a domiciliary basis. The study in Madras was carried out in an urban setting,[14] and the Hong Kong experience was also taken from a predominantly urban setting with a very high population density.[25] In contrast, in Africa at the time, typically 85% of the population lived in rural areas with low population density and scarce health services infrastructure. It was decided that there, hospitalization had to be kept as an option when supervised treatment could not be guaranteed on an ambulatory basis, which in some areas was the rule rather than the exception. This is not to say that hospitalization was necessarily forced on patients; an option of self-administered 12-month treatment remained available. Mitchison has characterized this decision (in his words "the insistence on the requirement to treat patients initially in hospital") as a "retrograde step" and a mistake.[26] Nevertheless, some countries have opted for a similar strategy as the programs collaborating with The Union, using hospitalization to supervise treatment. As an example, when short-course treatment was implemented in Cambodia in 1994, 75% of the patients were hospitalized during the intensive phase of treatment.[27]

Looking at cost-effectiveness, the evidence on hospitalized versus ambulatory or outpatient treatment is mixed, but where the hospitalized version is

superior according to the provider's perspective, it may not be so from the patient's point of view.[28] In 1991, the World Bank studies conducted in the African countries collaborating with The Union concluded that hospitalization could improve the cure rate and thus be cost-effective.[29] These studies did not take into account direct and indirect costs of hospitalization incurred by the patients, an important weakness.

Operational features of drug regimens

The discovery that anti-tuberculosis drugs could and should be administered in a single daily dose considerably simplified the organization of treatment. In the programs collaborating with The Union, treatment was administered on a daily basis, with the exception of the continuation phase of the regimen for previously treated cases. A health worker supervised the treatment originally whenever streptomycin was administered, and later on, with implementation of short-course treatment, whenever rifampicin was administered. This was done to guarantee that all drugs were taken simultaneously, in the correct dosages, and by the correct patients. When streptomycin was part of the treatment, tablets were to be swallowed at the time of the streptomycin injection. Treatment could be omitted on Sundays if necessary.[6,30] Treatment was self-administered in the continuation phase of the short-course regimen. In this case, the patient was usually given a month's supply of drugs at a time and instructed to return when the supply was finished rather than on a certain date. Thus, patients who attended late obviously did not take the drugs daily, thereby signaling irregularity in treatment.

According to Styblo, the continuation phase of the regimen for previously treated cases was intermittent (three times a week) only if it could be fully supervised. Otherwise, treatment was to be daily, which was a good deal more expensive.[9]

Intermittent treatment

The origin of intermittent therapy dates back to Madras in around 1960.[5,31] According to Fox, supervised intermittent chemotherapy was shown to be an effective alternative to self-administered daily treatment, and as such improved the control of chemotherapy.[32] It also reduced the risk of drug toxicity. Intermittent treatment was used selectively by Sbarbaro in "skid-row" populations in the United States as early as 1965, and it was adopted in Czechoslovakia in 1972.[32] Finally, intermittent treatment was recommended in the report of the Expert Committee of 1974.[33]

Intermittent regimens (12 months of twice-weekly treatment with streptomycin and isoniazid) were used as early as the 1960s. Later, short-course regimens with intermittent application of drugs were studied. Whereas both the

twice- and thrice-weekly application were studied, the only intermittent short-course regimens the WHO recommends rely on thrice-weekly application in the continuation phase.[34,35]

Intermittent treatment was originally developed to make supervised treatment easier by reducing the number of appointments during care. Now, as then, intermittent treatment is a tempting strategy not only because of easier supervision, primarily in urban areas, but also because it is cheaper (in terms of drug cost). The Committee on Treatment of The International Union Against Tuberculosis and Lung Disease in 1988 warned, however, that intermittent treatment should not be used purely as a cost-saving measure;[36] instead, such treatment must be fully supervised, which also incurs cost.

In 1970, it was pointed out that the studies on intermittent treatment did not separate the contributions of intermittency and supervision because the intermittent regimens were all fully supervised.[37] In 1999, an operational evaluation of a partly supervised, fully intermittent (three times a week) 6-month short-course regimen in Sulawesi, Indonesia, referring to patients registered from 1993 to 1997, reported good results.[38] Treatment was directly observed once a week in the intensive phase and once a fortnight in the continuation phase, but was otherwise self-administered. The main concern with such a strategy is development of acquired drug resistance. Ideally, outcome measures would include relapse and acquired drug resistance rates, but for this study, smear conversion (at two months in new cases and at three months in retreatment cases) and treatment success rate were the outcome measures used. A later study in Sulawesi found high relapse rates (7%) in new smear-positive patients registered for partly supervised, fully intermittent treatment with a 6-month short-course regimen from 1999 to 2001 (the findings of this study were inconclusive but suggested that relapse might be related to the use of four-drug fixed-dose combinations).[39]

Whereas it was recognized that intermittent regimens might facilitate implementation of directly observed treatment programs in urban areas, recommendations concerning intermittent treatment were in fact cautious, and daily treatment was considered safer for self-administered treatment. The Union was reluctant to approve intermittent treatment in the intensive phase within developing countries and never endorsed twice-weekly regimens. It is generally accepted that as many as 50% of patients miss an occasional appointment for medication. In twice-weekly regimens, there is no safety margin. If a dose is missed, a patient receives only a single one in a week; if a dose is delayed, there is an unacceptably long interval between doses. Either interruption invites the possibility of developing drug resistance. Consequently, it seems controversial to recommend twice-weekly regimens except in settings where regularity of treatment is guaranteed (for example, in clinical trials). In a multi-center, randomized controlled trial reported in 2004, a regimen with a daily intensive

phase (two months) with EHRZ was shown to be superior to a regimen with an intermittent (three times a week) intensive phase in terms of culture conversion (86% versus 77%).[40]

Fixed-dose combinations

Fixed-dose combinations of anti-tuberculosis drugs were introduced as a safety mechanism in the programs collaborating with The Union, as discussed in Chapter 9. The possibility of confusing fixed-dose combinations of rifampicin and isoniazid for single preparations of rifampicin poses the threat of causing errors in treatment.[41] No such risk existed in programs assisted by The Union because rifampicin was only available in a fixed-dose combination, and the isoniazid tablets procured for the programs (and used, for example, in preventive chemotherapy) appeared quite different from the fixed-dose combination.

Blister packs

Although blister calendar packs may facilitate logistical and handling procedures, Trébucq has pointed out that the notion that they enhance treatment completion is unfounded.[42]

Injections

Streptomycin, the sole essential anti-tuberculosis agent available only as a parenteral drug, was part of all treatment regimens originally introduced in the programs collaborating with The Union. This was considered an advantage; at the time, it was widely believed that patients in developing countries placed a greater value on treatment with injections than treatment with tablets. It was thus convenient to use the streptomycin injections as a justification for hospitalization or daily attendance at a health facility for supervision of treatment, and this practice was widely employed. The mounting prevalence of HIV infection in African tuberculosis patients made use of injections in the programs contentious. At the early stages of the pandemic, in the 1980s, the issue of proper sterilization was emphasized,[43] and in 1991 the requirement of "one needle and one syringe for one injection" was adopted.[8] Injectable drugs were regarded with considerable unease, and their use threatened to become a logistical nightmare. Programs in countries with high or increasing HIV prevalence needed to discontinue injections. Elsewhere, program administrators, expecting the worst, sought to phase out injections as well as part of their preparedness strategy. Replacing streptomycin with ethambutol, an orally administered drug, in the intensive phase of the short-course regimen for new cases was the alternative. This substitution was not thought to negatively affect the efficacy of the regimen. The issue of adherence and treatment supervision, however, remained. The findings of a U.S. study from the 1970s had suggested that injections promoted superior clinic attendance.[44]

Box 4.1 Injections and adherence to anti-tuberculosis treatment

In a retrospective study in Tanzania, referring to the period from 1992 to 1993, the expected and observed attendance of patients was measured at two outpatient clinics in Dar es Salaam.[45] Expected attendance was daily in the first month and three times a week in the second. The unit of measurement was the number of expected patients each day, that is, group attendance. No significant difference was observed in attendance between periods when patients always and never received streptomycin injections as part of directly observed treatment in the intensive phase of treatment. If anything, it seemed that attendance increased during periods without injections in one district. The authors speculated that this might be a result of reduced waiting times.

In a before (1992) and after (1993–1994) comparison of hospitalized intensive phase treatment of new smear-positive patients in Cotonou, Benin, no difference was observed in defaulter rate at the end of the intensive phase.[47]

In a qualitative study from Vietnam's Quang Ninh Province (1996), patients expressed fear of injections as one reason for nonadherence.[46]

A randomized controlled trial (1,023 patients recruited in 1994–1995) in urban settings in Madagascar compared treatment efficacy and tolerance of 8-month regimens, including either streptomycin (SHRZ) or ethambutol (EHRZ) as a fourth drug in a fully supervised intensive phase of treatment of new smear-positive cases.[48] There was no significant difference between the regimens with regard to compliance with treatment, the number of patients lost or who died, or bacteriological response (sputum smear microscopy) during the intensive phase. The combination of EHRZ was better tolerated. The results of the two groups remained comparable during the continuation phase. Compliance was considered good when the patient received the full course of treatment, and overall absence did not exceed seven days in the intensive phase and 30 days in the continuation phase (treatment was extended accordingly). Overall, 192 patients (19%) were lost during follow-up (one fifth of these in the intensive phase) and 4% died. Of those alive at two months, 22% were still smear-positive.

Operational studies were conducted to examine the role of injections in adherence to tuberculosis treatment (Box 4.1). These studies were directed at patient adherence measured by treatment regularity and dropout rates rather than the adherence of health personnel to the policy of direct observation of treatment. These studies showed that injections were not important for patient adherence. If anything, the results suggested the contrary—that injections might actually reduce adherence.[45,46]

Eventually, more and more programs replaced streptomycin with ethambutol in the intensive phase of treatment of new cases. The process of changing the short-course regimen for new smear-positive cases in Nicaragua is presented in Box 4.2. As opposed to treatment of new cases, there was no obvious alternative to streptomycin in the retreatment regimen. With the change in

Box 4.2 Replacing streptomycin with ethambutol in short-course treatment for new smear-positive cases in Nicaragua

In the early 1990s, 67% of new cases reported to the tuberculosis program in Nicaragua were pulmonary smear-positive cases, and 33% were pulmonary smear-negative or extra-pulmonary cases. Of all cases registered in the program, 11% were previously treated. It was estimated that 65% of the streptomycin used in the program was dedicated to short-course treatment of new cases, 24% to treatment with the 12-month regimen, and 11% to treatment with the regimen for previously treated cases. The estimate assumed that 95% of new smear-positive cases were enrolled in short-course treatment (and the remaining 5% in the 12-month regimen), and 30% of smear-negative and extra-pulmonary cases were enrolled in short-course treatment (the remaining 70% in the 12-month regimen). All previously treated cases were enrolled in the retreatment regimen. Substituting streptomycin with ethambutol in the intensive phase of treatment in all new cases would, according to this scenario, reduce the use of streptomycin to roughly 10% of what it was at the time. As a first step, however, it was decided to perform the change only in the short-course regimen.

In any policy change, there are several phases: a trial or pilot period (with possible study effect), an expansion or post-trial phase (when practices may still be favorably influenced by the motivation brought by the change), and finally the period in which the novelty wears off and routine sets in. In this particular change, there were several issues to consider. There was the question of efficacy and effectiveness of the two regimens. The former was not considered a problem. The latter would be roughly assessed by routine cohort evaluation in the program (before and after the change). Then there was the matter of treatment adherence. Adherence would be assessed in a controlled trial. Finally, an important question arose: what would happen in the long run regarding directly observed treatment? This issue primarily concerns compliance of health personnel.

A controlled trial of compliance in selected Managuan health centers in 1992 detected no difference in adherence with or without streptomycin: 40% and 45% of patients missed at least one appointment for daily directly observed outpatient treatment in the intensive phase in the ethambutol (105 patients) and streptomycin (95 patients) groups, respectively.[49] The final results of treatment were comparable in the two groups. The treatment regimen for new smear-positive cases was changed mid-year in 1993, replacing streptomycin with ethambutol in the intensive phase.[49] Routine reports of treatment outcomes in the program are summarized below. Factors other than the change in regimen are likely to have influenced outcome of treatment in the period.

Year enrolled	1991	1994	1996	1998	2000
Patients	1,242	1,590	1,663	1,653	1,432
Success, %	74.7	80.8	79.4	82.2	82.5
Failure, %	2.1	2.6	2.8	1.7	1.3
Death, %	4.0	4.5	4.3	4.0	4.8
Default, %	13.5	6.6	8.3	8.7	9.4
Transfer out, %	5.6	5.4	5.3	3.3	2.0

treatment of new cases, however, the use of streptomycin was greatly reduced in the programs.

Drug tolerance

Generally speaking, drug tolerance was not a problem in the tuberculosis program until the HIV pandemic. The occurrence of adverse reactions is more common in HIV-positive patients. Thioacetazone in particular is badly tolerated by HIV-positive patients, and with rising HIV prevalence, serious adverse reactions to thioacetazone were increasingly witnessed and eventually led to changes in the treatment algorithm, as discussed in Chapter 3. Adverse effects to anti-tuberculosis drugs and their management are discussed in detail in Rieder's *Interventions for Tuberculosis Control and Elimination*.[34]

Monitoring response to treatment

Standardizing the procedures for treatment is important where follow-up is carried out by paramedics, and also where reducing redundant investigations can lighten the financial burden on patients.[50] It is prudent to ask whether it is necessary or wise to perform follow-up tests on all patients as a routine or only on those who are irregular or have unsatisfactory clinical responses to treatment.

In clinical practice, following the patients' clinical condition and paying attention to their comments and complaints is critical. For this, it is necessary to give each patient sufficient time and space for communication. Whereas in the pre-chemotherapy era the course of fever in tuberculosis patients was considered important, and persistence of fever after several weeks of bed rest was associated with progressive disease, the course of fever in patients treated with modern anti-tuberculosis drugs is variable[51] and of little use in case management. The patient's general condition, symptoms (cough, for instance), and body weight are important and relevant in monitoring progress. In isolation, these are poor surrogate markers of treatment response,[52] but if the patients do not gain the weight lost in the course of illness and their general condition does not improve or deteriorates, this may support the value of a positive follow-up smear (see below). Body weight is, however, not always recorded and sometimes not even measured in routine practice, a fact that also raises questions as to whether or not correct doses of medications are being prescribed. In a study referring to a sample of patients registered in 1996, body weight was recorded on the treatment cards of 53% of the patients in the sample from Nepal, 65% in Kenya, and 95% in Senegal.[53]

A hospital-based study published in the 1950s found that improvement detected on chest radiography in a group of 96 patients did not correspond to bacteriological progress:[54] six patients had demonstrable cavities on chest radiography months after sputum culture became negative, and two of these

showed complete healing in the walls of the cavities on histological examination. Other studies confirmed that radiographic resolution lags behind clinical response and is inadequate as a marker of treatment response.[55,56]

In clinical trials, progress during treatment was assessed mainly by the results of sputum culture,[55] with the purpose of evaluating and comparing different treatment regimens. It is difficult to use culture to monitor treatment of individual patients in routine practice because it takes a long time to get the results of culture, particularly when solid media are used. The reliability of culture examination during follow-up is, however, generally regarded as superior to that of smear examination, although culture is neither simple nor a perfect test in this respect.

The monitoring of response to treatment in the model program is carried out by sputum microscopy and not by culture or radiography, primarily because bacteriology is considered more reliable than radiography and the short turnaround time associated with sputum smear microscopy—as well as easier access to services—gives microscopy advantages over culture. The problem with available studies on sputum examination during treatment is the use of different recruitment criteria (case and treatment characteristics), different procedures in collecting and processing of sputum samples before smear microscopy (for example, spot specimens or morning specimens, centrifugation or concentration of specimens, or none), different technology, different criteria for positive results, and different standards for comparison (such as culture, radiography, treatment outcome, or clinical relevance).

Assessing progress during treatment

In the Kolin, Czechoslovakia, study in the 1960s, where a regimen of streptomycin, isoniazid, and PAS was administered in new culture-positive cases, 41 out of 348 patients (12%) were found to be positive by culture after three months, and only three (1%) after six months of treatment.[57] Only two patients failed to convert sputum altogether (0.6%); one of them had atypical mycobacteria, and the other suffered severe drug intolerance. Thus, in the early days of chemotherapy, it was clear that the timing of culture conversion was variable, that not all late converters failed therapy, and that failure was not always the result of drug resistance.

In 1966, Devadatta et al. used data from three clinical trials in India to study the efficacy of sputum smear examination relative to that of culture in assessing the progress of patients during treatment.[55] Atypical mycobacteria were uncommon in this setting. The data concerned 532 new patients treated with isoniazid with or without PAS, who submitted two overnight collection specimens monthly. Specimens were examined by fluorescence microscopy, and the cut-off for a positive smear result was set at four acid-fast bacilli detected in the smear. Favorable outcome was defined as all cultures negative or

Table 4.1 Correct predictions of treatment outcome with smear compared to culture examination in treatment of pulmonary tuberculosis

	Month									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*12*
Smear, %	62	73	82	85	87	90	87	90	89	92
Culture, %	47	66	78	89	92	92	93	94	94	95

Data from Devadatta et al., 1966.[55]

a single isolated positive culture in the last three examinations (in months 10, 11, and 12). The prognostic value (percentage of correct predictions regarding outcome of treatment) of sputum examination in the first two months of treatment was low but improved with time in treatment, as shown in Table 4.1. The study concluded that the examination by smear of an overnight sputum specimen was of great prognostic value, making it possible to predict correctly from four months onwards the outcome of treatment in at least 85% of the patients. Examination of two smears at a time did not significantly improve the prognostic value. Furthermore, it was argued that the slight comparative advantage of culture over smears (of the order of 5%) in the trials was likely to disappear under routine conditions in treatment programs where operational problems —such as long specimen transport time and contaminated cultures—would occur. Finally, whereas evaluation of treatment outcome by smear examination seemed to overestimate treatment efficacy in the trials, it was argued that this margin of error would likely be offset by an increase in sample size and would be less important in treatment programs having large patient numbers. Thus, in the early days of 12-month treatment, it was recommended that sputum be examined at six months or later, one smear at a time, to detect treatment failure.[33,58] This reasoning seems to partly explain definitions and practices that are still with us today. A comparable analysis for short-course treatment was never published, and today many would argue that smear examination overestimates treatment failure.

In 1978, Aber and Nunn noted that the most informative measure of the efficacy of short-course regimens was the bacteriological relapse rate occurring after treatment was completed.[59] They examined factors that might be prognostic for the occurrence of relapse in data from two East African trials where treatment included rifampicin (and usually pyrazinamide) for one to two months. They studied severity of disease and extent of cavitation on chest radiographs, results of sputum culture, viable count, and smear examination. Only the last measurement was practical for use in developing countries, and

thus it was important to consider how other parameters were related to it. They found that pre-treatment assessment was not particularly useful to predict relapse: the extent of cavitation was the factor most correlated with relapse. When considering pre- and in-treatment parameters, positive culture at two and three months was the dominant correlate with relapse rate, with the pre-treatment extent of cavitation being of next importance. They concluded that the pre-treatment extent of cavitation was a useful marker and one likely to correlate with the pre-treatment bacterial content of the lesion. Thus, quantification of bacilli in the initial smear was important in predicting the response to treatment.

Discordance between sputum culture and smear microscopy

Early chemotherapy studies reported a strong correlation between results of sputum culture and smear microscopy during treatment. Whereas discordance —that is, culture becoming negative faster than smear examination—was not unknown,* this phenomenon, often referred to as "non-viable bacilli," appeared to become more frequent and pronounced when rifampicin was introduced.[61–63] The reliability of a positive microscopic examination even decreased with time in treatment in U.S. trials from 1969 to 1970.[62] The regimens tested in these trials did not include pyrazinamide or streptomycin, however. The specific dose of rifampicin might also be important in this context: a daily dosage of less than 9 mg per kg of body weight seemed to affect the rate of sputum conversion.[64] The standard dose today is 10 mg per kg.[4]

In 1973, Hobby et al. in New York speculated that negative culture while a patient was in treatment could be explained by a low residual of viable bacilli and/or high drug concentration in the sputum, resulting in continued antimicrobial action of the drugs in vivo.[63] Experimental work suggested that the latter was not correct, however.[65] In a small study where only two patients received pyrazinamide, 5/28 cases with susceptible organisms had positive smears (concentrated sputum) and negative culture in treatment, and 3/31 had positive smears and cultures with resistant bacilli.[63] The study's findings concluded that although it did not allow species identification or permit differentiation between viable and non-viable bacilli, sputum microscopy should still be used to monitor response to treatment in smear-positive patients, as it offered the advantage of rapid results and useful information on the burden of acid-fast bacilli.

The smear-positive, culture-negative phenomenon was not discussed in the reports from the clinical trials of short-course regimens in the 1980s.[66,67] The issue of non-viable bacilli did not go away, however, as is discussed below.

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*As an example, four weeks after culture-negative samples were obtained, bacilli were demonstrable on smears in 15% (3/20) of the patients in a small U.S. study in the 1960s.[60]

Smear conversion at two months

When are smear-positive patients expected to convert to negative smears? As discussed in Chapter 3, timing of smear conversion depends on the treatment regimen. With the introduction of short-course regimens, the smear conversion rate came to be defined as the number of new smear-positive cases who were negative at the end of the second month of the initial phase of short-course treatment, out of all new smear-positive cases registered in the respective period.[68] Given a short-course regimen with four drugs in the intensive phase, which factors have proven links to late sputum smear conversion? A high positive grade on an initial smear (that is, at diagnosis),[23,69–75] extensive, advanced, or cavitary disease on an initial chest radiograph,[23,69,70,76] irregular

Box 4.3 Studies on smear conversion at two months in short-course treatment

A prospective cohort study in Uganda included 457 previously untreated smear-positive patients (28% HIV-positive) admitted from 1991 to 1993 and treated with SHRZ. Treatment was directly observed in the intensive phase. In the event of a positive smear at two months, HRZ was continued for a third month. The continuation phase of treatment was with self-administered HT. A failure to convert at two months was associated with initial smear grading, but neither HIV infection nor drug resistance affected smear conversion (2 of 225 persons had multidrug resistance, prevalence of resistance to streptomycin was 18%, and resistance to isoniazid, 5%).[74]

A case-control study followed 297 smear-positive tuberculosis patients in an urban area in Madagascar in 1999–2000: 152 were smear-positive and 145 were smear-negative at two months.[77] Treatment was with EHRZ in the intensive phase. A single sputum smear was taken at two months, and the intensive phase prolonged if the smear was positive (that is, the two groups did not receive the same treatment). Treatment was with HT in the continuation phase. Of those who were smear-positive at two months, 51% were negative by culture, 12 (8%) eventually failed treatment, and 4 (4.6%) relapsed. Of those negative at two months, 22 (15%) were culture-positive, and one of them failed treatment. Of the 13 failures, 11 were smear- and culture-positive at two months; 1 was smear-positive, culture-negative; and 1 was smear-negative, culture-positive. The number of defaulters was much higher than failures in this study (54 versus 13). The investigators raised the question whether it is necessary to examine a smear at five months if the smear at two months is negative.

In a recent case series reported from New York (U.S.), of 100 hospitalized, smear-positive tuberculosis patients who ultimately converted to smear-negative, the mean number of days in treatment before the first of three consecutive negative sputum smears was performed was 33 (median 23).[23] Cavitary disease, numerous bacilli on the initial smear, and no prior history of tuberculosis were independently associated with an increased number of days to smear conversion. HIV infection did not increase the time to conversion.

Table 4.2 Factors affecting sputum smear conversion at 2 months

Factor	*Effect*
Cavitary disease	Delayed sputum conversion
Numerous bacilli on smear	Delayed sputum conversion
Previous treatment	More rapid sputum conversion?
Drug resistance	Variable, depending on the pattern and prevalence of drug resistance in study subjects and on treatment regimen
HIV status	No effect
Irregular treatment	Variable, probably depends on level and nature of irregularity
Drug regimen	More rapid smear conversion in short-course compared to 12-month regimens

treatment,[75] and drug resistance[70] have all been shown to be associated with a positive smear at two months. Some of the studies concerned are presented in Box 4.3 and the results are summarized in Table 4.2.

The effect of adherence on smear conversion is not well studied, partly because sputum conversion is often investigated where treatment is well organized. It has been stated that viable bacilli on any follow-up smears are often attributable more to nonadherence than to drug resistance.[78] This, however, is likely to depend on the setting. According to Chaulet (1987), irregular treatment or treatment of insufficient duration mainly results in failure when more than 25% of a treatment regimen's doses are omitted.[79] As is the case with irregular treatment, the effect of drug resistance on smear conversion can only be studied in a setting where there is significant drug resistance. In one study, new cases had a longer time to smear conversion than previously treated cases.[23] The investigators speculated that this phenomenon might have to do with priming of the immune system. HIV infection appears not to have an independent effect on time to smear conversion,[23,74,80] and smears can still be used to monitor treatment response in the HIV era. Finally, it is important to note that when confronted with unexpected results of follow-up smears in routine practice, laboratory error needs to be considered.

In national programs in high-prevalence nations, it is common to find 75% to 85% smear conversion at two months in short-course treatment. The exact proportion depends upon case-mix (for example, grading of initial sputum smears, extension and character of lesions on radiography, drug resistance), operational quality (regularity of treatment, for instance), laboratory quality (the sensitivity of the smear examination), and the criterion used for a positive result.

The purpose of sputum examination during treatment

The main questions regarding sputum smear examination during treatment are whether it is useful or not, and for what? First, consider what kind of a test it is. Is it a diagnostic or a screening test picking up an abnormality? Diagnostic tests are assessed for validity and reliability, and a screening test is studied in a cross-sectional survey where it is compared to another test or to a gold standard (such as culture or clinical relevance). Is it a test for prognosis? Does it predict adverse outcome (that is, treatment failure or relapse)? Such results would be addressed in a longitudinal cohort study. If it predicts adverse outcome, can something be done to prevent it? That is, does it help in case management? A prospective trial, preferably randomized, would answer this question.

If the smear reliably detected something that was likely to influence treatment outcome were it not addressed, then smear examination would be useful and would have immediate implications in case management. If the smear detected something that was either irrelevant for outcome or likely to disappear anyway (such as non-viable bacilli), it would be redundant. In other words, follow-up smear examination is important if it detects something that necessitates or justifies changes in treatment or in case management.

In the Union model, the purpose of sputum examination during short-course treatment was twofold. First, the examination was intended to strengthen the short-course regimen for new smear-positive cases by identifying patients who were likely to benefit from early modification of the treatment regimen, namely a prolongation of the intensive phase. Such patients were detected by sputum examination at two months in treatment of new cases and can be referred to as "late converters." This step was considered important because the continuation phase of the short-course regimen for new cases was weak (isoniazid and thioacetazone). The second purpose of smear examination during treatment was to identify patients who might benefit from late modification of treatment. These cases are referred to as "treatment failures" and were to be detected at five months of treatment or later and enrolled on a retreatment regimen.

The first objective could have been partly achieved with a different approach, studying the grading of positive smears at diagnosis (that is, "*if* 3+ *then* prescribe prolonged intensive phase") or a more stringent approach, looking at both initial and follow-up smears ("*if* 3+ on initial smear *and* smear-positive at two months, *then* . . ."). This might not capture all cases whose treatment is irregular, though. Irregularities were expected in the programs, and thus the strategy was cautious and aimed at over-treatment rather than under-treatment so as to prevent development of drug resistance and minimize relapses. A further possible version of the strategy would be the following: "*if* 3+ on initial smear *and/or* smear-positive at two months *then* . . ."). As it turned out, however, the criterion of a positive smear at two months was used, demanding im-

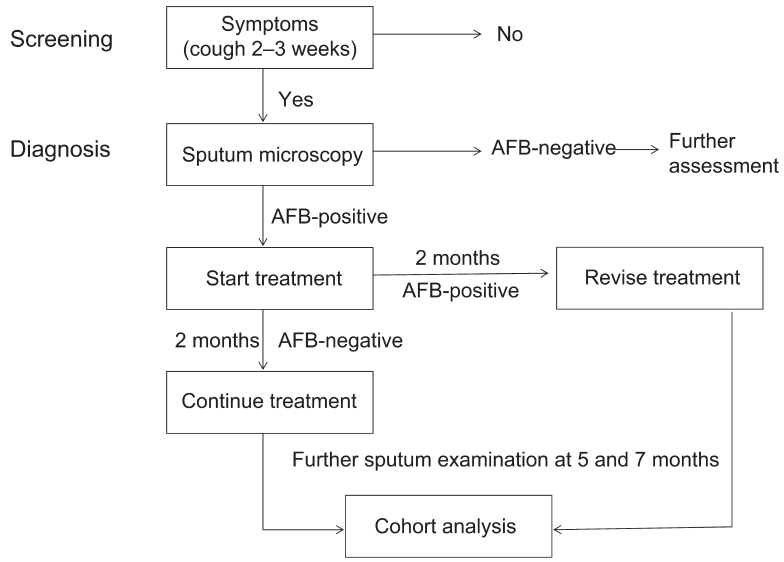
mediate local action. In this context, follow-up sputum examination is a process criterion and can be used in quality assurance. The action required is a careful re-assessment of the case and prolongation of the intensive phase of treatment with the aim of reducing the risk of failure and relapse. Thus, the examination of a smear at two months becomes an explicit measurement of quality of care. If sputum examination is not performed, the results not recorded, or the intensive phase not prolonged when the result is positive, then there is a quality problem.

Smear conversion can also be monitored at the program level, where it may indicate a variety of aspects such as overall quality of care, adherence to guidelines, case holding, laboratory quality, and appropriateness of the treatment algorithm. Smear conversion was not made part of routine surveillance in the Union model, however (see Chapter 8), but it was to be studied during supervision of services. This is discussed further in Chapter 10.

Timing of sputum examination during treatment

The recommendations of the policy model regarding sputum smear microscopy during treatment are summarized in Figure 4.1. Sputum examination is

Figure 4.1 Timing and interpretation of the results of sputum examination (Union model)



AFB, acid-fast bacilli.

performed only if action depends on the results. In patients who are classified as new smear-positive, sputum is examined at two months (if positive, the intensive phase is prolonged), at five months (to detect treatment failure and switch to the retreatment regimen), and at the end of treatment to detect treatment failure or discharge the patient as cured. But, should the timing of follow-up sputum examination refer to treatment time or calendar time? This question arises because in practice, when treatment is irregular, its duration is often increased, corresponding to the gaps introduced by nonadherence. In the Union model, patients who miss appointments have the time of treatment missed added to the originally planned duration.[6] In routine practice, calendar time of follow-up sputum examination thus varies according to the regularity of treatment. Perhaps this issue was never explicitly addressed in recommendations because it was assumed that treatment would be fairly regular.

How many follow-up smears at a time?

According to the Union model, one specimen only is taken in a follow-up sputum examination, but a positive smear needs to be repeated to confirm failure.[6,81] The former was not explicitly stated in the Orange Guide, however, except in relation to determining the needs for laboratory supplies.[81] In Nicaragua, two smears were examined at each follow-up examination.[82] (The WHO recommended that two smears be taken each time as a routine.[83])

In 2004, Urbanczik et al. reported that, in the context of a clinical trial, they examined two early morning sputum samples by microscopy at two and five months of treatment.[84] Some subjects were positive only on the first sample, and some only on the second. The latter would have been missed had only a single sample been examined at two months of treatment. Rieder, in his study involving Cambodian refugees in the 1980s, found that sputum smear conversion was 85% when looking at a single smear at two months but 75% if three smears were examined and any of the three was positive.[72] The strategy of taking only one smear can be interpreted as looking for consistently smear-positive subjects. The practical implications of this may be insufficiently studied. A retrospective study of laboratory registers in India suggested that if a morning specimen is taken, a second smear adds little. If, on the other hand, the specimen is a spot specimen, many positives—especially scanty-positives—are missed if one specimen only is examined. Whether this is an advantage or a disadvantage is debatable. Because of non-viable bacilli, being positive on the second smear is of lower specificity, and given the use of rifampicin throughout regimens, it threatens to misclassify too many as failures.

It can be argued that if a positive smear is missed at two or five months, it should be picked up with the smear examination at the end of treatment if it is clinically relevant. Similarly, if a positive smear is missed at the end of treatment, it should be picked up as a relapse further on if it is clinically relevant.

Regarding treatment failure (see below), a conservative strategy such as that of the Union model is justified because it is a serious matter to submit a patient to eight months of fully supervised retreatment.

Interpretation of the results of sputum examination during treatment

What should constitute a positive smear during treatment? This issue was not explicitly addressed in the recommendations either. Generally speaking, scanty-positive results were considered doubtful and inconclusive.[85] Some experts contend that because of non-viable bacilli and the serious consequences of a classification of treatment failure, the criterion for a positive smear in follow-up should be strict. Further, it has been suggested that it is advisable to consider the positive grade of a positive follow-up smear compared to the positive grade on the initial smear (that is, to look at the trend in positive grade for an individual patient).[86] In 2005, the technical staff of the Tuberculosis Division of The Union proposed applying a higher cut-off point for labeling a follow-up smear as positive than for one in diagnosis: at least one plus positive (that is, not "scanty") and/or at least two positive samples (a positive result must be confirmed with another positive result).[87]

Prolongation of the intensive phase in late converters

In the Union model, patients whose smear was positive at two months were considered at risk for adverse outcome, given the weak continuation phase in short-course treatment of new smear-positive cases. Trébucq and Rieder have pointed out that this concern was supported by indirect evidence: observations from the results of clinical trials.[88] It was common in clinical practice in industrialized countries at the time to prolong treatment in cases with numerous bacilli on smears and extensive cavitary disease, a protocol that was supported by studies. This is not a comparable strategy, however: an intervention that is prolonged in the intensive phase and one whose total duration of treatment is prolonged do not constitute the same intervention.

In 2006, Van Deun et al. provided evidence from a prospective trial in Bangladesh[75] supporting the recommendations in the model. They found that extension of the intensive phase in cases with a positive smear at two months reduced failure and relapse within two years of completing 8-month short-course treatment with isoniazid and thioacetazone in the continuation phase, such that these outcomes occurred at a rate comparable with those of cases with a negative smear at two months. In contrast, in the group with positive smears at two months who did not have the intensive phase extended, the failure rate was 8.2% versus 3.3%, and the relapse rate 3.7% versus 2.1% compared to the group with negative smears at two months. Van Deun et al. argued

that although these findings might well apply to a short-course regimen with ethambutol replacing thioacetazone in the continuation phase, they should not be extrapolated to treatment with 6-month regimens using isoniazid and rifampicin in the continuation phase, nor to settings with a higher prevalence of drug resistance. They pointed out that in spite of a significant reduction in the relative risk of failure and relapse (rare adverse outcomes), the absolute gain from extending the intensive phase of treatment was modest when considering that all patients must undergo quality sputum examination at two months and, in their setting, the intensive phase had to be extended for 20 patients to prevent one smear-defined failure or relapse.[75]

Evolution of recommendations on follow-up sputum examination

The policy in the Tanzanian program in the late 1970s involved 12-month treatment, and sputum smears were to be examined at six, nine, and 12 months to detect treatment failure, relying upon morning specimens when possible.[30] The introduction of short-course treatment changed the recommendations concerning sputum examination during treatment and, for a different purpose (as discussed above), smears were to be taken at two months.

According to the 2000 version of the Orange Guide,[81] sputum smear examination should be performed at two, five, and seven months in new smear-positive cases on short-course treatment.* Originally, it was recommended that in the event of a positive smear at two months, sputum examination should be performed every week and the continuation phase started when the smear was negative.[89] The first edition of the Orange Guide recommended prolonging the intensive phase for two to four weeks.[6] This was later simplified further, and the 1996 version of the Guide advised prolonging the intensive phase for one month and then starting the continuation phase without a new smear.[90] In the 2000 version, a note of caution was introduced, pointing out that this was a safe practice as long as the continuation phase was conducted with HT. Using HE† in the continuation phase, however, might carry a risk of extending drug resistance in patients with initial resistance to isoniazid.[81] As discussed in Chapter 3, there is no easy solution to this challenge.

It is sometimes asked whether it is necessary to examine the sputum of all patients at all scheduled follow-up times, especially if the smear is negative at

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*During retreatment, the timing of the follow-up sputum examination is the same as in treatment of new cases, except that the first examination is done at three months rather than at two (that is, at the end of the intensive phase in retreatment). Depending on the setting, positive follow-up smears may not call for modification of the retreatment regimen but could be important for infection control and/or for triggering drug susceptibility testing.

†Or HR (but that regimen is not recommended in the Orange Guide).

two months, the patient shows convincing clinical improvement and has difficulty expectorating. Some would even suggest performing sputum examination only if the patient's clinical condition and apparent progress in treatment are unsatisfactory, which conforms to the argument of performing tests only on good clinical indication. In situations where paramedical personnel are in charge of treatment, it may be safer to examine sputum from all patients at all scheduled follow-up times. On the other hand, where well-trained and experienced specialists are in charge, a more lax position may be justified, although this is debatable. The disadvantage of examining follow-up smears from all patients routinely is that the positive predictive value of the test would be expected to decrease, and in most settings treatment failure cannot be routinely confirmed by culture. Indeed, this is another thorny problem. Some go so far as to say that if the patient cannot expectorate spontaneously, the sample should be collected by sputum induction, gastric lavage, or other invasive procedures. This, it can be safely argued, is taking matters too far. Whereas such procedures may be justified in the process of differential diagnosis of difficult cases, when choosing the right treatment, performing such procedures simply for the register is unwarranted.

Finally, what if the patient is sputum smear-negative at diagnosis or has extra-pulmonary tuberculosis? Very rarely does a smear-negative patient develop smear-positive disease during treatment. If the clinical condition and cough worsen during treatment of a smear-negative patient, performing a sputum examination is indicated;* otherwise, not. It should be noted, however, that in the second edition of their technical guidelines, in 1997, the WHO recommended that sputum examination be performed in all smear-negative cases at two months in the event that an error at the time of diagnosis occurred or that treatment was irregular.[91] In cases where the sputum is positive at two months, they recommend evaluating the case as a treatment failure and registering the patient as a previously treated case. The Orange Guide's position on this matter is, as always, not to standardize management of rare events and exceptions.

Workload in the laboratory

When deciding on the policy of sputum examination during treatment, it is important to consider the laboratory workload, and this was indeed part of the rationale when the policy model was developed. At the time, it was common to examine the sputum of tuberculosis patients every week until smear conversion, and monthly thereafter. In the programs collaborating with The Union,

*In this case, further tests would be indicated for differential diagnosis if the sputum is still negative because the patient may have another disease.

the workload in follow-up was reduced to only three sputum examinations during treatment, one smear at a time. Some, though, regard even this number of sputum examinations to be too much.[92,93] Typically, such observations come from a centralized service where chest radiography is used as a first test in assessment of tuberculosis suspects and where the proportion of those smear-positive among those undergoing sputum examination is consequently high. As shown in Box 4.4, in decentralized services, where this proportion is low, the relative workload when performing three follow-up sputum examinations during treatment is also low. The argument for decentralized tuberculosis services is accessibility. In a decentralized service, the bulk of the work in acid-fast microscopy will be for examination of tuberculosis suspects rather than for follow-up examination during treatment. It makes more sense to reduce the number of slides examined per suspect rather than to reduce follow-up examinations, in case high laboratory workloads are a concern. It should be noted, however, that if the treatment regimen is different from what is recommended in the Union model, the policy on timing of follow-up sputum examination ought to be critically appraised with the treatment regimen and case management in mind.

Box 4.4 Relative workload in sputum microscopy for follow-up examinations

If three smears are examined per tuberculosis suspect in the process of finding smear-positive cases, and a single smear in each follow-up sputum examination (at two and five months and at the end of treatment)—

given that,	the relative workload in follow-up is
5% of suspects are positive	5%
10% of suspects are positive	9%
20% of suspects are positive	17%
30% of suspects are positive	23%
50% of suspects are positive	33%

For comparison: If two smears are examined per tuberculosis suspect and a single smear in each follow-up sputum examination—

given that,	the relative workload in follow-up is
5% of suspects are positive	7%
10% of suspects are positive	13%
50% of suspects are positive	43%

(Relative workload refers to proportion of all slides examined in the laboratory.)

Operational deficiencies

It is well known that policy is not always reflected in practice, and in this respect laboratory tests, for diagnosis or follow-up, are no exeption.[94] To give an example, a retrospective record review in Malawi, referring to patients registered in 2001, found that approximately three out of four patients had results of sputum examination recorded corresponding to two, five, and seven months of treatment.[95] Although 82% of the smears were taken at what the investigators classified as acceptable timing—that is, within what they determined to be a reasonable time frame—this proportion was 71% and 78% for smears at five months and seven months, respectively, and lower if considering only follow-up examinations with positive results. This could reflect a practice where smears are eventually examined when there is a strong clinical indication or it could signal irregular treatment associated with positive follow-up smears. However, it was not clear whether the time range in this study was measured in terms of calendar dates or number of days in the treatment cycle. A calculation based on calendar date might at least partly explain the findings. Performing such exercises during supervision allows an exploration into individual cases, explaining why the timing of sputum examination is irregular (see Chapter 10).

Discharging the patient

When is treatment completed?

What treatment completion in routine practice actually refers to is seldom discussed. Definitions may be based on calendar dates, an absolute number of doses of medications, a proportion of prescribed doses, or some combination thereof. Two issues are involved: regularity and duration of treatment. The former is relevant when considering drug concentrations in serum and the emergence of drug resistance; the latter, when considering bacterial persistence. In practice, the prime concern is treatment failure and relapse. Strictly speaking, complete treatment is 100% of the prescribed doses. Missing an occasional dose should not be a problem, however, particularly in the continuation phase of treatment when bacterial load is low.

In clinical trials, treatment regimens are described in terms of drugs, dosages, dosing schedules, and calendar time. Treatment is expected to be regular in this context. In a study of 287 highly selected cases recruited in two Indian clinical trials in 1978,[96] 49% did not miss a dose during the intensive phase of treatment. The remaining 51% had the daily intensive phase period extended to complete the prescribed number of doses. The number of doses compensated per patient ranged from 1 to 36, and the number of treatment gaps per irregular patient ranged from 1 to 4. During the biweekly continuation phase, 66 out of 183 (36%) patients had the treatment period extended, and the

number of doses compensated per patient ranged from 1 to 10. In a U.S. clinical trial in the 1980s, where treatment was self-administered, patients who reported missing more than 14 consecutive days of treatment were required to complete 100% of the assigned doses before stopping treatment, but otherwise patients were required to complete at least 80% of the assigned regimen.[97] In a clinical trial in Hong Kong (1981), 19 cases (5%) were excluded for missing at least 14 days of treatment in the intensive phase or at least four weeks in total, on account of drug toxicity.[98]

In routine practice, treatment can be quite irregular and is often completed within a longer time frame than is prescribed. How much of a problem does such irregularity constitute, and how should it be managed? Should "missed doses" be compensated for and if so, how? Some publications define "adequate treatment" as a certain proportion of prescribed doses taken within a certain time frame, such as 80% of a 6-month short-course regimen in eight months.[99] If a two-month daily intensive phase means 60 doses, 80% would amount to 48 doses. If, over a period of eight months, 48 doses in the intensive phase of a 6-month regimen are administered along with 80% of the prescribed dosage in the continuation phase, can the same failure and relapse rates be expected as those in a clinical trial? What if the allowed time to completion is 12 months? What if the intensive phase is even less complete but compensated for with a more complete continuation phase that still results in 80% of prescribed doses being taken? Might different definitions of treatment completion in this respect in different programs explain some of the differences in treatment results at the program level as well as different rates of relapse and even drug resistance?

If only 80% of the prescribed doses are required, then skipping treatment on Sundays (which would represent 15% of the treatment) and still maintaining a two-month treatment in the intensive phase is clearly not a problem. But what if treatment is not administered on Saturdays and Sundays? Is that safe practice? And what about safety and management of irregularities in intermittent treatment? A variety of strategies for compensating for missed doses in practice exist: for example, adding double the number of missed doses at the end of treatment,[100] adding the exact number of missed doses in all cases, or adding the number of missed doses at the end of scheduled treatment only if the number exceeds a certain percentage of scheduled doses (such as 20% or more).[101]

In the Orange Guide, poor adherence was addressed by recommending extending the duration of therapy in terms of time. In the intensive phase, prolonging treatment for patients who had taken the regimen without interruption but had omitted treatment on Sundays was considered only of minor benefit. In contrast, it was advised that patients who were irregular in their collection of drug supplies in the continuation phase continue treatment until they had completed the six months of thioacetazone and isoniazid (in terms of the

number of tablets).[6] This was interpreted as extending the duration of therapy equal to the exact number of missed doses. Case management in the event of irregularities in the intensive phase of short-course treatment was not explicitly described, except to say that patients leaving the hospital before completing the intensive phase were to switch to the 12-month regimen.[6] In Nicaragua, where treatment was primarily administered on an ambulatory basis in the intensive phase, the standard procedure was to require the administration of 60 doses in the intensive phase and to compensate for any number of missed doses. Originally, patients who missed four consecutive appointments in the intensive phase were switched to the 12-month regimen. This was done not to "clean" the cohort (in order to document better treatment results), but rather to prevent drug resistance, given that this level of irregularity (missing four consecutive doses) was seen as an indication of further irregularity. This practice was later abandoned as the program matured. According to the 1994 Orange Guide, patients who occasionally miss an appointment during the continuation phase should add the missed time to the originally planned treatment duration, but up to a limit: a total duration of one year for patients on the 8-month regimen, and 15 months for patients on the 12-month regimen.[7] If treatment lasted longer, the patient should be declared a defaulter on the report of treatment outcome.

Communication with patients

Here, as always in one-on-one health education, it is important to establish a routine in terms of the frequency and means of contact, and to standardize the minimum information to provide to all patients on discharge from treatment. Patients need to know that they should return if symptoms recur and, ideally, they should be able to advise other patients with symptoms of tuberculosis to seek care. For the sake of consistency, it is good to have a checklist of what health workers should discuss with patients upon patient discharge.

Follow-up after treatment

When chemotherapy was first begun as a treatment program, patients were requested to attend for follow-up assessment at regular intervals for a number of years after treatment was completed or even for life. Improved treatment regimens and better organizational frameworks allowed health care officials to discontinue this practice, greatly simplifying case management.[33]

Even before the introduction of short-course treatment, relapses were rarely detected during scheduled follow-up. A study published in 1976 found that only one in four relapses were detected during routine annual checkups. In the remaining cases, relapses were noted when patients experienced symptoms that prompted them to attend in advance of their next scheduled visit.[102] Thus, routine follow-up after completion of treatment seemed to be a waste of

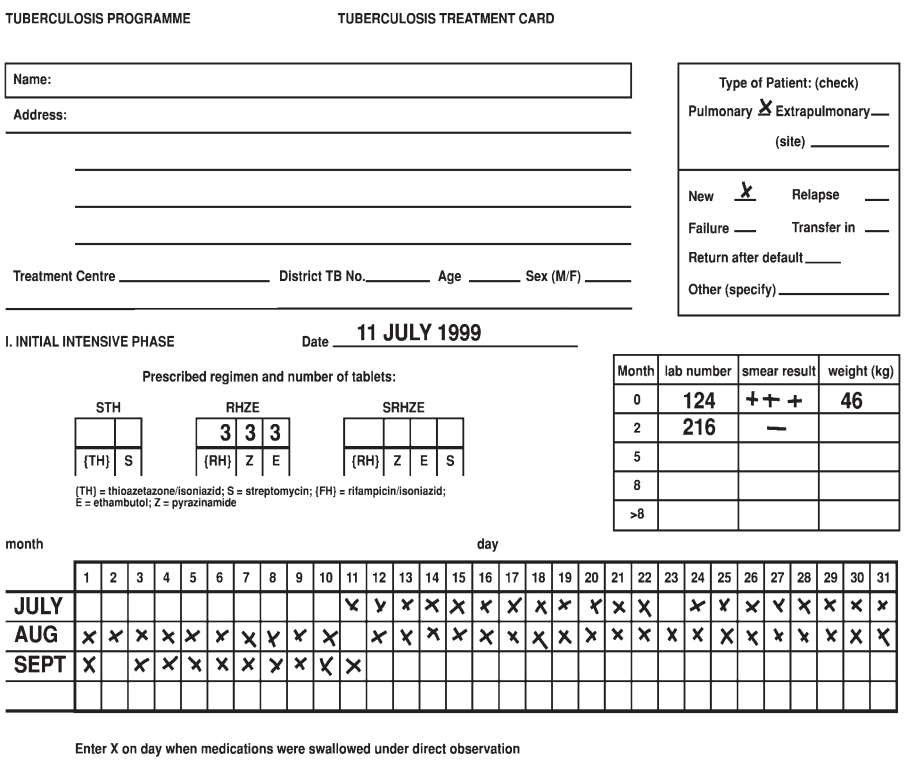
resources. Short-course therapy resulted in very low relapse rates that further justified abandoning scheduled post-treatment follow-up.

Accountability

The Expert Committees in 1964 and 1974 made various recommendations regarding records and operational assessment in tuberculosis programs.[33,58] In 1964, Horwitz and Palmer published a paper discussing case definitions and outcome analysis in tuberculosis programs based on experiences in Denmark, where notification of tuberculosis was made compulsory in 1905.[103] In their paper, they established the foundation for cohort analysis in tuberculosis programs as it is known today. In 1968, Fox pointed out that the high mobility of populations in many developing countries and the fact that patients were referred between health facilities at different levels required an information system capable of managing the transfer of patients between units so that patients would not be lost due to simple administrative hiatuses.[1] He also emphasized the importance of keeping treatment records in a calendar system according to a patient's next attendance date so as to detect and prevent default. It was Styblo, however, who actually tested a simple but comprehensive information system that has since been developed further. This system is presented in detail in Chapter 8. Suffice it here to review briefly the main components of the system.

A sputum request form and a laboratory register aids in managing patient recruitment. The register lists time, person, and place identifiers, and has columns for recording the reason for examination (diagnosis or follow-up) and its result. For information related to case management and program evaluation, case definitions are dealt with above, and reporting is discussed in Chapter 8. Each patient has a treatment card, and the information from the cards is summarized in a tuberculosis register. Details concerning the treatment regimen, dosage, and progress in treatment are recorded on the card, which provides a summary of the main events during treatment and facilitates case management and continuity of care. The card is an instrument used for monitoring regularity of treatment. Gaps in treatment, such as the number of missed doses, but not always the distribution (only if treatment is directly observed but not if it is self-administered), are clearly noted on the card. The card is depicted in Figure 4.2 (the front side) and Figure 4.3 (the reverse side, for continuation phase of treatment). When the patient receives directly observed treatment, a corresponding date on the treatment card is ticked. If the patient receives drugs to take at home a line is drawn corresponding to the period during which the drugs are meant to be taken. The tuberculosis register is divided into four parts: registration (time, person, place, and case identifiers); follow-up during treatment (results of sputum smear examination at predetermined intervals, as discussed above); outcome of treatment; and observations.

Figure 4.2 Tuberculosis treatment card, front side



TUBERCULOSIS PROGRAMME

TUBERCULOSIS TREATMENT CARD

Name:

Address:

Treatment Centre _____ District TB No._____ Age _____ Sex (M/F) _____

Type of Patient: (check)
Pulmonary X Extrapulmonary ___
(site) _____

New X Relapse ___
Failure ___ Transfer in ___
Return after default ____
Other (specify) _____

I. INITIAL INTENSIVE PHASE Date 11 JULY 1999

Prescribed regimen and number of tablets:

STH		RHZE			SRHZE			
		3	3	3				
{TH}	S	{RH}	Z	E	{RH}	Z	E	S

{TH} = thioazetazone/isoniazid; S = streptomycin; {FH} = rifampicin/isoniazid;
E = ethambutol; Z = pyrazinamide

Month	lab number	smear result	weight (kg)
0	124	+++	46
2	216	–	
5			
8			
>8			

month / day

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
JULY											X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
AUG	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SEPT	X		X	X	X	X	X	X	X	X	X																				

Enter X on day when medications were swallowed under direct observation

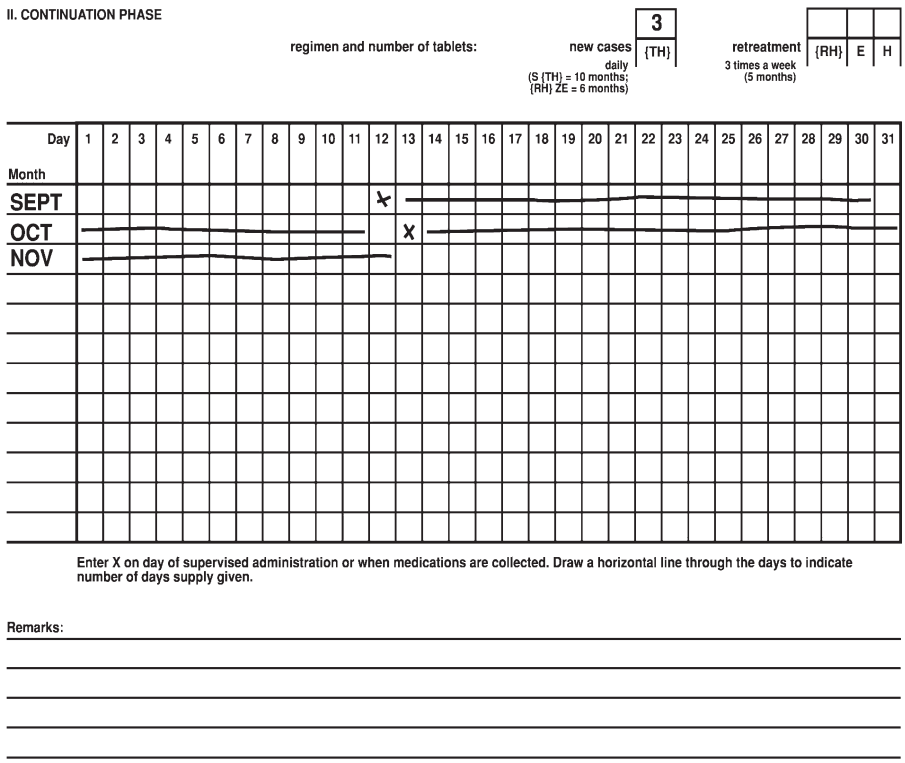
Outcome analysis

The Expert Committee of 1964 recommended that cohort analysis of drug administration records, covering complete groups of patients who began treatment within a given period, should constitute the basic method of operational assessment.[58]

In 1976, the results of a sample survey of treatment outcomes of patients notified in Scotland in 1968 were published, and a policy of routinely monitoring all notifications at diagnosis and at a point one year thereafter was subsequently instituted in Scotland in 1977.[104] It was argued that clinicians might be even more careful with their patients when they knew that they were expected to report on outcome of treatment. This strategy coincided with a decrease in the number of tuberculosis cases reported in Scotland and in the prevalence of patients with resistance to two or more drugs.[104]

In the 1980s, Styblo developed a method for cohort analysis of treatment

Figure 4.3 Tuberculosis treatment card, reverse side



results in the programs collaborating with The Union, and demonstrated that routine assessment was possible even in developing countries. In 1993, routine assessment was changed along similar lines in the United States; outcome information was added to the national tuberculosis surveillance system.[105,106] In the United States, it has been argued that this added data permitted analysis of characteristics of completers and noncompleters for better targeting of services,[105] and that cohort reviews introduced in 2004 were key to improving case management.[106]

Cohort evaluation of treatment results

Generally speaking, when discussing outcome assessment, five elements need to be clear: a description of the method by which the criteria were arrived at, the categories of patients to be assessed, the method for measuring outcome, the precise time at which outcome measurement should occur, and the sources

of information concerning patient characteristics and outcome.[107] In the Union model, case and outcome definitions were composed using information from various studies (clinical trials, surveys, and clinical outcome studies), and all sputum smear-positive patients were included in routine cohort analysis of treatment results. Emphasis was placed on smear-positive cases, given that such findings were considered reliable and of serious prognostic significance,[108] as well as being able to exclude faulty diagnoses with a high degree of certainty. The analysis is performed at a date when patients in the cohort can be expected to have completed treatment. The source of information is the tuberculosis register. As many have pointed out, care must be taken to include all tuberculosis patients and exclude those who do not have tuberculosis; otherwise, the recorded outcome statistics are difficult to interpret and are possibly misleading.[109] Cohort evaluation is discussed in detail in Chapter 8.

Whereas in some programs the results of treatment of smear-positive and smear-negative cases are similar—for example, in Nicaragua, where a comparison of treatment results in confirmed and unconfirmed tuberculosis cases registered in 1994 found an 83% treatment completion rate in the latter[110]—this is not invariably so. In recent times, partly as a consequence of the HIV pandemic and its implications for quality of care, it has been argued that outcome analysis should be performed routinely for smear-negative and extra-pulmonary tuberculosis cases as well as for smear-positive cases.[111] Studies in Malawi concluded that higher death rates[111] and higher default and transfer with unknown results[112] in smear-negative cases, as compared to smear-positive cases, might reflect a lack of attention paid to this group of patients. If this is the case, a routine cohort evaluation might help.

Definitions related to outcome of treatment

The aim of treatment is to prevent death and to render the patient permanently noninfectious. Thus, apart from the occurrence of death, the outcome of interest is treatment failure and relapse. What should be the gold standard in evaluation of treatment success? One option is the result of sputum culture at the end of treatment and the relapse rate. These parameters are used in clinical trials. Routine practice, however, involves different criteria. What difference does it make to determine that the culture is positive near or at the end of treatment? In such an event, the patient will probably have been discharged by the time the result becomes available, unless the specimen was taken a month before treatment is due to be discontinued. It was known from clinical trials that isolated positive cultures detected in follow-up toward the end of treatment or after treatment was completed were often clinically irrelevant in the sense that these patients did not fare differently than patients with no positive cultures during follow-up.[113] Thus, isolated positive cultures during treatment

in clinical trials were not considered to constitute treatment failure. Culture might do away with the problem of "non-viable bacilli," or at least reduce misclassification as failure based on smear examination. But does a culture that is negative toward or at the end of treatment provide conclusive evidence? The culture could be false-negative (particularly in high-prevalence countries where storage and transport of specimens are problematic). This is just to point out that culture is not necessarily an easy and straightforward test in monitoring treatment—there is no such thing as a perfect test. In any event, it was not and still is not realistic to use culture routinely in high-prevalence countries. One has to make do with microscopy.

In clinical trials, the definition of failure was usually the presence of at least two positive cultures from the six specimens obtained during the last three months of treatment. The definition of relapse was evidence of two or more cultures of at least ten colonies at different months in any consecutive three or sometimes four months.[114] There are many difficult issues in routine outcome assessment in tuberculosis programs, as will be discovered when looking at outcome definitions. What starts out as irregular treatment can end up as treatment failure (if the patient does not default before) or relapse (for example, if the failure is missed). Put another way, the definitions tend to blend into each other.

Definition and detection of treatment failure

Practically all patients enrolled in 12-month treatment with susceptible bacilli converted their sputum by six months of consistent chemotherapy. Accordingly, examination of sputum at this point in time would separate patients into two groups: those who were responding to treatment and were likely to be cured with further treatment, and those who failed to respond, mostly on account of bacterial resistance, for whom continuation of the standard regimen was unlikely to result in cure.[115] This observation underlies the definition of bacteriological failure in 12-month regimens. In their article of 1978, Grzybowski and Enarson argued that the fate of patients with pulmonary tuberculosis had not received the attention it deserved. They stressed that routine examination of sputum at five to six months of supervised treatment should be used in case management, and whenever possible those with positive sputum at this point in treatment should be offered an alternative drug regimen.[115] Thus, the operational definition of treatment failure in tuberculosis programs became the following: sputum smear-positive at five months or later during treatment.[7] But what was the rationale for using five-month sputum examination in short-course treatment? Was the definition simply carried over from the 12-month regimen? The same definition would not automatically hold true for 8-month or 6-month regimens. Or was the definition influenced by the fact that in the first five months of treatment, non-viable bacilli were a problem?

This was not clearly documented. Some reflections on detection and definition of treatment failure in tuberculosis programs are presented in Box 4.5.

The main question with monitoring by sputum microscopy is whether or not positive follow-up smears at five months or later are clinically relevant. Misclassification at two months is not harmful: it causes at most a strengthening of the treatment regimen without affecting the total duration of treatment. Misclassification at five months or later is a serious matter, however: it can cause an extra treatment episode if the result is a false positive or a missed opportunity to diagnose treatment failure, which can be harmful to the patient and to the community even though it should be picked up later as relapse if clinically relevant. The early recommendations in the Union collaborative programs were cautious and required a confirmation of a positive smear (at five months or at end of treatment) at least two weeks later, and a positive culture if possible.[6] Only if two specimens were positive on smear or culture was treatment to be considered to have failed.[30] The precautions can be understood in

Box 4.5 Reflections on the definition and detection of treatment failure

In chemotherapy studies in Madras, India, in the 1950s, smear-positive culture-negative results reached a peak (29%) at five months of treatment with isoniazid and PAS, but in two out of three instances this was an isolated phenomenon (occurring only on a single occasion) and was not associated with bacteriological status at 12 months.[2] According to Fox in 1964, it was exceptional for a patient to produce smear-positive culture-negative sputum samples frequently, and they were nearly always confined to scanty-positive smears.[116] Also, it was unusual for the sputum to remain consistently positive on culture but negative on smear.[116]

In a retrospective study of patients diagnosed from 1974 to 1978 in a Virginia (U.S.) sanatorium, the smear-positive (concentrated specimens), culture-negative phenomenon in treatment was seen in 20% of the patients from four to 20 weeks into treatment, its frequency related to the extent of disease and to treatment regimens containing rifampicin (usually without pyrazinamide).[70] All these cases converted to smear-negative with continuation of the same regimen, however, and the investigators argued that positive smears in the first 20 weeks of treatment should not be taken to indicate treatment failure.

In a retrospective chart review in the United States of 453 HIV-negative, previously untreated smear-positive tuberculosis patients from 1988 to 1992 who completed therapy and were able to produce a specimen at the end of treatment (that is, expectoration was still present), ten were found to have positive microscopy on one of two sputum samples taken (five in only one of the samples). Of these, eight had less than 10 bacilli (in concentrated specimens; that is, very few bacilli that might not be detected on routine microscopy in high-prevalence countries). Eight specimens were negative on culture and two grew atypical mycobacteria. Only one of the ten patients had clinical symptoms supporting treatment failure.[117]

(*continued*)

Box 4.5 ***Continued***

A publication from Canada in 1999 joins the above study in questioning the policy of basing identification of treatment failure on smear examination.[118] In a population-based historical cohort study including 428 patients with culture-proven pulmonary tuberculosis registered from 1988 to 1995 in British Colombia, 30 patients (7%) were positive at 20 weeks (five months), but only 23% of the 30 had positive cultures. This finding was not explained by atypical mycobacteria. The seven patients who had positive cultures had less progress on radiography, a higher prevalence of drug resistance, and were less compliant with treatment—all factors associated with treatment failure. Sputum specimens were concentrated, but it is not clear how the specimens were obtained; that is, whether they were all spontaneously expectorated sputum. Furthermore, the case-mix might not be comparable to treatment programs in high-prevalence countries. The 7% smear-positive at 20 weeks is higher than that found in routine practice in high-prevalence countries. In fact, the 23% of the 7% who were "true failures" in the Canadian study (1.6%) is closer to the proportion of failures reported in most programs in high-prevalence countries.

In a prospective study in Bangladesh referring to patients registered in 2000–2001, culture-negative, smear-defined failures were documented and constituted a higher proportion of those failures positive at two months than those negative at two months.[75] On the other hand, only two out of three smear-positive relapses were confirmed by culture, suggesting that transport delays were responsible for suboptimal culture sensitivities in this setting. Van Deun et al. suggested that true relapse and failure* frequencies may fall in between the rates based on smear and culture criteria.[75]

A retrospective analysis of Bangladeshi laboratory registers from 2004 found that scanty bacilli (less than 10 per 100 HPF) were reported in almost 50% of "positive" follow-up series (27.5% having 1–3 bacilli, and 19.3% having 4–9 bacilli). As a rule, only one smear was taken at each follow-up examination, and thus it is not known how many of these results could be confirmed by a second sample. The significance of scanty follow-up smears at the end of the intensive phase of treatment in this setting was suggested by their association with smear-defined treatment failure and unfavorable outcome overall (including default, death, and passively recorded relapse).[85]

*Failure was defined by them as smear-positive (the cut-off for positive smear being 4 acid-fast bacilli in 100 oil immersion fields) at five months or later in treatment, confirmed by at least one more positive smear from two morning samples examined two to four weeks later. [75]

light of the fact that observations in clinical trials had shown that isolated positive cultures occurred but were not associated with adverse outcome of treatment, that positive smears could not always be confirmed by culture, and that laboratory errors did occur.[119]

In 2005, the technical staff of the Tuberculosis Division of The Union concurred that a definition of treatment failure based on sputum smear examination at five months might be unreliable, especially in patients with high initial

bacillary loads and when careful microscopy detects low numbers of acid-fast bacilli.[87] Thus, two positive smears continue to be required to declare a case a failure. Should the second smear be negative, treatment is continued as planned, and cure declared on the condition that smears at the end of treatment remain negative.[87] Finally, it is important to emphasize that when looking at the results of follow-up smears, one should keep in mind whether or not treatment was likely to be taken regularly.

Treatment failure versus nonadherence

When sputum converts from positive to negative during treatment and then reverts back to positive (or from a high positive grade to a low one and then back to a high positive grade), this effect is referred to as the "fall-and-rise phenomenon." Originally, this phenomenon was seen with inadequate treatment and referred to the fall of susceptible bacilli and the subsequent rise of resistant mutants. One of the classic maxims in tuberculosis control, however, stated that the rise is most often due to patients ceasing to take their drugs.[120] Kent et al. in Kenya, after examining records of 311 patients treated in 1964–1965 and 283 comparable cases from controlled clinical trials, pointed out that "treatment failure" often occurred with drug-susceptible organisms under routine conditions, whereas in drug trials, failure was usually with drug-resistant organisms.[121] This indicated that, under routine conditions, many patients simply did not take their drugs and drug resistance did not develop. It seemed there were three main reasons for apparent treatment failure: insufficiently effective regimen, the presence of initial drug resistance, and failure to ingest an adequate quantity of the regimen. Similar observations were made elsewhere: Pamra et al., in a retrospective analysis of 984 consecutive patients on domiciliary treatment in New Delhi, India, in 1965–1966, concluded that irregular treatment contributed considerably to treatment failure, more so than initial drug resistance (although acquired drug resistance was an important contributing factor to treatment failure).[122] A study in Hong Kong in the 1970s found that apparent treatment failure was attributable to a failure to self-administer drugs in the continuation phase of treatment more than it was to drug resistance.[123] A retrospective study in Algeria in the early 1970s revealed that, under routine conditions, the rate of bacteriological failure of 12-month treatment was four times less than the rate of organizational failure.[124] Accordingly, persistence of positive sputum during treatment was primarily regarded as an indicator to review the situation but not necessarily to change treatment.[120]

Though certainly relevant and important, eventually this became conventional wisdom: poor adherence to treatment was the principal cause of treatment failure and was more important than drug resistance.[120,124,125] Clearly, however, this would be context-specific and should not have been expected to apply everywhere and indefinitely; for example, it would depend on program

organization and performance, the treatment regimen, and pattern and level of drug resistance. The assumption that poor adherence was the principal cause of treatment failure should not be expected to hold true in well-organized and well-executed directly observed treatment programs. A consequence of the fact that the assumption was generalized was that patients who did not convert or converted only temporarily during treatment—including those who left the program—were all classified as treatment failures. This position is reflected in the first edition of the Orange Guide.[6] This approach seemed confusing to many practitioners and, it can be argued, may have impeded sensible operational evaluation in some programs. Consequently, the revised, third edition of the Orange Guide in 1994 distinguished between "smear positive" (failure) and "defaulter" (lost) in outcome assessment, and differentiated "failure" and "return after default" in registration of cases for retreatment.[7] This change is reflected in the guidelines issued by the WHO in 1997.[91]

The bottom line is that the former practice allowed an important detail to be lost, with potentially serious consequences for program evaluation and policy development. Some experts insisted that the attention to detail encouraged by the later recommendations was likely to be futile since there would be gross misclassification. Misclassifications of previously treated cases in many programs at the outset should be regarded, it can be argued, as a challenge to improve later classification of cases and outcomes.

Definition of treatment defaulter

"Defaulter" is an unfortunate term because it can be understood to imply a moral judgment, namely that the patient is at fault.[37,126] An alternative term would be "lost," referring to "lost from sight"[6] or "lost to follow-up,"[8] which suggests responsibility on the part of the provider. Nonetheless, the term *defaulter* has become firmly established in tuberculosis surveillance, and thus it is used here.

In a randomized controlled trial investigating adherence to treatment in Bangalore, India, in the early 1970s, the term defaulter was defined as a patient who had not returned within two months of the last missed appointment.[127] The rationale behind the cut-off point was not documented—and probably was arbitrary—but two months leaves ample time for the patient to return on his own initiative or be traced by the treatment supervisor. The definition used in the 1994 edition of the Orange Guide is a patient who has failed to collect medication for more than two consecutive months after the date of last attendance,[7] whereas previously it referred to those who had defaulted for more than three months after the start of treatment.[8] In the continuation phase, two months from the date of last attendance means the patient has gone one month without drugs, or two months if in the intensive phase of treatment. Some programs have used different definitions in the intensive and continua-

tion phases. The definition given above refers to a consecutive period of absence irrespective of the amount of treatment left. It is also necessary to set a limit of how much time to allow for a given treatment episode in the event of repeated, shorter periods of absence (and thus a patient who at the time of evaluation of treatment results—for example, 12 to 15 months after the close of the quarter in which the patient was entered into the tuberculosis register—is still in treatment; that is, the patient has not completed the prescribed regimen) before the subject is to be deemed a defaulter.

Definition of relapse

The definition of relapse in tuberculosis programs in developing countries involves sputum smear examination. In the original version of the Orange Guide, from 1986, relapse was defined as patients with smear-positive pulmonary tuberculosis who were previously treated for active tuberculosis (bacteriologically confirmed or unconfirmed) and declared cured after completing a course of anti-tuberculosis chemotherapy.[6] A change introduced in 1994[7] stipulated that patients could be classified as relapses only if they previously had smear-positive tuberculosis. Some experts argue that this condition is too strict. Revised international definitions published in 2001 clarified that the patient needed to have been declared "cured" or "treatment completed."[128]

What is categorized as relapse in programs can be either a consequence of endogenous reactivation of disease (even a "missed" treatment failure) or a new infection (sometimes referred to as reinfection or exogenous reinfection). The relative contribution of reinfection among cases classified as relapses in programs increases in step with the incidence of tuberculosis,[129] as the higher the risk of infection, the higher the risk of reinfection. A study referring to the period from 1992 to 1998 in a South African area with a very high incidence of tuberculosis found that in 12 of the 16 relapse cases (in HIV-negative persons) studied, the RFLP patterns of the strains of *M. tuberculosis* responsible for the disease differed between the two episodes, indicating exogenous reinfection.[129] This discussion has since been taken further, however, by evidence of the occurrence of "mixed infections," which means that RFLP is not as reliable a tool for this classification as was previously thought.[130,131] This discovery might have implications for treatment policy, program evaluation, and the interpretation of the findings of clinical trials.

Relapse, nonadherence, and treatment failure

Analysis of data from clinical trials (short-course treatment) found a correlation between relapse and the following features: the age of the patient (older patients with large numbers of bacilli being more likely to relapse), pretreatment extent of cavitation, and positive cultures at two or three months of treatment. Thus, factors related to the bacterial content of the lesion are

important.[59] Whether relapse is associated with drug resistance depends on the prevalence and pattern of drug resistance, the drug regimen, and adherence to the regimen.

A study referring to patients registered in Blackburn, U.K., in the period from 1978 to 1987 found that compliance (graded by physician assessment as "good," "fair," or "poor" based on clinic attendance and reports of home visitors, including results of pill counts) was the major determinant of relapse (defined as clinical, radiological, or bacteriological recurrence of disease within 36 months of cessation of treatment). Age, though, was also significantly associated.[132] Compliance was worst in those 15 to 29 years of age, and best in those 60 years of age or older. A study in the tuberculosis program in South India reported that relapse after treatment with a fully intermittent (three times per week) regimen of rifampicin throughout demonstrated a linear relation between the extent of irregularity during treatment and rate of relapse.[133] Nearly 33% of the patients in this study were irregular, 16% defaulted, and the overall relapse rate was 12%. Roughly two thirds of the relapses occurred early, that is, within six months after completing treatment. Among 236 retreatment cases included in a study in Cotonou, Benin (referring to the period from 1992 to 2001), 57% of relapses and 72% of returning defaulters were put on retreatment within 12 months of stopping their initial treatment.[134]

Thus, relapse is related to irregular treatment. If relapse occurs shortly after treatment is completed, it could represent a missed failure either if sputum was not examined at the end of treatment or if there was a laboratory error. This is why, in the old classification system from the 1960s, patients were eligible to be defined as relapses only if they had achieved a certain "disease-free" period (recurrent disease within two years of completing treatment had to be defined as the same episode of disease and not as recurrence). No such timeline (that is, "disease-free" period) is used in the current definitions in control programs. The timing of disease recurrence and interpretation of such data can be regarded as topics for operational research, rather than surveillance.

Death

In outcome analysis in tuberculosis programs, death is recorded if it occurs while the patient is on treatment, regardless of the cause of death. This practice dates back to 1964, as discussed by Horwitz and Palmer.[103] The exact cause of death is not always known. Death during treatment has been associated with late diagnosis, advanced age, HIV/AIDS, and other concomitant diseases.

Almost one in four smear-positive tuberculosis patients in Baltimore from 1993 to 1998 died while on tuberculosis treatment in spite of a good program.[135] Most of the mortality was the result of co-morbid illness rather than tuberculosis. This is not surprising in a setting where tuberculosis has become concentrated in older persons with chronic diseases. If deaths, irrespective of

their cause, are recorded in tuberculosis programs, then deaths can be excluded from comparative analyses of sites where the causes of death differ (old age or HIV, for example). Information on death in many countries is notably inaccurate, and this limitation should be kept in mind when interpreting the results of cohort evaluation. This matter is discussed further in Chapter 8.

Treatment completion and cure

Reflecting on outcome definitions in tuberculosis, especially cure and relapse, an anonymous article published in 1982 pointed out that the views of clinicians and bacteriologists sometimes conflict.[136] Knowing that isolated positive cultures can occur without consequent adverse outcomes, most clinicians would be content with observing an otherwise well patient.[136] The anonymous writer suggested—and he has a point—that although an agreement may be reached on the definition of relapse, defining the term "cure" satisfactorily may prove impossible and discarding it altogether might be better since the term has little bearing on clinical management. Defining adequate treatment should be sufficient.

A somewhat amusing debate on the definition of "cure" took place in the early 1980s.[113,137–140] The following definition was put forward:[137] "A patient's sputum should be rendered negative by both smear and culture at least six months before completion of therapy and remain negative for life." The aforementioned anonymous writer commented that such a definition was obviously flawed, given that it ignored the possibility that the patient could be reinfected and implied that he must be followed for life and in fact could not be classified as cured until he died.[136] Such a definition is hardly useful in clinical trials or operational assessment. Thus, one must come up with alternative definitions depending on the purpose of the exercise.

As discussed further in Chapter 8, the definitions of "cure" and "treatment completed" assume that sputum is examined at certain points during treatment. Subjecting all patients—and not only those where it is indicated on clinical grounds—to follow-up sputum examination at certain time points during treatment is the price of standardization. As advised above, one should take care not to overburden patients unnecessarily with demands to submit a sputum specimen, for example, for the sole purpose of forcing a case to fit a definition. Inside every case is a human being.

Operational deficiencies

As a rule, neither practices nor surveillance are perfect in tuberculosis programs. Contrary to what some might think, this is not only the case in low-income countries. According to program management reports in the United States in 1990, approximately 24% of patients failed to complete therapy

within a 12-month period, and in some areas this proportion was as high as 55%.[141] A retrospective survey in the United States referring to 800 patients registered as relapses in the period between 1981 and 1982 found that 25% did not meet the criteria for recurrent disease.[142] Of the 601 remaining cases, 20% had not had any treatment prescribed on the previous account, 20% were prescribed inadequate or inappropriate treatment, and 33% had been noncompliant with previously prescribed treatment. Some of these figures can be explained with changes in definitions and in the classification system and, it can be argued, demonstrates that a surveillance system will never capture the complexities of tuberculosis. Another perspective, however, suggests using the findings to improve practice. This is in fact the purpose of information systems, which will be discussed in Chapter 8.

Summary and conclusions

When examining case management strategies and accountability, a number of controversial issues appear, such as the role of hospitalization, methods of monitoring progress during treatment, and the definition and management of treatment failure.

Different issues can be distinguished within the debate on hospitalization versus ambulatory treatment: the best interest of the patient, and immediate and future infection control. Whereas early studies suggested that ambulatory treatment was a safe policy, investigators demanded that certain requirements be met if ambulatory treatment was to be made national policy. These qualifications were largely ignored in many countries, which resulted in low quality and unsafe ambulatory services. Furthermore, in policy making one needs to consider different scenarios and, rather than issue an edict recommending "all ambulatory" or "all hospitalized" treatment, to take note of services infrastructure and access in different locations and geographical settings. Although the evidence showed that uniform hospitalization was not an essential part of infection control strategies or necessary for cure, this was not to say that there was no need for hospital beds for the treatment of tuberculosis.

In monitoring response to treatment, the policy model recommended sputum smear microscopy at predetermined intervals during treatment. It has been argued that the model is too demanding in this respect for tuberculosis programs in high-prevalence countries. A reasonable simplification proposed is to perform laboratory follow-up only if the patient's clinical course is unsatisfactory.[143] Such a protocol, however, seems to demand relatively high clinical skills of those caring for tuberculosis patients. In many settings, paramedical personnel are responsible for the process, and thus standardization might be safer. A certain flexibility is called for, nevertheless, when patients cannot spontaneously produce good sputum samples toward the end of treatment.

Given the treatment algorithm recommended in the Union model, the results of smear examination at two months are used in case management to alert the attending health worker to reassess the situation and to detect patients who might benefit from prolonging the intensive phase of the 8-month regimen for new cases, that is, to strengthen the treatment regimen in a targeted manner with minimum workload. This strategy is supported by evidence from a trial in Bangladesh. The aim of sputum smear examination at five months and at the end of treatment is to detect treatment failure. Ideally, when studied, this strategy should be compared to a gold standard such as culture confirmation and clinical and epidemiological relevance. Whereas it is recognized that smear microscopy cannot distinguish live bacilli from dead bacilli—reducing its utility for treatment monitoring—smear microscopy is still recommended for this purpose because it is the only technique widely available in the field, and it is more accurate than chest radiography and more rapid than culture.[87] The operational strategy is conservative: for classification of outcome as treatment failure, repeated positive samples are needed, and scanty-positive results are considered inconclusive. Some over-treatment in the programs in connection with sputum microscopy may result nonetheless. When in doubt, it is good practice to refer patients to medical officers or specialists and to study drug resistance in previously treated cases whenever possible.

Outcome assessment is performed for operational purposes in tuberculosis programs. Its aim is not clinical or epidemiological research but rather to improve the organization of services and identify problems for further study. Many difficult issues surface when trying to establish outcome measures for routine assessment in tuberculosis programs: the problems of scanty and non-viable bacilli and false-positive laboratory results for the detection of treatment failure; the causes of treatment failure (bacteriological versus organizational failure or nonadherence); the issue of early failure (in treatment) versus "late failure" (relapse); and the issue of true relapse (endogenous reactivation) versus reinfection. The bottom line is that the outcome definitions should serve the purpose of the assessment. Outcome evaluation is discussed further in Chapter 8.

Ensuring regular and complete treatment is a central issue in tuberculosis programs and a determining factor for outcome regardless of the limitations in outcome definitions. Nonadherence may be an early warning sign of imminent default or death and is associated with treatment failure, drug resistance, and relapse. The next chapter turns to case management strategies aimed at monitoring and improving adherence to treatment.

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5

Adherence to treatment and case-holding strategies

A drug prescribed is not the same as a drug ingested.

This last chapter on operational strategies examines treatment adherence and case-holding strategies. Some of the approaches discussed in the previous chapter, such as hospitalization and various tactics to do with the drugs and regimens (intermittent treatment and fixed-dose combinations, for example), can also be regarded as case-holding strategies. One of the most heavily debated among the operational strategies in tuberculosis control is directly observed treatment. Accordingly, it features prominently in the current chapter. After considering adherence to treatment in general, the background and development of the policy of directly observed treatment is reviewed. Finally, the chapter looks at other case-holding strategies: incentives, retrieval of non-attendees, and health education and counseling.

Adherence to treatment

Adherence to medical advice or medication is a multi-faceted subject. Global statements such as "up to one half of the people with tuberculosis do not complete their treatment"[1] are common but meaningless at best. Generally speaking, studying adherence is fraught with difficulties. Adherence is a highly context-dependent variable, and that fact may explain some of the disparity among reported results of compliance studies.[2] When reading and interpreting the literature, it is important to consider how compliance is defined, measured, and analyzed.[2] The following discussion aims to address a number of questions. How should treatment adherence be defined in tuberculosis programs? How can it be measured and studied? What are the determinants of poor adherence? What are the consequences? Can health workers predict poor adherence? How can adherence be enhanced?

Definitions related to adherence to treatment

Adherence to chemotherapy has several dimensions: a patient may fail to take any medication, may discontinue therapy prematurely, or may continue to

take the medication but deviate from the prescribed regimen.[3] Definitions of adherence range from percentage of prescribed tablets consumed in a given time span to classifications such as errors of omission, dosage, timing, or purpose.*

An ideal definition of adherence refers to the dosage, timing, and manner of medication, as well as the duration of treatment. As an example, in the tuberculosis program in Nicaragua, new smear-positive cases were treated with an 8-month regimen (2EHRZ/6HT), with the drugs administered simultaneously in a single daily dose as prescribed according to the patient's body weight. Strictly speaking, complete treatment constituted 60 doses under direct supervision in the intensive phase and six monthly drug collections for the continuation phase of treatment, the first coinciding with the last day of attendance for directly observed treatment. Complete treatment could be accomplished in 240 days with 100% adherence. In practice, however, irregularities occur: to give just a few examples, treatment is often omitted on Sundays in outpatient settings, patients do not show up for all of their appointments, and treatment is temporarily discontinued because of other illnesses or adverse effects. The management of irregularities varies depending on the setting, but as a general rule, duration of treatment is extended in case of noncompliance.

Adherence to a given medication regimen is a correlate of clinical outcome.[3] In tuberculosis treatment, failure and relapse (and acquired drug resistance) depend partly on adherence to treatment. Ideally, the difference between adherence and nonadherence would be determined biologically, with nonadherence being defined as the point at which the therapeutic outcome of permanent cure becomes unlikely.[4] Generally speaking, this point is seldom known precisely, and thus arbitrary cut-off points are applied in practice.[3] Variation in cut-off points will affect the sensitivity, specificity, and accuracy of the measurement.

Early reports noted a lack of evidence that minor irregularities in antituberculosis treatment prevented sputum conversion to negative, and that a surprisingly scant correlation existed between regularity and response to chemotherapy—with the exception of complete cessation of treatment.[5] Thus, provided the regimen was adequate, there seemed to be a considerable margin of safety.[6] It was also observed that the consequences of various types of irregularity were likely to differ, that the bacteriological consequences of gross irregularity early in treatment were probably worse than the same degree of irregularity in the later phases of treatment.[5] A U.S. study in the 1970s documented supervised intermittent 2-drug regimens in which individual missed treatment rates were as high as 12% without demonstrating adverse effect on treatment outcome.[7] The investigators concluded that up to 15% of the intermittent doses could be

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*E. C. Wright quoted in Farmer,[3] p. 1075.

missed without adverse effects on patient outcomes. In 1983, Fox pointed out that introduction of short-course regimens reduced the compliance required of the patient and the risk of therapeutic failures associated with premature discontinuation of treatment.[8] According to Fox, the evidence showed that treatment effectiveness declined gradually as the duration was shortened below six months, but even with treatment for three months about 80% of the patients enrolled on the most potent short-course regimens were most likely cured. Further, even in the first three months of treatment, the omission of some doses probably would not appreciably alter the regimen's success, and an even shorter duration of treatment might achieve a substantial rate of cure. In any case, if bacteriological relapse occurred, it was almost invariably with fully susceptible organisms, facilitating successful retreatment.[8]

Three types of nonadherence are commonly distinguished in anti-tuberculosis treatment: total default, irregularity of attendance, and irregular medication.[9] In the modern tuberculosis program, default (dropout) is clearly defined whereas irregularity is not. A definition for irregularity, though, can be derived from the definition of default. The term "defaulter" refers to patients whose treatment is interrupted for two consecutive months or more[10,11] or who do not complete a full course of treatment in a given time period.* Although the definition of default is an operational one with program evaluation as its primary purpose, it is also relevant for case management. Strictly speaking, anything between 100% adherence and default is considered irregularity, but "significant" or "important" nonadherence is often defined specifically by the inclusion of cut-off points. To give an example, in a study in Zaire in 1991, patients were considered compliant if they completed at least 11 of the 12 months of the standard regimen, at least 56 of the 60 doses of intensive phase and never interrupted therapy for more than two consecutive weeks.[12]

Some irregularity in treatment is common in any setting. A compliance trial in selected health centers in Managua, Nicaragua, in 1992 found that 40% to 45% of the patients missed at least one out of 60 consecutive appointments in the intensive phase.[13] Similarly, more than one half of the patients in a case-control study in Bangalore, India, in 2003 missed at least one dose of treatment whether in the case group (defaulters) or control group (completed treatment).[14] A study conducted in urban Chilean tuberculosis clinics in the 1980s† found that noncompliance decreased from 22% in 1978 to 7% in 1982.[15] Thus, the occasional missed appointment is common, and adherence to treatment in a given setting is not a constant.

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*In the Union model, those who are still on treatment at the time the treatment results are evaluated, which is 15 months after the closure of the quarter in which the patient was entered into the tuberculosis register.[10]

†Cited in Homedes and Ugalde,[15] p. 307.

Measuring and studying adherence to treatment

Assessment of the degree of adherence can be difficult. Various methods have been tried: self-report (patient interviews), collateral reports (physicians, nurses, or family members), appointment keeping, directly observed treatment, pill counts, biochemical tests, electronic monitoring, and biological markers.[3,15] None of the methods is perfect and, strictly speaking, all methods of adherence monitoring constitute an infringement on patients' privacy.

In 1979, Feinstein claimed that the best way to find out what a patient had done was simply to ask the patient directly.* While self-reporting is considered unreliable by many because it tends to overestimate compliance, interviewing the patient is nevertheless the most widely applicable method of measuring compliance, and careful questioning will identify more than one half of those who are noncompliant without falsely labeling many of the compliers.[15,16] Furthermore, one can detect most nonadherent patients by watching for nonattendees and non-responders as well as by asking non-responders about their compliance.[16]

Pill counts refer to counting the number of pills that the patient has not taken in a given time period and calculating an adherence ratio (for example, $(60 - 12)/60 = 0.8$).[3] This simple method is generally considered to overestimate compliance but to be more accurate when conducted on unannounced home visits rather than at predetermined clinic visits. However, it does not reveal the pattern of nonadherence.[3,17] Although direct observation of treatment should reveal the pattern, it is considered by many to be neither practical nor required in most situations. Moreover, it is not foolproof in the case of deliberate noncompliers.[3]

Measurement of an expected biological effect—such as heart rate treated with beta blockers—can sometimes be used in measuring adherence.[2] Biological effects, because they often are the ultimate goal of therapy, may seem perfect adherence markers. The problem with this method is that absence of an expected effect may or may not be the result of nonadherence.[2] Nevertheless, most health professionals would agree that definitions of adherence ideally should be outcome-oriented and shift from strict adherence to a regimen toward therapeutic efficiency.[2] In accordance with this belief, ethical standards for adherence research dictate that attempts to increase adherence should be judged by their clinical benefits, and not simply by their effects on adherence rates.[18]

Homedes and Ugalde emphasize that patient adherence and prescribing practices should always be examined together and as part of an overall assessment of quality of care.[15] When the quality of care is not guaranteed, efforts to improve adherence might be undesirable. For example, if the diagnosis is

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*Quoted in Homedes and Ugalde,[15] p. 297.

wrong, noncompliance might be an appropriate response. An even more complicated issue is the paradoxical impact on HIV drug resistance of good adherence to anti-retroviral treatment.[19] The longer a dose is delayed in anti-retroviral treatment, the lower the drug concentration falls and the more virus replication occurs, and intermittent therapy and poor adherence are the principal factors leading to drug resistance.[20] Thus, in a scenario where anti-retroviral treatment programs implement direct observation of treatment once a day when treatment twice a day is prescribed, good adherence as measured by attendance could hinder success if it puts the patient in the 80% to 90% adherence window, which seems to promote drug resistance.[19] Similarly, it can be argued that observing one out of two to three weekly doses in intermittent anti-tuberculosis treatment could promote drug resistance.

Care is needed when generalizing the results of compliance studies between diseases and settings. In this context, Homedes and Ugalde specifically point out that whereas in industrialized countries self-medication and patient autonomy are celebrated, in low-income countries, self-medication may be encouraged by poor and unaffordable health services coupled with few regulations controlling the sale of drugs, or weak enforcements of existing regulations and aggressive marketing by the pharmaceutical industry.[15] In the West, patients make reasoned decisions about their treatment, experimenting with dosage or combination of drugs, discontinuing regimens and trying alternative therapies.[15] Much of the support for the type of illness self-management encouraged in the West results from studies of chronic degenerative diseases. It is reasonable to question the applicability of patient autonomy to life-threatening conditions or diseases with serious individual and public health consequences and for which there is a known cure. The implications of contagious and degenerative diseases are very different, and it is implausible, to say the least, that helping patients adhere to treatment regimens for diseases such as tuberculosis and malaria could be construed as a manipulation to foster professional control or promote biomedicine, as is sometimes done.[15]

Finally, adherence studies should always be part of a process to improve adherence.

Tuberculosis programs

In 1987, Chaulet summarized the following methods used to assess adherence in tuberculosis programs:[21] when treatment is directly observed, the ticks on the treatment card can be counted; when treatment is self-administered, appointment regularity, patient interviews, and pill counts can be reviewed; indirect measurements at the program level include the defaulter rate as measured in cohort analysis, the proportion of previously treated cases among patients registered in the program, the consumption of anti-tuberculosis drugs against case notifications, and the incidence and nature of drug resistance.

In the Union model, treatment was directly observed in the intensive phase of smear-positive cases, and the degree of adherence could be assessed directly from the treatment card by looking at the number of dates (or doses) noted. When treatment was self-administered, as in the continuation phase of treatment in new cases, appointments (drug pick-up dates) were not fixed; instead, patients were to attend when they had taken all the tablets issued to them, or preferably a few days before so as not to run out of their prescribed medication. Thus, the interval between pick-up dates was a measurement of adherence, even though it did not give exact details of patterns of nonadherence.

Studies on adherence to anti-tuberculosis treatment

As a general guide, studies in compliance trials having a single intervention group and a control group must include more than 60 patients per group in order to have a power of at least 80% to detect an absolute difference of 25% in the proportion of patients judged to have adequate adherence.[18] As always in tuberculosis research, smear-positive cases should be analyzed separately, and the quality of diagnosis needs to be assured. One of the problems with studying defaulters is that they are difficult to track down; that is, participation rates are low, and thus the results may be biased.

Regularity of treatment can be measured with the following calculation: expected duration of treatment divided by actual duration of treatment (in number of days) for the intensive and continuation phase, respectively,[22] with the increasing value reflecting decreasing regularity. When studying timing of default, one can measure the actual number of doses (days) divided by the expected number of doses (days), with a declining value reflecting decreasing completeness.

Regularity of treatment can be regarded as a continuous variable (using a sliding scale) or a dichotomous variable ("regular" versus "irregular"). Default could be a dichotomous variable, although timing of default is likely to be important. Adherence can be treated as an independent variable or a dependent one.[2]

Finally, what about markers of treatment efficacy? Is smear conversion (for example, at two months of treatment) such a marker or at least an acceptable proxy marker? Outcome of treatment (death, default, failure, and success), but ideally drug resistance and relapse rates, are the ultimate—and therefore preferred—outcome measures.

Causes of poor treatment adherence

Anti-tuberculosis treatment is relatively simple: it is temporary, taken as a single daily dose, and unlikely to result in major adverse effects. Nevertheless, nonadherence is common. Determinants of adherence are sometimes divided

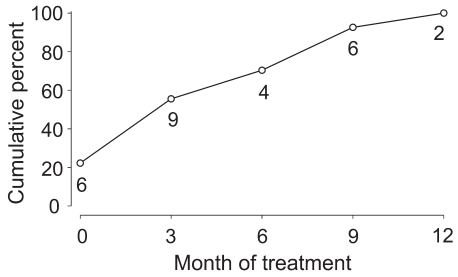
into four types of factors: characteristics of the treatment or regimen, patient factors, the relationship between provider and patient, and the system of care. To some extent, however, these factors are interrelated, making it difficult to distinguish one from another. In the early 1970s, researchers observed that if there was a high defaulter rate, the system and services were mainly at fault.[23] In recent times, the wider social system has been increasingly blamed for treatment default—just as it is for the persistence of tuberculosis in general. As Farmer pointed out in 1997, throughout the world, those least likely to comply are those least able to comply.[24] In this context, he quoted Barnhoorn and Adriaanse's 1992 study in India, in which these two socioeconomic variables were the strongest predictors of adherence to anti-tuberculosis treatment: monthly family income (whether looking at total or per capita income) and type of family dwelling.[24]

The defaulter problem, in terms of magnitude and immediate underlying causes, is compound and context-specific to an important extent. Traditionally, the defaulter problem was explained by the fact that patients felt better after only a short time in treatment and subsequently dropped out of the program as symptoms subsided. The results of a study conducted in a centrally placed facility in Addis Ababa, Ethiopia, in the early 1980s suggested that whereas the single most common cause of default was clinical improvement before completing therapy (22%), other reasons accounted for the majority of program defaults.[25] These findings keenly emphasize the importance of analyzing the immediate causes of default—especially in areas beleaguered by such a problem—for information that might lead to default-reduction actions in response.

Another widely cited explanation for default involves geographic proximity to health units. The relationship between adherence and physical distance from health units is complex, however. In a case-control study carried out from 1997 to 1999 in the Oromia Region of Ethiopia's Arsi Zone, health stations had the highest defaulter rates, followed by health centers and hospitals.[26] Moreover, in a 2003 retrospective case-control study in an urban setting in Bangalore, India, the median distance traveled by patients, two km on average, was no different for those who defaulted and those who completed treatment.[14] In addition, access to services and hospitalization plays a controversial, influential role in adherence. A 1993 study in Canada reported that compliance was higher among those initially hospitalized (the average stay in hospital was 17 days),[27] but these findings contradict those of a 1999 study conducted in Uganda.[28] Changing health units during treatment may also contribute to default.[29–31]

In the predominantly urban environment of Hong Kong in the 1960s, a relatively high proportion (17.5%) of tuberculosis patients defaulted.[9] Alcoholism and drug addiction were among the recognized reasons for default. Another

Figure 5.1 Timing of default in a trial in southern India

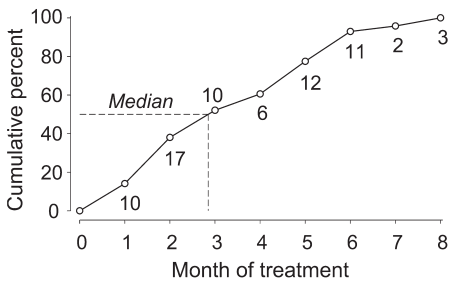


Adapted from Toman,[33] p. 211.

problem altogether involved patients who attended public clinics for confirmation of a diagnosis made by another treatment provider to which they then returned for treatment. This is a common finding in pluralistic health systems with insufficient coordination regarding tuberculosis control. In 1992, Rubel and Garro in the United States stressed the fact that adapting the services to patients' lifestyles was often ignored by tuberculosis programs.[32] This is particularly true in the context of changing social patterns in industrialized countries in recent times, such as the United States and the former Soviet Union. On the other hand, in low-income countries, the failure to provide accessible health services of reasonable quality is an important culprit of default.

When studying treatment regimens for causes of default, the role of injections, the duration of treatment, and reliance on daily instead of intermittent regimens frequently recur as important factors. Intermittent treatment and injections are discussed in Chapter 4. Many examples of high defaulter rates and early default exist in the literature, irrespective of the regimens used. In a random sample from a routine service in Kenya, where an 18-month regimen was used, the majority of those who defaulted left treatment during the first six months after enrollment.[33] In a 1974 randomized controlled trial of compliance in Bangalore, India, in which a 12-month regimen was used, drop-out was highest in the first three months of treatment[34] (see also Figure 5.1). A retrospective review of routine reports and registers in 95 Nicaraguan health centers in 1995 reported that when a short-course (8-month) regimen was administered, 149 out of 1,504 patients (10%) did not complete a full course of treatment.[35] Of 71 consecutive defaulters in 1993–1994, 27% left the pro-

Figure 5.2 Timing of default in the tuberculosis program in Nicaragua



Data from Cruz et al.[35]

gram before completing the intensive phase of treatment (two months), and 93% before completing six months of treatment (see Figure 5.2). Quarterly reports showed a decrease in defaulting from 15% in the 1990 cohort to 7% in the 1994 cohort, all while using an 8-month regimen. A study in Hong Kong referring to patients registered in 1999 found that 41% of those who eventually defaulted did so within the first two months.[36]

The expected duration of treatment is important. It was agreed early on that defaults commonly occurring even in the first few weeks of regimens of 12 to 24 months in duration did not necessarily mean that the same problem would result in short-course treatment. In other words, if patients anticipate 6 to 8 months of treatment, they may well endure. If the expected duration of the treatment is unspecified or not communicated to the patient, the patient, lacking a concrete goal in mind, may be less likely to persevere. Finally, some practitioners have argued that patients' swift improvement in short-course treatment—as compared to the slower progress in 12-month regimens—could encourage early default.

At which stage in the course of treatment a patient drops out of the program is important. The causes of early default may well be different to those of late default. Furthermore, the proportion of defaulters who return to treatment is related to the timing of default. In Nicaragua in the mid-1990s, the number of patients registered as returning defaulters in the program was comparable to the number of early dropouts (before completing two to three months of treatment) in 8-month treatment of new smear-positive cases in the previous year.[35] This dynamic has to do with the consequences of default: the longer the treatment duration before default, the more likely it is that the patient will be permanently "cured." Examples of studies are presented in Box 5.1.

Consequences of poor treatment adherence

Poor adherence to anti-tuberculosis treatment can lead to longer, more severe illness and even death, as well as delayed smear conversion, prolonged infectiousness, treatment failure, relapse, and drug resistance. Therefore, poor adherence to treatment is a concern for the community as well as for the individual. In a retrospective study in New York, reported in 1997, 48% of 184 culture-positive patients were nonadherent (nonadherence defined as not keeping clinic appointments for at least two consecutive months or three or more months in the course of a year). Of the 88 nonadherent patients, 89% did not keep clinic appointments for at least two consecutive months, 6% did not keep clinic appointments for three or more months in the course of a year, and 6% refused treatment from the start. On average, nonadherent patients took three to four times longer to convert to negative culture than adherent patients, were

Box 5.1 Examples of studies of adherence to treatment

In a U.S. clinical trial, carried out in the 1980s and comparing 9-month and 6-month regimens, noncompliance occurred in 29% and 17% of patients during treatment—a significant difference.[37] Treatment was self-administered, and patients were seen every two weeks in the first eight weeks and every four weeks for the remainder of therapy. Noncompliance was defined as missing at least 14 consecutive days of treatment or two clinic appointments.

A study of patients registered in 1985 in Escourt and its surroundings in the United Kingdom found that adherence to treatment (defined as a patient attending the clinic 80% of the times scheduled for the full course of treatment) was poorer in rural areas than in urban ones and the more remote the clinic, the worse the adherence.[38] The investigator speculated that health personnel in rural areas were generally poorly trained, in-service training was nonexistent, clinical staff received little or no encouragement or recognition, contact with medical colleagues was lacking, and the workload was excessive.

A case-control study in India's Wardha District that collected interviews from 52 compliant tuberculosis outpatients and 50 noncompliant ones from 1988 to 1989 (noncompliance was defined as failing to take drugs for more than 15 days) found that many patients were noncompliant simply because they forgot to take the medicine.[39] This behavior is potentially amenable to action such as the implementation of reminders. In this study, rural patients who had their medications delivered to their door were more compliant, and professional and family support was critical in improving compliance whereas support from friends seemed to have the opposite effect. The investigators conjectured that friends, misinformed about the treatment, might have discouraged compliance.[39]

A study conducted in Taif, Saudi Arabia, from 1996 to 1997, found that among Saudi nationals, female patients were more likely to default than males, the opposite being the case among non-Saudi nationals.[40] (Default was defined as a patient failing to attend a first appointment after discharge from the hospital, followed by unsuccessful attempts at retrieval.) Elderly and previously treated patients were more likely to default.

In Madagascar's Tamatave Province, a retrospective case-control study in an urban setting, including 38 smear-positive patients who defaulted from treatment in 1993 and 111 controls who completed treatment under comparable conditions, found that default appeared to be linked to transportation time, the sex of the patient, patient information, and the quality of communication between patients and health workers.[29] The investigators concluded that improved communication skills and attention from medical staff could encourage more patients to complete treatment. In this study, treatment was given via a 12-month regimen, and default was defined as interrupting treatment for more than one month. As is common in studies of defaulters, this research could only trace and include 40% (38/95) of consecutive defaulters; consequently, the results may be biased.

more likely to acquire drug resistance (this finding was not statistically significant, though, and reinfection not excluded), and were less likely to complete treatment.[41]

From the community perspective the most serious consequence of poor adherence to treatment is drug resistance. Incorrect treatment (monotherapy or effective monotherapy) and the so-called "sequential regimens mechanism" resulting in functional monotherapy are often identified as the culprits of acquired drug resistance. But can resistance result solely from taking drugs irregularly?

Drug resistance is commonly associated with previous treatment. In Algiers, in the period from 1987 to 1990, repeated courses of treatment were linked to increasing drug resistance. The proportion of any drug resistance among groups of patients having undergone one (27 patients), two (22 patients), or three or more (32 patients) previous courses of treatment was 33%, 64%, and 100%, respectively, or 22%, 54%, and 97% if looking at multidrug resistance (in a program using a 6-month regimen with rifampicin throughout).[42]

Mitchison has described the potential mechanisms for drug resistance during "correct" chemotherapy, provided there are repeated cycles of killing and regrowth as might occur with irregular treatment even if all drugs are ingested simultaneously when taken.[43] Drug resistance by these mechanisms would be more likely to occur early in treatment, when bacterial counts are high, and with widely spaced intermittent therapy. Repeated cycles of killing and regrowth could explain drug resistance surfacing during chemotherapy and also drug resistance in relapses after chemotherapy. This, Mitchison argued, emphasizes the importance of fully supervised drug taking. His argument seems to imply that abrupt interruption of treatment (that is, one-time, clear-cut dropout) threatens less—if it does at all—to engender drug resistance than does continuous irregular treatment. Default is nonetheless often preceded by a period of irregularity. But are these speculations relevant for tuberculosis programs?

An illustrative example can be found in a report from Ivanovo Oblast, in Russia, a setting of increasing drug resistance. The report refers to patients registered in April through June of 1999. Treatment "interruption" was defined as a patient discontinuing medication for two to eight consecutive weeks but eventually restarting treatment. In contrast, a "successful treatment" described patients completing 6-month treatment regimens within 12 months (provided they could not be classified as treatment failure or default).[44] Of 54 new smear-positive patients, none of whom had multidrug resistance at the start of treatment, 15 (28%) interrupted treatment: 3 during the intensive phase, 10 during the continuation phase, and 2 during both phases. The median number of interruptions was 2 (range 1–6). All in all, 31 patients completed treatment, 6 failed, 12 defaulted, and 5 died. For those who completed treatment, the

median duration of treatment was 10 months (range 6–18). Clearly, someone completing a 6-month regimen in 12–18 months in this setting has received highly irregular treatment, inviting repeated cycles of killing and regrowth. Treatment was commonly interrupted repeatedly before default, and thus repeated cycles of killing and regrowth may occur in defaulters as well.

Predicting adherence to treatment

Some health workers with experience treating tuberculosis patients—particularly nurses who have close, frequent contact with patients—claim that they can predict which patients will likely have difficulty adhering to treatment. Even though this ability has not been documented systematically, it is reasonable to believe that health professionals can develop an intuition about treatment adherence. After all, some health workers are more successful than others in curing tuberculosis patients in otherwise similar settings. Identifying those who are at risk of defaulting and responding to their needs so as to facilitate treatment adherence involves instinct as well as motivation, skills, and experience. An anonymous 1972 editorial in *Tubercle* observed the following:

> Knowledge of human nature and skills in advising, encouraging, reassuring, convincing, and if need be, dominating patients are essential attributes for all clinicians. If the system in which they are working is efficient, it should not be difficult for good clinicians to obtain good results. If the system is inefficient, it may be impossible. But standardization and "mass-production" methods are not necessarily incompatible with efficiency and personal service. Indeed they may make personal service easier. The service may have to be given by less well-trained and experienced staff. But if the system within which they are working is efficiently organized, they will be freer to devote time to individuals; and the "clinical approach" of humanity and understanding does not necessarily require long interviews and discussions, nor is "clinical work" limited to medically qualified staff.[23]

If it were possible to predict nonadherence before treatment began or shortly thereafter, efforts and resources could be targeted at patients who are at risk of nonadherence rather than those who are not.[45] One classic maxim of the tuberculosis literature, however, states that adherence cannot be predicted at the level of the individual patient. This observation is not entirely borne out by the evidence, though. Various risk factors for nonadherence and signs of imminent default have been identified in different contexts.[36,46] Good tuberculosis programs, where health services factors play a lesser role, often pinpoint some warning signs of default. Some examples of studies into the matter are presented in Box 5.2. Ideally, any risk factors identified, regardless of the setting, would be examined to determine their sensitivity, specificity, and predictive value before an evaluation of their overall usefulness was rendered.

Box 5.2 Patients at risk for default and signs of imminent default

In a 1974 study in Bangalore, India, men were more irregular in adhering to treatment than women.[34] This observation contradicted previous ones from India and early observations from Nairobi, Kenya.[6] While many later studies have found that default is more common among male than female tuberculosis patients, this should not be taken for granted in any given setting, but rather should be investigated locally.

It is common to find that default is associated with previous default. A study in Argentina in the 1980s reported that among 390 patients receiving ambulatory treatment at a hospital, 38% did not complete treatment. Defaulting often occurred early in treatment, and once patients defaulted, they were at increased risk of defaulting again.[47] Default has been linked to previous default in studies in the Netherlands, in the 1990s;[48] Saudi Arabia, from 1996 to 1997;[40] Benin, in the period from 1992 to 2001;[49] Bangalore, India, in 2003;[14] and Hong Kong, in 2004.[36] This phenomenon shows more than anything else that an underlying problem has not been identified and/or solved.

A retrospective record review in Canada, referring to the year from 1987 to 1988, found that at the time of the first follow-up visit, tuberculosis patients identified by nurses to have suboptimal compliance were more likely to fail to complete therapy than those not identified thus.[27] Similarly, a Hong Kong study reported that an irregular initial adherence pattern was a risk factor for default.[36] In a 1992 study of health centers in Managua, Nicaragua, defaulting occurred mainly in the continuation phase of treatment and was associated with young age, male sex, and regularity of treatment in the intensive phase. Males who attended irregularly in the intensive phase were at greatest risk of default.[13] A study in India referring to patients registered from 1999 to 2000 found that one fifth of all registered patients took their drugs irregularly (according to the definition used in the study) during the intensive phase of treatment, and 40% of them eventually defaulted.[50] Investigators concluded that when patients do not attend for scheduled appointments, health workers need to take prompt action to counsel the patients or consider changing the treatment site or the treatment observer to suit the patients' preferences.

A prospective study conducted in 2002–2003 in Greater Banjul, the Gambia, identified risk factors for default and specified when they exerted greatest influence over patients during treatment: defaulting was more likely among those who doubted that treatment would work (particularly in the first 90 days of treatment) than those who did not doubt the treatment's efficacy, and among those who incurred significant time or money costs traveling to receive treatment (more important after 90 days of treatment).[46] All forms of tuberculosis were included in the study, and treatment was intermittent (three times a week) and directly observed. The study looked at irregular treatment, defined as missing three consecutive appointments (occurring in one out of four patients) and default (8%). The authors suggested a policy change: after three months of directly observed treatment, the rest of the treatment course should be home-based and self-administered to prevent dropout in the later stages of treatment.

Strategies to improve treatment adherence

Munro et al. reviewed health behavior theories in 2007 and concluded that the little empirical evidence on their effectiveness in promoting treatment adherence was fragmented and contradictory.[51] They point out that the applicability of many of the theories to contexts other than those in which they were developed is unproven. The issue of infectiousness and the potential for drug resistance make achieving adherence to anti-tuberculosis treatment an urgent concern, but large-scale implementation of some of the more complicated interventions based on behavior theories may be time consuming, complicated, and costly.[51] Arguably, adherence to anti-tuberculosis treatment does not really call for behavior change, because treatment is temporary. Changing patient behavior seems more appropriate in promoting long-term adherence to treatment of chronic conditions. Furthermore, research on adherence in tuberculosis tends to indicate that poor adherence is related to factors outside of the patients' control, such as the organization of clinics and services and social forces such as poverty and migration.[51] Thus, Munro et al. conclude, as have many before them, that interventions to improve results in tuberculosis treatment should focus primarily on providers, the provider-patient relationship, the health system, and contextual factors.[51] Some of these factors are discussed in Chapter 7.

Homedes and Ugalde divide patients roughly into four categories: those who are motivated but lack knowledge, those who are knowledgeable but lack motivation, those unable to comply due to external constraints, and those who simply behave contrary to the advice and recommendations of heath care providers.[15] A good rapport between patient and provider is likely decisive for adherence. In Chaulet's words, "When the thinking behind the health care services is centered around the thinking of the patients—that is, when it is focused on meeting their needs—it will be possible to bring the treatment received into line with the treatment prescribed (p. 24)."[21] Chaulet emphasized that health personnel must ask about the patients' conditions and circumstances and then see to it that they receive necessary support. According to him, health workers also need to identify risk factors for nonadherence and prescribe any appropriate supervised therapy. Increased attention to patients via increased attention to staff—in the form of training, supervision, and motivation—is also effective. This is discussed in Chapter 10.

Directly observed treatment

In the mid-1950s, irregularity in outpatient treatment of tuberculosis was recognized as a problem in developing countries, and in response, supervised treatment was recommended. Subsequently, other developments that aimed to facilitate supervised treatment and improve regularity in self-administered

treatment came into being, such as intermittent regimens introduced in the 1960s and short-course treatment in the 1970s.[52] Further strategies included fixed-dose combinations, an intervention directed at helping health workers and patients to adhere to recommendations.

Tuberculosis is an important disease that affects vulnerable populations in rich and poor countries alike. Regardless of the national setting, problems of poverty, social marginalization, and substance abuse may compound the already difficult circumstances of tuberculosis patients, thereby posing obstacles to treatment adherence. Directly observed treatment has come to be a widely acknowledged strategy to improve treatment adherence for tuberculosis control and to prevent or reverse problems of (multi-) drug resistance. Not everyone endorses the strategy, however.

Historical background

Many people associate the term "directly observed treatment" with short-course chemotherapy. In the Union model, directly observed pill swallowing was specifically recommended in the 1980s when rifampicin-containing regimens were introduced, and the WHO definitively linked the term "directly observed treatment" (DOT) with short-course regimens in the 1990s, when they gave their new tuberculosis control strategy the name DOTS (for directly observed treatment, short course).

The idea of health workers supervising the administration of anti-tuberculosis treatment, as well as the term "directly observed treatment" itself, predate short-course chemotherapy though. In an article published in *Tubercle* in 1958, Fox discussed the problems of self-administration of drugs in the context of leprosy programs and anti-tuberculosis chemotherapy studies in Madras, India.[53] Similar concerns arose from the results of drug trials in Nairobi, Kenya, in the late 1950s[17] and in the Kolin studies in Czechoslovakia in the 1960s.[54] In contrast to patients who self-administered their treatment drugs, Fox noted in his article, a group of hospitalized patients in Madras had no real difficulty taking their medicine regularly under direct observation.[53] These experiences form the basis of the argument for a policy of directly observed treatment as opposed to self-administered treatment. Although these early findings cannot be applied as prima facie evidence for the present day short-course regimens and contexts, they may explain the traditional belief among tuberculosis physicians that drug taking—particularly in the intensive phase of treatment of smear-positive patients when bacterial load is high—was best guaranteed with hospitalization where treatment could be strictly supervised.[55] Direct supervision of drug administration in the intensive phase was certainly deemed more important than direct observation in the continuation phase, in which the number of bacilli in lesions was by then greatly reduced and the risk of selection of resistant mutants much decreased, if not negligible.[56]

It has been debated to whom credit for the strategy of directly observed therapy is due.[57,58] When answering this question, it is important to remember that at that time—just as is true today—tuberculosis experts sat together sharing ideas during committees, meetings, and conferences. Tracing the origins of ideas may be tricky, therefore, and largely irrelevant. With this caveat, the origins of supervised and directly observed treatment are reviewed in Box 5.3.

In the early days, directly observed treatment was used on a small scale in various countries. More precisely, it was applied in selected cases of treatment adherence problems, for example in Santiago, Chile, in the early 1960s.[65] In the programs collaborating with The Union, country-wide expansion of short-course regimens was accomplished in the 1980s. In accordance with the concerns raised by Fox and Mitchison, universal supervision of treatment rather than selective supervision was considered essential to ensure correct and regular treatment in the programs. Supervised treatment was implemented as a strategy primarily to minimize relapse and prevent drug resistance. As discussed elsewhere, hospitalization was often involved to allow treatment supervision in the African countries collaborating with The Union and also in difficult settings in Nicaragua. It is sometimes stated that The Union advocated universal hospitalization for directly observed treatment.[57,66] Such an approach, however, was the decision of local policy makers in Africa.[67] The Union did recommend hospitalization in areas where ambulatory treatment was not feasible. Despite

Box 5.3 The origins of supervised and directly observed treatment

In 1962, Fox raised the issue of entirely supervised treatment, declaring it both important and feasible: "[t]he studies at the Madras Center have shown that self-administration is a problem . . . Even a year of supervised administration in a sanatorium does not avoid subsequent irregularity (p. 310) . . . long-term daily supervised administration can be organized under special circumstances even in developing countries (p. 321)."[6] Even so, Fox warned that organizing supervised treatment on a wide scale would be difficult, especially if entrusted to staff other than highly trained paramedical personnel.

The unreliability of self-administered treatment was documented in clinical studies in Czechoslovakia's Kolin District in the early 1960s. With a regimen of a total duration of 18–24 months, 43% of the patients did not take their PAS regularly at home, and nearly one in five patients did not take their isoniazid regularly.[54]

A scholarly paper published in 1963 revealed that in chemotherapy trials in Nairobi, Kenya, where 12-month treatment was self-administered on ambulatory basis (with patients attending at clinics once a month and the staff making sporadic surprise home visits), only about one half of the patients received at least 85% of the drugs prescribed in the first six months of treatment, and even fewer patients received them in the subsequent six months.[17]

Box 5.3 *Continued*

A paper from Madras, India, in 1964 concluded that "Irregularities in drug-taking . . . may lead to unfavorable therapeutic results; this might be avoided by supervised administration of the drugs. Daily supervision is clearly impracticable in developing countries but regimens in which the drug is administered intermittently—say, twice a week or less frequently—are, if effective, more likely to gain general application (p. 247)."[59]

In early experiments with directly observed treatment in the largely urban setting of Hong Kong in the 1960s, up to 30% of the patients discontinued therapy prematurely even if organization in the clinics was patient-centered.[9,60] Daily supervised therapy apparently was not a viable answer to the problem of compliance, given that both patients and staff seemed to tire of the routine.[60]

A 1969 clinical trial in Singapore, that compared twice-weekly supervised treatments with streptomycin and isoniazid to self-administered treatments with isoniazid and PAS in the continuation phase after a three-month daily intensive phase of all three drugs, found that major interruptions of treatment occurred more frequently in the self-administered regimen (12/155 compared to 3/163) than in the supervised ones.[61] However, in 14% of those allocated to the supervised intermittent regimen, it could not be fully implemented.

In a randomized controlled trial of compliance in an urban setting in Bangalore, India, reported in 1974,[34] 232 patients were allocated to a twice-weekly regimen with streptomycin and isoniazid given under supervision: of the 232, 58 patients (25%) refused to start treatment, 52 of them opting for an unsupervised regimen instead. The main reasons given for refusal to adhere to the regimen were unsuitability of working hours (25 patients) and distance from home to the center (19 patients). Of 242 patients allocated to a self-administered regimen with isoniazid and thioacetazone, only 3 refused. If, in this study, distance from the center affected adherence among the group receiving supervised treatment, in a rural setting it can be expected that supervised treatment on ambulatory basis would have been even less feasible. Thus, in spite of the optimism expressed by Fox and coworkers, supervised treatment on an ambulatory basis was indeed a challenge.

Eventually, in the 1980s, short-course treatment was introduced in low-income countries, and in 1991 the efficacy of fully intermittent (three times a week) short-course treatment for smear-positive pulmonary tuberculosis was established based on results of clinical trials in Hong Kong.[62] The introduction of short-course treatment into low-income settings was a milestone in facilitating supervised treatment in general, and the proven efficacy of fully intermittent short-course treatment was undertaken specifically to facilitate fully supervised ambulatory treatment in urban settings.[63]

In 1986, Mitchison and Nunn emphasized that the clinical trials had shown that initial rifampicin resistance greatly compromised the results of short-course treatment, and widespread rifampicin resistance would threaten the success of short-course chemotherapy.[64] Thus, they advised, in order to minimize the chances of acquired rifampicin resistance, the drug should be used only in properly designed and supervised treatment regimens.

the fact that Mitchison refers to this advice as "a mistake,"[57] in light of the rudimentary and low quality health services prevailing in many developing countries at the time—particularly in rural areas—this counsel was probably wise. However, one might have expected that, after a quarter of a century, the health services would have advanced and the programs would have evolved.

Terminology

Mitchison claims that supervised treatment was inaccurately renamed "directly observed treatment."[43] "Supervision of treatment" is a broader term because supervision is more than direct observation of a patient swallowing tablets. Arguably, supervision of treatment can be undertaken only by properly trained health personnel—with or without the application of directly observed pill swallowing.

What did supervision of treatment imply? The report of the Expert Committee in 1964 pointed out that intermittent treatment had the advantage that it could be "entirely" supervised, thus overcoming the major difficulty of irregularity inherent in the long-term self-administration of drugs.[68] The Expert Committee of 1974 noted that "careful" supervision was required to ensure that a patient actually received the full course of a self-administered regimen.[69] Such careful supervision apparently included surprise checks, pill counts, and analysis of the patients' urine for traces of anti-tuberculosis drugs.[69] The Committee acknowledged, however, that this kind of supervision often was not possible, and that administering intermittent regimens under "full" supervision, with treatment directly observed, represented an alternative approach.[69]

An anonymous editorial published in *Tubercle* in 1970 discussed this issue. The author's comment makes for interesting reading, as it touches on issues that figured in a debate that took place a quarter of a century later.

> "Supervision" can have several meanings in the context of medical treatment. It may imply only indirect overseeing of and responsibility for the actions of others—as a physician supervises his staff. Or it may imply direct overseeing by one person of a particular action of another, in order to ensure that the action is taken. It is in this sense that it is usually, and should be, applied in the treatment of tuberculosis. In a "supervised regimen" each dose of drugs is seen by some other person to be swallowed by or injected into the patient, and the supervisor is responsible to the physician who is ultimately in charge of treatment. The responsibility for regular drug administration is removed from the patient and put onto someone else. This responsibility covers more than just watching drugs being swallowed; it includes taking whatever action possible to keep the patient attending regularly for treatment. The action varies with the circumstances, ranging from merely reporting a missed attendance to the clinic to initiating or taking steps to find out why the attendance was missed and to encourage regularity in future. The supervisor may be the patient's general

> practitioner, a member of the clinic staff or a person employed by some other organization—a hospital, factory health department or public health authority. The person need not be attached to a medical unit. Anyone with the necessary authority, who will assume the responsibility for taking appropriate action, can supervise drug administration. It could be done by any person in authority within a community or, in the case of a child, by a parent.
>
> Regimens in which the drugs are self-administered cannot by definition be supervised in this sense: but they can be monitored. Warnings of irregularity can be obtained by keeping accurate records of attendance, drugs issued and appointments, by surprise home visits, urine testing, tablet counting, and frequent interrogation of the patient . . .
>
> Supervision and monitoring are not mutually exclusive procedures. A supervised regimen can be monitored, checks being made not of the actions of the patient but of the supervisor. And supervision by non-medical people could be more widely used in regimens at present classed as monitored self-administered.[5]

With time the term "supervised treatment" came to be widely used for various procedures, and eventually became largely devoid of meaning. As an example, there was "intensely" supervised treatment and "strictly" supervised treatment, and "complete" and "direct" supervision of treatment. This vocabulary was not always defined precisely, but seemed to imply that treatment can be partly or loosely supervised and that supervision can be incomplete or indirect. The term directly observed treatment suffered a similar fate. Recent definitions of directly observed treatment refer to the practice of "a second person" administering tablets and observing that they are swallowed[4] or "people" directly observing patients taking their drugs.[70] In a Cochrane review published in 2006, directly observed treatment is defined as an appointed "agent" (such as a health worker, community volunteer, or family member) who directly monitors patients swallowing their anti-tuberculosis drugs.[70]

In 1968, Fox emphasized the importance of flexibility in the organization of directly observed treatment in which the convenience of the patient is considered as much as the convenience of the supervisor.[71] According to Fox, though, treatment was always administered by health workers: patients attended a dispensary either in a clinic or a factory, a doctor's surgery, or a conveniently situated health center or hospital; or, a public health nurse visited them at home or at their place of work. In the programs collaborating with The Union, supervised treatment and directly observed treatment always referred to activities carried out by health personnel as opposed to laypersons (see Box 5.4).

The position of the policy model

The terms supervised, directly supervised and fully supervised treatment frequently appeared in the reports of the expert committees, though rarely was

Box 5.4 The Orange Guide on supervision of treatment

The first recommendations were published in 1986, at the time when short-course treatment was being expanded in the programs collaborating with The Union. Although supervision (in hospital, if necessary), had been recommended for 12-month treatment in smear-positive cases prior to the introduction of short-course regimens, the procedures were reinforced with their introduction.

The first edition of the Orange Guide, published in 1986, specified the following:[72]

Regularity of chemotherapy: "Frequent and careful supervision is required to ensure that the patient actually takes all the drugs prescribed. Respected individuals in the community . . . can be a great help to the health workers in their tasks of ensuring compliance." (p. 18)

Inpatient versus outpatient treatment: "In developing countries, even though the policy states that treatment should be mainly ambulatory, hospitalization is recommended to ensure that the initial intensive phase of treatment (two months) is received without defaulting if patients cannot attend for daily treatment because they live far away from the nearest health unit or if the health staff think that a smear-positive patient will not manage to receive the full initial phase otherwise." (p. 19)

Appendix A: "Patients under treatment are closely supervised by the health workers."

Appendix E (on short-course chemotherapy): "Patients from rural areas will, as a rule, have the intensive phase of treatment as in-patients, since every dose of drugs should be given under strict staff supervision. The oral drugs must be swallowed under direct supervision of a member of staff. Rifampicin should never be handed out to the patient. Patients who left the hospital before having completed two months of treatment are to receive treatment with isoniazid and thioacetazone until treated for 12 months. In urban areas, patients are to receive the intensive phase of treatment . . . on an ambulatory basis provided that they can attend daily (except on Sundays) for supervised treatment at the treating center."

In the fifth edition of the Orange Guide, published in 2000, the position was essentially the same:[10]

"What is directly observed treatment and how is it used? To achieve cure, it is vital that the patient takes the total quantity of medication prescribed. To ensure that this occurs, frequent and careful supervision is necessary. Whenever rifampicin is given to a patient, a health worker must directly observe that the patient swallows every dose of the combination of medications given. This will require the patient to be present for direct administration on a daily basis for the total period during which rifampicin is given. This is usually accomplished on an ambulatory basis if the patient can attend the treatment center daily. Occasionally, it will require that the patient has accommodation arranged at the treatment center, in a hostel, or in some other location. The continuation phase does not contain rifampicin and is usually given in monthly supplies for daily, self-administered intake (except in the case of retreatment, where rifampicin is given). This limits the duration of time required for the patient to attend the health services daily, freeing the patient to return to normal daily activities after the intensive phase, when the patient is usually strong enough to do so." (pp. 12–13)

this terminology clearly defined, nor was a firm stand taken regarding its application. In the late 1970s the use of short-course treatment was still rare in developing countries. Indeed the introduction of short-course treatment met with criticism among experts due to previous difficulties in ensuring patient adherence to treatment. To be on the safe side, Styblo opted for a strategy of universal directly observed treatment in smear-positive cases. He stressed the fact that the first two months of treatment were decisive in more than one way.[73] This intensive phase of treatment, 60 doses of four drugs, was to be given under strict supervision because during that period 80% to 95% sputum conversion could be attained. If strict supervision could not be guaranteed on an ambulatory basis, the patients could be hospitalized for 60 days.* If the patients then continued, regularly or irregularly, with an inexpensive drug combination of isoniazid and thioacetazone that was distributed in all health centers, the sputum conversion rate most probably would remain very high.

In the first years of the collaboration, patients who had been enrolled in short-course treatment were switched over to the 12-month regimen at the first sign of nonadherence during the intensive phase. For the purposes of this treatment regimen, nonadherence was defined as leaving the hospital (self-discharge) or missing four consecutive daily doses in outpatient treatment. This was done out of concern for the creation of drug resistance. This practice was later abandoned when the programs were up and running. A 12-month regimen was always an option, however, if directly observed treatment was not possible. Such cases were never excluded from analysis, that is, the results of 12-month treatment were always reported, and coverage of short-course treatment was one of the operational indicators in program evaluations.

Finally, in the Union collaborative programs, paramedical workers were not always very skilled clinicians. Therefore, as a minimum they were to observe pill swallowing. Any personal skills were then considered a bonus, but were difficult to predict and evaluate.

As discussed in Chapter 3, the operational advantage of the 8-month regimen over the 6-month regimen was that the former required only two months of directly observed treatment, given that rifampicin is not used in the continuation phase. But is direct observation of treatment necessary at all? Many have pointed out the fact that there is no (or insufficient) scientific evidence that directly observed treatment is, in and of itself, superior to self-administered treatment.[70,75,76] In the programs collaborating with The Union, many other elements were introduced at the same time as direct observation of pill swallowing, and thus these programs cannot claim to have undisputed evidence that directly observed treatment is superior if all other elements were controlled for.

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*Hospitalization was inexpensive in these countries at the time. The cost per hospital day in Tanzania was estimated as equivalent to US$1.50 in 1990.[74]

Directly observed treatment in practice

In 1958, Fox pointed out that the best way to impress upon a patient the necessity of taking medicine was unknown and might well vary from country to country.[53] An editorial published in *Tubercle* in 1970 recognized that supervised treatment was not necessarily superior to self-administered treatment, but could give either better or worse results. Furthermore, the issue could be studied but the results would not necessarily be the same in all conditions because economic, social, and geographical factors could affect the results.[5]

The extent to which self-administration of anti-tuberculosis treatment is a problem is in fact likely to depend on the setting. In an area where treatment results are good with self-administered treatment, directly observed treatment seems less likely to improve program performance. A good situation may change, however. For example, if the patient population becomes increasingly confined to marginalized individuals, as occurred in industrialized countries, directly observed treatment may become necessary even where it was not before. This scenario provides a strong rationale for continuous monitoring of treatment results in tuberculosis programs. When considering whether and how to best implement directly observed treatment, one ideally would look first at adherence and defaulter rates. If such rates reveal problems, then the next step is to look at the system characteristics and any patient circumstances that might explain the problem, and finally to consider whether and how directly observed treatment could ameliorate the situation.

Many argue that directly observed treatment alone is not enough to improve treatment results, and that although the success of the DOTS strategy has been documented in many observational studies, the impact of directly observed treatment cannot be isolated from other components of the strategy.[19,77] Apart from the example of the Union model itself, numerous other examples indeed illustrate this phenomenon. One can cite, for instance, a retrospective study in Newark, New Jersey (U.S.), referring to patients registered from 1994 to 1996. The study reported a reduction in treatment duration following the introduction of a comprehensive case management strategy that combined universal, directly observed treatment with surveillance, public health, and clinical care activities under a nurse case manager. This program's success relied on more regular treatment and increased treatment completion rates.[78] This research leads back to the discussion in Chapter 2, where it was argued that strict adherence to experimental design, which can result in a weak intervention, is rarely implemented in programs.

Undeniably, opinions on directly observed treatment are divided. Critics of the strategy argue that it is authoritarian, alienating to patients, and prone to decreasing responsibility for self-care.[77,79] Others characterize it as a caring strategy that places the responsibility for treatment where it belongs, namely

with the treatment provider. In a 1996 qualitative study in South Africa, supervised treatment was interpreted by patients as distrust.[80] On the contrary, interviews with patients in Ho Chi Minh City, Vietnam, in 2001 found that most patients viewed the daily monitoring as a sign of professionalism and care and preferred the national program's structured approach over that of other service providers.[81] In this study, reported reasons for a dislike of directly observed treatment involved the time and travel required and the level of cost and inconvenience incurred.

Two issues worth considering are the question of whether or not directly observed treatment should be universal (that is, for all tuberculosis patients) or targeted (that is, for some patients only), and the matter of identifying the selection criteria (such as smear-positive cases, retreatment cases, only in the case of demonstrated nonadherence or a risk of nonadherence). Further, should every dose be directly observed or only some doses, and should there be directly observed treatment for the entire duration of treatment or only in the intensive phase?

In the 1990s the issue of universal strategy versus targeted strategy was debated in the United States (Box 5.5). An interesting aspect of the debate concerned federal funding. If federal funding is tied to a specific strategy (directly observed treatment, in this case), it is reasonably likely that everyone will choose it, even those with completion rates higher than 90%. The question then arises whether or not the funds are wisely spent. The same question can in fact apply to the DOTS strategy in general—or any strategy, for that matter. When funding or grants are conditional on adopting a certain policy—be it health reform, DOTS, or directly observed treatment—the policy under discussion will be adopted.* Whether or not an officially "adopted" policy is then implemented is another question. In sum, funding tied to particular policies does not necessarily constitute a litmus test of a given policy's effectiveness or appropriateness. A scenario in which funds are linked to a universal strategy or a targeted one can, however, influence the debate over such policies.

Some arguments for universal directly observed treatment rely on the notion that nonadherence is hard to foresee, without taking into consideration the fact that some nonadherence is relevant for the outcome of treatment and some not. The objective is cure without relapse or acquired drug resistance. Some public health professionals argue for a universal strategy on the basis that failing to treat even a single case of tuberculosis can produce mini-epidemics. This argument is also weak because such failures can occur despite a strategy of universal directly observed treatment.

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*This is a variation on "Sutton's law." Sutton robbed banks because "that's where the money is." Apparently, Sutton never said this himself; nonetheless, it is one of the classic quotations in the literature.[82]

Box 5.5 Universal or selective observation of treatment: the debate in the United States

A national tuberculosis program was established in the United States in 1944, and short-course treatment was introduced in 1972.[83] Although directly observed treatment had previously been used in several settings, it emerged as the standard of practice in the 1990s after the resurgence of tuberculosis in the late 1980s.[83] In 1993, the federal Advisory Council for the Elimination of Tuberculosis recommended expanded use of directly observed treatment if the treatment completion rate (within 12 months of starting treatment) was below 90%.[84] According to Binkin et al., while approximately 30% of the patients received directly observed treatment throughout their course of therapy (a higher proportion for at least some period of their therapy), this proportion varied importantly from only selected patients in some settings to 90% of patients in other settings.[83] Criteria for receiving directly observed treatment included belonging to a locally defined high-risk group for defaulting (such as previous default, drug resistance, and previous treatment failure).

An article published by Bayer et al. in 1998 discussed the irrationality of universal recommendations. The article pointed out that in the United States, directly observed treatment had a marked impact on treatment completion rates in jurisdictions with historically low rates, but that treatment completion rates higher than 90% could be attained with far lower directly observed treatment rates than those proposed by advocates of universal supervised treatment.[85] A 1993 policy change specifying expanded directly observed treatment (DOT rate) meant that 49.4% of those on a tuberculosis regimen received directly observed treatment in 1994, compared to 16.8% in 1990. Looking at the relationship between DOT rates and treatment completion, Bayer et al. divided jurisdictions into three categories based on treatment completion rates: "low" (below 70%), "intermediate" (70% to 89.9%), and "high" (90% and above). Bayer's research team found that although the overall DOT rate in "high" jurisdictions rose almost five-fold, the treatment completion rate changed little. In the "intermediate" category, the picture was mixed, and in the "low" category, six out of eight jurisdictions had changed from their original categories. Having a raised treatment completion rate (89%), New York was among the jurisdictions moving from a "low" completion rate category to an "intermediate" one in 1994, even though the DOT rate was only 30% to 40%. In Washington, DC, treatment completion actually declined in spite of an increase in DOT rate. Thus, universal directly observed treatment is neither necessary nor sufficient to improve treatment completion rates where these are low.

Those in favor of targeting directly observed treatment suggest that a tuberculosis program should focus on defaulters and patients in real need of support,[86] using pre-treatment risk factors for adverse outcome[87] or early signs of nonadherence or imminent default to select patients for directly observed treatment, rather than disciplining those who already are motivated and have sufficient support to adhere to treatment. Some examples supporting a targeted strategy are presented in Box 5.6.

Box 5.6 Selecting patients for directly observed treatment

The recommendations in the Union model are to prescribe directly observed treatment for new smear-positive patients in the first two months of treatment (when bacillary load is high), late converters (smear positive at two months), and previously treated cases (throughout retreatment).

In Blackburn, U.K., treatment results for the period between 1988 and 2000 were acceptable with a selective strategy: 23 of 205 patients (11%) were enrolled in directly observed treatment upon the first sign of noncompliance.[88]

In a retrospective record review referring to patients registered in 1994–1995 in the Gambia, treatment failure was associated with high initial bacterial load, and a positive smear at two months predicted default.[89] The data suggest that these factors could be used to recommend directly observed treatment in the intensive and continuation phase, respectively, in close accordance with Union recommendations.

A 2002 observational study in South Africa's Northern Cape Province suggested directly observed treatment had no effect on new cases, whereas patients on retreatment fared better on it.[90] The investigators suggested that patients most likely to benefit from directly observed treatment—such as those previously treated—should be targeted for it. New cases constituted 83% of all cases in this setting, and thus retreatment presumably accounted for about 17%. It can be argued that 17% is a high proportion and therefore new cases should be targeted somehow to minimize retreatment cases in the first place. Indeed, about 30% of the new cases were not successfully treated, and defaulting was the main problem.[90] In the study, previously treated patients—especially failure cases and patients returning after default—were more likely to choose unsupervised treatment, a finding that argues against supporting the patients' choice in this setting.

Health providers have always argued that long-term daily treatment supervision is difficult and usually impracticable.[5] Tuberculosis programs frequently tended to allow self-administered treatment. With expansion of the DOTS strategy in the late 1990s came pressure to implement universal directly observed treatment. Program staff then devised strategies to delegate the task of direct observation of treatment to laypersons (such as volunteers, employers, and shop keepers), and even home-based treatment has come to be referred to as "family DOT" rather than family-supported self-administration of treatment, or simply domiciliary treatment, both of which seem to be more appropriate terms. Arguably this course of events is a response to the pressure to implement the DOTS strategy (see Chapter 6) and universal directly observed treatment: whatever adaptation is made, it must still be called "DOT."

Decentralizing directly observed treatment

A widely used argument for decentralization of care is that the services are overburdened and cannot cope with their caseloads. Problems should not be

transferred from overburdened health services to the community, however, without considering how to strengthen and support the peripheral level of care entrusted with taking on the additional tasks (see Chapter 7). Delegating directly observed treatment to overloaded nurses at the health center level or to untrained and undervalued community members carries obvious risks for case holding and cure.[91]

Some public health officials argue that once supervision in directly observed treatment is shifted from health workers, the entire effort is compromised, not only in terms of weak supervision.[92] Once laypersons are recruited to serve as treatment observers, an important question arises: how can neighbors be trusted with a supervisory task that the patient's own family cannot? And if the patient's family can be trusted with the task, why then cannot the patient? What about confidentiality and patients' right to privacy? The answers to these questions are not obvious. Furthermore, when volunteers are recruited, one needs to consider why they would take on such responsibility and whether it is reasonable to request it of them. Guilt represents a potentially controversial consequence of delegating responsibility for treatment to a family member or a friend, and significant guilt may be induced if the treatment fails or the patient dies.

Some public health professionals have raised concerns about directly observed treatment. They worry that the cost, inconvenience, and stigma associated with visiting a health center or community volunteer on a regular basis could reduce treatment seeking and completion rates.[93] Another concern involves confidentiality and the controversial nature of recruiting and training citizens to watch one another. In some settings and instances, confidentiality is less of an issue—such as when family members observe treatment rather than when members of the wider community are involved—but exceptions do exist. Situations involving vulnerable groups such as daughters-in-law in India represent one such example. Confidentiality is particularly relevant in contexts where tuberculosis is a socially stigmatizing disease. Having the patients choose a treatment observer may circumvent or minimize this dilemma. The issue of confidentiality is likely to be context-specific, and similar strategies may yield varying results when applied in different settings. A 1992 qualitative study in South Africa found that the clinic was the supervision option patients considered to be the most discreet.[94] In a study in Pakistan in which community health workers observed treatment, confidentiality was identified as an issue, particularly by women.[95] In this setting, confidentiality was an issue even when family members were involved, although this was the case to a lesser extent.

An overriding issue regardless of which parties are involved is the matter of who travels to whom for directly observed treatment: the patient to the treatment observer or the treatment observer to the patient. A patient's access to care and convenience is not automatically guaranteed merely by decentral-

ization. Even if village health workers are closer to where rural patients live, they are not necessarily close. When directly observed treatment is delegated to laypersons, who, then, should the health personnel supervise: the patients or the treatment observers? How often should they interact and where (that is, who should visit whom)? Time spent counting tablets and supervising supervisors is time that otherwise could be spent on direct patient care. Furthermore, adding intermediaries may alienate the patient as well as add another layer of irregularity. For example, in one case in Pakistan, a patient's cousin—a truck driver—was the selected treatment observer, but because the cousin was frequently away for as much as two weeks at a time, he failed to ensure treatment regularity.[95]

Finally, is directly observed swallowing necessary? It may seem that if patients attend, the attendance is recorded, the patients receive the medicines and then go and swallow them by themselves, that plan should be fine. Why would a patient attend and then not take the medicines? Some argue that the patient might attend and then take the medicines later or not all in one dose, or that the drugs might end up with someone else. Perhaps the bottom line is communication between patient and provider. If mutual trust and effective communication are established, the patient will confide in the provider, and the provider will thus know if the patient is adherent or not. However, not everyone is capable of establishing mutual trust and effective communication.

Supervision of treatment by health personnel

Various categories of health personnel have been given responsibility as treatment observers in different settings: nurses, auxiliary nurses, medical assistants, midwives, and community or village health workers.

In a retrospective record review in the Gambia, referring to adult smear-positive patients registered from 1994 to 1995, smear conversion and cure rates were higher when directly observed treatment was provided by specialized tuberculosis workers in health centers than nonspecialized staff at the peripheral level, and positive smears at two months predicted default.[89] The results of this study raise questions about the regularity of treatment, as well as decentralization, training of health personnel, and program supervision. The investigators concluded that, in spite of a plan relying on directly observed treatment, irregularities occurring at the peripheral level could result in self-administered treatment.

Mixed results are reported when community health workers act as treatment supervisors. The quality of directly observed treatment administered by community health workers depends greatly on the character of the personnel and whether they are willing to visit patients' homes or are otherwise conveniently located for the patients. Other related factors include the working conditions: community health workers who are overworked and poorly paid may

be unmotivated and unwilling to take on the role of treatment supervisor. As Khan et al. in Pakistan point out, the commitment of dissatisfied public sector workers cannot be taken for granted.[95]

A qualitative study in Andhra Pradesh, India, suggested that tribal populations readily accepted traditional healers as treatment observers, and that public health providers were positive about their involvement as well, since they felt overburdened with other activities.[96]

Involvement of laypersons and volunteers

In spite of the widespread enthusiasm for and experiments with involvement of laypersons and volunteers in directly observed treatment, it is difficult to find convincing evidence that such strategies are sensible or useful in the long term.

A 1996 qualitative exploratory study in Vietnam's Quang Ninh Province revealed that tuberculosis patients avoided telling their employers about their disease out of fear of repercussions in the workplace and of losing their jobs.[97] Thus, "workplace DOT" seems inappropriate in this setting.

In a pilot project initiated in 1996 by a nongovernmental organization in Elsies River, a community 15 km west of Cape Town, South Africa, the involvement of volunteers did not significantly improve the adherence of adult patients to anti-tuberculosis treatment.[4] Treatment supervisors included eight salaried health advisors responsible for the recruiting, training, and supervision of 88 volunteers from the community, the majority of whom were married women recruited from church organizations. Despite a variety of supervision options available, only 68% of notified tuberculosis patients took 75% or more of their medications during the 6-month treatment period, and no substantive difference in adherence was related to the different supervision options.

Studies in Thailand have found the involvement of laypersons and volunteers, other than family members, to be rejected by patients.[98–100] While there may be various reasons for this (such as incompatibility of the strategy with urban lifestyle, poor training and supervision of volunteers in rural settings), it is likely that when given a choice of home-based treatment (as was the case in all the studies) patients will choose that option.

Finally, family-supported treatment has an advantage over the recruitment of volunteers, given that the latter are becoming increasingly overloaded by requests for help from many different health programs.[93] The fact that some programs compensate such workers for their efforts while others do not further erodes volunteers' incentives to provide free services.[93]

Treatment supported by family members

The idea of involving families in tuberculosis treatment is not new. In 1958, Fox made the following observation:

> [A]n attempt is always made to get another member of the family actually to watch the patient swallow the cachets. On occasion, it has been necessary and possible to arrange for a neighbor to perform this function. Since in the Madras Center the other family members are always seen at the outset, there is an excellent opportunity to involve the whole family group in the treatment and explain to all the importance of regularity for the future of the patient and his family . . . the explanation is always given in simple language, using homely similes of a type which the family understands.[53] (p. 271)

In the event that self-administered treatment is not a choice, many patients will opt for family-supported treatment over treatment from health workers, if given a choice. To give an example, 86% of the smear-positive patients who opted for directly observed treatment in a retrospective study of patients registered from 1996 to 1997 in Thailand's Yasothorn Province chose a family member as a treatment observer.[98] As noted previously, entrusting family members or other persons having close relationships with the patient with the responsibility of giving medicines to patients can be problematic. Some individuals may feel that a heavy burden has been placed on their shoulders, and emotional ties can interfere with the process in an unpredictable way.[101] Finally, it can be difficult to interpret the results of trials that include randomization to a family supervision arm, because cultural norms demand varying degrees of family support for family members.[95]

Homedes and Ugalde have noted that, in many low-income countries, family cohesiveness is still very strong and the family's potential role in patient compliance should be taken into consideration.[15] Garner and Volmink argue that this cultural feature gives credence to treatment managed within the family rather than imposed by health workers—regardless of whether or not family members actually directly observe pill swallowing.[102] Some investigators in South Africa, though, are of the opinion that poor family dynamics frequently make family members unsuitable as treatment supervisors.[4] Thus, it may be unwise to rely upon families to improve compliance unless the specific family dynamics are well understood. On the other hand, the family can be involved whether or not directly observed treatment is part of the program. For example, in 1982 a case-control study in Mexico that evaluated a multidisciplinary family supervision program in tuberculosis cases with adherence problems reported favorable results.[103]

The option of self-administered treatment

Self-administered treatment is the least demanding strategy from the patient's perspective and should be used as much as possible. According to a qualitative study in Pakistan, patients on self-administered treatment were more regular in taking their medicines and expressed more satisfaction with the treatment

process than did patients on directly observed treatment.[95] This is apart from the fact, however, that the results of treatment in the study setting, a compliance trial, were not satisfactory in any of the patient groups studied.[104]

If given a simple choice between directly observed and self-administered treatment, many patients are likely to select self-administered treatment. The Union collaborative programs required two months of directly observed treatment for a short-course regimen, thus compounding the choice. In some other programs, the options for treatment observation are presented to patients in the order of priority as ranked by the program: clinic-based, first; then community-based; then family-based; and finally—and only if the patient will not agree to any of the preceding options—self-administered treatment is put forth as an alternative to denying treatment or risking patient refusal of treatment.

Ideally, patients should decide whether or not treatment is directly observed and, if so, the person responsible for observing them take the medicines. Having patients choose between directly observed treatment and self-administration is not always wise, however. When patients known to be at risk for default opt for self-administration (as in the example from South Africa cited in Box 5.6), problems may arise. It is important to consider why patients choose a particular option and why patterns of patient choice differ between health units. When the unit of analysis is the health center, comparisons must be made carefully because the case-mix may differ.

In clinic-based programs, health personnel use treatment cards to record adherence to treatment (see Chapter 4). Usually, when directly observed treatment is decentralized, as in community-based programs, the treatment observers keep such cards. In a study in South Africa, patients on self-administered treatment were provided with a treatment card which they filled in themselves in between monthly visits to the clinic.[90] This policy is sensible; such cards are simple to use and may effectively alert patients to take their medicine. This way, the patients are empowered to engage in their own treatment.

Operational deficiencies

A retrospective study in India's Kerala state, corresponding to registration in the period from 1995 to 1996 and relying on patient interviews, found that roughly one quarter of 200 consecutive new smear-positive patients had received self-administered treatment even though their treatment was recorded as directly observed.[105] This was in spite of a policy of universal directly observed treatment (by health workers or community volunteers), and demonstrates that policy is not always reflected in practice. The investigators concluded that the policy of universal treatment observation was unrealistic and suggested that a treatment regimen without rifampicin be considered for those patients for whom directly observed treatment was impossible to guarantee.

Researchers conducting a study in Thailand from 1999 to 2000 interviewed patients and treatment observers and found poor compliance with the principles of directly observed treatment.[99] Patients often ended up self-administering their treatment in spite of having started off in a clinic-based directly observed treatment program, and especially if they had chosen to be supervised by a family member. Similarly, a study carried out in Senegal from 2001 to 2002 found that the policy of directly observed treatment was not reflected in actual practice.[106]

Historically, deviations from directly observed treatment have always occurred; in the future, this is likely to be the case as well. However, it must be remembered that directly observed treatment is not an end in itself but rather a means to a rapid and permanent cure of tuberculosis without acquired drug resistance or relapse.

Studying the effects of directly observed treatment programs

The design of directly observed treatment programs—and that of the studies that assess and compare those programs—must be carefully thought out. A prospective study in Bangkok's metropolitan area provides an illustration of the importance of a well-designed program.[100] The study's researchers reported that direct observation of treatment at health centers was presented to patients as the preferred option. However, if patients could not attend a health center for some reason, they were asked to choose between family-based and community-based treatment observation. If patients could not accept any of these options (for example, if they lived alone or worked long hours), they received self-administered treatment. This program strategy could be criticized with the argument that someone who lives alone should be offered support such as home visits or hospitalization. In the study, patients were excluded from the analysis if they were physically or mentally ill, born outside of Thailand, or unwilling to participate in the study. In an operational study this could be criticized, as it may bias the results and overestimate success. Examples of directly observed treatment programs and their evaluation in two settings in the United States are presented in Box 5.7.

It has been pointed out that many studies of directly observed treatment do not provide valid measurements of its effectiveness, and thus it is not strange that there are conflicting results.[111] Studying the effects of directly observed treatment and comparing different strategies is difficult. What study design should be used? The findings of descriptive studies, such as longitudinal intervention studies ("before–after" design), may be difficult to interpret if other changes are made in the study period (for example, improved drug supply or changes in the organization of services) or if the case-mix changes. Controlled intervention studies, in particular the randomized controlled trial, may not be an appropriate study design, given that adherence to therapy is complex and

Box 5.7 Experience with directly observed treatment in two settings in the United States

At about the same time that Tanzania entered into collaboration with The Union, a directly observed treatment program was implemented in Baltimore, Maryland (U.S.). From 1978 to 1992, the tuberculosis rate in Baltimore declined by 64%, and its ranking for tuberculosis fell from second highest among "large" cities in the United States to the twenty-eighth highest, probably the result of a policy change that called for the expansion of directly observed treatment, which was the only major policy change in the period.[107] Initially, in 1978, clinic-based directly observed treatment was used selectively for "high-risk" patients: the unemployed, homeless, or addictive substance users. In 1981, the program was expanded city-wide using a community-based strategy of home visitation for treatment.[108] Teams consisting of a nurse supervisor and an outreach nurse provided directly observed treatment at the patient's home, workplace, school, drug treatment facility, city jail, nursing home, or clinic. The number of teams was adjusted over time in response to the city's caseload; each team managed 25 to 35 patients at a time. From 1978 to 1981, about one quarter of all the patients were treated with directly observed therapy;[107] in 1984, this proportion was 54%; and in 1993, 87%.[108] Baltimore experienced a 52% decline in tuberculosis incidence between 1981 and 1992 and reported the highest completion rate (90%), whereas in the five cities compared, the average incidence decreased by a mere 2%.[107,108]

In 1994, Weis et al. evaluated the effects of a policy enacted in November, 1986, that mandated universal directly observed treatment in Tarrant County, Texas, where previously directly observed treatment was used only in selected cases (patients considered at risk for nonadherence).[109] The researchers compared a group of 407 episodes of tuberculosis from the seven-year period preceding the policy change to 581 episodes in the six years following the policy change. The comparison demonstrated that the policy of universal directly observed treatment spurred a statistically significant decrease in drug resistance in new and previously treated cases, in relapse rate (from 21% to 6%), and in the number of relapses with multidrug resistance (from 25 to 5). These results were obtained in spite of higher rates of illicit drug use and homelessness in the period following the policy change and a general increase in the rate of tuberculosis. In the period after the new policy was enacted, 10% of the patients received unsupervised treatment. Treatment included a 6-month regimen, a daily phase of two to four weeks (with treatment self-administered on weekends) followed by intermittent treatment. Nurses, public health investigators, and community service aides performed treatment observation in a setting of the patient's choice, such as in the clinic, at home, or in a workplace. The investigators emphasized that to be successful, directly observed therapy must be individualized and not intrusive. It is of particular note that the program was implemented with existing resources. In 1999, a retrospective economic evaluation compared the total costs related to the treatment of tuberculosis patients registered in Tarrant County in the period 1980 to 1985 and 1987 to 1992.[110] The study reported that costs dropped between the two periods compared, the result of shorter duration of treatment, fewer hospitalizations, and shorter hospital stays. Relapse or acquired drug resistance occurred in 1.2% of the patients in the latter period, compared to 10.9% of the patients in the former one, and treatment for relapse and acquired resistance during the latter period accounted for 6% of the costs involved, compared to 36% for the former period. Thus, in this setting, universal observed treatment was more effective and less expensive than a selective strategy.

involves many context-specific variables and confounding factors.[112] Which of the following should be measured: outcome (cure, failure, and relapse); process (adherence); or impact (multidrug resistance and tuberculosis incidence)?[113] Some public health researchers have noted that short-term treatment results are not the appropriate outcome measure; rather, one should look at drug resistance and relapse.[114] Examples of studies of directly observed treatment are presented in Box 5.8.

The study from Pakistan referred to in Box 5.8 was published in 2001 and stimulated lively debate.[104] Although other constraints may have compromised the benefits of directly observed treatment in this setting, it may be the case that directly observed treatment cannot guarantee better results than self-administered treatment. Analyzing the trial results, some researchers have argued that the study sites—the province (Punjab) or the facilities (tertiary care centers)—were selected out of convenience and cannot be considered representative of Pakistan.[118] Some have also contended that the study was performed prematurely, as general program strengthening had just started when patients were recruited.[117,118] Indeed, the investigators themselves emphasized that the timing of the study coincided with substantial improvement in treatment results (from 26% to 60%), irrespective of the method of treatment supervision. A transitional period is not the ideal time for a compliance trial such as this one. To avoid such scenarios, operational research should be conducted in coordination with national programs. On the other hand, a subsequent so-

Box 5.8 Examples of studies of directly observed treatment strategies

In a randomized controlled trial in district and provincial hospitals and tuberculosis referral centers (Zonal TB Centers) in Thailand, which recruited new smear-positive tuberculosis cases registered from 1996 to 1997, direct observation of treatment embedded in a good primary health care structure and including home visits by health workers yielded significantly higher cure rates than self-administered treatment.[115] In the group with directly observed treatment, 7% of the patients defaulted compared to 13% in the control group (self-administration). Treatment results (completion rates) were better at provincial and district hospitals than at referral centers; in the former, there was a significant difference between the two groups (81% for directly observed and 69% for self-administered treatment groups), but in the latter the difference (72% versus 66%) was not significant. No difference existed between completion rates with supervision by health center staff, community members, or family members (79%, 74%, and 77%, respectively). In the group supervised by health center staff, patients met their supervisor daily, whereas if community or family members were selected to support treatment, the health center staff visited patients' homes twice a month during the initial two months and then once a month for the remaining four months, which may not be feasible in most developing country settings,[104] such as sub-Saharan Africa.[116]

(*continued*)

Box 5.8 *Continued*

A randomized trial in Pakistan compared three modes of administration of treatment in the intensive phase of an 8-month regimen: self-administered treatment (drug collection by the patient twice a month), treatment directly observed by family members (drug collection by patient or family member twice a month), and treatment directly observed by health workers (at a health facility of the patient's choice, provided certain access criteria were met, or by community health workers, with the patient attending six times a week).[104] In cases of imminent default, patients were switched to self-administered treatment rather than having them drop out altogether. In the continuation phase, drug pick-up was scheduled twice a month for all patient groups. A total of 497 new smear-positive cases were enrolled from 1996 to 1998. No difference was observed between the strategies in terms of treatment success rate, which was 65%, 62% and 67% in the three groups, respectively. Defaulter rate was high in all groups (30% to 40%), however, and in addition a substantial number of patients under health worker supervision changed to self-administered treatment after allocation.[95,117]

A randomized trial was conducted in Swaziland, recruiting from 2000 to 2002.[116] All forms of tuberculosis were included but, for part of the analysis, adult and child cases were analyzed separately, as were smear-positive cases (290 for community health worker DOT [CHW-DOT] and 296 for family DOT [F-DOT]). The trial compared CHW-DOT programs in which patients visited their health worker, who provided supervision, with F-DOT programs in which family members chosen by the patients performed supervision. In this program, patients still had to visit a community health worker every week. There was no comparison group with self-administered treatment. The results showed a high cure rate (80% to 83% after excluding those who were known to have died), and a borderline but insignificant difference favoring supervision by community health workers. When the trial's results were compared to earlier ones, the findings demonstrated important improvements, which could be explained by other components of the DOTS strategy. The investigators concluded that further studies were needed.

A cluster randomized trial in hill districts in Nepal recruited smear-positive adult patients from 2002 to 2003 (districts were the unit of randomization).[93] Community directly observed treatment (community DOT) was defined as a strategy with daily supervised therapy and patient tracing, if needed, performed by a female community health volunteer or a village health worker, with drugs provided to the supervisor every month. Family-based directly observed treatment (family DOT) involved daily treatment supervised by a household member selected by the patient, with drugs provided to the patient's supervisor every week. In both strategies, patients could opt for a program featuring directly observed treatment conducted at a health center (center-based DOT), and 10% of the community DOT patients and 15% of the family DOT patients made such a choice. Community DOT and family DOT programs achieved success rates of 85% and 89%, respectively. No comparison was made with self-administered treatment programs. The investigators concluded that both strategies could achieve international targets for treatment success, but warned that care should be taken in extrapolating the findings of this study to other settings.

cial study involving patients from the trial and exploring background issues gave useful information for policy development, such as some of the constraints and barriers patients met and why they defaulted or moved between study groups.[95] Thus, it was asserted that a study (but perhaps not a trial) should be performed early on in program reform to guide policy change. The strength of the trial in Pakistan lies primarily in the problems that were reported. In the setting of many if not most countries, problems are bound to arise. If they are not identified and acknowledged, they cannot be addressed.

Systematic reviews comparing directly observed treatment with self-administered treatment and comparing different methods of direct observation of treatment largely ignore the issue of context when they pool results from programs and settings that are not obviously comparable. Examples of such contextual elements include the following: different countries with different populations, varying program quality, different recruitment criteria and participation rates, and different completeness of follow-up. Such reviews may be misleading, and it is tempting to argue that it is more informative to look at individual studies. The strategy of directly observed treatment is yet another problematic policy issue that does not lend itself easily to orthodox research methods. In 2001, Auer presented an interesting approach to discussing or summarizing the issues and evidence related to directly observed treatment.[119] Table 5.1 is a modified and expanded version of his summary grid.

Ignoring, for the most part, the complexity of the matter, systematic reviews are undertaken nevertheless. In 2006, a Cochrane review concluded that there was no evidence and thus no sound reason to advocate the routine use of directly observed treatment to improve cure rates until there was a better understanding of the situations in which it might be beneficial.[70] One could turn this argument around and say that there is no evidence and thus no sound reason to discontinue direct observation of treatment where such programs are in place and results are good, until the issues involved are better understood.

In conclusion, when studying the effects of directly observed treatment, it is important to define the context and the strategies being tested. Whereas a drug is a drug (if it is of good quality and the dose is standardized), strategies for directly observed treatment are complex, not easily standardized, and often ill-defined. Ideally, tuberculosis control should be well organized when comparing different strategies of directly observed treatment. Results in preventive chemotherapy programs and tuberculosis treatment programs should not be mixed, as is sometimes done. These are two different interventions. Smear-positive cases should be analyzed separately. There should be a comparison with self-administered treatment (which is the least demanding approach from both the patient's and the provider's perspective), and any supervision by a

Table 5.1 Assessment of a DOT policy

	DOT at health facility	*DOT by community health worker**	*DOT by laypersons**	*DOT by family members**	*Self-administered treatment**
Adherence					
Detection of adherence					
Adverse reactions					
Progress monitoring					
Smear conversion					
Treatment completion					
Default					
Failure					
Relapse					
Drug resistance					
Convenience†					
Burden†					
Cost†					
Cost-effectiveness					

Adapted from Auer.[119]
*The frequency and nature of support and supervision from health personnel and the required attendance at health units vary, and this may influence the results.
†For provider and patient.

health unit should be meticulously described (including, for example, frequency of home visits, clinic attendance, drug collection or delivery). Consecutive cases ideally should be recruited without exclusions. Alternatively, exclusions should be clearly defined and justified. Analysis by intention to treat may be desired, but this can be tricky if patients move between groups after randomization with or without knowledge of the investigator, and thereby can jeopardize the analysis (as in the case of the trial in Pakistan[95]). If costs are studied, all costs should be included whether met by the patient, the provider, or the treatment observer. Outcome variables are ideally failure, relapse, and acquired drug resistance rates. Treatment completion rate, smear conversion, and adherence can be looked at as well (in decreasing order of preference if it is to be used for the main analysis). If randomization is a feature of the trial, the method of analysis must correspond to the randomization method: patients or clusters (health units, districts, for instance). The bottom line is that operational strategies to promote adherence, and directly observed treatment in particular, do not easily lend themselves to assessment by randomized controlled trials.

Incentives, inducers, enablers

Incentives, inducers, and enablers are not an inherent part of directly observed treatment, but rather are different interventions that can be implemented with or without direct observation of treatment. Many questions need to be considered when such programs are implemented: Who should pay? How should the program be managed? Is it sustainable in the long run? Should incentives be universal or should they target selected groups of patients? Are there any potential harmful effects? Many of the studies on the subject involve marginalized populations in cities in rich countries and thus the results are not applicable in low-income countries.

Often, incentive programs involve small rewards to attract patients to the program with the goal of improving adherence to treatment. As an example, in a directly observed treatment program serving an inner city population in Fulton County, Georgia (U.S.), the introduction of incentives (grocery coupons) coincided with increased treatment completion rate ("before–after" design).[120] Patients who demonstrated nonadherence by missing at least 25% of their scheduled directly observed treatment doses over a three-week period were eligible for incentives. Of 185 patients starting treatment in the study period (1996–1997), 55 (30%) were enrolled in the incentive program.

Whereas some argue for improved nutritional and economic assistance for tuberculosis patients,[121] the case can be made that these are wider public health issues that are better dealt with by general social policies at the population level than within the tuberculosis program. In this context, structural, operational, and financial links between the social and health sectors are important.[122] Social legislation and support as a rule is absent or inadequate in low-income countries, although some exceptions do exist. In Cuba, from 1965, patients with tuberculosis were given sick leave from work and received their full salary during the entire treatment period.[123] As a result, they did not have the added worry of losing their job (if they had one), which is a burden in many countries (such as Vietnam, to give one example[97]). This is a very important issue, and tuberculosis programs should intervene in this respect. On the other hand, linking benefits such as economic subsidies for housing or food, or "sickness pension" to an infectious disease such as tuberculosis can be controversial if it deters patients from completing treatment. Another matter worth considering is that purchasing compliance may have negative long-term consequences if it becomes financially unsustainable, difficult to manage, or a constant subject for exploitation or negotiation.[124]

Retrieval of non-attendees

If, as in the Union model, a defaulter is considered to be someone lost from sight, the terms "defaulter tracing" or "defaulter retrieval" are misnomers, as it

is too late to trace or retrieve patients once they have been classified as defaulters. The period of nonattendance before default should be used for tracing patients and persuading them to continue to attend for treatment. Some refer to this as "late patient" tracing. The utility of this strategy is likely to depend on the prevalence of nonattendance and default in the program and on the nature of the defaulter problem.

Yet again the question arises as to whether or not to use a universal or targeted strategy, such as trace only in case of smear-positive patients and/or only in the intensive phase. Other questions to consider are how quickly retrieval action should be instituted in cases of no-show, what actions should be taken, and when to give up the effort.

Occasional nonattendance is common in ambulatory treatment. As a rule, it is not necessary to take immediate action in the case of a missed appointment; this is likely to occur in as many as half of the cases, and most of the patients will return spontaneously. It is common to choose a threshold for action arbitrarily (for example, a few days in the intensive phase or on a particular day of the week), but this could be based instead on analysis of records in the program.

Actions that have been used for patient tracing include prompts and reminders (by a letter or a messenger, for instance) or more definitive actions such as home visits. The retrieval rate may depend on the definition of noncompliance, that is, the threshold for initiating retrieval action. The underlying reasons for noncompliance, the retrieval rate, and the overall gain for the program are likely to differ with the prevalence of noncompliance. Studies of retrieval strategies ideally include an element of comparison, such as comparison of results with different retrieval actions or comparison with a scenario where no retrieval action is performed. Table 5.2 demonstrates the variation in the potential gain for a program (measured by success rate) depending on noncompliance and retrieval rates, assuming fixed death (5%), transfer out (3%), and failure (2%) rates. The real gain is further compromised by the treatment completion rate among retrieved patients. Where there is a large potential gain from tracing (15% to 20%), the underlying problem likely has to do with the organization of services, and "late patient" tracing is unlikely to fix such a problem.

Finally, at what point should efforts of retrieval be abandoned and the case declared a defaulter? The Union policy of two months after last attendance may seem too long if treatment is directly observed but realistic in self-administered treatment with monthly drug pick-up dates. For the sake of simplicity, it was decided to have only one definition.

Some examples of studies of retrieval of late patients are presented in Box 5.9.

Table 5.2 Gain in treatment success rate in programs with variable nonadherence and retrieval rates

Retrieval rate %	*Fixed death, failure, and transfer rates* %	*Non-adherence* %	*Treatment success** %	*Maximum gain in success rate* %	*Realistic gain*† %
	10	5	85		
25			86.25		
50			87.5	2.9	2.2
75			88.75		
	10	10	80		
25			82.5		
50			85.0	6.3	4.7
75			87.5		
	10	15	75		
25			78.75		
50			82.5	10.0	7.5
75			86.85		
	10	30	60		
25			67.5		
50			75.0	25.0	18.8
75			82.5		

*Assuming that 100% of retrieved patients complete treatment.
†If 75% of retrieved patients complete treatment.

Communication, health education, and counseling

Communication between health practitioners and their clients is sometimes characterized by mutual misunderstanding between the two.* Some argue that nurses are able to communicate with patients better than physicians because of their closer cultural proximity and fewer time pressures.[15] This explanation is likely to be context-specific.

Health education has been defined as a process of motivating patients to adopt behavior that is beneficial to their health.† The effect of health education in routine clinical practice is difficult to study. Were health education measures undertaken? Were such measures recorded (that is, is there a data source)? Did the patient understand the health education information? Was it effective (in other words, did it result in the desired patient behavior)? Generally speaking,

*A. Kleinman, cited in Kroeger,[127] p. 152.
*L. W. Green, quoted in Dick and Lombard,[128] p. 181.

Box 5.9 "Late patient" tracing

In Hong Kong in the 1960s, the defaulter rate was 17.5%, and default tended to occur early in treatment: Almost one in four defaulters left within the first five or six months of treatment, mostly in the first three weeks.[9] Tracing was only successful in about 50% of the instances where it was tried.

In a randomized controlled trial in Bangalore, India, in the 1970s, the first retrieval action was a letter after three days' absence, and the second was a home visit made eight days after posting the letter.[34] In a group of patients on supervised treatment, patients returned to treatment before a home visit was made in 66% of the instances, and in 67% of the instances where a home visit was made.

In a study in India reported in 1981, 81% of the patients on self-administered 12-month treatment with monthly drug pick-up appointments missed an appointment at some time, two to three times on average.[125] The study compared two strategies of patient tracing: a letter (if the patient had not attended within three days of the due date) plus a home visit (a week after posting the letter, that is, on day 11) as opposed to a visit (on day 4) and a repeat visit (on day 11) in case of a no-show. The findings suggested that the latter policy resulted in earlier retrievals but not more of them. In the latter group, there was little added success with further visits at one and two months, suggesting that if initial visits are unsuccessful, there is not much point in continuing retrieval activities. The retrieval rate was high in this study, approximately 80%. The study, however, excluded a large proportion of patients (60%) who were regarded as unstable residents or as noncooperative, which is a flaw in a study of this kind. It is precisely in such cases that adherence is expected to be the worst and retrieval action important but probably of limited success. Another weakness in this study was the absence of a comparison with a scenario without retrieval action.

In a study in Cambodia reported in 1992, tracing was initiated if a patient failed to return for drugs after either ten days in the daily intensive phase or 45 days in the continuation phase (that is, 15 days after the due date for monthly drug pick-up).[126] The first action was a reminder (a letter delivered by a community nurse, a family member, or a neighbor) and the second reminder was a home visit. Out of 171 patients registered during the study period, 46 were eligible for retrieval at some point in treatment, 57% of these were met at home, 81% of those met at home returned to treatment, and 76% of those who returned completed treatment. This translates into a patient retrieval efficiency rate of 35%. There was no comparison group without retrieval action.

A study carried out from 1996 to 1997 in a chest hospital in Taif, Saudi Arabia, tested a retrieval system to improve patient return for follow-up and drug collection after a period of hospitalization.[40] First, program administrators waited two weeks, then phoned, and finally a social worker was sent on a home visit. Of 628 patients, 358 (57%) did not attend the first outpatient clinic visit. The retrieval system was successful in bringing back only 83 patients (a 23% retrieval rate), even if the administrators offered to arrange follow-up at a nearby facility. The retrieval system helped to reduce the default rate only from 57% to 44%. The results of this study demonstrate the importance of program structure. Centrally located hospitals often have a problem with case holding that cannot be solved by implementing a retrieval system. This topic is discussed in Chapter 7.

the evidence of effectiveness of patient education for enhancing compliance is inconsistent, and this observation is borne out by experiences and studies in the field of tuberculosis. It is clearly possible to increase knowledge about a given disease and its treatment without improving compliance, and the mastery of factual knowledge about the disease is not necessary for adherence.[2,46,60] Examples of some studies on health education are presented in Box 5.10.

Studies aside, common sense suggests that it is important to communicate few but clear messages in health education. It is best to have standardized core messages so that the information provided to patients is complete and consistency between health workers is maintained. Ideally, patients with tuberculosis should know what tuberculosis is, how it is spread, how transmission can be limited, and that it can be cured. They need to have a clear concept of what the treatment entails—what medications are used and for how long, how progress during treatment is monitored, and what are the medications' possible adverse effects. It is particularly important that patients know the planned duration of treatment; otherwise they do not know what they will face in the process. To promote adherence, patients need direct and continuous support and feedback throughout treatment.

Generally speaking, it is possible to utilize some of the time spent in health facilities for health education, whether the clients are tuberculosis suspects, tuberculosis patients, family members, or individuals attending for an entirely different motive. Stigmatizing messages that frighten and misinform with alarming content, such as "Keep a safe distance from tuberculosis patients, let them eat separately, do not share their cutlery, and let them sleep in a separate room" (or even outside the mosquito net!), are all too common in "health education" even to this day. Such a misguided, counterproductive approach is likely to increase the burdens of addressing the disease itself and the public heath issue in general.

Summary and conclusions

Adherence to treatment is a central issue in tuberculosis control. Irregular treatment predicts imminent default and is associated with treatment failure, drug resistance, and relapse. These hazards form the justification for supervising anti-tuberculosis treatment. It is agreed that properly trained health workers should supervise the treatment. A team of a doctor and a nurse ideally performs this activity. That strategy, however, requires a well-organized and fully staffed health service. As this is not always the case, supervision of treatment is frequently delegated to medical assistants and auxiliary nurses.

Supervised treatment may or may not be directly observed, and where it is, this can be done on an ambulatory basis or in a hospital, by the treatment supervisor or by someone else, such as another health worker or a layperson.

Box 5.10 Studies on health education in tuberculosis treatment

In an article in 1975, Curry, based on numerous discussions with patients in San Francisco, U.S., listed the following complaints as frequently occurring ones: a lack of continuity in medical care, the tendency of health personnel to communicate with each other rather than with the patients, the failure of health personnel to communicate medical information in a manner understandable to the patients, and the attitude of health personnel (for example, punitive, judgmental, disparaging, or arrogant).[129] This information was used to reorient the clinical services.

In 1997, Dick and Lombard reported the results of a controlled intervention study in Cape Town, South Africa, to assess whether a combined strategy of a patient-centered interview plus a patient education booklet (in the form of a photo novel) would increase the rate at which patients with pulmonary tuberculosis adhered to their prescribed treatment program.[128] The cut-off point for nonadherence was set at 75% of expected doses actually taken by the patient, and adherence was monitored on the basis of attendance for directly observed treatment. Home visits were made if two consecutive appointments were missed. Consecutive patients were enrolled in the study, 60 each in the "intervention" and in a "control" clinic. In the intervention clinic, the booklet was used, and the nurses were trained in interviewing techniques. The study concluded that the risk of nonadherence was significantly reduced in the intervention compared to the control clinic.

In Tanzania's tuberculosis program, health education was provided to patients on an individual basis and in groups. In a study in rural and urban settings in Tanzania's Mwanza Region, 296 patients with smear-positive pulmonary tuberculosis were interviewed in 1998 to assess their knowledge of the disease.[130] Researchers from the study found that the most important sources of information about tuberculosis were health workers and former tuberculosis patients, whereas informational posters were the least important sources of information. The investigators were surprised by the patients' limited knowledge of tuberculosis, given the good treatment results reported in the study area. It has been shown, however, that patient knowledge of the disease is not necessarily or always related to treatment success; furthermore, the measurement of knowledge about tuberculosis is not standardized.

Results of a randomized controlled trial of the impact of intensive patient counseling on treatment adherence conducted in a mission hospital in the outskirts of Pakistan's Sialkot City were reported in 1999.[131] Counseling was given at the start of treatment and at each subsequent visit for ambulatory patients, and every week for hospitalized patients. A total of 1,019 patients were included in the trial. The outcome measure used was treatment default (international definition). Defaulter rate was very high in both groups: 54% and 47% in the control group and intervention group, respectively, suggesting serious problems in the services. The investigators concluded that intensive counseling had a limited impact on treatment adherence. Clearly, though, until the organization of services has been improved, it will be difficult to interpret the findings of such a trial, as structural issues outweigh other considerations.

According to the policy model of The Union, directly observed treatment is the role of trained health personnel. If laypersons are involved, issues of confidentiality, accountability, remuneration, and sustainability arise. When family members are involved, this is best referred to as domiciliary therapy—one form of self-administered treatment. Family dynamics need to be understood and defined when a family member is assigned as treatment observer.

Ideally, patients would be involved in the choice of treatment supervisor as well as treatment observer when directly observed treatment is used. This precludes orthodox research design (randomized trial) when comparing treatment observers, given that the resulting patient groups will not be comparable. An operational service evaluation using cohort analysis is a realistic assessment method. Monitoring and identifying individual patients who need support for adhering to treatment is important in case management. Endorsing and supporting the patients' choices may not be wise if they are at risk of defaulting.

An important explanation of why opinions on directly observed treatment are divided is that the strategy is often ill-defined and not easily standardized. With regard to other adherence-promoting strategies, incentives may be useful but are difficult to manage and may not be appropriate in low-income countries. Furthermore, studies on the utility of patient tracing and health education are inconclusive.

In all case-holding strategies, the question exists as to whether they should be universal or targeted. When contemplating policy change, the bottom line always is to look at what you have. Are the results obtained with the existing strategy good enough? If not, analyze the problems and assess the resources and options at hand. Revise the strategy, pilot, and then reassess the situation. When studying treatment adherence, the proper outcome measures are acquired drug resistance and failure and relapse rates. Yet these are difficult to measure in most settings. Thus, surrogate measures are frequently used.

This chapter concludes the review of operational strategies and of the Union policy model apart from the supportive strategies, which are examined in Part II. The next chapter, however, follows the Union model into the World Health Organization, via the World Bank, and then into the global health arena.

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6

Global tuberculosis control

"You can take a tuberculosis program to the people, but you cannot make them accept it if they don't want to. If after careful, sympathetic explanation they still don't want it, then there is something wrong with the program for those particular people in that particular environment."[1]

When tuberculosis reemerged on the international health agenda, Styblo found himself at center stage. This chapter explores the similarities and differences between the policy model and the DOTS strategy of the World Health Organization. It recounts the origin and development of the DOTS strategy, along with some of the criticism it faced and its current position and course. Finally, the future prospects of tuberculosis control are discussed, including the impact of drug resistance and HIV on the tuberculosis situation and the implications for the control policy.

The model hits a policy window

In her 1991 article "A Tale of Two Cities," Brudney demonstrated what a powerful tool international comparisons can be when used wisely.[2] Shunning diplomatic phraseology, she compared the tuberculosis control program in New York City, a megalopolis in a rich and powerful country, to a control program in a poor country, and found the New York program lacking.

The international health community was caught off guard when, in the mid-1980s, the number of reported cases of tuberculosis started to rise in the United States as well as in Africa. By 1990, the link between HIV and tuberculosis was well documented,[3,4] as was the high risk of infection among vulnerable and marginal groups in large cities.[5,6]

Triggered by the upsurge of tuberculosis and its underlying factors, interest in tuberculosis control in low-income countries was renewed for a number of players, including the Commission on Health Research for Development, with its secretariat at Harvard, and the World Bank. From then on, the issue of tuberculosis control moved rapidly onto the international scene.

The response of the World Health Organization

In 1989, the WHO strengthened its Tuberculosis Unit, which had all but disappeared.[7] In 1991, the forty-fourth World Health Assembly (WHA) adopted a new strategy and endorsed global targets for tuberculosis control.[8] In that same year, the World Bank China project was initiated,[9] through which the WHO, together with Styblo himself, set about testing their new model. Soon, projects were introduced in a number of other countries. The stakes were high, and success was important.

In 1993, the WHO declared the spread of tuberculosis a global emergency,[10] and formally launched the DOTS strategy in 1994. Some researchers have suggested that this tactic was instigated by an advocacy expert,[11] and it can be argued that, after DOTS implementation, advocacy drove the WHO's response to the global emergency, while technical and operational issues took second place. As a rule, advocacy campaigns primarily target donors and policy makers. The DOTS campaign used operational terms such as "directly observed treatment," and bold statements concerning drug resistance were at the center of the campaign. While advocacy was important in the launching of the DOTS strategy,* an unfortunate collateral effect of the high-profile campaign made it difficult for health professionals to address technical and operational issues sensibly later on.

The WHO explained its new policy in 1994 in its "Framework for Effective Tuberculosis Control."[10] In 1995, the Global Tuberculosis Program was established, roughly 20 years after it was suggested in the 1974 report of the Expert Committee.[12] The new program was dismantled in 1998, however, in a wave of integration that swept through the WHO and resulted in its reorganization.[13] At the beginning of 2001, the main units of the program were regrouped into the Stop TB Department.[13] According to Raviglione and Pio, in their review of the evolution of WHO policy recommendations,[13] the expansion of the DOTS strategy was deemed too slow.† In addition, at the turn of the century, the WHO embraced a multisectoral approach for implementing programs based on advocacy, social mobilization, community involvement, and the engagement of private, for-profit providers.[13]

In 2002, an Expanded DOTS Framework was developed,[14] and in 2006, the "new WHO Stop TB Strategy" was introduced.[15] In addition to a sharper focus on HIV-related and multidrug-resistant tuberculosis, the issues addressed in the Expanded DOTS Framework were mostly nontechnical and heavily influenced

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*It is debatable for whom it was most important. It has been pointed out that the WHO has come to depend partly on collaboration with agencies that directly fund programs in low-income countries.[11] This can be seen as a conflict of interest.

†It can be argued that slow progress was, at least partly, a result of the strategy being ill adapted to complex health care systems.

by health sector reform policies: a multisectoral approach, an emphasis on partnerships with the private sector and nongovernmental organizations, and economic analysis. The most recent WHO strategy broadens its scope even further to promote tuberculosis control as "an element for" health system development, a basic human right, and an integrated part of poverty-alleviation strategies.[13]

DOTS

In 1982, Bignall, when offering his opinion on why tuberculosis was not under control, mentioned—among other things—that one of the many weaknesses of the control strategies of the previous 30 years had been the widespread eagerness to adopt dogmas and then apply them uncritically in all circumstances; for example, integration, ambulatory treatment, and giving priority to treating smear-positive cases.[1] He pointed out that the carefully worded recommendations of expert committees were never intended to be obeyed unthinkingly throughout the world.

In the early 1990s, when the WHO launched the revised tuberculosis control strategy, the director of the WHO tuberculosis program pointed out several reasons for the past failure to achieve sustained progress in tuberculosis control in low-income countries. According to Kochi, although identifying *what* should be done had long since been documented, explaining *how* to do it under different circumstances had never been properly clarified.[8] He recognized that some technical policies had been taken as dogma, a situation that discouraged results-oriented and locally appropriate approaches. While these were sound observations, the WHO essentially perpetuated the situation by establishing new dogmas.

When the WHO adopted Styblo's model as the foundation of its new policy recommendations, the model was modified and eventually branded and marketed as a global solution. The alternative would have been to put forward the basic policy principles and encourage and assist with local policy formulation in different settings. Initially, with the original 1994 framework, it seemed that this would indeed be the case.[10] In reality, a product—complete with brand name and bulleted points—was presented as if it were the one and only complete and final policy.* As mentioned above, some scientists suggest this was the doing of advocacy experts. One can also speculate that this approach was justified within the WHO as necessary if any progress was to be made in the overhaul of tuberculosis control programs that was needed in many—but by no means all—countries. Ultimately, this tactic may have done the policy more harm than good in various ways.

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*This has since changed, and the WHO has acknowledged that implementing the DOTS strategy requires flexibility, with adaptation to a broad range of contexts and community needs.[16]

First, there was the "brand name." The name chosen by the WHO for its new recommendations was DOTS, or Directly Observed Treatment, Short-course. It is arguable whether brand names and acronyms facilitate or impede communication. In this case, the use of the acronym generated endless confusion, misunderstandings, and debates;[17,18] and considerable effort went into discussing, explaining, and opposing it—an effort that would have been better spent on something else. Some health professionals have criticized the acronym for its emphasis on only one element of the strategy, directly observed treatment,[19,20] despite the DOTS strategy's having five "pillars," as explained in Box 6.1. In 2006, a Cochrane review referred to DOTS as a version of DOT promoted by the WHO.[21] Perhaps DOT was emphasized because of the weakness of the case-holding component of tuberculosis programs up to that point.

Second, what the WHO presented was referred to as a "policy package" rather than a general approach. Again, one can speculate that an internal decision was made that a "package" would be simple to follow and easy to market. This presentation, however, backfired. Ogden has pointed out that while guidelines are necessary, they are not sufficient; and, more important, they need to be adapted to the social, economic, and health services contexts in which they are applied.[22] Guidelines also need to reflect the epidemiological situation. It was naïve of the WHO to assume that the package could ever be complete or that one size would fit all. When the policy package was inevitably found lacking, rather than unpacking the contents and laying them out in a general, adaptable approach, alternative packages were designed. As a result, many different packages were on display, and a new tactic emerged—sometimes referred to as the "supermarket approach"—in which national tuberculosis programs

Box 6.1 Acronyms and terminology

DOTS (Directly Observed Treatment, Short-course): A brand name given by the WHO to a national strategy for tuberculosis control. The strategy has five pillars: government commitment, case detection by quality-assured sputum microscopy among symptomatic patients self-reporting to the health services, directly observed short-course treatment, an uninterrupted supply of medicines, and a system for recording and reporting.*

DOT (directly observed treatment): Refers to the administration of treatment and aims to improve case management, ensure adherence to treatment, and prevent drug resistance, failure, and relapse.

S or SCC (short-course chemotherapy): Refers to treatment regimens of less than 12 months' duration.

*The exact wording when describing the pillars has varied with time and in different documents.

"go shopping" and select what they can afford or what they wish to implement, with or without external donors paying for it.

In this environment, the DOTS strategy came to be referred to as "classical DOTS,"[23] while the variants are referred to as DOTS-Plus strategies. Perhaps it is time to contemplate this approach and where it is leading. Arguably, the successful branding of the strategy had negative repercussions for tuberculosis program development. In fact, DOTS can be seen as an obstacle in policy development. The policy package is in the way; policy makers frequently stumble over it, trying to get around or beyond it.[24,25] If it were not for DOTS, there would be no need for DOTS-Plus. Policy makers could simply discuss tuberculosis control, tuberculosis policy, and context using conventional vocabulary, instead of terms like DOTS-based tuberculosis control, standard DOTS,[26] DOTS-only,[27] DOTS-Plus,[28] or PPM-DOTS,[24] often without properly defining the terms.* Furthermore, DOTS is sometimes treated as if it were a simple, dichotomous variable, as is the case when DOTS and non-DOTS patients, programs, or areas are compared.

Some scientist argue that the WHO predominantly focused on changing clinical practice but neglected such contextual factors as social, political, organizational, and financing issues—factors that may limit the benefit of improved clinical management.[29] Whereas the DOT of the DOTS strategy became fashionable, action plans that would result in effective tuberculosis control did not feature prominently early on in the DOTS campaign.[30] In essence, issues that did not explicitly make it onto the "bulleted list" were relatively neglected. Supervision and quality assurance were not properly acknowledged and addressed; the same can be said for coordinated services and referral systems.

Third, there was the matter of ownership. Arguably, the DOTS strategy was marketed as a global one owned by the WHO. One of its five pillars is government commitment.[10] While achieving government commitment in member states might be an important part of an international organization's strategy (or that of a nongovernmental organization, for that matter), it is difficult to see why government commitment would feature as a pillar of a national or local control strategy. Furthermore, when a policy is claimed or owned by an organization, the owner may become defensive and protective of it. In the context of public health in general, evidence seems to be selected to fit a specific policy, or may even be deliberately manipulated by those with vested interests in the policy. This has given rise to the term "policy-based evidence" rather than "evidence-based policy."[31] The best way for the WHO to avoid this type of criticism would have been to encourage independent research and evaluation of DOTS to produce policy-free evidence. Instead, the WHO was the acting force behind both the implementation and "external" evaluation of tuberculosis

*PPM stands for public-private mix.

control programs when DOTS was first presented. Even more recently, reports of impact evaluation in tuberculosis control have been challenged,[32,33] as have "the WHO party line" and policy development,[34] and DOTS-Plus[34–37] and its promotion by WHO as a feasible and cost-effective strategy in low- and middle-income countries.[38] The advantages of making a clear distinction between the political side and the action side of programs have been detailed in the context of general WHO reform.[39] On the other hand, it is also argued that the core functions of international health agencies should be the surveillance and control of diseases that represent a regional or global threat, including involvement or intervention in both the planning and implementation of national health policies.[40]

Another matter closely related to that of ownership of tuberculosis control policies—and not limited to the WHO—is the one of stakeholders. During the policy formulation process, tuberculosis specialists may be seen as a tightly knit, inward-looking group pushing their professional interests.[41] If they are seen as having a vested interest in the policy, they are more likely to be excluded from participation in discussions regarding changes in the health sector as a whole.[41] This could compromise the potential of tuberculosis programs in the long run.

The WHO was criticized for using a top-down approach in its response to the upsurge of tuberculosis and in promoting the DOTS strategy.[42] This did not sit well with those involved before the WHO moved in or with those who wished to become involved. Moreover, as discussed below, it seems the WHO did not always realize when the standardization of practices was necessary and justifiable and when it was not. Arguably, policy adaptation and development were compromised for the sake of marketing and advocacy. DOTS appeared at times to divide existing programs and the international community alike rather than providing a comprehensive and coordinated approach. Finally, the WHO was perceived as considerably success- and target-driven. Some researchers have suggested that, as a result of this drive, DOTS itself may have led to questionable practices that challenge the reported success of the strategy.[22,43–46] Others regard this as premature criticism referring to temporary situations in expanding programs.

Recent global initiatives

Since the 1990s, various organizations and agencies have joined in the race to control tuberculosis, and new supra-national players have emerged on the scene. In May 2000, the WHA called on international organizations, donors, foundations, and the international community at large to participate in the Global Partnership to Stop TB, whose aim is the elimination of tuberculosis as a public health problem.[47] While hosted by the WHO, the partnership intends

to strengthen networking to create a global movement against tuberculosis.[43] The Union, along with many other organizations, joined the Stop TB Partnership and endorsed the Expanded DOTS Framework.[14] The Secretariat of the Stop TB Partnership is placed in the WHO, as is the Global TB Drug Facility, a mechanism that supplies the drugs needed for DOTS expansion. Various working groups have been established to cover the different technical areas of the partnership's activities, an arrangement similar to that of The Union (see Chapter 1). Finally, the Stop TB Partnership has a Task Force for Advocacy and Communications, and a sister body that provides financing support to the Secretariat and the working groups.

In April 2001, the United Nations Secretary General announced the establishment of a public-private partnership fund: The Global Fund to Fight AIDS, TB and Malaria, an initiative apparently triggered by the perceived lack of progress toward meeting the Millennium Development Goals.[48] Many policy experts feared this was yet another international, donor-driven initiative that would fail because of lack of attention or a tangible commitment to building capacity and infrastructure in order to implement and sustain effective programs. These critics argued that international aid should be used to support system development, with the aim of improving the delivery of health services.[49] Indeed, The Global Fund, as it is commonly called, has been criticized for creating a duplication of administrative effort at ministry level,[48] as well as for pressing disease treatment priorities in its desire to achieve short-term results.[50]

It is beyond the scope of this publication to detail all the initiatives and activities in the international health arena. It is important to emphasize, however, that despite the fanfare associated with global programs, it was, it is, and it will continue to be primarily national and local actions and commitments that determine the degree of success in tuberculosis programs.

The DOTS strategy

Chapter 2 stated that the challenge for the WHO was to demonstrate how the policy model it adopted from the Union collaborative programs could be adapted and implemented in different settings. In many ways, the WHO failed in this task. These failures mainly involved the methods used in piloting the policy package, recruiting patients, and defining success. Furthermore, some of the changes introduced in the treatment algorithm were controversial. Insufficient rigor on the one hand and inadequate adaptation to local circumstances on the other resulted in the partial failure of implementation (see Box 6.2).

In the early phase of the 1990s campaign to improve tuberculosis control, several programs featured prominently: China, India, Peru, and Russia. All used a 6-month regimen with rifampicin throughout, some fully intermittent (for example, India[55]). In Peru, the treatment algorithm used was deemed by outside

Box 6.2 Adaptations of the policy model in the 1990s

According to Wilkinson and Gilks, the Chinese Tuberculosis Control Collaboration used a process of experimentation and adaptation to design and implement a tuberculosis control program that was actually very different from the standard programs assisted by The Union: no inpatient therapy, an intermittent regimen, and directly observed treatment throughout.[51] Other differences included screening by fluoroscopy and offering a 6-month treatment regimen for new cases (rifampicin throughout). While there was inpatient treatment taking place in China, the hospitals providing it were not included in the project. Further weaknesses in the China project have been brought to light, such as the selective recruitment of patients and noncompliance with the policy of directly observed treatment.[44,52]

Quoting the *WHO's Treatment Observer* of March 24, 1997, Heifets and Cangelosi recall how WHO used Peru as an example of the success of the DOTS strategy: tuberculosis was defeated by a model DOTS program, making it virtually impossible for a patient to develop incurable multidrug-resistant tuberculosis.[53] At the same time, a group of researchers argued that this was not the case, based on their experiences in Peru. Farmer et al. demonstrated how patients with initial resistance to isoniazid and rifampicin developed additional resistance to two other drugs through treatment in the DOTS program, a phenomenon labeled the amplifier effect.[54] In 1998, enlightened by their experience in Peru, Farmer and Kim suggested the term "DOTS-Plus" to describe a strategy to address multidrug-resistant tuberculosis.[28]

experts to be controversial. Ironically, Peru became the cradle of DOTS-Plus.[28,54] It is tempting, in the case of Peru, to argue that had there been a less top-down approach and more involvement with regional experts at the outset, the course of events might have been different. In Russia and the countries of the former Soviet Union, where drug resistance, including multidrug resistance, was a serious problem, the treatment algorithm seemed even more inappropriate.[56] In China and India, the project structure and patient recruitment strategies were found by outside experts to be controversial, and these countries became examples of settings with low case detection.[32,57] It took roughly a decade for the WHO to acknowledge that program structure was important or, quoting Dye et al., that the DOTS strategy would have to "penetrate" the variety of health care systems that diagnose and treat tuberculosis.[58]

Technical and operational aspects

The Union collaborations involved national programs implemented in places with uniform health care systems where there was commitment to countrywide expansion with the involvement of local leadership from the start. In the early stages of the DOTS strategy, DOTS programs or projects were sometimes

isolated phenomena in pluralistic health care systems or separate projects running within existing tuberculosis programs. These were two quite different scenarios, and the situation raised concerns as to program comparability, risk adjustment, and patient selection.

Short-course treatment was already in use in many places where the DOTS strategy was introduced (for example, it had been used for a decade in Peru[54]), and thus the principle of gradual implementation of short-course treatment with careful monitoring of performance was not applicable. Instead, the implementation of the strategy became phased revisions of existing tuberculosis programs, and it was common to hear talk of "new" national programs or "revised" national programs, "DOTS areas" and "non-DOTS areas," and even "DOTS patients" and "non-DOTS patients," giving rise to controversial comparisons. Meanwhile, short-course treatment was sometimes, but not invariably, used in non-DOTS areas and/or for non-DOTS patients, often uncontrolled.

In some countries, the method of choosing areas in which to introduce the DOTS strategy was criticized as selective rather than representative, and there were even allegations that individual patients were selected so as to maximize the likelihood of a successful evaluation. In addition, the definition of a non-DOTS patient was unclear. Was it a patient treated with a 12-month regimen or a self-administered short-course treatment? A patient diagnosed on the basis of radiology? A patient who was not registered and/or reported? Or a patient whom the government was not committed to cure? It was also unclear what it meant to treat patients in "a DOTS-compliant way."[59]

The perceived focus on directly observed treatment as central to improving treatment adherence and achieving cures in tuberculosis programs was criticized as inappropriate.[60,61] Volmink et al. argued that various co-interventions —for example, the use of incentives, the tracing of noncompliers, the legal sanctions in place, patient-centered approaches, staff motivation, supervision, charismatic managers, enthusiasts, and additional external funds—were not made explicit and/or were poorly described, and their influence on improving results was not assessed.[60] Others have suggested that it was funding rather than directly observed treatment that was important for success.[62]

The DOTS strategy is not uniform. The intervention or change made to existing tuberculosis control programs depends on what measures are already in place. Therefore, one would not expect the same effect to be achieved in all settings. Even when fully implemented, DOTS programs are not necessarily identical in different settings; they may differ in terms of structure, recruitment strategies, treatment regimens, and treatment supervision. Thus, "DOTS" and "non-DOTS" strategies are not clearly differentiated, and it is at best naïve to treat them as such.

Perhaps forced by the circumstances, the implementation of the DOTS strategy was often success-driven. The DOTS demonstration areas did not always

reflect what was likely to happen if implementation were complete, that is, used in the health care system country-wide, with no exclusions. It is even claimed by some researchers that DOTS programs rejected patients who were unlikely to adhere to treatment.[43,45] Mobile populations were excluded in some settings, for example, the "floating population" in China[52] and "extra-territorial patients" in Russia. Furthermore, seldom if ever did the picture presented to policy evaluators include non-DOTS areas or non-DOTS patients, or even the results of retreatment in DOTS areas (even if the technical recommendations of the WHO[63] stated that treatment evaluation should cover the entire program and all diagnosed cases). This backfired, as it gave rise to suspicion and criticism. Perhaps, within the WHO, it was considered important to start somewhere, and perhaps it was hoped that when good results were demonstrated, everyone would want to adopt the program.

As mentioned above, while the initial framework presented by the WHO described a comprehensive approach,[10] this effort eventually drowned in the advocacy campaign. DOTS came to emphasize clinical and curative care aspects and surveillance, but neglected some core public health functions that are important in any setting, and even more so in pluralistic health care systems.

Recruitment of cases

The coverage of short-course treatment in new smear-positive cases was an important operational indicator in the programs collaborating with The Union. Its implications for the overall outcome of treatment in smear-positive cases, and thus for tuberculosis control in general, were monitored. The 12-month regimen was used during the expansion phase of the programs, while prerequisites for the full expansion of short-course treatment were being implemented.

Comparing the outcome for patients given the short-course treatment with the outcome of those given the 12-month regimen was not meaningful, as patients were selectively recruited into the different treatment groups. The selection criteria used in programs collaborating with The Union were explicit: those who were able to accept directly observed treatment were enrolled in short-course treatment, and those who were not received 12-month treatment but were included in the evaluation. Apparently, various other and sometimes highly controversial enrollment criteria came to be used in some DOTS programs. A tuberculosis control program must not discriminate against patients by refusing care, and it is not justifiable to refuse available treatment to patients in a control program. In the case of habitual defaulters who have had opportunities to be cured, it may be justifiable to impose conditions before allowing them into a treatment program, such as direct observation of treatment and/or hospitalization. An obsession with a target cure rate, however, can result in all other objectives being ignored.

Operational research gathered from 1996 to 1998 in two DOTS pilot sites

in New Delhi, India, revealed that 37% and 49% of eligible patients received short-course treatment in the two clinics, respectively.[45] The remaining patients rejected or were denied short-course treatment—some, it was argued, on highly questionable and discriminatory grounds. In practice, the personnel applied an algorithm for DOTS recruitment with criteria such as proof of residence, duration of stay in the area, having a permanent job or government employment, and "impression" or "convenience," as judged by the health staff after visiting the patient's home. All this seemed to the investigators to amount to an effort to determine how likely the patients were to "spoil" the results of the "DOTS cohort." Critics concluded that the staff of these clinics had developed a strategy for maintaining the cure rate—that is, the program goal—but it was one that worked against basic tuberculosis control principles by failing to provide the best available treatment to infectious patients. Thus, it was argued, the clinics' work was oriented toward project success rather than tuberculosis control, and the focus was on maintaining cure rates rather than on curing patients.[45] This led people to question the nature of DOTS; if it is not a tuberculosis control strategy, then what is it?

Modifications in the treatment algorithm

With the new strategy came new terminology. Cases and treatment regimens were grouped into Category I, Category II, and Category III. A patient would not first receive the Category I, then the Category II, and finally the Category III treatment regimen, as some might assume. Rather, the classification referred to the relative priority of treating a case.[63] Category I was for new smear-positive cases (and seriously ill smear-negative and extra-pulmonary cases), Category II for previously treated smear-positive cases (and exceptionally smear-negative), and Category III for smear-negative and extra-pulmonary cases (unless seriously ill). Under this classification system, various treatment regimens could be accommodated under each category, except for Category II, for which there was only one option. Policy makers were to compose a treatment algorithm by selecting a regimen from each category. There was also a Category IV, devised for chronic cases, but the treatment of these patients was given low priority. Grouping the regimens into categories may have simplified the presentation of the DOTS strategy, but it unfortunately blurred the strategy's details.

Category III

The 1964 Expert Committee report suggested that a definitive diagnosis of tuberculosis be made if a person was found to be bacteriologically positive. It was recommended that so-called suspect cases—those people whose tuberculosis was detected through chest radiography but who were bacteriologically negative—not receive anti-tuberculosis treatment, but that their status be followed by the programs to see if they progressed to smear-positive tuberculosis.[64] This

recommendation was put forward under conditions that still prevailed in India in 1977, where as many as 70% of pulmonary "cases" were diagnosed solely on the basis of chest radiography.[65]

In 1991, the WHO recommended that patients with smear-negative pulmonary tuberculosis be treated, based on studies published in the early 1980s reporting the outcomes for smear-negative patients in Hong Kong, where a strict diagnostic process was applied.[66,67] Also based on the results of clinical trials in Hong Kong,[68] the WHO endorsed a regimen of a shorter duration (four months) than was recommended for smear-positive cases and that used three as opposed to four drugs in the intensive phase (as bacterial load in smear-negative cases is lower than that in smear-positive cases and selection for resistant mutants less likely).[63] The problem with this recommendation was that the rest of the world did not use the strict diagnostic process utilized in Hong Kong.

In the guidelines published in 1993,[69] recommendations for smear-negative Category III cases included a regimen with rifampicin, isoniazid, and pyrazinamide (daily or three times a week) in the intensive phase, followed by two months of isoniazid and rifampicin (daily or three times a week), or alternatively 6HE, 6HT, or 2HE/4H. This regimen could be used except in pulmonary cases with parenchymal involvement exceeding a certain size on chest radiograph. In extra-pulmonary cases with incomplete remission of signs and symptoms, it was recommended that the continuation phase be extended, administering isoniazid alone for an additional four months. This was altogether different from the straightforward, careful, and somewhat conservative recommendations made in the Union model.

According to the trials conducted in the 1980s in Hong Kong, a longer course of treatment was needed to cure smear-negative tuberculosis if the culture was positive. However, while the relapse rate was considered too high (13%) for culture-positive patients in the 2- to 3-month regimens tested,[67] this was not the case with the 4-month regimen.[68] In high-prevalence countries, as a rule, it is impossible to distinguish between culture-negative and culture-positive cases (since cultures are not routinely performed). Therefore, all smear-negative cases need to be enrolled in a regimen that is able to cure culture-positive tuberculosis. Some would even argue that the regimen has to be safe for use in smear-positive tuberculosis as well, as laboratory services may be weak and program procedures not always followed.

In the 1986 Orange Guide, the simplest regimen put forth was a 2-drug regimen (12HT).[70] It was harmless in terms of producing serious drug resistance not easily cured by the retreatment regimen. The 4-month regimen recommended by the WHO in 1993 (2RHZ/2RH) had the potential to create drug resistance if the organization of the treatment was deficient. The second edition of the WHO guidelines, released in 1997, recognized that its recommendations were primarily intended for countries with a high incidence of tuberculosis,

where the bulk of the tuberculosis problem (95%) was found.[71] The 4-month regimen was no longer recommended, and treatment was always administered on a daily basis in the intensive phase. Finally, in the third edition of the guidelines, released in 2003, it was recommended that four drugs be administered in the intensive phase for all new cases (except noncavitary, smear-negative disease in HIV-negative patients; patients known to have fully susceptible organisms; or young children).[72]

Category I and Category II

Guidelines issued by the WHO in 1991[63] and published in 1993[69] endorsed a 6-month treatment regimen with rifampicin throughout for new smear-positive cases (under Category I). The intensive phase required daily treatment, as did the other treatment options in this category. Supervision of treatment was not particularly stressed, except in areas with high HIV prevalence. There was, however, no modification of the retreatment regimen (Category II) compared to the Union model algorithm. The WHO recommended that retreatment be fully supervised, at least in the intensive phase (three months), and in case of a positive smear at four months, that sputum be sent for culture and susceptibility testing.[63]

In a 1994 document, it was acknowledged that, in countries where HIV infection was common and there was only a weak capacity for supervision of treatment, self-administered ethambutol and isoniazid in the continuation phase of an 8-month treatment course might be a wiser choice than the continued use of thioacetazone on a programmatic basis.[73] In this context, the WHO advised strengthening the retreatment regimen with pyrazinamide throughout.[73] This recommendation, however, never made it into the published treatment guidelines.[71] Furthermore, in the 1997 guidelines, thioacetazone stopped being recommended as an option in the continuation phase of treating Category I cases.[71] There was now more emphasis on treatment supervision than in the previous version of the guidelines, and directly observed treatment was specifically mentioned.

In 2000, Bastian et al. referred to treatment recommendations such as those in the programs collaborating with The Union as algorithmic approaches to diagnosing multidrug-resistant tuberculosis.[74] They claimed that this approach was not only inaccurate but also dangerous and costly—even in a good program, where multidrug-resistant cases might eventually be cured. This, however, is a misinterpretation of the Union model's recommendations, which were not put forward as an algorithm to diagnose multidrug resistance but rather to prevent its occurrence. With the introduction of the 6-month treatment regimen for new cases, the algorithm was weakened.

As mentioned in Chapter 3, it was assumed in the retreatment regimen used in programs collaborating with The Union that relapses and failures had

resistance to streptomycin and/or isoniazid,[75] because these drugs had been used widely under inadequate control. This assumption was supported by cohort evaluation of treatment results and by drug resistance studies conducted in previously treated cases in Tanzania.

This assumption should not have been expected to apply globally or indefinitely, and it should have been reconsidered when the DOTS strategy was launched in different settings. Furthermore, the Union collaborative programs had never tested an algorithm using a 6-month regimen. The DOTS strategy nevertheless endorsed a 6-month treatment course with rifampicin throughout for new smear-positive pulmonary tuberculosis (Category I)—without preconditions, without stressing the supervision of treatment, and without modifying the regimen for previously treated cases adopted from programs using the Union algorithm.

At the time, many clinicians and public health experts argued that the treatment regimen suggested for previously treated cases was unsuitable if those failures had completed a treatment course in a reliable program that used a 6-month regimen for treating new cases. At a minimum, these concerns should have led to a careful study to assess the situation. The WHO's justification for using the same Category II regimen for retreatment cases (that is, irrespective of the Category I regimen) was the dogma that "operational" or "program" failure did not necessarily imply the presence of drug resistance. The counterargument, however, was that, if the program is well organized, treatment failure is likely to be due to bacterial resistance, whereas if a program is weak, it is better not to use rifampicin throughout in new cases.

The fact of the matter is that in the early 1990s, many programs were using 6-month regimens with rifampicin throughout anyway, and some were already struggling or beginning to struggle with complicated drug resistance, including multidrug resistance. In Latin America, the 6-month regimen had been used on a wide scale but in tandem with different regimens for failure cases—regimens that included second-line drugs. Some of these programs were performing quite well, for example those in Chile and Venezuela. Others, such as Peru, were not. A problem of multidrug-resistant tuberculosis was exposed when Peru implemented the DOTS strategy, and was compounded by the DOTS treatment algorithm.[76] The amplifier effect set in and, primarily because of the WHO's premature boasting, multidrug resistance became an embarrassment.[54] This problem should have been foreseen and could have been prevented with proper piloting and careful adaptation of the DOTS strategy.

While tuberculosis programs employing short-course regimens and sound control policies had been shown to decrease the prevalence of drug resistance in a number of countries in the early days before the DOTS strategy,[74,77] these successes concerned poly-resistant, but not multidrug-resistant, tuberculosis.[28] In places where it was firmly established, particularly in Russia and the coun-

tries of the former Soviet Union, multidrug-resistant tuberculosis did not go away easily with the implementation of DOTS. Health providers claimed that using a DOTS treatment algorithm was nonsensical in these settings and, some argued, even harmful.

The idea that multidrug-resistant tuberculosis would simply disappear with the implementation of DOTS programs was challenged by a project conducted in Peru.[28,78] Investigators stated that the amplifier effect from using short-course treatment in the DOTS program had contributed to a large outbreak of multidrug-resistant tuberculosis in Lima.[28] In a case series, more than 90% of patients who were smear- and culture-positive after treatment with a directly observed short-course regimen using rifampicin throughout were found to have multidrug-resistant tuberculosis, and thus were unlikely to be cured by the DOTS retreatment regimen (Category II).[79] Accordingly, a retrospective study of Category I failures registered for retreatment in northern Lima, conducted from 1997 to 2001, suggested* that the Category II treatment regimen did not make sense.[80] In 2001, the Category II regimen was discontinued for use in Category I failures in Peru.[81]

Arguably, as a result of the rivalry between policy stakeholders, the issue of preventing and treating multidrug-resistant tuberculosis was not studied objectively. Rather, the discussion became polarized, and considerable effort went into fortifying positions on both sides. It took roughly a decade for the WHO to acknowledge the flaw in the treatment algorithm introduced by the 6-month regimen. In the third edition of the WHO guidelines, published in 2003, it was finally spelled out that new smear-positive cases that failed a 6-month treatment regimen that used rifampicin throughout were likely to be multidrug-resistant (if the treatment was reasonably regular and particularly if it was directly observed) and that those patients required a modified retreatment regimen (Category IV).[72] The guidelines recommended that drug susceptibility testing be performed whenever possible before starting the Category II regimen in failure cases. These recommendations were very much in line with earlier recommendations in programs such as those in Chile and Venezuela.

Even if multidrug resistance is more common in failures of Category I programs than in other patients eligible for retreatment, those failures do not automatically become the most important source of multidrug-resistant tuberculosis in a given setting. A greater number of multidrug-resistant cases might actually arise because of partially treated patients (defaulters) or patients previously treated outside of the program. It depends on the quality of the program and the characteristics of the area's health care system, and cannot be known for sure unless studies of drug resistance are carried out in all categories of previously treated cases.

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*The study design and sample size were not optimal for drawing a conclusion on the issue.

Category IV: DOTS-Plus

A study conducted in Algeria in the 1970s concluded that systematic drug susceptibility testing in new, untreated cases was not necessary and much less important than making improvements in the organizational aspects of a program and treatment supervision aimed at preventing treatment interruption.[82] According to the data, performing susceptibility testing before starting treatment overestimated the number of failures, doubling the number of patients who needed a second-line regimen. A somewhat similar debate took place later, but in a different scenario: with multidrug-resistant tuberculosis. Some health professionals argued that treatment failure should be allowed to happen, while others argued that drug susceptibility should be tested at the start of treatment in places where drug resistance was prevalent, or treatment would result in the amplification of drug resistance.

With the introduction of short-course treatment, initial drug resistance became irrelevant, as rifampicin-based regimens were quite effective in spite of resistance to isoniazid and/or streptomycin, and at this time rifampicin resistance was rare. In their article in 1999, Heifets and Cangelosi argued that, as of the late 1990s, initial resistance to rifampicin was no longer rare and, accordingly, the opinion that drug susceptibility testing is too expensive, unnecessary, or impractical as a tool for modifying treatment on an individual basis (because of the long turnaround time) was no longer justifiable in countries with high levels of drug resistance.[53] According to them, depending on the levels and nature of drug resistance, programs may at a certain point need to perform drug susceptibility tests in all new cases and modify individual treatment regimens according to the results. Reports from countries with serious drug resistance problems tend to agree with this view.[56]

The position of the Tuberculosis Division of The Union in 2005 was that the use of drug susceptibility testing for individualizing treatment regimens has inherent limitations and may be dangerous.[83] According to The Union, any case of multidrug-resistant tuberculosis detected by drug susceptibility testing should be offered an appropriate standardized treatment regimen based on second-line drugs. When available, surveillance data from chronic patients on those drugs for which drug susceptibility testing is more reliable, such as kanamycin and fluoroquinolones, should be used to determine this regimen.[83] Otherwise, they argue, the probability of resistance to the main second-line drugs must be estimated by the extent of the drugs' previous use. This is essentially the same logic applied in the development of the treatment algorithm in the Union model.

Supervision of treatment

The recommendations of the WHO concerning treatment supervision and the direct observation of treatment have lacked consistency.[84] In the WHO's

1993 technical guidelines, recommendations on supervision of treatment were vague.[69] The term "fully supervised treatment" was used, while "directly observed treatment" was not. Emphasis was put on supervised treatment in Category II cases until they were smear-negative, and on intermittent treatment. Adherence was addressed by recommending fixed-dose combinations in daily self-administered treatment. Daily supervised treatment for the first month in Category I and Category II treatment was only mentioned in relation to settings with high levels of HIV infection. There was no mention of who should supervise treatment or how.

In the revised guidelines, published in 1997, the term "directly observed treatment" was used.[71] Directly observed treatment was recommended in the initial phase of treatment in all smear-positive cases and in the continuation phase when the regimen contained rifampicin, that is, as in the original Union model. The guidelines specified that the supervisor, who could be a health worker or a trained community member, should watch the patient swallow the tablets. The third edition of the guidelines, published in 2003, is in agreement with this but specifies in addition that members of the patient's family should not serve as treatment observers.[72]

The journey and the destination: objectives, targets, and rationale

The Expert Committee of 1964 stated that the efficiency of tuberculosis programs could be estimated quantitatively in terms of the proportion of a community that was served and the number of patients who completed treatment annually. They did not, however, elaborate on how coverage was to be measured, nor did they clarify the latter indicator. Geographical coverage, patient access, and case detection make the measurement of these indicators difficult.[85]

With the 1990s launch of the new WHO tuberculosis control strategy came an emphasis on developing targets and indicators.[8] The WHO's priorities were to improve the cure rate, and once this was achieved, to expand service coverage. The proposed global target of the new strategy was to cure 85% of detected new smear-positive cases and to detect 70% of existing cases by the year 2000.[10] The time it would take to achieve a 50% reduction of tuberculosis incidence in low-income, developing countries with poorly developed health services was thought to be 10 to 12 years. The WHO believed that by implementing the DOTS strategy, tuberculosis deaths could be halved in a decade and the global epidemic controlled.[86]

Mathematical modeling and estimates of disease burden

In 1965, Waaler et al. suggested it might be more promising to use mathematical modeling when studying tuberculosis epidemiology rather than in economics

and other social sciences, where the operating agent is the unpredictable *Homo sapiens*.[87] Today, however, it can be convincingly argued that *Homo sapiens* is indeed an important operating agent in tuberculosis epidemiology.

The tuberculosis disease burden on a community must be estimated when planning services and activities and when speculating on program impact. This is true for both considering the implementation of a new program or the continuation of an existing one. There are several potential sources of information for estimating the disease burden and/or the expected volume of services. If a good notification system is in place, then routinely gathered information will provide figures on actual case findings and trends, which reflect the expressed need or demand for services. At the time The Union started its collaboration with national programs, however, routinely collected information on tuberculosis was scarce in partner countries.

In 1981, Styblo and Rouillon discussed the unreliability of notification data in developing countries: the services and thus the detection of cases were incomplete, the information systems deficient, and the reference population (including its age distribution) often unknown. While acknowledging the importance of reporting for the assessment of treatment results as well as for the amount of work performed and the functioning of the services, they stressed the need for a measurement of disease burden independent of the program and its information system.[88] The key parameter they proposed was the annual risk of tuberculosis infection in a community, calculated from the prevalence of infection in children as measured in tuberculin surveys. The disease burden could then be estimated and described by applying three assumptions: first, the incidence of tuberculosis was twice the mortality rate, and the prevalence twice the incidence. Thus, if tuberculosis mortality equaled 1, then incidence equaled 2 and prevalence 4. Second, a 1% risk of infection corresponded to a rate of 50 (40 to 60) smear-positive cases of pulmonary tuberculosis per 100,000 population. Third, 50% of all tuberculosis cases are smear-positive. The second assumption, often referred to as Styblo's formula, has been widely used in mathematical modeling, target setting, program evaluation, and cost-benefit analyses to this day.

In 1995, Rieder demonstrated that estimating the expected number of cases using Styblo's formula is controversial.[89] The ratio of (risk of) infection and (incidence of) disease is subject to systematic variations caused by epidemiological changes such as occur as a result of intervention (case finding and treatment) or an HIV epidemic, for example.[90] Therefore, tuberculosis incidence estimates based on Styblo's formula for individual communities are uncertain, let alone those for provinces and districts. For demonstration purposes, some examples are provided in Box 6.3.

Thus, it is difficult to use prevalence of infection or estimates of it when planning supplies and services or when setting targets for case detection. The

Box 6.3 Examples comparing estimates of risk of infection and case notification

Based on a tuberculin survey conducted in Nicaragua from 1992 to 1994, the annual risk of infection was estimated as 0.4%.[91] The actual reported rate of new smear-positive cases was 38 per 100,000, making the actual case-detection rate 190% of what Styblo's formula estimated. Calculations based on the annual risk of infection underestimate the disease burden in this setting.

A similar observation was made in Cambodia, where the estimated tuberculosis incidence based on a survey of annual risk of infection in urban areas was 2.4 times lower than the actual tuberculosis notification rate in 1995.[92] There may, however, be a denominator problem here, as patients presenting in urban areas may live in rural areas, and thus the notification rate in urban areas could be inflated.

A tuberculin survey conducted in Vientiane, Laos, from 1995 to 1996 estimated the annual risk of infection as 1.3%.[93] The expected rate of smear-positive tuberculosis based on this annual risk of infection was 65 per 100,000, whereas the reported rate was 37 per 100,000. The calculated case-detection rate was accordingly 57% (37/65) using Styblo's formula. In this setting the calculation might well reflect the reality, although this is difficult to verify.

relationship between the annual risk of infection and the rate of smear-positive tuberculosis is not constant over time and depends on intervention, among other things. However, evaluating changes in this ratio could be a valuable tool for monitoring the efficacy of a tuberculosis program.[94]

Another alternative is to measure the prevalence of disease. The main problems with this involve difficulties in conducting tuberculosis prevalence surveys and interpreting the results. Again, it seems that recognizing a trend would be more useful than making a single estimate. Ideally, the ratio of prevalence to incidence will be reduced with intervention—approaching 1 and then dropping below 1—as, if there is high case detection, the average duration of disease (or rather, infectiousness) is shortened to less than a year.

Even if tuberculosis surveys are performed, however, it is not easy to get an accurate case-detection rate based on a cross-sectional survey. Those patients diagnosed in a survey would most likely have been diagnosed eventually when their symptoms progressed.[52] Furthermore, incidence cannot be calculated from survey data without precise measures of the duration of illness.[95] Surveys are nevertheless conducted. A 2001 report from South India highlights an unfavorable situation as judged by a survey, in which a decline in incidence was measured in spite of a stable prevalence of smear-positive tuberculosis and no measurable decrease in risk of infection.[94] The investigators concluded that the ratio of prevalence to incidence increased over time, suggesting ineffective treatment and the pooling of partially treated cases.[94]

Styblo's mathematical model[96] (see Chapter 2) and formula were not emphasized in the Union collaborative programs as they were in the DOTS era. Prevalence and incidence are epidemiological terms that belong in the field of research, and are not useful vocabulary in the routine work in tuberculosis programs. For example, several definitions of a "prevalent case" have been used, none of them practical in day-to-day work. While it is important to understand the epidemiological terms, it is unwise for program workers to translate them literally into formulas or for policy makers to plug in numbers at every step. There are too many ill-defined and interrelated factors for this to be a sensible approach. For the purpose of policy formulation, the null state needs to be understood (this depends on the setting and is not always studied well enough), as do the underlying forces that drive the spread of tuberculosis in a community (this is reasonably well researched) and the actions taken to counteract them. Program workers then need to decide which actions to implement and finally how to assess progress and the outcomes of the intervention in a sensible way.

Objectives and targets

As stated in Chapter 1, ideally, targets should be specific, measurable, adaptable, reasonable, and time limited. The targets for tuberculosis control endorsed by the World Health Assembly in 1991 (85% cure ratio and 70% case detection) were based on Styblo's mathematical model (presented in Chapter 2). These targets were set for tuberculosis programs. It is interesting to contemplate what implications such targets have for the care of individual patients. A public health program with an emphasis on the quality of care, for example, on curing patients, ideally benefits the individual patient. There is, however, a potentially harmful problem with emphasizing targets: in the race to reach the target, some people are excluded from care.

The targets endorsed by the WHA were originally set for the year 2000, then postponed to 2005, and later it was stated that if countries did not reach these targets by 2005, they should aim to reach them "as soon as possible thereafter."[97] In 2005, governments, donors, and other supporting agencies were starting to ask for proof that DOTS was having the expected epidemiological impact.[98] As the evidence was not obvious, it is tempting to argue that target-setting backfired.

Since the turn of the century, all discussions in the international health arena have revolved around the Millennium Development Goals: the goals from the Millennium Declaration adopted by the General Assembly of the United Nations (UN) and signed by 189 countries in September 2000. Their reference point is the year 1990, and they are to be reached by 2015. In all, there are 8 goals and 18 targets, and 48 indicators for monitoring progress. Goal 6, Target 8, and Indicators 23 and 24 concern tuberculosis. Arguably, the UN should focus on international poverty reduction and the goals and targets concerning

debt relief and fair trade—not on communicable disease. These are truly international issues that affect the wider public health, and the specific targets can actually be addressed by the international community. Humans are essentially the sole factors influencing these issues. Furthermore, meeting these targets will indirectly aid in the control of infectious diseases, including tuberculosis. The problem with creating specific, global targets concerning the health and diseases of populations is that local circumstances differ widely, and there are many forces at play—not just the human factor.

Another issue with the UN's international public health goals is responsibility. Who exactly is responsible for achieving the global epidemiological targets in disease control? To whom is the UN addressing its goal of hitting global targets for the reduction in incidence, prevalence, and mortality from tuberculosis? In addition to this ambiguity, it must be noted that progress toward meeting most of these communicable disease targets cannot be measured easily.

Within the Millennium Development Goals, Target 8 specifies the following: "[to] have halted by 2015 and begun to reverse the incidence of malaria and other major diseases," tuberculosis being one of the other major diseases.* The indicators for monitoring progress are prevalence and death rates (Indicator 23) as well as case-detection and cure rates in DOTS programs (Indicator 24). Indicator 24 refers directly to the targets endorsed by the World Health Assembly in 1991. The Stop TB Partnership elaborated on the specific goal of Indicator 23.[97] The aim was set at halving tuberculosis prevalence and death rates by 2015. The prevalence target is in line with Styblo's original predictions of tuberculosis control in high-prevalence countries. The death-rate target is not well defined. The current goals and targets are summarized in Box 6.4.

Enarson et al. have pointed out that the global targets in tuberculosis control focus on disease—incidence, prevalence, and death—whereas for elimination, a reduction in rates of infection must be the measure of progress, the ultimate target being to reduce infection.[25] Improved or new tools are needed for measuring progress in this respect.

Measuring progress toward meeting current targets

None of the global targets referring to disease burden (incidence, prevalence, and death) are easily measurable, be it at global, national, or local levels, except perhaps the elimination target, if that is understood to refer to notified cases. The prevalence of tuberculosis is not routinely measured and not easily measurable (except in countries where prevalence is accurately reflected by a health surveillance system), and the measurement of death rate can be approached in several ways, none of them perfect. Whichever method is used, documenting a trend might be possible. The main problem with taking all the measurements

*United Nations, http://www.un.org/special-rep/ohrlls/lldc/MDGs.pdf

Box 6.4 Goals, targets, and indicators in tuberculosis control

Millennium Development Goals

Goal 6: Combat HIV/AIDS, malaria and other diseases

Target 8: To have halted by 2015 and begun to reverse the incidence of malaria and other major diseases

Indicator 23: Prevalence and death rates associated with tuberculosis

Indicator 24: Proportion of tuberculosis cases detected and cured under DOTS

Stop TB Partnership targets

By 2005: At least 70% of people with sputum smear-positive tuberculosis will be diagnosed (that is, under the DOTS strategy) and at least 85% cured.

By 2015: The global burden of tuberculosis (per capita prevalence and death rates) will be reduced by 50% relative to 1990 levels.

By 2050: The global incidence of tuberculosis disease will be less than one case per million population per year (note that this is the elimination goal from 1991, as discussed in Chapter 1).

is primarily, but not exclusively, a denominator problem. It is also debatable how much priority should be placed on obtaining accurate measurements of disease prevalence and incidence, other than improving routine notification and surveillance. Another problem is with assessing the impact of the DOTS strategy, as it was not implemented in virgin territory but rather in areas where there were already intervention programs in place, but little information on their effects (for example, how many deaths were prevented).

The denominator is missing for the 70% case-detection target, although estimates have been produced. Furthermore, in Africa and comparable settings, the denominator should have constantly increased as a result of the HIV pandemic. Erroneous estimates used for the denominator could explain a low case-detection rate in a country. Another explanation for an erroneously low case-detection rate would be that not everyone was included in the numerator, as has occurred in places where DOTS has been implemented in pluralistic health care systems (for example, Bangladesh, China, India, and Vietnam). The implementation of the DOTS strategy in pluralistic health care systems was flawed. To some extent, the interventions were each based in vertical or semi-vertical tuberculosis services without adequately addressing coordination and referrals, and often excluded the private sector altogether. This is not to say that a new indicator is needed to track programs in health care systems that are a public-private mix, but rather that a system for universal, mandatory notification is necessary.

Some experts have said that the reduction of tuberculosis deaths has not

always been a priority for tuberculosis programs, because death as a treatment outcome is not associated with ongoing transmission and therefore is not relevant to the public health objective of breaking the cycle of transmission.[99] This is misleading. The prevention of premature death is always a public health objective and has been an objective of tuberculosis treatment from the start. With the introduction of effective chemotherapy, however, death from tuberculosis has become a rare event and thus has lost its practical importance as an epidemiological indicator.

As a result of HIV infection, more patients started dying while on tuberculosis treatment, but not necessarily from tuberculosis. A high general (for example, age-related) and specific (for example, HIV-related) mortality in population groups will be reflected in tuberculosis programs in both low- and high-burden countries. How, then, to deal with the statistics? The World Health Report counts deaths among HIV-infected persons as AIDS deaths, whereas the Stop TB Partnership death rates include HIV-positive patients because, they claim, they want to reduce the burden of tuberculosis among all groups, not just among HIV-negative patients.[97]

Some policy administrators argue that the number of cohort deaths—what is measured in tuberculosis programs—is insufficient as an indicator in epidemiological surveillance regarding the impact of tuberculosis programs and that measuring progress toward reaching targets for reduced tuberculosis deaths requires improved national vital registration systems so that a more accurate determination of tuberculosis mortality can be made.[99] It is important, however, not to fall victim to the targets—improving the mortality statistics because there is a mortality target. As a rule, someone setting a target would identify the data source before deciding on that target. Cohort deaths is an operational indicator and suffices as such, as further discussed in Chapter 8.

Finally, what does a global, a regional, or even a national cure rate measure? These rates are subject to what is referred to as the fallacy of the mean. As an example, compare overall figures for the United States to the figures for selected cities.[100] From 1976 to 1980, 83% of patients completed 12 continuous months of chemotherapy. That seems acceptable until the data are broken down: the rate was 36% in Chicago as opposed to 94% in El Paso. From 1986 to 1990, the U.S. completion rate was 84%, ranging from 54% in New York City to 96% in San Francisco and 99% in El Paso.

The role and consequences of reward and punishment

Performance-related payment schemes have been applied in a variety of circumstances, targeting workers at all pay scales. These schemes were originally used in production lines in factories, where it was easy to monitor output (for example, pairs of blue jeans produced) and where bonus payments were used to boost production and meet deadlines. When applied in different circumstances,

the temptation to exploit the system arises—something that is difficult to do on the production line.

Performance-related payment schemes are frequently linked to target setting. Such schemes assume that health professionals will work harder if they receive direct rewards. While this may or may not be true, strategies based on this ideology have proved difficult to manage in tuberculosis programs and in the health services in general. The issue is complicated, and the pros and cons vis-à-vis improving salaries across the board should be carefully considered. Introducing pay-for-performance schemes can be costly, and sustainability needs to be considered up front. There is also the risk of exploitation and cheating. Finally, the schemes might alter working morale irreversibly, as once incentives and bonus payments have been introduced, it would be difficult to withdraw them without risking performance deterioration to below pre-scheme levels.

Does paying for performance promote quality? A 2005 U.S. study looking at performance in preventive services (screening for cervical cancer, mammography, and hemoglobin) concluded that paying clinicians to reach a common, fixed performance target might produce little gain in quality for the money spent and would largely reward those with higher performance at baseline.[101] In a study of performance-related payments to general practitioner practices introduced in the United Kingdom in 2004, where a variable number of points was tied to 146 performance criteria (referring to clinical care for ten chronic diseases, organization of care, and patient experiences), targets were met for 83% of eligible patients. The practices participating in the experiment earned nearly 97% of the possible points available—a considerably higher proportion than the 75% expected, contributing to a budget deficit in the National Health Service. It also left policy makers wondering whether the targets were set too low, whether the physicians improved their practices or improved documentation of care to meet the new standards, or whether they skewed their results by excluding patients whose care did not meet the performance criteria.[102,103] A small number of practices appeared to have achieved high scores by excluding great numbers of patients through exception reporting. Interestingly, marked improvements in the quality of care had been achieved before the introduction of the pay-for-performance scheme.[102] The investigators concluded that the scheme was costly in terms of both bonus payments and information technology systems.

In the tuberculosis program in Malawi (2005), a system was piloted to see if staff at central and regional levels could fill out a self-assessment form related to the tasks they were expected to perform during that period, and whether the system could help the tuberculosis officers achieve certain key program targets.[104] The form dealt with meetings, supervision, and training activities. The self-assessment reports were submitted twice a year to the Tuberculosis Program Steering Group, consisting of senior ministerial staff and representatives of international development organizations. To some, this might seem patron-

izing, if not reminiscent of colonialism. The staff received a performance-related allowance if they accomplished what was expected of them in the self-assessment forms. Such systems raise many questions, apart from those raised in the British study cited above. What about differences in setting? Targets may not be equally easily accomplished everywhere in Malawi. And if some staff receive bonus payments, what is given to other staff—peripheral staff who do not have access to the donors but without whom no targets would ever be met?

Special care must be taken when dealing with targets that are linked to surveillance and epidemiological indicators. In Vietnam, it is acknowledged that a bonus system that includes payment to laboratory workers for positive smears and payment to community health workers for each patient cured encourages some health workers to falsify data in order to boost performance.[105]

Finally, there is the question of error reporting and disclosure systems. These can be seen as the opposite of bonus or incentive systems, as disclosure of suboptimal performance can be seen and felt as punishment. In a 2005 study conducted in the United States, most hospital administrators expressed substantial concern about the impact of mandatory, non-confidential reporting systems on hospital internal reporting.[106] They feared that, as a result of such a policy, information on performance problems and errors would be withheld. It may also be difficult to interpret and use such information, as seen, for example, when looking at the results of the Hospital Quality Alliance program in the United States, which found that performance varied not only among hospitals but also across indicators.[107]

The worst consequences of target setting, with or without performance-related payment schemes, are patients being excluded from care or discriminated against in some way. Examples are presented in Box 6.5 (see also the

Box 6.5 Targets: is everyone included?

As Hippocrates did before him,[108] the Roman doctor Galen warned his colleagues against visiting patients in the late stages of tuberculosis, lest their professional reputations be damaged.[27]

An article from modern-day Vietnam (2001) discussed the various ways in which patients may be excluded in tuberculosis programs.[109] In some districts in Ho Chi Minh City, a patient has to agree to daily attendance for directly observed treatment, sign a written agreement, and pay a deposit in order to register for treatment in the program. A patient may need to have a permanent address and present proof of permanent residency in Ho Chi Minh City. Incentives are paid to health workers for each patient cured. This may discourage health workers from registering patients who are likely to default.

In a retrospective review (reported in 2002) of a referral hospital in Riyadh, Saudi Arabia, it was found that a great proportion of patients were deported (27%), and therefore treatment results were not known.[110] This is one aspect of globalization.

Box 6.6 Challenges facing tuberculosis control in China

A vertical tuberculosis dispensary system works only if there is wide agreement among other care providers regarding the referral of patients to the vertical system and/or the coordinated supervision of all facilities (a public health function). Styblo referred to this as the "flow" of a program, and it should be piloted before DOTS expansion.

An internal assessment of the World Bank–assisted Chinese tuberculosis control project was reported in the *Bulletin of the World Health Organization* in 2002. The assessment, which used routinely collected data from 1991 to 2000, led to the conclusion that DOTS could be expanded rapidly on a large scale. Investigators found that the global target of an 85% cure rate had been reached rapidly and that the level of drug resistance was probably reduced, but that case detection had not reached the 70% global target—even though the notification rate for smear-positive cases doubled in the first five years of the program.[9] The "DOTS detection rate" was estimated as 53% in 1998.[9] In spite of a very high cure rate (more than 90%), the proportion of previously treated patients among those newly registered as smear-positive varied between provinces, but was approximately 20% overall as of the seventh year.[9]

An article published in *Health Policy* in 2005, referring to the period up until 2002, suggested that China faced four main problems in tuberculosis control: low case finding (that is, referring to cases detected within the DOTS system), even as low as 30%; low rates of treatment completion outside the DOTS system, where as many as 70% of patients did not complete treatment; an increasing proportion of multidrug-resistant tuberculosis; and lack of effective tuberculosis control in rural migrants, referred to as "floating populations."[52] These are exactly the issues that a public health program needs to address, preferably in the pilot phase.

The same article pointed out that as many as 80% of tuberculosis patients in China were diagnosed at general hospitals rather than in tuberculosis dispensaries at the time, and that as few as 15% of these patients were subsequently registered within the tuberculosis dispensary system (and thus counted by the DOTS system).[52] Formerly, only patients who sought care at the tuberculosis dispensaries (perhaps no more than 20% overall) would be treated free of charge, not those who sought care at general hospitals or township health centers.[52] Furthermore, in a revenue-driven system, Chinese patients were made to pay for all kinds of things, including unnecessary treatments and tests.[52] The stigma attached to tuberculosis in China is thought to be a problem, as is the lack of worker protection. Members of the working population may lose their jobs because of their tuberculosis status, which is likely to prevent them from seeking care within the DOTS system.

An article published in the *Lancet* in 2007 reported that, from 2003 to 2005, improvements were made in the Chinese program, resulting in an 80% case-detection rate (up from about 30% in the period from 1996 to 2002) without significantly affecting the reported cure rate (which is high in China, roughly 90%).[115] Thus, it seems that in 2005, China was able to achieve the global targets.

examples of India, discussed above under Recruitment of Cases, and China, in Box 6.6).

In conclusion, epidemiological targets and indicators involve working with estimates. The use of case-detection and cure rates in calculating indicators is problematic. On a local level, it is wiser to focus on performance indicators—on process and quality of treatment. This is discussed further in Chapter 10. Ogden suggested that it is important to shift thinking away from control and to start focusing on care.[22] In fact, they are the same thing. The best way to achieve control is to focus on care. No targets will be reached, whether those of control, containment, elimination, or eradication, unless all patients are included and treated. Focusing on achieving targets now may hinder tuberculosis control in the long run.

Current position and course in tuberculosis control

Toward the end of the twentieth century, many experts believed that the main challenges in controlling tuberculosis were those arising from the integration of tuberculosis control programs into the general health services and the quality of the overall functioning of the health services, rather than technical problems, such as insufficient diagnostic tools and drug resistance.[30] Interestingly, this is similar to the conclusion drawn by the Study Group in 1980, as discussed in Chapter 1.[111]

The problem with DOTS programs in many countries is low DOTS coverage rates and, inevitably, low case detection (DOTS detection rates). Many policy analysts are concerned that case finding is underemphasized in the global control strategy.[57,112–114] If there is low case detection, then effective cure rates are not guaranteed, no matter how high the rate is within DOTS projects. To illustrate some of the controversial issues involved in case detection and reporting, the example of China is presented in Box 6.6.

Currently, a division within the international policy community seems to be emerging. On one side are those who believe tuberculosis control policy is complex and needs to be simplified, and on the other are those who believe the policy is too simple and needs to be more sophisticated (the DOTS-Plus lobby). The fact of the matter is that tuberculosis control requires a relatively complex intervention that demands human resources and capacity.

Some health professionals argue that the WHO oversimplified its policy, perhaps because of its early enthusiasm, eagerness to raise funds, and focus on targets. Voices are now emerging that doubt the feasibility* of the DOTS strategy and point out that the lack of human resources and other shortcomings in capacity cannot easily be compensated for with money.[116] Health policy analysts

*Feasibility is defined here as a match between technical complexity and capacity.

holding this opinion state that reducing the technical complexity of the strategy is crucial in order to compensate for the capacity gap when scaling up to meet the Millennium Development Goals.[116] At the other extreme are the voices claiming that, despite the substantial success of DOTS expansion, most countries will probably not meet the Millennium Development target of halving the prevalence of tuberculosis and the associated death rates by 2015 unless the current policy is amended to include various DOTS-Plus strategies.[117] It seems that neither group is convincingly suggesting that stronger health care systems and public health functions are necessary; rather the focus is still on technical issues and targets and goals (or else both groups use them to justify their positions).

In a broad sense, there are two main problems with the DOTS strategy. First, DOTS does not prevent the increase in incidence of tuberculosis in settings with high HIV prevalence. Second, DOTS—or rather, the way it was applied—has not lived up to expectations within pluralistic health care systems. To the former problem, there is no obvious solution. The latter problem seems to require more, or rather different, political commitment and modifications in the application of DOTS, paying more attention to inclusion and the coordination of different service providers and to regulatory functions and quality assurance, that is, strengthening public health medicine.

Can tuberculosis be controlled?

In a paper published in 1998, Dye et al. applied a mathematical model to investigate the potential effect of the DOTS strategy and forecast the effect of improved case finding and cure rates on tuberculosis in different parts of the world.[118] They predicted that in countries where the incidence of tuberculosis is stable and HIV is absent, a control program that reaches the WHO case detection and cure targets would reduce the incidence of tuberculosis by 11% per year, whereas this effect would be smaller where rates have been declining for some years. According to the authors, HIV causes an increase in tuberculosis incidence but does not reduce the preventable proportion of cases and deaths. Their overall conclusion was that the potential of the DOTS strategy was greater in many developing countries than was the effect of introducing chemotherapy in industrialized countries 50 years earlier.

Nevertheless, at the dawn of the twenty-first century, criticism of the DOTS strategy was mounting. The inability to prevent the increase of cases in sub-Saharan Africa in the wake of the HIV pandemic is widely interpreted as a failure of the WHO's tuberculosis control strategy. A 2004 article went so far as to claim that with the DOTS strategy, the needs of millions went unmet and that no current epidemiological studies support the DOTS-only or DOTS-first approach.[119] On the contrary, there is indeed evidence to support the latter—or

rather to support making case finding and treatment the first priorities in tuberculosis programs—with the aim of controlling transmission from currently active cases and to prevent drug resistance. A telling example is from Russia and Eastern Europe, where low cure rates in DOTS programs suggest that if you do not do DOTS-first, chances are it will be too late.[74,120] On the other hand, it seems reasonable to argue that, instead of having a single global strategy, local control programs should take note of key epidemiological characteristics, such as the prevalence of tuberculosis, (multi-) drug resistance, and HIV, as well as available resources.[119]

Some criticisms of the DOTS strategy as listed by skeptics in 2005,[121] and comments in its defense are presented in Table 6.1. Apart from the critique of the strategy itself, some argue that technical excellence is not the main issue; programs that do not take into account factors that sustain the presence of tuberculosis in communities may fail to control the disease in the long run.[122]

Table 6.1 Critique and defense of the DOTS strategy

Critique	*In defense*
The strategy does not rely on protecting susceptible people from acquiring disease	It can be argued that this is a misinterpretation
Transmission occurs before diagnosis and treatment	An accurate measurement of levels of pre-treatment transmission and its relevance seldom exist, but programs can achieve rapid detection (short delays before diagnosis) suggesting little pre-treatment transmission
The initial symptoms are non-specific	Whether and how much of a problem this is varies by setting and may be difficult to pinpoint
The sensitivity of direct sputum microscopy is low	Sensitivity for infectiousness is high and low case detection is often due to poor access to services and poor proficiency rather than low sensitivity of sputum microscopy
There are patient and doctor delays	Delays can be addressed if the matter is carefully studied
Inadequate attention is given to smear-negative cases	The majority of patients in many programs are reported smear-negative, and considerable effort is devoted to them
Little attention is given to preventing disease in infected subjects	This criticism is legitimate but it is difficult to come up with a solution, and it is not clear how much the time frame of tuberculosis control can be shortened

Squire and Tang, speculating on why tuberculosis prevalence declined faster in World Bank–funded Chinese provinces than in unfunded provinces, even if they also adopted the DOTS strategy, have suggested that stronger health systems in the generally richer areas funded by the World Bank, rather than the DOTS strategy, may have been important in achieving effective tuberculosis control.[33]

Resistance to anti-tuberculosis drugs

While a number of experts claim that multidrug-resistant tuberculosis is likely to remain a localized problem,[123,124] others[125] describe it as a pandemic,* a phenomenon threatening to destabilize global tuberculosis control.[127]

Despite the fact that multidrug-resistant tuberculosis has been around since at least the 1970s, as demonstrated by results of treatment in patients registered in a U.S. referral hospital from 1973 to 1983,[128] the phenomenon was generally considered to be confined to previously treated patients whose treatment had been mismanaged in some way. It was the occurrence of multidrug-resistant strains† in patients who had never been treated with anti-tuberculosis drugs and the nosocomial spread of multidrug-resistant tuberculosis in HIV-positive patients in U.S. hospitals in the early 1990s that caused alarm and attracted attention to the problem.[127,130–132] Typically, the patients involved in these outbreaks developed tuberculosis within three to four months of exposure, and 80% to 90% went on to die within two months. Following the outbreaks in New York City, analysis of records showed that multidrug resistance had been on the increase in the city since the early or mid-1980s.[133]

These and subsequent accounts of multidrug-resistant tuberculosis brought to light the circumstances of socially disadvantaged groups in large urban areas in the United States and later in Europe as well: poverty, unemployment, homelessness, and substance use. In the early 1990s, there were reports of problems with multidrug-resistant tuberculosis cases in Africa.[134] Then there was the case of Peru, as discussed above, and what seemed to be an alarming problem in Eastern Europe, after the dismantling of the Soviet Union. It seems likely that the increase in drug resistance in Eastern Europe in the 1990s was a by-product and not the cause of an increase in tuberculosis;[135] that is, there was inadequate response to a deteriorating epidemiological situation brought about by socioeconomic collapse.

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*The definition of a pandemic is an epidemic occurring over a very wide area, crossing international borders, and usually affecting a great number of people.[126]

†In the short-course chemotherapy era, multidrug resistance is defined as resistance to at least isoniazid and rifampicin. Apparently, initial resistance to rifampicin became significant along with the widespread use of this drug in the mid-1980s.[129]

Already in 1993, Kochi et al. reported that in response to the threat of multidrug-resistant tuberculosis, the WHO proposed a three-pronged approach: rapid strengthening of national tuberculosis programs to prevent the problem at the source, the establishment of a global drug resistance surveillance system, and the development of new regimens to cure multidrug-resistant tuberculosis.[129] The results of the effort to expand drug resistance surveillance are evident in reports from numerous surveys published in 1997 and 2000.[136,137] A meeting in 1998 acknowledged multidrug-resistant (MDR) tuberculosis as a global problem that needed to be addressed by what became known as the DOTS-Plus strategy.[28] In 1999, Heifets and Cangelosi pointed out that while at that time rifampicin resistance was a surrogate marker for multidrug resistance, the nature of serious drug resistance and thus its definition was likely to evolve.[53] Today, outbreaks of what is referred to as extensively drug-resistant (XDR) tuberculosis, involving resistance to second-line drugs as well as to rifampicin and isoniazid, have been reported in settings with high HIV prevalence in South Africa.[138]

Two issues are relevant when considering drug resistance in tuberculosis: the impact of drug resistance on tuberculosis in the community and the implications of drug resistance on the control policy. Some prefer to regard tuberculosis, multidrug-resistant tuberculosis, and even the recently defined extensively drug-resistant tuberculosis as separate epidemics. While it is not disputed that drug-resistant tuberculosis can be transmitted from person to person, dividing the epidemic is not in line with the Union model, which stresses the importance of viewing the overall picture and the context in which drug resistance develops in the first place.

Drug resistance does not challenge the rationale behind the tuberculosis control model, but it does mean that new drugs need to be introduced to replace those lost to resistance. New drugs are primarily needed in areas where the prevention of drug resistance has failed, and occasionally for patients elsewhere. Other changes to control programs proposed in areas with high levels of multidrug resistance include the implementation of routine culture and drug-susceptibility testing and even individualized rather than standardized treatment,[74] but opinions differ on this. The need to strengthen tuberculosis programs so that new drugs are used rationally when they become available cannot be overemphasized. Some have argued that the management of multidrug-resistant tuberculosis may call for individual measures, which are in the domain of specialists rather than that of planners. This view can be interpreted as placing the management of multidrug-resistant and extensively drug-resistant tuberculosis outside of the tuberculosis program.

Testing has been done to ascertain whether drug-resistant strains of *M. tuberculosis* are equally as virulent as non-resistant strains. HIV infection, however,

Box 6.7 Response to multidrug-resistant tuberculosis

A population-based prospective study conducted from 1995 to 2000 in southern Mexico, where there was a moderate rate of multidrug resistance (20.7% of new cases were resistant to at least one drug, and 3.3% were multidrug-resistant), and prevalence of HIV infection was low (2% among the 94% of participants who agreed to be tested), demonstrated significant reductions in a number of parameters (reported incidence of tuberculosis, clustering of pulmonary tuberculosis cases, treatment failure, drug resistance in previously untreated cases, and multidrug resistance) when a program compatible with the DOTS strategy was introduced.[142] Second-line drugs were not available locally, but multidrug-resistant cases were referred to a national institute for treatment. A quarter of all cases in the study period were previously treated (52% of them were resistant to at least one drug). The proportion of retreatment cases decreased between the first and second year of the intervention. Neither significant transmission of drug-resistant bacilli nor amplification of resistance was documented in this study.

may change the pattern of circulations of strains[139] so that any selective disadvantage of less virulent strains might become irrelevant in the compromised host. On the other hand, the high death rate in HIV-infected tuberculosis patients may curtail the patients' ability to transmit the mycobacteria. (This may change with improved anti-retroviral therapy.)

The most important information to have when assessing the epidemiological impact of drug resistance and the need and methods to address it is the proportion and distribution of drug-resistant cases in the community, the community's social mixing patterns, and patient survival rates. Whether or not special measures are needed to achieve tuberculosis control in countries with significant levels of multidrug resistance has been debated. The question is the identity of DOTS-Plus: a humanitarian gesture, clinical medicine, or a control strategy? Dye and Espinal (2001) argue that if multidrug-resistant tuberculosis can persist in self-sustaining transmission cycles, containment will require a high cure rate for resistant cases as well as non-resistant cases.[123]

A decline in tuberculosis or multidrug-resistant tuberculosis in areas of high incidence may result in part from an exhaustion of the supply of persons highly susceptible to tuberculosis infection, that is, epidemic burnout. In an area of high HIV prevalence, transmission may be checked by a high mortality rate. Where there is a high prevalence of HIV infection, drug resistance can spread quickly, and outbreaks or epidemics of drug-resistant tuberculosis can easily emerge. Where this has occurred so far, patients have died quickly, which limited the outbreaks.[140] In such a situation, it is debatable whether second-line anti-tuberculosis drugs, or new drugs for that matter, are useful. The situation may evolve too quickly for any drugs to be of much use. As an example,

in New York, the mortality rate of the 297 patients involved in the 1990s outbreaks was approximately 70%, and the median interval from diagnosis to death was four to sixteen weeks.[141]

Where HIV is not prevalent, the course of the multidrug resistance problem is different: slower and more persistent, as in the case of Eastern Europe. In these situations, the rationality of the response is likely to be more important than its rapidity. It is important to introduce second-line anti-tuberculosis drugs or any new drugs cautiously so as not to create ever more resistant strains. An example of a response in a setting with a moderate rate of multidrug resistance is presented in Box 6.7.

The impact and implications of the HIV pandemic

In 1937, Wade Hampton Frost stated that the tubercle bacillus was losing ground and that the eventual eradication of tuberculosis required only that the balance against it be maintained.* He did, however, identify two possible but unlikely forces that might halt or reverse the downward trend of tuberculosis: a decrease in human resistance to the disease or a fundamental change in the bacillus. Twenty years later, Feldman optimistically noted that since Frost's observation, effective drug therapy had joined forces with the natural decline in tuberculosis, accelerating the downward trend.[143] Twenty years after that, both of the forces that Frost thought unlikely actually developed.

Impact of HIV on tuberculosis

Early on in the HIV pandemic, health professionals hoped that a major HIV epidemic could be prevented in settings with a high prevalence of tuberculosis infection. This was not to be. Perhaps this course of events was inevitable, although it is tempting to argue that important opportunities to minimize the current wave of tuberculosis in Africa were missed.

The first impact of the HIV pandemic on tuberculosis was to put this old scourge back on the international health agenda, which is why some health professionals at the time referred to HIV as "a blessing in disguise." In retrospect, had there been more effort to control tuberculosis in Africa before the HIV pandemic, could the pandemic's devastating consequences on the tuberculosis situation have been prevented? This question is perhaps best answered by contemplating in a given setting what could have been achieved before the HIV pandemic if short-course treatment had been successfully expanded country-wide. This hypothetical situation assumes that the tuberculosis problem would be reduced by 50% in fifteen years with a fully expanded control program.[144]

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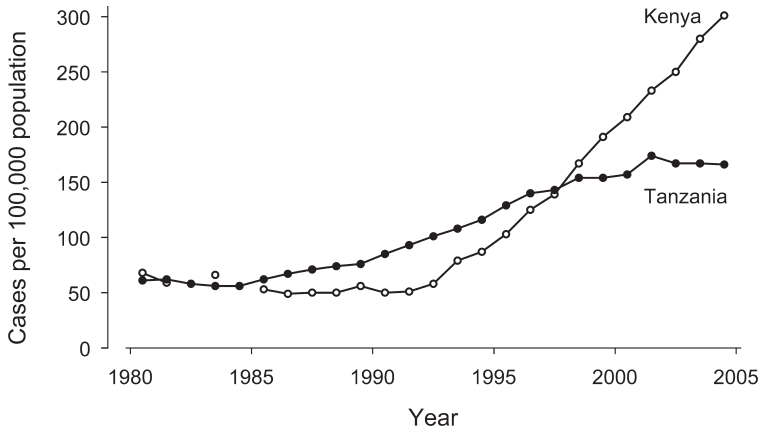
*Frost, quoted in Feldman,[143] p. 1236.

National expansion of a tuberculosis control program frequently takes at least five years. Fifteen years after expansion, cohorts born after the intervention, and thus less exposed, start to enter adulthood. It then takes 30 years to replace heavily infected with lightly infected adult cohorts in the 15– 45 years age group. Thus, instituting national tuberculosis control programs in 1955 would have made a significant difference. Starting a program in the 1970s, however, would have left people in the 15–45 years age group quite heavily infected during the spread of HIV, from 1985 to 1995.

In a 1990 study of the dual epidemic in Mbeya, Tanzania, the tuberculosis patients with the highest HIV prevalence (72.5%) were those 25–34 years old.[145] Without HIV infection, according to the study, the tuberculosis case rates would probably not have increased at all after 1985, and might have decreased.[145] Those aged 15–24 years at the time of the study were born between 1966 and 1975, before the implementation of short-course treatment. Thus, considering that HIV results in reactivation of remote infection, it is in fact not until 2000 to 2010, when cohorts born after the introduction of effective tuberculosis control in Tanzania reach the age of highest risk for HIV infection, that the full effect of the national program on the dual epidemic can be expected.

Another approach when speculating on the impact of the HIV pandemic on tuberculosis control would be to examine what actually occurred with regard to the tuberculosis situation in comparable countries with different control programs. From looking at Figure 6.1, it is possible to speculate about the

Figure 6.1 Notification rates of tuberculosis in Kenya and Tanzania, 1980–2004

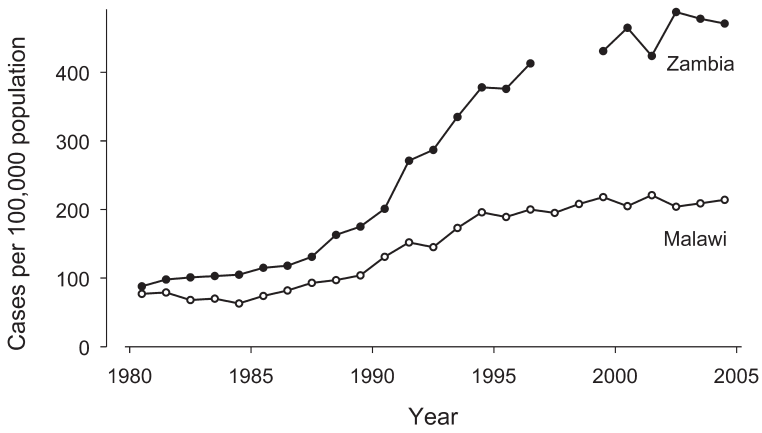


Source: World Health Organization.[146]

reason why the (reported) tuberculosis rate increased more in Kenya than in Tanzania (by a factor of 5.0, from approximately 60 to 300 per 100,000, as compared to a factor of 2.8, from approximately 60 to 170 per 100,000).[146] Short-course treatment was introduced a decade later in Kenya (1993–1994)[147] than in Tanzania. The risk of infection was increased in some areas of Kenya, according to a report on a survey conducted from 1994 to 1996.[147] This was not the case in Tanzania, where the annual rate of infection did not increase over a 20-year period (1983–2003) in spite of a doubling of the notification rate for smear-positive tuberculosis.[148,149] The prevalence of HIV may, however, have been significantly higher in Kenya than in Tanzania from 1995 to 2000.[150] Similarly, Figure 6.2 compares Zambia (an increase in tuberculosis by a factor of 5.4, from approximately 90 to 490 per 100,000)[146] with Malawi (an increase by a factor of 2.75, from approximately 80 to 220 per 100,000).[146] Again, however, HIV prevalence may have been significantly higher in Zambia than in Malawi.[150]

These are only speculations, and such comparisons are fraught with difficulties. Where there is a better health system, communicable disease control is likely to be more effective, including tuberculosis control. Success in tuberculosis control depends to a large extent on the health system and the general health services. If this is also true for HIV prevention (which is not obvious), a better health system may result in a more limited HIV epidemic, which in turn would result in a smaller impact on the tuberculosis situation. A better tuberculosis program is likely to be more effective in dealing with the problem, which

Figure 6.2 Notification rates of tuberculosis in Malawi and Zambia, 1980–2004



Source: World Health Organization.[146]

also may moderate the effect of the HIV pandemic on tuberculosis. Thus, when the HIV pandemic hits two countries with similar baseline tuberculosis rates, if there is a smaller increase in tuberculosis in one country, that country may have a better health care system—one with interventions to control tuberculosis, differences in epidemiology, and interventions to control HIV, or (most likely) with a combination of these factors.

Finally, there is concern that Africa will not achieve the target of an 85% cure (or success) rate because of HIV mortality, even if the target could be reached globally. Looking at this target from another angle, aiming for fewer than 15% of patients to have an unfavorable outcome (and excluding deaths), only four of 25 countries with high HIV prevalence reached that target: Malawi, Mozambique, Tanzania, and Kenya.[151] The figures are only comparable, however, if all those lost from sight (defaulters) are verified, as there may be deaths among them.

Impact of HIV on tuberculosis control policy

It has been heavily debated whether the current tuberculosis control policy is appropriate for use in areas with high HIV prevalence. Many scientists argue that DOTS is not enough.[152,153] When considering the prevention and control of a dual epidemic, other than the prevention of HIV infection, two methods come to mind: prevention of tuberculosis in dually infected persons (tuberculosis preventive chemotherapy or anti-retroviral therapy to prevent immunosuppression), and prevention of transmission from HIV-positive tuberculosis patients (case finding and anti-tuberculosis treatment).

As predicted by Styblo in 1990, a tuberculosis control policy aimed at curing infectious patients does not prevent an increase in the number of tuberculosis cases in areas hard hit by HIV if the prevalence of tuberculosis infection is high.[154] Surplus cases arise partly from the pool of young adults infected with *M. tuberculosis* when HIV strikes. At best, a control program can minimize the number of persons infected further on as a result of the excess tuberculosis cases in HIV-infected persons; that is, reduce a second and further waves of tuberculosis. Stated another way, tuberculosis control could minimize the increase in transmission.[154] Such a policy can also prevent deaths from tuberculosis in HIV-infected tuberculosis patients, but unless the HIV infection is treated with specific anti-retroviral treatment, these lives are only temporarily saved, as the patients will die of other causes as a result of their underlying HIV infection.

The suggested modification to the tuberculosis control policy in the new scenario is twofold: first, implement preventive chemotherapy programs for HIV-positive persons infected with *M. tuberculosis* in order to prevent progression from tuberculosis infection to disease, and thus prevent or minimize an increase in tuberculosis incidence. One of the challenges of this strategy involves recruiting participants into the preventive chemotherapy program. Sec-

ond, expand anti-retroviral treatment programs for HIV-positive persons. These two strategies can be seen as competing for the attention of the global health community, as it may not be realistic, or even necessary, to implement both.

Preventive chemotherapy programs

A 1993 joint statement issued by The Union and the WHO declared that the primary objective of a tuberculosis program was the interruption of transmission by curative treatment of infectious cases and that there was insufficient information available to recommend that tuberculosis preventive therapy for co-infected individuals be implemented in program settings worldwide.[155] Lately, it has been increasingly argued that unless preventive chemotherapy for HIV-infected persons and the contacts of smear-positive tuberculosis patients is incorporated into the policy, tuberculosis will not be controlled.[156,157] When the incidence of tuberculosis decreases in a population, the preventive chemotherapy component becomes relatively more important. While it is true that if preventive chemotherapy were to be successfully implemented, it would enhance the control of tuberculosis in the long run, its added potential for reducing transmission in high-prevalence countries is of a smaller magnitude and comes into effect later than that of case finding and treatment.

Using mathematical modeling, Heymann (1993) predicted a great effect from using preventive chemotherapy in Africa,[158] and Brewer et al. (1996) concluded that in the United States, a combination of targeted preventive treatment in addition to case finding and the treatment of patients was needed in order to reach the national goal of elimination.[159] In 2004, they argued that, based on mathematical models and computer simulations, the treating of both latent and active tuberculosis was likely to be more effective at reducing tuberculosis in HIV-infected populations than strategies focusing on treating only active tuberculosis.[119] Predictions based on this ideal are, however, variable. In 2004, Guwatudde et al. concluded that the impact of preventive chemotherapy on tuberculosis case rates in populations in sub-Saharan Africa was likely to be small,[160] the maximum effect being a 15% to 20% reduction in the prevalence of tuberculosis after 16 years of implementation if 75% to 100% coverage was achieved. Their sensitivity analysis suggested that preventive chemotherapy had a greater effect when DOTS targets are met and a smaller effect when transmission is high; in other words, a greater effect when tuberculosis has been substantially controlled. None of these predictions addresses the feasibility of implementing preventive chemotherapy programs.

Anti-retroviral treatment programs

Anti-retroviral treatment programs recruiting HIV-positive persons into tuberculosis programs before those persons succumb to the bacillus would aid in tuberculosis control. If HIV-positive persons are recruited into tuberculosis

programs at the point of tuberculosis diagnosis, an anti-retroviral treatment program's impact on transmission is likely to be far less or even negligible, but possibly fewer patients would die while on tuberculosis treatment. The latter still needs to be convincingly proven, however.

Reducing mortality is always a public health intervention. If provided early on in the course of HIV infection, perhaps anti-retroviral treatment makes more sense than preventive tuberculosis treatment, as it more directly addresses the suffering of HIV-positive persons. Studies suggest that there is potential in exploring ways of reducing the incidence of HIV-associated tuberculosis.[161] The potential of recruitment into anti-retroviral treatment programs among smear-negative tuberculosis suspects who do not have tuberculosis has been noted.[162]

Voluntary counseling and HIV testing

Voluntary counseling programs and HIV testing that identifies patients with tuberculosis do not reflect innovations in disease control; rather, they borrow an element that has always been part of the tuberculosis policy model: the notion that all health services personnel should be on the alert for tuberculosis symptoms even when the patients have contacted the services for other reasons. Today, this is not least directed at those who come into contact with HIV-infected persons in their work. The step beyond case finding and treatment of infectious patients, however, is to identify persons who are infected with *M. tuberculosis* but are not yet sick or infectious. They have no symptoms and thus need to be actively sought out. When the tuberculosis policy model was formulated, this objective was discarded as unachievable in the context of low-income countries. Even if today a new risk group can be identified and targeted for this activity—that is, HIV-infected persons—preventive chemotherapy programs still have to be proven feasible and efficient on a large scale in settings with a high prevalence of tuberculosis and HIV.

Surveillance

Some researchers have suggested that tuberculosis and HIV-related tuberculosis should be subject to separate surveillance (stratified surveillance), given that tuberculosis incidence and trends may differ in the HIV-positive and HIV-negative subpopulations of a community.[152] A similar claim has been made for tracking multidrug-resistant tuberculosis and even for relapses and reinfection. However, it is difficult to judge the thoroughness of any surveillance system, and it is especially difficult in low-income nations and in countries with high HIV prevalence.

One way to approach the question of whether tuberculosis can be controlled is to refer to global targets. According to Dye (2006),[135] based on the latest assessment of trends, the Millennium Development Goal—to have halted

by 2015 and begun to reverse incidence—should not be hard to achieve. Indeed, case-notification rates have been steady or falling for at least two decades (since before DOTS) in South-East Asia and the Western Pacific, much of Europe, Latin America, and the Eastern Mediterranean.[135] In sub-Saharan Africa (since the mid-1980s)* and in Eastern Europe (since the mid-1990s),† the rates have been increasing, but in both regions the rate of increase has slowed since the mid-1990s. The incidence in Eastern Europe might now be in decline, and HIV infection rates seem to be stabilizing.[98,135] On the other hand, the targets set by the Stop TB Partnership to halve the prevalence and death rates globally between 1990 and 2015 are much more of a challenge, according to Dye, especially in Africa and Eastern Europe.[135]

The wider public health agenda

As the 1980 Study Group pointed out, socioeconomic conditions are related to both the incidence of tuberculosis and the performance of control programs.[111] Thus, economic development based on basic egalitarian principles is paramount for the ultimate control of tuberculosis.

In recent years, tuberculosis has revealed itself as a moving target. The goal of eradication has slipped away, and globalization may have made other goals, such as elimination, to some extent less appealing. Some researchers argue that in modern times, infectious diseases have increased partly because of increased poverty and as a product of widening social inequalities, that infectious diseases should be treated as sociomedical rather than simple medical phenomena, and that a narrow medical focus is insufficient to tackle communicable diseases in the long run.[163,164] In the rich countries of the world, the resurgence of tuberculosis coincided with increased urban poverty and marginalization as well as with HIV/AIDS.[43] Some contend that globalization may have contributed to the spread of multidrug-resistant tuberculosis, via deterioration in public health programs and decreased social support for vulnerable groups, and that the policies of the aid community (for example, structural adjustment programs) may have made matters worse in poor countries.[43]

Finally, some assert that in an environment emphasizing health sector reform, cost-effectiveness, competition, and market approaches, events have created inequity in primary health care regarding equity and access to comprehensive health services, with serious consequences.[165] Whereas access to health services improved from 1980 to 1990, it may have worsened since then.[49] Given the dependency of the tuberculosis control strategy on health infrastructure, this is a discouraging trend.

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* Primarily as a result of the HIV pandemic.

† Due to socioeconomic and structural factors.

Globalization and global approaches

The term *globalization* refers to "the increasing interconnectedness of countries through cross-border flows of goods, services, money, people, information and ideas; the increasing openness of countries to such flows; and the development of international rules and institutions dealing with cross-border flows."[166] Globalization is not a new phenomenon; economic migration has been a motivating force throughout human history.[167] However, the department of economics and statistics of the Organization for Economic Cooperation and Development (OECD) reported in 1991* that the world economy was further from full integration than it had been in 1914, when there was more free trade, capital movement, and migration. Contemporary globalization may be of a different character and more complex than in earlier times, widening the gap between the rich and poor and creating inequities within as well as between countries.[43]

Recently, international and national policy processes have been converging. According to Kumaranayake and Walker, what has been referred to as a global approach was spearheaded by the World Bank's 1993 World Development Report and its background studies,[168] among them the studies on tuberculosis control in Africa. They argue that due to the influence of the World Bank, emphasis has been placed on economic approaches to priority setting, and the direction in policy making has been centralized by international agencies with a focus on mortality and morbidity rather than on broader public health gains. These generalizations are increasingly being applied in disparate settings, and little attention is being paid to local details, even if many "cost-effective" interventions are not as effective as promised because of the limitations imposed by failures of systems or the behavior of people.[168]

The tendency to centralize policy making is indeed widespread. In 1995, De Cock and Wilkinson maintained that because the WHO declared tuberculosis a global emergency, having a uniform international response using the same strategies and drugs is logical.[169] Apart from the fact that the logic in this statement is not obvious, such a view seems to disregard the importance of context. In 2002, Porter et al. presented tuberculosis as an example of how health policy is shaped by globalization and how globalization in turn is reinforced by such health policies.[43] According to them, the links between globalization and tuberculosis are threefold. The recent resurgence of tuberculosis took place within the context of contemporary forms of globalization. In response, the DOTS strategy was introduced and promoted worldwide as a gold standard. Finally, the promotion of the DOTS strategy raises questions as to how to define "global": to what extent can the strategy be considered truly global?

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*Quoted in Wheen, p. 256.[167]

It is not being disputed that the improvement of socioeconomic conditions is important for tuberculosis control. This has been argued for decades. Even so, no country—however poor—can accept the improvement of its socioeconomic conditions as the basis of its tuberculosis policy.[96] Tuberculosis control remains the immediate objective of tuberculosis programs. While it is important to move ahead with the wider social and public health agenda, it is unethical to wait for the results of their implementation when there is a way to reduce current suffering by applying the biomedical approach. Patients cannot be ignored when effective treatment is available.

Summary and conclusions

When the WHO stepped up its commitment to tuberculosis control in response to a worsening epidemiological situation, they turned to Styblo for advice. This collaboration became the basis of the DOTS strategy, which was launched in the early 1990s. While the WHO was successful in catalyzing tuberculosis program reforms in many countries, its adaptation of some of the technical policies and its methods of promoting the strategy have been criticized. Policy adaptation and development were compromised for the sake of marketing and advocacy. The organization's top-down approach was ill received, and appeared at times to divide and split tuberculosis programs rather than promoting a comprehensive and coordinated public health approach. Finally, the WHO is perceived as considerably success- and target-driven. It has even been suggested that, as a result of this, DOTS itself may have led to questionable practices that challenge the reported success of the strategy.

Since the conception of the policy model, the HIV pandemic has been gaining force in Africa. As a result, tuberculosis control efforts on the continent were severely undermined. The relevance of the DOTS strategy in the African setting is increasingly being questioned. Where HIV infection has contributed to outbreaks and epidemics of drug-resistant tuberculosis, at the same time it undoubtedly facilitated the control of outbreaks of multidrug-resistant tuberculosis in many settings. Whether this will change with the increasing use of anti-retroviral treatment remains to be seen. Where multidrug resistance has emerged and reached critical proportions in the absence of HIV, it has proven more difficult to control. Technological development has not kept up with the need for new tools, a need primarily brought about by drug resistance. Experts have not kept up with policy development. Whereas many researchers agree that a revised control policy is required, primarily due to HIV, a tangible alternative has not materialized. Meanwhile, the effort toward case finding and treatment continues throughout low-income countries.

When contemplating ways to improve tuberculosis control, it is common to focus exclusively on technology: how existing technology in diagnosis and

treatment can be improved or new technology invented and put to use. One can also focus on improving operational aspects relating to diagnosis and treatment or address the program and health services structures and the information, surveillance, and quality-assurance systems, or materials management. These issues are addressed in Part II. All of this together determines the results of a tuberculosis program, and this is in essence what the policy model was all about. Whether and how operational strategies can be improved depends on the setting. Only after careful analysis can specific recommendations be made. As a rule, any such recommendations should be context-specific rather than universal.

There is a tendency to be all-inclusive when "global" recommendations and strategies are devised. Consequently, the complexity increases. Whereas it is relatively easy to standardize diagnosis and surveillance, this is not the case with patient care and treatment where, as recent experiences show, universal recommendations can be controversial. It may be unwise to put forward global recommendations other than for a general approach when the terrain is as variable as it is in different countries and different parts of the world. Overstandardization may create more problems than it solves.

Some argue that, in an increasingly interconnected world, infections know no borders and thus social quarantine is fiction.[170] Nevertheless examples suggesting the contrary abound. Even if tuberculosis is transported across national borders within the human body, the fact of the matter is that, in modern times, tuberculosis largely respects the border between the rich and the poor. If it were not for the considerable degree of protection provided by social quarantine, many communicable diseases would surely have been more convincingly addressed at the global level in recent history.

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PART II

Supportive Systems

7
System design

Consider the characteristics of the system that is in place, its strengths and weaknesses. If it is not possible to fix all the weaknesses, at least acknowledge them.

Health systems vary greatly. The health system in any given region or country has evolved alongside, and under the influence of, other aspects of society. Sometimes it seems as if the health care system developed to serve the interests of health sector professionals rather than the patient population it intends to serve. Systemic features, including organizational, institutional, social, and political constraints, frequently limit the implementation of technological solutions. Health professionals with a clear understanding of health system design could better perform important structural activities such as supervision, coordination, and referral.

It is not always clear how outcomes are linked to structures in health care. It is tempting to think that, with sufficient focus and a willingness to adapt any given strategy or program to the existing systems, any health care system could mount a successful intervention. Given that tuberculosis control involves detecting the disease and curing infectious patients, health services clearly are the vehicle for the control strategy. Because tuberculosis is uniformly, if unequally, distributed in populations in low-income countries, it is something all health institutions can expect to deal with regardless of the disease rate.[1] Integrating a response across the entire health care system is the goal of good system design.

In the past, vertically organized tuberculosis programs in low-income countries failed primarily due to a lack of infrastructure and access for the population. The vertical approach taken by specialists failed to consider the wider processes needed to make the intervention work. The primary health care approach failed due to an insufficient understanding of the issues involved and lack of real commitment to tuberculosis control. A lack of dialogue between the two approaches further contributed to the failure of both. A successful tuberculosis program requires an analysis of how the structure of the local health system and services—as well as other local dynamics—can best provide safe, high-quality tuberculosis services.

System design is a complex issue. Topics this chapter will examine include infrastructure, human resources, and organizational issues. It will also include principles and lessons learned from the development of the Union model and examples from other settings. The focus is on the organization of tuberculosis control within general health services, which involves a holistic examination of the health system with particular emphasis on access, decentralization, integration, and coordination. Clinical guidelines and case management programs, which can also be classified as structural elements, are covered in Part I. Finally, system design involves information and materials management, the training and qualifications of health personnel, and assessment and monitoring systems. All these are dealt with in subsequent chapters.

Background

Structure in health care is a means to an end.[2] Structural factors are important determinants of people's behavior[3] and are likely to affect provider satisfaction, although this factor is rarely the focus of evaluations.[4] The structure and organization of health services influence the scope and volume of the services delivered.[5,6] To the extent that structural characteristics influence the quality of care, efforts to improve health care by changing the structure of the health services might pay off in the long run.[7] However, there is little evidence regarding what specific structures best support high-quality health care.[2] As a result, recommendations on structure frequently rest on expert opinion rather than on empirical evidence.

Discussions of structural issues are often complicated by the fact that important terminology is often insufficiently explained. In particular, terms such as "decentralization" and "integration" are often used without specifying what is being decentralized or integrated, and how.[8,9] This confusion is further compounded by disorganized and chaotic implementation in the field. The many pilot or demonstration projects that have been launched are sometimes badly prepared and insufficiently evaluated. A long-term commitment to structural innovation that is guided by local conditions and implemented incrementally is rare.

With regard to tuberculosis control, "structure" refers to a functional structure and organization within a wider context. This structure depends on the physical and organizational aspects of the health system and services as a whole. It is appropriate to consider health services structure in general before discussing its impact on tuberculosis programs.

Health systems and health services

Roemer defines a "health system" as the combination of resources, organization, financing, and management that culminates in the delivery of health services

to the population.[10] He examined health systems using a conceptual matrix with two dimensions: the economic level of the country and the social policy of its health system. In his comparison of health care systems in Tanzania and Nicaragua (two of the countries where the Union model was developed) during the mid-1980s, Roemer placed both systems in the same category with regard to policy.* Both systems had universal and comprehensive health system policies. Economically, he placed Tanzania among the very poor nations, but identified Nicaragua as having a developing and transitional economy.†

Health systems change in response to economic, political, and demographic forces, as well as changes in technology. The latter half of the twentieth century saw major political changes in both Nicaragua and Tanzania. The availability and delivery of health services were high on the agenda of the emerging governments in both nations. This is relevant when discussing the development of the Union model. The model's developers considered political commitment a prerequisite for implementation. As the political scene evolved, many people speculated about the long-term effects of changes to the health systems that resulted from political shifts. Fortunately, the public tends to resist efforts to roll-back policies that bring about positive changes. Politicians, fearing disapproval, are hesitant to reverse successful innovations.[10,12] The banal force of inertia also helps sustain a firmly rooted program, even when enthusiasm and motivation wane. Firmly established routines resist change.

Toward the end of the twentieth century, a wave of reforms that apparently originated with the World Bank and the International Monetary Fund washed over health systems in middle- and low-income countries. Many criticized this "one-size-fits-all" approach to reform.[13] These critics emphasized that a coherent approach to health system reform requires a thorough understanding of the historical, political, and socioeconomic contexts of health services development and an analysis of the workings of the existing system.[8] Chaulet claims that the rapid implementation of health sector reforms had a negative impact on tuberculosis control in several African countries.[8] These reforms organizationally and financially damaged existing tuberculosis programs by shrinking or eliminating

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*Comparisons across health systems are fraught with difficulties. Health systems are not static, nor do they necessarily function as they are supposed to. It is difficult to measure output and outcome in health care. Caution is called for when generalizing results.[11]

†For comparison: of the very poor economies at the time, Ghana, Kenya, and Bangladesh were classified by Roemer as having health systems policies that were entrepreneurial and permissive; India's were welfare-oriented, and China's and Vietnam's were socialist and centrally planned. Of the developing and transitional economies, the Philippines and South Africa were classified as having entrepreneurial and permissive health systems policies, and Brazil was classified as having a welfare-oriented one. Examples of affluent industrialized economies with universal and comprehensive health system policies are Great Britain and Norway.[10]

the programs' central units; tying up the supply of anti-tuberculosis drugs in defective, inefficient, and irresponsible pharmaceutical supply systems; and provoking bureaucratic conflicts with those in charge of general health information systems. Furthermore, some reforms arbitrarily reduced the number of hospital beds available for tuberculosis patients without redistributing human and financial resources to the ambulatory services that were expected to cope with a newly increased patient load. These effects were not limited to African systems. In Nepal, the tuberculosis program effectively stopped functioning in 1997 as a result of reforms. The primary cause: insufficient communication between those responsible for the cross-governmental decentralization and those responsible for the tuberculosis program.[14]

Infrastructure, power structure, and qualifications of staff

The building blocks of a health system

Even if health care systems vary greatly, some universal elements do exist. A health system invariably has a central ministry of health or its equivalent, although its scope of work varies among countries.[10] Historically, ministries of health usually originated in an effort to combat epidemics. Controlling communicable diseases and maintaining vital statistics are the oldest functions of ministries of health.[10] These activities are often carried out by institutions that are detached from, but administratively under, the ministry of health.

Traditionally, health systems in developing countries have three levels beyond the national level: provinces (states, regions), districts (counties, areas), and communes (municipalities, communities). The population represented by each level may vary considerably between countries. Health systems often include separate or parallel military, police, and penitentiary systems. Public health programs require serious political commitment to cross all these divides.

Where public sector services are strong and well distributed, the private market is likely to be relatively small.[10] In low-income countries that feature a prominent private sector, private practitioners operate mainly in urban areas. These practitioners may be engaged entirely in private practice or overlap in the private and public sectors. As a rule, regulation and licensing of the private sector is poorly developed in low-income countries. This is due in part to under-staffed monitoring and supervision systems.[15,16]

Whereas the public sector should lead the health system in a direction likely to maximize its contribution to the health of the population, the private sector, due primarily to its fragmented nature and profit motive, is at best only a complement to public sector services.[15] Influencing private providers to harness the underutilized potential of the private sector is a challenge. As discussed elsewhere, the effects of one-off training opportunities do not last long, and providing private practitioners with access to diagnostic facilities and medicines

for priority conditions can be difficult in an under-resourced health sector.[16] However, "resourcing" the private sector, as this strategy is sometimes called, in return for accountability has the advantage of facilitating the full description and quantification of the total expressed need for medical care. This aids in the realistic estimation of a nation's total resource requirements.[17] Partnerships that encourage cooperation between the various private and public providers and aim to improve the coordination, continuity, and quality of care are considered by many to be the best hope for further positive developments.[18]

Finally, most health care systems include nongovernmental organizations and voluntary contributors. The primary advantage of nongovernmental organizations is flexibility. These groups tend to be more open to innovation and change than governmental systems. One of the first diseases against which extensive voluntary efforts were mobilized was tuberculosis.[10] Historically, voluntary organizations typically acted ahead of governments. Their role changed as governments assumed responsibility for some of the tasks they pioneered.[10] In recent times, as national authorities attempt to reduce costs, this trend seems to have been reversing. Governments, health programs, and professionals are attempting to push responsibility for health care to the personal level:[19] the patients, their families, and volunteers are expected to perform medical and health-related chores for the community. One of the objectives of this strategy is to reduce the burden on hospitals and health facilities.[20] Another development that merits reflection is the rise of opportunism in international health. The rampant lobbying for various international health causes can come, at times, to resemble a marketplace. When funds become available, nongovernmental groups move in from all directions. Sometimes these groups have little experience with foreign health care systems. They may not respect the context of their work or concern themselves with the long-term effects and sustainability of interventions.

Community participation

"Community participation" is a term widely used but vaguely defined. In an article published in 1998, Tenner and Vlassoff discussed community participation in the context of malaria control. They pointed out that although the community itself is often referred to as the desired recipient of health interventions, it may be the least important intervention point in terms of the potential for successful disease control strategies.[21] In their view, the important intervention points are persons, households, and services. The authors suggested that programs rethink the concept of community participation. In 2003, Raeburn and Macfarlane claimed that evaluations of community-driven interventions are difficult to perform and usually so subjective as to prevent one knowing whether such programs can or should ever be brought to scale.[22]

Whereas ideally community participation emerges locally and spontaneously, in the course of time it tends either to become institutionalized or to

die out. In Nicaragua, there was considerable motivation for voluntary and community-based work in the wake of the Sandinista revolution in 1979. However, community participation eventually came up against serious political, financial, and administrative constraints, and the status of community health workers remained marginal except during short-term campaigns run by the Ministry of Health.[23] Nicaraguans seemed to expect the government to provide more and better services than local volunteers. In 1992, Garfield and Williams argued that the need for and motivational support of community participation in health care were greatest immediately after the revolution in Nicaragua.[23] Over time, the need for volunteer labor diminished or volunteers' roles changed as the health services were expanded, and the government gradually resumed responsibility for health care. This makes sense, and some argue that increasing need for voluntarism is a sign of insufficient or declining government commitment.

The arguments for community-based approaches to health care are often negatively formulated. Proponents point to inadequate health infrastructure, inaccessible outpatient services, overburdened health facilities, and other insufficient resources. They hope that "community participation" will result in communities taking more financial and social responsibility for providing health care.[24] Others argue that community health worker schemes will not solve the problems of inadequate health infrastructure, access problems, and lack of resources. If anything, community-based programs may provide welcome excuses for governments not to assume full responsibility for the provision of health services. They may even deter much-needed investments in the proper decentralization of infrastructure and health care. Some supporters of community-based programs argue that the incremental costs of involving the community are often small, as they mainly concern training and supervision.[25] In reality, the costs and the logistics involved in training and supervision of community health workers and volunteers are often underestimated, and these activities are simply neglected.

In the long run, community participation tends to become institutionalized. Once institutionalized, it may lose originality and spontaneity and become an empty bureaucracy without any meaningful contribution. There is also a potential for exploitation, such as when community organizations become political recruitment venues or conduits for propaganda,[23] when the strategies used by the organizations infringe on privacy and civil liberties, or when financial motives outweigh service concerns.

Health facilities and personnel

General ambulatory care facilities, which provide both preventive and ambulatory care and basic laboratory services, are usually referred to as "health centers." Smaller "subcenters" may serve as satellites. Peripheral even to these there may be "health posts," often staffed with a single health worker. Then there is

the "dispensary," a poorly defined but widely used term. Finally, there are specialized clinics that cater to subgroups of patients or populations. Although the size of the population served by health facilities obviously decreases at each level of the system as one moves from the center to the periphery, the absolute numbers served vary substantially in every setting and cannot be taken for granted.

The scope of so-called "general hospitals" varies among countries. For example, a general hospital may exclude maternity cases, cases of infectious diseases, and may not serve prisoners.[10] Historically, tuberculosis was managed in special hospitals, but this has changed with advances in technology. Few countries still maintain a system of special tuberculosis hospitals and clinics.

It is one thing to have a health facility in place; it is another thing to staff, equip, and supply it; and yet another to provide the services as expected. Limited opening hours and absenteeism among the staff are problems that plague the health services of many low-income countries and affect the utilization of health services. This is partly due to the fact that the staff may need to earn a living elsewhere. For example, a study in Uganda in the 1990s revealed that most health units included in the study were open for only two to three hours in the morning.[26] Investigators described two main patterns. In the first pattern, high informal charges at the facilities and high incomes earned from them went together with high outpatient attendances and high numbers of hours worked. In the second pattern, high rates of drug leakage and low drug availability went together with limited working hours and low utilization of the services. Indeed, informal charges and drug leakage are well-known strategies that health workers use to "correct" their salaries. While some would call this corruption, the matter is in fact complex.

"Community health workers," another ill-defined term, may operate independently or be attached to health facilities. Whether multi- or single purpose, community health workers and other auxiliary medical personnel are a prominent part of the human resources of health services in low-income countries. Under the influence of the WHO, the scope of health services provided by community health workers, even those with very limited training, has expanded, and although they theoretically work under supervision, the extent of this guidance is frequently quite meager.[10] Some of the controversies concerning community health workers are presented in Box 7.1.

Health services development

Generally speaking, institutions and power structures change gradually. Health services organization and policies, and the relative proportions of health service personnel and facilities of different types that have evolved over time, can distort the judgment of the "need" for health care[5,6] and are likely to influence policies along lines different from actual needs or trends at any given place and time.[10,15] Professional organizations, whose members are often strong

Box 7.1 Community health workers

The definition of a "community health worker" is notably inconsistent. One definition includes only nurse aides and orderlies as community health workers.[27] Conversely, Maher et al. define a community health worker as a community member who is involved in health activities in the community to which she or he belongs, is not a formal government employee, and may or may not receive a financial or other material incentive.[24] Policies of remuneration and incentives for community health workers, if they are not government employees, are controversial. They raise questions concerning sustainability and competition with salaried health workers, and seem to go against the spirit of voluntarism that is the ideal motivation for community participation in the first place.[23]

Some see community health workers as the cornerstone of primary health care in rural areas in low-income countries.[28] The low-cost, readily available, and appropriate care that community health workers provide is considered essential to ensuring access to health care.[28] On the other hand, some regard community health workers as inappropriate for providing curative health services in cities.[29] In urban areas, there is frequently a surplus of more competent care providers, and the insufficient difference between community health workers and laypeople, particularly women, makes using their services not worthwhile.[29] Sauerborn et al. list three approaches to the evaluation of community health worker strategies: measuring the impact on morbidity and mortality, which is difficult; assessing the degree to which community health workers attain their goals; and studying the utilization of their services by the population, since unused services cannot be useful.[28] They also point out that comparative research in this field is difficult because of the different status, training, and tasks of community health workers in different settings.

A household survey in Burkina Faso's Solenzo District in the 1980s found that community health workers (in this case, laypersons chosen by villagers to undergo training as community health workers) added little to self-referral.[28] According to the survey, there seemed to be little demand for the services of community health workers even in a rural context. Community health workers were only consulted in nine percent of mild illnesses. In cases of serious diseases where community health workers were supposed to identify the illness and refer the patient to a health facility, the villagers bypassed them. The investigators concluded that it is important to consult with the community before embarking on community health worker strategies; to include women; to improve training and supervision; and to consider issues of regular pay, professional recognition, and a career perspective. Many of these priorities seem to be aimed at turning community health workers into conventional health professionals and rendering the lay health worker irrelevant.

Other researchers have advocated the increased involvement of women in community health care organizations on the basis that women seem to be more diligent and less likely to be motivated by ambition or the hope of material reward.[30] In the era of increasing awareness of gender equality concerns, it is tempting to debate whether exploiting theses allegedly feminine characteristics is justified (particularly in low-income countries where women are already overburdened with work to

Box 7.1 *Continued*

support their families). Furthermore, there is the question of what is voluntary. All kinds of pressures can be exerted on individuals—and on women in particular—to "volunteer."

Finally, a rivalry can develop between professional health workers (physicians, nurses, auxiliaries) and lay health workers.[23] Whereas community health worker strategies seem to work best if the workers are well trained, have broad responsibilities, and dispatch medicines (that is to say, when they resemble professional health workers), this is also when their involvement is most likely to be resisted by professionals who can then refer to arguments related to quality of care.

stakeholders, influence national health system policies.[10] This aside, deliberate planning of health services is a challenge. One of the dilemmas concerning primary health care has been whether to create facilities that people do not want and may not use spontaneously and then educate or direct people to use them, or whether to educate people in the absence of facilities until a consumer demand is created.[11] In the tuberculosis programs collaborating with The Union, quality and safety came first with the aim of establishing a good service that would then be able to respond competently to rising demand. It was assumed that the service would advertise itself. This line of thinking was in accord with the recommendations of the 1974 Expert Committee on Tuberculosis.[31] Some observers may see this as a "top-down" approach since the design of the tuberculosis program and services in low-income countries was influenced by expert opinion.

As background to further discussion of the collaborative programs and the model, Box 7.2 presents a comparison of the health systems in Nicaragua and Tanzania in 1986, during the early years of their collaboration with The Union.

The volume-outcome relationship in health care

Most health professionals agree that a certain volume of work is needed in order for health workers to become proficient at a particular task and to maintain proficiency over time. This phenomenon, which is referred to as the "volume-outcome relationship," has been studied in some detail, although less so for ambulatory services and medical interventions than for hospital-based services and surgical interventions. A large study of acute care hospitals in the United States in 1984 found strong and consistent evidence that high volume was associated with better outcome for surgical patients, regardless of the complexity of the procedure, and for the specific medical conditions studied.[32,33] It could be that high-volume units perform well because of the experience gained ("practice makes perfect"), or it could be that well-performing units attract patients

Box 7.2 Comparison of the health systems in Nicaragua and Tanzania in 1986*

In 1986, Nicaragua was an example of a low-income country that illustrated the importance of political commitment to the development of a national health system characterized by a reasonable balance between centralized policy making and decentralized implementation. After the 1979 revolution toppled the dictator Anastasio Somoza Debayle, Nicaragua developed a health system that entitled everyone to basic health services. Many difficulties obstructed the implementation of this policy objective, including a civil war in which health facilities and personnel were among the targets of anti-government guerilla forces. Prior to the revolution, there were 172 health centers and health posts in the country, but only 20% of these were in rural areas where more than 40% of the population lived. Utilization of these facilities was low. In 1979, a health service unification law brought nearly all government health activities under the jurisdiction of the Ministry of Health. In 1986, the population of Nicaragua was roughly 3.3 million (a decade later it was around 5 million). The administration had, at this time, been decentralized to six health regions and three special zones. The next level of administration consisted of 90 health areas, each with a population of 20,000 to 50,000. In each area there was a health center with at least one physician and several auxiliary personnel. In addition there were 379 health posts, each intended to serve 5,000 to 10,000 people. Attendance at health facilities increased. In rural areas, there were outreach workers (*brigadistas*) in villages. These workers were usually volunteers and were considered agents of the community rather than the Ministry of Health, even if they operated under supervision of the health posts. The share of traditional healers in health care declined as that of the national health services increased. There was never a ban on private medical practice in Nicaragua, and the great majority of pharmacies were privately owned and operated, but drug prices were regulated by the government and kept low. In 1986, 284 private pharmacies existed. At the time, about two thirds of physicians were general practitioners and roughly 90% were government employed (but could have a private practice on the side). As for financing, it is estimated that as much as 50% of health system costs came from public and 50% from private ("out-of-pocket") sources. The National Tuberculosis Program was one of the priority health programs in the Ministry of Health. Diagnosis and treatment of tuberculosis were free of charge in government health facilities. Private pharmacies were not allowed to sell anti-tuberculosis drugs, and the share of the private sector in tuberculosis treatment was small. In the 1990s, the health administration was decentralized further with "local health systems" (SILAIS) replacing the regional level. A clear division separated clinical and administrative duties. The importance of building capacity and allowing time for supervision was acknowledged.

The United Republic of Tanzania was formed when, after independence, the former British colonies of Tanganyika and Zanzibar united in 1964. In subsequent years, major policy changes were launched under the leadership of Julius Nyerere. In comparison to Nicaragua, Tanzania had a larger population (23 million in 1986), was less urbanized

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* Source: Roemer, *National Health Systems of the World.*[10]

Box 7.2 Continued

(14%), and was at a lower economic level.* Another important difference to account for when considering tuberculosis control is the profound impact of the HIV pandemic on Tanzania. In 1986, the country was divided into 20 administrative regions (plus Zanzibar) and 104 districts. The districts were subdivided into divisions of about 50,000 people on average. In 1984, there were health centers in 66% of the divisions staffed by medical assistants. Each health center had 10 to 20 dispensaries as satellites. Dispensaries were staffed primarily by rural medical aides and commonly served 5,000 to 10,000 people in several villages. In some villages there were village health workers. Mission health facilities dating from the colonial period were mostly integrated with the government services in the rural areas where they were typically located. Private medical practice was legally prohibited in 1980 as part of the government policy to provide free care for everyone. Traditional healers were not as prominent in Tanzania as in many other African countries, perhaps partly due to a British law from 1928 (outlawing witchcraft for healing). It is estimated that three quarters of health system costs came from public, while only one quarter of the financing came from private sources. Despite good intentions and ambitious plans, health services were always understaffed. Personnel at the regional and district levels were overburdened with clinical work, which left little time for management and supervision. In conclusion, although primary health care was reasonably accessible at the time (roughly 70% of the population lived within five km of a health facility) and health services were provided free of charge, the quality of the services was not always high.

*The Nicaraguan economy deteriorated after the mid-1980s, due primarily to the civil war and its consequences. As much as 40% of the government budget was spent on defense, resulting in a great loss of opportunity to build other sectors as planned.

with their good reputation and become high-volume units secondarily ("selective referral").[34] Both factors may play a role, and the importance of each may differ between diagnoses and procedures. In a systematic review of research on volume and outcome from 1980 to 2000, Halm et al. found evidence of varying magnitudes of association between high volume and outcome. For example, there was a strong association between higher volume and better outcomes for AIDS treatment. They concluded that differences in case-mix and in processes of care between high- and low-volume units could partially explain the associations they observed, but they stressed that the clinical and policy implications of these findings were not entirely clear.[35] A 2006 study of clinical care for ten chronic diseases within primary care practices in the United Kingdom found that small practices performed marginally better overall than large ones, but there was greater variation in the performance of small practices (very low-volume practices were excluded).[36]

Even when there is evidence that an adequate volume of a given procedure or caseload is necessary to support specialized facilities, services, and skills, exactly what quantity is sufficient is usually less clear, and policy recommendations are usually based on expert opinion rather than on demonstrated association with quality.[7] The usefulness of standards related to structures of health services is further limited when experts disagree. Clearly, whatever the minimum or threshold volume, volume in and of itself does not guarantee quality. Some physicians with large caseloads have been found to provide less than optimal care,[7] and greater hospital size has been associated with poorer outcome.[33] High volumes require generous staffing, as unreasonable workloads will negatively affect quality. One can further speculate that very high volumes may result in low-quality care, as the services become less accessible, more mechanical, and less personal. For many conditions, transfer-out rates rise with volume, and this may cause problems in itself.[34]

Decentralization

The term "decentralization" is used when describing different approaches to transferring power from central to local authorities in the health system.[37,38] "Delegation" refers to the assignment of responsibility for specific tasks to peripheral units with overall control remaining centrally; whereas "devolution" refers to the transfer of power, that is to say responsibility, authority and accountability, resulting in peripheral units coming outside of the direct control of the central power.[37] The stated intention of decentralization is usually to improve the responsiveness, quality, and efficiency of health care services through local involvement, direct accountability, and increased flexibility to adapt to local circumstances and changing conditions.[37] Success in decentralization depends, to a large extent, on local capacity and resources.

It is a common misconception that decentralization saves resources. In a decentralized system, it usually costs more to ensure a consistent level of high-quality services. Service delivery costs per person reached are not fixed. The cost per person served increases as population density decreases, an important factor where population density is low.[39] Generally speaking, when services are expanded, the average unit cost can be expected to fall during the early expansion stage, then level off, and finally increase as less populated areas are reached.[40]

Decentralizing supportive services, such as monitoring and quality assurance, poses several unique problems. Contrary to what is sometimes stated, decentralizing supervision does not guarantee frequency of supervision. The content or quality of supervision may actually suffer when supervision is decentralized.[41] Training and supervision are important, but often neglected, cost items in decentralization. Quality assurance is difficult in a decentralized system with many low-volume units.[7] However, too much centralization can also

negatively affect quality and is likely to reduce access. The key is defining a volume range sufficient to support proficiency, and then decentralizing up to that point to facilitate access. In the tuberculosis program, consider acid-fast microscopy (a laboratory procedure) on the one hand and case management (medical intervention) on the other. Theoretically, different volume ranges may apply to different elements of the program. Furthermore, procedures such as microscopy and case management can be broken down into smaller tasks, each with different volume ranges again.

Rural and urban health services

The definitions of "urban" and "rural" are not straightforward and differ among countries. Sometimes the meaning of these terms is based simply on absolute population figures. For example, in Nicaragua in 1986, the term urban referred to a population of over 2,000.[10] A complex definition was used in the 1981 census in India. To be classified as urban, an area needed to have a minimum population of 5,000, a population density of at least 400 people per square km, and at least 75% of the male working population had to be engaged in nonagricultural activities.[42] Another complex definition was used in the 1995 census in Laos. A village had to satisfy at least three of five conditions to be classified as urban: a market in the village, access by a road for motor vehicles, a location in the municipal vicinity where the district or provincial authority is located, a majority of households electrified, and a majority of households serviced by tap water supply.[43] Given the variety of definitions available, one can conclude that cities and metropolitan areas form only a part of what are defined as urban areas.

Problems in health services development in metropolitan areas are typically linked to rapid population growth that outpaces resource allocation, whereas the problems in rural areas tend to be associated with traditional shortages of facilities and, in some settings, what is referred to as "cultural lag."[44] It is common to talk about an urban bias in health care; that is to say, there is more or better provision of health services in urban areas. While this may be the case, this is not invariably so. In some low-income countries where the large majority of the population lives in rural or semi-rural areas, the primary focus of the government has been to establish rural health services. The development of metropolitan health services has been taken for granted and, as a result, is relatively neglected. An urban bias in tuberculosis control sooner or later backfires, as it did in Beijing, where the proportion of migrants among notified tuberculosis cases increased from one in ten cases in 1993 to one in three in 2005.[45] The majority of migrants to Beijing are young people from rural areas who engage in manual labor. Their access to tuberculosis treatment is inferior to that of permanent residents, and according to routine reports, treatment results for migrants were unsatisfactory from 1997 to 2004.[45]

Urban and rural health services are interrelated. Where rural health services are nonexistent or of low quality, rural populations tend to make use of city-based services. This can result in a deterioration of the quality of care if urban services become overwhelmed. Inefficient referral systems also lead to an influx of self-referred patients from rural areas to urban health facilities. In tuberculosis programs, this may result in a high defaulter rate, when patients are lost during follow-up, or a high transfer-out rate, as patients are directed back to their area of residence once a diagnosis has been established. These indicators, particularly the transfer-out rate, can be seen as an indirect indicator of coverage and real access to services.

The recent rapid growth in metropolitan populations in many low-income countries has been accompanied by the spontaneous appearance of settlements where disadvantaged populations come to live.[29] These settlements possess insufficiently developed health infrastructures. In the Kenyan capital of Nairobi, at the turn of the century, notified tuberculosis cases increased 30 fold in 20 years, with more than 75% of the patients coming from the informal settlements and slums that were home to more than 50% of Nairobi's population.[46] With urban planning lagging far behind, the population of these informal settlements is likely to seek care, not necessarily in the nearest health facility, but in centrally located facilities. Although this is conveniently explained by the fact that central facilities are better equipped and staffed and therefore attract patients, other, more banal, explanations exist. It is unlikely that new and marginalized populations are familiar with facilities other than those centrally located. In fact, the health facilities closest to them may not necessarily be planned for them. There is also the issue of transport, which in many urban areas tends to take people toward the center of the region. Locations in the periphery are rarely directly linked. If no nearby health facility exists, it is often most convenient to travel to a centrally located facility. The common result is that central health facilities are congested. It is important to decongest central facilities by continuously and systematically decentralizing services as the population increases. This decentralization process requires ongoing planning and monitoring.

Ultimately, it may not be possible for all rural areas to achieve sufficient volume to maintain the quality of certain services. However, it may be difficult to separate the effect of "rurality" from other factors, such as personnel and other resource issues.[47] Qualifications of staff in rural areas are often inferior to those in urban areas, but not invariably so. Smaller units (in terms of volume) may not be able to recruit highly qualified staff, but closing facilities in response to low quality may diminish general access to care. It is important to decide what can and should be done locally and when patients should be referred to a more central facility.[47] In low-income countries, quality-assurance programs

and supervision of services are important both for providing professional backup for low-level staff and to make up for the relative lack of opportunities for professional interaction locally.

When comparing urban and rural health services, it may not be appropriate to pool rural units together to produce an aggregate statistic for comparison to urban settings. In this context, Rosenblatt emphasized the importance of looking at the overall system when planning and assessing health services.[47] He encouraged a population-based approach to quality of care that focuses on broad organizational aspects both for systems of care for individual patient groups and for specific clinical conditions. This approach to quality of care is an important addition to the narrow focus on technical issues. Foster raised a similar point when she suggested that a strategy of reimbursing cost of transport might be wiser than reaching out with fixed health facilities or mobile teams.[39] Finally, the same types of services may not be suited for rural and urban areas. For example, due to high transport costs, ambulatory services may be much more expensive for patients in rural areas than a hospital stay.[11] It is important to consider all these issues when planning health services and strategies.

Referral systems

Policy makers often focus on improving coverage by expanding service delivery with decentralization, but less attention is given to the issue of access to referral. Local availability of health care in a given area is only one aspect of access to care. When discussing relevant access, it is just as important to consider the quality and safety of the care provided. In this context, access to referral is an important feature of health services. It is the functioning of the entire system of care that determines whether or not individuals receive high-quality care, which is reflected in Rosenblatt's insistence on focusing on populations in quality assurance.[47] To reiterate his point, assessment of the quality of health care in rural areas is not merely an issue of comparing quality in rural health facilities to that of urban health facilities. A real evaluation must look at the entire system, including referral to the more advanced care in urban areas, with the aim of creating a decent network of health care services.[47] He also pointed out a common weakness in studies of rural care, as self-referred patients never show up at local centers and thus do not feature in the studies. These self-referred patients may fare differently, perhaps better and perhaps worse, than those who seek care locally.

This leads to the issue of the coordination of access. It is important that, in the network of care, there be a single structure responsible for the case management of an entire illness episode, rather than dispersing the responsibility to fragmented segments of the health care system, such as laboratory

services, hospitals, and ambulatory care. This is the rationale behind the tuberculosis management unit: a specialized group responsible for the overall management of tuberculosis control in a region. This unit is presented later in this chapter. Finally, when considering referral systems, the possibility of insufficient communication between facilities in the health care network must be addressed.

Access to health care

Access to health care is a complex subject. There is no standard definition or measure of access. Access, an elusive term, is largely a political matter. But an accessible health service is only one of the goals of health systems, along with quality, and cost containment. All three are interrelated.

Some social scientists argue that if variation in the use of health services is a function of need, then there is equity of access. However, if that variation is a function of availability of services, or the way they are organized, or a function of the predisposing or enabling characteristics of individuals other than age and sex, then the services are not equitably distributed.[48] For example, when the severity of illness predicts utilization of services, there is more equitable access in the system than when access barriers (such as ethnicity, income, and insurance status) predict utilization.[48,49] In a framework presented by Aday and Andersen in 1981,[48] characteristics of the health system—such as availability of services (volume and distribution) and their organization (entry to and structure of the services)—are structural indicators, whereas constant or variable characteristics of the population at risk (predisposing factors, enabling factors, and need) are process indicators of potential access to health care. In contrast, utilization of services (type, site, purpose, and timing) provides objective indicators of access, whereas consumer satisfaction (regarding convenience, availability, financing, provider characteristics, and perceived quality) provides subjective indicators of realized access.

Utilization of services: need versus demand for health care

Broadly speaking, there are two main approaches to health care. One is based on the need for health care and the other on the demand for health care. Neither approach is straightforward. Who should define the "need," and what does "demand" measure? When evaluating the demand for health services, consideration must be given to how demand is created, expressed, and influenced. As for utilization of health services, although there is no definition of how much health services should be used, it is certain that people cannot use what is not there. Therefore, research on health care seeking behavior that addresses how people act given the current organization of resources and services

should ideally be designed to provide insight into how people would behave given a different organization.[50] This is obviously difficult. As McPake et al. point out, "utilization" as a measure assumes that reasonable alternatives exist as well as an ability to pay for them, neither of which may be true.[26]

Proponents of demand-based approaches to health care assume that the operation of a market for health care creates a system that is both the most efficient system and the most responsive to individual desires.[51] The main problems associated with this approach are that it does not acknowledge that, in reality, consumers often have little choice; it does not account for inequitable physical and financial access barriers; and it ignores community health.[51] Critics of needs-based approaches point out that such approaches tend to rely on objective, technocratic measures of community need rather than the perceived needs of individuals and the community itself.[51] Critics claim that in almost all systems, need has been categorized primarily by epidemiological assessments. They further argue that when health professionals determine so-called essential need for health care, there are likely to be implicit assumptions and value judgments concerning the appropriate level of care as well as how much of what services is required, although perceived need and patients' knowledge about available services are no less important.[48] Perceived quality of care and user satisfaction may affect both the initial contact with health services and a patient's adherence to medical advice and treatment.

Priority setting in health care always involves making value judgments, and the key question is whose values should count. Historically, in the case of communicable diseases, "communities" have often responded by discriminating against those who are inflicted by diseases such as leprosy, tuberculosis, and AIDS. This primitive attitude, while cruel, is logical in terms of individual and community self-interest. It takes exceptional individuals, who are also members of the community, to act differently and more humanely. In this situation, someone with unusual values or specific knowledge explains to the community how it should act and why. It may be argued that patient groups, voluntary organizations, experts, and vertical programs—which are all part of the community—have frequently taken on this role.

Approaches to studying the utilization of health services

It is often difficult to interpret the findings of studies that measure overall access to or utilization of health care. What does utilization measure? When is decreased utilization a danger sign? Ideally, studies need to examine what population's attendance is diminished and why. A focus on a specific condition or disease helps further clarify study results.

In 1983, Kroeger[3] suggested that, when studying how individuals end up using or not using different kinds of health services, one can investigate either

the pathway to care* or the determinants of the use of care.† He distinguished between predisposing factors for utilization of health services (demographic characteristics, household and family composition, smoking, education, attitude, role, and responsibility); enabling factors (quality of care, communication, doctor-patient relationship, accessibility, referrals, health insurance, and income security); and health services system factors (referral practices, structure of the health system and services, and the sociopolitical macro-system). He also listed factors associated with the illness itself (acute versus chronic, severe versus trivial, and infectious versus noninfectious) and expectations of benefits. All these variables may contribute in triggering different decisions in the selection of alternative types of health care in individual cases. Kroeger pointed out that some of these variables inevitably change in the process of development, others may be influenced by health policy (geographical accessibility, cost, and quality), and still others by public education, although here undisputed evidence is scarce.

Factors associated with utilization of health services

Even the simplest type of access, namely geographical access, is still rudimentary in some low-income countries. In Ethiopia at the turn of the century, the majority of the population, an estimated 60%, lived farther than ten km from a health facility.[52] Even if equality in geographical access is achieved, differences in quality of care may persist.[53] The relationship between access, or even contact with medical services, and subsequent health is not guaranteed.[48] Access to poor-quality health care is irrelevant and may even lead to poorer health if, for example, drug resistance develops as a result of contact with the health service. There is no real equity in access unless the quality of services provided is comparable. For this purpose, it is important to establish criteria for what is appropriate care for any particular illness.

It is generally accepted that those who live close to health facilities and can afford care use those services more than those who live far away. Distance decay‡ in utilization of health services makes an argument for spatial or geographical location-allocation models, models based on distances to health facilities, when planning health services.[54] However, the relationship between

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*The pathway to care: a patient recognizes/realizes symptoms; resorts to self-care and/or lay consultation with a relative or friends; proceeds to care seeking and may shop around; the providers respond; and finally, the patient either adheres to the remedy/advice or does not.[3]

†Determinants of the use of care: the recognition of symptoms and the significance placed on them by the patient after considering their seriousness and potential consequences; barriers to care (structural, economic, geographic or communication barriers); and faith in the system.[3]

‡The term "distance decay" refers to the inverse relationship between rate of utilization of health services and distance.

the utilization of health services and distance is not constant, and geographical distance is not the sole concern. Distance can be measured in various ways, such as linear distance, actual distance, travel time, or cost of travel.[54] The hierarchical nature of health services is also an important factor, as attendance is affected by the level of the health facility within the system, a phenomenon that argues for simple hierarchical location-allocation models placing facilities from the highest to the lowest level in centers of strictly decreasing population.[55] In addition to the distance to and level of health facilities, a multitude of other variables affect their utilization.

According to a 1983 study in Nigeria, the type of illness was another important factor, followed by quality of care. Tuberculosis was an example of a disease where distance had virtually no impact on utilization rate.[54] The distance from a health facility was positively related to the duration of illness prior to the acquisition of treatment. Neither distance to the nearest health facility, nor population, nor access to modern transportation provided reliable predictions of utilization rates in individual villages. The investigators concluded that the optimal size of a service area varies greatly according to the type of facility, the type of illness, and the age and sex of the patient. This is an important point to consider when planning health services in general and tuberculosis services in particular.

A study in Burkina Faso found an age bias in health care utilization in favor of adults, suggesting a focus on economic survival with households favoring productive members of the family when it comes to health care expenditures.[56] The underlying rationale of this strategy is to maintain the health of all household members in the long run. This suggests that tuberculosis care would be granted priority by households. The same phenomenon has been reported from Bangladesh (1989), where Pryer specifically pointed out the potential impact that tuberculosis can have on the nutritional status and survival of children and on the welfare of the entire family when men are affected.[57]

Examples of factors affecting the utilization of health services according to studies reported in the 1980s are presented in Box 7.3.

Financial policies

The pros and cons of charging fees for using health services were discussed at considerable length in the last quarter of the twentieth century. Proponents of user fees argue that fees not only provide additional revenue for health services, but they also improve the quality and scope of the services and promote efficient resource utilization by discouraging unnecessary use of health care.[61] Others argue that there is no such thing as trivial consultations in rural areas in low-income countries. Therefore, there is no reason for introducing fees that discourage utilization.[62] Opponents of user fees caution that the fees often raise relatively little revenue, may discourage legitimate utilization of health services,

Box 7.3 Factors affecting the utilization of health services in the 1980s

Factors frequently mentioned as affecting the utilization of health services in Nigeria include the availability of experts and medicines, prompt attention, the manners of health personnel, the presence of relatives living in the hospital town who will accommodate those accompanying the patient, and the cost and ease of transport.[58]

In a rural area in Nigeria, distance decay varied according to the type of facility, sociodemographic variables, and illness. Distance decay was greater when looking at female utilization compared to that of males.[54] Similarly, in Nepal, the restricted mobility of women was found to affect utilization of services.[59]

In Ethiopia, utilization rates varied with the type and duration of illness, socioeconomic level, age, and sex.[44] The quality of services and perceived efficacy of treatment were often more important considerations in the selection of services than cost. In a study that revealed a steep distance-decay gradient and underutilization of services, the type and cost of transport, type of illness, the patient's preferences, socioeconomic status, and referral patterns influenced utilization.[60]

Severity of disease and perceived treatment effectiveness were the most important determinants of health-seeking behavior in a study in Burkina Faso.[28] Availability, distance, and the cost of travel and drugs were important service-related determinants.[28]

In a study of leprosy patients in Nepal, distance afforded welcome anonymity for patients eager to disguise their disease.[59] Traveling a long distance for a diagnosis did not affect adherence to treatment. The same may not apply for other diseases, as the consequences of diagnoses vary. Being diagnosed with leprosy often results in rejection by the community. In Nepal, default from treatment was greater among those with no disabilities, which makes sense in light of social consequences mentioned above.

and do not necessarily improve the quality of care.[61] A study in Kenya drew attention to the fact that, in the reality of low-income countries, cost-sharing revenue was often used to prevent deterioration in services rather than to improve quality.[61]

The level of the health system at which fees are introduced is important. Once again, it is important to look at the complete picture. In contrast to the Bamako Initiative model,[63] where fees were typically introduced at the primary care level, some propose that there may be a greater role for introducing fees in hospitals, a strategy that might encourage the appropriate use of referral systems.[62] Implementing user fees for comparable types of services at one level of the health system and not another can act as a referral mechanism in favor of the free-of-charge level. Theoretically, user fees can be implemented to direct utilization to peripheral and general health services. These are referred to as "by-pass fees," and are intended to deter patients from inappropriately using the services of referral hospitals. The assumption is that second- and third-level

referral hospitals should not offer general outpatient services or provide first-level inpatient care unless such services are explicitly required as, for example, in the case of a district where there is no other alternative for the type of care in question.[64] For this strategy to succeed, the services at the primary care level must be competitive.

It is also important to consider the point in the process of a health care interaction at which user fees are introduced. Registration or consultation fees paid before the patient is seen may dissuade people from seeking care. On the other hand, if only drug fees are introduced, the most acutely ill patients, those most in need of medical services, and those most in need of exemption, can be identified before the issue of payment arises.[37] For example, after a first attempt to introduce a registration fee in the Kenyan health services in 1989 failed, a later attempt with the gradual introduction of treatment fees from 1991 to 1994 succeeded, at least partially, as judged by a greater reduction in the overall decrease in utilization of services when compared to the earlier attempt.[61]

When determining the amount of user fees patients will tolerate, data on "willingness to pay" should be used carefully. The poorer the person, the more likely it is that the expenditure reflects an extraordinary situation and cannot be taken to represent an amount people would be willing or able to pay on a regular basis.[39] In addition to user fees, patients usually are faced with other expenditures, such as transport and opportunity cost.

Typically, fee exemption policies for safeguarding the access of vulnerable groups are components of user-fee programs. However, the design and execution of such policies is a challenge. Exemption policies are among the determinants of actual revenue collection in the programs. Procedures for exemption must be feasible from an administrative viewpoint, should exempt the correct groups, and should prevent abuse, as exemption policies are open to exploitation by those who run or work in the system. Exemptions can be made based on types of services, drug categories, or health conditions.[37] Although tempting, direct exemption of the poor as a group has proven difficult.[65] It is difficult to exempt the most economically disadvantaged because they may not attend the services in the first place if there is a fee. Furthermore, poverty is relative and difficult to define. As discussed in Chapter 9, it is common to classify tuberculosis as an exempt health condition. A potential negative aspect of exemption policies is the possibility that the service, because it is no longer a source of revenue, will no longer be a priority and will be ignored in future plans.

Health programs

A "health program" has been defined as a formal set of procedures to conduct an activity,[66] or a set of activities and tasks aimed at dealing with a particular problem.[9] Arguably, health resources would have limited impact on populations

if they were not organized into programs.[10] Strategies need to be supported by tactical programs or plans of action that are feasible, acceptable, and safe both to the staff who must carry them out and to the intended beneficiaries.[11] The cardinal rule of medicine, "first do no harm," is as true in public health as it is in clinical practice.[11]

The most prominent debate concerning health programs in general and communicable disease control programs in particular revolves around the issue of "vertical" versus "integrated" approaches. The terms "vertical" and "integrated" are often vaguely defined, and the debate is confusing. The discussion below borrows from a 1997 analysis by Criel et al.[9]

Operations of programs: integration versus differentiation

There is evidence that specialization by physicians, medical institutions, and primary care practices improves quality of care for specific conditions, whereas specialists are likely to be low performers outside of their area of expertise. Consequently, many consider it important to have a "gatekeeper" who refers patients to the relevant specialists.[7,67] This is how specialists and generalists complement one another. It is important to keep this in mind when organizing the delivery of health services and programs.

In the second half of the twentieth century, the development of national health systems was, to varying degrees in different countries, marked by two major trends: the establishment of so-called "vertical programs" for specific health problems, each with its own specialized infrastructure and staff, and the contrasting development and expansion of a general health services infrastructure.[68] The first vertical programs were programs for the control of yellow fever in Brazil in the 1890s.[68] The creation of the WHO in the period after the Second World War brought a rapid increase of vertical programs for communicable disease control in developing countries, most notably a program for malaria and, in the 1950s and 1960s, specific programs for numerous diseases, including tuberculosis.[68] An appreciation of the importance of a health services infrastructure as a prerequisite for the development of any health services, including disease-specific programs, was lacking at this time.[68] Eventually, it was acknowledged that individual programs would not reach universal coverage; and integration, with the aim of more widespread and comprehensive health services, became the focus of a policy change in developing countries in the early 1970s, with a transition to primary health care in the 1970s and 1980s.[68] It was during this period that the Union model was developed. The tuberculosis program in Nicaragua is exemplary in this respect. It took full advantage of the expansion of the general health services in the 1980s. The supervisory system, using semi-specialized supervisors, was integrated into the administrative structures of the Ministry of Health—rather than the curative care structures—and drug supply was channeled through the general system of medical sup-

plies. As a result, there were no physical structures specifically for tuberculosis control apart from one sanatorium, which gradually developed into a national referral hospital for difficult cases.

Criel et al. define a "vertical structure" as being staffed by specialized personnel highly qualified in a particular field, but not necessarily with a formal specialist qualification, who are responsible for dealing with a single or a limited number of health problems.[9] They define a "horizontal structure" as a health facility in which a multi-function staff is responsible for dealing with a wide range of health problems. A vertical structure can be either periodic or permanent, centralized or decentralized.* A horizontal structure is, by definition, decentralized and permanent. Importantly, both the horizontal and the vertical approach aim to improve the care provided to the population. A vertical program may or may not depend on a vertical structure. Whether or not specialized vertical structures are used, and at what level of the system they are operational, is variable. According to Criel et al., "integrated health care" refers to prevention, promotion, and curative care being provided by a single operational unit. They emphasize that both vertical and horizontal structures can provide integrated health care. An "integrated health system" is a system whose various components, such as the basic health services and referral facilities serving a defined population, are organized and coordinated so as to constitute a single entity with a common objective. Finally, they acknowledge that the term "integration" commonly refers to different phenomena, such as the integration of all or some specific program activities into the total of activities provided by a multi-functional health service, the integration of services in the execution of a particular program, and even the collaboration or fusion of two programs.

Integration of program activities into the general health services

If a program is a set of activities and tasks aimed at dealing with a particular problem, then it is these activities and tasks that are integrated into the general health services rather than the entire program.[9] The important question is, which activities can and should be integrated, where, and how? For example, it may be justified to decentralize diagnosis activities to a different level than treatment activities or reporting, as mentioned above in relation to the volume-outcome relationship. Although standardized case management may be relatively easily integrated into the basic health services, activities requiring the involvement of specialized personnel, such as quality assurance, are not.

Criel et al. point out that the nature of integration is context-specific and may change over time.[9] When considering integration, they advise, in addition to spelling out the justification and objectives of integration, contemplating the potential benefits and limitations, as well as the preconditions and

*Note that "vertical" and "centralized" are not synonyms.

practicalities that must be addressed for successful integration. They summarize the preconditions of successful integration in the following way: existence of functional basic health services, choice of an appropriate time for the integration, acceptance by all parties of a transfer of decision-making power, and review—and possibly remodeling—of program objectives. In their view, too late or too much decentralization occurs when the problem that a program is targeting is so rare that the specific caseload (actual rather than estimated or predicted caseload) of the multi-functional health personnel is so low as to prevent a guarantee of proficiency. Integration can also occur too early. This could happen when the target problem is still new and relatively rare or when the intervention is still under development, an example being HIV/AIDS in the 1980s.

With regard to the objectives, Criel et al. warn against a narrow focus on the quick epidemiological impact of integration. They take case finding and treatment of tuberculosis as an example. According to them, the primary objective of integration should be to improve the care to the patients. Therefore, absence of impact on the recorded frequency of tuberculosis after integration would not necessarily mean that integration had failed. Both the objectives of integration and the terms of reference for its evaluation must be clear. The objectives should be realistic and the multi-functional health services should not be expected to achieve results that are impossible.[9]

The rationale and motivation for integration should be positive (for example, promoting improved access, reducing patient stigma, and improving early detection and treatment) and not negative (such as lacking the resources to run a vertical structure).[9] Numerous problems can be encountered in the process of integration: resistance by specialists or others who fear for their careers and employability or fear a deterioration in quality of care; resistance by the peripheral services that do not agree to take on responsibility for the activities or fear increased workload, stigma, or possible risks involved (such as the risk of infection); resistance by donors who may be concerned about the difficulties of raising funds for integrated services, may worry that funds will not be well used, or fear that there will be less (or less measurable) effectiveness; and, finally, resistance by patients who may fear losing privileges or receiving inferior care.[9]

Integration may result in a drop in the technical quality and efficacy of a program, so planners must decide how much compromise is safe. Because decentralized programs incur different—though not usually fewer—costs, resources have to be allocated in different ways. Some of the cost of integration can be recovered if vertical structures are discontinued, but such structures often remain. Finally, Criel et al. point out that unexpected benefits may occur if integration improves the skills of the general services over and above the specific program activities.[9]

Integration calls for supplementary training, appropriate instruction manuals, and closer supervision.[9] Whether supervision is one of the activities re-

quiring involvement of specialized personnel—or, how far toward the periphery supervision should be provided by specialists as opposed to managers of the basic health services—is debatable.[9,68] Supervision requires not only supervisory skills, but also special knowledge of the disease or problem. Consequently, supervision should not be integrated. The conclusion may rest on how supervision is defined, which is a question of identifying which program, which activities, and which level of the health services are being referred.

The main argument against vertical supervision is the potentially confusing overlap and contradictions that may arise from having various specialists supervise the same group of people. This may be more of a theoretical than a practical problem, at least when considering supervision at the district level. Besides, the criticism misses the point: who is capable of providing useful support for the staff in question? Another argument claims that, when specialists supervise their work, multi-functional health services are reduced to a vehicle for serving different vertical programs. For example, with home-based care for AIDS patients, the services can be seen as benefiting the AIDS program at the cost of other activities of the general health services.[9] Though this may seem a strange argument at first glance, it reflects a certain absurdity in the reality of health systems in low-income countries. If the objectives of the AIDS program or of hospital-based HIV/AIDS projects do not coincide with those of the general health services, then that is a problem in itself. There needs to be agreement on the objectives of the care of AIDS patients and on the roles and responsibility of different parties in the health system. Furthermore, whatever activities are to be integrated, the basic health services must be strengthened and supported in such a way that they can accomplish their tasks. After all, the basic health services, the hospitals, and the vertical programs are all part of a health system that serves the same population.

Even if having a multi-functional supervisor does not contradict the involvement of a specialized supervisor at a particular time, either on request by the multi-functional supervisor or on a regular basis, there remains the question of whether this results in the unnecessary duplication of work. There is also the worry that having a multi-functional supervisor may disconnect the health workers on the ground from specialist support, making them dependent on an intermediary who may be too busy to follow up. The argument for the necessity of a "gatekeeper" does not apply in this instance, where the focus is on the supervision of management of specific cases and specialized programs. Finally, it has been pointed out that, at the district level and beyond, the multitude of specialized programs falls on the shoulders of a small team and that this is where integration occurs by necessity if not by choice.[68] It is easily argued that having specialized supervisors travel beyond a certain level in the health system is not realistic. Public health officials considering the decentralization of specific activities should take note of this.

Integration of services in the execution of a program

When case finding, treatment (particularly if prolonged) and contact tracing are components of a disease control strategy, a program must cut across the boundaries between the hospital and ambulatory facilities, specialized and nonspecialized facilities, and the different components of a health system and services, such as the civil, prison, and military sectors. Doing so benefits both individual patients and the community. Individuals move between facilities (hospitals and ambulatory units) and sectors (in and out of prison), and patients in different facilities and sectors are connected by epidemiological links. In the case of tuberculosis, this fact is so obvious that it needs no lengthy justification and, indeed, it causes less debate than the issue of integration of program activities into the general health services. Nevertheless, in certain settings, there is resistance from different stakeholders for reasons similar to what is described above. Recently, this has been particularly notable in the former Soviet Union, where it concerns primarily the civil versus penitentiary sectors, but is also a consequence of a highly vertical specialized structure within the civil health services.

Collaboration or fusion of programs

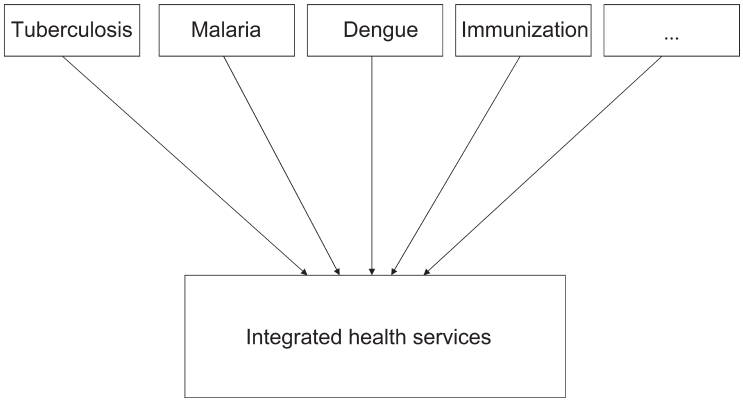
Despite the benefits of integration, it may be difficult to justify the joining of two or more programs. When fusing programs, the same issues raised by the integration of program activities into multi-functional health services must be considered.

The central goal in integrating communicable disease control is to integrate program activities into the general health services while, at the same time, preserving the degree of specialization needed for every case. This is more important than the combination or fusion of any two programs. Even when programs are part of primary health care and integrated into the general health services, a certain level of specialization is necessary. In the case of tuberculosis control in low-income countries, the coordination of technical aspects and supervision by specialized personnel are conditions for integration. With specialization, higher levels of quality of diagnosis, chemotherapy, treatment of complications, and understanding of patients' problems are achieved. Fusion of two programs at the central level may force fusion at the intermediate and local levels. However, the existence of separate programs at the central level does not prevent integration at the intermediate and local levels, which provides for more flexibility in the organization of disease control at all levels.

Disease-specific versus task-specific programs

"Vertical," "horizontal," and "integrated" are complex terms, and there are many ways of looking at integration. Carlson, when discussing the term "multi-

Figure 7.1 Disease-specific vertical support

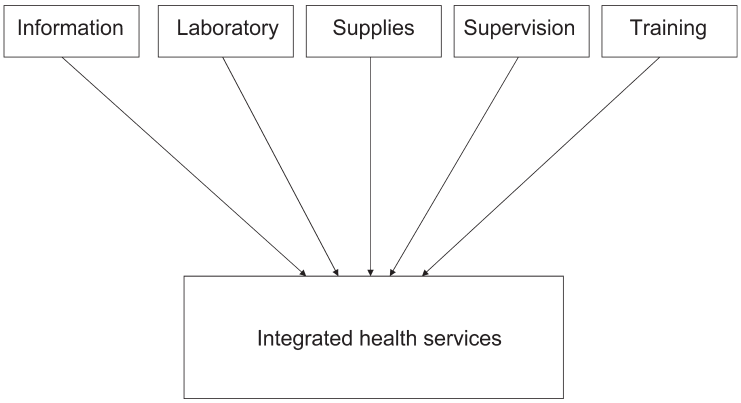


disciplinary," talks of both integration across health professions and integration across medical specialties.[4] Yet another dimension to consider is the multitude of tasks in various programs, such as training, supervision, materials management, and surveillance.

In low-income countries, a need for a certain verticality in the support to the basic health services, both technical and managerial, exists now and will continue to exist in the near future. How should this support be provided? The term "vertical" can refer to the direction of support—from a central level to an intermediate level and to a local one—and the nature of the support, that is to say, specialization. A disease-specific approach is depicted schematically in Figure 7.1, and a task-specific approach is described in Figure 7.2. Which is more vertical in terms of specialization?

In appropriately decentralized health services in low-income countries, it is ideal that managers and supervisors of communicable disease control programs have knowledge and experience concerning all the factors relevant to the outcome of the program, which makes the managers multi-functional even if their program deals only with one disease. This implies that they need to be familiar with diagnostic procedures, treatment and case management, materials management, data collection, analysis and interpretation, quality assurance, and evaluation. Arguably, this diversity of tasks makes their assignment more interesting and thus increases motivation. This type of "specialization" can be viewed as an "integrated" approach and may be sensible in the context of public health programs in low-income countries, even if it seems to contradict the prevailing interpretation of and direction in specialization within the health services in industrialized countries.

Figure 7.2 Task-specific vertical support



Coverage of health services and programs

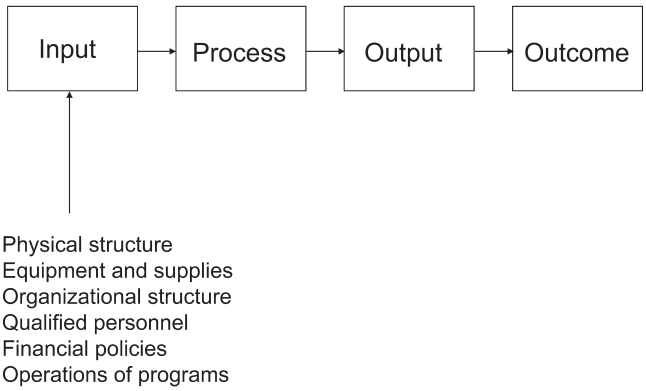
Coverage is an important indicator for any health program. Just as there is little point in having good coverage if the services are of low quality, there is little point in having excellent services if they only reach a small proportion of the population. In low-income countries, often a small proportion of the population supposedly covered utilizes a large proportion of services provided by health facilities. As previously mentioned, studies have shown that people travel farther for more specialized or higher-quality services. Generally, a very low proportion of those attending dispensaries are from outside their planned service area, whereas this proportion is higher in hospital outpatient services and highest for hospitalized patients.

"Coverage" of health services can be defined as a measure of the extent to which the services rendered cover the potential need for services in a community, expressed as a proportion in which the numerator is the number of services rendered and the denominator is the number of instances in which the services should have been rendered.[66] An obvious limitation of this measure is the difficulty in estimating the need for services, as discussed above. Coverage estimates depend on how the target population is calculated, and there are many problems associated with this. Surveys are often difficult to accomplish, and their results are subject to variation and may be difficult to interpret.[20]

System design in tuberculosis control

In the simple model in Figure 7.3, "system design" refers to the input, which provides a framework for the process described in Part I. An effective system

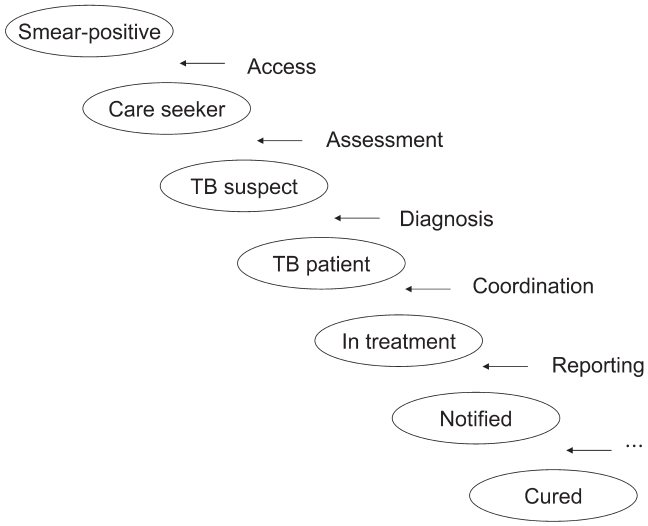
Figure 7.3 Tuberculosis control model



delivers a high output of cured patients, whether as a proportion of the total number of patients registered and treated (cure rate) or of the actual number of infectious cases in the community, which depends on case detection. It is difficult to estimate the latter and the former is easily measured, but the measure is most meaningful if it reflects the total effort at diagnosis and treatment of tuberculosis in a country or region.

The output in tuberculosis programs is the end product of the complex sequence of events as depicted in Figure 7.4. A person develops infectious tuberculosis and, looking only at structural characteristics, whether, when, and where he or she seeks care depends on access and utilization of health services. Whether, where, and when a care seeker is recognized as having symptoms meriting assessment for tuberculosis depends on the qualifications of health personnel and access to referral. Whether and when a care seeker is correctly diagnosed as having or not having tuberculosis depends on the skills of the staff in the diagnostic services, primarily the laboratory services, and on coordination between the clinical and the laboratory services. Once the diagnosis of tuberculosis is established, whether and when the patient is treated depends largely on coordination between the laboratory and the clinical services. If and when the patient is cured depends on case management, that is to say on the technical and communication skills of the clinical personnel; but also on the structure, function, and coverage of the tuberculosis program and the health services; and, finally, on the circumstances of the patient. Whether or not there is reliable information for optimal functioning of the program (for example, whether the program can obtain the necessary supplies for diagnosis and treatment of patients) depends on the coverage and reliability of the information system. All of this, taken together, reflects the quality and safety of the tuberculosis services.

Figure 7.4 The multiple steps in tuberculosis control



There is some evidence that structure influences the outcome of case finding and treatment activities in tuberculosis programs. In the late 1970s and throughout the 1980s, a series of studies was conducted in Kenya looking at the structure and organization of tuberculosis services (see Chapter 2).[69–75] These studies concluded that tuberculosis should be managed at the district hospital.* Further decentralization of services could not be recommended given the low quality of the peripheral services at the time, the lack of training, supervision, and motivation of the staff at the peripheral services, and the poor communication between health facilities.[72,73,75] Patients attending the peripheral services who complained of a prolonged cough were to be referred to "chest clinics" at district hospitals for assessment for tuberculosis. This method of case finding appeared to be effective within a radius of approximately 15 km.[73] The investigators emphasized that tuberculosis control was critically dependent on the improvement of the organization and efficiency of primary health care facilities at the peripheral level, including the training of staff and the establishment of referral systems.[75]

The Kenyan case-finding studies were the foundation of system design in the Union collaborative programs in Africa. In Nicaragua, where the context

*The population in the four study districts in Kenya ranged from 279,000 to 473,000 at the time.[74] Note that this is more centralization than currently recommended by The Union,[76] as discussed further on.

was different, the program took a more decentralized approach to fully utilize the expansion of primary health care in the country at the time. Various studies have since looked into the effect of decentralization of services, which will be discussed later. There have also been studies that examined referral systems and the transfer of tuberculosis patients between health units. Some of the key issues in system design for tuberculosis control are presented below: namely vertical and integrated program components, the volume-outcome relationship, population-based planning, the level and nature of decentralization of activities, the role of different health care providers, and referral systems. The term "tuberculosis management unit" is used in order to facilitate the understanding and discussion of system design based on the Union model.

The tuberculosis program

In a 1968 publication, Mahler, then the Chief Tuberculosis Medical Officer of the WHO, criticized tuberculosis specialists for their vertical approach, reflected in the centralization of tuberculosis services into specialized institutes and clinics that were separated from basic health services, located mainly in cities, and served only a small proportion of the population.[77] Mahler pointed out that a large share of national budgets for tuberculosis control went to central institutes, radiology services, and the treatment of unconfirmed cases rather than to strengthening the basic health services to deal with tuberculosis: training their personnel, securing an uninterrupted supply of anti-tuberculosis medicines, and improving case holding. Mahler had a point in that tuberculosis institutes, with their sparse network of specialized tuberculosis clinics, were ineffective at tuberculosis control. He stressed that, with simplified and standardized technology, tuberculosis control was almost entirely an organizational problem, requiring managerial skills. He described an integrated national tuberculosis program within the basic health services, with specialized support from a tuberculosis managerial team that included a tuberculosis physician, a record organizer, a BCG vaccination organizer, a case-finding organizer, and a treatment organizer; one team per one half million population. The strategy subsequently developed in the programs collaborating with The Union is simpler and more convincingly integrated than what was described by Mahler. Notably, the recording system is simpler; essentially, one supervisor takes the place of the five-member managerial team; and the system is more decentralized.

The 1974 Expert Committee recommended that tuberculosis programs should be integrated into community health structures, networks of permanent health services that people could consult if they felt ill.[31] Their report defined the role of the usual three levels. The central level was responsible for policy making, planning, programming, coordination, training, direction, and

evaluation. The intermediate level was responsible for supervision, in-service training, evaluation, and referral services. Finally, the actual delivery of services occurred at the peripheral level. It specified that the network should include private practitioners, outpatient departments of hospitals, health centers, dispensaries, and health posts. With the simplified and standardized technology available, diagnosis and treatment of tuberculosis could be carried out at any health institution and by a large number of personnel, including auxiliaries, if they were properly trained and supervised. One criticism is that these recommendations were not followed up in such a way as to better define how exactly these networks should function. Further, it was unclear how quality, safety, and efficiency should be monitored and who would be responsible for seeing that it was accomplished. This "lapse" left the door ajar for uncontrolled implementation of tuberculosis treatment with potentially serious consequences.

In some countries, such as India,[78] the specialized tuberculosis clinics that Mahler criticized subsequently developed into vertical tuberculosis control centers or district tuberculosis centers with managerial and supervisory functions added to their clinical duties. Importantly, their mandate concerning supervision did not reach beyond the public sector. In other countries, such as Tanzania and Nicaragua, where arguably there were no elaborate vertical program structures in place to begin with, tuberculosis services came to be integrated into the general health services. In addition, a supervisory system emerged within the intermediate and central administrative structures within, or parallel with, the ministries of health, under either a division or a department of communicable disease control or chronic or curative care.

The Union model program

In the model, a central unit heads the national tuberculosis program. The functions of the central unit are policy formulation, including preparation and continuous updating of a tuberculosis manual with clinical guidelines and recommendations on program management; providing an advisory role regarding recommendations on structure, functions, and the staffing of the health services, including referral mechanisms; personnel development and regulation; surveillance and evaluation; control of materials management; monitoring and supervision of tuberculosis services; and the preparation of necessary documents and plans for financing purposes as well as for guiding the overall implementation of the program.

In small countries (in terms of population), the central level, by necessity, requires multi-functional personnel. In larger countries, central level personnel can have responsibility for specific tasks (such as training, information, supply, supervision, or evaluation) or for specific administrative areas (such as zones or provinces).

At the health services level, paramedical personnel (medical assistants, nurses, auxiliary nurses, and laboratory technicians) do the bulk of the actual implementation with minimal, but essential, back up by physicians.

Vertical and integrated elements

As discussed above, vertical and horizontal approaches to health programs are not necessarily mutually exclusive. The tuberculosis program is an example of a program where specialization and integration are combined.[79] The general health services are very important for tuberculosis control because success depends largely on the coverage, capacity, and quality of the curative care services. The activities of case finding, diagnosis, and treatment of tuberculosis patients take place at the health services level, with the participation of all types of health facilities. These services are fixed, not mobile. The vertical support system, on the other hand, can be described as a mobile team of public health professionals responsible for the training, supervising, monitoring, and coordinating of program activities.

The specialized or semi-specialized* support system is organized from central to intermediate level and from the intermediate level to the health services level. As depicted in Figure 7.5, the national policy for tuberculosis control is formulated at the central level, with consultations throughout the system, in coordination with those responsible for setting the general health policy in the country. At this level there is also coordination regarding information and supplies, as discussed in Chapter 8 and Chapter 9. The support to the health services level includes clinical and managerial guidance, coordination and consultations, training, supervision, monitoring, and evaluation.

Some differentiation is recommended at the health services level. Even if the services are offered within the primary health care system, personnel should be dedicated to program management and the treatment of tuberculosis patients. This is recommended in order to improve the continuity of care, result in better support for the patients, and promote better case holding. The dedicated staff member—the *tuberculosis manager*, sometimes called the focal person—is the person who meets with the "vertical" supervisor, so it should not be a problem that the different programs all descend on the peripheral services, as they will to some extent meet different focal persons if the service is well organized.† It is the responsibility of the tuberculosis manager to coordinate program activities within the facility and the service area. The supervisor may provide advice in this respect.

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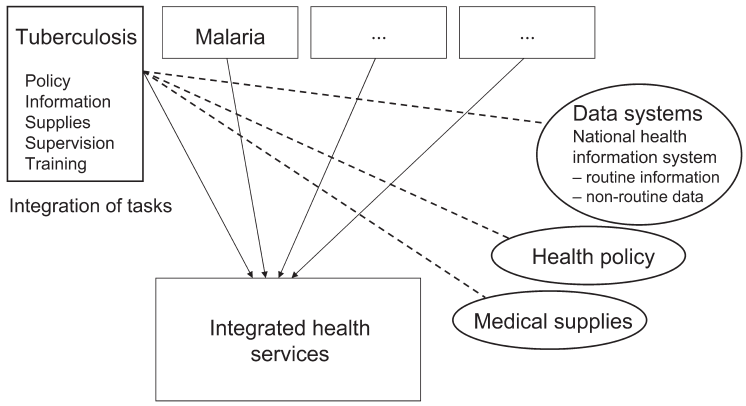
*The supervisor at intermediate level may be responsible for several programs.

†The designated staff may, however, have several responsibilities, depending on the setting and the level of the facility.

Figure 7.5 Vertical support in tuberculosis programs

Arrows indicate supervision, and dotted lines coordination. The national policy for tuberculosis control is formulated at the central level, with consultation throughout the system, in coordination with those responsible for setting the general health policy in the country. At this level there is also coordination regarding information and supplies. The support to the health services level includes clinical and managerial guidance, coordination and consultation, training, supervision, monitoring, and evaluation.



An important role of the tuberculosis program is the integration of different services within the overall health system in the execution of the program. Low case-detection rates in national programs are sometimes, as in the case of China, due to the fact that many patients are detected and treated in health facilities that are not considered a part of the tuberculosis program, such as private sector facilities, prisons, nongovernmental organizations, and even general hospitals. This is an anomaly. Collaboration between ministries of health, justice, home affairs or the interior, defense, and law enforcement is important for the coordination of tuberculosis control efforts.

Collaboration with other programs

In the past, in countries like Tanzania and Mozambique, tuberculosis control was sometimes integrated with leprosy control. This was initiated by a directive of the Minister of Health of Tanzania in a brief given to the international consultation exercise that launched the first collaborative program (see Chapter 1). Among the arguments for a combined program were the fact that tuberculosis and leprosy are mycobacterial diseases, so both interventions require skills in acid-fast microscopy; both diseases, albeit to a different degree, are stigmatizing; both programs were to an important extent donor-dependent;

the strategies, staff and training requirements, logistics, and information needs were similar; and, it was argued, a combined program would make better use of resources. In recent years, as leprosy has become a very rare disease, it has been increasingly discussed if and how tuberculosis control could be integrated with other programs. Two main options have featured prominently in these discussions. One option is functional integration based on a "symptomatic approach" to health care with establishment of a lung health program, the justification being that it improves care of patients by strengthening skills in the differential diagnosis of lung disease in adolescents, adults, and the elderly.[8] The other option is integration with the HIV/AIDS program.

The most obvious advantage of the former option is that it puts the patient at the center and responds to the needs and expectations of patients who contact the health services because of respiratory symptoms.[8] This approach requires the development and application of decision-making algorithms that can be adapted to the situation and the level of health personnel in different settings. Such a plan has the potential for improving the quality of care, the competence of health personnel, referral mechanisms, and, by extension, the overall efficiency of care delivery.[8] Advocating for this approach, Chaulet points out that many countries have a problem with a large number of smear-negative cases registered for anti-tuberculosis treatment.[8] With the implementation of a lung health program, it should be possible to lower this proportion to below 15% to 25%.[8] It can be argued, however, that many programs have performed just as well in this respect without implementation of a lung health program. For example, the proportion of smear-negative cases among new cases of pulmonary tuberculosis in Nicaragua was 24% to 28% from 1999 to 2003, and the proportion is even lower if relapses are included.* Still, a lung health program might improve the management of other lung diseases and is therefore a convincing integration into the general health services.

The latter option, fusion with the HIV/AIDS program, is considered increasingly relevant as the impact of the HIV pandemic on tuberculosis control has become more and more obvious and as the strategy of the HIV/AIDS program develops. With case-finding and treatment activities, the HIV/AIDS program starts to resemble the tuberculosis program and could build on the many lessons learned in the field of tuberculosis control, and vice versa. Furthermore, in some settings, the majority of tuberculosis patients are HIV-positive. In such a setting, a combined program puts the patient at the center. Proponents make the case that a combined tuberculosis and anti-retroviral treatment program would be a powerful combination in sub-Saharan Africa, where it is predicted that, in 2020, tuberculosis and HIV infection together will account for 92% of adult deaths from infectious diseases, up from 60% in 1990.[80] A report from

*Source: Annual reports of the Nicaraguan Tuberculosis Program.

Malawi describes the first steps in developing a country-wide anti-retroviral treatment program based on the lessons from the tuberculosis program and recognizing the need for simplicity and standardization.[81] However, the feasibility and efficiency of such a program is yet to be demonstrated. It remains to be shown that anti-retroviral treatment programs can be successfully managed on a large scale in low-income countries.

The tuberculosis control strategy is, by now, well established, straightforward, and relatively easy to apply. In contrast, the anti-retroviral treatment program is complicated and, in many ways, still poorly defined. It has a certain similarity with tuberculosis programs in the pre-chemotherapy era and also with the so-called DOTS-Plus strategy for multidrug-resistant tuberculosis, which is far more complicated than the Union model. As with DOTS-Plus, the arguments for starting anti-retroviral treatment programs are often defensive, such as the argument that the drugs are being used anyway, so it is better to provide treatment within a structured framework.[82] Once the anti-retroviral treatment strategy is fully developed, integration with tuberculosis control may be ideal at the service delivery level, where patient care is by necessity integrated, but not the central level. Nor is it necessarily convenient to have a single "integrated" program manual. This is not strictly necessary, and the pros and cons should be considered. One thing to consider is that at this early stage, frequent updating may be needed regarding HIV/AIDS care but not for tuberculosis.

When discussing the collaboration or fusion of programs, another issue worth considering is the recent tendency to fragment existing programs. There has been a tendency to split the tuberculosis program up into different entities. There is the DOTS strategy, which by now is sometimes called "classical" DOTS, and there is DOTS for prisoners, DOTS for refugees, and—in some settings—even DOTS for VIPs. There is also the DOTS-Plus strategy or strategies. It seems increasingly necessary to stand guard and insist that there should be one national tuberculosis program for the sake of continuity of care, visibility of consequences, comprehensiveness of evaluation, and the facilitation of policy making, prioritizing, and financing.

The health services level

The WHO lists prevention and control of endemic diseases as the role of primary health care, whereas some list the definitive diagnosis and treatment of tuberculosis as a specialized activity to be carried out at secondary care level.[10] The issue is debatable, as is the issue of the border between primary and secondary care. This is also a question of policy and cost. In the 1960s there was debate regarding how decentralized the various activities of tuberculosis programs regarding diagnosis, treatment, and evaluation could or should be in developing countries.[83] Some were optimistic regarding centralization, seemingly underestimating the logistical problems involved and the importance of capac-

ity building for tuberculosis control in the long term. At the other extreme, there were those who promoted decentralization, seemingly underestimating the need for training and supervision.

In the 1960s, it was commonly believed that people preferred specialized services and institutions to multi-functional health services. A study conducted by Nagpaul et al. in India challenged this view.[78] That study, which was based in the specialized tuberculosis services in Bangalore District, revealed that neither the general health services nor the population, not even urban residents, used the specialized tuberculosis clinics in the city as expected. As a rule, individuals did not go directly to the tuberculosis clinics, but rather sought care elsewhere when they developed symptoms, and other health care providers did not necessarily refer to the tuberculosis clinics as expected. Eventually, patients found their way to the clinics, either on their own initiative (presumably because their problems were not being solved elsewhere) or because they were referred to the clinics by other care providers (see Table 7.1). The majority of those attending the specialized clinics, whether they were urban or rural residents, were self-referred (see Tables 7.1 and 7.2). Most had received nonspecific treatment, but some had been partially treated for tuberculosis by the time they attended the clinics, and prevalence of drug resistance in this group was high. The investigators concluded that the general health services should be properly equipped and prepared to diagnose and treat tuberculosis, preventing any early mismanagement of the disease and making routine referral unnecessary. In other words, tuberculosis services should be an integral part of the general health services.

A study reported by Gothi et al. in 1970, also from Bangalore, came to a similar conclusion.[84] Their study was based in dispensaries within the general health services and showed that patients with symptoms of tuberculosis did not bypass the general services for the specialized clinics. The investigators

Table 7.1 Reasons for attendance at tuberculosis clinics*

		Source of previous treatment			
Reason for attendance	*Attendance*	*None n* (%)	*General hospital n* (%)	*Private practitioner n* (%)	*Other, or no data n* (%)
Self-referral	1220	479 (39)	304 (25)	287 (24)	150 (12)
Referred	780	NA	497 (64)	209 (27)	74 (9)
Total	2000		801	496	224

*Bangalore District, India, 1960s. Adapted from Nagpaul et al.[78]
NA, not applicable.

Table 7.2 Distribution of care seekers at tuberculosis clinics and case yield by residence and reason for attendance*

	Urban attendance			*Rural attendance*		
Reason for attendance	*n* (%)	*Cases n*	*Case yield %*	*n* (%)	*Cases n*	*Case yield %*
Self-referred	1024 (63)	57	6	196 (54)	26	13
Referred	611 (37)	52	9	169 (46)	30	18
Total	1635 (100)	109	7	365 (100)	56	15

*Bangalore District, India, 1960s. Adapted from Nagpaul et al.[78]

concluded that dispensaries should be involved in diagnosis and treatment of tuberculosis.

The obvious advantage of having the tuberculosis services within the general health services is that they improve coverage and prevent the tuberculosis program from receiving partially treated patients. Nagpaul et al. concluded that services should take note of the social expectations and behavior of the population, such as the utilization of services.[78] They also concluded that all facilities participating in tuberculosis control should be able to diagnose and treat tuberculosis. The Union recommendations do not agree with this last point. Instead, they advise that the roles and responsibilities of each type of health facility be clearly spelled out, aiming for appropriate level of implementation of the various activities in the tuberculosis program.

In the model, all health facilities within the general health services, whether private or public, should be able to identify and refer patients with symptoms of tuberculosis. An adequate volume of specimens is considered necessary to guarantee proficiency in acid-fast sputum microscopy, so this procedure should not be performed in all health facilities. However, what constitutes adequate volume in acid-fast microscopy is not entirely clear. To date, this matter may be insufficiently studied. The participation of health facilities in treatment of tuberculosis depends on the setting and should, as a minimum, be under the supervision of designated units, as discussed further on. Still, there is little hard evidence regarding this matter and recommendations of volume ranges are not easy to make. Adequate volumes are likely to be context-specific and depend on variables such as training and supervision. Some examples from the field are presented in Box 7.4.

The tuberculosis management unit

In the Union model, specialized or semi-specialized personnel ("tuberculosis managers") have overall responsibility for tuberculosis control within the area

Box 7.4 The volume-outcome relationship in tuberculosis services

In the Bangalore District of India, with a population of 1.3 million and 15 microscopy centers (average population per center approximately 85,000), a study of nine centers from 1963 to 1965 supported the decentralization of microscopy to this level, but demonstrated that supervision and quality control were essential in order to achieve uniform quality in such a network.[85,86] Quality assessment identified centers with suboptimal performance (three out of the nine centers included in the study) and the nature of the problems (smear preparation, staining, and reading). The error rate depended on the method used in identifying errors and varied importantly by center. Overall, under-diagnosis (false negatives) was an important problem, whereas over-diagnosis (false positives) was less common and was traced to fewer centers.

A study group in 1980 advised that the level to which microscopy should be decentralized needed to be studied.[87] Many have since warned against the further decentralization of microscopy, arguing that the prevalence of tuberculosis is low compared to many other infectious diseases. Fewer than five smear-positive cases can be expected in a year at a typical health center covering 10,000 inhabitants,[88] and it is considered difficult to maintain a high quality of acid-fast microscopy with a low workload. Experts in the United States claim that, to maintain proficiency, a minimum of 500 slides should be processed in a laboratory annually,* but this presumably refers to a low-prevalence setting.

In rural areas in the Philippines, a health care facility covers a population anywhere from 10,000 to 60,000, and rural laboratories may examine, on average, 40 to 100 tuberculosis suspects annually (corresponding to 100 to 300 slides) with 10 to 20 smear-positive examinees.[89] A study in 2004 found that the differences in quality between large and small centers were not significant, but that the differences between cities and provinces were.[89] All laboratories located in the cities processed over 1,500 slides annually, but 60% of laboratories in the provinces processed less than 500. Factors other than volume may impact proficiency, such as qualifications of staff, training, supervision, and quality-improvement procedures. As discussed elsewhere, variability is likely to be greater among low-volume providers, making quality assurance even more important despite the fact that, in a decentralized system, it is a logistical challenge and labor intensive.

In a clinical trial in the United States in the 1980s, self-administered noncompliance was positively associated with large clinic size, defined as enrollment in a clinic with more than 55 study patients (enrollment in the trial took place in October, 1981 to March, 1986).[90]

A U.S. survey carried out in California's San Diego County in the late 1990s suggested that specialists in pulmonary medicine and infectious diseases and physicians who had treated six or more patients in the past two years were more likely to give answers in agreement with health department policies.[91] However, response rate was low in this survey and the measure of quality was indirect (that is, cases were not reviewed).

(*continued*)

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*Quoted in Endo et al.,[89] p. 293.

Box 7.4 *Continued*

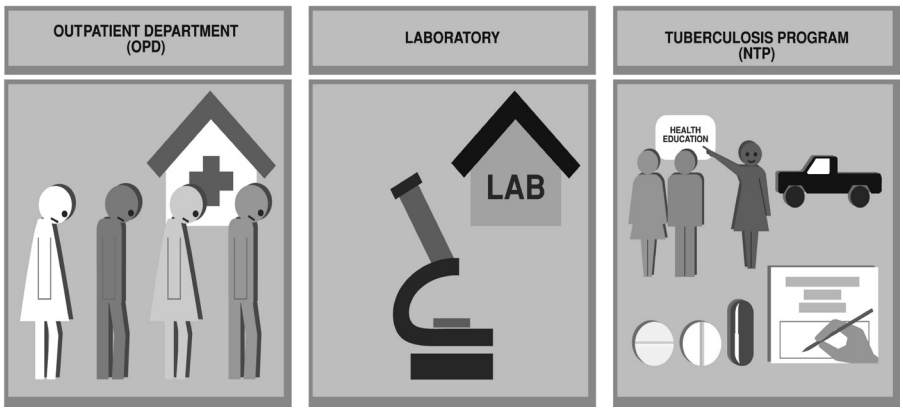
In Botswana, a study found that, in 1997, being diagnosed in a hospital outpatient setting versus a clinic and being diagnosed in a high-volume versus a low-volume unit were both risk factors for treatment delay or nonregistration.[92] The definition of a "high-volume clinic" in this study was one that saw 15 or more patients in the 19-week study period, while a "low-volume clinic" saw fewer than 15 patients in the same period.[92] The median number of patients seen in high-volume clinics was 20 (equivalent to 55 per year) and in low-volume clinics it was four (equivalent to roughly 10 per year).

A 2000 to 2001 study in Djibouti suggested that there was a negative relationship between volume and performance. The relationship ceased to be significant as more established centers became, with experience, more capable of dealing with a high workload.[93] The investigators concluded that the optimum workload per facility in Djibouti was 50 to 200 smear-positive patients a year, depending on experience.

An observational study in the Northern Cape Province in South Africa, from 1999 to 2000, found that rural residence was associated with a higher likelihood of successful treatment outcome. This was thought to result from the fact that rural clinics in the study tended to have fewer patients than the urban settings. The nurses at these clinics generally had more time to trace defaulters and bring them back to treatment.[94]

served by what is referred to as a tuberculosis management unit.[76,95] The tuberculosis management unit is located within the general health services, ideally in health centers. As depicted in Figure 7.6, the health center has a triage (outpatient clinic) where patients with symptoms suggesting tuberculosis are identified and referred for sputum examination, a multi-purpose laboratory where

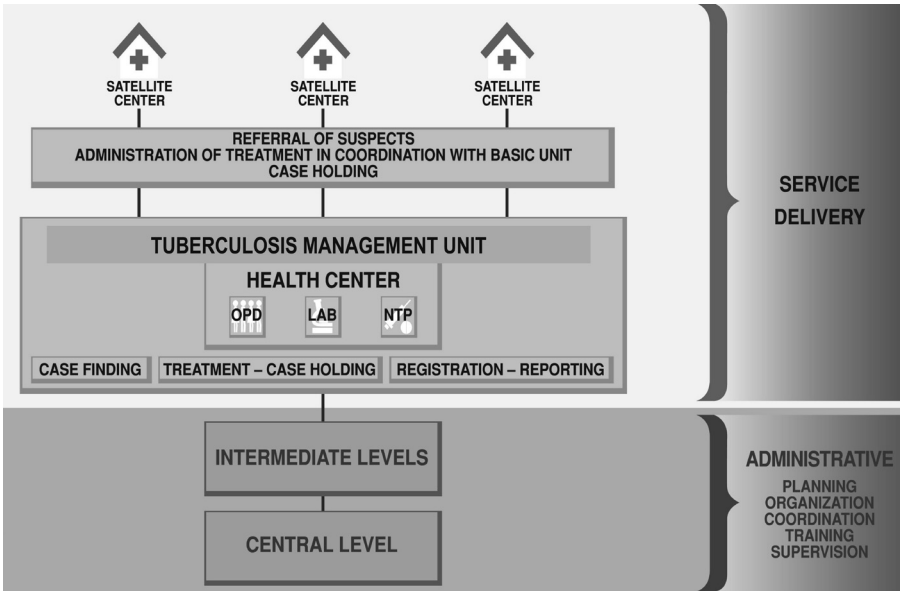
Figure 7.6 The tuberculosis management unit



acid-fast microscopy is performed, and a tuberculosis clinic, where patients are registered, enrolled in treatment, and supported throughout treatment.

Many activities are performed in health facilities granted the status of tuberculosis management units: planning and organization of tuberculosis control in a defined area, diagnosis of tuberculosis by sputum smear microscopy, registration and notification of cases, materials management, treatment and follow-up of tuberculosis patients, reporting of outcome of treatment, and health education and support to patients. The tuberculosis management unit is linked with more peripheral health facilities that serve defined subpopulations. These are referred to as "satellite centers." The role of satellite centers in tuberculosis case finding is important and, depending on the setting, satellite centers can be involved in treatment of tuberculosis under the supervision of tuberculosis management units. The role of satellite centers can be summarized as referral for assessment of symptoms and follow-up of tuberculosis patients during treatment. A supervisor from the intermediate level of the health care system, who is supported by the central level, supports the tuberculosis management unit. The tuberculosis management unit, in turn, supports the satellite centers. The resulting organizational structure of the tuberculosis program is depicted in Figure 7.7.

Figure 7.7 Organization of tuberculosis services



OPD, outpatient department; LAB, laboratory; NTP, national tuberculosis program.

Hospitals

In the majority of tuberculosis cases, hospitalization is not needed and can be harmful if it increases the risk of nosocomial transmission of *M. tuberculosis*, which is particularly worrisome in the era of HIV/AIDS and multidrug-resistant tuberculosis. The logical role of hospitals in tuberculosis control is the prompt diagnosis of tuberculosis in patients who happen to be admitted to hospital for whatever reason, and the management of severe and complicated cases and comorbid illnesses. Nevertheless, where there are hospital beds, they tend to be used, and not only in developing countries. A study in Italy, reported in 1999, showed that pulmonary centers with beds hospitalized 88% of their tuberculosis patients. By comparison, pulmonary centers without beds hospitalized only 28% of their patients.[96] The majority of hospital centers (64%) claimed to hospitalize all tuberculosis patients, but the majority of non-hospital centers claimed to hospitalize only selected cases. In a study in Malaysia in the 1980s, 90% of tuberculosis patients were hospital referrals.[97] Similarly, a study in Australia, reported in 2001, found that 90% of tuberculosis patients had tuberculosis treatment initiated in a hospital.[98] In Managua, Nicaragua, where it is program policy that health centers are responsible for managing tuberculosis, a review found that 74% of sputum smear-positive patients had been diagnosed in health centers, suggesting that no more than 26% were diagnosed in hospitals.[99]

Hospital emergency departments are important entry points for high-risk population groups in cities. In low-prevalence countries, tuberculosis may be largely confined to marginalized urban population groups, and these groups frequently use hospital emergency departments rather than other health facilities, as demonstrated for example in a Canadian study in the 1990s.[100]

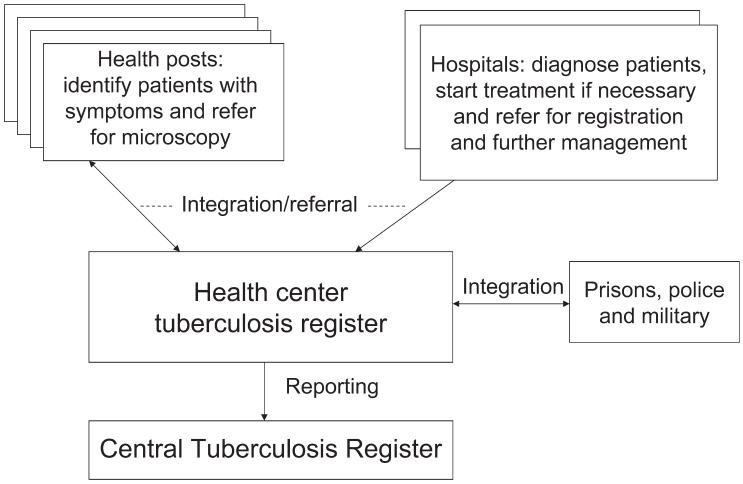
Finally, in some settings, hospitalization of tuberculosis patients is a complex issue. A 1999 to 2002 study conducted in Samara Oblast, Russia, found that socioeconomic factors influenced hospital admission patterns and the length of stay for tuberculosis patients when hospitalized, as the providers of tuberculosis services attempted to mitigate the lack of social care provision for patients.[101] Male, unemployed, and disabled adults were more likely to be hospitalized. The investigators pointed out the importance of addressing the links between the health system and the social sector when implementing policies aimed at minimizing hospital stays.

Coordination of reporting

In the Union model, the tuberculosis management unit keeps a tuberculosis register and reports to the Central Tuberculosis Register. As a reporting unit, it keeps track of the entire process of care, with the main purpose being continuity of care and visibility of consequences. Figure 7.8 demonstrates coordination of reporting in a system where health centers serve as tuberculosis man-

Figure 7.8 Coordination of reporting in tuberculosis control

In this example, health centers serve as tuberculosis management units, health posts as satellite centers, and hospitals refer patients to the health centers. There is coordination with other sectors, such as the prison sector, to avoid double reporting and to allow both continuity of care upon imprisonment and continued treatment for prisoners who have not completed a full course of treatment when released. Coordination with the private sector is also important.



agement units, health posts as satellite centers, and hospitals refer patients to the health centers. There is coordination with other sectors, such as the prison sector, to avoid double reporting and to allow both continuity of care upon imprisonment and continued treatment for prisoners who have not completed a full course of treatment when released. Coordination with the private sector is also important.

Where hospitals and chest clinics play a large role in tuberculosis care, it is important that the tuberculosis program acknowledge this reality. Coordination with hospitals and chest clinics in Yogyakarta, Indonesia, resulted in a large increase in notification of cases in 2004 compared to 2000.[102]

Decentralization of tuberculosis services

The public sector services

There is no absolute rule for the planning of all health services. For example, the management of diarrhea would, ideally, primarily take place in the household, whereas malaria and acute respiratory infections may need to be managed in peripheral facilities at least in rural areas. By comparison, tuberculosis

is a relatively rare disease, even in high-prevalence settings. Most people never get tuberculosis and most people who are examined for tuberculosis do not have it. Its onset is often insidious and its treatment is comparatively complicated and of long duration. Not only absolute caseloads but also relative caseloads diminish with decentralization of services, as the prevalence of tuberculosis is related to population density.[103]

One of the studies carried out in Bangalore in the 1960s showed that distance from specialized tuberculosis clinics in cities affected the attendance of both rural and urban residents.[78] Distance seemed to exert a continuous selection process. Beyond a limit of five km from a clinic, the number of attendants decreased and the case yield among attendants increased. In this study, the effect of distance was overwhelming compared to the impact of the number of symptoms or their duration. While those with longstanding and serious symptoms will sometimes travel far for treatment, the important questions are: at what cost do patients make a long journey for care, and how many patients with tuberculosis do not make the journey at all? This is a strong argument for decentralizing the services. On the other hand, the quality of health care is important for safety as well as impact. Access to low-quality health services is not real access. Decentralization, therefore, must be properly planned, managed, and evaluated.

As a general rule, population-based planning[67] can be appropriate for tuberculosis programs in high-prevalence countries. Taking into account quality, accessibility, and cost of services, a convenient organizational level for the tuberculosis management unit is a center of diagnosis and treatment serving, on average, a population of 50,000 to 150,000 persons.* Further centralization may jeopardize both accessibility and quality of care. Further decentralization may also affect quality, make evaluation difficult, and increase the cost. Apart from this general rule, population density and local characteristics are important and must be taken into account. Table 7.3 shows how the estimated workload varies with the rate of tuberculosis and population size. For example, in a setting with a notification rate of 200 new smear-positive pulmonary cases per 100,000 population in urban areas and 50 per 100,000 in rural areas, it should be possible to maintain proficiency in a network having one tuberculosis management unit with laboratory services for 100,000 population, with the equivalent of a full-time laboratory technician in the urban setting and a part-time technician in the rural setting. Often it is preferable to have services more centralized in

*The term "district" is not uniformly defined, so it is not used here. Even if a district is sometimes defined as an administrative unit serving a population of 100,000 to 200,000,[41] the population in districts varies greatly between, and even within, countries. Therefore, it may be confusing to use the term district in planning. For example, in India the so-called District Tuberculosis Program referred to districts with population of 1.5 million.[104]

Table 7.3 Estimated annual workload by rate of smear-positive tuberculosis and decentralization of services

Rate PTB-positive	*Population served*	*PTB-positive cases annually*	*Slides examined**	*Technicians required†*	*On treatment in any given month‡*	*Intensive phase*	*Continuation phase*
200	150,000	300	9900	1.7	200	50	150
200	100,000	200	6600	1.1	133	33	100
200	50,000	100	3300	0.6	67	17	50
100	150,000	150	4950	0.8	100	25	75
100	100,000	100	3300	0.6	67	17	50
100	50,000	50	1650	0.3	33	8	25
50	150,000	75	2475	0.4	50	13	38
50	100,000	50	1650	0.3	33	8	25
50	50,000	25	825	0.1	17	4	13
25	150,000	38	1238	0.2	25	6	19
25	100,000	25	825	0.1	17	4	13
25	50,000	13	413	0.1	8	2	6

*Assumption 1: 33 slides examined per smear-positive case diagnosed.
†Assumption 2: one full-time technician examines 6000 slides per year.
‡Assumption 3: treatment with 8-month regimen.
PTB-positive, pulmonary smear-positive tuberculosis.

urban areas, but it should be kept in mind that the need for staffing does not necessarily decrease except in the laboratory if, with the centralization, fluorescence microscopes are introduced. The centralization of sputum smear microscopy, however, renders the services less accessible.

It can be quite difficult to establish microscopy services in peripheral units and, sometimes, most of the patients continue to be diagnosed elsewhere and are either registered locally or recorded as "transfer-in." While the notification rate may seem to suggest that proficiency can be maintained, if none, or only a few, of the smear-positive patients are diagnosed locally, then this is doubtful and it should be questioned whether the local laboratory is reliable enough to be trusted with follow-up examinations. This situation reflects failure in decentralization with regard to the laboratory component of the tuberculosis services.

Examples from the field regarding planning and decentralization of the public sector services are presented in Boxes 7.5 and 7.6.

Throughout the years, there has been some concern that the structure described above does not guarantee access to diagnosis and treatment. An article from India published in 2002 suggested involving accessible private sector laboratories.[110] An earlier article from 1985 suggested that "community health

Box 7.5 Population-based planning

In Nicaragua (population 5.3 million in 2002 with over 50% urbanization), the tuberculosis management unit was the health center. There were roughly 160 health centers with laboratories for an average of approximately 33,000 inhabitants per tuberculosis management unit, the ratio generally being higher in urban and lower in rural areas. Health posts referred care seekers with symptoms of tuberculosis to the health centers, and hospitals referred tuberculosis patients to health centers. The health centers were responsible for the registration and reporting of tuberculosis patients to the Central Tuberculosis Register via the intermediate level. A nurse or auxiliary nurse was responsible for all aspects of the tuberculosis services in a health center, supported by a general physician. The nurse coordinated with other members of the health center staff and peripheral health posts, depending on local circumstances.

The population of Laos was approximately 5.5 million in 2000. Urbanization was only 15% and population density was very low: on average 19 persons per square km.[43] Population size varied from 70,000 to 700,000 by province. Population density varied from 8 to 135 people per square km. Population also varied importantly by district, from 8,000 to 124,000. The tuberculosis management unit was in the district hospital. However, not all district hospitals qualified. Those serving very small populations were not designated as tuberculosis management units. In the least populous provinces there was only one tuberculosis management unit, located in the provincial hospital. In the first five years of the program (from 1995 to 2000), an attempt was made to involve district hospitals serving small populations but the results were not encouraging.

An article from Nepal described the decentralization of tuberculosis services to ten units: a general hospital and nine health posts, in an area with a population of 648,000. Case rates were lower in remote and hilly areas compared to subtropical plain and urban areas. The authors claimed that it was difficult to maintain proficiency in acid-fast microscopy in health posts with very low workloads.[105]

guides" (one for every village of 1,000 people) and "community health workers" (one for 5,000 population) should collect sputum samples, prepare fixed smears to send on to a health center, and administer anti-tuberculosis treatment in case a patient is diagnosed as having smear-positive tuberculosis.[111] Sending unprocessed sputum samples is generally not recommended, as there is a certain risk involved with such a strategy. It is preferable to send fixed sputum smears. The problem with this strategy, however, is the possibility that the sputum samples or their preparation will be of low quality and cases might be missed. While such problems could be detected by a quality control system, it is a logistical challenge establishing effective quality control within such a network. Furthermore, peripheral units and community health guides involved in tuberculosis treatment must be supervised. Experience shows that little time is spent on supervision at the most peripheral points in general health services.[27]

Box 7.6 Decentralization

An intervention study in a rural district with a population of 230,000 in South Africa looked at the effects on outcome when decentralizing tuberculosis treatment (1998).[106] The patients were diagnosed in the district hospital, received treatment as inpatients for three to four weeks, and then continued treatment depending on area of residence. The patients residing within the area served by six randomly selected peripheral clinics continued treatment at the hospital outpatient department. Patients residing within the area served by another six clinics continued their treatment at those respective clinics. The overall results showed 75% treatment success. Treatment success rate was worse for patients from outside the district (58%), which is a common finding and demonstrates the importance of studying why patients seek care outside their district of residence and how the overall system can better serve these patients. On the other hand, reasonably good results were obtained for district residents regardless of decentralization (82% versus 88%). Decentralized services were better accepted by the patients and should be preferred in this setting, as it does not seem to jeopardize outcome. In this example, the district hospital functioned as a tuberculosis management unit and the 12 peripheral clinics served as satellite centers. While it is a debatable strategy to decentralize acid-fast microscopy to all the peripheral clinics, access could be improved over and above having only one tuberculosis management unit in this population of 230,000. The decision whether to establish additional tuberculosis management units would depend on population density and distribution, disease burden, and the mobility of the population.

A study of patients registered from 1992 to 1997 in the Rakai District of Uganda found a 92% treatment completion rate among survivors, compared to 57% in a district where services were not decentralized.[107] The population of the Rakai District was 450,000, with about 80% of the population living within an hour's walking distance of a health facility. Tuberculosis services were reorganized so that five health facilities provided acid-fast microscopy services (two hospitals and three health centers). The average population per laboratory was 90,000. Additionally, treatment was administered in 15 peripheral health units that were distributed fairly evenly throughout the district. All in all, there were 20 treatment units (one per 22,500 population). Chest radiography services were only performed in the hospitals. In the comparison district, patients were hospitalized for the intensive phase of treatment in six health units and some were later referred to peripheral units for the completion of treatment. By contrast, in the Rakai District, treatment was on ambulatory basis from the start, and the entire course of treatment provided in a single health unit.

A 2002 study in Ethiopia found that a higher defaulter rate was recorded in health stations than in health centers, even if the former were considered more accessible.[108]

In the late 1990s, Sudan followed the recommendations of The Union in decentralizing diagnosis and treatment of tuberculosis from large tuberculosis institutions to tuberculosis management units in selected primary health care clinics based on the population served (an average population of 100,000). In 2003, El Sony et al. reported on the effect of decentralizing tuberculosis services in three sites (Khartoum, Red Sea, and Gadaref States).[109] They found that two thirds of all patients were diagnosed in referral hospitals and one third in primary health care facilities, but observed a trend

(*continued*)

Box 7.6 *Continued*

in favor of the latter during the study period (1997–2001). The findings suggested that a higher level of access existed for female and elderly patients in primary care facilities than in the referral hospitals. A higher proportion of patients were treated with short-course treatment in the primary care clinics than in the hospitals (76% versus 62%), evaluation was more complete (95% versus 72%), and among those evaluated there was a higher success rate (75% versus 67%) and a lower defaulter rate (12% versus 17%) in the clinics.

A study in Djibouti (2000 to 2001) found that urban decentralization of directly observed treatment increased the chances of treatment success among smear-positive patients.[93]

Consequently, the long-term feasibility and safety of such a strategy may be questioned.

"Community-based" services and community participation

As previously mentioned, "community-based services," "community health workers," and "community participation" are widely used terms that are often vaguely defined. What is community contribution to tuberculosis care? According to Maher et al. in 1999, the overall responsibility for tuberculosis control should always remain with the program, and community activities should be part of, rather than substitutes for, the activities of a national program.[24] They define "community health workers" as community members who are involved in health activities in the community but are not formal government employees and who may or may not receive incentives.[24] Others reserve the term "health worker" for qualified and (government) employed personnel only. In 2000, Hadley and Maher divided community involvement into "formal" and "informal" involvement, the former describing community health workers, village health workers, and traditional birth attendants who play a part within the infrastructure of the health services and the latter describing the participation of neighbors, family members, and others in support to patients.[30] Others might classify only the latter as community involvement, which seems more straightforward.

In 1986, the Orange Guide encouraged "indirect" (presumably corresponding to "informal," above) community participation, arguing that it might contribute to case finding by encouraging people to seek medical advice if they develop symptoms referable to tuberculosis.[112] It might also contribute to treatment by encouraging the patients' compliance.[112] Maher et al. argue that the establishment of a tuberculosis program is a prerequisite for teaching the community how to contribute to the work.[25] They point out that, in the period since the 1980s, many countries have implemented tuberculosis programs, thus pav-

ing the way for community contribution. Others might see this as a "top-down" approach. Hadley and Maher list potential forms of community involvement in tuberculosis control: raising awareness of the disease and its treatment, referring individuals for case detection, providing access to drugs via either community drug schemes or free distribution of drugs, addressing stigma, facilitating adherence to treatment, administering directly observed treatment, "late patient" tracing, and providing general support to patients.[30]

Those in favor of providing care for tuberculosis patients "in the community" claim that doing so will reduce patient load on hospitals and health centers, decrease costs to patients and their families, improve adherence by making treatment more accessible, and reduce transmission of *M. tuberculosis* in health facilities.[25] Others look at community-based care as a vertical approach that allows vertical programs to bypass, rather than contribute to, the basic health services. Some even argue that community-based care could increase stigmatization if it is interpreted as a strategy of turning away patients with infectious diseases. However, the main concerns associated with community participation are quality of care, motivation, accountability, and long-term sustainability.

It is important to acknowledge that community involvement is not a magic bullet and that if the tuberculosis problem—or any other health problem—is not manageable within the health service, then there are several options for action: improving and adapting the health service or changing the approach (to abandon the strategy of directly observed treatment, for example). In any case, more resources are needed. Last but not least, when contemplating community participation in tuberculosis treatment or curative care in general, conflicting priorities in this field and competition with other community health work, other community work, and other work of community members must be considered.

Some examples from the field are presented in Box 7.7. The participation of laypersons in directly observed treatment is discussed in Chapter 5.

The private sector

Involvement of the private health sector in tuberculosis control is not a new idea. Wherrett (in 1957) and Fox (in 1968) discussed the importance of coordination and referrals between different health providers and sectors.[83,117] Continuous reporting of notifiable diseases, for which it is mandatory that cases be brought to the attention of health authorities, is the cornerstone of disease control strategies.[11] Regarding tuberculosis, mandatory reporting of disease occurrence is important for bringing together all those involved in diagnosis and treatment of tuberculosis for a concerted effort to control the disease. However, the private sector is often poorly regulated in low-income countries. The necessary legislation is often lacking, and in any case, enforcing mandatory reporting when it comes to the private sector is a challenge in any country. A study

Box 7.7 Experiments with "community participation" in tuberculosis control

A 2001 report from Ethiopia described "TB clubs" made up of tuberculosis patients who supported each other and, at no cost to the health service, identified and advised people who might have the disease.[52] Attendance for scheduled treatment appointments improved with the establishment of these clubs. This initiative led to the formation of local tuberculosis community associations. Membership in these associations was open to all interested parties, as opposed to the clubs, where membership was restricted to patients.[113] This type of community participation resembles what occurred in Western countries in earlier times. The project in Ethiopia, however, was not sustained.

A 2002 report from South Africa looked at the motives of lay volunteers in tuberculosis control.[114] The study was performed in the Northern Cape Province, an area with high unemployment. Lay volunteers, who received four days training, administered treatment to patients at home. There were many volunteers per clinic, the large majority of whom were young females. Although they did not receive any monetary incentives, the hope for eventual remuneration was found to be the strongest factor motivating them to join the program. As the novelty of the project wore off, interest waned. Within a year of joining the program, 22% of the volunteers had dropped out, three out of four because they had lost interest or desired paid work. These results raise concerns for sustainability of the strategy in the long term.

Another study in South Africa, reported in 2002, investigated the involvement of indigenous nongovernmental organizations in the community-based administration of treatment.[115] Again, the issue of expectations for funding surfaced. Lack of adequate funding limited the scope of activities of the participating organizations, and one of the consequences was lack of reliable information about the impact of their involvement. This left potential financiers of the scheme skeptical of the value of involvement of nongovernmental organizations. Another problem identified was rivalry and competition among the organizations.

In the 1990s, community care organizations sprang up in relation to HIV/AIDS programs, and many of them claimed to provide tuberculosis care. In 1997, Maher et al. reviewed several such projects in sub-Saharan Africa. Most of the programs concerned hospital-based organizations that provided care through mobile teams to patients initially seen at the hospitals.[25] They found that performance was poor: delayed diagnosis of tuberculosis, shortages of anti-tuberculosis drugs, low treatment completion rates, high default rates, inadequate recording, little interaction with local tuberculosis programs, and inadequate training of the staff.[25] They concluded that the general health services had failed to recognize the potential of community care services for tuberculosis control, but also acknowledged the lack of sustainability and high turnover of workers in the community-based programs, issues that are likely to limit the impact of such programs in the long run.

A study of three home-based care organizations and a hospice project in Lusaka, Zambia (2005), where one half of the care recipients were tuberculosis patients, found that management was undermined by poor record keeping, shortages in anti-tuberculosis drug supply, stigmatizing health education, limited supervision of the caregivers, and poor coordination with the district health services.[116] As is often the case, the majority of the volunteers were middle-aged women, relatively well educated, and poor. The involvement of the organizations was not a direct government initiative, but rather seemed to have emerged in the community in response to need.

in South Korea in the 1990s found that 50% of the general practitioners surveyed did not notify the health authorities of new cases of tuberculosis.[118] The main reasons they gave were that they were not aware that this should be done and the complicated paperwork involved. In this respect, there are two main problems related to an unregulated private sector: the size of the tuberculosis problem is underestimated by official statistics and the output of total control efforts is unknown, that is to say, evaluation is incomplete. As a result, there will be an underestimation of the need for public financing of treatment for tuberculosis and, in a worst case scenario, the public sector will be confronted with drug-resistant cases who have previously been treated in the private sector.[119]

Regarding tuberculosis, individual private practitioners are often low-volume providers.[120] In many Asian countries, private practitioners commonly constitute the first provider contact for patients with tuberculosis. At the turn of the century, studies of a rural area in Nepal and of mixed rural and urban populations in South India found that every other tuberculosis patient had first contacted a private health care provider, whereas only one quarter had contacted a government medical establishment as a first choice.[110,121] Private practitioners, for various reasons, may be reluctant to refer tuberculosis patients to the public services where there is a national tuberculosis program, and may prefer to operate alone.[122,123] Various studies suggest that a longer delay in diagnosis occurs when private practitioners are the first care providers consulted and that poor performance among private practitioners can be expected in tuberculosis treatment. A prospective comparative cohort study in Ho Chi Minh City, Vietnam, found that treatment success was considerably worse in a "semi-private" chest clinic (49%) than in the national program (85%)—even if there was considerable overlap of the public and private sector in this setting, that is to say, if the private clinic was on the premises of a government hospital and the chest specialists from the hospitals worked after-hours in the clinic.[124] The services at the clinic were fully paid by the patients (out-of-pocket) even if one quarter of the patients had no regular income. The difference in outcome did not appear to be explained by patient-related factors. The findings suggest that a private health care market might attempt to meet patients' demands by compromising safe treatment strategies and, therefore, may fail to produce optimal public health outcomes.[124]

Private pharmacies are an important source of medical care in many developing countries. Their role may include dispensing anti-tuberculosis medicines.[110,125–127] The private distribution of these drugs constitutes a threat for tuberculosis control; the uncontrolled sale of anti-tuberculosis drugs is a risk factor for the development of drug resistance. It is difficult, if not impossible, to know whether patients who receive anti-tuberculosis medicines from private pharmacies actually have tuberculosis. It is commonly recognized in low-income countries that regulatory approaches to controlling the pharmaceutical

Box 7.8 Tuberculosis and the private sector

In 1999, it was reported from Ho Chi Minh City, in Vietnam, that private pharmacies constituted a weak link in the referral chain, delaying the diagnosis of tuberculosis.[125] The study found that the delay was due more to inability of health care providers to detect tuberculosis than to underutilization of the health services, and concluded that diagnostic procedures needed to be improved and referral chains strengthened. This study, which was based in the tuberculosis program, also confirmed the phenomenon that many programs in settings where there is a prominent private sector face: tuberculosis patients who are diagnosed by private practitioners receive treatment, then interrupt it, and, eventually, seek care in the public sector services (in this study, on average 4.2 weeks after interruption of treatment, with a range of 1 to 16 weeks), by which time they are smear-negative.

In 2001 a "public-private mix" project was launched in Ho Chi Minh City, linking private providers with the tuberculosis program. Two years later, a borderline increase in notification was observed. However, problems occurred at several levels: many patients were not assessed with sputum microscopy or were sent to private and non-credited laboratories; many who were advised to contact the national program were not willing or able to do so; and many of those diagnosed with tuberculosis defaulted before starting treatment.[128] Furthermore, in a project that did not involve free or subsidized drugs for private clinics, there was low treatment success with a high defaulter rate in private clinics (34% among new smear-positive cases).[129] This was in spite of a financial incentive for private providers linked to the completion of treatment. The reason most commonly reported by patients for defaulting was that they could not afford treatment (38%). In this setting, many private providers made a fair share of their income from selling drugs to patients. Another project, involving pharmacies in Ho Chi Minh City, reported limited success.[130]

A 2001 report from India described a "public-private mix" in Hyderabad where a nonprofit hospital recruited private practitioners to refer patients and provided tuberculosis treatment in collaboration with small hospitals operated by private practitioners.[131] It is of note here that there were practically no public sector services in the study area. All 358 physicians practicing in the area agreed to participate, and 59% referred at least one patient. One half of the 2,244 care seekers assessed at the hospital in the study period were self-referred, and 43% of all referred patients had tuberculosis. The proportion of smear-positive tuberculosis among cases was rather low, but reported treatment success was high. Private practitioners applied radiology prior to referral in 80% of cases. The investigators commented that they possibly only referred patients who could not afford to pay for their services. The services at the main hospital, diagnosis of tuberculosis and initiation of treatment, were free of charge for all patients. Directly observed treatment was provided free of charge in conveniently located facilities. Private practitioners who provided space and staff for treatment observation found that doing so did not interfere with their routine work. Furthermore, being considered as an official center increased their status in the community, and care of inter-current illnesses during and after a full course of anti-tuberculosis treatment may have increased their patient population and earnings in the long run.

Box 7.8 *Continued*

An experimental project in Kannur District, in Kerala State, India, encouraged notification of smear-positive cases after assisting in the implementation of sputum microscopy in private sector laboratories.[132] The project was developed and implemented by the local tuberculosis program with minimal additional financial or external technical assistance, and participants received no incentive other than training and supervision. Evaluation assessed the contribution of private laboratories to notification of smear-positive cases to the national program in the study period (2001–2002), and whether notification was complete (allowing for three months' delay in registration for treatment). The evaluation found that private laboratories had detected 17% of notified cases and that their cases were more likely to be new cases and female. Forty-three percent of cases identified in the private laboratories could not be matched with a notification to the national program. This project represents a promising first step in addressing the issue of mandatory notification of tuberculosis.

sector, widely endorsed on paper through national legislation, are difficult to enforce.[127]

In line with recommendations of the WHO, increasing emphasis has been placed on involving the private sector in the tuberculosis control network. When considering involvement of the private sector, the approach can target clinicians, laboratories, and pharmacies. Some examples from the field are presented in Box 7.8.

To this day, it is frequently argued that patients prefer to contact private practitioners, either because of confidentiality and privacy issues related to stigma[131] or for more personalized services and convenient opening hours.[122] However, patients may use the services of private practitioners simply because they exist and the public services do not, or because the latter do not function properly. Collins et al. point out that involving private practitioners in a meaningful way requires a strong national tuberculosis program, but in many countries the program is weak.[13] If this is the case, they argue, the program needs to be strengthened before attempting to involve private practitioners. But the very act of strengthening the public services is likely to reduce the importance of private practitioners. Consequently, the critical policy question in many countries is whether private practitioners should be ignored, important though they seem to be, to concentrate instead on strengthening the public services currently used only by a minority of patients, or whether time and effort should be invested in attempting to involve a group that, by its very nature, will be hard to influence and control, given weak national tuberculosis programs.[13] Some attempts at involving the private sector in tuberculosis control are presented in Box 7.9.

Box 7.9 The public-private dilemma in policy development

A 1998 study in Nepal found that as many as 50% of all patients in an urban municipality (Lalitpur) in the Kathmandu Valley received treatment in the private sector.[127] The investigators encouraged collaborative efforts between private and public sectors. In another setting, Nawal Parasi, substantial changes occurred in utilization of services over the course of a few years, as management units were opened and improved in the public sector services. In 2001–2002, 77% of women and 80% of men with tuberculosis symptoms consulted at government facilities, compared to 30% and 32% in 1997–1998.[133]

A 2001 study in Cochabamba, Bolivia, suggested that the private sector contributed little to managing tuberculosis and that there was a small market for anti-tuberculosis drugs in private pharmacies.[134] Apparently, anti-tuberculosis drug sales had declined dramatically in the last few years before the study, something that private pharmacies attributed to the increasing visibility of the national tuberculosis program that provided free treatment in public health centers.

With implementation of structural adjustment policies in Nicaragua in the 1990s, financing of public services was reduced. It is claimed that, as a result, the government health services lost some of their prestige and the private sector burgeoned.[135] In 1998, first-line health services offered free health care to women, children under five, and to sufferers of a few priority diseases, such as tuberculosis.[135] A study of three sites in 1999–2000 found that, overall, 35% of patients whose sputum had been examined for acid-fast bacilli had consulted a private practitioner at some point.[135] Time to sputum examination and money spent by the patient were lower for those who exclusively used the government services. Whereas in this situation some would argue for strengthening the private sector for detecting tuberculosis, it can also be argued that this kind of information should be used to boost the credibility of the public services.

Coordination of access and referrals

The tuberculosis program is an end point in the route to tuberculosis treatment, not a starting point. Success in tuberculosis control depends on the efficient recruitment of patients. Recruitment of patients depends on the health system in general much more than on the tuberculosis program. However, the tuberculosis program and specialists can and should take the initiative in pointing out weaknesses in the health system and further developing it to stimulate the recruitment of patients.

Recommendations on structure for tuberculosis control are primarily made based on access and quality of services. Many studies have found that people with tuberculosis will travel long distances to seek care. While this could be interpreted as "willingness to travel" for care, it simply reflects the fact that quality care, or any tuberculosis care for that matter, was not available nearby. The patients included in these studies may have made enormous sacrifices to make

the journey, and it is impossible to say how many other potential patients either perished along the way or were not able to start the journey in the first place and never had a chance to be recruited. Health care should be provided as close to the patient's home as possible. To safeguard quality, however, it is not recommended to decentralize every activity of the tuberculosis program to the most peripheral health units. The main concern is, therefore, the overall structure and coordination within the health system, including access to referral. Supervision and quality assurance at every level, linkage, and crossroad within the system are crucial so that problems are detected and access is facilitated. For example, a report from Malawi, where there was a relatively high transfer-out ratio (13%), found that patients tended to transfer out early in treatment, suggesting a problem in the organization of tuberculosis services, and that the quality of data and evaluation of treatment results for transferred patients was poor.[136]

The referral system aside, when considering access, there is access to and utilization of the health services in general and also the question of the skills of the health personnel. There is also the question of whether services for diagnosis and treatment are provided within the same facility and, even when they are, if the coordination between the two services within a given facility is adequate. Once treatment is started, there is the concern of continuity of care and the final outcome.

Factors that influence access to tuberculosis services

Any delay in the diagnosis of tuberculosis is of concern for various reasons. It may increase the overall cost to patients, compromise outcome, and result in increased transmission.[137] Delayed diagnosis may cause patients to suffer more advanced disease, more complications, and a higher mortality.[138–140] Factors causing delay have been related to the patient or to the health system. Delays from the latter are frequently, but not invariably,[141] found to be longer,[138,139,142,143] and may be more pronounced when patients seek care in outpatient clinics or health centers as well as in rural areas.[138,139,141]

Looking at the pathway to tuberculosis care in a chronological order, there is a time period from the onset or awareness of symptoms until the patient seeks care. It then takes time for the diagnosis to be established once the patient has consulted a care provider. There may be delay when the patient is or is not referred on to another provider. Finally, delays in starting treatment once the diagnosis is established may arise. When these phenomena are studied, it is important to consider the context: the local health policy, including that of the tuberculosis program; the characteristics of the health system; and the circumstances of the population.

It is complicated to study delays in the pathway to tuberculosis care. It cannot be overemphasized that the system does not start at the threshold of

the tuberculosis program. Even when patients knock on the door of the program, they generally are coming from somewhere else within the health system, either self-referred or referred by a layperson or a health professional. It is important to start by defining what is expected to happen given the local policy and what is likely to happen in practice in the study area. Assuming that the tuberculosis services are integrated into the general health services, as in Nicaragua, the following might apply regarding smear-positive pulmonary tuberculosis: first, as a rule, patients would not know that they have tuberculosis and would not be expected to go directly to the tuberculosis nurse, although a few might do just that, if, for example, they are the neighbors or relatives of tuberculosis patients. Most people would seek care in the nearest government health facility or the one they usually visit when they are ill, which for some people would be a hospital, a private practitioner, or a private pharmacy. Second, the symptoms ideally should be recognized right away as meriting assessment for tuberculosis, and the patient should be referred for sputum examination or, if in a health post or at a private clinic, referred to a health center for the same purpose. This is unless patients seek care very early in the process of illness, in which case they might escape assessment for tuberculosis at the first visit even if procedures were correctly followed. Third, given a spot-morning-spot strategy for sputum collection (see Chapter 3), the diagnosis of smear-positive pulmonary tuberculosis could be confirmed by sputum examination on the day after the patient contacts a health center or a hospital, at the earliest, although a positive result already on the spot sample should alert the health worker in charge of infectious tuberculosis on the very first day of attendance. A study would then measure what actually happens compared to the ideal pathway and analyze the influence of different variables.

Serial studies of the pathway to tuberculosis treatment can provide useful information in program evaluation and guide program development,[138] but only if they are well formulated. First, they should focus on sputum smear-positive cases because these are the main sources of transmission and are easily defined. A common weakness in studies of this kind is to analyze smear-positive and smear-negative cases together as one group. Another weakness is to include patients who are detected as a result of screening high-risk population groups, as opposed to those detected from consultations due to symptoms. The former procedure does not reflect care seeking. Finally, it can be difficult to determine the duration of symptoms in patients with chronic underlying pulmonary conditions, such as asthma, and such cases are often excluded.[138]

Definitions of delays en route to tuberculosis care

"Patient delay" is usually defined as the time from onset (recall or awareness) of symptoms—which is often difficult to estimate—to first contact with a health care provider. "Provider or doctor delay" is defined as the delay from contact

with a care provider or doctor until diagnosis or initiation of anti-tuberculosis treatment. Many prefer to talk about "health services delay" or "health system delay" to underline the importance of structural factors. This last group looks at the time from first contact with the health care system to first sputum sample and the time from the first sputum sample, examination, or positive result of acid-fast microscopy to the initiation of treatment.

While it can be useful to divide the total delay into patient delay and health system delay, and the latter then into delay in diagnosis (part of this is referral-system delay) and delay in starting treatment once the diagnosis is established, this is an oversimplification. There may be misclassification of patient delay as provider delay if the patient does not follow the advice of the provider,[110] and misclassification of health system delay as patient delay if patients delay seeking treatment due to health system characteristics.[144] Poor perception of health services among users influences patient delay in seeking care for tuberculosis.[49,144,145] Furthermore, patient and system delays may be interdependent. If patients attend very early in the disease process, this may result in a longer delay on part of the provider even if legitimate procedures are followed. Studies have documented an inverse relationship between patient and provider delay.[142] It has been suggested that part of the explanation of longer provider delays for women might be that women consult earlier. The same is true for private practitioners and outpatient services. As a rule, they are consulted as a first choice and thus earlier in the process of illness. Finally, there is likely to be a difference in the way public and private providers operate in low-income countries: the former are more likely to act according to guidelines.[110]

There is no concrete scientific evidence to rely on when attempting to define a reasonable time to diagnosis and treatment for tuberculosis. Attempts to define "acceptable" health system delay, from the first consultation to diagnosis and then treatment, and an "acceptable" period from the onset of symptoms to commencement of treatment, both need to take note of the prevalence of tuberculosis.[146] In high-prevalence areas, delays might be expected to be shorter because the disease is relatively common and health professionals should be on the alert. In reality, delays are sometimes longer in high-prevalence areas,[138] the result of inadequate health services. Any definition of acceptable delays would also need to consider the prevalence of HIV/AIDS, which may hasten the progress of tuberculosis and cause patients to seek care earlier. In such cases, however, patients also could delay seeking care due to increased stigma.[147] Finally, the setting and the coverage and organization of the local health services are important: for example, industrialized versus developing countries, rural versus urban settings. As a gold standard, the referral system and the laboratory investigation for tuberculosis (sputum smear microscopy) should be completed within a week.[148] In areas with difficult access, this may be unreasonable. In other words, delay is an indicator of the accessibility and utilization of health services.

The most important aim of studies looking at delays in the diagnosis and treatment of tuberculosis in low-income countries is to investigate delays related to the health system, as such delays are not uncommon and should be amenable to intervention.[145,149,150] Interventions directed at patients are not likely to be useful when the determinants of delay in care seeking primarily relate to the health services rather than the patient's knowledge and understanding of tuberculosis.[144]

Finally, average delay is one thing, but, as is discussed in detail in Chapter 10, the main information for action may be found in reviewing cases that fall above the average, particularly those with exceptionally long delays. Both qualitative as well as quantitative information is useful here. Information from cases with shorter than average delays can, however, also provide valuable insight for improving the services.

Results of studies on delay en route to tuberculosis care

Examples from a number of recent studies in this field are presented in Box 7.10. To emphasize the importance of context, no attempt has been made to synthesize this information. Ideally, information for action is collected, analyzed, and interpreted locally.

In summary, the pathway to tuberculosis care, in particular the expected time and sequence of events in the diagnosis of tuberculosis, can vary substantially between and within countries. As a rule, more than one visit is expected before diagnosis. Ideally, no more than two or three visits should be necessary: one for nonspecific treatment or antibiotics (which is not always necessary), one for a spot specimen (patients are admitted for the night if they travel far), and one for submission of further specimens (at which time the results of the first spot specimen should be available). Unsurprisingly, provider delay in hospitals is shorter than in outpatient services; hospitalized patients are likely to be more severely ill and easier to diagnose, especially if they have smear-positive tuberculosis. Also, longer delays for rural patients, resulting from difficult access, are to be expected. The association of delay with the number of pre-diagnosis encounters with care providers and the number of providers—that is to say, with a convoluted pathway to care—emphasizes the need to simplify and improve referral systems.

Urban tuberculosis control

If health services in rural areas are poorly distributed or of low quality, then health facilities in urban areas will attract patients from rural areas. This may be a problem for tuberculosis control if patients cannot attend facilities in the cities for the entire duration of treatment. Treatment results in urban centers will then be poor, with high transfer and defaulter rates. According to data from the National Tuberculosis Center in Nepal, in 1995 only 39% of the patients

Box 7.10 Delays en route to tuberculosis care

Very short delays were reported in a hospital-based study in northern Thailand, where one half of all tuberculosis cases were co-infected with HIV.[148] The short delay was in spite of the fact that roughly one half of the patients included in the study lived outside of the central district where the hospital was located. Patient delay was reported as 10 and 15 days, respectively, for HIV-positive and HIV-negative new smear-positive tuberculosis cases. Provider delay was reported as one week. For women, patient delay was shorter, but provider delay longer. Hill tribe people had longer patient delay. Most of the patients attended the hospital in response to symptoms, but some attended for routine checks (these were not excluded). A study in southern Thailand measured a median patient, health system, and total delay of 4.4, 2.8, and 9.4 weeks, respectively.[151] This study included both smear-positive (79%) and smear-negative cases. Delay was not associated with smear status, but there was longer delay in mild illness.

Data from Ghana support the view that patients with HIV co-infection present earlier than those with pulmonary tuberculosis alone. A study conducted in a referral hospital in Ashanti Region revealed a total delay of four months in the diagnosis of smear-positive tuberculosis.[138] The mean number of consultations before diagnosis was 4.2, and 85% of patients first sought care from conventional medical practitioners, whether in government, private, or mission facilities. Doctor delay was longer than patient delay and was strongly associated with rural residence, but rural patients did not delay care seeking compared to urban residents. There was also longer doctor delay for female cases and longer delays for inpatients as opposed to outpatients, whereas patient delay was equal. This suggests that severe disease is related to health system delay rather than late care seeking in this setting. The authors concluded that tuberculosis services were too centralized.

A study in Queensland, Australia, that looked at symptomatic cases, excluding those found in screening programs, revealed a median patient delay of one month and a health system delay of 11 days in smear-positive tuberculosis.[149] There was a longer health system delay for women and the elderly. As expected, migrants had a shorter delay because, in Australia, migration from a high-prevalence country is a known risk factor, and care providers are aware of this. There was similar patient delay in sputum smear-positive and sputum smear-negative cases, but the health system delay was shorter in cases of smear-positive tuberculosis.

A study in a mixed urban, semi-urban, and rural population in South India, including new smear-positive tuberculosis patients over 15 years of age, reported median patient, health system, and total delays of 20, 23, and 60 days.[110] Patient delay was longer for men, and longer if the patient had initially contacted a public service provider, resided more than two km away from a health facility, or was an alcoholic. A health system delay of more than one week was recorded in 69% of the cases. This delay was longer if the first contact was with a private provider, if the duration of cough was short, if there was alcoholism, and if the patient resided more than two km from a health facility. Only one in five patients made a single visit to a care provider, which is a common finding: patients need to make more than one visit to a care provider to be diagnosed with tuberculosis. After the strengthening of the tuberculosis program, a

(*continued*)

Box 7.10 *Continued*

later study found an increase in the proportion of patients attending the government services, and median patient delay was no longer associated with the type of provider contacted.[152]

A study in a rural area in Nepal that recruited smear-positive and smear-negative patients found a longer delay in diagnosis of women (3.3 months) than men (2.3 months), and more women died shortly after diagnosis, which could be associated with more advanced disease due to a long delay in diagnosis.[121] Patient delay and the number of visits to a health provider before diagnosis did not differ by sex. A longer delay was found for both sexes if the patients had contacted private practitioners. For women, it was particularly traditional healers who delayed the process.

A study in four districts in Vietnam reported a longer provider delay for women than for men with new smear-positive tuberculosis.[153] Rural and highland residence was a risk factor for longer provider delay. Only 9.4% of male and 6.3% of female tuberculosis patients came directly to the district tuberculosis unit. This behavior might have been predicted because in most health systems patients would first present elsewhere. The key issue is to make sure that those who first attend to patients know when, how, and where to refer for assessment for tuberculosis. The authors, however, speculated that patients might be avoiding the district tuberculosis unit for fear of social isolation and stigma attached to tuberculosis, a poor understanding and undervaluation of symptoms, or limited access to the district tuberculosis unit.

A study of consecutive cases with active tuberculosis in Los Angeles, California, measured self-reported delay in seeking care.[49] The response rate was 60%, and the study found that 20% of respondents had delayed obtaining care for more than 60 days, during which period a patient exposed, on average, eight contacts. Delay was more common in the unemployed, those concerned about health care costs, those expecting prolonged waiting-room time, those who believed they could treat themselves, those anticipating difficulty in getting an appointment, those uncertain where to get care, and those fearing immigration authorities. In other words, the study revealed access barriers. On the other hand, illness severity ("need") had little impact. Consequently, structural characteristics were the main concern, and the authors concluded that improving the availability of services for high-risk groups could substantially reduce delay in seeking care and might limit the spread of tuberculosis. They emphasized that most patients sought care due to symptoms rather than as a result of screening. This was an important finding in a setting where there was strong belief in prevention via the screening of high-risk groups.

A median total delay of 12 weeks to diagnosis of smear-positive tuberculosis was documented in Kweneng District, Botswana, with a median patient delay of three weeks and a system delay of five weeks.[142] The median number of visits to a health provider before diagnosis of tuberculosis was two and the median interval between the first and second visits was three weeks. Although 93% complained of cough at the first consultation with a health provider, only 36% of the patients had a productive cough of more than three weeks, which was a definite indication for sputum examination in this setting. At the second visit this proportion was 69%. This may be part of the

Box 7.10 *Continued*

explanation why patients need to make repeat visits before a diagnosis of tuberculosis and why investigators stressed the importance of communicating with patients and encouraging them to return if symptoms persist or worsen. However, the study also revealed that only 38% of the patients who complained of having had cough for more than three weeks at the first visit had a sputum examination, which reflects poor performance on behalf of the health workers.

A study of smear-positive tuberculosis patients conducted in government hospitals in five districts in Malawi found a median time from cough to first submission of a sputum specimen for acid-fast microscopy of seven weeks and a median duration of cough before diagnosis of eight weeks.[154] Most provider contacts (75%) were with health centers or hospitals, and the most common reason for selecting a certain provider was proximity to home (55%). Usually the patient made the decision where to go (45%), whereas another family member made this decision in 24% of cases, and a health worker in 20% of cases. More than one half of the patients believed they might have tuberculosis before the diagnosis was made. This proportion would be expected to be lower where tuberculosis is less common.

A 1998 study in the Mwanza Region of Tanzania reported a median total delay in the diagnosis of smear-positive tuberculosis of 185 days, with longer patient delay than system delay.[141] Patient delay was significantly longer in rural areas, as was system delay. Median patient delay was 120 days and system delay to diagnosis was 15 days. All but 11% of the patients were enrolled in treatment within three days of diagnosis. Patient delay was longer for those who first visited a traditional healer, which was more common in rural areas. The majority of patients in both urban and rural areas had their diagnosis established in hospital. The main issue here seems to be access to health services and referral.

A study in the Gambia in 1997, which included 152 tuberculosis patients, found the median delay from onset of symptoms to initiation of treatment to be eight to nine weeks.[139] The delay was shorter in young patients and longer in rural areas. The presence of haemoptysis shortened the delay. A longer delay increased the risk of death. At first visit to a care provider, only 23% of the patients had a cough, whereas this proportion was 98% once they reached the tuberculosis program. The median number of providers seen prior to starting anti-tuberculosis treatment was four.

A study of centralized urban tuberculosis services in Lusaka, Zambia, measured the delay from onset of symptoms to diagnosis in smear-positive and smear-negative tuberculosis patients, and found that delay was associated with female cases, the number of health-seeking encounters prior to diagnosis, being diagnosed as an outpatient, and having visited a private practitioner or traditional healer.[155] Another study from Zambia used a different approach, studying adult patients presenting with a cough of any duration to health centers in Lusaka, irrespective of whether or not they had tuberculosis.[144] This study found that only one third of patients had delayed seeking care for more than one month. Delay was associated with age, severity of illness, poor perception of the health services (particularly expectations of drug shortages), prior attendance of a private clinic, and distance from a health center.

who came from rural and remote districts completed treatment.[105] Consequently, improving health services in rural areas is important to obtain good tuberculosis control results in urban health facilities. That said, urban health facilities sometimes blame poor results on the fact that many of their patients are from out of town. This claim should not be accepted uncritically, as these facilities may mainly serve the urban population. For example, a 1970 study in Bangalore showed that 83% of the patients in urban tuberculosis clinics were from the city and 17% from the surrounding rural areas.[78]

In 1963, Andersen and Banerji summarized the weaknesses in urban tuberculosis control in India,[156] weaknesses that characterized tuberculosis services in urban areas in many countries at the time and may persist in some cities even today. They highlighted two important points, both of which are still valid. First, administrative and organizational issues in control programs merit priority because technology, while important, is largely useless if it is poorly implemented. Second, success in urban tuberculosis programs is impossible without the country-wide implementation of good-quality services. Otherwise, rural patients will be attracted to urban health facilities, only to vanish from the system once they are diagnosed. Andersen and Banerji described how little was achieved by urban Indian tuberculosis services, in spite of considerable work in case finding, due simply to weak treatment organization (see Box 7.11 for details).

Health services in large cities are, as a rule, more complex than rural health services and tend to be more vertical and specialized. In the 1960s, Indian cities featured specialized tuberculosis clinics, whereas the national tuberculosis program was integrated into the rural health services in rural areas. At the time,

Box 7.11 Urban tuberculosis clinics in India in the 1960s

In Bangalore City, with a population of 1.2 million, 784 consecutive patients diagnosed at the Tuberculosis Demonstration and Training Center during a two-month period in 1961 were included in an evaluation reported in 1963.[156] Of the 784 patients, 84 did not return to learn the results of their diagnostic test; 46 were enrolled in treatment but never came under the proper control of the clinic; 138 lived outside the city limits and were lost and not traced; 48 who claimed they resided in the city when treatment was started left the city; and 173 were treated elsewhere in the city. Only 295 (38%) of the patients diagnosed remained under control at the clinic. Of these, only 156 (53% of the 295 and only 20% of the 784) followed the treatment at the clinic with what was considered an acceptable degree of regularity. In summary, the clinic clients could be divided into three groups: those who were treated at the clinic, those who were treated elsewhere in the city, and those who came from outside the city. The investigators concluded that diagnosis and treatment of tuberculosis should be decentralized and implemented within the general health services.

Nagpaul et al. argued that there was no logic in organizing urban tuberculosis services differently from rural services.[78] They felt that the convoluted path to specialized tuberculosis clinics in urban areas put rural patients at an advantage for care. Their basic arguments still hold true, and more recent publications from India claim that the organization and delivery of tuberculosis services in urban areas still lag behind their rural counterparts for various reasons.[157]

Even if population density is high in urban areas, population-based planning still applies in cities. High case rates, urban poverty and complex social problems, transport difficulties, and overcrowded large hospitals and clinics all justify population-based planning in urban general health care and tuberculosis services in particular. This issue has for a long time been grossly neglected in most large cities in low-income countries. Decentralized treatment in health centers with tuberculosis registers and microscopy services can be considered the ideal organization in urban tuberculosis control. When reforming a centralized specialized service, management and guidance is very important during the transitional period.[158] In large cities, the situation is further complicated due to the multiplicity of private and public providers and different government sectors (penitentiary, police, and military, for example). This complexity necessitates sufficient public health human labor to integrate the services and coordinate all tuberculosis activities within a city.

With coordination and integration of tuberculosis services in cities, case finding may increase, with additional cases being reported to the tuberculosis program, cases that either had not been reported previously (an increase in notification) or had not been detected previously (a true increase in case detection). Consequently, such intervention may result in better evaluation and in better tuberculosis control. Several examples from urban tuberculosis services are presented in Box 7.12.

Although it is important to decentralize the services, there is a limit to how far this decentralization should go. Apart from the volume-outcome relationship, decentralization is also costly in terms of training and supervision. With the 18 health centers in Managua (see Box 7.12), the tuberculosis program trained and supervised 18 semi-specialized nurses, and a nurse managed, on average, 30 new cases of smear-positive pulmonary tuberculosis in a year (making the ratio of health worker to patient 1:30). For comparison, in Riga, Latvia, it was decided to offer training to all primary health care staff in the city in 2002–2003. The ratio of trained health workers to annual number of new smear-positive cases was 2:1.* Clearly, this is much less efficient training, and it seems unlikely that it would be feasible to supervise all the trained staff on a regular basis. In a similar situation, a very decentralized service in San Diego County, California, used a strategy in which only the physicians who reported

*Author's observations during field visits.

Box 7.12 Urban tuberculosis control

In a paper published in 1970, the general health structure in the city of Bangalore (population 1.4 million), India, was described as being composed of the following: four large hospitals, eight municipal health centers, 19 general dispensaries, and numerous private practitioners working independently.[84] Additionally, there was a tuberculosis control center and two sanatoria. Given the general rule of one tuberculosis management unit per 50,000 to 150,000 people, the organizers of a tuberculosis program in a comparable setting would need to decide whether only the municipal health centers should be designated as tuberculosis management units, offering services for acid-fast microscopy and anti-tuberculosis treatment (on average 175,000 population per unit), with dispensaries serving as satellite centers. The other option is to have health centers and dispensaries function as tuberculosis management units (on average 52,000 population per unit). Such decisions depend on the local setting, available resources, and the rate of tuberculosis. Ideally, the role of the hospitals should be limited to diagnosis, treatment initiation when necessary, and the subsequent referral of patients to tuberculosis management units. Coordination and quality assurance should be the responsibility of tuberculosis supervisors. In the example above, specialized tuberculosis health facilities would eventually have become obsolete.

One quarter of a century later, in Zambia in 1995, 88% of the 6,948 tuberculosis cases registered in Lusaka Province (population 1.55 million) were diagnosed at the chest clinic of a tertiary referral hospital: the University Teaching Hospital. Patients needed a referral from a government clinic in order to attend the hospital. Interviews with 202 patients identified various access barriers including service-related costs, transportation costs, expenditure for special foods, and loss of income.[159] In this very centralized structure, the investigators expressed concerns about the risks associated with decentralization.

A retrospective study conducted in 1997 in Karachi, Pakistan, reported a 70% loss to follow-up among tuberculosis patients treated at a tertiary care teaching hospital in the city.[160] The majority of the patients were lost during the intensive phase of treatment. This percentage proves how unsuitable this type of health facility is for managing tuberculosis cases and underlines the need for a proper structure with designated tuberculosis management units.

Nicaragua is one of the countries that participated in developing the Union model. Its capital, Managua, had an estimated population of 1.3 million in 2001. There were 18 health centers designated as tuberculosis management units. The average population per unit was roughly 70,000. A review of 466 new smear-positive tuberculosis cases registered in health centers from July 1, 1994, to June 30, 1995, found that 74% of the cases had been diagnosed in health centers.[99] The remaining 26% were diagnosed elsewhere, presumably in hospitals, and then referred to the health centers for registration and treatment.* In Nicaragua, hospitals do not report tuberculosis cases to the Central Tuberculosis Register, and reporting is the responsibility of the health centers. It is the role of tuberculosis supervisors to monitor whether or not tuberculosis patients diagnosed in hospitals are effectively referred to health centers according to their area of residence.

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*In the late 1980s in Nicaragua, it was independently estimated that 70% of all health care visits occurred at health centers and 30% at hospital outpatient departments.[10]

Box 7.12 ***Continued***

For comparison, in 1996, the Kinondoni District in Dar es Salaam, Tanzania, had a similar population to that of Managua, but reported four to five times as many tuberculosis cases. Yet, there was only one laboratory for diagnosis of tuberculosis and six treatment units.* This was a grossly insufficient infrastructure at the time, but it has since changed. Likewise, in Nairobi, where one quarter of Kenya's tuberculosis patients are registered, a similar problem of congested urban services was addressed by increasing the number of centers with staff trained in tuberculosis treatment from four to 33 in five years.[161]

When a national tuberculosis program was launched in Laos in 1995–1996, the Vientiane Municipality had a population of approximately 500,000 and an average population density of 135 people per square km.[43] The municipality was divided into nine districts: four centrally located urban districts with 50% of the population, surrounded by three semi-rural districts with 40% of the population, and two rural districts to the west and the east containing 10% of the population. It was decided that the tuberculosis management unit would be in the district hospital, or rather district centers, as not all the facilities had beds. The population served by tuberculosis management units ranged from 20,000 to 110,000.[158] It was difficult to establish and maintain quality in units serving small populations.

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*Author's observations during field visits.

a tuberculosis case were sent a package of educational materials and invited to the annual day-long tuberculosis education course conducted in the county.[91]

It is not uncommon to find that supervision in accessible urban areas is relatively neglected. It is often assumed that urban health services perform well and need less supervision or, because they are close and accessible to the supervisor, it is less important to plan ahead for supervision in cities. This is a serious mistake. The role of the tuberculosis supervisor or coordinator is very important in urban tuberculosis control, and frequently more complex than in rural areas. It is also important to define the roles and responsibilities of the different people in the tuberculosis control. The design of the training and supervision programs in urban areas should keep this in mind.

The Union model recommends that the responsibilities of the urban health centers or tuberculosis management units encompass the diagnosis, registration, reporting, and treatment of patients who present with symptoms of tuberculosis, and the follow-up, registration, and reporting of tuberculosis patients referred to them from hospitals. Outreach workers for special groups and marginalized populations may be needed in large cities depending on the setting, as conventional ambulatory services often do not meet the needs of such groups. The tuberculosis supervisor, a public health professional, should be responsible

for coordinating the work of hospitals, ambulatory services, and outreach services. Coordination and overall integration of services and sectors—such as the industrial health sector, penitentiary system, and private sector—are very important aspects of tuberculosis control in cities and should also be the responsibility of the supervisor. A study in Botswana (2000) demonstrated the importance of the records and registers that form the information system in the tuberculosis program for the purpose of coordination and supervision.[92] The fact that these tools are not appropriately used for coordination and management is an all-too-common weakness.

Coverage of the tuberculosis program

The main problem for the tuberculosis program in terms of estimating coverage is that prevalence figures are not available and, therefore, the true "need" cannot be determined. The results of surveys of prevalence of infection are often difficult to interpret, and tuberculosis surveys are generally considered prohibitively resource demanding. So, how to measure coverage of tuberculosis services?

Methods based on the provision of services and population data are likely to be the most widely applicable. Reasonably accurate estimates of population size are usually available. However, how well official estimates reflect the actual population size in different settings is debatable, especially in rapidly expanding urban areas and in highly mobile populations in low-income countries. This problem apart, it is possible to estimate the population "served" by a program after defining what is referred to by "served." For example, the definition could be "the proportion of (the total population living in) districts providing acid-fast microscopy and treatment of tuberculosis at the district level," or the "population per tuberculosis management unit." A reasonably clear idea of the coverage of services can be obtained by combining information on access to health services in general—and routine information on tuberculosis (notified cases and trend and transfer-out and default rates in anti-tuberculosis treatment)—in addition to qualitative and quantitative information from periodic studies on delays in diagnosis and treatment of tuberculosis.

After the WHO revised its recommendations, defined the "DOTS strategy," and the term "DOTS" became widely used, the WHO defined "DOTS population coverage" as the percentage of people living in areas where the health services have adopted the DOTS strategy, expressed as a proportion of the national population, but recognizing that the population units nominally covered do not necessarily provide full access to "DOTS services."[162] The term "DOTS population coverage" is used to monitor progress during the geographic expansion of "DOTS programs."[162] However, this term has certain limitations, as the "expansion" of changes in a program or a service is not as clear-cut as the expansion of a new treatment, program, or service. Moreover, as mentioned

earlier, an important problem in tuberculosis control is the fact that the total number of cases diagnosed and treated is usually unknown in low- and middle-income countries with diverse and poorly regulated health systems. It is difficult to estimate whether the different patient populations—those treated under the DOTS strategy and those not—are comparable, or what differentiates the DOTS strategy from other alternatives. Consequently, the practical meaning of the term "DOTS population coverage" is not always clear and, as a minimum, depends on the context. The WHO recognizes that interpretations inevitably differ by country.[162]

Summary and conclusions

Whereas system design may be the most important subject in tuberculosis control, it is undoubtedly the most neglected. Historically, a narrow technical focus was applied in efforts to control the disease. This approach retarded progress in the coverage of tuberculosis services and in program management. The development of the Union model addressed the issue of structure and management in the context of low-income countries. However, tuberculosis is a moving target, and populations and systems change. Consequently, tuberculosis programs need to be dynamic. Recent developments in many settings are encouraging.

A vertical program does not necessarily use a vertical structure. Important issues when contemplating structure include centralized services versus decentralized ones, permanent services versus periodic services, and multi-functional or polyvalent services versus specialized services. Regarding community participation in tuberculosis control, it is important not to conflate decentralization within formal health services and voluntary participation of laypersons. These are two different strategies and should be evaluated separately.

Although it is agreed that a certain volume of work is needed in order for health workers to become proficient at particular tasks and to maintain proficiency over time, a lack of hard evidence precludes recommending exact volume ranges for the different tasks in the tuberculosis program. Adequate volume ranges are likely to be context-specific, and depend on variables such as training and supervision.

It is important to acknowledge that the different activities in a tuberculosis program—such as the identification of persons with symptoms requiring assessment for tuberculosis; acid-fast microscopy; registration and reporting of cases; and initiation, continuation, and reporting of the results of anti-tuberculosis treatment—cannot all be implemented in every health facility or at the same level of the health services. Therefore, it is crucial to define the roles and responsibilities of the many different parties in the health system. This includes defining where the overall responsibility for coordination, management, and

monitoring of tuberculosis control services should lie in order to guarantee continuity of care, visibility of consequences, and a complete evaluation of efforts to combat the disease. In the Union model, the overall responsibility rests with the tuberculosis management unit.

It cannot be overemphasized, particularly in nations with diversified health systems, that what counts is the total effort dedicated to treating tuberculosis in a country. The most important aim of a national tuberculosis program should be to have official statistics reflect that total effort.

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8
Information

Why do we need information in the tuberculosis program?

The current era is sometimes referred to as the Information Age. Accordingly, a high value is placed on health sector development projects that focus on health information.[1] True believers in the power of information say that it is essential for making decisions. The underlying assumptions are that uninformed decisions could have a negative impact on the health sector and that useful decisions cannot be made if information is lacking.[1] However, rational decision making, especially at higher levels of the health system's hierarchy, does not automatically follow from an improvement in information. In reality, important decisions, particularly those that involve politicians, are often based on tradition or political expediency rather than on information.[2]

The political character of decision-making within the health sector does not encourage the collection of information. This is a challenge and a frequent source of frustration for those working within the public services. A positive point is that the more routine the decision and the less conflict it engenders, the more likely it is to be based on information.[3] Thus, it is more likely that information is used in case management and in program management than at the higher echelons of the health system. The current chapter discusses information in terms of case and program management, and does not attempt to address the use of information for advocacy and lobbying. Instead, it examines the Union's model tuberculosis information system against the background of communicable disease surveillance, compares it with health information systems in general, and contrasts the situations in industrialized and low-income countries.

Background

Information on health can be divided into routine information and non-routine information. Information derived from health facilities is typically a register or health statistics generated from routinely collected data and reports

within the health system. Non-routine information includes surveys and information generated by evaluation and research. For example, community-based or population-based sample surveys can disclose problems that are unknown, not acknowledged, or not addressed by the health services. Ideally, a national health information system will use a combination of routine and non-routine data collection methods. The WHO proposed categorizing a routine health information system under five interrelated subsystems: epidemiological surveillance (for certain infectious diseases, environmental conditions, and risk factors), routine service reporting, special programs (including tuberculosis control), administrative system, and vital statistics.[4] This chapter deals with routine information in tuberculosis programs.

Problems often arise with routinely collected data, such as difficulties in ascertaining cases, variations in diagnostic criteria, unsuitable formatting of records, and inconsistencies in data presentation.[5] Most of these problems can be overcome by well-designed information systems.

The need for information systems that ensure health services are delivered according to standards has been increasingly acknowledged.[6] Styblo stressed this point in the 1970s. He emphasized that surveillance should be an integral part of tuberculosis programs and should involve both surveillance of the epidemiological situation and surveillance of the control measures applied.[7] With technical support from The Union, a system of recording and reporting data was developed and tested in several national tuberculosis programs in the early 1980s.[8–10] Today, this information system is seen as an element that is indispensable to the success of tuberculosis programs.[8,9]

Definitions, objectives, and changing attitudes to information

Attempts to collect information on health and disease go back a long way. For example, the Commission of Tables, founded in Sweden in 1749, registered vital statistics and causes of death beginning in the mid-eighteenth century, earlier than in any other European country.[11] Traditionally, health information systems were oriented to collect information on diseases, an activity known as "surveillance," and on health services output, such as discharges from the hospital. The term "surveillance" refers to continuous analysis, interpretation, and feedback of systematically collected data, using methods distinguished by their practicability, uniformity, and rapidity rather than by accuracy or completeness.[12]

Surveillance is the foundation of disease control efforts. The term *disease surveillance* can be defined as "the continuing scrutiny of all aspects of occurrence and spread of a disease that are pertinent to effective control."[13] Disease surveillance is usually a passive activity, that is, one based on reports.[14] In its simplest form, disease surveillance is limited to the number of cases and deaths,

the latter used as an indicator of disease severity. Although information collected using surveillance has been used to monitor secular trends in disease occurrence, identify outbreaks of diseases, set priorities, establish baseline and evaluation of interventions, and study the natural history of diseases in populations over time,[14] it is generally agreed that the main objective of disease surveillance is to detect changes and sound an alert for further investigation and action. A relevant example regarding tuberculosis is the recent increase in incidence, which was subsequently found to be a consequence of the spread of HIV, and increasing drug resistance. Sentinel surveillance is a subtype of facility-based data collection in which certain sites are selected to record and report specific events or activities in greater detail than is routinely done. One of the objectives of using sentinel sites is to improve the complexity of data for use at higher levels.[15] The personnel in sentinel sites receive special training and supervision for this purpose.

In recent years, it has been emphasized that the objective of information systems should be to improve action. In the case of health information systems, the goal is to improve health services management through information support. Accordingly, health information systems are increasingly regarded as tools for improving the efficiency of health services.

Too much time and emphasis is typically placed on attempts to create perfect systems before any information is collected.[16] Cibulskis and Hiawalyer, in the context of implementation of an information system in Papua New Guinea, pointed out that data analysis, even from imperfect systems, can stimulate greater interest in information.[16] In turn, this interest is likely to improve the quality and completeness of reporting and encourage a more methodical approach to planning and monitoring services. Increased attention to information and detail can thus initiate a process which itself leads to improvements, including improvements in information. There are many examples to support this view. In the Czech Republic, the introduction of cohort analysis of results of anti-tuberculosis treatment is reported to have resulted in more complete information on patient outcomes.[17] In Moldova, computerization and analysis of information in the national tuberculosis reference laboratory highlighted gaps in routinely collected data. This analysis suggested a discrepancy between policy and practice and provided material for stimulating discussions on surveillance, case management, and clinical practice in general.[18]

If information systems are to fulfill their potential as aids to improving health service, they need to be designed to support the decisions and actions of health personnel.[1] Generally speaking, data lose operational significance when they are transmitted and processed centrally.[19] This has to do with the context surrounding data. When removed from their context the data lose some of their significance. It is increasingly acknowledged that data should be useful at the local level, that is, be relevant at the source. Tuberculosis programs that

collaborated with The Union respected this principle. The information system, originally created on the recommendations of expert committees brought together by the WHO, was later adopted by the WHO as the model information system for tuberculosis programs. [20,21]

A vertical versus an integrated approach to information support

Are so-called "unified" national health information systems effective enough for tuberculosis programs to rely on them for information acquisition, or should a specific system be implemented in tuberculosis programs? After a seminar held in Benin in 1995, which brought together representatives from both systems and across six West African countries, the participants concluded that the two systems were complementary rather than overlapping, a fact they believed should be emphasized and utilized. According to Trébucq et al., who reported from the seminar, the unified system is important because it collects information on health infrastructure, demographic variables, and other data. This allows tuberculosis control activities to be put into perspective. However, they asserted that what is of value in the tuberculosis program is direct management of the information resulting from its activities.[10] The seminar proposed that both systems be continued and that the flow of information between the two should be organized at all levels of the health system.

Much has been written about "vertical" versus "integrated" approaches to information systems. In their introduction to a book on the design and implementation of health information systems, Sauerborn and Lippeveld argue that elimination of duplication and waste requires a unified information system rather than coordinated parallel systems using separate data collection instruments, handled by separate staff, and supervised by program-specific supervisors.[6] This conclusion is debatable. They state that the presence of strong vertical programs often causes delays in data transmission and a lack of feedback at the local level. This is also arguable. Trébucq et al., reporting from the seminar in Benin, claimed that only the data generated by the tuberculosis program were reliable and complete or arrived quickly enough to be of use in program management.[10]

Sauerborn has suggested that there are cultural and psychological differences between "data people," who collect, analyze and report information, and "action people," who use information.[3] Although presumably the term "action people," refers to health care practitioners, it is less clear to whom the term "data people" refers. It could be scientific researchers or personnel of the health agencies who are officially responsible for surveillance and data systems, such as epidemiologists and bio-statisticians, or even program managers. Even if there were differences between data people and action people, the issue is less relevant at peripheral levels in the health system. Indeed, as pointed out by

Sauerborn, it is not uncommon at the services level for the health care practitioner to also be the provider and user of information, as well as the decision maker.[3] Styblo emphasized that the staff responsible for executing a program, be it prevention, diagnosis, or treatment, should have a general understanding of surveillance and its importance.[7] A recent U.S. study demonstrated the importance of combining surveillance, public health, and clinical care activities under a case manager.[22] It can be argued that, in the tuberculosis program, information is ideally collected, aggregated, analyzed, and interpreted at all levels by those who produce and use it. An argument against this approach can be found in situations in which the staff in charge of assessing the data also collects it. The reliability of that data sometimes becomes questionable, particularly when incentives are tied to good performance, such as case finding or favorable treatment results. In such a scenario, a conflict of interest clearly exists. Therefore, it may be controversial to link financing or monetary incentives to epidemiological or performance indicators. In an example cited from the Philippines, where resource allocation was based on population figures, it was in the interest of the peripheral health stations not to report deaths, because doing so would result in reduced allocation.[23] When motives work at cross purposes, quality information collection suffers.

Advocates of unified health information systems claim that although successful information systems have been developed on a small scale, such as for individual districts or programs, the sustainability of these initiatives is often doubtful.[16] They also question the relation of such initiatives to the development of national information systems.[16] Whereas this may be true in some settings, there are examples to the contrary. Moreover, it seems that large-scale unified national health information systems in low-income countries are often supported by external donors and thus face problems in terms of sustainability. Jayasuriya, in his paper on information systems for health services in developing countries, casts the Philippines as an unfortunate example of attempts to implement a single comprehensive information system for all preventive programs.[23] Such failures are not unheard of, and are part of the reason why there is reluctance to replace existing information systems with new ones that have not proven effective. To give an example, in the Czech Republic, according to tuberculosis experts, liberalization of the health system in 1989 caused both the deterioration of information on tuberculosis control and the fragmentation of organization, responsibilities, and funding for public health services.[24] With the discontinuation of a centralized vertical notification system, which had ensured completeness and validity of the information, the number of notifications dropped by one half. In 1996, however, regional tuberculosis consultants were appointed to supervise notification, and the system gradually improved. In Nicaragua, a decade after withdrawal of all support from the donor that originally assisted the tuberculosis program, the vertical information

system that was introduced in 1988 was still being sustained by national efforts. When it was proposed that a unified health information system be introduced there, the tuberculosis information system was well established and accepted by all involved. It already had been proven useful at all levels. The national health authorities made sure that the system continued, but coordinated it with the new unified system.

Cibulskis and Hiawalyer claim that follow-up on missing reports in a system, data quality control, data summary, and provision of feedback are best managed and financed by a single unit at the national level rather than being transferred to provinces or split among separate programs at the central level.[16] Such an approach is disputable. In fact, they acknowledge that a different strategy may be preferred, particularly if the monitoring capacity of individual programs is well developed and program staff are motivated to seek and use the information. The latter is indeed a sign of successful implementation.

Finally, it should be pointed out that a unified health information system has not been the rule in industrialized countries in the recent past, not even with regard to a unified communicable disease surveillance register. In the European Union, subsystems were developed, such as EURO-TB and EURO-AIDS, which collected detailed information but fed it into a larger system. The same is true in the United States. If such systems are being developed and run in industrialized countries today, why should low-income countries act otherwise? Until unified systems have been convincingly shown to provide the support needed for action, there will be reluctance to rely only on them for information.

Communicable disease surveillance versus information on tuberculosis

Classical disease surveillance implies continuous comparison of the actual number of cases with the expected number. Even if it is recognized that many outbreaks are first detected by clinicians, it is claimed that an important aim of a modern notification system for communicable disease control is to give a central agency the power to detect outbreaks of diseases for rapid application of preventive measures.[25] The commitment and ability to act, however, are not always equivalent to the desire to collect information. Sandiford et al., in 1992, argued that centralized surveillance systems are typically ineffective for detecting and controlling outbreaks of disease.[1] According to them, disease episodes are usually reported to national offices where responses are far too slow to be effective, if they even occur at all.

Frequently, too much routine data are collected as opposed to not enough, and the information generated by information systems is not continuously analyzed.[19] As a result, it is seldom up-to-date. Generally speaking, it is important to reduce data collection but increase data use. It can be argued that sur-

veillance should prioritize important health problems where there is a well-formulated response.[1] With regard to communicable disease control, tuberculosis is clearly one such problem. It is tempting to go a step further and argue that collecting data exclusively on the number of cases detected without paying attention to the quality of the response is of limited value. In 1976, Styblo wrote that surveillance of tuberculosis should deal with two distinct subjects: surveillance of the tuberculosis situation and monitoring of the response.[7]

As a rule, tuberculosis prevalence is high in low-income countries. The primary aim of information in this context is not one of detecting outbreaks. On the other hand, the application of anti-tuberculosis treatment is a challenging task in many of these countries, one that needs to be carefully monitored with the aim of preventing an adverse outcome of the intervention itself. Thus, in the case of tuberculosis, an emphasis on the quality of the response is important. This is not only the case with regard to low-income countries. In the 1970s, it was estimated that between 20% and 30% of tuberculosis patients in the United States failed to complete anti-tuberculosis treatment within the prescribed 24-month period, but this fact provoked little sustained public health attention.[26] Tuberculosis control is not unique in this respect, and tuberculosis programs can serve as an example for other programs, such as programs for sexually transmitted disease and HIV/AIDS.

The setting of industrialized versus low-income countries

Regarding communicable disease control in general and tuberculosis control in particular, surveillance systems in industrialized and in low-income countries may not be entirely comparable. In industrialized countries, there is great concern and even fear of outbreaks and micro-epidemics of infectious diseases. In this context, major emphasis is placed on rapid response. Although this is also important with regard to epidemic and emerging infectious diseases in other countries, a host of predictable and familiar communicable diseases are part of life in most low-income countries. An important focus in communicable disease control in low-income countries is therefore on sustained commitment rather than rapid response.

In industrialized countries, with new technologies and methods in food manufacturing, processing, and distribution, for some time there has been a particular focus on food-borne diseases. Even more recently, other transmission routes—such as occur in SARS (severe acute respiratory syndrome) and avian influenza—have captured enormous attention. Aggregation of data from different sites is considered critical to allowing discovery of outbreaks that can spread rapidly with modern communication and transport. It is argued that if data are not aggregated in a timely manner, an outbreak could easily be missed in the early stages. All of this may not be of equal concern in low-income

countries where populations are busy tackling classical problems with well-known causes and consequences.

On the other hand, many low-income countries are going through an urbanization process in which people from remote areas migrate to towns and cities for economic reasons, among others. Consequently, problems of low-quality health services in remote areas, which result in selection of drug-resistant bacterial strains, can spread. This problem has not received sufficient attention. Where health services are decentralized, quality assurance is essential. Information and quality-assurance systems must reach remote locations not so much with the aim of obtaining aggregate statistics to detect or investigate outbreaks, but rather in order to prevent, detect, and correct poor responses. In tuberculosis programs, poor response may lead to drug resistance and thus complicate communicable disease control locally as well as elsewhere further on.

Implementation and running of information systems

Good information systems may fail to take hold if they are poorly implemented.[16] Before expansion, testing on a limited scale should always be done. Discontinuation of a previous information system is important when implementing a new one, but may need to be gradual because it is often an uncomfortable process for those involved. The tuberculosis information system had been used for a decade within national tuberculosis programs collaborating with The Union before it was promoted at the international level. In Nicaragua, one of the collaborative programs of The Union, where short-course anti-tuberculosis treatment was introduced gradually from 1984 to 1989, a new information system was only implemented nationally in 1988, after it had been tested on a smaller scale.[27] The previous system was then abandoned for all practical purposes, but lingered on as part of the general surveillance system. In Laos, on the other hand, there had been no functional system in place previously. Starting in 1995, the Union tuberculosis information system, which was by then the internationally recognized system, was introduced in steps simultaneously with other elements of the tuberculosis program.

In order to decentralize decision-making and build capacity at the peripheral level, information systems need to be decentralized. One must first consider the technical skills of those who will collect the data at the local level as well as the available diagnostic equipment in peripheral health facilities.[6] Furthermore, it is widely acknowledged that publication of a manual (guidelines), training and subsequent supervision of health personnel, motivation, and feedback are all important factors in successful implementation of information systems.[1] Finally, it is important to organize the printing and distribution of any forms and registers centrally, rather than expect this to be done at local levels.[16] Anyone who has been through the cycle described above understands the

tremendous effort required to establish and maintain a well-functioning information system in any country, let alone in a low-income country. It is easy to suggest changes to a system and always tempting to request more detailed data collection and reporting. However, it is cumbersome to implement changes effectively on a large scale. Thus, changes to an established system should be carefully justified before they are implemented.

The focus of a good information system is on the local level. Ideally, problems should be identified in individual health units, and timely and effective action should be taken locally in response. If power, responsibility for decision-making, and accountability do not exist locally, information systems will remain blunt tools.

Sometimes information systems are perceived to be merely instruments of control designed for those at the top to check on achievements and targets they set, but of little value for the staff at the local level.[19] If this is so, either the design is inappropriate or implementation has failed. Ownership is an important issue when implementing information systems. Top- and middle-level managers must be willing to let go and, at the same time, actively contribute to capacity building at the local level. Information empowers, which may explain reluctance on the part of top- and middle-level managers to decentralize systems. Reluctance to fill in forms and report activities may indicate that the system is seen as someone else's rather than one that is useful for local management and decision-making. This attitude can be influenced by training and supervision that emphasizes local ownership and utilization of the data. Training is also important in order to develop the skills needed to convert data into information through analysis and interpretation.

Using information generated by the systems

Information plays multiple roles with regard to interventions. It plays a prospective role in planning, a continuous role in case management and quality assurance, and a retrospective role in evaluation—learning what works and what does not. Before any health intervention becomes part of standard practice, it should be evaluated, ideally with randomized controlled clinical trials. The impact subsequently observed rarely equals that seen under such experimental conditions. In real-life settings, the impact of an intervention is first studied in pilot projects (feasibility studies). Further evaluation is then required to ensure that a positive impact will exist in routine practice. This is where studies of effectiveness and health information systems come into play.[1]

Using the information collected in a system is a critical factor for the system's sustainability.[16] The information is ideally used for encouraging a more rational approach to decision making at all levels, the aim being to improve the operation of health services. Data use at the local level is particularly critical.

The presence of personnel whose key role is to monitor the reliability of the data, making comparisons and relating performance to standards, is also important.[1] This is a significant role of supervisors. Eventually, routine data should inform overall national health policies and strategies and can be used when negotiating with donors. Such a scenario, however, involves the "higher echelons" where, as mentioned earlier, decisions are less likely to be based on information.

Reluctance to use data that has been collected may arise from a lack of confidence in the quality of the data or from uncertainty as to how it should be processed. It is essential to look at poor data quality as a consequence, rather than as a cause, of the underutilization of data.[1] When data are used, anomalies and errors are detected and corrected. If genuine efforts are made to analyze and use the data, detection and correction of errors should occur naturally. Thus, it is important to ritualize data analysis and interpretation. Just as clinicians make rounds, public health specialists analyze data with the objective of identifying areas where corrective action or further investigation is warranted. It can be argued that it was an error in the report of the 1974 Expert Committee on Tuberculosis[21] to emphasize surveys and not routine collection of reliable data. It is true that, at the time, tuberculosis notification data were inaccurate and incomplete. However, such flawed data were primarily due to a lack of effort, as was subsequently shown in the programs collaborating with The Union, in which a reliable and complete surveillance system was implemented. This system came to accurately reflect the disease burden over time in the collaborating countries.

Reluctance of managers to share information with others for mutual benefit is a well-known constraint in most settings.[1] It applies to managers at all levels. This phenomenon can be addressed in training and in regular meetings by discussing the various roles and responsibilities of each player and emphasizing the importance of teamwork. If the different roles are understood and mutual benefits experienced, there should be no reluctance to share data.

Generally speaking, disease surveillance is more effective in countries with nationalized health systems than in those with independent private clinics and laboratories. A national information system, however, does not provide useful information for policy and planning if much of the need for health services is expressed by visits to a private health sector, or a paramedical or alternative medicine sector that does not participate in the system. In other words, the coverage of information systems is important.

The role of technology in information systems

Increasingly, computer systems and software packages have become major items of expenditure for health services. Sandiford et al. noted that in the same way that medical symposia are used to promote pharmaceutical and medical

equipment, international and national informatics conferences are now used to sell hardware and software products for health information systems.[1] They also assert that there is a tendency by all disciplines to exaggerate the benefits and minimize the constraints involved in implementation of computerized health information systems.

Jayasuriya has been critical of interventions for improving health information in low-income countries with computerization. He points out that although investments in information technology have escalated, the failure rate of applications is of concern.[23] A focus solely on technology (computers, software, etc.) in such projects instead of non-technological elements (such as a sensible design, training, and supervision for information gatherers) is inappropriate and may partly explain the failure rate.

The stated objectives when computerizing information systems include saving time, improving the timeliness of reporting, and making data handling and analysis easier. A less common objective, but one that may be relevant in countries with a bad system to start with, is to improve and simplify the system. Though it is widely acknowledged that computers can improve efficiency and assist in data analysis, many would argue that computerization will not, in and of itself, solve problems of inappropriate information systems nor will it do away with the need for on-the-spot supervision of systems. In fact, it can be argued that only an appropriate and functioning information system merits computerization. Sandiford et al. pointed out that what causes problems in many countries is the excess of routinely collected data, not the lack of them.[1] Further, there is an almost universal reluctance to reduce the data set because someone can always find a reason why certain data might be needed, even if they have never been used. A two-step process in computerizing the system offers a chance to rationalize data collection, that is, to limit the amount of data collected on the basis that doing so is appropriate for sensible use of the data.[1] The first step is to continue to collect the data manually but not to enter them onto the electronic database when the system is computerized. Once it becomes apparent that the data are not missed, those items can then be removed altogether.

The tuberculosis information system

Background and purpose

A common generalization about disease surveillance is that it simply counts the number of cases detected. Tuberculosis programs, however, are concerned with what happens after the detection of cases. This is where the intervention can go seriously wrong, and as a result, the number of people living with tuberculosis (that is, the prevalence) can actually increase. This should not happen when effective treatment is available.

Cohort analysis* in tuberculosis has been carried out for a long time. Survival analysis predated chemotherapy, and it is interesting to examine early attempts at data collection and analysis in the field of tuberculosis. In 1919, Rutledge and Crouch reported what they referred to as the "ultimate results" in cases of tuberculosis seen in a sanatorium.[30] They used two main case definitions: "ever smear-positive" and "smear-negative." They subdivided the former category further based on radiological findings ("incipient," "moderately advanced," and "advanced" tuberculosis) and the latter according to how likely tuberculosis was to have been the correct diagnosis ("probable," "possible," and "not clinical" tuberculosis, which might be translated as "doubtful"). Looking at how the patients fared over time, they divided patients into groups according to how long they had been out of the sanatorium at the time of analysis. They defined three outcome categories referring to the time of analysis: "alive," "died of tuberculosis," and "died of other causes." Of the 245 patients in their research who had been out of the sanatorium for more than eight years at the time of analysis, the survival status was the following: of 187 "ever smear-positive" cases, 79% had died, and of 58 "smear-negative" cases, 22% had died. Tuberculosis was considered to have been the cause of death in only about one half of the smear-negative cases.

The value of outcome analysis was realized early in the history of tuberculosis chemotherapy. Such analysis was part of the studies of the efficacy of treatment regimens in clinical trials, in which the outcome categories were "failure" and "relapse" among the cases of survivors available for analysis. Soon thereafter, it was recognized that outcome analysis was also essential to studying effectiveness or efficiency in the routine application of chemotherapy. In 1964, Horwitz and Palmer discussed the difficulties in establishing case definitions and outcome definitions in tuberculosis. They put forward what can be seen as a precursor to modern cohort analysis, emphasizing the point that hospitals, clinics, and physicians throughout the country must participate.[31] At that time, the practice of reporting new cases and relapses separately as well as reporting cures in pulmonary cases had recently been introduced in Denmark. This allowed for the calculation of a national cure rate.[31] Horwitz and Palmer made the point that relapses were just as much, if not more, a part of the burden of tuberculosis and a source of new infections in the community. They suggested reporting what they referred to as "lethality index," including all deaths occurring among persons with active tuberculosis, irrespective of

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*The term "cohort" originally referred to a component of a population identified by period of birth (that is, birth cohort), but has broadened to describe any designated group of persons who are followed over a period of time.[28] Thus, a cohort can be understood as a clearly defined group of persons studied over time.[14] In epidemiology, the term is often used to designate a group of people who share a common experience or condition, such as exposure.[29]

whether they were attributed directly to the disease, a practice that is still in use today. In the 1964 Expert Committee report, it was noted that cohort analysis of drug administration records, covering complete groups of patients who began treatment within a given period, should be the basic method of operational assessment in treatment programs.[20] In 1974, the Expert Committee recommended monitoring the output of cured patients, but also looking at failure rates, case-fatality rates, and relapses.[21]

In the programs collaborating with The Union, emphasis was placed on simplifying and standardizing data collection in general and on implementing cohort analysis in accordance with recommendations of the expert committees. As a result, reporting of the "prevalence" of tuberculosis, that is, reporting patients "on register" at the end of a year, which was widely practiced at the time, was discontinued. End-points were defined with the aim of evaluating the efficiency of treatment programs. The result of these efforts was that both outcome analysis and the previously monstrous tuberculosis register, which had attempted to keep patients under lifelong surveillance, became manageable in the context of low-income countries. This was significant for two reasons: first, in countries with a high prevalence of tuberculosis, it was important to decentralize case management and information management; second, in low-income countries, decentralization meant delegating responsibility to lower cadre personnel. Thus, the recording and reporting system had to be simple, straightforward, and relatively easy to implement and supervise. In retrospect, it can be said that these same characteristics are also desirable in middle- and high-income countries.

Today, it can still be argued that the primary aim of information in the tuberculosis program is to monitor the quality of intervention. There are five important reasons for collecting information on tuberculosis (see Box 8.1). For everything but the first, aggregated data are sufficient.

Nothing can replace the routine information system for its purposes. On the other hand, for the purpose of policy making, planning, and implementation, the system does not collect all the information required. To avoid duplication of efforts, the tuberculosis information system should be effectively linked with relevant statistical registers and information systems in any given country (Figure 8.1). Additionally, there should be periodic external evaluations as well as operational research. Tuberculosis should be featured in health interview surveys where doing so is feasible.

There are many ways to describe information systems. The definitions used in the Union model and the components of its system (that is, forms, registers, and reports) will be described first. Then the structure and implementation of the system and the flow of data within it will be discussed, as well as the issue of converting the data into information and using it. Finally, quality assurance and validation will be covered.

Box 8.1 The purpose of collecting information in the tuberculosis program

Individual case management
To facilitate clinical decision making and guarantee rationality and continuity in case management. To prevent mistakes that may have serious consequences for the individual patient. To detect early warning signs for action, and thus increase the probability of a favorable outcome.

Epidemiological surveillance
To monitor the course of tuberculosis in the community over time. All care providers who deal with tuberculosis should be included and know their role and responsibility vis-à-vis the tuberculosis register.

Outcome evaluation
In the field of tuberculosis control, this is now widely acknowledged as an indispensable part of any treatment program. Bad treatment results at the program level are a warning sign for future increases in caseload and drug resistance.

Management and administration of the program
Knowledge on the burden of disease as measured by the health service can be used to estimate the need for infrastructure, staffing, medical supplies, and other resources (inputs). For this to be a realistic estimation, the coverage of the information system is important. Otherwise, the total need for resources may be underestimated.

Evaluation
The information is used for continued self-evaluation in the program, quality assurance and motivation, and to assist evaluation of impact. For impact evaluation, the coverage of the information system is important, as the evaluation is incomplete unless all treatment providers are included and participate.

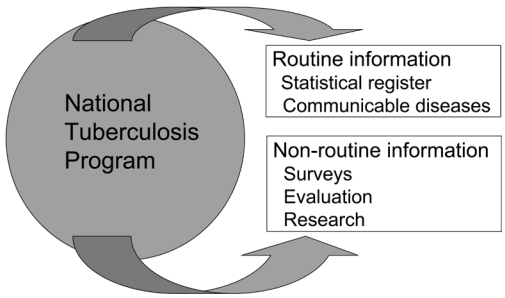
Case definitions and components of the system

Definitions are the foundation of any information system. In the past, it was difficult to agree on classifications and definitions in the field of tuberculosis because each medical branch—bacteriologists, clinicians, epidemiologists, health officers, pediatricians, pathologists, and radiologists—had their specific working methods and objectives and thus their own criteria.[32] It was eventually agreed that the definitions should be practical, applicable, and serve the purpose of tuberculosis control (see Box 8.2).

It is not uncommon for beginners in the field of tuberculosis to get upset when individual cases do not easily fit the definitions. When this happens only occasionally, it does not imply that the definitions need to be updated. Even if definitions are frequently found to be lacking, this may simply indicate operational problems. Rather than the definitions, the issue of how the system,

the practices, the services, or the tuberculosis program itself needs to change should be considered. International definitions for tuberculosis have been agreed upon and published, and the minimum routine data that need to be collected are clearly defined.[33,34] It is interesting to note that the definitions used in the programs collaborating with The Union are relatively robust. In spite of global expansion of the model information system, the definitions have not changed substantially since the early phase of the collaborative programs. This may reflect a sensible foundation and careful and extensive piloting of the system in different settings.

Figure 8.1 Health information



The central issue in the tuberculosis information system is that a cohort of patients must be followed continuously to determine if they get cured without relapse. This concern is also carried through in supervision and self-evaluation. The term *cohort* refers to consecutive cases, and is defined as "a group of patients diagnosed and registered for treatment during a specific time period."[33]

Definitions of cases and outcomes

Infectious disease specialists, when discussing routine surveillance, argue that the system's sensitivity for detecting cases needs to be high, given that the main task of a surveillance system is what is referred to as "cluster alert," that is, the detection of sudden changes in incidence.[25] On the other hand, the specificity need not be so high. In modern communicable disease surveillance in Europe, it is common to have different levels of case definitions: possible, probable, and definite (or confirmed) cases. This is complicated and invites problems if care is not taken to ensure that a case has one and only one definition. In other words, a case should not be entered in a database as "probable"

Box 8.2 Kurt Toman, on definitions (1979)

A definition is a basis for action, a working definition, determined by its practical applicability rather than the degree of completeness. A definition is not right or wrong, but should be judged in the light of a stated purpose and should contribute to meeting the agreed purpose (pp. 4–5).[32]

and then later be changed to "definite" after it is confirmed. Such practices invite difficulties when it comes to guaranteeing the reliability of the database at any given point in time.*

In 1973, Horwitz and Comstock pointed out that case definitions can serve several different purposes.[37] The most essential characteristic for judging infectiousness and for the short-term success of therapy is whether direct smear microscopy can confirm the presence of acid-fast bacilli. On the other hand, radiological appearance is crucial for long-term prognosis when looking at pulmonary function. Because a discrepancy between bacteriological and radiological indices exists, Horwitz and Comstock concluded that the latter should be discarded as a basis for definitions in tuberculosis programs because it depends on interpretations and clinical judgment.

The basic principle, that tuberculosis case finding and treatment should be regarded as a functional entity, is an argument against having one definition for surveillance and another for treatment. Using a definition with high sensitivity in which all "cases" were to be enrolled in treatment would lead to the unnecessary treatment of many patients. For the individual, this might imply useless and potentially harmful treatment, and delay or prevent correct diagnosis and treatment. At the programmatic level, high sensitivity is likely to result in a waste of resources and can take the focus away from the real problem. Thus, in the tuberculosis information system, there is emphasis on specificity of the definitions as well as the quality of the data.

In the Union model, any person enrolled in treatment for tuberculosis should be recorded.† Since the 1970s, it has been recommended that new cases of smear-positive pulmonary tuberculosis be reported separately and used as an epidemiological index, in light of the fact that they are the most significant sources of infection.[7] All cases of tuberculosis should undergo an assessment with this in mind; that is, the sputum of all new patients should be examined for acid-fast bacilli before treatment is initiated. It is also recommended that cases who come to the attention of the tuberculosis services but who previously

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*Some tuberculosis programs use different levels of case definitions (for example, the tuberculosis program in Taiwan) and allow cases to change category. However, these programs determine the case rate for any given year only at the end of September of the subsequent calendar year.[35] Nevertheless, a 2003 study in Taiwan found substantial misclassification of notified tuberculosis cases.[36]

†A key issue in the definition of "possible" and "probable" tuberculosis cases is the clinician's decision to treat with anti-tuberculosis treatment. It is important that the emphasis then be on a full course of anti-tuberculosis treatment rather than the questionable practice of "trial treatment" in which patients are enrolled on anti-tuberculosis treatment as an aid to diagnosis. In trial treatment, the patient's condition is observed, and if it improves, treatment is continued. If it does not, treatment is discontinued, and the patient is "taken off the register" (that is, the patient is not considered a case). Trial treatment is not recommended as a diagnostic aid in the Union policy model.

have received anti-tuberculosis treatment be reported and evaluated separately, the justification being that they are more likely to have drug-resistant tuberculosis and thus should receive a different treatment regimen. In addition, the proportion of such cases out of all cases is an indicator of program quality.

According to current international definitions, a case of tuberculosis is a patient in whom bacteriology has confirmed tuberculosis, or whom a clinician has diagnosed.[33] A definite case is a patient with a positive culture for the *M. tuberculosis* complex. In countries where cultures are not routinely available, a patient with two sputum smears that are positive for acid-fast bacilli is considered a definite case. There is further detail regarding localization of disease as pulmonary or extra-pulmonary, and previous treatment status.

In the tuberculosis information system there are categories for registration of patients on diagnosis (which can be referred to as entry categories) and six mutually exclusive categories for results of treatment in smear-positive pulmonary tuberculosis (which can be referred to as outcome or output categories). These are presented in Boxes 8.3 and 8.4. As a rule, a case should be recorded only when the final entry category has been determined. For outcome analysis, the first event is recorded.

The rationale behind definitions of adverse outcome in the program is in some ways more practical and less scientific than the rationale behind the case

Box 8.3 Mutually exclusive categories for registration of tuberculosis patients at diagnosis[33]

New: A patient who has never had treatment for tuberculosis or who has taken anti-tuberculosis drugs for less than one month.

Relapse: A patient previously treated for tuberculosis who has been declared cured or having completed treatment, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

Failure: A patient who, during treatment, is sputum smear-positive at five months or later during the course of treatment.

Return after default: A patient who returns to treatment with positive bacteriology, following an interruption of treatment for two months or more.

Transfer in: A patient who has been transferred from another tuberculosis register to continue treatment.

Other: All cases that do not fit the above definitions. As a rule, in a well-functioning program this category needs to be used only rarely. This includes—

Chronic cases: Patients who are sputum-positive at the end of a retreatment regimen.

Box 8.4 Mutually exclusive categories for evaluating the results of treatment of smear-positive pulmonary tuberculosis patients[33]

Cure: A patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.

Treatment failure: A patient who is sputum smear-positive at five months or later during treatment.

Died: A patient who dies for any reason during the course of treatment.

Defaulter: A patient whose treatment was interrupted for two consecutive months or more.

Transfer out: A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

Note that *treatment success* is defined as the sum of patients who are "cured" and those who have completed treatment.

definitions (see Chapter 4). Although it is important, when interpreting the results of a treatment program, to be able to exclude patients who died during treatment, it is less important, and in fact often quite difficult, for those responsible for the program to determine the exact cause of death. The definition of failure was originally based on studies of the results of 12-month treatment. Then, it seems, it continued to be used when short-course treatment (8-month regimen) was introduced to treat new smear-positive cases in the programs collaborating with The Union.* It was important to set the time of failure at a point in treatment in which it was unlikely that the patient would be rendered permanently cured without modification of treatment (thus the five-month period noted in the definitions above). At that time, the patient was re-registered† and enrolled on the regimen for previously treated cases. In the programs col-

*The definition of failure of retreatment was defined as smear-positive at the end of treatment (eight months) primarily in order to allow all patients on retreatment to complete a full course of treatment before discharging them as treatment failures, as there was no other treatment option available for them.

†This point was not clearly spelled out in the Orange Guide, however, and practices in the Union collaborative programs may have varied. In the author's experience, some health workers are confused in the management of relapse cases and returning defaulters, and record their sputum examination as "follow-up" and, instead of re-registering "failure" and "return after default" cases, they continue case management under the same registration number (and line in the tuberculosis register).

laborating with The Union, the continuation phase of treatment in new cases was always self-administered; the patient would attend on a monthly basis to pick up a fresh supply of drugs. Patients who missed their monthly appointments were allowed one month to show up on their own initiative or to be traced by the program staff before closing their cases. Therefore, the definition of "defaulter" was determined as two months from the last attendance at a health facility. For the sake of simplicity, this definition was made applicable to any treatment regimen in the program.

Components of the tuberculosis information system

Many factors need to be considered when designing data collection instruments, including relevance, feasibility, layout, and clarity. In the tuberculosis program, information is collected on a minimum number of variables, but enough variables to support and summarize case and program management and to allow for surveillance and outcome analysis. Information on risk factors is not reported, as it is the topic of special studies and not part of routine data collection. There are six key components in the tuberculosis information system at the services level, as listed in Box 8.5. These components, depicted in Figure 8.2, constitute the tuberculosis information system developed

Box 8.5 Key components in the tuberculosis information system

Request for sputum examination: A form completed by the health worker who identifies a symptomatic patient and refers the patient to the laboratory for sputum examination.

Tuberculosis laboratory register: A list that provides the characteristics and details of the activities in the microscopy laboratory. There is a separate line for each examination (that is, the serial smears for diagnosis or an examination for follow-up during treatment).

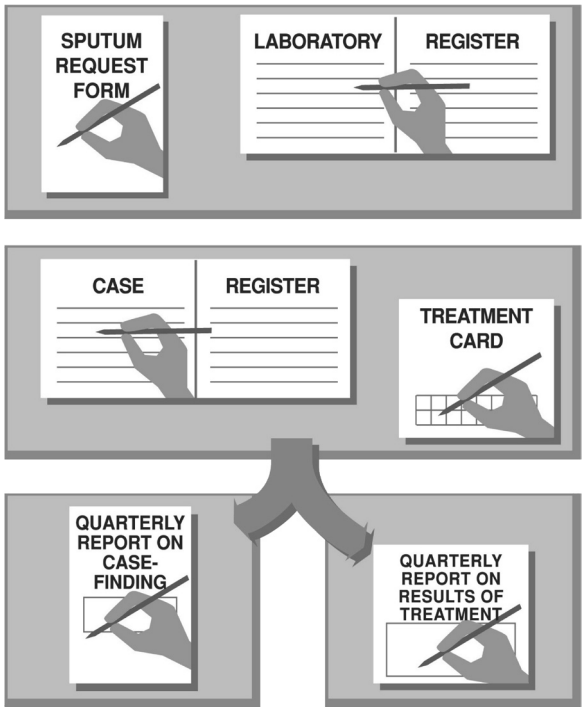
Treatment cards: A record providing detailed information on the treatment and adherence of individual patients for the purpose of aiding rational case management.

Tuberculosis case register: A line listing where information on individual patients is summarized to facilitate overview of the situation in general regarding case finding and treatment. There is a separate line for each case (that is to say, for each illness or treatment episode). A patient registered as a new case may, at a later date, be re-registered as a relapse, a returning defaulter, or a treatment after failure case.

Quarterly report on results of case-finding activities: A report filed at the close of a calendar quarter with information on the number of cases registered in the quarter.

Quarterly report on results of treatment: A report describing the outcome of treatment of smear-positive cases registered in a particular quarter.

Figure 8.2 Schematic presentation of the tuberculosis information system



in programs collaborating with The Union. Importantly, the system links the laboratory and treatment services and can be used as a tool for coordinating these services.

The simplicity of the design provides the staff at the local level with a strong incentive for using the system. Although keeping the system simple and straightforward is recommended, there is a common tendency at the central level to add more components. At times, there has been a tendency at the international level to request more detail and more reports. A common set of additional components are typically requested: forms for requesting culture of mycobacteria and drug susceptibility testing (these are clearly needed where these procedures are performed); patients' identity cards; individual notification forms; referral and transfer forms; a transfer-in register; a "cough register"; duplicate tuberculosis case registers; a chronics register; a register and a treatment card for multidrug-resistant tuberculosis cases; report on smear conversion; and forms related to supply management, laboratory quality control, and supervision. Of these, two are indispensable in any setting: a form for referral

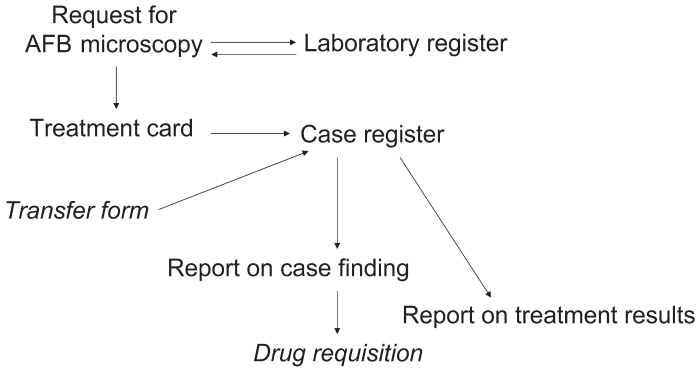
and transfer of patients between health facilities and a form (or forms) for materials management.

The importance of keeping routine data collection to a minimum cannot be overstated.[19] Any changes to data collection instruments require added effort for designing, printing, and distributing new forms, not to mention the effort in retraining health personnel. Finally, there is the continuous effort of collecting and reporting the data. Changes to the information system, particularly in the direction of increasing data recording and reporting, should never be attempted without careful consideration and pilot testing.

It is difficult to justify why detailed information on every single aspect of the program should be transmitted centrally. The more forms, registers, and details requested, the more difficult it is to manage and supervise the system and the worse the program will look to outside observers, which is an important consideration. Furthermore, it is important to remember that those who work at the health services level have jobs to do apart from filling out forms and transmitting data. The situation could be compared to a factory production line. Production is likely to suffer if those working on the line are constantly preoccupied with filing reports. It would be far better if they could keep their minds on the production line and concentrate on running it smoothly. Rather than having workers fill out constant reports, a supervisor can pay a visit from time to time to see how things are going on site. During these visits, the supervisor can verify that the few reports that are required and transmitted are reliable. Similarly, in the tuberculosis program, it is not necessary to have very detailed information sent to the central level, let alone the international level. Minimum information should be reported. Greater detail can be obtained during supervisory visits. After all, the detailed information should be used locally, where appropriate action can be taken promptly. At the intermediate and central levels, the information is primarily used for planning, program management, monitoring, and evaluation. A good tuberculosis program has a strong services level. It is likely to pay off in the long run to emphasize thorough training, decentralization, local empowerment and ownership, and supportive supervision (a public health function).

Figures 8.3 and 8.4 depict the classic version of the tuberculosis information system (the model) and a more complex one with additional components. Generally speaking, it is wise to reduce the number of times that information must be transcribed. At every step in an information system, there is the potential for a loss of or error in information. Every step must be supervised. If additional components are implemented, such as duplicate case registers (as in Botswana[38]), a cough register (as in Malawi[39]), and transfer-in register (as in Malawi[40]), these involve more steps to be supervised and validated. As discussed above, it is good practice to test all new ideas in a pilot project before embarking on nationwide implementation. This is true of any components

Figure 8.3 The model tuberculosis information system. The system is made up of six universal components. Transfer forms and drug requisition forms are two important additions (*in italics*) that need to take note of local characteristics.



AFB, acid-fast bacilli.

added to the information system. It is also important to keep in mind that what works in a pilot may not work in routine practice, after the novelty of and enthusiasm for the new component have faded.

Details concerning the forms used in individual case management and materials management are discussed in corresponding chapters. Only the quarterly reports are discussed in detail below. Before that, however, it is valuable to first consider the structure for implementation of the system and the data flow within it.

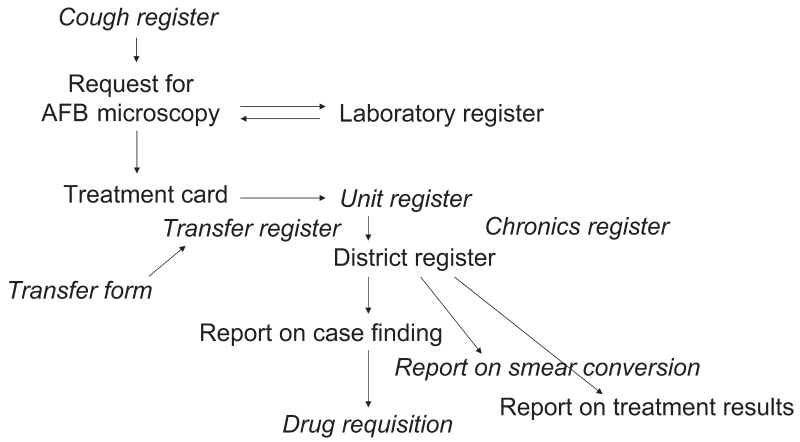
Structure, implementation, and data flow

Historical background

The actual implementation of the information system depends on the organizational structure in the health services. Just like all other components of the tuberculosis program, the information system must fit into an established or emerging health services structure.* Early on, Styblo's approach was to have

*As an example, the population of Tanzania increased from 15 million in 1977 to 23 million in 1986, and was 28 million in 1995. In 1977, the intermediate level of the tuberculosis program consisted of four tuberculosis officers: two stationed in Dar es Salaam and one each in Mwanza and Kibongoto.[41] In 1988, the intermediate level had been decentralized, with the appointment of regional tuberculosis coordinators in each of the 20 administrative regions.[42] The number of districts increased from 81 in 1977 to 105 in 1988, and the average district population from 185,000 to 230,000.

Figure 8.4 A complex version of a tuberculosis information system. In this model, various components (*in italics*) have been added to the system, increasing its complexity. At every step in an information system, there is the potential for a loss of or error in information. Every step must be supervised.



AFB, acid-fast bacilli.

the provincial (regional) level responsible for keeping tuberculosis files and reporting to the central level.[7] Provincial (regional) tuberculosis coordinators would base their quarterly reports to the central level on district registers. Styblo justified this "decentralization" as necessary in high-prevalence countries.[7] Whereas this may have been regarded as a decentralized surveillance system compared to the one in Europe at the time, today this can be seen as a vertical system, but one that undoubtedly reflects the situation in Africa where peripheral services were rudimentary and ill prepared at the time to take on responsibility for reporting. In the long run, however, the emphasis on regional and district levels in Tanzania may have resulted in a rather centralized and top-down structure becoming firmly rooted. However, it must also be admitted that this is unlikely to have been solely a failure of the tuberculosis program, but rather reflects a general failure to systematically decentralize and strengthen the peripheral health services. Eventually the Tanzania tuberculosis program introduced unit registers (at subdistrict level). The district tuberculosis coordinators traveled in the districts and updated the district registers with information from the unit registers. This change represented delegation of the task of registration (keeping a register), but without responsibility for reporting.

In Nicaragua, the situation was different. Any recommendations for centralization were strongly resisted, as this went against the promises of the

revolution concerning the establishment of primary health care. Most activities of the tuberculosis program in Nicaragua were, therefore, quite decentralized from the start. The unit of registration in Nicaragua, the health center, corresponded (in terms of population served) to a subdistrict in Tanzania, for example. Even if Styblo recommended that regional "coordinators" keep tuberculosis files, this was never convincingly implemented (except in one region). The "supervisors," as they were referred to in Nicaragua, completed the quarterly reports based on the tuberculosis registers kept by the health centers. Later on, from 1990 to 1992, the tuberculosis program emphasized the principle that ownership and accountability (including reporting) should reside with the health center.

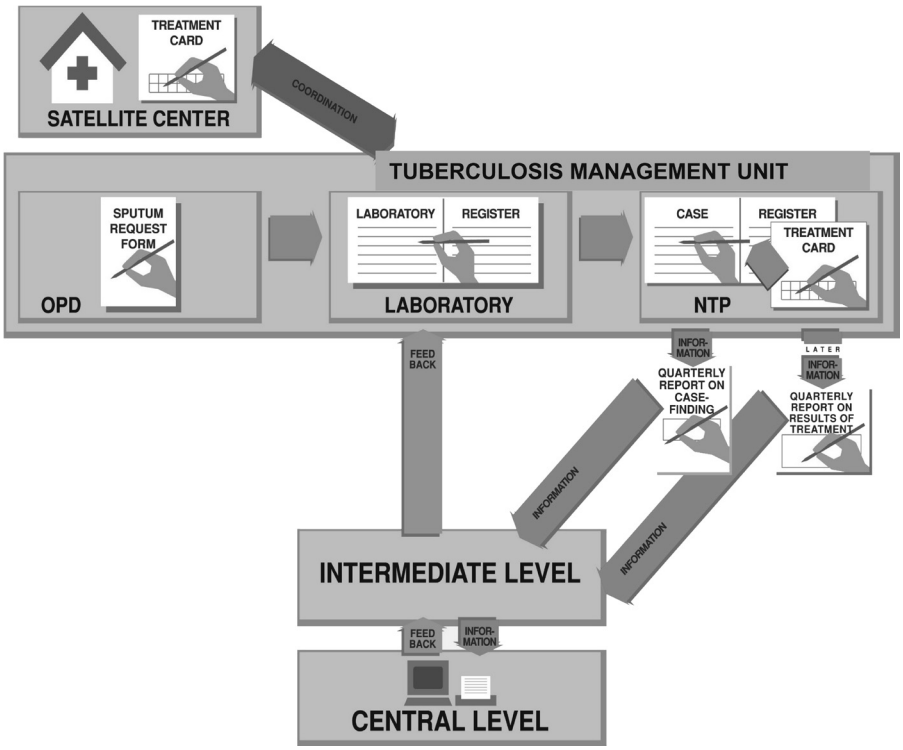
The model in modern times

As discussed in Chapter 7, the "tuberculosis management unit" is defined as a health facility with a triage facility (outpatient department), a laboratory where acid-fast microscopy is performed, and a tuberculosis clinic. Ideally, the laboratory and case registers are kept at the tuberculosis management unit. The tuberculosis treatment card is kept where treatment is administered. This may be at the tuberculosis management unit or, in case of difficult access, the administration of treatment may be delegated to satellite treatment centers that operate in coordination with the tuberculosis management unit. The intermediate and national levels operate with the quarterly reports from the tuberculosis management units and any additional information that they may wish to collect during supervisory visits. Summary sheets are sometimes prepared from the quarterly reports at the intermediate level. Alternatively, photocopies of original reports from tuberculosis management units can simply be sent on to the central level. Data transmission in the information system always reflects the administrative structure of the health system. Information should flow in both directions; data are reported from the periphery to the center, and feedback flows from the center to the periphery. Figure 8.5 is a schematic presentation of the model information system.

The recorded data are used locally for day-to-day decision-making at the services level. Delays in horizontal transmission, for example from laboratory to the personnel involved in treatment, should be minimal. Other than that, the speed of data transmission is not crucially important. Consequently, quarterly reports are used in vertical (between levels) transmission of data.

In an African setting, it is common that laboratory services are less decentralized than the treatment units and that tuberculosis coordinators travel around to update the tuberculosis registers from health unit (or subunit) registers. The coordinators then file quarterly reports on case finding and results of treatment based on their registers. This is a less convincing example of a decentralized system than the Nicaraguan example above. The coordinators can be

Figure 8.5 The tuberculosis information system fitted into the health services structure. Data transmission always reflects the administrative structure of the health system. Information should flow in both directions; data are reported from the services level to the center and feedback flows from the center to the services level.



OPD, out-patient department; NTP, national tuberculosis program.

seen as the owners of the data that are collected for them by the personnel of the health units. As there are more steps in this system, there are also more opportunities for the introduction of data errors when the information is transcribed from one register to another. However, with a more decentralized system, quality may be poor unless there is effective supervision. This means that there is no less work in a more decentralized system; the work is simply of a different nature.

The treatment cards are retained at the health facility where treatment is administered because there should be a "paper trail" within the health facility for recording follow-up. In many countries, there are also miniature tuberculosis treatment cards that patients keep. The main advantage of the miniature

tuberculosis cards is that patients can then present their cards should they unexpectedly seek care in a different unit. However, this is only helpful if the patient cards are continuously updated, which is not always the case in practice.

So-called "tickler files" for filing the active treatment cards in a tuberculosis clinic are useful, making it is easy to follow adherence.[15] When the patients attend, their treatment cards are placed in an appropriate slot in the file according to the date of the patient's next appointment. At the end of each working day, the cards of patients who missed their appointments are placed in a "late patient" slot instead. These patients can then be followed up according to policy.

Easy-to-fill-in forms make the work of collecting and reporting data easier. In the programs collaborating with The Union, the definitions of important terms were printed as footnotes in the case registers. Instructions were printed on the reverse side of the reporting forms for easy reference. Ideally, the tuberculosis program manual should contain a section with instructions for recording and reporting. It is especially important that both the treatment cards and the registers are printed on good-quality paper suitable for the local conditions. These records may need to last in conditions of high humidity without much protection.

Implementation of the information system requires ongoing training and the regular supervision of all personnel involved in recording and reporting. There is commonly a high turnover of staff at peripheral level in the health services in low-income countries, and it is important that new staff members be oriented on how to record and report data when they are recruited.

In some countries, special staff or clerks are responsible for "paperwork," including reporting. In the tuberculosis program, it is ideal if the user of the data is the same person who records the data and completes the reports. Arguably, this will result in data of superior quality and reliability than when these responsibilities rest with a freestanding vertical information structure. If the data have meaning for those who report them, reporting can act as the first level of feedback.[10] However, this does not guarantee the quality of the data. One reason for poor quality of data is a lack of motivation in the health workers responsible for recording and reporting. Regular supervision encourages both respect for documentation and the use of the data collected. Periodic or regular operational meetings are useful for feedback. Moreover, collaboration among colleagues can facilitate the exchange of information on patients transferred or referred between units, resulting in more complete information.

Computer support

Despite the critical remarks regarding computer technology earlier in this chapter, it must be acknowledged that most tuberculosis programs appropriately feature some computer support. In low-income countries, this usually takes

the form of computerized quarterly reports at the central and, less often, intermediate levels generated and manipulated by common software packages, such as spreadsheet or database programs. However, several attempts have been made to pilot and run more elaborate computerized systems, such as the Epi Info "electronic tuberculosis register" piloted in Botswana[38,43] and the Epicenter Program sponsored by the WHO. The trend toward increasing computerization will undoubtedly continue, and such systems will be further developed in the near future.

In Botswana, the software for the computerization of the district tuberculosis registers was developed to aid with the efficient collection, compilation, and analysis of tuberculosis data on a continuous basis. A district in Botswana has, on average, a population of 50,000 to 100,000. The software became operational in 1996, but was revised repeatedly until the year 2000. The software completely replaced manual compilation of data at the district level, but the district tuberculosis coordinators updated their data source, their own manual tuberculosis case register, from unit registers during supervisory visits. From the district level to the national level, data were managed on diskettes. In 2002, it was reported that, while user acceptance was high and the quality of data improved,* timeliness remained unchanged because the critical factor in this respect was the availability of supervision when the coordinators updated their registers.[43] Several factors were identified as critical for success of the computerized system: a well-functioning paper-based system; involvement of the staff of the tuberculosis program, the national health information system, and the relevant health facilities; ongoing rather than one-time training; and, finally, supervision and backup support. Training and supervision are the same factors known to be important for a reliable paper-based system. In other words, computers are not short cuts for strengthening surveillance and program management at the peripheral level. On the contrary, the computer system is an added element to implement, needs staff to maintain it, and requires additional training. When implemented, a successful and continuously supported computerized system saves time and may increase the reliability of reports in the long run, particularly in areas with high caseloads.

A note of caution is due here. Investment in computers for entering information at a peripheral level should not be a program-specific goal, because computerization is unlikely to be sustainable in most countries with a high prevalence of tuberculosis. In Botswana, both computer illiteracy and high staff turnover slowed the process of implementing the electronic register. The system developed in Botswana can probably only be recommended for countries where

*This could be a study effect because more attention was paid to recording and reporting than before computerization.

there is already a sustainable computer network within the general health infrastructure. Finally, to avoid the logistical difficulties of having to send diskettes or CDs by mail or other means, an electronic system should not be implemented until solutions to link sites electronically are in place.

Converting data into information

The objective of information systems is not simply to produce information but to help people make use of it.[3] The data collected in tuberculosis programs give information on the outcome of patient care, the effectiveness of the program, and the program's adherence to standards. The information is used in case management, planning, programming, training, quality assurance, and evaluation. The use of information in case management, in materials management, and in quality assurance (supervision and monitoring) is dealt with in later chapters. The records and registers can also be systematically studied or randomly sampled and analyzed for more detail when necessary.[9] The rest of this chapter covers reporting, that is to say, how standardized information generated by the system is processed for the purpose of surveillance and outcome analysis. For this purpose, the data sources are the quarterly report on case finding and the quarterly report on results of treatment, which are based on the tuberculosis case register. A parallel source for case-finding data is the register in the laboratory, which may report its activities separately. Unless there is coordination between the two sources, parallel reporting may confuse matters. With good coordination, the parallel source can serve as a validation mechanism.

Until a report is received from every health unit in the system, case information should be considered incomplete. Still, there comes a point when efforts to obtain the information should be stopped. Health professionals should not spend undue effort getting perfect statistics, but should instead concentrate on the patients currently under their care and on obtaining good results in the future. Attempting to estimate the number of cases missing is not recommended, as it then becomes difficult to estimate the quality of the final data. If there is missing information, the final statistics should include a note indicating the number of units that did not report. If appropriate action is taken concerning non-reporting units, the problem should diminish over time.

Lack of respect for negative results is an all too common phenomenon. Negative results are important information. A blank cell cannot be assumed to represent a negative result. It is simply missing information. It should be stressed in training that if there are no cases to report or evaluate, a zero is written in the corresponding cell.

The information obtained from the quarterly reports is listed in Box 8.6.

Box 8.6 Information obtained from quarterly reports

Number of cases by category: This is classical surveillance and the information is necessary for estimating the need for supplies for diagnosis and treatment.

Proportion of sputum smear-positive out of reported cases: This measure is calculated from the information on the report on case finding. This gives an indication of the use of sputum microscopy for (confirmation of) diagnosis. If this proportion is low or decreasing, further investigation is warranted.

Age and sex distribution of new sputum smear-positive cases*: Tuberculosis shifts to older age groups when transmission decreases. Styblo pointed out that it was especially useful to look at the trend in the rate of new sputum smear-positive tuberculosis among young adults (15 to 29 years), as a decline in the case rate in older age groups may lag behind, the result of endogenous exacerbation of old infections.[7]

Proportion of previously treated among sputum smear-positive cases: This measure is calculated from the information on the report of case finding. If this proportion is high or increasing, further investigation is warranted.

Proportion of sputum smear-positive cases that complete treatment: This measure is calculated from the information on the report on results of treatment. This is an important indicator of the quality of the response and of the long-term impact of control activities. If this proportion is low, additional information is available by looking at the categories of adverse outcome. Further investigation may be warranted depending on the suspected causes of the problem.

Proportion of "cured" among successfully treated cases: This proportion provides an indication of the comprehensiveness of sputum smear examinations and the precision of follow-up.

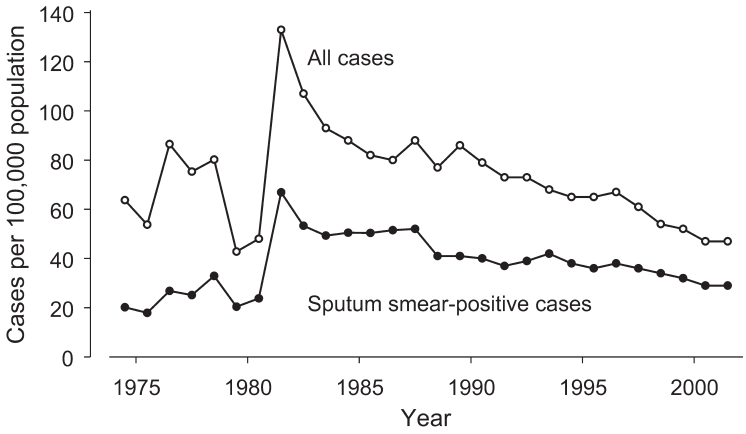
*In some settings, age is not reliably recorded, and patients may not even know their exact age.

Quarterly report on results of case finding

In pulmonary tuberculosis, there are four ways to classify a smear-positive patient on entry to the tuberculosis program: new, treatment after relapse,* treatment after failure, or treatment after default. There are also smear-negative pulmonary tuberculosis cases and cases of extra-pulmonary tuberculosis. Finally, there are those patients who are transferred in. Most of the data processing in the program involves sputum smear-positive cases, as these are the main sources of transmission.

*The term "relapse," as used in the tuberculosis program, does not distinguish between those reinfected and those suffering the reactivation of an old infection. "Recurrent tuberculosis" might be a better term, but the term relapse is by now firmly rooted in many programs.

Figure 8.6 Tuberculosis case notification rates in Nicaragua, 1974–2001



Data from annual reports of the Nicaraguan tuberculosis program.

All cases, whether enrolled in treatment or in which there is an intention to treat, are reported. A case should be reported even if the patient dies or is lost from sight before treatment is started. The quarterly report on case finding includes the number of cases by category (person), but also indicates the time of occurrence of disease (corresponding quarter) and the place (reporting facility*). Age and sex are reported for new sputum smear-positive cases only. Otherwise, no specific information on risk factors is included. Risk factors are considered the subject of research, not routine reporting.

A report on case finding is completed at the end of a quarter. However, where culture of mycobacteria is used routinely in the diagnostic process, it is reasonable to finalize the statistics in July for the first quarter of a year and the statistics for the whole year in April of the subsequent year, or even later if drug susceptibility is to be reported as well. Even where culture is not used, it may also be reasonable to expect to finalize yearly national statistics in April of the subsequent year, allowing for delays and difficulties in communication.

The results of case finding can be expressed as absolute numbers by category of case or as case rates, which take population figures into account. As an example, the case notification rates in Nicaragua from 1974 to 2001 are presented in Figure 8.6. Prior to 1980, the statistics were not reliable, and bacteriological confirmation was low. Case detection, undoubtedly low in this period,

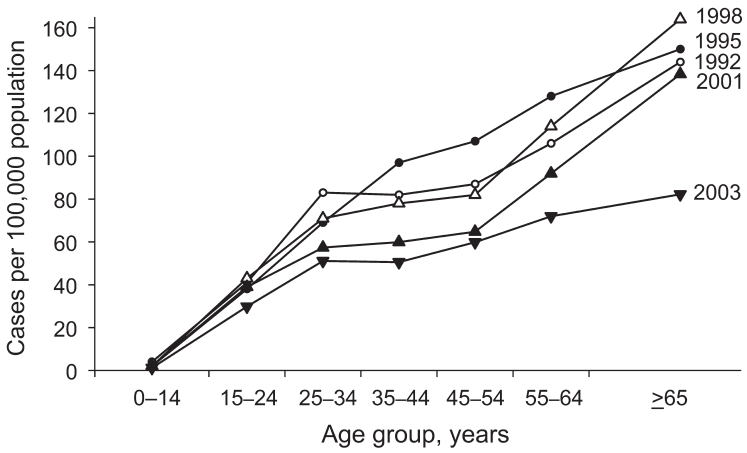
*It is preferable that a health facility close to where the patient resides or where he or she is expected to stay throughout treatment be responsible for reporting the case.

was seriously disrupted prior to and during the revolution of 1979. Starting around 1980, the primary health care network was strengthened and expanded. Tuberculosis services were, at the same time, integrated into the primary care services, and the number of tuberculosis cases reported increased impressively. Reports rapidly reached a peak, and then the case rate decreased to a level that may reflect the incidence of tuberculosis when the services were fully expanded. Since then, the rate has continuously declined.

Age and sex are reported for new sputum smear-positive pulmonary cases only. To give an example, Figure 8.7 demonstrates the decrease in age-specific rates in Nicaraguan males over time. A marked decrease is eventually seen in all age groups.

Tuberculosis is a public health problem, and it is recommended that notification of tuberculosis cases be mandatory. At the same time, it is important to avoid double or multiple reporting of cases. Generally, in low-income countries, it is not possible to compare identity or social security numbers to prevent double reporting. The alternative is to set clear rules regarding who reports a case, to whom, when, and how. For example, in Nicaragua, the health center is the reporting unit. If a patient is diagnosed with tuberculosis in a hospital and treatment is started there, policy dictates that the patient be referred to a health center for continuation of treatment. The hospital does not notify the case to the central registry; instead, the health center notifies the case when the patient presents for registration and the continuation of treatment. Obviously,

Figure 8.7 Decrease in age-specific rates of new smear-positive pulmonary tuberculosis in Nicaraguan males



Data from annual reports of the Nicaraguan tuberculosis program.

this leaves the possibility that a patient who does not follow the recommended procedure or who dies is never reported. Ideally, program supervisors visit the hospitals in their area on a regular basis* or coordinates with hospitals in some other manner so as to be informed about the details of patients diagnosed in the hospitals. The supervisors keep records of patients diagnosed in hospitals and verify whether these patients show up at the assigned health centers as planned. If a patient does not show up as planned, the supervisor can register the patient in the corresponding health center all the same. Attempts can be made to trace patients to determine their whereabouts and condition. A patient may, for example, be registered in a different center. At any rate, such patients should be accounted for in the statistics even if they are lost from sight after discharge from the hospital. Even if this is not the fault of the personnel of the health center or the hospital, it indicates a problem in the service area that needs to be addressed.

To prevent double or multiple reporting of the same patient, clear rules are needed regarding the registration and reporting of patients who are transferred from one reporting unit to another before treatment is completed. If the unit where the patient was diagnosed has already registered and reported the case, the second unit registers a "transfer in." The second unit should not notify the case to the central registry, but should eventually report the results of treatment to the original unit, which is responsible for reporting the outcome of treatment to the central registry. If the first unit receives no information on the outcome of treatment, they simply report a "transfer out" to the central registry. Further investigation should reveal if a problem of default is masked by a reported transfer out.

Notification delays can occur and, for the sake of consistency, it is important to determine which dates to use when reporting cases: the date of diagnosis or the date of registration. Notification delays can be substantial where it is routine to wait for the results of culture. This is usually not a problem in high-prevalence countries, where diagnosis is confirmed with smear microscopy. Generally speaking, when looking at trends in case finding, notification delays are not an important problem in tuberculosis programs if the delays are consistent, that is to say, unless there are changes in reporting practices over time.

Notification of tuberculosis may be incomplete even when it is mandatory. Contrary to what many believe, where nominal notification is on an individual basis, notification may be more incomplete than when quarterly reports are used, as in the model tuberculosis program. In the model program, a reminder can be issued or an inquiry made when a quarterly report is not received on the due date.

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*The visits have the added value of maintaining awareness of tuberculosis and the tuberculosis program among the hospital staff.

Quarterly report on the results of treatment

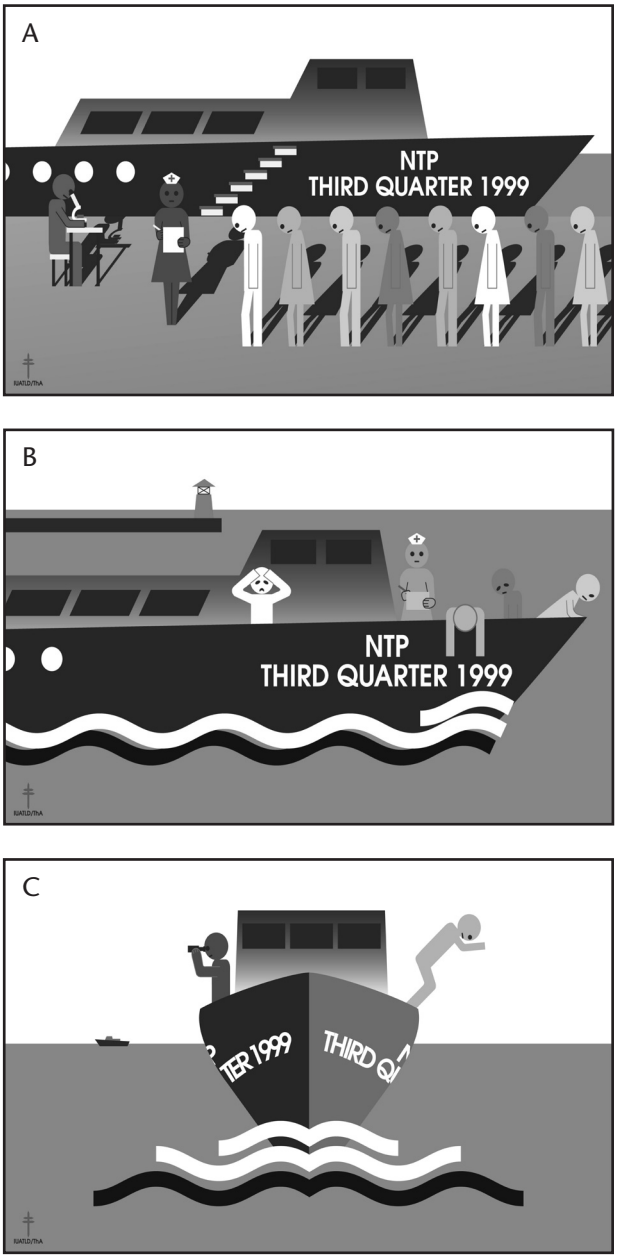
Cohort analysis evaluates the output or outcome in tuberculosis programs. The main aim of this analysis is to evaluate operational aspects of the program and, further on, the overall impact of the intervention rather than the treatment results of individual patients.

The cohort analysis is based on linking reports on case finding and reports on the results of treatment. The basic principle is that what goes in (entry, or case finding) must come out (output or outcome, that is, the treatment results of cases). Consecutive cases are evaluated without exclusions. Minimally, the outcome of all cases of pulmonary sputum smear-positive tuberculosis is evaluated on a routine basis. The outcome of other cases (smear-negative pulmonary and extra-pulmonary cases) can be evaluated as well, but it should be reported separately because it is important to distinguish between sputum smear-positive cases and others. The results of cohort analysis are not used in short-term planning of services and activities, but the routine reporting of results of treatment should ideally encourage good performance. The cohort method can also be used in interim evaluation (see Chapter 10).

Cohort analysis requires a cohort definition and outcome categories. The "definition of the cohort" refers to the time when patients are registered. There are six outcome categories (defined above): cured, treatment completed, failure, died, defaulted, and transferred out. One, and only one, option should be reported for each patient, and it is the event that occurs first that is reported. Cohort analysis is demonstrated abstractly in Figure 8.8, where the tuberculosis program is depicted as a boat. In Figure 8.8A, patients are registered one by one as they are enrolled in treatment after having been subjected to sputum examination. At the end of the quarter, embarkation is closed and a report on recruitment in the quarter is filed (case finding). The treatment can be likened to a long journey over potentially rough waters. Dedicated crewmembers provide continuous support and encouragement to the passengers throughout the journey (Figure 8.8B). They are constantly on the lookout for individuals who, for some reason, wish to abandon ship (Figure 8.8C). There needs to be a strategy for preventing this, as well as procedures to be followed when passengers go missing (Figure 8.8D). Finally, when the journey is over, the boat comes in, and it is time to report the results (Figure 8.8E). All passengers must be accounted for, as the report filed on disembarkation is compared to the report filed on embarkation.

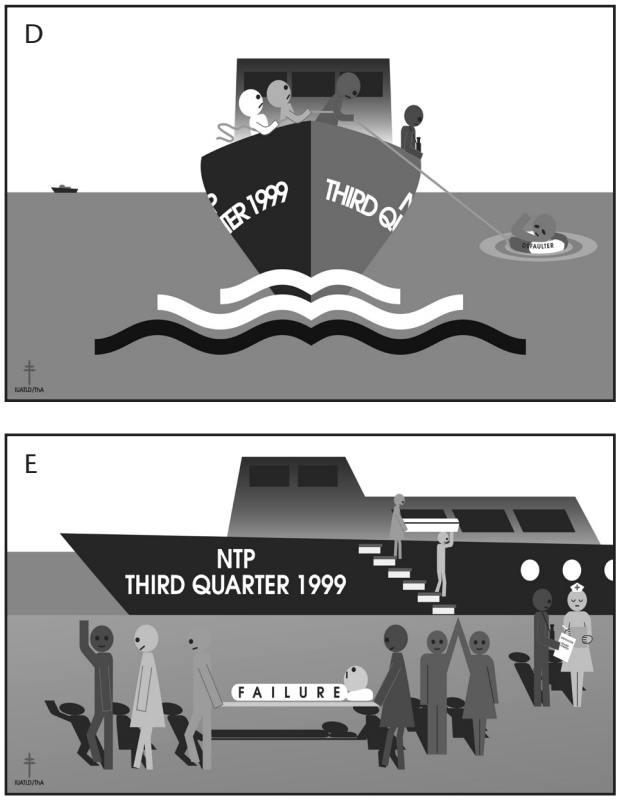
"New" is the only entry category of previously untreated smear-positive cases. In contrast, there are three classifications for previously treated smear-positive cases on entry: "treatment after relapse," "treatment after failure," and "treatment after default." Previously, the last two categories were not included in the quarterly report on case finding.[44,45] Later, this was changed[33,46] in response

Figure 8.8 Cohort analysis. A) Case finding and registration. B) Treatment and case management. C) Vigilance.



NTP, national tuberculosis program.

Figure 8.8 Cohort analysis. D) Defaulter prevention. E) Evaluation of treatment results.



NTP, national tuberculosis program.

to the argument that it was easier to include all cases than to tease out which cases should be reported and which not. For maximum detail, the categories are evaluated separately, but the overall results in treatment of sputum smear-positive tuberculosis would include all entry categories.

Cases registered as "transfer in" are not included in the cohort analysis of the facility to which they were transferred. Whenever possible, the treatment results in such cases should be reported to the transferring unit, which will take note of the results in their report. While this means that the results of a reporting unit do not only reflect their own efforts at case holding, but also the efforts of the units they communicate with,[47] transfer of patients between units is not a major operational problem if evaluation in the program is complete and treatment results are good. Although the "transfer out" and "transfer in"

options in the recording system may have been designed primarily to avoid double reporting,[48] a high transfer-out ratio indicates a problem in the organization of services. This problem needs to be solved before a meaningful evaluation can be based on the cohort analysis.[49]

In the tuberculosis program, case management and surveillance are based on illness episodes. There is a definition of "defaulter" to determine when the "episode" ends in case of dropouts. Some practitioners are reluctant to accept this procedure, wishing instead to keep the case open in the hope that the patient will eventually return to treatment. The same is true for the definition of failure; they hope that one day (perhaps with modification of treatment) the patient's sputum will become smear-negative. This misses the point of the outcome analysis: to evaluate the efficiency of the system of care and how well it performs in ensuring regular treatment and permanent cure within a reasonable time frame, thereby minimizing transmission.

The number and proportion of defaulters and the number of cases returning after default are indicators designed for the purpose of operational assessment. In some programs, a proportion of patients remain categorized as "still on treatment" a long time after treatment should be completed, as judged by the duration of the treatment regimens used. "Still on treatment" is not a valid outcome category. There should be a pre-set date when a cohort is closed for evaluation. The date when the report is due must take note of the length of the treatment regimens used and recognize that some irregularity may occur. For example, if the longest regimen in a treatment program is 8 months, a reasonable date for evaluation is one year after the last date for entering the cohort. This would allow for irregularities and slow communication. It would also coincide with the end of a quarter, which is convenient since the system is based on quarterly reports. If the treatment regimen is 6 months, then the reporting date might be 9 months after the end of a quarter, or else it might still be 12 months because it is more convenient and less confusing (when a report on case finding in a quarter is completed, the treatment results for patients registered in the corresponding quarter in the previous year is made). On the due date, patients who have not completed treatment should be assigned to a valid outcome category, such as defaulter, unless they can be classified as treatment failure, given that their treatment will have been unreasonably irregular.

There is one exception to the rule that consecutive cases are evaluated without exclusions: programs where there is a treatment option for multidrug-resistant cases. Although it is essential to decide a time limit for final (national) statistics on treatment results, it is important not to wait for results of treatment in new multidrug-resistant cases* before reporting any treatment results

*That is, patients who are shown to have multidrug-resistant tuberculosis already on diagnosis.

in a program, even if this means excluding these multidrug-resistant cases from the analysis temporarily, as explained below. This is because the duration of treatment is so much longer in multidrug-resistant cases. On the other hand, it can be argued that those patients who acquire multidrug-resistant tuberculosis during treatment should be evaluated as failures.

The results of cohort analysis are reported as rate or ratio—for example, cured as a proportion of all cases registered.[45] It has been pointed out that the denominator for official statistics should be all cases diagnosed rather than treated.[50] Even though the exact meaning of "registered" may be unclear, all cases that are diagnosed should be registered for treatment (this is comparable to analysis by intention to treat). Reported results of treatment of smear-positive patients registered in Nicaragua in 1993 are provided in Table 8.1 as an example. What the table does not show is that the success rate in new smear-positive tuberculosis patients varied considerably when looking at individual health departments (58% to 97%). The main problem was defaulting, which also varied importantly between departments. More detail regarding the results of retreatment could be obtained by looking at results in the different categories of retreatment cases separately.

It is important to analyze the results of treatment in sputum smear-positive cases separately and to divide these cases into new and previously treated cases, as shown in Table 8.1. It should be acknowledged that the picture is incomplete if only new cases are considered, as is all too common. Usually, however, the number of previously treated cases is small compared to the number of new cases. Consequently, the treatment results in previously treated cases do not influence the overall results importantly, even if they are different from the results of new cases. However, this is not invariably so. Where the proportion of previously treated sputum smear-positive cases is high and the result of treatment in such cases is considerably worse than in new cases, it could significantly influence the overall results in the program.

Table 8.1 Results of treatment in smear-positive cases registered in Nicaragua, 1993

	n	*Success* %	*Failure* %	*Died* %	*Default* %	*Transfer* %
New smear-positive	1695	78.2	2.7	3.7	10.0	5.4
Retreatment	317	71.9	6.0	3.2	13.2	5.7
Total	2012	77.2	3.2	3.6	10.5	5.5

Data from annual reports of the Nicaragua tuberculosis program.

Table 8.2 Retreatment cases in three settings

Setting	*Year*	*Sample*	*n*	*Relapse cases* %	*Returning defaulters* %	*Failure cases* %
Nicaragua*	1996–1997	Routine reports	577	62	26	13
Benin/Cotonou†	1992–2001	Selected (37% of all cases)	236	48	17	36
Botswana‡	1999	Representative survey	144	62	24	13

*From annual reports of the Nicaragua tuberculosis program.
†From Gninafon et al.[51]
‡From Talbot et al.[52]

Retreatment cases represent additional transmission over and above what is expected when looking only at new cases, and thus it is not illogical to lump them in with new cases for overall program evaluation and impact assessment. The proportion of the different categories of previously treated cases among all cases of retreatment varies. Examples from Nicaragua, Benin, and Botswana are given in Table 8.2. When the source is routine reporting, there may be misclassification depending on the health workers' skills at obtaining and recording accurate information. There may be misclassification in the data from Nicaragua in Table 8.2, given that it comes from routine reports. The data from Benin[51] and Botswana[52] are from studies, and so should reflect minimal misclassification. The sample in Benin was, however, selected rather than representative, and returning defaulters are underrepresented and failure cases are overrepresented.

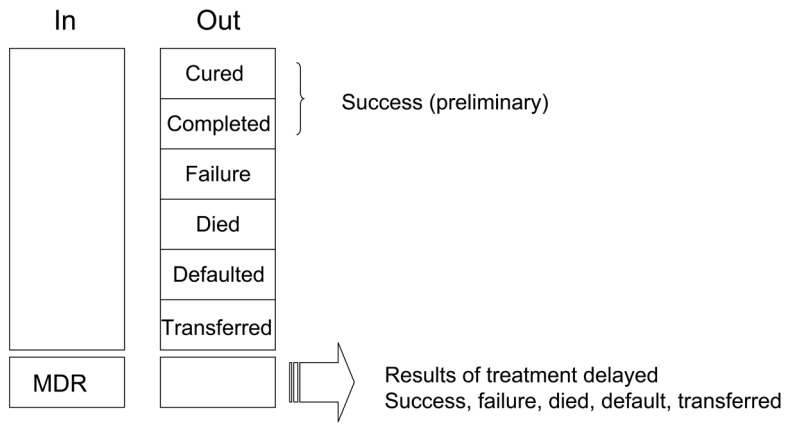
Information on the results of treatment is valid only if all the cases in the service area are included in the cohort analysis. Any selection criteria or exclusions must be described and explained in order to allow a meaningful interpretation of the data. It is often asked if all treatment units must participate in cohort analysis on a routine basis. Some argue that a representative sample of patients or units could give a reliable estimate of treatment results for predicting impact. Although this is a valid argument, representative sampling of patients or treatment units is difficult to do in practice. Furthermore, participation in routine outcome evaluation encourages accountability and stimulates case holding, which must be considered an important parallel effect of the exercise.

Multidrug-resistant tuberculosis

A policy regarding information management in multidrug-resistant tuberculosis is still in the development phase. Meanwhile, when making analyses from the

tuberculosis case register in settings where there is routine drug susceptibility testing at the time of diagnosis, a high prevalence of multidrug-resistant tuberculosis, and a treatment program for such cases, it may be useful to have the bacteriological confirmation of multidrug-resistant tuberculosis on entry override any type of patient case-finding category. This means that multidrug-resistant cases would be temporarily excluded from analysis of results of treatment, as demonstrated in Figure 8.9. A comparable procedure can be applied to patients who acquire multidrug-resistant tuberculosis during treatment. Eventually, such cases can be analyzed with other failure cases. How much the treatment results in multidrug-resistant tuberculosis influence the final overall results in the program depends on the proportion of multidrug-resistant tuberculosis in the material, the results of treatment in multidrug-resistant cases, and the results of treatment in other case types. The results of treatment from Lithuania are presented in Table 8.3 as an example. Even if the results in multidrug-resistant cases are quite poor, they do not greatly influence the overall results because they only account for roughly 12% of all cases. Nevertheless, the poor results are of great concern because these patients can be expected to remain infectious for a long time compared to other cases. What this means for transmission of *M. tuberculosis* in the community depends to a great extent on their socialization patterns. However, the main problem regarding multidrug-resistant cases in most settings is that many, if not most or all, multidrug-resistant cases are

Figure 8.9 The tuberculosis information system and multidrug-resistant tuberculosis



MDR, multidrug-resistant.

Table 8.3 Results of treatment in smear- and/or culture-positive new cases and relapses of pulmonary tuberculosis registered in Lithuania, 1993

	n	*Success* %	*Failure* %	*Died* %	*Default* %	*Transfer* %
New cases*	1086	76	2	10	11	—
MDR new cases	71	46	13	15	23	—
Relapses*	253	63	10	13	14	—
MDR relapses	120	36	13	27	23	1
Total	1530	70	5	12	13	—

Source: Arnadottir T, Blondal T. Report on project #69, April 2004. Task Force on Communicable Disease Control in the Baltic Sea Region. (Data from the National Tuberculosis Registry, Lithuania.)
*Excluding MDR cases.
MDR, multidrug-resistant.

not registered and not treated. In other words, the coverage of treatment is usually not known when estimating the impact of a treatment program for multidrug-resistant tuberculosis.

Analysis and interpretation

Interpretation of data cannot be standardized. Interpretation requires in-depth knowledge of the program and the context. What follows are only general observations and some examples.

Making comparisons between, for example, past and present performance, actual and planned performance (targets), and units or regions can be useful. Comparisons with mean performance are sometimes used to identify units that must be prioritized for intensive support. However, although there may be "good" and "bad" results, the terms are relative. If a facility with bad results is improving, then that is good. When comparing sites, the two sites must truly be commensurate. Comparison between countries is always difficult. Social and cultural factors differ considerably between countries, as do health systems and policies. Strategies—including recruitment into cohorts—may differ, and prevalence and patterns of drug resistance may vary, which will affect the values of indicators. In short, comparisons should always be made cautiously.

When data are overly processed, the information becomes meaningless for decision making. One example is what is referred to as the "fallacy of the mean." For example, a cure ratio of 85% at national level may sound good, but if the range is from 60% to 100%, then clearly there are units or areas in need of support and other units where credibility could be questioned.

If all patients who seek treatment in a program are treated and included in

the cohort analysis, the results of the cohort analysis evaluate the quality of the treatment program. However, whether or not the results are useful in predicting impact or speculating on the future course of tuberculosis in the community depends on the coverage of the program and of the information system. They are not useful in a setting where a large proportion of tuberculosis patients receive no tuberculosis treatment or receive treatment in a parallel or private sector which does not participate in the surveillance system.

Case finding

Generally speaking, validity is the most important problem in the interpretation of notification data.[25] Validity in this context refers to whether the data really measure what they are intended to measure.[28] Does notification reflect the incidence of the disease? Do any changes observed (trends) represent changes in incidence or something else? Assessment biases can pose a problem. Examples of such biases include access to and utilization of the health services, advocacy, reporting practices, incentives,* and changes in detection methods, such as new diagnostic tests or screening programs. Any changes in assessment biases over time pose a problem in interpretation of trends.

Changes in definitions introduce numerator problems in notification data. A more common problem is determining what denominator to use when calculating rates. Accessibility and attendance patterns can distort the actual geographical distribution of disease. Patients do not always opt to visit the health facilities assigned to them, or even those closest to their homes. Furthermore, administrative boundaries change. Demographic transition and migration further complicate the picture. Finally, populations are not homogeneous, and the proper interpretation of notification data would require stratification based on risk groups, which is very difficult if not impossible to accomplish on a routine basis.

Results of treatment

Although it is true that tuberculosis mortality data largely lost their value as an indicator of the size of the tuberculosis problem once anti-tuberculosis treatment was widely implemented,[21,31] a high death rate in a tuberculosis program which cannot be explained by a high prevalence of HIV infection, other comorbidities, or the advanced age of patients, can be considered to indicate an inadequate program. Consequently, tuberculosis mortality data are a useful indicator of the quality of tuberculosis control.[53] Tuberculosis deaths may be

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*One such example is from Taiwan, where linking reimbursement of drug fees to notification and introducing a notification fee resulted in an increase in reported cases.[35] The source of the increase was primarily from without the tuberculosis program, especially from general hospitals, and many reported cases could not be confirmed.

associated with inadequate or irregular treatment, insufficient access to health services, delay in diagnosis or drug resistance (or multidrug resistance), and also with preventable transmission of *M. tuberculosis*. However, the measurement in cohort analysis is "known death during treatment" (also referred to as "cohort deaths") rather than death from tuberculosis. How reliable an indicator this is depends on many things, such as whether the diagnosis of tuberculosis is always correct, whether the person completing the register is aware of all deaths, and whether the actual cause of death is always known.[53] To overcome some of these problems it is important to compare sites, look at trends, and conduct special inquiries or investigations in tuberculosis programs where the reported death rate is high. Verbal autopsies can provide information on tuberculosis deaths in the community that were not detected by the program.[54] In areas where HIV infection is common among tuberculosis patients and treatment of HIV infection is implemented, death as measured by the tuberculosis program could be an indicator of the quality of HIV care. Styblo, when speculating on the impact of the tuberculosis program, calculated the cure rate after excluding from the denominator those who died before treatment completion.[55]

Treatment failure is also a complex indicator. Failure can be managerial in origin, caused by a flaw in the administration of treatment or inadequate treatment regimens, or the result of the use of low-quality drugs. Apparent failure can also be explained by the presence of non-viable bacilli in sputum (see Chapter 4) or low-quality laboratory services (false-positive results), which should be detected with regular laboratory quality control. Treatment failure can also be a consequence of drug resistance. In a well-functioning program, treatment failure on "rifampicin-throughout" regimens is a good marker for multidrug-resistant tuberculosis.[56,57] Finally, early "relapse" soon after completion of treatment may indicate "missed" failure (that is, failure that went undetected and unreported).

It may be difficult to interpret a high proportion of defaulters without further investigation. The problem could be disguised mortality. If not, poor services or uncaring health workers, insufficient or ineffective communication with patients, services that do not fit the conditions and circumstances of the patients, in addition to any other problems in the organization or coverage of the services, all can contribute to a high defaulter rate.

If there is a high proportion of "transfer out," the cohort analysis is incomplete. A high transfer-out ratio indicates a problem of organization, access, or coverage of the services or a problem in information flow. A retrospective study in Malawi, referring to patients registered in 1999, found that the quality of data for patients who transfer was poor.[40] Transfers of patients are frequently seen as a challenging management task in high-prevalence countries, which is perhaps not strange when, in the 1990s, it was even considered difficult to track results of treatment if patients moved across state lines in the United States.[58]

Good results may also need analysis and interpretation. In case of a very high "cure" ratio, the credibility of the data should be considered. Perhaps some patients are excluded from the analysis, such as those lost from sight after diagnosis and before registration for treatment, migrants, or unaccounted deaths in hospitals. In case of very low "failure" ratio, the ability of the laboratory to detect failures should be investigated. A very low "death" ratio may indicate that patients die at home or in a hospital without any notification to the tuberculosis program.

Finally, regarding outcome assessment, "treatment after default" and "treatment after relapse," just like the hospital readmission rate, are "proxy" indicators for treatment outcome because patients only come back if they are not permanently "cured" (or become reinfected).

Case finding and treatment as a functional entity

It is important to look at the big picture when interpreting information from tuberculosis programs. Considering only one aspect of a program at a time may be misleading. For example, information referring to patients with pulmonary tuberculosis registered in Nicaragua from 1989 to 1995 is presented in Table 8.4.

Table 8.4 Analysis of PTB cases registered in Nicaragua, 1989–1995

	1989 %	*1990* %	*1991* %	*1992* %	*1993* %	*1994* %	*1995* %
Proportion smear-positive among new PTB cases	54.7	56.6	57.8	61.8	70.0	66.5	64.7
New smear-positive cases reported, *n*	1472	1478	1434	1552	1714	1615	1568
New smear-positive cases evaluated (percentage of reported cases)	100.6	101.8	101.9	99.4	98.9	103.2	102.8
Proportion of new smear-positive cases treated with the short-course regimen	78.5	82.4	85.0	88.7	95.4	95.4	95.3
Overall cure rate in all smear-positive PTB cases	68.8	69.8	70.3	73.1	77.2	78.1	79.9
Retreatment cases evaluated, *n*	368	337	375	337	317	269	289
Proportion of retreatment of all smear-positive cases evaluated	20.1	18.3	20.4	17.9	15.8	13.9	15.2

Data from annual reports of the Nicaragua tuberculosis program, and reports of technical consultants of The Union.
PTB, pulmonary tuberculosis.

The table shows that bacteriological confirmation in new cases improved gradually from 1991 to 1993, when it reached 70%. Between 1991 and 1992, the bacteriological status of new cases was systematically checked during supervision, and this clearly had an impact. From 1994 to 2003, bacteriological confirmation was, on average, above 70% (information not presented). The table also shows that the number of new smear-positive cases increased in 1992 and 1993. This statistic must be interpreted with improved bacteriological confirmation in mind. It is likely that a new baseline was reached in 1993. Since then, the trend in new smear-positive cases has been a decline. Evaluation (outcome analysis) is complete throughout the period. In 1994 and 1995, however, there is a trend that warrants investigation. Further, the table shows the final stage of expansion of short-course treatment from 1989 to 1993, when maximum coverage was reached, at roughly 95%. There continued to be exceptional patients who could not accept directly observed treatment, which was a prerequisite for short-course treatment in Nicaragua at this time. As of 1993, these exceptions were so few that they did not influence the overall results of treatment. Consequently, from 1995 onwards, it was no longer necessary to include expansion as a routine indicator in program monitoring, unless findings during supervisory visits would suggest the contrary. The overall cure rate in the program is low, but improves gradually. Table 8.1 was only a snapshot, but here the visible trend is reassuring. Also, the analysis is complete and has become more meaningful with improved bacteriological confirmation in new cases occurring during the period. More detail could be obtained by looking at the trend in defaulting, failure, and transfer out, and by looking at the different treatment regimens separately (for new and previously treated patients). It could be argued that the improvement in treatment results is too slow, but more information is needed before evaluating that claim. Finally, the table shows, as expected, that the number of cases on retreatment decreases as treatment results improve, which is a good sign. Looking at the different categories of previously treated cases would produce even more detail. Arguably, the proportion of retreatment out of all cases is rather high, even if it has decreased. Further information would be needed to elaborate on this issue.

When considering the long-term impact of a program, one can speculate about what the output as measured by the program means for the ongoing transmission of *M. tuberculosis* in the community. To state that death as a treatment outcome is not associated with ongoing transmission and, therefore, is not relevant to the public health objective of cutting the cycle of transmission,[59] is an oversimplification. With the death of a patient, transmission is certainly permanently arrested. However, death—if the result of tuberculosis—may be associated with an above average duration of transmission before the death occurred. In most cured patients, transmission will have been arrested permanently. However, some will relapse. These patients are likely to contact

the services again, where they will be registered as relapses and captured by the surveillance system as such. In a portion of defaulters, transmission will have been permanently arrested. The shorter the treatment before default, the higher the risk that the patients' condition will worsen and they will become infectious. They are then likely to return to the services, where they will be registered —and spotted by the surveillance system—as "return after default." Failure in new smear-positive cases means a prolonged period of transmission. This is captured by the surveillance system when they are re-registered as "treatment after failure." When retreatment fails, there may be no further treatment option. These patients will continue to transmit *M. tuberculosis*. For how long generally depends on the setting, for example, the prevalence of HIV in this patient group. The problem is complicated, as these patients will generally transmit multidrug-resistant bacilli. One needs to reflect on all these factors when considering the long-term impact of tuberculosis treatment programs.

Data validation

In the tuberculosis program, "data quality" refers to how well the data reflect the truth regarding activities within the program, not how well the data reflect the quality of laboratory results or the true disease burden out in the community. The former is the subject of laboratory quality control and the latter is the focus of community-based surveys.

"External validity" refers to whether findings can be generalized to other settings. This is not relevant for the routine tuberculosis information system because the data collected are used for case management and program monitoring locally, as discussed above. Information from a particular unit (service area) is not used to evaluate other units (service areas).

"Reliability" or "repeatability" refers to whether the information collected reflects the reality in the program: if two reports of the same results are sent, are they the same? This is an important issue for all information systems. The quality of the data obviously depends on the system functioning well at all levels. Impediments to data quality include inappropriate forms, poor recording and reporting, and errors in processing.[60] Reliability will improve if the information is verified systematically during supervisory visits[27] and used in operational research.[39,49,61] Quarterly operational meetings of tuberculosis program staff from different units may also be used for exchanging and verifying information. Such meetings were established in the program in Nicaragua in 1992. The meetings were useful for the purpose of improving information in the program. Similar meetings established in Malawi are reported to have been successful.[61]

Box 8.7 Simple validation of quarterly reports

Step 1: All units listed as reporting units in the program should report quarterly. There should be one report on case finding and one report on the results of treatment. If a report is not received on the due date, an inquiry should be made.

Step 2: In the quarterly report on case finding, the sum total of cases should be in accordance with the number of cases in individual categories. Furthermore, the number of new smear-positive cases should square with the number of cases reported in the cells for age distribution. Finally, the report should be compared with previous reports from the same unit. If there are important and unexpected differences, an inquiry should be made.

Step 3: Looking at the quarterly report on the results of treatment, the number of cases evaluated by category should be compared with the report on case finding for the corresponding quarter. If there is discrepancy, an inquiry should be made. The sum totals should also be checked. Finally, the report should be compared with previous reports on results of treatment from the same unit. If there are important and unexpected differences, an inquiry should be made.

Regular supportive supervision and feedback are an important incentive for staff to report quality data.[60] Simple validation of quarterly reports should be performed routinely at all levels where reports are received.[27] Box 8.7 shows how this can be done. Validation during supervisory visits, where reports can be compared directly with original data sources (registers, treatment cards, and other records), is important. The methods used during supervision in the tuberculosis program are presented in Chapter 10. Comparing actual and expected consumption (based on case-finding reports) of all or selected anti-tuberculosis drugs on a regular or ad-hoc basis is another validation mechanism. This is discussed in Chapter 9.

Action should be taken promptly when errors in recording or reporting are suspected. Usually, these are unintentional errors caused by staff that are new or inexperienced and need guidance. This guidance can be provided "on-the-spot" during supervisory visits or in formal training sessions. It may also happen that data are intentionally misreported or distorted in some way. This may occur if health workers fear reprisals for poor performance, if there is peer pressure and performances are being compared, or if there is a monetary or other incentive in inflating performance.[60] An amusing example of unintended consequences of incentives on data quality can be found in the "fee for rats killed" policy that was introduced in response to a rat infestation problem in China.[60] To maximize their potential gain, individuals began to breed rats in order to kill them and collect the fees. In each of these cases, the reports arrived on

time and showed that the worker had met the reporting requirements for the given month.

Errors can occur during transcription, transmission, and processing of data at all levels of an information system. This is one of the reasons for minimizing the number of levels and keeping the system simple and straightforward. In Botswana, for example, information generated by an electronic tuberculosis register suggested that an unacceptably high proportion of pulmonary tuberculosis patients did not have pre-treatment sputum smear microscopy performed. Validation was done by cross-checking the electronic register and paper-based laboratory registers.[38] The results showed that, in reality, microscopy had been performed in the majority of these cases, but that the information was not always transcribed locally and therefore had not made its way into the electronic register. The investigators concluded that reinforcement was needed for information on indicators to be transferred as expected. A general lesson from this study is that every step in the information circuit represents a potential opportunity for introducing discrepancies. Consequently, every step needs to be supervised. In the case of Botswana, information on the results of sputum smear microscopy needed to travel from the laboratory register to the treatment cards and the unit register.[38] From there, the data traveled to the district register. Finally, the data traveled to the national electronic register.

It should be stressed that data sets are seldom error free. The goal is to try to ensure that there are as few errors as possible and that these few errors are random rather than systematic. Random errors are likely to cancel out in the final estimate and should not bias evaluation or decision making at higher levels.

Proposed modifications

It has been suggested that the tuberculosis information system could be simplified. One suggestion is to prioritize data on smear results at presentation, rates of adherence and completion of therapy, and mortality rates.[62] Others suggest that it would be sufficient to report the number of cases registered (so that drug requirement can be estimated) and the number of defaulters (so that case holding is guaranteed), leaving all other information in the tuberculosis register to be used only for supervision purposes.[63] These suggestions are, in fact, quite similar to the current recommendations, except that the latter requires the classification of registered cases and result of treatment in all cases. This simplifies things if one assumes that it is easier to include all patients in an outcome evaluation than to include only some (those who default). Adherence rate (other than treatment default) is a complicated measure and perhaps best left for operational studies in areas where surveillance and supervision suggest there are problems.

The international perspective

Surveillance of a transmissible disease like tuberculosis is important on the global level, particularly with the considerable mobility of populations in modern times. To facilitate mutual understanding between countries, it is important to have universal agreement on methods and definitions, including both case definitions and outcome definitions. A tuberculosis information system, if universally adopted, would enhance communication between countries. In order to encourage consistent use of definitions, the WHO (whose mandate includes developing norms and standards in international health) recently took the initiative to publish agreed international definitions.[33] As previously noted, these definitions are consistent with those published in the Orange Guide,[34] which in turn are based on the practices and experiences in the Union collaborative programs.

Although reports issued by the WHO on the global tuberculosis situation, as well as regional reports such as the EURO-TB reports for Europe, are useful, it must be kept in mind that the coverage, reality, problems, and challenges that lie behind seemingly similar reported indicators may be quite different. In other words, comparability is not guaranteed. Still, averages are calculated and comparisons are made. Some of the averages are meaningless because they are calculated for vast territories that have a wide range of values. It must be stressed that it is the values and trends in specific locations that are important for action in tuberculosis control locally, and by extension, ultimately for the global situation.

Summary and conclusions

When applied to information systems, the terms “vertical” and “integrated” can be misleading. A unified health information system, separated from other aspects of the health services, can be seen as a vertical approach to information. However, in programs traditionally referred to as vertical, such as the tuberculosis program, information is integrated with other activities and used in everyday decision making at all levels.

It is important to avoid overlap between parallel information systems. The tuberculosis program should not collect data that are collected elsewhere and should feed into a national health information system, which in turn should avoid collecting routine health unit-based data on tuberculosis in a parallel system. It is crucial to decide who collects what information and how systems will collaborate. Once these decisions have been made, they must be fully implemented. Whether implementation succeeds or fails will depend on the availability of staff, training and supervision of health personnel, the relevance of the system(s), and, most importantly, on the commitment to use the information generated.

There are frequent and important problems with routinely collected data in health care. However, these problems can, to a large extent, be overcome by well-designed information systems. The primary role of information systems is to support decision-making and action at the local level. In terms of surveillance, a focus on outcome is important in tuberculosis programs.

Finally, information is just one of many inputs into the decision-making process at administrative levels. Political decisions are not necessarily driven by knowledge and information. Advocacy, leadership, and lobbying are just as important here. In this respect, the role of the tuberculosis program does not end with the publication of annual reports. A report is merely the first step in the continuous process of influencing decision-making and shaping future policies.

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9

Materials management

How is drug supply managed in tuberculosis programs? Do the same principles apply as in the general health services?

The availability of drugs may be the most important factor determining patterns of health care use. As one woman in Tanzania put it, "People go anywhere where drugs are available."[1] Materials management is a key component of tuberculosis control, but it is often a major weakness in treatment programs. This chapter looks at medical supply systems in general and the methods recommended in the Union collaborative programs in particular. It identifies differences between tuberculosis programs and the general health services, differences that warrant methods of drug financing, management, and distribution that deviate from standard methods.

The materials management cycle can be divided into four basic functions: selection, procurement, distribution, and use.[2] In the case of tuberculosis programs, selection concerns setting a national policy on diagnosis and treatment of tuberculosis, defining treatment regimens, and publishing clinical guidelines; procurement involves quantifying requirements for drugs and materials, selecting procurement methods, managing proposals and contracts, and assuring the quality of products; distribution includes customs clearing, stock control, store management, requisitions, and delivery to depots and health facilities; and use refers to diagnosing tuberculosis, prescribing and dispensing anti-tuberculosis drugs, and patients consuming such medications.

Issues concerning the selection and use of anti-tuberculosis drugs are discussed in Part I. The current chapter focuses on inventory management and quantifying requirements for drugs and materials related to the diagnosis and treatment of tuberculosis, requisition of medications and materials, distribution to health facilities, and store and stock management. Other aspects of procurement and distribution, while very important for the functioning of tuberculosis programs, are beyond the scope of this publication. The reader is referred to other publications for details on managing drug supply in general[2] and procurement of anti-tuberculosis drugs in particular.[3]

The discussion in this chapter borrows from *Managing Drug Supply*, a publication of Management Sciences for Health (MSH) in collaboration with the WHO and the Action Programme on Essential Drugs.[2]

Background

"Essential drugs" is defined as a limited range of affordable drugs to meet the basic needs of a population. The idea of working with a limited range of drugs goes back a long time; consider, for example, the few medicines carried by physicians on home visits and aboard ships.[2] A basic list of medicines for entire populations was developed in Norway before 1940 and, as early as the 1950s, Papua New Guinea had a policy based on a list of essential drugs.[2] In 1975, the WHO defined the concept of essential drugs, and in 1978 in Alma Ata, they recognized essential drugs as one of the elements of primary health care.[2] Over time the list of essential drugs has grown. Relevant to this chapter, the list contains the first-line anti-tuberculosis drugs: ethambutol (E), isoniazid (H), rifampicin (R), streptomycin (S), pyrazinamide (Z), and thioacetazone (T).

A 1991 quality survey of Papua New Guinea's hospitals found that all of the institutions included had experienced drug shortages during the past year: 85% cited shortages at area medical stores as a reason; other reasons cited were late placement of orders and late shipments.[4] At the time of the survey, three hospitals had no stock of an essential anti-malaria drug, and four other hospitals were out of stock on two other medications. Interestingly, the investigators weighted drug supply at 10% of the total score for quality, whereas clinical care was weighted at 52%. Very little emphasis is placed on drug supply issues in spite of the fact that the health services depend on a stable drug supply for standard treatment of common diseases.

In 1982, Bignall, discussing his personal view on why tuberculosis control had failed, underlined the importance of drug supply: "Drugs . . . must reach the patient and not rot in a central store or be sold on the 'black market (p. 172).' "[5] Drug supply is commonly one of the weakest points in the health systems and tuberculosis programs of developing countries. Availability of drugs influences the quality of care as perceived by patients, and is an important determinant of the utilization of health services.[6,7] Medical supply procurement and distribution methods are highly variable depending on the setting. Ideally, this function is handled in an integrated system for all medical supplies. However, the country needs a strong, competent, and properly controlled pharmaceutical sector for it to succeed. Even if there has been recent progress in this sector, there is still a long way to go in many countries. As an example, a recent study carried out in Ugandan health facilities estimated that 67% of the drugs leaked out of the public system.[7] The investigators described various leakage mechanisms, such as ghost patients, drugs not being given to real patients according

to prescriptions, or simple theft of drugs from the shelves. The findings suggested that high-level officials or employees were involved in the leakage problems. When drug leakage of this magnitude occurs in tuberculosis programs, the fact that infectious patients may not receive optimal treatment or be treated at all due to a lack of drugs is not the only problem. There is also no way of knowing whether the drugs that leak out of the system are used safely. Thus, there is the threat that improperly administered drugs could create drug resistance, which in turn could undermine the very efforts of the program itself.

On the basis of ethical grounds and for disease-control purposes, the Union collaborative tuberculosis programs intervened in order to ensure that antituberculosis drugs were supplied to all treatment centers. They also needed to ensure the rational use of the drugs supplied to the programs. Historically, practices in the various programs collaborating with The Union ranged from vertical supply systems, which may or may not have used state storage mechanisms, to fully integrated systems with strong coordination between the national tuberculosis program and the national system for medical supplies. The approach chosen by any given program depended on the context and, undoubtedly, so did the success.

Drug supply, financing, and sustainability

Three main mechanisms for drug distribution exist in low-income countries: a private commercial sector largely concentrated in urban areas, a private nonprofit mechanism commonly used by nongovernmental humanitarian organizations, and the governmental sector.[8] In some African countries, private nonprofit organizations may be responsible for as much as one quarter of all health care provided.[8] These organizations, commonly serving remote areas of limited commercial appeal and often skillfully managed, frequently charge user fees and apply cross-subsidization.[9] Apart from their incomplete coverage—a serious drawback—some observers contend that this mechanism has been more successful in distributing drugs in sub-Saharan Africa than the governmental sector.[9] It is debatable, however, whether humanitarian organizations have prevented development in the public sector by providing partial relief without completely resolving the issue of drug supply and distribution.

In affluent countries, the private commercial sector has a leading role in drug supply for the general population. In developing countries, though, the private for-profit sector has historically failed to supply drugs to more than the wealthiest of their population. People in rural areas specifically have suffered a lack of access to essential drugs.[8] With this in mind, these countries' governments, often with donor support, attempted to supply and distribute essential drugs free of charge to patients.[2,8] However, due to the failing economies of developing countries, partly rooted in deteriorating terms of trade,[10] government

financing of health services diminished and free drug policies were deemed unsustainable.[2]

Public sector systems are expected to reach everyone, not only those who are easy to reach, or those who can afford to purchase high-priced drugs.[8] While increasing the population served results in larger purchases, and consequently lower unit prices (that is, economies of scale), if that population is hard to reach the matter is more complex. The average cost of supplying a population increases when services are extended to remote areas. This is due to transport costs, spoilage, etc., and may result in "diseconomies of scale."[8] For this reason, the private commercial sector shies away from operating in such areas. With fiscal crises, the increasing demand for services, and growing populations, implementing drug-financing strategies that ensure equal access to an uninterrupted supply of medicines is enormously challenging for governments.

In 1985, the World Bank first raised the controversial issue of introducing user fees for financing health services in poor countries, and in 1987 they officially promoted the idea.[11] The Bamako Initiative, presented by UNICEF in 1987, launched an internationally financed fund for essential drugs in sub-Saharan Africa.[12] Community drug programs were linked to the stated goal of the Bamako Initiative to strengthen and increase access to primary health care.[12,13] These initiatives sometimes formed part of broader cost-sharing programs, where fees were charged not only for medicines but also for consultation, diagnostic procedures, and hospitalization.

The term "revolving drug fund" refers to programs where fees are charged for drugs and the drug supplies are replenished using the income.[2,14] Theoretically, a revolving fund needs a onetime start-up capital investment to purchase the initial stock of essential drugs and then runs on the income from drug fees (thus the term "revolving"). Not to be confused with private pharmacies in a private for-profit sector where the primary objective is to maximize profit, revolving drug funds seek mainly to maximize access to drugs and improve the quality of care. Revolving drug funds were typically implemented in rural areas where competition with the private commercial sector was unlikely.

Those opposed to revolving funds point out that a large part of the income is spent on operating the fund itself and that government spending on health may decline as a result of the introduction of drug fees. As a consequence, overall financing of health care may remain the same or even decrease.[2] They argue further that revolving funds do not guarantee improved drug availability and other quality measures; that fees create a conflict of interest that can encourage overprescribing; and that drug fees may reduce overall utilization of health services with serious consequences for the population.[15] In many settings, however, drug funds were a response to declining utilization in the first place.[10]

Revolving drug funds did in fact prove difficult to implement.[9,14] Capital-

ization and operating costs were frequently underestimated, and implementation was often insufficiently planned, with too rapid expansion.[14,15] Revolving funds tended to decapitalize and thus stopped revolving. Few examples of successful large national revolving funds exist. For various reasons—such as pricing below true replacement costs, failure to collect payment, and underestimation of losses from theft and deterioration—costs recovered from user fees introduced in health services in developing countries have been low,[14] frequently less than 10% of recurrent expenditures.[2] This proportion is somewhat higher when looking only at drug funds as opposed to the broader cost-sharing programs designed according to the Bamako Initiative. As a result of lower than expected revenue, systems relying on user fees have not necessarily improved drug availability. A World Bank evaluation found that utilization of health services and quality of care frequently declined with the introduction of user fees, sometimes dramatically.[2] Drug availability increased in less than one half of the countries studied, but where it did, utilization of services tended to increase. Virtually no large-scale program generated sufficient funds to cover all non-salary costs where this was the objective.

In Cameroon, one of the few examples where equity, access, and quality improved under a system of revolving funds, utilization of services increased with the introduction of a revolving fund. It covered 62% of recurrent costs in the third year of implementation.[10,13] This example underscores the fact that even in a relatively wealthy nation such as Cameroon, implementation of a revolving fund takes time, and success depends on donor support to subsidize recurrent costs for a minimum of five years. Phased implementation, training, management, and supervision were also identified as key elements to success.

Cost-sharing strategies and private sector involvement promise greater coverage of essential drugs needs so that public resources can be used for prevention, communicable disease control, and the poorest segments of the population.[2] In theory, diagnosing and treating tuberculosis as priority interventions for public financing could increase the sustainability of tuberculosis programs in the long run. However, given the practical experiences, it may be unrealistic to expect this to be the case in the near future.

Low-income countries are still far from self-sufficient regarding pharmaceuticals. Donors and, particularly, bilateral and multilateral aid agencies are often reluctant to subsidize recurrent costs such as drugs and pharmaceuticals,[9] in part because it requires long-term commitment. Politically motivated donors find it difficult to make such commitments knowing how frequently and unpredictably political priorities shift.

When the programs are well run and they clearly express what resources are needed, governments should find it easier to take over program financing in the long run. The Nicaraguan government, which assumed responsibility for financing anti-tuberculosis drugs in their national tuberculosis program in

the mid-1990s, provides an example of sustainability. A number of factors contributed to this course of events: they chose a low-cost option in treatment strategy; they used generic drugs of good quality at low cost; the program used well-established quantification of requirements and costs; there was visible success when examining program indicators; donor support for recurrent costs existed for a decade; and there was consistency in the dialogue between the donor* and the government throughout.

Special considerations concerning anti-tuberculosis drugs

While tuberculosis is no longer regarded as a disease requiring hospitalization, its treatment in the ambulatory setting is subject to certain conditions.

Exemption from user fees

Exemption policies to safeguard vulnerable groups' access to health care are usually included in user-fee programs. The public health arguments in favor of exemption policies are strong. As an infectious disease with consequences not only for the individual patient but also for public health—considering both the risk of infection and the risk of development of drug resistance—tuberculosis is commonly classified as an exempt health condition.[14] Tuberculosis, often considered a marker of poverty, affects the poor disproportionately with its relatively costly treatment. Exempting tuberculosis patients from user fees is an indirect way of exempting the poor. As a consequence of scarcity of resources or problems of overdiagnosis, exemption is sometimes granted only to smear-positive patients and to the most seriously ill smear-negative patients. However, this controversial policy can compromise credibility, affecting case detection. The credibility of the health services depends partly on satisfying all users.

From an administrative perspective, exempting tuberculosis patients is both practical and feasible, and preventing abuse is relatively easy if tuberculosis cases are clearly defined. These characteristics are considered prerequisites for making a condition exempt from user fees.

Directly observed treatment

In ambulatory settings, health workers may need to administer anti-tuberculosis drugs in directly observed treatment programs, instead of allowing self-administered treatment. Even if the health services rules allow it, dispensing medicines directly to the patient from a pharmacy or rural dispensary may contradict the policy of a tuberculosis program. Dispensing anti-tuberculosis drugs to patients via the tuberculosis program goes well with exempting tuber-

*A Norwegian nongovernmental organization.

culosis patients from payment of drug fees (the patient does not need to go to the pharmacy and the issue of payment never arises).

Fixed-dose combinations

Because anti-tuberculosis drugs should never be used in isolation but always in combinations of two or more drugs, the argument for introducing combined formulations of drugs is strong. Some health professionals justify fixed-dose combinations based on the advantage they have over single compounds in facilitating adherence to treatment—for both the patient and the practitioner—and in preventing drug resistance. However, combined formulations go against the essential drugs doctrine that stipulates that essential drugs be available as single compounds,[2] and tuberculosis experts have debated intensely over fixed-dose combinations. The arguments against the combinations may originate with a strong statement issued in 1969 by the National Academy of Sciences in the United States, condemning the use of fixed-dose combinations of antimicrobial agents in general, although this statement did not address the treatment of tuberculosis.[16]

Many developing countries have been using fixed-dose combinations of isoniazid and thioacetazone extensively since the early 1960s.* The programs collaborating with The Union in the early 1980s also used fixed-dose combinations of isoniazid and rifampicin.[18] The Union's Committee on Treatment, in 1988,[19] and the WHO, in 1991,[20,21] both recommended the use of fixed-dose combinations. By 1994, these combinations were available at prices comparable to those of single preparations.[22] In 1995, two- and three-drug combinations containing rifampicin were included on the WHO model list of essential drugs,[23] and recently a four-drug combination was added.[24] As the number of fixed-dose combinations of anti-tuberculosis drugs found on essential drugs lists increases, programs must adapt.

Fixed-dose combinations prevent monotherapy (other than functional monotherapy), and provided that bioavailability is guaranteed and the dosage of each ingredient meets the requirements of a defined population group, fixed-dose combinations facilitate delivery of accurate dosages. These combinations are expected to reduce the development of drug-resistant tuberculosis. Those in favor of fixed-dose combinations claim that their use simplifies treatment, minimizes prescription errors, increases both patient and provider compliance, and reduces the risk of misuse of rifampicin for conditions other than tuberculosis.[25–27] They also argue that fixed-dose combinations facilitate drug supply management and prevent out-of-stock situations, during which some drugs are

*Thioacetazone was well tolerated in South America and by East African populations (before the HIV pandemic) but less well tolerated for example by the Chinese population of Hong Kong and Singapore.[17]

continued while others are not available. Some believe, however, that the variety of fixed-dose preparations, combinations, and dosages available has complicated supply management and has not helped the market expand, a necessity for lowering drug prices.[23,26] Technical experts and organizations eventually unified their recommendations on combinations, hoping to influence the market and prices. The resulting formulations aided the standardization of case management recommendations.[28]

Opponents of fixed-dose combinations emphasize that bioavailability of rifampicin in combined formulations is difficult to ensure.[26,29] They also argue that fixed-dose combinations, unless available in a variety of dosages, lead to inappropriate dosing, causing adverse effects in patients of low body weight, with consequent noncompliance.[30] Management of these adverse effects is more difficult with the combination drugs. The expiration period of fixed-dose combinations is shorter than that of some of the single drugs, which may lead to increase in drug waste. Also, the use of fixed-dose combinations does not do away with directly observed treatment programs, as drug resistance can develop if there are multiple interruptions of treatment.[31] Or, if patients reduce the number of tablets they are taking without being instructed to do so, the concentrations of all the drugs in the combination would drop to subinhibitory levels.

As more and more fixed-dose combinations become available, concerns grow regarding quality and, in particular, the bioavailability of rifampicin in the various products. Low rifampicin bioavailability in fixed-dose combinations is a known problem.[32] A joint statement from the WHO and The Union, approved in October 1993 and published in 1994, reemphasized the importance of demonstrable bioavailability of rifampicin in fixed-dose combinations.[33] However, only recently, in 1999, was a quality-assurance protocol for assessing rifampicin bioavailability in combined formulations published.[34]

Restrictions on the importation and sale of anti-tuberculosis drugs

Realistic laws and regulations are needed with serious consequences for the lack or misuse of drugs.[2] In many developing countries, the private pharmaceutical market is largely uncontrolled and partly operated by laypeople rather than qualified pharmacists. Control over the quality of antibiotics, especially anti-tuberculosis drugs, on the market as well as the prescription and use of these drugs is important. Substandard products and inappropriate use leads to the development of drug-resistant organisms, which may result in serious public health problems. Multidrug-resistant tuberculosis is a noteworthy problem today in areas where poorly run tuberculosis programs have operated.

Regulations regarding the importation and licensing of pharmaceutical products are important public health measures for tuberculosis control in developing countries, and restrictions on the sale of anti-tuberculosis medicines are essential to preventing or arresting the development of drug resistance. The

1964 Expert Committee on Tuberculosis recommended that anti-tuberculosis drugs be made available only to physicians and others authorized by the health authorities.[35] Few low-income countries, however, have attempted, let alone succeeded at, implementing such restrictions. In Nicaragua, restrictions on the sale of anti-tuberculosis medicines on the private market appeared to work well in the 1980s and 1990s when import of pharmaceuticals was well regulated.[36] However, such measures are not easy to implement when a flourishing private drug market exists and powerful interests are at stake. Some experts believe that legislative action, such as requiring labels ("For tuberculosis treatment only" or "Available free of charge only in health services linked to the National Tuberculosis Program"), might help in reducing the misuse of anti-tuberculosis drugs as well as in preventing pilferage within the government sector.[23]

Materials management systems

Five basic systems exist for the organization of drug supply within the government sector: a central medical store, an autonomous supply agency, direct delivery, a prime vendor, and a fully private system.[2] Except for the private system, all of the above take advantage of economies of scale wherein a central authority purchases large quantities of medicines for which they can negotiate favorable prices.

In a central medical store system, the traditional system in developing countries, a central unit procures and distributes medical supplies, usually under the Ministry of Health or an autonomous or semiautonomous agency.[2] In a direct delivery system, a government office still undertakes procurement but the supplier distributes directly to peripheral points. For a prime vendor system, the government contracts an agency independent of the supplier to manage distribution. Private pharmacies provide medicines in a fully private system with or without the government taking measures to ensure equity. Mixed systems are common; the various types of units, services, or drug categories go through different management mechanisms.

Depending on where the responsibility for needs assessment and requisition lies, one of two common supply systems is used: "pull," or requisition, systems and "push," or allocation, systems.[2] In a pull system, health facilities order drugs from a supplier according to a local determination of need. In contrast, in a push system, a central authority determines, based on a distribution plan, the quantities to be sent to health facilities. The advantage of the pull system is the close involvement of the staff assessing needs and managing the inventory at health facility level. Generally, a pull system is preferable if sufficient management capacity exists or can be established locally and competent staff can be well trained. The success of the system depends to a large extent on supervision and monitoring.

Finally, systems are referred to as "loose drugs systems" or "kit systems." In the former, the supplier dispatches quantities of loose drugs according to the number of tablets, capsules, or vials ordered. In the latter, either requirements for individual cases (that is, full treatment courses) determine the packaging and dispatching of the drugs; or packaging and dispatching are "service based" or "population based," and the amount required by a health facility is estimated based on morbidity patterns and population. Population-based estimates tend to over- or underestimate demand unless sufficient attention is paid to identifying the realistic target population.[14] Population-based estimates can also be very inaccurate if drawn from burden of disease estimates rather than actual utilization of services.

Materials management in tuberculosis programs

Whether in a vertical materials management system or in a national system for medical supplies, important general principles regarding the estimation of requirements and the distribution and monitoring of supplies for diagnosis and treatment must be established.

Materials management is a very important element of treatment programs. Surprisingly often, program personnel pay little attention to this subject, and as a result, it is commonly a major weakness in national tuberculosis programs. Medical staff are usually interested in issues related to diagnosis and treatment, and many consider materials management tasks to be complicated and cumbersome, if not boring. They tend to postpone or even ignore these tasks altogether until a crisis looms. Materials management may be improved by integrating it within a general materials management system rather than entrusting the job to medical staff in a vertical program. However, integration per se does not guarantee accurate results. Here, as in the information system, keeping supply management simple is crucial to maintaining staff motivation and guaranteeing task completion. Success, whether in a vertical or an integrated system, will depend on following an agreed upon process and monitoring performance.

When discussing materials management systems, record keeping and requisitions must be considered, as well as the frequency with which orders are placed, distribution mechanisms, and the balancing of service and stock levels. In any inventory management system, different drugs and facilities usually require different methods.[2] Special programs such as the tuberculosis program may use a unique method for quantifying requirements and ordering drugs.

Consumption is relatively stable in tuberculosis programs—even when there are upward and downward trends—which makes materials management easier. The system recommended by The Union is simple and straightforward, and problems are often the result of insufficient follow through on the process and a lack of interest.

Traditionally, the materials management systems in the Union collaborative programs stocked loose drugs, recorded inventory received and distributed on stock cards, and placed orders quarterly at intermediate and peripheral levels and annually or semiannually at the central level. Requisition forms included reports on stock levels at the time of the order. As a rule, distribution was quarterly to intermediate and peripheral levels, and the service and stock levels were balanced, equivalent to a three-month consumption estimate at intermediate and peripheral levels but six- to twelve-month consumption estimates at the central level depending on the setting.

The design of the system

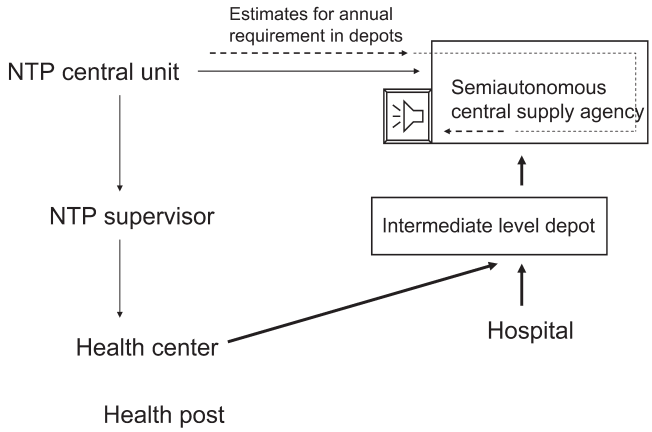
Public sector supply systems in developing countries are frequently three-tier systems, with central, intermediate (for example, regional or provincial), and peripheral (district, for instance) level depots. The service levels—hospitals and tuberculosis management units—are supplied from the depots. Different distribution methods may be used in getting supplies to the depots and to the service levels.

Ideally, intermediate and peripheral levels are responsible for quantification, requisition, and accountability in a decentralized pull system, but procurement remains at the central level to better guarantee high-quality drugs at reasonable prices. "Inventory management" is defined as the management of the routine ordering process.[2] Someone, preferably the tuberculosis manager, at the management unit is responsible for this activity. Supporting this manager is very important initially to build up the local capacities for inventory management. Frequent turnover at the peripheral level or assigning these duties to lower level employees often hampers the efforts at capacity building in low-income countries, and can hinder implementation of a "pull" system. At depot levels, either the tuberculosis supervisor or special logistics coordinators, working closely with the supervisor, are responsible for inventory management.

In Nicaragua, The Union procured anti-tuberculosis drugs annually upon receipt of a requisition from the central unit of the tuberculosis program. Since 1991, the program in Nicaragua has used a mixed model for materials management: a pull system with built-in central monitoring and control. Centrally assigned quotas based on case finding in the previous year serve as a control mechanism, as in an allocation system. The central unit of the tuberculosis program transmits this information to the semiautonomous central supply agency, CIPS (Centro de Insumos Para la Salud) at the beginning of each year. The central supply agency compares this information to quarterly requests from the intermediate level and sounds an alarm if too little or too much product is "pulled." Estimates and requisitions at all levels are based on the number of cases registered or reported. The system is demonstrated in Figure 9.1. The

Figure 9.1 Tuberculosis materials management system in Nicaragua in the 1990s

The dotted line indicates the central control loop; the heavy arrows indicate drug requisitions, and the light arrows indicate supervision. The central unit estimates annual requirement from case-finding reports of the previous year. Health centers and intermediate depots base quarterly requisition on case-finding reports in the previous quarter. Hospitals may use a different system based on past consumption or critical stock level. When a case-finding report is sent from the intermediate level to the national tuberculosis register, a form with calculations of drug requirements and requisition is sent as well. A simpler requisition form is sent to the central supply agency at the same time. A comparable process should be in place as regards requisition from the services level to intermediate-level depot.



NTP, national tuberculosis program.

central unit is thus informed of irregularities and can investigate and advise. The central unit also visits CIPS sporadically for a visual stock count, to inspect stock cards, and to review the distribution to intermediate level. In addition, they make occasional visits to intermediate and peripheral levels as part of the overall tuberculosis supervisory system.

Quantifying requirements

Anti-tuberculosis drugs and treatment supplies

Estimates of drug requirements can be drawn from an analysis of epidemiological profiles, case notification, services utilization, or past consumption.[37] Pharmacists generally favor the consumption analysis method, and epidemiologists usually prefer the morbidity analysis method.[2]

Data on drug consumption ideally give the most accurate prediction of future needs, if the data come from a stable supply system with a relatively uninterrupted and full supply line.[2] In reality, however, consumption data are often misleading. For example, if past shortages or drug donations are not accounted for, the real need is underestimated.[14] Furthermore, consumption data may or may not reflect rational prescription and use of drugs. Therefore, the consumption analysis method may be unrealistic and can perpetuate irrational use of drugs if it is not linked to other information.

The morbidity method forecasts the theoretical quantity needed for the treatment of specific diseases.[2] Reliable data on morbidity patterns and patient attendances are required, and the analysis projects drug needs, assuming some standard treatment guidelines. This is sometimes described as a complex and time-consuming method, and there can be major discrepancies between projections and utilization.

The Union recommends a modified morbidity method. Surveillance reports and treatment guidelines are used for predicting requirements; these are then adjusted by noting stock levels at the time of requisitions (the stock level reflects actual consumption).

The treatment regimens, described in the tuberculosis program manual, determine the drugs that need to be available and the full treatment course length. The dosage and strengths of the drugs used in national programs should be fixed and match those published in the manual. The number of tablets of the different drug formulations needed for an average adult's full treatment course is calculated for each regimen. Dosages determined using weight brackets would be calculated using the average or the heaviest weight bracket.

The quarterly reports on case finding determine the number of patients to be treated. According to practices outlined in the fifth edition of the Orange Guide, the exact number of patients enrolled in each treatment regimen should be reported.[38] For each treatment regimen, the number of tablets is multiplied by the number of patients. The total requirement for each drug in a quarter is the sum of the drug requirements for all regimens used in the program.

The same method is used at all levels. When determining the annual quantity needed at the central level, the number of patients reported in a year is used. The method is demonstrated in Table 9.1, using information on case finding from the tuberculosis program in Nicaragua.[39]

Table 9.1 is easily adapted to the treatment regimens and drug formulations used in any program,* including blister packs, kits, or different fixed-dose

*The examples presented in this chapter use either the fifth version of the Orange Guide[38] or the forms that were used in specific programs at the time the data were generated. As recommended dosages and drug presentations may vary or may have changed, the drug presentation and drug requirements per regimen may not equal the latest recommendations.

Table 9.1 Hypothetical requirement based on case finding in third quarter of 2001, Managua, Nicaragua*

	A *2[RH]ZE/6[TH]*			B *2S[TH]/10[TH]*			C *Retreatment*†			D *Requirement Total*
Item	*Cases*	*Factor*	*Total*	*Cases*	*Factor*	*Total*	*Cases*	*Factor*	*Total*	*(A + B + C)*
[RH] 150/ 75 mg	120	× 210	= 25,200		× 0	= 0	22	× 540	= 11,880	37,080
Z 400 mg	120	× 210	= 25,200		× 0	= 0	22	× 320	= 7,040	32,240
S 1 g		× 0	= 0	66	× 60	= 3,960	22	× 60	= 1,320	5,280
[TH] 150/ 300 mg	120	× 180	= 21,600	66	× 360	= 23,760		× 0	= 0	45,360
H 100 mg		× 0	= 0		× 0	= 0	22	× 100	= 2,200	2,200
E 400 mg	120	× 150	= 18,000		× 0	= 0	22	× 450	= 9,900	27,900

Source: Ministerio de Salud, Managua, Nicaragua.[39]
*As recommended dosages and presentation of medications may vary or may have changed, the requirement may not equal that in the latest recommendations.
†Retreatment regimen: 2S[RH]ZE/1[RH]ZE/5[RH]E3H3.
R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; T, thioacetazone; S, streptomycin.

combinations.[24] To treat any adverse effects in regimens using four-drug fixed-dose combinations, a program should order additional single formulations for use at referral units. Ordering single formulation quantities equivalent to 5% of the total requirements should be sufficient.[23] Needles, syringes, and diluents need to be ordered for streptomycin injections—one disposable needle and one disposable syringe for each injection.

In summary, when quantifying the requirements of anti-tuberculosis drugs, what is needed is a list of the drugs used in the tuberculosis program, the clinical guidelines, and actual data on the number of tuberculosis cases seen at health facilities.

Laboratory supplies for acid-fast microscopy

At the national level in the programs collaborating with The Union, 5% to 30% of the tuberculosis suspects were positive on sputum examination.[40] This information can be used to calculate the need for laboratory supplies. The ratio reveals how many tuberculosis suspects on average are examined to diagnose one smear-positive case.

To give one example, if the proportion positive among tuberculosis suspects examined in the laboratory is 10%, then on average 10 tuberculosis suspects need to be examined to diagnose 1 smear-positive case. If 3 smears are

Table 9.2 Estimated quantity of microscopic slides required for sputum microscopy in different scenarios

Number of slides for tuberculosis diagnosis				*Number of slides for follow-up examinations*			
Positive in laboratory	*Suspects per case*	*Slides per examination*	*Total*	*Number of examinations*	*Slides per examination*	*Total*	*Grand total*
5%	20	3	60	3	1	3	63
	20	2	40	3	1	3	43
	20	3	60	3	2	6	66
10%	10	3	30	3	1	3	33
	10	2	20	3	1	3	23
	10	3	30	3	2	6	36
20%	5	3	15	3	1	3	18
	5	2	10	3	1	3	13
	5	3	15	3	2	6	21

initially examined for each tuberculosis suspect and 3 follow-up examinations of 1 smear each are performed during each positive patient's treatment, then 33 slides and sputum cups are needed: $(10 \times 3) + 3 = 33$. If 5 ml of staining solution is needed for each smear, then 165 ml of staining solution is needed for each smear-positive case: 33×5 ml.

These calculations are easily adapted for any setting. What needs to be known, to work out the requirement for laboratory supplies, is the expected or estimated proportion positive among tuberculosis suspects examined in the laboratory, the policy of the program regarding the number of smears to be examined in the assessment process, the frequency of follow-up sputum examinations during treatment, and the number of smears to be examined each time. Table 9.2 demonstrates a few different scenarios.

Drug requisitions

The "drug pipeline" is defined as the total storage capacity that must be filled in a drug supply system, that is, the stock levels within the system and the number of supply points at each level.[2] The safety stock levels and reorder frequency should be fixed in a tuberculosis program. Reorder frequency determines the approximate reorder quantity when the pipeline is full and consumption is stable, as is usually the case in tuberculosis programs. There may

be slight variations, however, due to irregularities, such as when patients are transferred out, transferred in, die, or default. Not following treatment guidelines, unexpected donations, and inventory shrinkage will also result in irregularities. By taking account of actual stock levels when requisitions are made, adjustments can be made. To detect irregularities in need of investigation, consumption can be monitored facility by facility, comparing expected against actual reorder quantities.

Drug requisitions in the model program

The materials management system in the Union collaborative programs linked drug requisitions to case-finding reports, as demonstrated in Figure 9.2. Placing drug orders quarterly, at intermediate and peripheral levels, allowed requisitions to coincide with quarterly case-finding reports. Full courses of treatment were ordered for the number of patients enrolled according to the previous quarter's report.

"Drugs on hand" is defined as drugs on outstanding orders plus drugs in the store, not counting expired drugs or drugs that will expire before they can be used. Before an order is placed, the quantity of drugs on hand is noted.

To prevent shortages and stock-outs as a result of unforeseen events, lead time and the maintenance of a reasonable safety stock level should be considered. "Lead time" is defined as the time between placing an order and receiving the goods. "Safety stock" (also called "buffer" or "cushion") is sometimes

Figure 9.2 Quarterly report on case finding linked to drug requisition

Table 9.3 Hypothetical drug requisition for fourth quarter of 2001

Item	E *Running requirement (= D)**	F *Reserve requirement (= E)*	G *Currently in stock*	*Total order (E + F − G)*
[RH] 150/75 mg	37,080	37,080	30,100	44,060
Z 400 mg	32,240	32,240	28,900	35,580
S 1 g	5,280	5,280	4,980	5,580
[TH] 150/300 mg	45,360	45,360	42,100	48,620
H 100 mg	2,200	2,200	1,500	2,900
E 400 mg	27,900	27,900	28,700	27,100

*From Table 9.1.
R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; T, thioacetazone; E, ethambutol.

defined as the stock that should always be on hand to prevent stock-outs.[2] This is misleading, however, as the safety stock should be used if needed—which is its intended purpose. Actual stock levels will fall below the safety stock levels when unexpected events occur.

Table 9.3 demonstrates calculations for a requisition at the intermediate level based on the requirement calculated in Table 9.1 and hypothetical stock levels. The calculation is for one quarter's requirement, and the intermediate level safety stock policy for this example requires a quantity equal to three months worth of supply.

On the national level there is usually a different reorder frequency and reserve level. Table 9.4 demonstrates the calculation for a drug requisition made at the central level on April 10, 2002, to a foreign supplier. For this calculation, the orders are made annually, and the reorder quantity is equal to one year's requirement. The desired reserve stock is also equal to one year's requirement, that is, six months of safety stock and six months of stock for expected lead time; the stock level in the central store at the time of the order is noted as well. The information on case finding comes from Nicaragua's tuberculosis program in 2001.[39] The shipment would have been expected to arrive in early October 2002.

The relevant unit sizes need to be clearly identified when transcribing the information from calculations onto the final requisition form. The unit size could be individual tablets, boxes of 1,000, 500, or 100, or some other unit, and the order quantity would be rounded up to be even with the unit sizes.

In summary, to complete a drug requisition, the following quantities need to be known when the order is placed: an estimate of the working stock needed (that is, the drug requirement in between orders), obligatory safety stock,

Table 9.4 Hypothetical drug requisition at central level on April 10, 2002, based on surveillance in 2001, Nicaragua

	A *2[RH]ZE/6[TH]*			B *2S[TH]/10[TH]*			C *Retreatment*			D
Item	*Cases*	*Factor*	*Total*	*Cases*	*Factor*	*Total*	*Cases*	*Factor*	*Total*	*Total (A + B + C)*
[RH] 150/ 75 mg	1510	× 210	= 317,100		× 0	= 0	324	× 540	= 174,960	492,060
Z 400 mg	1510	× 210	= 317,100		× 0	= 0	324	× 320	= 103,680	420,780
S 1 g		× 0	= 0	775	× 60	= 46,500	324	× 60	= 19,440	65,940
[TH] 150/ 300 mg	1510	× 180	= 271,800	775	× 360	= 279,000		× 0	= 0	550,800
H 100 mg		× 0	= 0		× 0	= 0	324	× 100	= 32,400	32,400
E 400 mg	1510	× 150	= 226,500		× 0	= 0	324	× 450	= 145,800	372,300

	E *Running requirement (D from above)*	F *Reserve requirement (= E)*	G *Currently in stock*	*Total order (E + F − G)*
[RH] 150/ 75 mg	492,060	492,060	485,000	499,120
Z 400 mg	420,780	420,780	405,000	436,560
S 1 g	65,940	65,940	63,500	68,380
[TH] 150/ 300 mg	550,800	550,800	525,000	576,600
H 100 mg	32,400	32,400	35,500	29,300
E 400 mg	372,300	372,300	369,000	375,600

Source: Ministerio de Salud, Managua, Nicaragua.[39]
R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; T, thioacetazone; E, ethambutol.

expected lead time, and inventory of the stock on hand. When fully implemented and with adequate pressure in the pipeline (see below), the materials management system should run smoothly. If the requisition process is followed, the pipeline will maintain pressure and there should be no stock-outs. Adjusting orders for minor irregularities can be done as orders are prepared and the stock on hand is reviewed.

Reserve level and inventory control models

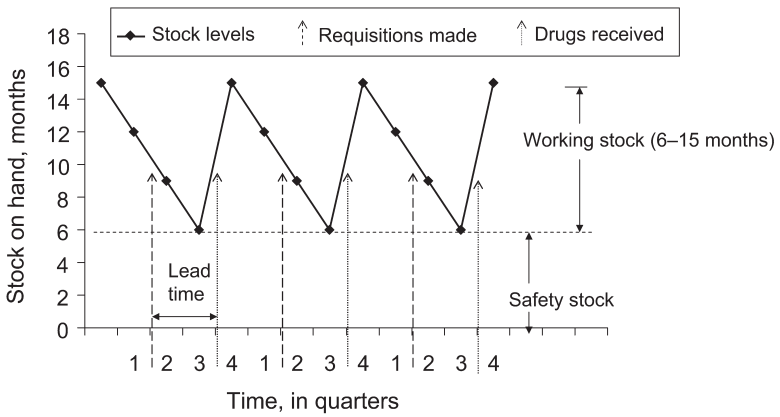
The average monthly stock requirements and the expected lead time in months both contribute to the calculation of a reserve level. A tuberculosis program, which is country-wide and must never run out of drugs, must have a high reserve level. Although drug consumption is relatively stable in tuberculosis programs, there could be unpredictable fluctuations in lead time. To calculate a

safe reserve level, multiply the average monthly requirement by the number of months of expected lead time, plus a safety stock, which is also measured in months and depends on the setting. By increasing the safety-stock level and decreasing the reorder frequency, inventory-holding costs (that is, storage costs) go up because more storage space and staff are needed. There is also higher risk of spoilage and theft with high stock levels. So, while it is not recommended to carry very high stock levels, the levels must be high enough to prevent stock-outs.

Figure 9.3 demonstrates an inventory control model at central level. In this example, annual orders are scheduled for April 10, and, with a lead time of six months, the shipment is expected in early October. Every quarter, supplies are distributed to the depots at the intermediate level (on April 15 in the second quarter, for instance). Reserve stock level is equal to six months' safety stock plus the amount required for lead time (six months' worth in this example). In a perfect situation, the actual stock level would fluctuate from six to 15 months' requirement. Figure 9.4 gives a more realistic picture of what might happen in practice, assuming some irregularities. Comparable models can be drawn for intermediate and peripheral levels.

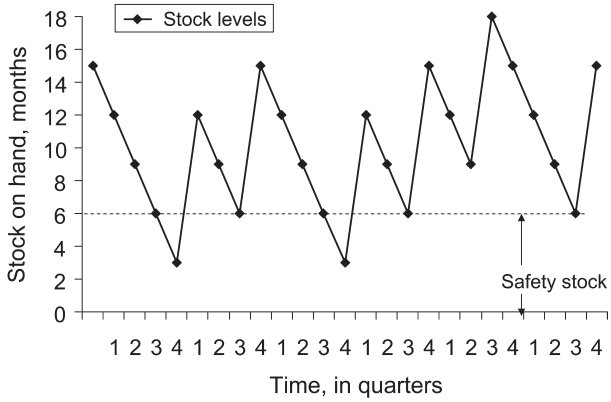
Figure 9.5 shows an inventory control model using a lower safety-stock level but equal lead time and reorder frequency. The stock level in this example fluctuates between three and 12 months' requirement, lowering the inventory holding costs, an advantage particularly in countries with very large caseloads. The same would happen if reorder frequency were increased to twice a year, for example. The disadvantage of ordering biannually is that procurement

Figure 9.3 Inventory control model at central level



Adapted from Management Sciences for Health and Euro Health Group.[2]

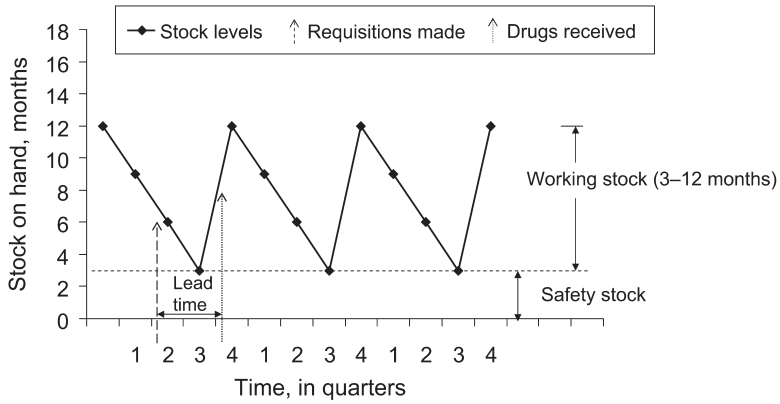
Figure 9.4 Realistic inventory levels at central level



is a cumbersome process involving a lot of paperwork and much effort following up on the order and in retrieving the goods when they are in-country. These drawbacks must be weighed against the problems of carrying high stock levels.

When setting the reserve levels and reorder frequency in a program, one needs to take note of local conditions; it may not be possible to give a fixed formula for these parameters. The optimal levels and frequencies are likely to

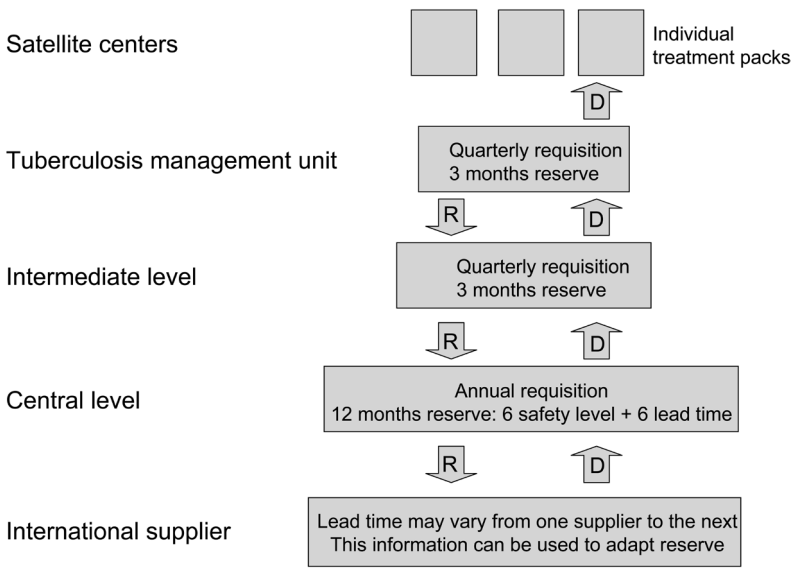
Figure 9.5 Inventory control model with reduced safety-stock level and lower inventory cost



vary between countries and may also vary within a country, as conditions are not often uniform throughout a country. The Orange Guide recommends a reserve level of three months at both the peripheral and intermediate levels, for a total of six months.[38] These are minimum levels, and for some settings they may be too low, such as if the lead time is especially long or variable. Furthermore, a safety stock level of six months is recommended at the central level, as shown in Figure 9.6. The reserve requirement at the central level may be quite large if an international supplier is used; the lead time requirement expands because of the lengthy shipping period.

After analyzing the lead time for a setting and considering the local conditions, the reorder frequency and reserve levels should be adjusted accordingly. Drug orders should be regular and scheduled. In a fully expanded and well-functioning tuberculosis program, emergency orders should not occur but can be justified by unexpected irregularities. Emergency orders may be expensive, but so are inventory costs. In Nicaragua there were no substantial problems with inventory shrinkage in the 1990s, even with its high stock levels. Some countries could have considerable problems with drug leakage and theft, and unfortunately, such countries tend to also have other problems requiring high inventory levels.

Figure 9.6 Drug requisition and distribution system in the tuberculosis program



Lead time and expiration margins

In theory, domestic lead times—from central to intermediate level, and from there to the services level—should not be unusually long because they do not involve production but simply distribution from one warehouse to another warehouse and then to the health facilities. In reality, however, in-country lead time can be surprisingly long because of unreliable transport systems or shortages of funds to pay for transport. These problems can be very difficult to solve. Variable lead times for in-country orders suggests a failing distribution system that should be investigated and improved.

Lead time may be longer for remote areas in a given country or locations cut off from major supply routes during part of the year. Timing requisitions from such areas and distribution to them is key; reorder frequency and safety stock levels may need to be adjusted according to regional limitations.

International orders require expanded lead times not only because of shipping and complicated paperwork, but also because they involve manufacturing schedules. Accounting for these expanded schedules in the ordering cycles is simple when the lead time is reasonably stable. Highly variable lead times are a problem. Reserve-stock levels need to be high enough to cope with the worst-case scenarios, and maintaining reserves increases inventory costs. To protect the stock levels, lead time should be calculated based on past performance rather than promised delivery dates. Fluctuating lead times could warrant switching suppliers.

High reserve levels and narrow expiration margins that are constricted by the travel time of drugs arriving from overseas suppliers increase the risk of spoilage. Table 9.5 demonstrates an analysis of expiration margins on shipments received in Laos from 1995 to 1998.[41] During that period, anti-tuberculosis drugs had expiration margins of 36 to 60 months (3 to 5 years),* depending on the product, at the time of manufacture. It is reasonable to request that, upon delivery of a shipment, at least 75% of the full expiration period remain.[3] As seen in the table, the expiration margin is acceptable in most of the shipments received from 1995 to 1998. In February 2000, though, a shipment of the rifampicin-isoniazid and the ethambutol-isoniazid combinations had a period of only 16 months remaining, and the isoniazid in the shipment had only ten months remaining when received by the program.[42] Such unacceptable occurrences should be reported and investigated. Perhaps the drugs were shipped late, transport time was excessive, or customs held the shipment for a prolonged period. The actual cause must be discovered so that similar problems can be prevented in future shipments.

Insufficient remaining shelf-life spans on received drugs have been reported

*The lower limit has since been reduced to two years.

Table 9.5 Analysis of expiration margin on receipt of shipments, Laos, 1995–1998

Item, number of tablets	A *Expiration date*	B *Date received*	*Margin (A – B), months**
[RH] 150/100 mg			
176,000	November 1997	March 28, 1995	32
310,000	April 1998	August 11, 1995	32
294,000	February 1999	November 29, 1996	27
320,000	March/June 1998	February 23, 1998	25–28
Z 400 mg			
146,000	February 2000	March 28, 1995	59
250,000	February 2000	August 11, 1995	54
352,000	April 2002	October 6, 1997	52
330,000	May 2002	February 23, 1998	51
E 400 mg			
153,000	December 1997	March 28, 1995	33
270,000	December 1997	August 11, 1995	28
238,000	March/Nov. 1999	November 29, 1996	27–36
320,000	April 2002	February 23, 1998	50
[EH] 400/150 mg			
467,000	February 1998	March 28, 1995	35
432,000	February 1998	August 18, 1995	30
1,741,000	Dec. 1998/May 1999	November 29, 1996	25–30
1,550,000	May/June 2000	February 23, 1998	27–28

Source: Arnadottir.[41]
*Margin is months until expiration (useful life of stock).
R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol.

in Cambodia as well.[43] Sometimes drugs with a narrowed expiration margin are offered at discounted prices. Well-organized tuberculosis programs with high working-stock levels would be unwise to spend funds on larger than routine drug requisitions. Purchasing drugs with a narrow expiration period may result in drug wastage rather than savings.

Special situations

Irregularities

Whereas it is convenient for quarterly orders and drug distribution to coincide with the rhythm of surveillance reports, as noted earlier, reorder frequency and reserve level may need to be adjusted in remote areas or due to seasonally difficult travel (for example, during the rainy season).

It may be necessary to adjust for drug losses or increase in case finding. Minor fluctuations are automatically taken into account when taking note of stock on hand at the time of the order. If necessary in a rapidly expanding program, an increase in case finding can be estimated (as percentage, for example) and added to the calculated requirement or the final order. Major irregularities, such as when a shipment is lost, a lot expires or will expire before it can be used, or when an entire shipment is stolen, are accounted for if the damaged or missing stock is not counted as stock on hand. This will temporarily increase the order quantities above the usual and expected numbers as based on case-finding reports, and may require an emergency order in between scheduled orders.

If reorder frequency is high when compared to the usual lead time or if lead time is highly variable, the stock on order—that is, quantities in transit—can be problematic. As a rule, stock on order should be included in the stock on hand quantities when placing a requisition.

Hospitals and satellite units

The workings of the supply system for central, intermediate, and peripheral depot levels are different from those needed by tuberculosis management units at the services level, unless such units have a reasonable and stable caseload. The supply system as described above will not necessarily perform well if there is a very low or highly variable level of activity.

In countries where tuberculosis programs are based in health centers, as in Nicaragua, hospitals need to be supplied as well, even if they do not report cases. Consumption in these hospitals is relatively low and highly variable; the same is true of satellite centers or health posts covering small populations and operating in coordination with tuberculosis management units. A perpetual order system is convenient when consumption fluctuates significantly. In a perpetual order system, orders are placed whenever stock falls below a critical point. Because the lead time from the municipal and provincial stores to the hospitals is short, they do not usually need large safety stocks or even scheduled orders. For satellite centers, drugs should be requested whenever a patient is diagnosed and enrolled in treatment. Having one treatment course in stock at such centers, however, could allow treatment for a patient to begin without delay. Generally, patients are diagnosed and registered at a tuberculosis management unit, treatment begins, and the drugs are sent to the satellite center. The satellite centers do not need to order drugs or have any stock above what is required to complete treatment of patients under their care.

Starting a new program

The number of levels in the distribution system, the frequency of requisition and delivery, and the safety stock at each level influence the amount of drugs needed to fill the drug pipeline. The pipeline for a new program must be filled

when the materials management system is implemented. If information on morbidity and demand for services is unavailable at the outset, the pressure in the pipeline could take one to three years to build up. In the meantime the materials management system will be incomplete and will not function smoothly. If the program is phased in, the pipeline needs to expand at the same pace, and irregularities may occur in some sections until the program is fully expanded.

Starting a new program where case-finding reports are nonexistent or unreliable means requirements will need to be estimated from other data. Estimates of disease burden or of the annual risk of infection are highly questionable and often inaccurate when compared to statistics in a real-life setting within the health services. Real figures (rates) from neighboring or comparable countries or areas are more reliable for estimating long-term drug requirements, and as a basis for the initial requisition and distribution of drugs and supplies. These estimates should be used only for the initial requisition. It is extremely important that as soon as possible after start-up, requisitions be based on actual case-finding reports rather than estimates. The figures can be adjusted for an expected increase in case finding as discussed above, but preferably they will be based on observed trends. Projections and estimations from project proposals or planning documents should not be used in actual drug requisitions after the initial order. In new programs, emergency orders or drug wastage (expired drugs) is tolerated. Both, however, signify a waste of resources and should not occur after the start-up period. Box 9.1 summarizes the 1995 start up of a national tuberculosis program in Laos.

Box 9.1 Expired drugs during implementation of the tuberculosis program in Laos, 1996 to 2000

There was little information for planning in 1995 when the first drug requisition was placed in Laos. As time went by, information became available from the surveillance system. Small quantities of drugs expired in the provinces and in peripheral health units during the first five years of the program. Most notably, 400,000 tablets of the ethambutol-isoniazid combination expired at the central level before it could be used.[42] While this may seem like a large quantity, in relative terms this was roughly the requirement for one quarter in the year 2000, and it was equivalent to 2.6% of the total drug requirement for this product during the first five years of the program, 1996 through 2000. Including the quantities that expired in the provinces and districts, less than 5% of all the ethambutol-isoniazid purchased expired in the first five years of the program; an even smaller percentage of the other drugs expired during the period. The total wastage in the first five years of the program can be roughly estimated at 2% to 3% of the total amount spent on drugs.

Changes in treatment policy

Careful advanced planning of changes to treatment regimens, such as switching from an 8-month to a 6-month regimen, or drug formulations, such as moving to fixed-dose combinations, will minimize waste.[24] Without early attention to the details, stock-outs may be more likely to occur. Estimating the quantity in the drug pipeline and accurately timing the new policies allows the reserve stock to be used before the changes take effect. The old formulations need to be cleared out, and the pipeline should be filled with the new formulations simultaneously with the start of the new treatment strategy. In addition to the materials management planning, revised clinical guidelines should be published and distributed. Health workers may need training, depending on the nature of the changes. Box 9.2 describes the process of changing the treatment policy in Nicaragua in 1992–1993.

Box 9.2 Changing the treatment policy in Nicaragua in 1993

In late 1991, the program staff discussed whether to replace streptomycin injections with ethambutol as a fourth drug in the intensive phase of short-course treatment of new smear-positive tuberculosis. The discussions began because it was expected that the number of HIV-positive tuberculosis patients would increase. An all-oral regimen would simplify logistics, a desired collateral effect, as the need for needles and syringes would be reduced. However, the medical staff did not know if the streptomycin injection was important for adherence to treatment. Patients might be reluctant to attend a health center daily if no injection was given.

A controlled trial of compliance was undertaken in early 1992 to compare adherence to treatment with and without injection, looking at regularity of attendance in ambulatory treatment and sputum smear conversion at two months of treatment.[44] The results suggested that adherence was not affected by the proposed change in the treatment regimen, and toward the end of 1992, the program decided to go ahead with the change.

According to surveillance reports, an estimated 65% of the streptomycin was used in short-course treatment of new cases, roughly 24% was used in the 12-month treatment of other new cases, and 11% went toward retreatment. The program had a safety stock level of 12 months (in the whole country) and 6 months lead time in ordering from Europe. Considering the generous expiration margin of the streptomycin in stock, the timing of the country-wide change was set for June 1993, which meant that from July onward, newly recruited patients were to receive the new regimen. The drug order placed in January 1993 reflected the phasing in of the new treatment strategy. In the first half of 1993, an updated version of the tuberculosis manual was finalized and workshops and meetings were held to introduce the new strategy.

Drug distribution

Distribution networks in the government sector are usually comprised of a central or primary store serving the whole country, and intermediate stores which may or may not be on the site of regional and district hospitals. Stores at other health facilities are usually small, but they should have a safety stock of anti-tuberculosis drugs at a level similar to that of the tuberculosis management unit.

Distribution is via either a delivery system or a collection system.[2] Drug delivery can be linked with supervision of services; however, supervision is a mechanism for quality assurance, while drug distribution is a routine primary activity in the tuberculosis program. These two activities do not really belong together. Supervision, often a weak point in tuberculosis programs, can make the whole program vulnerable when it is linked to drug distribution.

Transport, usually the least reliable link in the distribution system, can be a source of great frustration.[2] Frequently underfunded and badly functioning, government distribution mechanisms create problems with irregular distribution and end-point shortages. In some settings, parastatal or private companies can be used for distribution. The private, for-profit sector may indeed be the ideal mechanism when it comes to drug distribution.[9]

Store and stock management

Inventory levels need to be high to avoid shortages but low to control costs. Holding stock in a materials management system ensures availability of essential items at all times. In the tuberculosis program, the great amount of safety stock required makes inventory-holding costs relatively high.

Buying drugs in bulk is cheaper. The drugs can be repackaged locally for smaller centers and individual patients. However, the original expiration dates on the drugs will change when they are repackaged; the new expiration date should probably not be more than one year after repackaging.[2] Proper storage in a clean and well-organized store, prompt release, and clear labeling of dispensed drugs, including expiration dates, are all very important. At the health services level it is common to find anti-tuberculosis drugs in mislabeled containers, in containers relabeled correctly but with expiration dates referring to the container's original product, or in containers with no expiration dates recorded on them at all. All of this is bad practice.

All depots need to keep stock record cards—a separate card for each drug—on which are recorded the amounts received and dispatched. The card is drawn periodically to check the balance against a visual stock count. The dates of movements should be noted on the card as well as the expiration dates of the lots received. An example of a card is presented in Figure 9.7.

Figure 9.7 Example of a stock record card

Drug: Ethambutol 400 mg

Received date	Quantity	Expiry date	Distributed date	Quantity	Receiver	Balance date	Quantity	Expiry date	Stock count
3/20/2003	1,000,000	09/2005				3/20/2003	1,000,000	09/2005	
			4/15/2003	30,000	AAA				
			4/15/2003	100,000	BBB				
			4/23/2003	75,000	CCC				
			7/16/2003	115,000	BBB				
			7/16/2003	29,000	AAA				
			7/17/2003	69,000	CCC				
						8/1/2003	582,000	09/2005	582,000
								Shrinkage	0
			10/16/2003	28,000	AAA				
			10/17/2003	92,500	BBB				
			10/20/2003	68,000	CCC				
			1/15/2004	103,000	BBB				
			1/15/2004	25,000	AAA				
			1/20/2004	74,000	CCC				
2/10/2004	1,000,000	06/2006							
						2/10/2004	191,500	09/2005	
						2/10/2004	1,000,000	06/2006	
						2/10/2004	1,191,500	total	1,190,000
								Shrinkage	1,500
						3/1/2004	1,190,000		

Records must always be kept up-to-date, and subtractions from stock must also be recorded, such as for expired drugs, lost drugs, or spoiled drugs. Inventory and stock management benefits from regular supervision. In Nicaragua's integrated supply system, tuberculosis supervisors visit the depots periodically and perform physical stock counts. Their assessment is external to the supply system, and the visits assure an effective link between the tuberculosis program and the supply and distribution system.

When drugs are dispatched, the FEFO (first-expiration first-out) rule should

be used to minimize loss of drugs due to expiration. The drugs to be dispatched first should be situated in front of other drugs on the shelves.

Expiration date analysis

Expiration date analysis, if used regularly, can help to prevent wastage of drugs by detecting problems while they can still be prevented. Comparisons of expiration dates to inventory levels determines how much stock is at risk of being wasted.[2] This type of analysis is demonstrated in Table 9.6, using information from Laos.[41,45] First, a physical stock count is conducted, and expiration dates of each lot are noted. Then the expiration margin—that is, the useful life of the stock—is calculated (as in Table 9.5). After calculating the annual requirement (as in Tables 9.1 and 9.4) and dividing it by 12 to obtain the monthly requirement, the stock is converted from tablets into months and compared to the useful life of the stock. If the months until expiration are greater than the stock position in months (that is, a negative value in column G in Table 9.6), and the estimated need is realistic, there should be no risk of wastage. If there is a surplus in months, this quantity is likely to expire before it can be used. In the example from Laos, in Table 9.6, clearly five months' worth of the ethambutol-isoniazid combination with expiration date May 1999 is at risk of expiring at the country level. Since there are two lots of the combination, assuming that the one with the closer expiration date (May 1999) is used first, this quantity must be subtracted from the expiration margin of the lot with the later expiration

Table 9.6 Analysis of expiration dates and inventory levels, Laos, January 1999

Item	A *In-store, number of tablets*	B *Expiration date*	C *Margin, months (B − date)*	D *Annual need*	E *Monthly need (D/12)*	F *In-store, months (A/E)*	G *At risk, months (F − C)*	*At risk, number of tablets (E × G)*
[RH] 150/ 100 mg	541,445	June 2000	18	453,300	37,775	14	– 4	
Z 400 mg	561,360	April 2002	40	460,500	38,375	15	– 25	
S 1 g	92,711	March 2002	39	48,000	4,000	23	– 16	
[EH] 400/ 150 mg	1,254,186	May 1999	5	1,444,500	120,375	10	**5**	652,311
[EH] 400/ 150 mg*	1,550,000	June 2000	**18**	1,444,500	120,375	13	– **5**	
H 100 mg	12,800	Dec. 2001	36	12,000	1,000	13	– 23	
E 400 mg	358 ,312	April 2002	40	331,500	27,625	13	– 27	

Source: Arnadottir.[41,45]

*In this case, we need to correct the margin (18 − 5 = 13) as the May 1999 lot will be used first.

R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; E, ethambutol.

date (June 2000) as it will not be used until the other is finished. In Table 9.6, the second lot of the ethambutol-isoniazid combination, with an expiration date of June 2000, is close to being at risk, but it might just be possible to use it all before the expiration date. This depends largely on the stock level in the provinces and districts.

Large quantities of expired drugs have been found in some settings.[43] Expired drugs accumulate in stores if they are not destroyed. When evaluating a program, consider the proportion of expired drugs to drugs used in the program over time and find out why the drugs were not used before they expired. In the example from Laos, above, with hindsight, the expected case finding was overestimated at the start of the tuberculosis program, particularly regarding patients recruited for the 12-month treatment regimen. Looking at the quantity of drugs in store, according to column F in Table 9.6, it is seen that the stock is balanced at the level of 13 to 15 months for everything but streptomycin and the ethambutol-isoniazid combination, that is, the drugs used in the 12-month regimen, where the quantity in store is equivalent to the requirement for 23 months. As the streptomycin has a wide expiration margin, the analysis shows that it is not at risk of expiring; in contrast, some of the ethambutol-isoniazid combination will be wasted. The quantity at risk should not be distributed to the provincial level in excess of need only to then blame the expiration on them. It should be acknowledged that this quantity will expire and the focus should be on improving planning and management of supplies for the future. The option of donating drugs at risk of expiring to another country in need could be examined, but such donations are controversial and should be made only if agreed to by the tuberculosis control authorities in the recipient country, and provided there is a guarantee that the drugs can be used. Usually, a surplus at country level simply needs to be destroyed.

Expiration date analysis can and should be performed periodically at all levels. If the surplus in the example above had occurred at provincial or district level, to prevent wastage, one would have considered the option of redistribution within the country.

Inventory shrinkage

Inventory shrinkage is defined as the beginning inventory plus drugs received minus drugs distributed and ending inventory,[2] as shown in the examples given in Box 9.3. This should be studied periodically, quarterly perhaps, and if there is considerable shrinkage further investigation into the cause is warranted.

The role of computers

Computer spreadsheets are useful in materials management, particularly in programs with large caseloads.[46] They are useful for calculating needs and requisi-

Box 9.3 Inventory shrinkage

BI + DR − DD − EI = Inventory shrinkage, where BI is beginning inventory, DR is drugs received, DD is drugs distributed, and EI is ending inventory.

Example 1: 1,000,000 + 500,000 − 400,000 − 1,100,000 = 0
Example 2: 1,000,000 + 500,000 − 400,000 − 800,000 = 300,000 (shrinkage)
Example 3: 1,000,000 + 500,000 − 400,000 − 1,300,000 = −200,000 (surplus)

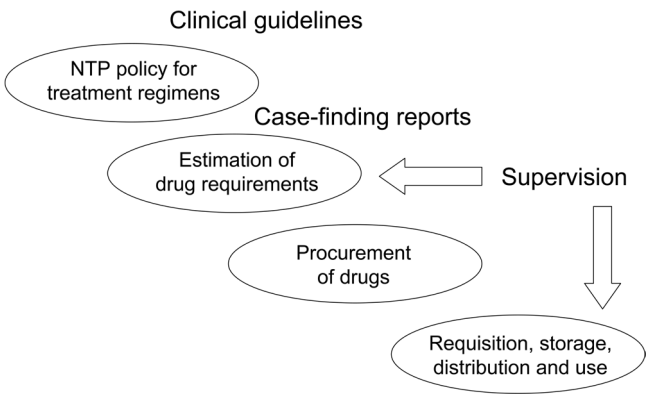
Surplus and shrinkage should be investigated if the quantity is significant.

tions, as demonstrated above, for monitoring distribution and consumption (as demonstrated below), and for studying scenarios and options (so-called "what if" analyses).

Supervision and monitoring

The materials management system is closely linked with surveillance (information) and supervision in the tuberculosis program, as depicted in Figure 9.8. Requirements are estimated using clinical guidelines and case-finding reports. If drug requisitions are missing or erroneous, someone, ideally the tuberculosis supervisors at intermediate and central level, should take corrective action. Tuberculosis supervisors should understand the methods used in inventory management and be able to analyze information on supplies and stocks. They should

Figure 9.8 Drug-supply management in tuberculosis control



NTP, national tuberculosis program.

regularly study the information provided on the quarterly requisition form and perform analyses for the districts or provinces under their responsibility.

Analysis of information on stock levels and supplies includes estimating the quarterly and annual requirement, monitoring distribution (quarterly and annually), and reviewing stock levels at the end of the year. If the annual distribution to each level corresponds approximately to the estimated annual need based on case-finding reports, then the supply system is functioning well. Every drug must be assessed to determine if its consumption is balanced and follows the treatment policy. If it is not, then inquiry into possible causes should be made.

Some drugs are more likely to leak out of the supply pipeline than others. The anti-tuberculosis drugs most likely to leak are rifampicin and streptomycin, because they can be used for treatment of other diseases. When a parallel private for-profit sector or a black market exists for the drugs, all of the drugs—rifampicin, isoniazid, pyrazinamide, and even ethambutol, in single formulations or in combinations—are at risk of leaking out.

Specialists in the field of drug supply management have designed numerous indicators to monitor drug supply.[2] A simple set of indicators for requisition, distribution and consumption, stock levels, and inventory shrinkage suffices in tuberculosis programs. The questions to be asked are the following: is there regular requisition? Regular distribution? Balanced consumption? Balanced stock? Inventory shrinkage? All can be answered with a "yes" or a "no" after proper analysis and a review of the actual numbers. If the answer to any of the first four questions is negative, or there is apparent inventory shrinkage, then a justification should be sought and further investigation made before a judgment is passed. Some examples from real situations are presented below for demonstration purposes.

Examples from the field

Management of the drug supply was weak throughout the first five years in the national program in Laos. The system was vertical, with a central tuberculosis store at the National Tuberculosis Center in the capital, Vientiane. Table 9.7 shows the distribution of drugs from 1998 to 2000* to the Vientiane Municipality and five provinces selected for the purpose of this example.[42,47,48] According to Table 9.7, drugs were distributed from the central store to the Vientiane Municipality quarterly in 1999, but quantities were irregular and overall the distribution was not balanced. There was greater than expected distribution of the rifampicin-isoniazid combination and to a lesser extent the

*This information is taken from the records in the central tuberculosis store and may have errors. The quantities in the table ideally should be checked against the quantities received in the provinces. This can be done during supervisory visits to the provinces.

Table 9.7 Analysis of requisition and drug supply to provinces, Laos, 1998–2000

	% of annual need				Distribution in 1999					Estimated need
Destination	*1998*	*1999*	*2000*	*Average*	*Q1*	*Q2*	*Q3*	*Q4*	*Total*	*1999*
Vientiane Municipality										
[RH] 150/100 mg	98	160	137	132	0	11,000	13,000	8,000	32,000	20,010
Z 400 mg	53	109	110	91	1000	11,000	0	10,000	22,000	20,250
S 1 g	83	115	115	104	600	350	0	150	1,100	960
[EH] 400/150 mg	86	141	115	114	21,000	23,000	13,000	12,000	69,000	49,050
E 400 mg	63	117	101	94	0	8,000	1,000	8,000	17,000	14,550
Oudomxay										
[RH] 150/100 mg	54	104	98	85	7,000	16,000	14,000	0	37,000	35,580
Z 400 mg	53	109	97	86	8,000	16,000	15,000	0	39,000	35,940
S 1 g	178	197	54	143	2,000	2,000	2,500	0	6,500	3,300
[EH] 400/150 mg	139	131	64	111	28,000	57,000	64,000	0	149,000	113,400
E 400 mg	41	109	92	81	6,000	12,000	10,000	0	28,000	25,800
Vientiane Province										
[RH] 150/100 mg	85	75	104	88	3,000	0	8,000	0	11,000	14,760
Z 400 mg	73	67	83	74	3,000	0	7,000	0	10,000	15,000
S 1 g	37	152	144	111	3,000	0	0	0	3,000	1,980
[EH] 400/150 mg	193	77	201	157	3,000	19,000	19,000	0	41,000	53,100
E 400 mg	63	139	121	108	4,000	5,000	6,000	0	15,000	10,800
Khammouane										
[RH] 150/100 mg	57	118	14	63	3,000	11,000	12,000	22,000	48,000	40,710
Z 400 mg	54	118	13	62	4,000	10,000	13,000	22,000	49,000	41,430
S 1 g	149	130	8	96	150	1,050	800	1,200	3,200	2,460
[EH] 400/150 mg	133	100	46	93	0	33,000	16,000	50,000	99,000	99,450
E 400 mg	40	111	10	54	4,000	6,000	16,000	33,000	59,000	29,850
Savannakhet										
[RH] 150/100 mg	87	76	125	96	0	39,000	0	25,000	64,000	84 ,660
Z 400 mg	82	68	68	73	0	32,000	0	26,000	58,000	85,620
S 1 g	99	24	74	66	0	1,500	0	0	1,500	6,180
[EH] 400/150 mg	98	71	138	102	0	90,000	0	81,000	171,000	241,200
E 400 mg	85	85	71	80	0	22,000	0	30,000	52,000	61,500
Champassack										
[RH] 150/100 mg	43	123	42	69	0	27,000	9,000	41,000	77,000	62,550
Z 400 mg	46	111	27	61	0	23,000	6,000	41,000	70,000	63,270
S 1 g	230	78	80	129	0	4,000	100	2,000	6,100	7,860
[EH] 400/150 mg	94	99	93	95	0	110,000	0	115,000	225,000	227,250
E 400 mg	56	51	41	49	0	16,000	7,000	0	23,000	45,450

Q1, first quarter; Q2, second quarter; Q3, third quarter; Q4, fourth quarter; R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; E, ethambutol.

ethambutol-isoniazid combination. This would require further investigation. In the Oudomxay Province, no distribution occurred in the fourth quarter of 1999, but sufficient amounts of all drugs were distributed during the year. The oversupply of the ethambutol-isoniazid combination could be because the 12-month regimen was used more than expected, perhaps due to problems with guaranteeing directly observed treatment. However, there was a relatively higher oversupply of streptomycin. Streptomycin could have been used for diseases other than tuberculosis, which is common where resources are scarce, morbidity is high, and the only drugs guaranteed are those in the tuberculosis program. The same phenomenon is revealed by the figures from the Vientiane and Khammouane Provinces. Table 9.7 shows that the Savannakhet Province was undersupplied in 1999, with partial correction in 2000; intermittent shortages may have occurred, and further investigation would have been merited at the time.

Oversupply and particularly theft and corruption are sensitive issues. Tables 9.8 and 9.9 show the results of an analysis made in a country with a chronic oversupply problem. In a situation of oversupply, careful documentation and analysis are an important basis for discussion, allowing the involved parties to explain or defend the situation. In this case, despite quite generous orders in 1995, emergency orders were placed in between the regular orders. The oversupply was very high for the rifampicin-isoniazid combination and for pyrazinamide, which are valuable drugs for treating tuberculosis patients. Even with this oversupply at the country level, it was not uncommon during supervisory visits to find situations of stock-outs at peripheral levels. For com-

Table 9.8 Analysis of drug requisitions made over a 5-year period in country X

	Tablets ordered (×1000)						*Requirement*	*Surplus tablets*	*Surplus patients*
Item	*1991*	*1992*	*1993*	*1994*	*1995*	*Total*	*(×1000)**	*(×1000)*	*(no.)†*
[RH] 150/ 100 mg	4600	2640	5850	5500	6200	24,790	16,740	8026	38,219
Z 500 mg	2700	2105	3700	3450	5440	17,395	14,400	2995	14,262
S 1 g	2100	1110	1300	1860	1370	7,740	6,504	1236	20,600
[TH] 150/ 300 mg	8600	3700	1600	1600	5200	20,700	26,010	−5310	
E 400 mg	2600	404	2300	1800	500	7,604	5,760	1845	

* Estimation is generous, based on reported case finding in 1994 × 6, allowing accumulation of 12 months' reserve.
† The surplus equals this number of patients fully treated with short-course treatment.
R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; T, thioacetazone; E, ethambutol.

Table 9.9 Scheduled and emergency drug orders in country X, 1995

Item	Scheduled orders		Emergency orders		Total ordered	Annual requirement	Proportion ordered, %
	May 18	*September 1*	*June*	*October*			
[RH] 150/ 100 mg	1,950,000	3,150,000		1,100,000	6,200,000	2,655,000	234
Z 500 mg	2,200,000	2,440,000	800,000		5,440,000	2,295,000	237
S 1 g	770,000	600,000			1,370,000	1,086,000	126
[TH] 150/ 300 mg	3,000,000	2,200,000			5,200,000	4,460,000	117
E 400 mg	0	500,000			500,000	880,000	57

R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; T, thioacetazone; E, ethambutol.

parison, Table 9.10 presents recommendations for the annual central level drug requisition in Laos in 1997.[45,49] Even with substantial operational problems in this new program, the amount of drugs ordered was reasonably close to the annual requirement.

Finally, stock indicators used in quality assessment must be part of a larger picture and need to be explained and applied reasonably. Fearing the repercussions of not heeding indicators, some individuals may rigidly adhere to them, provoking unintended adverse consequences. As an example, on a field visit to a depot store in an African country it was noted that there was sufficient stock on hand. Discussions with the storekeeper revealed that he had not dispensed drugs upon request from health facilities. He had understood that to get a favorable evaluation he must have a high stock level at all times.

Table 9.10 Example of drug requisition for Laos, 1997

Item	Estimated annual requirement 1997	Order	
		n	%
[RH] 150/100 mg	425,820	382,691	90
Z 400 mg	432,300	468,641	108
S 1 g	59,760	57,438	96
[EH] 400/150 mg	1,586,700	1,301,109	82
E 400 mg	311,100	436,858	140

R, rifampicin; H, isoniazid; Z, pyrazinamide; S, streptomycin; E, ethambutol.

Summary and conclusions

Using examples from tuberculosis programs, this chapter has discussed inventory management, including calculation of requirements, requisitions, stock management, and monitoring. Tuberculosis programs are different from the general health services in terms of issues related to the financing and management of drug supply. Anti-tuberculosis treatment should be free of charge to patients because treatment of tuberculosis carries public health benefits and risks beyond those for the individual patient. In ambulatory settings, anti-tuberculosis treatment may need to be administered under the supervision of health workers in the context of directly observed treatment programs, instead of allowing self-administered treatment by patients. Thus, distributing the drugs directly to patients from pharmacies or dispensaries may contradict the policy of a tuberculosis control program. Finally, anti-tuberculosis drugs should be available as drug combinations in order to prevent the misuse of these drugs.

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10
Quality assurance

Quality assessment is an important tool for self-assessment. Supervision is for support, not punishment!

Research in the latter half of the twentieth century demonstrated that variations in the process and outcome of medical care are extensive and common,[1–5] whether in high-income or low-income countries. Some variation is inevitable and should be expected. It is argued that failure to learn from such variation is a more serious condemnation of health professionals than the variation itself.[6] Quality assurance is an important tool for identifying and minimizing variations that contribute to undesirable outcomes.

When the collaboration between The Union and Tanzania started, the quality assurance and primary health care movements were in their infancy. At the time, there was little understanding of quality assurance within the latter. Instead, the main emphasis was on quantity as measured by expansion and coverage.[7] Conversely, concern with quality of care had a great influence on the development of the model tuberculosis program. Its information system was designed and implemented in such a way as to facilitate quality assessment and monitoring. On-site supervision and support with the aim of improving performance was an important element of the model from the start. This was considered all the more important because, to a large extent, paramedical workers within the general health services carried out the work. Whether routine quality assurance was consistently performed as expected in the various programs as time went on is another matter.

Quality assurance aims to improve the level of health care based upon measures of quality,[8] and can be divided into three components: system design, quality assessment and monitoring, and quality improvement.[9] System design refers to measures used to safeguard and promote quality of health care.[9] Although quality assessment is often described as a research-related activity that aims to measure the quality of care, quality monitoring is primarily an administrative activity.[8] In the model tuberculosis program, both activities depend largely on routinely collected data. The term "monitoring" will be used to refer

to an ongoing activity that relies on information from quarterly reports; the term "quality assessment" will be used to refer to a periodic activity that relies primarily on records and information available at health units. Quality improvement involves the actions taken when quality is found to be poor.[9]

The present chapter deals with quality assurance as a regular program activity as opposed to other evaluation activities, such as program reviews and appraisal, which are beyond the scope of this publication. It discusses what quality assurance is, why and how it is done, who does it, and whether it makes a difference.

Background

Biomedical research is the foundation of modern Western medicine, and thus the legitimacy of the medical profession rests on a scientific tradition. Quality assessment has its roots in this same tradition.[6] Concern with variations in health care date as far back as 1913, when Codman suggested that hospitals should report the number of patients treated and the results of treatment. Furthermore, he suggested that all aspects of the care process be evaluated.[5] Later, in the 1960s and 1970s, clinical epidemiology* and outcome research† led to an erosion of the medical profession's scientific credibility and triggered extensive interest in variations in the quality of health care.[5,6] The sequence of events that followed was assisted by rapid progress in information systems, computer technology, and communication techniques, which made it easier to obtain and analyze data.[6]

In the 1970s, Williamson and coworkers reviewed the evidence related to medical care in three health conditions where it was widely believed that research had substantially improved outcomes.[11] They looked for documentation concerning the following: disease burden, natural history of the condition without health care, social and economic costs, achievable benefits with optimum application of available technology, and the benefits actually achieved in routine practice. Contrary to expectations, they found that the evidence base was scarce and that no common body of literature on best practices existed.

Early on, many physicians regarded measures of quality assurance as infringements upon their professional independence.[12] Even today, some physicians complain that quality-assurance programs rarely deal with important

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* "Clinical epidemiology" can be defined as epidemiological studies conducted in the clinical setting with patients as the subjects of study,[10] as opposed to "classical epidemiology," which studies populations.

† "Outcome research" is an umbrella term without a consistent definition. Generally speaking, it involves research which measures end results and is concerned with the effectiveness of health services and public health interventions.[5]

issues for patient care.[12] One may argue that this criticism is partly the result of the medical profession's reluctance to participate in the design and implementation of such programs. A further reason for skepticism among medical doctors was the lack of evidence that, as a whole, quality-assurance programs actually made any difference.[12] However, with repeated demonstrations of gaps in the evidence base in clinical medicine, increasing awareness of the limitations of controlled clinical trials,* and wider acknowledgment of the discrepancy between maximum achievable benefit and the results achieved in routine practice, such arguments sounded less convincing. Finally, some of the newer tools of quality improvement permit a better understanding of how errors enter into clinical practice and how the frequency of errors might be reduced.[12]

The 1990s have been referred to as "the era of assessment and accountability."[5] At the turn of the century, quality-assessment systems were widely used. Lately, there has been a tendency to assess different conditions or treatments separately rather than attempt to obtain an overall grasp of quality of health care.[8] This can be seen as a vertical approach to quality assurance, which reflects the fact that medical interventions are targeted toward specific conditions or diseases, and that it has proven difficult to interpret and then apply the results of outcome assessment except in specific interventions.

For several reasons, quality in health care was not addressed in developing countries in the past,[7] except in certain vertical programs. This may explain why complete integration with primary health care was resisted. Early on, in the 1960s and 1970s, the primary health care movement emphasized infrastructure (buildings and equipment), quantity, geographical access, and community participation, whereas little if any attention was given to the quality of care.[7] Even if supervision and control were acknowledged among necessary supportive activities,[14] these activities were not prioritized in practice. The Alma Ata Declaration in 1978 did not even mention quality.[7,15] It was not until the late 1980s that concern for quality of care surfaced in developing countries. Two things prompted governments to consider quality of care as an issue.[7] First, there was increasing evidence that patients did not utilize the first-line health services because of perceived low quality of care. Second, when user fees were introduced, it became clear that patients were reluctant to pay for low-quality services. In 1991, Nicholas et al. reported the results of a survey conducted in 12 low-income countries that indicated highly prevalent and serious program deficiencies in areas including diagnosis, treatment, patient education, and supervision.[16] Toward the end of the twentieth century, the quality of care

*The randomized controlled trial is widely considered the gold standard in methodology and the cornerstone of the medical profession. However, randomized controlled trials often recruit relatively young and healthy individuals rather than older patients and patients with co-morbid illnesses,[13] and thus the effect they demonstrate is often an exaggeration of what can be achieved in routine practice.

was still a limiting factor with regard to improving the health status of populations in developing countries. Even where serious problems of access to health services persist, issues of quality remain a high priority.[17,18]

Quality of care

Definitions of quality of care

Quality of care has many facets, and there are different approaches to defining it. In 1976, Rutstein et al. defined "quality" as the effect of care on the health of the individual and of the population.[19] Their definition was only concerned with benefit, "the effect of care" in reference to outcome. Donabedian, on the other hand, specifically mentioned cost and distinguished between the individualized and social definition of quality, the former referring to costs and benefits to individual patients, the latter recognizing the costs and benefits to those other than the patient.[20] Blumenthal spoke of the organizational perspective of quality of care, which considers the health of populations and the functioning of systems.[21]

Hermann et al. listed the domains of quality as the following: prevention, detection, access, assessment, treatment, coordination, continuity, and patient safety.[22] Donabedian talked of three interrelated components of quality of care: technology, interpersonal relationships, and setting.[23] According to Blumenthal, technical quality involves "doing the right thing right," and he distinguished two dimensions of technical quality: the appropriateness of services and the skill with which they are performed.[21] He claimed that, from the individual perspective, health care services need to be responsive to patients' preferences and values; patients' opinion of care is an important indicator of quality. Palmer spoke along the same lines when she included another dimension to quality of clinical care besides health outcome: the beneficiaries' satisfaction.[24] Accordingly, she listed as domains of quality issues such as timely and trouble-free implementation as it relates to patients' experiences in receiving care and communication with care providers.

Criteria and standards for quality of care

The criteria and standards of health care can differ depending on the definition of quality that is adopted. The criteria used can be implicit or explicit.

Setting standards for quality of care

Standards of care can serve as an operational definition of the quality of care.[25] According to Donabedian, "Criteria and standards should derive from a scientifically validated fund of knowledge. Failing that, they should represent the

best-informed, most authoritative opinion available on a particular subject. Criteria and standards can also be inferred from the practice of eminent practitioners in a community. Accordingly, criteria and standards vary in validity, authoritativeness, and rigor."[26]

Chassin, referring to how the U.S. Institute of Medicine defined quality of care in 1990, pointed out that health services should be consistent with current professional knowledge.[27] The scientific literature and current professional knowledge determine standards of care, which are therefore subject to change over time.[25] Standards may vary depending on the setting, particularly when looking beyond quality at the level of the individual patient.[25] Quality criteria are often categorized by the level of evidence supporting them.[28] From a scientific viewpoint, the strength of evidence increases with methodology according to this hierarchy: expert opinion, uncontrolled time series, case-control and cohort studies, controlled studies without randomization, randomized controlled trials, and randomized double-blind controlled trials.[29]

Although it is important to set standards and criteria for quality of care that correspond to appropriate objectives, it is not true that the longer the criteria list, the better.[30] The number and diversity of quality indicators increase the burden of data collection, and may reduce the usefulness of the results. Nevertheless, criteria lists had grown longer and longer until recently; the latest trend calls for shorter lists of so-called "core measures."[31] Here, as always, it is wise to keep it simple and straightforward.

By definition, a quality-assurance program promotes or acknowledges certain criteria and standards of care. If the package of care promoted by a program sets standards so high that care becomes too expensive in the setting where it is implemented, then the program may, in effect, decrease the overall quality of care available to the public.[32] Where resources are limited, a certain trade-off with regard to cost and quality may influence the final choice of criteria in a quality-assurance program.[32]

Implicit versus explicit criteria

Quality can be judged based on criteria that are either implicit or explicit. The term "implicit" means that there are no prior standards or agreements about what reflects good or poor quality. "Explicit" means that there are clear written standards. A panel of experts usually develops explicit criteria, whereas implicit criteria are derived from situations such as when an expert is asked to use personal knowledge and experience to judge the quality of care.[9] Some advantages and disadvantages of using explicit versus implicit criteria are listed in Table 10.1.[9,20,33]

Explicit criteria are easier to develop when practitioners use a written clinical guideline and when case management is standardized. Explicit criteria are particularly useful where reviewers are inexperienced; however, these criteria

Table 10.1 Comparison of implicit and explicit criteria

	Explicit	*Implicit*
Validity	Depends on who formulates the criteria and how consensus is reached	Depends on reviewer, whose judgment is influenced by professional background
Who can apply them?	Nonexperts	Experts
Advantages	Low cost (in assessment) Can be standardized More reliable?	Flexible, adaptable Allow a broader focus Better validity?
Disadvantages	Rigid, non-adaptable Forces a narrow focus Costly to develop	Prone to bias Reliability and consistency can be uncertain but are increased by using multiple reviewers

tend to be rigid and non-adaptable. Algorithms can add a dimension of flexibility to explicit criteria.[9]

According to Donabedian, the superior validity of an assessment that uses implicit criteria lies mainly in the ability to adapt to the special characteristics of any given case or context by adding more information, modifying the explicit criteria, or introducing additional criteria when relevant.[20]

Assessments using explicit and implicit criteria may elicit different results. Weingart et al. performed a retrospective chart review comparing explicit and implicit reviews of complications and quality of care in individual cases where nurses applied explicit criteria and physicians implicit criteria.[33] The two frequently came to different conclusions even if they used the same records. In discordant cases, physicians claimed that the complications were insignificant or attributable to related diagnoses or a preexisting condition. They asserted that the quality problems were unavoidable, insignificant mistakes in otherwise satisfactory care. The nurses and physicians in the study may have looked at different things, the nurses at specific tasks as dictated by the explicit criteria and the physicians at the overall case management. To evaluate the big picture, a reviewer needs flexibility to apply knowledge and experience. Flexibility, however, may introduce bias. Because process problems are such a common phenomenon, the physicians in the study cited above may have regarded substandard performance as the norm and therefore used other things besides process criteria to judge the overall quality of care.[33]

In conclusion, it may be best to use a combination of explicit and implicit criteria, the former for the purpose of identifying potential problems and the

latter for arriving at a more definitive judgment, which may require additional information. Another alternative is to use an interactive process that challenges reviewers to acknowledge process deficiencies while allowing for justification when discordance is detected.[33] This latter approach is in line with Donabedian's view when he claimed that criteria and standards should be flexibly adaptable to the finer peculiarities of cases and circumstances.[9] The interactive approach seems to go against rigidly fixed indicators such as those that are commonly advocated in assessment and monitoring programs. When using explicit criteria only, as in computerized quality-monitoring programs, there is a danger that the exercise will yield meaningless results. This is partly due to misclassification —where some problems are missed and others sound a false alarm. It is also because information on the nature of the problems may be lacking.

The structure-process-outcome paradigm

Although some measures of quality may depend on value judgments, some aspects and determinants of quality can be measured objectively.[10] In the late 1960s, Donabedian classified these into measures of structure, process, and outcome. His model, designed for the clinical setting, is a simplified version of a complex reality.[34] The terminology, structure-process-outcome, is widely used. Since its formulation, Donabedian's paradigm has influenced the various phases of the quality-assessment and performance-management movements.[8]

According to Donabedian, "structure" refers to material and human resources and organizational structure, "process" refers to activities related to giving and receiving care, and "outcome" refers to the effects of care on the health status of patients and populations.[26,34] Another term commonly used is "output," which is concerned with quantity, that is, the amount and nature of health services provided.[10]

Donabedian's model refers to types of information from which inferences can be drawn about the quality of care, and thus points to possible approaches to assessment, irrespective of the definition of quality used.[34] The validity of the approach that is chosen depends on the causal links between structure, process, and outcome.[20] These links ideally should be explained before the assessment is undertaken.[26] This is the role of the organizational and health care sciences.

Whereas Donabedian acknowledged that structure influences clinical performance and thus presumably the quality of care, he claimed that the relationship between structure and process in health care was weak.[9] He argued that although structural characteristics were important in system design, they were difficult to use in quality assessment due to the lack of proven associations.[26] Thus, although early structural data (for example, infrastructure, human resources, quantity of services, geographical access, and coverage) were the

only tools for measuring quality of care, with time they gave way to the use of process (such as diagnosis, treatment, prevention of complications, follow-up) and outcome data.[35]

In 1979, Palmer and Reilly pointed out that the scarcity of evidence of an association between structure and outcome might be partially due to the fact that the association had not been carefully studied.[35] They identified areas of interest for research that could have important implications for health policy, planning, and institutional management. Among these were referral mechanisms and coordination of access to different levels of care and clarification of the volume-outcome relationship. More recently, elements such as clinical guidelines, monitoring systems, and case management programs have been classified as structural elements and shown to influence quality.[13] Meanwhile, it has been acknowledged that using process and outcome data is not devoid of problems. Even where evidence suggests a relationship between the quality of medical care processes and the outcome of care, this relationship is seldom straightforward. Various confounding factors come into play, such as the utilization of health care, adherence, and overall health status reflected by the severity of illness and co-morbid illnesses.[36]

According to Donabedian, if the assumed causal link between process and outcome is valid, then the approach used in assessment—process or outcome—is irrelevant. A preference of one approach over the other is primarily a matter of convenience. One simply needs to formulate questions and determine where to obtain the information that is needed to answer them the most precisely and at the most reasonable cost.[9,23,26] For various reasons, process rather than outcome assessment is frequently preferred. Even when a linkage between process and outcome exists, faulty processes do not always result in adverse outcome, and they would go undetected if only outcome data were used. The time between performance of key processes and outcome of care may be long. Routine monitoring should increase the likelihood that action is taken to reduce the odds of an adverse outcome.[28] If an evidence-based clinical guideline describing a process of care to be followed exists, then a process assessment in quality assurance is important because of its potential for encouraging compliance.[13] Finally, the difficulties in interpreting outcome data make it attractive to use process assessment when the intention is to compare facilities or providers.[29]

Approaches to measuring the quality of care

There are several approaches to measuring the quality of care based on what is discussed above. These involve using explicit criteria for structural characteristics, for process variables (comparing what was done to what should have been done), or for outcome data (comparing actual and expected outcome); using implicit criteria for process or outcome data or both; or using a combination of

explicit and implicit criteria for process or outcome data or both. The explicit process method is the strictest and the implicit outcome method the least strict. Results of an assessment will vary according to the method used. However, if the assessment is carefully performed, it should vary in degree only, not in nature or direction.[28] When using a combination of explicit and implicit criteria, the former are applied first, with the objective of identifying cases with potential process problems (this is sometimes referred to as "flagging"), and the latter when reviewing the process of care in "flagged" cases.[9,20,32]

The flagging approach is tempting because minimally trained inspectors or even computers can apply explicit criteria. Developing an effective screening program using explicit criteria is not easy, though. Furthermore, routine care and monitoring is frequently inadequately recorded and may be more completely recorded when complications occur. When Iezzoni et al. conducted a controlled study looking at a quality-screening program, they found that process problems, many of them related to timing of events and monitoring, were quite common.[37] Contrary to what they expected, there was no difference in "flagged" and "non-flagged" cases in regard to process problems. Thus, in this example, the flagging was not a good indicator of the quality of care. It is possible that they did not use valid process variables, or misclassification may have rendered the flagging useless. The former can only be improved by developing better process indicators, which is not easy; the latter, by better information systems and respect for clerical procedures.

Quality assurance

Definition and objectives of quality assurance

"Quality assurance" has been described as a cyclical process by means of which the health care community assure themselves and others of the quality of care for which they have responsibility.[7] More specifically, "quality assurance" in health care is defined as a system of procedures, checks, audits, and corrective actions put in place to ensure that the health services are of the highest achievable quality.[10] "Quality control," a related term, is defined as the supervision and control of operations, usually involving sampling and inspection aimed at detecting and correcting systematic or excessive random variations in quality.[10] According to these definitions, the terms "quality assurance" and "quality control" overlap to a great extent. The term "quality assurance" will be used here mainly because of its broader definition, but also because of the negative connotation frequently associated with the terms "control" and "inspection."

Quality monitoring is primarily an administrative enterprise aimed at collecting a continuous flow of information about performance in order to determine whether a system is achieving its objectives.[38] Quality assessment, on the

other hand, is often described as a research activity or as the epidemiology of the management of illness or health. Here, the subject of study is the magnitude and distribution of quality and the manner in which it is affected by the characteristics of societies, organizations, practitioners, and patients.[38] As will be discussed later, the information used in quality assessment and monitoring is seldom precise enough or gathered under sufficiently controlled conditions to permit conclusions about the relative efficacy of varieties of care.[9] This is the role of clinical research and technology assessment, which establish the appropriate management of illness. Quality assessment, on the other hand, determines whether and how available technology is used.[38] Nevertheless, quality assessment can contribute to clinical research. If, during assessment, an association is suggested that cannot be explained by current knowledge, a resulting hypothesis can be put to study using sound scientific methods.[26]

Quality assessment is also to be distinguished from operational research* and health systems research.† "Operational research" can be defined as the systematic study, by observation and experiment, of the workings of a health service, with a view to improving the services.[10] Quality assessment and monitoring can identify problems, which can then be investigated applying methods of focused operational research. In this way, operational research contributes to quality improvement.

Chassin has pointed out that even if systematic analyses have revealed that the responsibility for errors often lies in faulty systems of care, considerable resources have been spent on "reactive quality assurance activities" within the health care sector, that is, in detecting bad patient outcomes and placing blame.[27] It is likely that mending the care delivery systems would be more effective in reducing errors.[12] Many health professionals have argued for a more proactive approach to quality assurance in health care.

System design

"System design" refers to the way the system of health care in general, or any particular health care institution or program, is set up with the aim of safeguarding and promoting the quality of health care.[9,23] This is the subject of Chapter 7.

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*Some investigators talk of "action research." Varying definitions are used for this term, but generally speaking, its purpose is to generate new knowledge and implement change.[39]

†"Health systems research" is a term used to describe a participatory and action-oriented research approach. It engages the very people involved in the delivery of health care in problem identification, data collection, and analysis, with the aim of stimulating local ownership of the research process and the results. This ideally should facilitate implementation of changes.[40]

Quality assessment

Quality assessment can be considered a requirement for good management and good clinical practice.[23] Its objective is health care itself, and by inference, the performance of those who participate in it or are responsible for it.[26] The methods used in quality assessment should be legitimate and fair, known to the person(s) whose performance is being assessed, and applied consistently and persistently without idiosyncratic variations and favoritism.[23] Monitoring of clinical performance should not be regarded as a policing activity, but rather as a valuable tool for self-evaluation.[23] It enables health personnel to measure their performance against their own expectations and the expectations of others as well as comparing themselves with others. Ideally, it serves as a motivation to perform better.[41] Whereas health care practitioners primarily use a case-by-case approach in their daily routine, quality assessment can add an epidemiological perspective, which requires a view of how groups of patients are managed by each practitioner and by practitioners collectively.[23] Those practitioners who give this exercise a sincere try usually agree that it benefits clinical practice.

As previously mentioned, quality assessment can be regarded as a research-related activity. It is useful to keep this in mind when designing and implementing quality-assessment programs. However, as will be discussed later in this section, there are important differences between genuine research and quality assessment.

The level and scope of assessment

Quality of care can be assessed at several levels, such as physician, health facility, administrative or geographical region, health sector, or health system.[28] Quality assessment can also address different aspects of care, such as technical performance of practitioners, personal interaction between practitioner and patient, patients' contribution to care, access to care, or the social distribution of access to or outcome of care.[9] Finally, assessment can address the management of a specific disease or symptoms.

Patient and community satisfaction with health services is an important aspect of the quality of health care.[18] However, patients frequently express satisfaction with any form of care experienced, and this may bias quality ratings, making them higher than the care they received warrants.[42,43] If users are able to select services, they are likely to rate the services they choose highly. Even when choices are severely restrained, people may convince themselves that they have received the best care they can afford.[44] Overall, although the results of patient and community surveys and opinion polls are thought-provoking, they often simply confirm known problems or, at best, are inconclusive and difficult to interpret. Although important, the management of the interpersonal process is seldom addressed in quality assessment because relevant information is

rarely available and not easily obtained.[26] Although patients may judge the quality of care subjectively, as a rule they have no standard against which to judge the technical quality of care, and they must rely on providers to monitor and maintain technical quality on their behalf.[32,41,42] As accountability in this regard is the obligation of health professionals and because it is easier to deal with data that can be objectively described or quantified, operational quality assurance usually begins with a review of technical performance, which it should always include.[32] Studies commonly reveal problems in this area, and thus reviews of technical performance are certainly worthwhile.[32]

Simple versus complex assessment

When implemented conscientiously, a simple method of monitoring can be more effective than a complex method implemented half-heartedly or not at all.[41] According to Palmer and Nesson, multiple task-oriented evaluations are more feasible for internal self-evaluation than the complex, multifaceted, all-in-one approach commonly used by external reviewers.[32] They emphasized a focus on patient care and the use of actual patient care data.

Vertical versus integrated assessment

A combination of explicit and implicit review requires that there be a certain level of expertise in a review team. This is less likely to be possible in "integrated" assessment. The one-task-at-a-time approach advocated by Palmer and Nesson acknowledges that the purpose of an operational quality-assurance program is to identify specific deficiencies that are amenable to correction.[32] They claimed that it is improbable that many aspects of care can be simultaneously assessed and improved. They specifically warned against the use of composite performance scores, because ultimately such aggregate measures tend to be meaningless when it comes to deciding on action for quality improvement. Instead, addressing particular small, discrete tasks of care individually in succession produces clear measurements.

Methodological considerations

Assessment design

Quality assessment is by definition retrospective in that it examines the quality of care that has been provided.* Quality assessment does not use a true prospective design or experimental design, because it does not set out to explore new ways of caring for patients or compare the relative efficacy of varieties of

*Strictly speaking, this is true for "quality assessment." Nevertheless, "quality-assurance programs" can use problem-solving strategies that trace care either backwards (from outcome to process) or forwards (from process to outcome). The former aim to improve care in future cases; the latter aim to enhance care in current cases as well.

care. Quality assessment usually involves an element of comparison, however, such as comparison with a quality standard or expected performance, with previous performance or with peers, between groups of patients (stratification), or even a proper case-control design.

In the early 1970s, Rutstein et al. advocated the use of negative indices as sentinel health events. In their view, the occurrence of an unnecessary disease, disability, or untimely death should trigger a search for underlying causes that might be prevented or treated,[19] that is, unfavorable outcomes should prompt an investigation of process. Therefore, a poor outcome would contribute to preventing such outcomes in future cases. Williamson's health accounting method is a comparable approach that uses normative group estimates to set standards for the percentage of patients having a favorable outcome.[32] If care fails to match the outcome standard, an investigation is conducted to identify the reasons for substandard results.

A major difficulty in using outcome assessment is that it is difficult to account for confounding factors that predispose toward poor outcome.[32] In other words, the so-called case-mix may differ from one care provider to another. Case-mix refers to characteristics of the disease or patients (for example, severity of illness, co-morbid illness, race, socioeconomic or behavioral characteristics) that can be seen as being outside the control of care providers. Attempts to correct for these differences with risk adjustment have proven difficult.[34] Donabedian warned that risk adjustment might not lead us in the right direction anyway.[9] A good-quality service should fit the clients, and a poor outcome should not simply be explained away as an unfavorable case-mix. In his opinion, over-adjusting might lead us to ignore some of the crueler realities of the health care system.[9] If the services do not fit the clients (as demonstrated by a high defaulter rate in tuberculosis programs, for example) or are not accessible (as demonstrated by severe disease on presentation, early death, or high defaulter or transfer rates), it is important to adapt the service. Ideally, quality assessment should guide us in this direction.

Those who criticize the outcome or negative indices approach point out that adverse outcomes are often delayed and thus require a long follow-up period (such as relapses),* are often relatively rare events that can be difficult to define or assess (such as functional status) and can thus be misleading (such as patient-reported outcomes), and finally that it may be difficult to time the assessment.[24,32] Although determining starting points is usually straightforward (for example, date of care seeking, registration in the laboratory, registration for treatment), determining end-points for outcome evaluation can be difficult (for instance, default and failure). Appropriate timing of outcome measurement

*This is partly solved in the model tuberculosis program by looking at "relapses" registered for treatment.

is important.[13] For example, in the tuberculosis program, all patients must have an opportunity to complete treatment even if treatment is not 100% regular; that is, there must be reasonable allowance for irregularities.

It can be argued that an assessment ideally should focus on early events in an attempt to prevent or reduce the chances of adverse outcome in individual cases. Strictly speaking, this is only possible if the assessment is based on items of process that are proven by research to be effective in improving outcome and that can be detected and acted upon in routine practice.[32] Frequently, however, process items are included based on the best available evidence and a value judgment about whether the items constitute a reasonable objective of patient care.[32] Krumholz et al. advocated using a process assessment in order to encourage health personnel to adhere to practice guidelines.[13] This is a valid argument when a clear evidence-based guideline exists, where the processes to follow are spelled out, or when paramedical workers with minimum training carry out the bulk of the work.

Slater defined what he called a "trajectory method" as an approach that combines process and outcome assessment and follows the course of patients from presentation to diagnosis and treatment and through final outcome assessment.[36] The entire process of care is then documented in a standardized manner, and the results are summarized at certain stages of the process.

As always, when making comparisons it is important to ensure that the data collected in the assessment conform to standardized definitions. As discussed above, it is debatable to what extent the data need to be from similar samples of participants, or otherwise whether risk differences should be adjusted for in the analysis or taken into account when interpreting the results. In tuberculosis programs, for example, it might be reasonable to adjust for drug resistance when looking at treatment failure and to take HIV prevalence into account when looking at the proportion of patients who die before completing treatment. Generally speaking, using outcome comparisons in coercive or competitive situations may produce perverse effects.[29] A tragic consequence would be if, as a result of perceived or actual competition, providers selected patients, excluding or transferring those likely to have a poor outcome,[24] a phenomenon which has been referred to as "dumping." In tuberculosis programs, these could be patients with severe disease or co-morbidity (such as HIV/AIDS or drug resistance), or they could be migrant workers, the homeless, or patients from far away. If the result of a quality-assurance program is that any of these are denied care or are excluded from analysis, then the program has defeated its purpose.

Study population and sampling

The study subjects in quality assessment can be single cases, selected cases, consecutive cases, or cohorts of patients. Random sampling is seldom applied.

Although random sampling is necessary to obtain an accurate view of how a practitioner, a health facility, or a system performs, in quality assessment, a more purposive method of selecting cases is often used to efficiently identify the cases most likely to have been mismanaged.[20] Thus, quality assessment frequently seeks out an illustrative view rather than a representative view.[26] A purposively biased sample might even include the worst examples of care,[9] that is, select cases with a particular type of adverse outcome such as "treatment failure." Because this is a serious and usually rare outcome, each and every failure case should be studied. On the other hand, in a setting with a high caseload and a high defaulter rate, the review might involve a sample of defaulters.

It is difficult to obtain meaningful data from health care providers that have a small caseload.[24] In a decentralized health service, all cases registered in such a health facility might be reviewed. Including older records in order to obtain a larger sample size does not solve the problem because there may be secular trends in the data.[24] The further back in time the review covers, the less it will be addressing recent performance. The circumstances may differ over time, and there may even be different personnel. Performance assessment is ideally derived from reasonably recent data.[24]

Gliebe encouraged an orientation toward the individual case as a solution to what he considered to be potential discrepancies between the results of process and outcome assessments and the problems of aggregating data.[45] Even if few would agree that carefully conducted process and outcome assessments result in seriously discordant results,[23,28] Gliebe had a point in that one can learn a lot from reviewing individual cases. As an example, this approach is widely practiced in the form of case conferences.

Because samples in quality assessment are seldom statistically valid probability samples, quality assessment is not "research" in the strictest sense of the word. The purpose of quality assessment is different. It is more managerial. Its main aim is to identify and correct the most serious flaws in health care and to create an environment of watchful concern.[26]

Measurements

A quality measure* is a quantitative measure† that can be used as a guide to monitor and evaluate the quality of care and supporting activities. A quality measure needs a numerator, a denominator, and a designated data source.[22] Standardized definitions and standardized data recording are important if quality assessment is to be based on health care records.

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*Some use the term "indicator" rather than "measure," and the term "performance" rather than "quality."

†Whereas both "qualitative" and "quantitative" information can be used in quality assessment, quantitative information has the advantage of measuring the magnitude of problems and any changes over time.

Validity, reliability, sensitivity, specificity, precision, and accuracy are important terms when discussing measurements. Validity of a measurement refers to how well a measurement procedure measures what it intends to measure. In the case of quality assessment: does it really measure quality? Reliability refers to repeatability or reproducibility, for example: would different reviewers come up with the same values (inter-rater agreement), or would a given reviewer be able to repeat the measurement with the same results (intra-rater agreement)? In quality assessment, "sensitivity" refers to how well the measurement performs in detecting low quality. "Specificity" refers to how well the measurement performs in assigning the status of good quality. To be able to judge this, there must be a defined standard. When applying a two-step procedure, as a rule, the first step should be highly sensitive (selecting all those instances that may be poor quality), and the latter should be highly specific (excluding those instances that were wrongly suspected in the first step).[20] "Precision" is a statistical term referring to standard errors in measurement. "Accuracy" refers to how well the measurement represents the true value. Although very important in research, accuracy and precision are not the primary aims in quality assessment. Finally, benchmarks refer to quantitative norms, which can be derived from best, average, minimum, or otherwise "acceptable" practice.

The construction of quality indicators is a daunting undertaking. Although it will never be possible to produce a completely error-free measurement of the quality of care, an effort should be made to use state-of-the-art measures.[28] The purpose of the measurement is important. If, for example, as discussed above, the aim is simply to identify cases that are probably mismanaged in order to study them in greater detail, precisely graded measures may not be necessary.[20,25] Obviously, however, the measures must be measurable. For example, it can be difficult to measure patient education: Was it performed? Did the patient understand? Did it result in "correct" patient action or behavior?

It is easier to come up with quantitative measures for standardized care than for individualized and vaguely described care.[22] If guidelines exist, then it is relatively easy to measure clinical performance in terms of adherence to the guidelines. A sample of patients to whom the guideline applies is the denominator of the rate. Those whose care matches the criteria defining conformity with the guideline represent the numerator.[24]

The ideal process measure has a documented process-outcome link, is applicable to a readily identifiable patient population, and is measurable through chart abstraction.[13] With regard to outcome measures, the outcome must be achievable by good care and attributable first to medical care and then to the provider's contribution to that care. Information on the outcome must be available, and the means to achieve the outcome must be considered as well as the consequences of taking and of not taking action.[30]

Palmer provided a useful summary of when to use process measures and

when to use outcome measures.[29] Process data are especially useful when time frames are short; when comparing providers; when processes of interest affect long-term outcomes; when quality assurance aims to improve delivery of care in current cases; when performance of individual providers is of interest; when there are low-volume providers; and when it is difficult to adjust or stratify for patient factors. Outcome data are particularly useful when it is acceptable to wait to observe long-term outcomes, especially if the interest is in the impact of entire programs of care on the health of a population. Large-volume providers can supply sufficient sample sizes to detect differences in outcome. Structure, process, and outcome measures are compared in Table 10.2.

Strictly speaking, if criteria based on structure or process data are to be credible, it should be shown beforehand that variations in the attributes they measure will result in differences in outcome (such as default, failure, death, or relapse).* If outcome data are to be credible, it should be demonstrated that differences in outcome will result if the processes of care that are under the control of health professionals are altered.[28] In practice, this principle is not always respected. In a review of quality indicators used in the field of mental health, Herman et al. found that measures based on fair research evidence were most common, and that only 20% of the indicators used were based on good research evidence.[22] Measures requiring only administrative data were more likely to be used than measures requiring other types of data. More than one half of the measures were insufficiently developed for implementation, and few measures had been tested for reliability or validity.

Data sources and methods for obtaining data

When designing a quality-assurance system, it is important to decide which methods of data collection can be used as well as the data sources, time, and personnel available.[32] Potential data sources and data collection methods include the following: clinical records (review, audit); structured or unstructured interviews with staff, patients, and family members; direct observation of the staff at work or of staff-patient interaction; and survey data. Each source will give different information. Which data source will give the best assessment of quality depends on the purpose of the assessment.[28] The availability of information, its completeness, and its susceptibility to manipulation are important considerations.[34] Finally, the cost of quality assessment should always be considered, and it should be acknowledged that quality-assurance systems might divert funds from other activities, such as patient care. Most quality-assurance

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* For example, in process assessment, it should be clear beforehand (and this is not the subject of quality assurance) that the action (such as directly observed treatment) is a valid measure of quality or that it is necessary, such as when a decision depends on it (for example, the 2-month sputum smear in the tuberculosis program).

Table 10.2 Comparison of structure, process and outcome measures

	Structure	*Process indicators*	*Outcome indicators*
Advantages	Important in design of systems	Provide timely information Process problems are common, thus easier to study Allows feedback concerning performance of the system "Actionability" (early action prevents adverse outcome) Easier to make comparisons Encourages compliance with guidelines	Comprehensible to consumers Summary (inclusive, integrative) variables, that is, reflect different things in antecedent care and possibly the interplay of several problems
Limitations	Causal relationship with outcome often weak Difficult to quantify	Difficult to establish causal relationship between process and outcome	Adverse outcome is rare, and thus difficult to study Information is delayed (after care is completed) Difficult to use in comparisons (case-mix, risk adjustment) Integrative, thus unable to isolate specific errors, to tell what went wrong in whose hands
Examples	Clinical guidelines Monitoring systems Systematic documentation Case management strategy Referral structure Decentralization	Refer to processes in diagnosis, treatment, prevention of complications, follow-up	Results of treatment Vital status Transmission Drug resistance
Utilization	Primarily in system design	In quality assessment and supervision at the level of individual providers or facilities	Primarily in evaluation of long-term impact of health programs

programs can anticipate limited budgets. Thus, where reliability and validity permit, they should prefer routinely available data sources and intervention mechanisms rather than special data-collection efforts and overlapping or duplicative efforts.[32]

Nicolas et al. conducted quality surveys in 12 developing countries.[16] They

concluded that direct observation using checklists was the best method for obtaining data during supervision; interviews with patients were second best; and record review, the poorest. Direct observation provided opportunities for personal feedback and motivation on site. Hermida et al. came to a similar conclusion when they studied data collection in supervision of the management of acute respiratory infections, diarrhea, and family planning in Guatemala.[46] The methods they compared were direct observation using checklists, structured interviews with mothers after they received care, and a review of medical records. Whereas sensitivity was found to be high for all three methods, the main problem was with specificity. Direct observation was found to have the best levels of sensitivity and specificity overall. The record review yielded the lowest specificity, mainly due to the fact that records were often incomplete.

Quality and completeness of recording is a frequently cited problem when using record reviews,[16,46,47] and not only in developing countries.[37,48] This is a separate quality issue, and good care and accurate recording are related.[25] With sufficient foresight, the routine medical record can be designed in such a way as to fit the quality-assessment exercise. In fact, record review can and should only be used if there is prior effort to implement a standardized recording system. Obviously, health workers may be reluctant to provide information on which their performance will be judged. If information pertinent to quality is routinely collected within the health system, quality assessment may be best performed on site.[17] In other words, supervisory visits provide an ideal opportunity for conducting systematic data validation and quality assessment. If there is a sensible and reliable recording system in place, then record review can provide an excellent basis for interactive discussions of discrepancies and for all kinds of feedback and motivation.[49] In fact, provided that the supervisor is skilled and experienced, even medical consultations,* a method that is frequently scorned, can achieve the same.

Information obtained in interviews is important for insight into political and administrative processes.[50] However, interviewing is a difficult technique. Extensive training and experience are needed to become a good interviewer for the purpose of systematic quality assessment. Additionally, interviews can be problematic for various reasons, such as mutual misunderstandings, fear of retribution, and vested interest in distorting the information. All of these contribute to inadequate, misleading, or even outright erroneous information.[50] In a study in Spain, physicians' agreement with quality evaluation criteria correlated significantly with self-reported compliance but only occasionally with actual compliance.[51] This study supports the view that interviews with health workers concerning their own performance are not a reliable tool in

*As opposed to systematic record review, medical consultation involves cases selected by the provider rather than the auditor.

quality assessment, but rather are seriously biased to an unknown extent. Furthermore, in this study physicians underrated the performance of their colleagues, which raises concerns regarding the reliability of peer ratings. Even if these results cannot necessarily be generalized to other professionals or nationalities, they do support the view that objective data should be preferred in quality assessment. Written sources of information should be consulted whenever possible.

Inter-observer variability is a problem when using on-site observation in data collection, and extensive training is needed if this method is to be applied sensibly. It can be argued that consistency in treatment and case-management protocols facilitates the use of standard observation instruments by observers with modest technical knowledge. However, as pointed out above, relying solely on explicit criteria has its limitations, such as lack of flexibility and adaptability, which may affect the credibility of the supervisor.

Finally, two things are worth considering when developing data-collection instruments for quality assessment. First, quality assessment ideally follows the route of the patient from the time of presentation at the health service or from diagnosis.[13] Second, it is important to link information from different units and/or sources during the quality-assessment exercise (for example, the laboratory and the tuberculosis register; the staff and the patients; hospitals, health centers, and satellite centers). The quality-assurance process can then be expected to facilitate continuity in care and stimulate the different players to work together to analyze and use the information they collect. Ideally, this is done using an interactive approach on site, for example, during supervisory visits. Linking information on continuity of care may, however, be difficult in large cities and in mobile populations that receive care from many sources.[25]

In conclusion, there is a difference between the inexperienced and the expert when it comes to measurements and data collection in quality assessment. Explicit criteria, standardization, and structured interviews as opposed to implicit criteria and unstructured interviews (which rely on personal experience to ask relevant questions and make sure that important issues are not overlooked) are more important for the inexperienced. Standardization can be accomplished with proper training and by using supervision guidelines and checklists.* On the other hand, very experienced supervisors can discreetly observe routines out of the corner of an eye, while simultaneously reviewing records. They can obtain important additional information and clues by interacting and talking with patients and personnel throughout the exercise. It is impossible to design foolproof criteria, which is why reviewers need to be trained or

*It is debatable, however, whether "standardized" supervision guidelines or standardized lists of indicators can be justified. Checklists and indicators should be context-specific. There are different realities and different problems in different settings.

experienced. Recent developments in quality-assurance methods, particularly in industrialized countries, tend to focus on using computers. This approach leaves no room for judgment. Computers, like the inexperienced non-expert, use rigid, explicit criteria. Another issue with computerizing quality-assurance systems is cost, considering the fact that computerized systems may require periodic updating of software, which is a logistical challenge.[8]

Interpretation of the results of quality assessment

Because quality assessment is not a research activity that requires great precision, it is not necessary to spend much time considering the accuracy of the results. However, when interpreting the results of quality assessment it is important to consider the validity of the results (whether any bias existed or systematic errors occurred), reliability, and whether the results can be generalized.

In theory, reviewers should judge quality as satisfactory if patients were cared for appropriately. Weingart et al. found that reviewers using implicit criteria were inconsistent in that they tended to judge process more harshly in cases with adverse outcome, even when care was identical in a matched case.[52] In other words, they seemed to be influenced by the outcome. One needs to keep this in mind when assessments focus on cases with adverse outcome. Using two or more reviewers may improve consistency.

Weingart et al. also found that poor documentation increased the odds of finding substandard quality.[52] Reviewers may assume (often rightly so) that poor documentation indicates sloppy care, inadequate attention to detail, or poor clinical judgment, rather than what it is, namely inadequate information from which to draw conclusions.

Generally speaking, small sample sizes make interpretation difficult. One must keep this in mind when looking at data from low-volume providers,[53] especially when looking at rare outcomes[24] or comparing providers.[54] Aggregating data from many low-volume providers (such as in rural areas) is controversial, because the providers are likely to differ in unknown ways.[55] Using scoring systems in data handling and analysis increases the limitations of the assessment.[9] Aggregated statistics and scoring systems may entirely obscure the objective of the assessment.[32]

Being that outcome is an integrative measure, it does not directly assess the quality of performance but merely permits inference about the quality of the process and structure of care.[34] Results based on outcomes are open to misinterpretation and misunderstanding if the problem of multiple causation is not understood.[34] Although comparisons are often difficult,[24] generally speaking it is easier to make comparisons when using process indicators, because process is less likely to be affected by patient characteristics than is outcome.

There is little evidence to support the supposition that the results from an assessment of one set of symptoms or disease (such as tuberculosis or malaria)

can be generalized to the quality of care for another set of symptoms or disease.[28] Thus it is not possible to generalize about quality on the basis of assessment of a single or a few conditions. Nor can generalizations be applied from one activity to another (such as information and supply), one service to another (such as triage, laboratory, and tuberculosis clinic), one unit or country to another, or from rural to urban settings.

Health professionals do not operate in a perfect world, and the benefit obtained in routine practice is usually different from the maximum achievable benefit under controlled experimental conditions. It is not practical for assessment criteria to incorporate all the rare circumstances that may affect clinical decisions.[56] Practitioners may have good reasons to deviate from expected paths, such as conflicting or uncertain information from the laboratory or patients not showing up on time for follow-up.[56] Although deviations from standards of care should be the exception rather than the rule, a reviewer should always listen to justifications before reaching a final conclusion. Rigidity is an acknowledged weakness of explicit assessments. The importance of discussing the results of such assessments with those being assessed, in order to allow them to explain and defend their actions and understand the setting and problems, cannot be overemphasized.

Finally, when health workers become familiar with the benchmark indicators used, they may be able to adjust for them without necessarily improving other factors equally important for quality.[53] Repeated quality assessment using the same indicators and benchmarks might then give a false picture. Nevertheless, as previously mentioned, it is important that quality assessment be a transparent process. With carefully designed, comprehensive quality-assessment instruments and good working relationships, this should not be a problem. After all, the purpose of quality assurance is to improve performance on the indicators used. At the same time, one should keep in mind that any deviations in quality, whether in a favorable or an unfavorable direction, can merit inquiry.[9]

Quality improvement

It cannot be stressed enough that the objective of quality assurance is not punishment but quality improvement. Well-designed quality-assurance systems result in improved performance with regard to the specific tasks, which are addressed in the assessment. The term "sentinel effect" refers to the phenomenon that the expectation that one's work might be reviewed results in better performance.[20] It can be speculated that quality assurance could even lead to a more general improvement in quality, that is, improved performance in tasks that are not specifically addressed in assessments. This is not well documented, however. Thus, it is important to select measurements carefully when designing assessment instruments and to address tasks and activities that are likely to

influence outcome. Certain kinds of explicit process criteria may encourage redundancies in care.[20] This should be avoided by using only relevant process indicators.

A review conducted by Palmer and Nesson identified feedback and reassessment among the least well-accomplished components of the quality-assurance cycle.[32] In a later study, where Palmer et al. specifically looked at these components, they found that taking action in response to results of low quality was generally associated with effectiveness of quality assurance.[57] The number of corrective actions taken made a significant contribution. Interestingly, however, there were problems that improved without any action and others that did not improve even if action was taken. The former is in line with the experience of many that simply exposing a problem can eliminate it. This is understandable, because practitioners may not be aware of problems until a systematic assessment is conducted. Indeed, this is why assessments are conducted in the first place. In the above-mentioned study by Palmer et al., the participants agreed with and believed they were following the review criteria.[57] When the results of performance assessment were presented to them, many of the participants were dismayed by the gap between intent and achievement. They were not doing what they intended to do or what they thought they were doing.

Even if taking corrective action is neither necessary nor sufficient for improvement,[57] often specific actions are needed to solve the problems identified by quality assessment. Interventions in response to issues of quality may include administrative actions, meetings, feedback, reminders, educational efforts, or focused operational research studies that will bring further understanding to the problems identified and test alternative solutions.[16,32]

Interestingly, meetings may have an impact irrespective of apparently negative attitudes among the participants as well as of the participants' ratings of meeting effectiveness.[57] Meetings provide a venue for communication, and important issues are raised that often set things into motion without specific action.

Donabedian suggested that education is more likely to be effective if the trainee is convinced that there is a problem, the training is pertinent to the setting and problem, and it is provided person-to-person. In addition, feedback is likely to be more effective if it is individualized, conveyed face-to-face by a respected person, and provides comparison with colleagues.[23] Ideally, continuing education and feedback are linked with supervision. Palmer et al. studied the contributions of different components of the quality-assurance cycle on performance.[57] No improvement was seen after practitioners became aware of patient-care guidelines and assessment criteria, but a statistically significant effect was observed after personal feedback based on the results of the assessment. Thus, it is not enough to introduce a guideline and train personnel. Personal feedback is necessary in order for quality assurance to have an effect. The

conclusion that physicians in a Spanish study tended to rate their own performance better than the average for their peers when presented with the results of assessment of group practice suggests that aggregate feedback may not be enough, that is, that personal feedback is superior.[51]

Although comparison with peers may be important in quality assurance, ranking providers and publishing the results of quality assessment are debatable methods opposed by many.[5,34,58] The information from quality assessment is primarily important for service providers so that they can correct errors and improve performance. There are many practical problems with publishing the results of comparative quality assessments. Even if valid measurements would allow ranking of facilities and providers, ranking is likely to change with time and may no longer be valid at the time that the results are published. Also, a facility or provider may rank high in one procedure and low in another. Therefore, it is not always obvious how ranking should be interpreted.[58]

Finally, there is some evidence that the effect of quality assurance starts to wane after 9 to 12 months, supporting the belief that repeated cycles are important.[57]

On-site supervision

It is argued that performance appraisal and feedback at the supervisory level and instruments for self-evaluation are of more value in managing a peripheral health service than monitoring based on reports.[59] On-site supervision allows an interactive approach to quality assurance. Those being supervised can participate in the quality-assessment exercise itself, and there is an opportunity for immediate personal feedback and training in response to detection of less than optimal performance.

On-site supervision is, if anything, more important in low-income countries, particularly in ambulatory and rural settings where there are fewer human resources and often lower cadres of staff. Although supervision is an officially recognized activity in the health services of many low-income countries and supervision schedules exist in writing, recommendations on frequency of supervision are not always respected.[16,53,60] There are many reasons for this. The most frequently cited is lack of transport, even if this is not always obvious, that is, where functioning vehicles exist at all levels of the supervisory system.[16] But transport, in the broadest sense, is more than just the vehicle: it involves travel authorization, compensation of travel expenses, and fuel. In some areas, safety of supervisory personnel cannot be guaranteed. On the other hand, the important role of supervision in problem solving is often poorly developed, and supervisory visits are not always convincingly devoted to improving service quality.[16] All too often, supervisors are not even trained in supervision. There is clearly a need for increased acknowledgment by top managers that supervision is important.[61]

Because supervision is a weak element in many low-income countries,[60,62] the question arises whether it is unrealistic to depend on supervision for quality assurance. One thing is certain: supervision exists only if a true commitment to it has been made, and not only in terms of policy and financial resources; the supervisory staff themselves must be committed to it. If supervision is not a realistic option, then what can replace it? Computerized information systems allowing distance-based monitoring are often suggested. There are many problems with such a strategy, however, as discussed in Chapter 8.

Operational research

As mentioned above, it is observed that sometimes a problem goes away when it has been identified. Although this may be frustrating for those hoping to study it further, from the point of view of the program it is an ideal development.

Sometimes, however, it is not all that easy to solve or understand issues, even when they have been identified. Even if the routine information and quality-assurance systems determine that the program is not producing the expected benefits, reasons for failure may be unclear. Non-routine information may be needed to sharpen the picture of the quality of care. Operational research can then provide the details needed to understand the problems, guide actions, and test different solutions.[16,17]

The ideas for operational research should preferably arise from routine quality assessment and monitoring. The primary value of operational research is for local use in quality improvement. When relevant, the experiences gained in the course of operational research can be shared more widely by publishing the results locally or internationally. After a problem is detected and understood, the cycle in operational research involves suggestion of a solution, implementation, reassessment, and interpretation (this strategy is sometimes referred to, in shorthand, as "plan-act-observe-reflect"). Until this cycle has been completed, operational research is incomplete and, strictly speaking, not appropriate for publication. As always with publication of research results, successes are more likely to be published than failures. One should be aware of this when browsing the operational research literature. It should also be kept in mind that operational research is only the first step in quality improvement, and expected benefits may be overestimated in the research phase. Usually there is extra motivation and enthusiasm during and for some period immediately following the research phase. Once the routine sets in again, the benefits achieved can be different.

Quality assurance in tuberculosis control

The criteria used in quality assessment of medical care refer to determinants of the resulting health status of individual patients.[35] In communicable disease

control, quality at the program level is concerned with epidemiological impact and health status of populations. Assessment criteria are defined accordingly.

The strategy for tuberculosis control is based on detection and cure of infectious patients. Therefore, the quality-assurance program is concerned with quality of care at the level of individual patients, even if the overall goal of the control program concerns the population level and prevention of new infections. In quality assessment, individual cases and cohorts of patients are studied. The questions that drive the assessment are whether patients are rendered noninfectious and achieve permanent cure. To come closer to the answers, it is necessary to consider the appropriateness of the strategy in the specific context where it is implemented, the skills of the providers, and the functioning of the overall system.

Going back to Palmer's definition of high-quality health care,[24] in tuberculosis programs, access is considered in population-based planning. Appropriateness and safety are addressed in the manual of the program, which recommends sputum smear microscopy and standardized short-course treatment. The elements of timeliness of care that health personnel can control are the delay in diagnosis once the patient has presented at a health facility, and the delay in starting treatment once a definitive diagnosis is made. Trouble-free implementation of diagnosis and treatment is largely limited by the setting, that is, what the patients would like most may not be realistic given the resources at hand. Considerations for safety may counteract access in some settings. The focus in terms of safety is on avoiding an adverse outcome of treatment, such as drug resistance and complications.

The domains of quality that are easily assessed in the tuberculosis program are the following: diagnosis, treatment, coordination within the system, continuity of care, and patient safety. It is more difficult to evaluate access to services, case detection, and prevention of infection overall, but nevertheless important clues can be obtained with careful assessment. Interpersonal communication, with regard to the patient-provider relationship and patient satisfaction, can be addressed by exit polls, but this would imply additional information over and above what is routinely recorded.

Quality assessment in the tuberculosis program is aimed at detecting system or provider failure as opposed to patient failure. System failures may be numerous and are usually amenable to correction. The primary concern is the quality of diagnosis and patient care. Therefore, quality assurance must focus on the network of sputum smear microscopy, the diagnosis of cases other than smear-positive, and case management.[63] However, it is also important to consider quality assurance of program management, that is, recording, reporting, and materials management.

A plan for diagnosis and case management was developed in the model tuberculosis program with the aim of designing a protocol that would enable

medical assistants, nurses, or auxiliaries to handle uncomplicated tuberculosis cases and to enable evaluation of the care given by them. The standards of care, evidence base, and appropriateness in a general context are dealt with in Part I. In what follows, a valid process-outcome link is assumed, so that compliance of health personnel with recommendations in the manual of the program serves as a measure of the quality of care.

The records and registers used in the tuberculosis program are useful tools for care providers. They are simple and straightforward, and include only variables that are important in clinical decision-making, quality assessment, and evaluation. These data sources should be available and complete because the care providers need them and use them in the day-to-day management of individual patients. Although medical records may be incomplete and unreliable, they will improve if the quality-assessment program insists on using them. Once the information system is successfully implemented, there should be high inter- and intra-rater agreement when conducting assessments using routine records. The tuberculosis case management and information systems allow quality assessments to be made using explicit criteria. However, it is recommended that an implicit analysis of cases that fail to meet the explicit criteria be performed.

Ideally, quality assessment in the tuberculosis program is performed during on-site supervision. Supervision is also an opportunity for on-the-job training of key health personnel. Although the regular supervisor of tuberculosis management units usually works alone, at the central level there may be a supervisory team, such as a physician, a nurse, and a laboratory person.[64] However, it is usually not realistic for all team members to participate in each and every supervisory visit, and care must be taken that pursuance of such ideal policies does not reduce the amount of supervision performed. It is important that supervision be conducted regularly. Among other things, the frequency should depend on performance. Frequent supervision is indicated immediately after implementation in a new site and whenever poor performance is suspected or confirmed by routine assessment or monitoring. Otherwise, it is recommended by The Union[65,66] that routine supervision become quarterly for all tuberculosis management units.* An example from Nicaragua is provided in Box 10.1.

Much has been written about "program-specific" supervision as opposed to "integrated" supervision. In order to provide useful support to personnel working at the peripheral level,[68] a supervisor needs to have considerable and relevant training and experience. In tuberculosis programs, the supervisor is, above all, a public health supervisor primarily concerned with disease control.

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* In Tanzania, the written policy early on was that district tuberculosis medical officers who were responsible for supervision should visit all units in their area on a monthly basis.[67] In other programs, the policy may have been different.

Box 10.1 Supervision frequency

In Nicaragua, the population per tuberculosis management unit was on average approximately 35,000 in 1998, with a total of roughly 160 health centers performing acid-fast microscopy. Recommended supervision frequency was quarterly for tuberculosis management units from the intermediate level (since the early 1990s this level is defined as integrated local health systems, "SILAIS") and annually from the central level to each of the local health systems. Scheduled and accomplished supervisions from central level from 1997 to 2001 are shown below. Sometimes more than one local health system was visited in the same trip. Rarely were planned supervisory activities fully accomplished. Assuming that in each supervisory visit in a local health system the central unit can visit three health centers, they might visit on average 25% of all units in a year and potentially all units in the country within four to five years. However, the most distant units are less likely to be visited by the central team. Quarterly supervision of all health centers is the responsibility of the local supervisor, not the central unit. The purpose of the central unit is to demonstrate supervision (that is, capacity building) and to support, strengthen, and evaluate the intermediate level. In addition to the supervision activities, the central unit organized quarterly meetings in Managua with the supervisors from all the local health systems.

Supervision from the central level in the tuberculosis program in Nicaragua*

Year	*Scheduled*	*Accomplished*
1997	12	10
1998	16	13
1999	18	15
2000	15	14
2001	12	11

* Source: Ministry of Health, Nicaragua, annual reports of the National Tuberculosis Program.

The supervisor needs to be competent in all aspects of the program and reasonably experienced both in clinical case management and in disease control and program management. It is also important to consider efficient use of resources and minimize personnel requirements for supervision. To make good use of resources, the tuberculosis supervisor should visit the triage (outpatient department or walk-in clinic), where patients with symptoms suggesting tuberculosis are identified; the laboratory, where sputum microscopy is performed; and the tuberculosis clinic. The supervisor should obtain a complete picture of the program, link different sources of information and, most importantly, stimulate coordination and teamwork. Inexperienced supervisors adhering stubbornly to rigid explicit criteria are not the ideal option for quality assurance in tuberculosis control. In the worst-case scenario, these types of supervisors can lead to undue dogmatism and deter flexibility, initiative, experimentation, and change.[25]

It is easy to select patients for review once they are diagnosed and registered for anti-tuberculosis treatment. However, it is more difficult to identify symptomatic patients in the triage unless they have been examined in the laboratory and thus are listed in the laboratory register. Quality control in the laboratory network is aimed at detecting the rate of missed diagnosis among examined symptomatic patients. It is difficult to go further than this in quality assessment without conducting special studies. A "cough register," whether located in the triage or in the tuberculosis clinic, does not necessarily solve this problem.* There may still be care seekers with symptoms of tuberculosis who do not appear in the cough register,[69] just as they may not appear in the laboratory register. The triage register ("walk-in log") could be systematically scrutinized for recordings of "respiratory symptoms" or "cough" as the reason given for attendance or, better still, patients in the triage could be sampled for interview. During routine supervision, these are actually inefficient techniques with a low yield, but the issue can be addressed in operational research and health-interview surveys.

The unit of measurement in the assessment is usually the "episode of care." This is made possible by standardized treatment regimens with a defined duration of treatment. To determine the end of a care episode in case of "drop-out" or unsuccessful treatment, definitions of "default" and "failure" exist.

Finally, the cost of quality assurance must be considered, including travel expenses of supervisors and opportunity costs. The approach to quality assessment described here uses measurements and criteria that do not require collection of new data but only compilation and analysis of existing data. However, it does require on-site visits and, as mentioned earlier, real commitment and dedication in order to accomplish regular supervision. Another limitation is that even if supervision is performed within government-run programs, if there is a large private sector in tuberculosis services, the overall share of the government sector in tuberculosis treatment may be low. As a rule, there is no organizational framework for supervision when it comes to the private sector. Establishing such a framework is a challenge.

Although on-site supervision is important, it is only one component of the quality-assurance system in the tuberculosis program. Other components are training of health personnel and program monitoring.

Training personnel for participation in tuberculosis control

Successful learning is most likely to occur when training is based in the real-life circumstances of the trainee, and when it is problem-based, driven by inquiry,

*A "cough register" is a separate outpatient register listing patients with cough of more than two to three weeks' duration who are referred for sputum examination (that is, "tuberculosis suspects").

and includes critical reflection.[39] A literature review conducted by Palmer and Reilly identified physician training as an important indicator of the quality of medical care.[35] According to their findings, duration was less important than the quality and the appropriateness of the training in relation to the actual or subsequent work of the trainees. Whereas participation in continuing education per se did not guarantee improvement or competence, they found evidence that specific courses and training programs could, at least in the short term, improve quality of care.

More recently, Davies et al. reviewed 50 randomized trials on continuing medical education in the United States.[70] Dissemination of clinical policies or practice guidelines alone showed a negative effect. Workshops or small group discussions without an attempt to facilitate performance by practice strategies were inconclusive. Chart reviews by supervisors and on-site information and feedback appeared to be more effective agents of change than printed materials. Prescribing, test ordering, and preventive actions seemed to be relatively easier to alter by training than clinical management and patient counseling. The latter needed more complex strategies, such as explicit instructions and opportunities to rehearse with "simulated" patients, videotapes, and role-playing. They concluded that an assessment of the training needs of individual trainees was important. Additionally, they found that continuing education is more likely to be effective when it is practice-based and uses what they refer to as "enabling" and "reinforcing" strategies.

On the one hand, this strongly supports the importance of on-site supervision to identify training needs of individuals and groups of health personnel, and on the other hand, to conduct one-on-one training during supervision. Although role-play and simulations are undoubtedly useful training elements, one should not underestimate the rich material available on site in practically any tuberculosis management unit in a low-income country. Systematic review of cases during supervision, and even what is usually referred to as "medical consultations," serve a similar purpose as simulations and role-play and are additionally truly relevant for the setting. The cases presented and reviewed represent actual cases and can, if the supervisor is competent and experienced, serve the purpose of a broad discussion on case management. This may not be well understood or appreciated by non-physicians and those who are inexperienced in clinical practice and supervision. The inexperienced may in fact need "dummy" cases in order to perform.

In low-income countries it is common to conduct short training courses immediately before implementation of a program. This activity is usually a waste of time and resources if it is not followed by supervision; training and supervision should go hand in hand. A 1996 study in Ghana showed that gains in knowledge following in-service training in clinical management of malaria deteriorated within a year.[71] An evaluation of the essential drug program in Angola in 1990 noted that health workers who had attended training courses

did not necessarily perform better than those who had not attended courses, and that training in week-long or shorter courses prior to program implementation was ineffective unless it was followed by refresher courses and frequent supervision.[72] A randomized controlled trial in South Africa in the late 1990s found that a simple intervention consisting of off-site training of primary health care workers, and involving tasks related to improving patient adherence, did not result in improved outcome of tuberculosis treatment compared with outcome in control centers.[73] On the other hand, a pragmatic trial in South Africa used on-site interactive training on respiratory care by existing nurse supervisors, with the primary goal—with regard to tuberculosis—of increasing case detection.[74] Clinics were ranked by size and randomly allocated to intervention or control arms. The effect on tuberculosis case detection was larger than expected and suggested improved clinical selection of cases for sputum sampling in the intervention group. This method of training appeared practical and feasible in settings of small towns and rural primary health care clinics.

In-service training for tuberculosis control

It is both logical and encouraging that training after medical school—if relevant for current or subsequent practice—has an impact on the quality of care, as reported by Palmer and Reilly.[35] It can be assumed that this is true for other health professionals as well. The focus here is on in-service training for personnel involved in tuberculosis control. The issue of background training of health workers is beyond the scope of this publication, except to note that the level of background training is important when considering curriculum and training methods used in the tuberculosis program. Thus, it is necessary to consider the different cadres of staff (for example, laboratory technicians, nurses, auxiliary nurses, medical assistants, general physicians, specialists, and social workers) who are involved in one way or another in tuberculosis control as well as their respective roles and responsibilities. Where there is a private sector dealing with tuberculosis, it is also important to consider what kind of training opportunities to offer private practitioners so that their activities do not counteract the efforts to control tuberculosis.[75,76] Private practitioners, as well as other health practitioners, often express a need for continuing education concerning tuberculosis management.[75,77,78] However, improvements following one-off training may be short lived,[71] and follow-up, monitoring, and supervision of the private sector is difficult for an under-resourced public sector that may be barely able to supervise its own personnel.[79]

Apart from training during supervision, the training activities in the tuberculosis program are threefold: training of new staff on recruitment, maintenance training or updating and motivation of previously trained staff, and training of middle-level managers whose role it is to coordinate and supervise tuberculosis control. The duration of training is less important than its content, methodology, and follow-up. As with supervision, it is important that the

training be focused and relevant for the current practice of the trainees. Therefore, program-specific training is easily justified, and "integrated" training is an inferior option, particularly if it is mostly a repetition of the more general background training of health personnel. The frequency of in-service training courses in a program must consider the need for training in any given setting, which depends on the absolute number of health workers and the turnover rate. Staff-turnover rate is variable but often high in the peripheral health service in low-income countries.

Training of new recruits should include specific instructions, case discussions, and practice. The program manual and a description of the roles and responsibilities of the different cadres of staff is the basis of the curriculum for training of new recruits. Application of knowledge is important, and case discussions and practical exercises are ideally based on actual cases from the daily work in the program. Such material already exists in all settings where tuberculosis patients are treated. Application of knowledge can be practiced with exercises based on the records, registers, and reports in the program, as well as in field visits.

It is not enough to receive a guideline and attend a training course. As discussed in detail further on, on-site supervision uses chart audits and clearly focused training tailored to individual needs. As a rule, health personnel genuinely intend to adhere to guidelines and may think they do so even when they do not. Health personnel are commonly surprised to receive feedback to the contrary, and are then likely to change their performance in adherence to the guideline without any further action.

Peer meetings are the usual venue for maintenance training. The agenda of such meetings includes eventual updating regarding the policy and strategy of the program, presentation and discussion of common knowledge gaps and operational problems identified during supervisory visits, and an evaluation of program activities with active participation of those attending the meeting.

Training of middle- and central-level managers should include all the topics covered in this publication, in addition to clinical tuberculosis, epidemiology, intervention strategies, mycobacteriology, and laboratory issues. Such courses should be organized in all large countries, whereas smaller countries might consider having their staff attend regional or international courses.

Two examples from national programs are presented in Box 10.2.

On-site supervision of tuberculosis services

The objective of supervision

The principal objective of supervision is to institutionalize quality of care assessment in the tuberculosis program. Although supervision is aimed at detecting

Box 10.2 Training of staff in tuberculosis programs

In Nicaragua,* the training of doctors, nurses, and auxiliary nurses for work in the tuberculosis program is always brief. Nurses, and occasionally auxiliary nurses, are responsible for the tuberculosis program at the services level, that is, in health centers serving on average approximately 35,000 inhabitants. Turnover of health workers at this level is high and varies from year to year. Public health workers supervise the program. On average there is one local supervisor per 300,000 inhabitants.

Until 1992, no distinction was made between initial training and maintenance training. Everyone received the same "package" during annual workshops of two to three days, which were organized region by region until 1991, and after decentralization, in each of the local health systems. There were no formal training courses for tuberculosis supervisors. In 1992, an annual international two-week tuberculosis course was launched in Nicaragua. At the first course, all the tuberculosis supervisors were trained. Subsequently, new supervisors were to be trained in the international course, Nicaragua being allotted one to three slots in the course annually. In 1992, it was also decided to distinguish between initial training of new nurses and the annual workshops for all staff involved in the program (nurses, doctors, laboratory technicians, and auxiliaries). Supervisors were to report to the central unit whenever new personnel were recruited to take responsibility for tuberculosis control in a health center, as a minimum at the quarterly meetings of supervisors in Managua. When a certain number had been recruited country-wide, a three-day training course was to be organized in a convenient location. It was hoped that this would improve the training of new recruits and result in changes in the content of the annual workshops to make them more interesting and motivating for experienced staff.

As of 1994, the system of perpetual training of new recruits based on demand was in effect. From 1994 to 1998, the demand for training courses varied, and six courses were organized in this five-year period (range 0–2 courses per year), training on average 20 to 25 persons annually (range 0–50 persons). For comparison, 400 persons on average attended the annual workshops of the program organized in the local health systems.

In a report from Malawi,† it was noted that tuberculosis officers at district level with three years of training in public health received a two-week course when they started working in the tuberculosis program.[80] The program organized a training course for ten people every second year. From 1995 to 1997, there were roughly 50 tuberculosis officers working at the start of a year (1 per 240,000 inhabitants), and on average 10% to 15% left the program every year during this period, mainly due to transfers to work in other posts or programs. The supply of training courses was considered insufficient compared with the need. The report concluded by emphasizing the importance of retaining staff in these specialized positions and the need to increase the supply of training activities.

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*The population was estimated at 5.34 million in 1992, and HIV prevalence was low.

†The population was estimated at 11.87 million in 1992, and HIV prevalence was high. It has been suggested that HIV prevalence influences staff turnover.

weaknesses, the purpose is to form a basis for discussion and quality improvement. It is important to emphasize local ownership of the data. The primary role of the supervisor is to build capacity for continued self-assessment. Therefore, the local personnel must participate during supervisory visits. Supervisors should use a well-defined methodology, give feedback, and leave a report.

As always in evaluation, it is important to involve the highest authority, as doing so may increase not only the effectiveness of quality assurance[25] but also political commitment. Thus, the supervisory visit usually starts with meeting the director of the unit or area visited. It then proceeds to the triage, the laboratory, the tuberculosis clinic, and the pharmacy or store where medical supplies are kept. A joint working session with all relevant staff should be organized for data collection. Eventually, the results are summarized and discussed in the group and then presented to the director. It is important to be critical but constructive and to leave a positive impression.

Supervision should not be rushed. It is crucial to reserve enough time to conduct a thorough assessment and address issues deemed vital not only by the supervisor but also by the local staff. Supervisors should decide beforehand what they want to address during a particular supervisory visit, but they should also be prepared to address unexpected results. Regular supervisors may not have the time or need to investigate every aspect in the course of each visit. They should keep copies of supervision reports for the units they are responsible for and should follow up on results and commitments.

The method of supervision

The epidemiological objective of tuberculosis programs is to minimize transmission in the community via early detection and permanent cure of infectious patients. Standardized strategies for tuberculosis detection and case management are used in the programs and described in clinical practice guidelines. The guidelines serve as a standard against which quality is assessed.

Assessment during on-site supervision uses an interactive approach. Generally speaking, it is not viable to use a computer to enter data on site. Doing so puts a barrier between the supervisor and the staff that are being supervised, and easily spoils the atmosphere (as judged by everyone except the person working on the computer). The assessment described here primarily uses process variables, with occasional structure and outcome variables. Explicit criteria are used coupled with implicit judgment when quality issues are detected; it is primarily experienced supervisors and experts who use the latter. A written checklist or guideline is considered necessary in some settings.* Even if supervision was always regarded as very important in the programs collaborating

*A checklist can be constructed based on the method presented here but should take note of the setting.

with The Union, the exact methodology was not clearly defined and was never documented in detail. Instead, it was passed on informally from person to person. Although the model tuberculosis information system was developed under the leadership of Styblo, it was Enarson—Styblo's successor at The Union—who formulated the approach to supervision that is described below. Enarson's recommendations, adopted in Nicaragua in late 1991, considerably influenced supervision methodology and clearly resulted in quality improvement when it was used consistently. Whether or not supervisors can master this supervision technique depends on their background and experience. A simpler approach to supervision would not require any abstraction. Rather, such an approach would instruct supervisors to review the records and registers one by one to determine whether standardized procedures were followed, without any attempt at analysis or reflection.[81]

The unit of assessment during supervision is the tuberculosis management unit. The primary unit of measurement is the episode of care. The overall approach follows the patient from presentation through diagnosis and treatment to final outcome assessment (trajectory method), focusing throughout on transmission. During supervision, however, the goal is not necessarily to follow the same group of patients throughout. Instead, the review may assess different patient cohorts for different indicators in order to assess the most recent situation, while obtaining a complete picture of how the entire process of care works. Sampling methods are variable depending on the indicator: selected patients, consecutive series, or cohorts of patients. Data collection is primarily based on a review of standardized medical records, registers, and reports; different data sources are compared when relevant. Additional information is obtained from direct observation of health personnel and of patient-health worker interaction, from interviews with health personnel and patients, and from inspection of physical stock counts for assessment of materials management. The assessment is divided in two parts, the first focusing on efficiency in reducing transmission and the second on program management.

Efficiency in reducing transmission

The first priority in tuberculosis programs is to permanently prevent transmission from known sources of infection, that is, patients diagnosed with smear-positive tuberculosis. This is a prerequisite for expansion of services. The measurements used are presented in Table 10.3. The focus is on pulmonary smear-positive cases, new cases or all cases, depending on the indicator. What follows is a brief description of the indicators, given one by one. (The indicator numbers refer to those used in Table 10.3.) Examples from the field are presented as well. Because information from supervisory visits is seldom published, some of the examples are taken from studies that have looked at issues similar to those addressed during supervision.

Table 10.3 Measurements in quality assessment: treatment of known patients

Indicator	*Measure*	*Data source*	*Period reviewed*	*Sampling*	*Numerator/ measurement*	*Denominator*	*Benchmarks/action*
01. Are all pulmonary cases examined by microscopy?	Process	Case register compared with laboratory register	Last full quarter*	Consecutive new PTB smear-negative cases (≥15 years) in case register	New adult PTB smear-negative cases with smear result in laboratory register	All new adult PTB smear-negative cases in case register	All new adult PTB smear-negative cases should have (2–3) specimens examined
02. Are all detected smear-positive patients treated?†	Process (structure)	Laboratory register compared with case register	Same as above	Consecutive smear-positive suspects in laboratory register, excluding follow-up examination	Number of smear-positive cases in case register	Number of smear-positive suspects in laboratory register	All smear-positive cases diagnosed should be registered for treatment; if not, why not?
03. Is there provider delay in starting treatment in smear-positive cases?	Process (structure)	Same as above	Same as above	Same as above	Subtract date of smear examination from date of start of treatment	NA	Depends on the setting; look at range and % with delay of 0–3 days, 4–7 days, and >7 days
04. What treatment regimens are used in smear-positive cases?‡	Process	Case register	Same as above	Consecutive PTB smear-positive cases registered	Number of PTB smear-positive cases with correct regimen	All PTB smear-positive cases registered	All patients should receive standardized regimen unless contraindicated
05. Is treatment directly observed (DOT)?	Process	Case register, treatment cards, interviews	Same as above	Same as above	PTB smear-positive cases on DOT	Same as above	All (if that is policy) should receive DOT; if not, why not?
06. Is treatment in the intensive phase regular?	Process	Treatment cards	Quarter ending ≥3 months back	Same as above (or random cases)	Actual duration of treatment (days)	Expected duration of treatment (days)	Not more than 15% excess time

07. Are "late converters" detected?	Process	Case register (treatment cards for details)	Same as above	Consecutive new PTB smear-positive cases registered	New PTB smear-positive cases with smear result at 2 months	All new PTB smear-positive cases registered and alive at 2 months	All should have smear result; if not why not?
08. Is treatment modified for late converters?	Process	Same as above	Same as above	New PTB smear-positive cases with positive smear at 2 months	New PTB smear-positive cases with positive smear at 2 months and intensive phase prolonged	New PTB smear-positive cases with positive smear at 2 months	All should have the intensive phase prolonged
09. Defaulting	Outcome	Same as above	Last 1–4 quarters evaluated (results of treatment)	Selected cases with adverse outcome: PTB smear-positive cases who defaulted	Treatment duration	NA	Review all cases carefully; look at timing of defaulting
10. Detection of "treatment failure" and subsequent case management	Process (structure)	Same as above	Last 1–4 quarters evaluated (reports on results of treatment)	Selected cases with adverse outcome: new PTB smear-positive cases who then failed	New PTB smear-positive cases who failed, were correctly evaluated and registered for retreatment	All new PTB smear-positive cases registered in the period reviewed who then failed	Review all cases, consider why they failed and how they were managed. If no failures, discuss
11. Transfer and referral of smear-positive patients	Process	Case register and supervisor's list of transfers[§]	Quarter ending ≥3 months back	Eligible cases on the supervisor's list of transfers	Cases registered as "transfer-in" in the case register	Eligible cases on the supervisor's list of transfers	Compare data sources case by case, all should be registered as "transfer-in"

*Assuming quarterly supervision (an alternative is to start with the latest patient registered and go backwards as time permits).
†This assessment is difficult if many patients are diagnosed in one health facility and then referred to another.
‡Look also at doses according to weight in a few randomly selected cases.
§This can be done only if supervisors keep a list of transfers and referrals within their jurisdiction.
PTB, pulmonary tuberculosis; DOT, directly observed treatment; NA, not applicable.

Box 10.3 Are "smear-negative cases" smear-negative?

In supervisory visits conducted in 1995, a review of 533 consecutive new pulmonary "smear-negative" cases registered in 95 Nicaraguan health centers revealed that 43% were children (less than 15 years of age). Of adult "smear-negative" patients, 20% had no record of sputum examination in their files.[82]

In the early stages of implementation of the Laos tuberculosis program, a review of 492 consecutive new cases registered in the National Tuberculosis Center in Vientiane showed that 40% were classified as "smear-negative," all were adults, and all had a record of sputum smear examination.[83]

A study in 40 Malawi hospitals showed that the proportion of new adult (15 years or older) pulmonary "smear-negative" patients who were considered to have proof of sputum smear examination increased significantly from 76% to 85%, and then to 89%, when comparing three 6-month periods from 1997 to 1998.[84]

Indicator 01. By measuring infectiousness, a trend in transmission can be documented. The question here is whether infectiousness as measured by acid-fast microscopy is actually investigated and documented in pulmonary cases. The purpose is twofold: firstly, surveillance, which concerns the trend in new cases of smear-positive tuberculosis in the population; secondly, the establishment of a baseline for follow-up during treatment in individual cases. If patients do not undergo sputum smear microscopy, smear-positive cases may be misclassified and thus escape adequate follow-up during treatment. These cases may even receive inadequate treatment (if there are different treatment regimens for smear-positive and smear-negative patients). See Box 10.3.

Indicators 02 to 03. These indicators address the coordination between the laboratory and the tuberculosis clinic, that is, whether infectious patients identified in the laboratory are all enrolled in treatment without undue delay so that transmission is promptly arrested. This evaluation may be difficult if a large proportion of patients is diagnosed or enrolled in treatment in a health unit different from the one where they are registered and continue treatment. Thus, these indicators evaluate structure as well as process. See Box 10.4.

Indicators 04 to 06. The aim of standardized and directly observed short-course treatment for patients with smear-positive tuberculosis is to efficiently and permanently reduce transmission, that is, to prevent relapse, drug resistance, and failure. The indicators measure components such as treatment regimen, direct observation of treatment, and regularity of treatment.

Indicators 07 to 08. In programs using the Union treatment algorithm, the purpose of performing sputum smear microscopy after two months of treatment in new sputum smear-positive cases is to identify patients who might

Box 10.4 Coordination at the services level

A review of 466 consecutive new sputum smear-positive cases registered for treatment in Managuan health centers from July 1, 1994 to June 30, 1995 found that 74% were diagnosed locally (that is, in the health center where they received treatment).[85] The rest were diagnosed and even enrolled in treatment elsewhere, mostly in hospitals. (Hospitals are not reporting units in Nicaragua. They must refer patients for registration and treatment in health centers.) Thus, 345 cases were available for analysis of coordination between the laboratory and tuberculosis clinics in health centers. The analysis revealed that 97% of the patients diagnosed in local laboratories were registered for treatment, 59% started treatment within three days of diagnosis, and 88% started treatment within a week. Although these results were considered reasonably good, there was room for improvement. The review also emphasized the importance of formal coordination between hospitals and health centers.

A retrospective record review in a hospital in Victoria, Australia, showed that 86% of 43 smear-positive pulmonary tuberculosis patients started treatment within three days of diagnosis.[86]

In 1997, a study in 43 central, district, and mission hospitals in Malawi revealed that of 3,482 smear-positive patients identified in the laboratories, 86% were registered in the tuberculosis case registers.[87] Of 2,975 patients who were registered for treatment and for whom the information was available, 85% started treatment within a week of diagnosis, 96% within two weeks, and 98% within three weeks. In three central hospitals, 40% of the patients identified in the laboratory were not registered for treatment as compared to 14% overall in the study. Performance was best in the district hospitals, where 8% went without registration. The share of the district hospitals in case finding in this study was 54% (of the total 3,482). The reason for non-registration was known in less than one quarter of those not registered for treatment (most common reasons were death, transfer, or default). Most likely, many patients diagnosed at the central hospitals went elsewhere for treatment, but to what extent they were simply lost is not known.

A study in a provincial hospital in Chiang Rai, Thailand, examined the effect of introducing an enhanced laboratory notification system.[88] The number of unregistered tuberculosis patients fell from 44 cases in 1994 to 0 in 1999. The time elapsed from admission to treatment initiation decreased from a mean of 5.5 days in 1997 to 3.1 days in 1999. This decrease was attributed to a reduction in time between laboratory diagnosis and treatment from 2.7 days to 0.6 days.

In a study in Ho Chi Minh City, Vietnam, in 2000, initial default (defined as a patient not being registered within four weeks of a positive smear in the laboratory) was found to be 8.3%. Initial default was higher in urban districts (9.8%) than in rural ones (4.8%).[89] The investigators were able to locate 50% of the defaulters for interview. The majority of the defaulters (65%) had been treated, mainly by private or semi-private providers, with anti-tuberculosis drugs that they had to pay for. Treatment completion was lower in the private and semi-private setting.[90]

benefit from prolongation of the intensive phase of treatment. If the smear is positive, the treatment regimen is modified and the intensive phase continued for a total of three months. It is assumed that, on the whole, this will contribute to permanently arresting transmission (that is, reduce the risk of failure and relapse). If sputum examination is not performed, there is no basis for a decision regarding the intensive phase of treatment. The indicators measure whether the examination is invariably performed and whether correct action is taken when the smear is positive (see Cohort analysis at two months of treatment, below).

Indicator 09. The longer the treatment, the more likely that transmission is permanently arrested, even if a full course of treatment is not completed. The indicator measures the duration of treatment in patients who default. The exercise also identifies patients who have defaulted and provides a basis for a discussion of the reasons behind this as well as the actions taken to prevent it. Although default is an outcome variable, the results and ensuing discussion may reveal structural problems. See Box 10.5.

Indicator 10. This indicator concerns the most serious adverse outcome in the program: treatment failure. Patients whose treatment failed continue to transmit infection, and in addition they may harbor bacilli resistant to medi-

Box 10.5 Are defaulters likely to spread infection?

A review of records of 71 consecutive defaulters among patients registered as new smear-positive cases in Nicaraguan health centers revealed that 27 (37%) left before completing the intensive phase of treatment (two months) and 93% before completing six months of the 8-month treatment regimen.[91] Thus, early defaulting was a problem. The male-to-female ratio in defaulters was higher than in new smear-positive cases reported. A separate study in selected Managuan health centers where defaulting occurred mainly in the continuation phase also showed absconding to be related to gender. It suggested that male patients who attended irregularly during the intensive phase of treatment were at increased risk of defaulting compared with female patients who missed appointments during the same phase.[92]

After excluding patients who lived outside the study districts, a study in the Oromia Region of Ethiopia found that roughly 11% defaulted.[93] Early defaulting was a problem, with 19% of the 155 defaulters leaving before completing the intensive phase (two months) and 50% within three months of starting treatment. Patients received treatment at hospitals, health centers, or health stations. The defaulter rate was highest at the health stations in spite of these being closer to patients' homes. Roughly 60% of the defaulters lived close to their treatment facility, but distance was not related to defaulting. Adverse effects of the medication and lack of knowledge regarding anti-tuberculosis treatment and its duration were contributing factors, however. Family support provided a protective effect.

Box 10.6 Treatment failure

A review of records during supervision in 95 health centers in Nicaragua showed that 42 of 1,531 patients registered as new smear-positive cases had a record of positive smear at 5 months or at the end of treatment (2.7%). All but one case had been correctly reported as "treatment failure." A total of 37 were registered for retreatment, and the remaining 5 were not registered for retreatment at the center where the failure was detected (they may have gone to another health facility). Of the 28 patients whose retreatment results could be evaluated (10 were still in treatment at the time of the supervisory visits), 19 were cured, 1 failed retreatment, 2 died, 5 defaulted, and 1 had been transferred out. Thus, one quarter of the patients who failed their original treatment in these centers may have escaped control. Even if the number of failures was small, the conclusion was that these results were cause for concern, and that efforts were needed to improve performance.

A Malawi study identified several programmatic deficiencies in the management of patients who failed first treatment: incorrect registration as relapse or no registration at all, delays in starting retreatment, and loss of follow-up (some of the patients may have died).[94]

cation.* Indicator 10 aims to measure whether treatment failure in new cases is detected (positive smears at five months or later during treatment) and correctly managed (registration for retreatment with a different regimen). Treatment failure is usually a rare outcome, and every case should be carefully reviewed to consider what might have caused the "failure." As opposed to the smear at two months, which should invariably be examined in new smear-positive tuberculosis cases (otherwise it is not possible to decide on continuation of treatment), sputum examination at five months and at the end of treatment is aimed at detecting treatment failure. Generally speaking, the longer the treatment, the less likely the patient is able to produce a good sputum sample if there is response to treatment. However, if there is poor response or no response to treatment, the patient as a rule should be able to produce a good sputum sample and thus failures should be detected even if sputum examination is not performed in every single case at five months and at, or shortly before, the end of treatment. This should be kept in mind when discussing the results. Even if failure is rare, if few or no failures are detected in a program, the quality of sputum examination should be questioned. See Box 10.6.

Indicator 11. When infectious patients are transferred to another treatment unit, they may never actually present there to continue treatment, and thus transmission may not be permanently arrested. It is only possible to measure efficiency in this respect if clear procedures exist regarding transfer and referral

*Drug resistance in failure cases varies considerably between settings, however, and depends on treatment regimens used as well as various operational factors.

Box 10.7 Are patients effectively transferred?

In 1998, 68 patients were "transferred out" or referred from the Vientiane National Tuberculosis Center to district health centers.[95] Record review during supervision revealed that 5 were not on the list of the supervisor. Three of the 68 patients had not presented at the district, but the others had presented without delay. The net error in registration was +2 cases, which corresponded to approximately 1% of all pulmonary smear-positive cases reported in the municipality.

A study of patients transferred between Malawi treatment units in 1999 exposed an inefficient transfer system, with discrepancies between transfer-in and transfer-out; patients were lost from sight in the transfer process, and there was incomplete and erroneous evaluation of treatment results in transferred cases.[96] The investigators stressed the need for improved supervision.

A 1993 California study found that patients who moved between jurisdictions defaulted more often than patients who did not move.[97] The level of transfer was 6% (147 out of 2,576), 3 out of 10 movements ended in default, but 40% of those who moved were diagnosed in prison.

of patients (a structural characteristic). In an effective system, it is also possible to measure the delay from transfer to presentation at the receiving unit and whether registration in the two treatment units is correct. See Box 10.7.

Case detection and access

Once treatment delivery and results are judged satisfactory, the second priority of the tuberculosis program is to detect a high proportion of the existing infectious cases in the community. The actual number of patients and the rate of tuberculosis in the community are not known, and the latter differs from country to country and within countries. This means that there is no real target and no denominator. Thus, no attempt is made to measure case detection precisely at local or even at intermediate levels. However, there are indicators that hint at case detection. These are presented in Table 10.4. A brief description of the indicators follows (the numbers refer to those used in Table 10.4). None of these indicators should be used in isolation to judge access and case detection, but together they may give a reasonable basis for reflection.

Indicator 12. As discussed in Chapter 7, population-based planning is used as a guide for decentralization of tuberculosis services. The target is one tuberculosis management unit for 50,000 to 150,000 inhabitants. As a rule, more centralization jeopardizes case detection and extreme decentralization may adversely affect quality. See Box 10.8.

Indicator 13. The aim of population-based planning is to guide implementation of tuberculosis control services within the general health structure. Adults attending the general health services are screened, first by symptoms

Table 10.4 Measurements in quality assessment: case detection and access

Indicator	*Measure*	*Data source*	*Period reviewed*	*Sampling*	*Numerator/ measurement*	*Denominator*	*Benchmarks/action*
12. Population served	Structure	Interview	NA	NA	Population served	NA	50,000–150,000
13. Assessment of patients with respiratory symptoms*	Structure	Laboratory register (Diagnosis column)	Last full quarter†	Consecutive entries for diagnosis, excluding follow-up	Entries for diagnosis with at least one positive smear	Consecutive entries for diagnosis (excluding follow-up examinations)	For example, 5%–15% (discuss findings that fall outside the range)
14. Utilization of services*	Structure	Case register (Address column)	Optional (not done every time)	Consecutive cases	Patients from outside the service area‡	All patients registered	If many from outside, discuss why this is so; do they default?
15. Death on treatment*	Outcome	Case register (treatment cards and/or interviews for details)	Last 1–4 quarters ready for evaluation of treatment outcome	Selected cases with adverse outcome: pulmonary smear-positive cases who died	Time (in days) from starting treatment to date of death	NA	Reflect on the findings and discuss

*Proxy for access.
†Assuming quarterly supervision (an alternative is to start with the latest patient registered and go backwards as time permits).
‡Variations: break down by distance in km (for example, 0–5 km, 6–10 km, 11–15 km, and so forth), or look at urban vs. rural patients.
NA, not applicable.

Box 10.8 Decentralization of tuberculosis services

In the 1990s, a tuberculosis management unit for an average of 35,000 inhabitants existed in Nicaragua. There was concern that overall performance was inferior in units where very few patients were diagnosed and treated, although this was not systematically investigated. The case is the same in Laos, where some evidence suggests that quality is inferior in low-volume units.

(cough of more than two to three weeks' duration) and then by sputum smear microscopy. In a decentralized program, it may be expected that 5% to 15% of those undergoing sputum microscopy at the primary level have smear-positive tuberculosis. The proportion is referred to as the "case yield among suspects." If the case yield is higher, the denominator may be deflated for some reason, such as with pre-selection of the persons attending the facility (the proportion positive may be higher in referral centers and chest clinics as well as elsewhere, if chest radiographs are taken routinely prior to sputum examination) or with low attendance (if patients only seek care in the case of prolonged or serious illness). Thus, this indicator, together with other information, is a useful hint

Box 10.9 Case yield in the laboratory

In the case-finding studies in Kenya (see Chapter 2), the case yield among tuberculosis suspects undergoing sputum examination increased as the distance they lived from the district hospital increased.[99] This rise is in spite of the fact that the rate of tuberculosis would be expected to decrease with decreasing population density because the distance from a district hospital increases.

In a study in the Bangalore District of India, the case yield was higher among rural residents (15.8% among 1,315 persons 20 to 59 years of age) examined by microscopy in tuberculosis clinics located in a city than among urban residents (7.6%) examined in the same clinics.[100] This suggests that distance is a barrier, resulting in a process of self-selection or referral among symptomatic individuals. Urban residents with symptoms attended more promptly when taken ill, with 61% visiting the clinic within three months of onset of symptoms compared with 42% of the rural residents. Nevertheless, even among the urban residents, distance influenced attendance at the clinics.

In a study of four countries, the case yield among persons examined by microscopy was 5.2% in Nicaragua, 17.3% in Malawi, 18.6% in Senegal, and 32.1% in Benin.[101] Although the sample of laboratories was not representative, a large number of laboratories were included in the study. The differences are striking. Of these countries, the laboratory network is most decentralized in Nicaragua, and thus access to diagnosis is probably greatest.

with regard to access to services and pre-microscopy assessment procedures.[98] If access is impaired, case detection may be low. If, on the other hand, the case yield is very low, pre-microscopy assessment may be too lax or sputum samples of bad quality. Finally, when looking at this indicator, one should consider whether the results of the laboratory are reliable. See Box 10.9.

Indicator 14. This indicator gives an idea whether the numerator in case detection may be inflated by attendance of patients from other areas, which would suggest impaired access to services elsewhere and an inflated detection rate locally. Patients from far away may have a problem with completing a full course of treatment, and thus this may adversely affect treatment results. See Box 10.10.

Indicator 15. Patients dying early in treatment may indicate impaired access, that is, patients present too late for treatment. This should, however, be interpreted with care, taking into consideration other reasons for death during treatment, such as HIV/AIDS. See Box 10.11.

Program management

If drug supply is insufficient, treatment of infectious patients may be interrupted or incomplete. Thus, a focus on transmission indicates a concern with materials management. Addressing this issue begins with asking health workers if they have experienced episodes in which patients did not receive treatment because supplies were interrupted. During the supervisory visit, the storage facilities are inspected and a physical stock count is made. Is the stock balanced? Are there any expired drugs? Are any drugs likely to expire? Ordering and receipt of supplies is also reviewed. Has there been a shortage of drugs? Is there evidence of inventory shrinkage? When drugs are distributed, is care taken to use the drugs closest to expiration date first? The methods involved in this assessment are presented in detail in Chapter 9.

Box 10.10 Utilization of services by residence

In the Vientiane National Tuberculosis Center, recorded place of residence for patients admitted in 1999 was as presented below. The addresses recorded were believed to be reasonably correct. Thus, the defaulter problem in the Center, which was 19% for new smear-positive patients registered in the first half of 1999, could not be explained simply by patients from distant provinces where the program had not been implemented seeking care there. The results suggested that it might not be very difficult to reduce the defaulter problem by at least one half.[102]

Address of 212 consecutive patients:

Vientiane Municipality, 173 (82%)
Vientiane Province, 22 (10%)
Other provinces, 17 (8%)

Box 10.11 Death during anti-tuberculosis treatment

A retrospective record review in Baltimore, Maryland (U.S.), prompted by a high case-fatality rate, revealed that 24% of the 174 new smear-positive patients included in the study died during anti-tuberculosis treatment (in 1993 to 1998).[103] Advanced age and co-morbid illnesses explained most of the deaths. The researchers considered the question of whether the high case fatality was a result of ineffective tuberculosis control. Judging by all other indicators, they found that the control program had been effective.

A treatment trial in North America (The Tuberculosis Trials Consortium) of 1,075 patients recruited from 1995 to 1998, recorded 71 deaths (6.6%).[104] Only one death was due to tuberculosis. Other deaths were related to co-morbid illnesses, such as malignancies, HIV, and alcoholism.

A retrospective study in 38 hospitals in Malawi revealed that 22% of patients with smear-positive tuberculosis registered in 1997 died before completing treatment.[105] Another 5% were lost during follow-up. Although information on HIV status of patients was not part of the study, HIV prevalence was known to be high. Death often occurred before anti-tuberculosis treatment was started (2% of all deaths) or shortly after starting treatment: 19% of those who died during treatment did so within a week of starting, and 25% died within two weeks. The proportion of smear-negative and extra-pulmonary tuberculosis cases that died was even higher. The investigators concluded that, to attempt prevention of early deaths, it was important to minimize the delay before starting anti-tuberculosis treatment, to consider adjunctive treatments such as an empirical course of antibiotics (or even anti-retroviral treatment), and to improve the routine diagnosis in smear-negative and extra-pulmonary tuberculosis.

An epidemiological study in Mwanza, Tanzania, found that 10% of the 561 patients included in the study died before completing anti-tuberculosis treatment. Another 12% either defaulted or were transferred out. Of the 561 patients, 26% were HIV-positive. Of the HIV-negative patients, 8% died during treatment compared to 16% of the HIV-positive patients.[106]

A hospital-based study in South Africa (1997 to 1998) identified distance traveled as a risk factor for death during treatment, but only amongst those traveling more than 60 km to reach the hospital.[107] Of patients who died during treatment, 75% died within the first two months.

If the information in the program is not reliable, it cannot be used in case management or to verify success in reducing transmission. Comparison of different data sources during supervision validates the information in the program. Selected treatment cards are compared with the register, and the case register is compared with the laboratory register. Quarterly reports on case finding and results of treatment are compared with the case register and treatment cards on site.[108,109]

Interim evaluation and preliminary results

A useful exercise during supervision is to obtain preliminary results of treatment in order to assess the latest trend in case holding. This is particularly important shortly after implementation in a new site and where there are problems in case holding.

As discussed in Chapter 8, results of treatment are evaluated in the tuberculosis program using cohort analysis. This evaluation is primarily for documenting the outcome of the intervention and predicting the impact of the program in the long run, but it is not useful for action in the short term. The final evaluation of treatment results does not identify early warning signs of program elements in need of correction, given that the results are final when the report is completed. For action to be taken, the problems must be identified in a timely manner. Assessment of recent trends in case holding uses the same principles as the final cohort evaluation. A cut-off point, which does not refer to a fixed calendar date but rather to treatment duration, can be inserted at any time during treatment. It is useful to look at the results at two months in new pulmonary smear-positive cases (this is sometimes referred to as smear conversion rate), and the results at five months (where 8-month treatment is used). The purpose is to identify operational weaknesses in order to take action and influence the outcome of treatment. This exercise is primarily important at the local level, which is why it makes little sense to report this information routinely to central level. How well such preliminary results predict the final outcome of treatment depends on the setting—the nature of eventual problems, the rapidity and nature of actions taken in response to unfavorable results, and the timing of the analysis (the further into treatment the analysis is performed, the more consistently it reflects the final results of treatment).

Cohort analysis at two months of treatment

Analysis of case holding at two months* of treatment can be performed when enough time has elapsed for all members of the cohort to complete the equivalent of two months of treatment. Three or four months after the end of a quarter, all patients enrolled in short-course treatment in the quarter can be expected to have completed the intensive phase, allowing for irregularities in attendance. All new smear-positive patients, and only new smear-positive patients, should have their sputum examined after two months of treatment.†

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*Note that this refers to the results of sputum examination at *two* months and not at two *or* three months.

†Previously treated patients undergo sputum examination at three months, and as a rule, new smear-negative patients do not undergo sputum examination during treatment (in any case they are not included in this exercise). In some programs, a smear examination is performed routinely at two months even in smear-negative cases. This is not strictly necessary and is not recommended in the Orange Guide.

Figure 10.1 The tuberculosis case register as data source for analysis of preliminary treatment results

Category of patient	Before treatment result/ laboratory no.	2-month result/ laboratory no.	5-month result/ laboratory no.	7-month result/ laboratory no.
New	+++/25	Negative/76		
New	++/29	+/89		
New	Negative/120			
Relapse	+++/144			

Figure 10.1 demonstrates a section from the tuberculosis case register. The first entry is a smear-positive patient with a negative smear at two months. The second entry is a patient with a positive smear at two months. The third (new smear-negative case) is excluded, as the exercise only involves new smear-positive patients. The fourth is also excluded (relapse).

The review would then continue case by case until the period intended for review had been covered. It might be that a smear was not taken for some reason even if the patient was attending for treatment. It might be that a patient died, was transferred out within two months of starting treatment, had defaulted, or was absent and at risk of defaulting (but not yet a defaulter since by definition a patient should be absent for two consecutive months before being classified as a defaulter). The summary results can be documented as shown in Table 10.5, which is an example from a 1997 supervisory visit in Nicaragua. There are two ways of looking at the results. First, of the 100 patients whose smear was examined, 94% had converted to smear-negative at two months of treatment. The important information, however, is the fact that only 86% of the total of patients had a smear examination at two months (100/116). Of eligible patients (alive and attending, excluding deaths and transfers), 88% had a

Table 10.5 Results at 2 months in treatment of new smear-positive cases

Total	*Smear-negative*	*Smear-positive*	*Smear not done**	*Died*	*Absent†*	*Transferred*
116	94	6	12	0	1	3

*The patient was attending for treatment but no smear examination was performed.
†The patient was absent (not attending) and at risk of defaulting or could be classified as defaulter.

Table 10.6 Comparison of results at 2 months in treatment of new smear-positive cases at two sites

Total	*Smear-negative*	*Smear-positive*	*Smear not done**	*Patient died*	*Absent†*	*Transferred*
Site 1 ($N = 91$)	59	8	19	1	4	0
Site 2 ($N = 51$)	41	6	1	1	1	1

*The patient was attending for treatment but no smear examination was performed.
†The patient was absent (not attending) and at risk of defaulting or could be classified as defaulter.

smear examination (100/113). The problem is that a smear was not examined in 12 cases. The question is, why not? Furthermore, since the decision to start the continuation phase depends on the result of sputum examination, one would also verify how treatment was continued in these cases.

In a similar example from Laos, where sputum examination was not always performed at two months and it was claimed that frequently patients were not able to produce a sputum sample at two months, it was convenient to perform a comparison with another treatment unit, as shown in Table 10.6. When comparisons are made, it is important that methodology and documentation are consistent. In Site 1, 19 patients did not have smear examination at two months even if they were attending for treatment. Four patients were absent and at risk of defaulting. In Site 2, this was not a problem. Why would patients invariably be able to produce sputum in one health facility and not in another? This problem was subsequently resolved without any further action. At the time of the supervision, the cases of the four patients at risk of defaulting would have been discussed. Sometimes default can still be prevented at the time of supervision.

Preliminary results of treatment

Table 10.7 shows how case holding is followed in a new site. It is done by following a cohort of patients through treatment, documenting the results at two months and at five months during two different supervisory visits, and then comparing this information with the final results of treatment, as reported on the quarterly report of treatment results and validated during a third supervisory visit. The example is from Laos. In this case, the results at two months do not predict the final results very well, whereas the results at five months do. Problems occurred mainly after the intensive phase treatment was completed. This kind of analysis is important after implementation in a new site until good results in case holding have been demonstrated.

Table 10.7 Evolution of treatment results in a cohort of new smear-positive cases after implementation of short-course treatment at a new site

Results (N = 176)	*Smear-negative* %	*Smear-positive* %	*No smear** %	*Patient died* %	*Default (or at risk)*† %	*Transferred* %
At 2 months	78	3	3	6	—	9
At 5 months	42	1	16	7	10	25
Final	42	1	16	8	14	20

*The patient was attending or had completed treatment but smear examination was not performed.
†The patient was absent and at risk of defaulting (preliminary results) or could be classified as defaulter.

When performing the exercises described above, it is also of interest to assess whether follow-up smear examinations during treatment are correctly timed, that is, to compare dates when sputum should be taken with when it is actually taken. In this case, it is necessary to consult the treatment cards and correct for eventual irregularities in treatment if the point of interest is "treatment time" rather than "calendar time."

The laboratory services

Quality control of sputum smear microscopy is largely outside the scope of this publication. Yet it is pertinent to mention that, for an efficient use of resources, tuberculosis supervisors can sample microscopic slides according to a pre-defined sampling method during laboratory visits. They can then deliver the slides to a designated reference laboratory for quality control of acid-fast microscopy. This system seems more realistic than one in which two persons travel for routine supervision of the tuberculosis services. An additional advantage of this arrangement is that the supervisor is not directly involved in the examination or re-reading of the microscopic slides but rather is an external observer.

Acid-fast microscopy is an inseparable part of the tuberculosis services, and the supervisor should always visit the laboratory as part of the quality-assessment exercise. By briefly assessing the work of the laboratory, the supervisor can detect obvious problems that are easily solved or that would otherwise merit a visit by a laboratory supervisor. The supervisor can verify the sputum collection strategy and the hours the laboratory is open for receiving and examining sputum, as well as the use of the laboratory register and the workload in the laboratory. The supervisor can also quickly check the status of the microscope

Figure 10.2 Examples of entries in the tuberculosis laboratory register

Serial no.	Date	Name	Sex	Age	Treatment unit	Patient's address	Reason for examination		Result		
							Diagnosis	Follow-up	1	2	3
1	2/9/2003	AAA	Male	12	X	. . .	✓		++	+++	++
2	2/9/2003	BBB	Female	55	Y	. . .		5 months	Negative		
3	2/9/2003	CCC	Male	34	Z	. . .		2 months	Negative		
4	3/9/2003	DDD	Male	79	X	. . .	✓		Negative		
5	3/9/2003	EEE	Female	24	Y	. . .	✓		+	++	+

by examining a few positive slides. All tuberculosis supervisors should be able to perform these tasks.

Here are some examples of questions asked when reviewing recording methods in the laboratory: Are the principles of registration and recording understood and followed? Is there one line for each individual (tuberculosis suspect) examined? Is the reason for examination always recorded (as diagnosis or follow-up)? Are examinations complete? Is the grading of positive slides recorded? Are positive results clearly recorded? The layout of the laboratory register is shown in Figure 10.2, with hypothetical examples demonstrating how it is filled in. One line is used for each examination, which can involve one to three specimens. In this example, three specimens should be examined in the case of diagnosis, but one in the case of sputum examination for follow-up during treatment.

It is possible to confirm that the policy is followed in terms of the number of specimens examined for diagnosis and follow-up. In the example in Figure 10.2, there is one entry (serial number 4) with incomplete examination. The workload—that is, the total number of slides examined—is nine slides in the example. The total number of examinations is five, three for diagnosis (3/5) and two for follow-up (2/5); there are two positive examinations out of all examinations made for diagnosis (2/3). Finally, when the proportion positive out of all examinations made for diagnosis has been calculated (see also indicator 13 in Table 10.4), one can estimate approximately the expected proportion of examinations for follow-up out of the total number of examinations.

Does supervision make a difference?

It has been shown repeatedly that supervision does influence performance and outcome. Simply paying attention to structure, process, and outcome, as is done in the approach described above, motivates health workers. In addition, it is

likely to lead to some improvement even without any further action because it focuses attention on important details and provides health workers with tools to assess their own performance and the overall program quality.

A province-based prospective controlled trial was conducted in the Philippines from 1991 to 1992, where supervisory practices had been found to be inconsistent, unstructured, and not allowing for follow-up of previous results. Health facilities were randomly selected for implementing supervision of primary health care services using a standardized methodology and supervision checklists with clearly defined indicators.[61] Before the intervention, a baseline investigation was performed in experimental and control facilities. After the intervention, all facilities were visited again. Performance had improved in both experimental and control facilities, suggesting a Hawthorne effect,* but the increase was greater in the experimental facilities (42% compared with 18%). In experimental facilities, but not in control facilities, there was correlation between the frequency of supervision and improvement, indicating that frequency of supervision is not the sole issue, but that the method used in supervision is also important. The supervisors and those supervised appreciated the checklist. They felt that it made the relations between them more professional. Those who were being supervised thought that the checklist was objective and the indicators served as reminders of important things. However, they felt that it was unfair that the assessment included things like drug supply, which they felt was beyond their control. This underlines the importance of defining and explaining who and what is being assessed with each indicator used.

Evidence that supervision has an effect on the quality of tuberculosis services has also been documented. In a randomized, controlled, health center-based trial conducted in Korea from 1980 to 1981, intensified supervision was used to motivate health personnel in experimental centers.[110] Treatment efficacy in experimental centers was 75.2% compared with 45.8% in control centers. In another example, from Algeria, it was reported in 1985 that case detection as well as treatment results were better in districts that were supervised than in districts that were not.[111] Information from Nicaragua suggests that regular, frequent, and intensive supervision of health personnel has a positive impact on treatment results.[112] Although not systematically documented, the experience in Nicaragua in the early 1990s suggested that changes in supervision methodology as described above resulted in supervision becoming a more powerful tool in quality improvement. The immediate effects were similar to the experience in the Philippines cited above. The relationship between the supervisor and the supervised became more "professional" as a result of a well-defined methodol-

*Being part of a study may affect performance, usually for the better. The mere knowledge of the study influences behavior, and this must be considered when comparing experimental and control groups.[10]

ogy. Those supervised considered the method fair and felt that they were active participants in the exercise. They understood what to improve and why.

Tuberculosis program monitoring

Routine program monitoring primarily concerns the results of case finding and treatment activities. Sputum smear microscopy is emphasized in order to follow the trend in transmission as measured by the reported number of pulmonary smear-positive cases. The goal in treatment is to reach a high cure (success) rate. However, it is more useful to look at negative indices, that is, treatment failure, default, death, and transfer, because doing so gives a clue as to the nature of quality issues. Treatment default and failure are particularly serious adverse outcomes in terms of transmission. A high proportion of transfer (and default) suggests a structural problem (access to diagnosis and treatment). If tuberculosis is the cause of death in reported fatalities, this may also indicate a structural problem. The main purpose of monitoring treatment results is to evaluate a program's impact over time. However, monitoring may also improve quality because health personnel are likely to be even more careful in their day-to-day work when they must report outcome (sentinel effect). A positive effect of monitoring was demonstrated in Scotland in the 1970s.[113]

Monitoring is performed by analysis of quarterly reports and drug requisitions. Monitoring draws upon variables of process and outcome, applying explicit criteria. The levels of assessment are the intermediate and national level. There is no sampling. Reporting of all cases is mandatory. A cohort approach is used following groups of patients from notification to outcome. A "cohort" is defined as patients registered for treatment in a given time period, usually one quarter of a year or an entire year. Data are collected exclusively from quarterly reports on case finding, results of treatment, and drug requisitions from tuberculosis management units. The indicators used in monitoring are presented in Table 10.8. The indicators are largely self-explanatory. Examples from the field are provided in Tables 10.9 through 10.12. Further examples and interpretation of indicators on case finding and results of treatment are presented in Chapter 8. Examples and methods for more detailed monitoring of drug supply are discussed in Chapter 9. Program evaluation visits to intermediate levels are recommended if quality problems are suspected or detected.

Examples from the field

Reported case finding in the first five years of the Laos tuberculosis program is presented in Table 10.9. There, case finding increased yearly with expansion of the program. Relapses were a low proportion overall. Excluding extrapulmonary tuberculosis, the proportion of relapses in 1999 was 2.4%.

The trend in new pulmonary cases and bacteriological confirmation in

Table 10.8 Quality monitoring in tuberculosis control

Indicator	*Measure*	*Data source*	*Period reviewed*	*Comparison*	*Numerator/measurement*	*Denominator*	*Benchmarks*
Results of case-finding activities	Outcome	Quarterly report on case finding	Semester or year	With previous year(s)	Number of cases (by category)	Use total population for calculating rate*	Depends on the setting; look at absolute number and rate
Proportion smear-positive among new PTB cases	Process	Same as above	Same as above	Same as above	Number of new PTB smear-positive cases	Total number of new PTB cases	Smear-positive ≥65% of new PTB cases
Proportion previously treated among PTB smear-positive cases	Proxy for treatment outcome	Same as above	Same as above	Same as above	Number of previously treated PTB smear-positive cases (or relapses)	Total number of PTB smear-positive cases	Depends on the setting
Results of treatment in smear-positive cases	Outcome	Quarterly report on results of treatment	Same as above	Same as above	Number of new PTB smear-positive cases with adverse outcome	Total number of new PTB smear-positive cases registered	Depends on the setting (<15%)
Drug consumption	Process	Quarterly drug requisition	Same as above	With case finding	Quantity of rifampicin (or other drug) distributed	Expected consumption of rifampicin (or other drug)	For example, ≤10% discrepancy
Reporting	Process	Quarterly report on case finding	Quarter	With expected reporting	Number of reports received	Number of reports expected	100%
Drug resistance	Outcome	Quarterly report on results of treatment (or drug resistance survey)	Year (or intermittent surveys)	Trend	Number of PTB smear-positive cases on retreatment who fail treatment (or detailed survey results)	Number of new PTB smear-positive cases registered in the period (or denominator from survey)	NA

*The use of this denominator has limitations, see indicator 14 in Table 10.4.
PTB, pulmonary tuberculosis; NA, not applicable.

Table 10.9 Tuberculosis case finding in Laos, 1995–1999

Year	*Total n*	*New PTB smear-positive n* (%)	*Relapse n* (%)	*New PTB smear-negative n* (%)	*Extra-pulmonary TB n* (%)
1999	2420	1710 (71)	55 (2)	491 (20)	164 (7)
1998	2133	1480 (69)	53 (2)	443 (21)	157 (7)
1997	1818	1199 (66)	24 (1)	457 (25)	138 (8)
1996	1259	824 (65)	21 (2)	312 (25)	102 (8)
1995	830	478 (58)	12 (1)	263 (32)	77 (9)

Data from the National Tuberculosis Program, Laos.
PTB, pulmonary tuberculosis.

Nicaragua in five periods from 1988 to 2002 is presented in Table 10.10. In late 1991, the supervision methodology was improved introducing—among other changes —a systematic review of whether all "smear-negative" cases had undergone sputum examination and were correctly classified. Although there was a decrease in the number of new pulmonary cases reported, the number of new smear-positive cases actually increased for a time, the result of more complete reporting of bacteriological confirmation. Then, a slight decline occurred between the third period (1994 to 1996) and the fourth (1997 to 1999), followed by a definite decrease when comparing the fourth and fifth (2000 to 2002) periods.

The proportion of relapses among all pulmonary tuberculosis cases registered in Nicaragua is rather high. Looking at three five-year periods from 1988 to 2002 (Table 10.11), the number of pulmonary cases registered decreased, but the proportion of relapses remained the same, at around 7%. A high relapse

Table 10.10 Bacteriological confirmation in new pulmonary tuberculosis in Nicaragua, 1988–2002

	1988–1990	*1991–1993*	*1994–1996*	*1997–1999*	*2000–2002*
New pulmonary cases, *n*	7661	7442	7390	6765	5793
Change, %	—	−2.9	−0.7	−8.5	−14.4
New smear-positive cases, *n*	4368	4700	4905	4882	4299
Change, %	—	+7.6	+4.4	−0.5	−11.9
Proportion smear-positive, %	57.0	63.2	66.4	72.2	74.2
Change, %	—	+10.9	+5.1	+8.7	+2.8

Data from the annual reports of the National Tuberculosis Program, Nicaragua.

Table 10.11 PTB relapses in Nicaragua, 1988–2002

	1988–1992	*1993–1997*	*1998–2002*
All PTB (including relapses), *n*	13,655	13,095	10,986
Relapses, *n*	1,001	893	791
Proportion relapses, %	7.3	6.8	7.2

Data from the annual reports of the National Tuberculosis Program, Nicaragua.
PTB, pulmonary tuberculosis.

rate might be explained by irregularities in treatment or the relatively weak treatment regimen used (8-month regimen with isoniazid and thioacetazone in the continuation phase). When looking at relapses, however, one should keep in mind the definition of relapse: a patient who was treated previously and declared cured but presents with sputum smear-positive tuberculosis. Cases registered as "relapses" may represent disease reactivation, reinfection, misclassification of patients treated after default or failure[94] or, if the "relapse" occurs very soon after discharge, a "missed" failure of previous treatment.

Treatment results of new pulmonary smear-positive tuberculosis cases in the first four years (1995 to 1998) of the Laos tuberculosis program are presented in Table 10.12. In 1994, 69% of the patients were enrolled on an 8-month short-course regimen. In 1998, this proportion was 92%. The remaining patients were enrolled on a 12-month regimen without rifampicin. As the program expanded, more patients were enrolled overall, and results of treatment improved. Looking at 1998, the number of cases reported (1,480) nearly matched the number of cases evaluated (1,488). This aggregate statistic, however, might disguise problems in the provinces.

Table 10.12 Results of treatment in new smear-positive tuberculosis in Laos, 1994–1998

Year	*Reported*	*Evaluated*	*Success* *n* (%)	*Failure* *n* (%)	*Died* *n* (%)	*Default* *n* (%)	*Transferred* *n* (%)
1998	1480	1488	1190 (80)	10 (1)	114 (8)	141 (9)	33 (2)
1997	1199	1118	900 (80)	13 (1)	74 (7)	99 (9)	32 (3)
1996	824	773	537 (69)	6 (1)	69 (9)	86 (11)	75 (10)
1995	478	442	273 (62)	9 (2)	25 (6)	112 (25)	23 (5)
1994		205	55 (27)	13 (6)	12 (6)	110 (54)	15 (7)

Data from the National Tuberculosis Program, Laos.

Summary and conclusions

The role of clinical research and technology assessment is to provide answers to questions concerning what should be done in health care. Quality assessment looks at whether care providers are doing just that and whether the outcome is as expected.

Although rapid expansion of primary health care was the trend in the 1970s and 1980s, the tuberculosis programs collaborating with The Union headed in a different direction: expansion guided by the principle that quality was more important than quantity. The information recorded in the model tuberculosis program can be used to monitor and assess different issues with reference to the patient, the staff, the unit, the service area, the program, and the health service. A practical approach taken in the model program is to define the roles and responsibilities of the different players in tuberculosis control and conduct quality assurance with this in mind. The model's primary focus is detailed quality assessment at the level of the tuberculosis management unit and monitoring at national and intermediate levels. Although quality assessment primarily uses process measures, outcome measures are used in program monitoring and when predicting the program's impact in the long run.

The overall objective of tuberculosis control is to detect patients with infectious tuberculosis and render them permanently noninfectious. The policy and manual of the program define the process of care and how different activities are supposed to be conducted. This is the standard to which performance is compared in quality assessment. Ideally, it is conducted during on-site supervision. In addition to being the venue for quality assessment, supervision provides an opportunity for on-the-job training of key health personnel. The methodology described in the chapter emphasizes the importance of generating ownership of the quality-assurance process through participation of local staff during supervisory visits, and capacity building for continued self-assessment.

The primary weakness of the quality-assurance system in the model program is its dependency on the mobility of specialized or semi-specialized supervisors, which for various reasons is often a limiting factor in low-income countries. Furthermore, where the private sector provides an important share of tuberculosis services, the supervision structure may not reach all service providers.

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