

TUBERCULOSIS

A MANUAL FOR MEDICAL STUDENTS

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World Health Organization
Geneva



International Union Against
Tuberculosis and Lung
Disease Paris

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FOREWORD

This manual aims to inform medical students and medical practitioners about the best practices for managing tuberculosis patients, taking into account the community interventions defined by the National Tuberculosis Programme.

It contains basic information that can be used:

- in training medical students, in supervised group work, presentations and discussions;
- in refresher courses for practising physicians, and for their personal study.

The manual has three sections:

- The first chapter combines essential **basic knowledge** about the tubercle bacillus, its mode of transmission, and the immunology, bacteriology and histology of tuberculosis;
- The second chapter is devoted to describing the disease in **the individual patient**: clinical aspects, treatment and prevention;
- Chapter three describes the basis for tuberculosis control in **the community**: epidemiology of tuberculosis and its control through the National Tuberculosis Programme.



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CHAPTER 1

THE BASIC SCIENCE OF TUBERCULOSIS

TRANSMISSION OF THE TUBERCLE BACILLUS IN HUMANS AND THE IMMUNE RESPONSE

Tuberculosis is a bacterial disease spread from one person to another principally by airborne transmission. The causal agent is *Mycobacterium tuberculosis* (the tubercle bacillus).

In a small proportion of cases, the bacillus is transmitted to humans from infected cows through drinking non-sterilized milk. This mode of transmission plays only a minor role in the natural history of the disease in humans.

Tuberculosis can affect any organ in the body. Pulmonary tuberculosis is the most frequent site of involvement; extrapulmonary tuberculosis is less frequent. Only pulmonary tuberculosis is infectious.

The natural history of tuberculosis

❑ Sources of infection

The main reservoir of *M. tuberculosis* is the patient with pulmonary tuberculosis. Such patients may have pulmonary “cavities” that are rich in bacilli (100 million bacilli in a cavity of approximately 2 cm in diameter).

The diagnosis of pulmonary tuberculosis is straightforward in such patients, as they almost always have chronic respiratory symptoms such as cough and sputum production.

The definitive diagnosis is simple when the patient has large numbers of bacilli in the sputum (more than 5000 bacilli/ml), as these can be seen on microscopic examination of a sputum smear; these patients are termed “smear-positive”.

Practical point:

Patients with cavitory pulmonary tuberculosis are almost always “smear-positive”, and are the main source of infection in the transmission of tuberculosis.

❑ Exposure and primary infection

When patients with pulmonary tuberculosis speak, and particularly when they cough or sneeze, they produce an aerosol of droplets from the bronchial tree, each of which contains a number of bacilli: these droplets are infectious.

The number of infectious droplets projected into the atmosphere by a patient is very high when coughing (3500) or sneezing (1 million). When they come into contact with the air these droplets rapidly dry and become very light particles, still containing live bacilli, that remain suspended in the air. In an enclosed space, the droplets can remain suspended for a long time, and the bacilli remain alive for several hours in the dark: these are “infectious particles”.

As direct sunlight rapidly destroys the bacilli, letting air and sunshine into rooms where tuberculosis patients live can reduce the risk of infection for those living in contact with them.

When people live or sleep near a patient, they are at risk of inhaling infectious particles. When a person inhales infectious particles, the large particles, are deposited on the mucous of the nasopharynx or the tracheo-bronchial tree and are expelled by mucociliary clearance. The smallest particles, less than a few microns in diameter, can penetrate to the alveoli.

The closer and the more prolonged the contact with an infectious patient, the greater the risk of infection, as this risk is linked to the density of the bacilli in the air the individual breathes and the amount of the air inhaled. As a result, children living in the same household as a source of infection are at a particular risk of becoming infected.

Practical point:

Two essential factors determine the risk of transmission of tubercle bacilli to a healthy subject: the concentration of the infecting droplets suspended in the air, and the period of time during which the exposed individual breathes this contaminated air.

When a few virulent tubercle bacilli penetrate into the pulmonary alveoli of a healthy person, they are phagocytosed by the alveolar macrophages, in which they multiply. Other macrophages and monocytes are attracted, and participate in the process of defence against infection. The resulting “infectious focus”, made up of the inflammatory cells, is referred to as a **primary focus**. The bacilli and the antigens that they liberate are drained by the macrophages through the lymphatic system to the nearest lymph node. Inside the lymph node, the T lymphocytes identify the *M. tuberculosis* antigens and are transformed into **specific T lymphocytes**, leading to liberation of lymphokines and activation of macrophages that inhibit the growth of the phagocytosed bacilli. The inflammatory tissue formed in the primary focus is replaced by fibrous scar tissue in which the macrophages containing bacilli are isolated and die.

This primary focus is the site of tuberculosis-specific **caseating necrosis**. This focus contains 1000–10 000 bacilli which gradually lose their viability and multiply more and more slowly. Some bacilli can survive for months or years: these are known as “latent bacilli”.

The same evolution occurs in the lymph node, leading to the formation of caseating lymph nodes that resolve spontaneously in the majority of cases towards fibrosis, followed by calcification.

Animal experiments have shown that 2 to 3 weeks on average after experimental infection, humoral and cell-mediated immunity (delayed-type hypersensitivity) occur simultaneously.

Delayed-type hypersensitivity is demonstrated by tuberculin skin testing. Tuberculin, which is prepared from metabolic products of *M. tuberculosis*, contains no live bacilli but consists of antigens related to the bacilli. When a tuberculin injection is given to a person who is already infected with *M. tuberculosis*, the patient develops a delayed-type hypersensitivity reaction. This appears after 48 hours as a local inflammatory reaction due to the concentration of lymphocytes at the site of injection.

This reaction, called the “tuberculin reaction”, can be observed and measured (Appendix 1). A person who has never been infected does not develop a delayed-type hypersensitivity reaction, and there is no significant reaction to tuberculin.

All of these clinical and immunological phenomena observed after infection of a healthy individual constitute primary tuberculous infection. They furnish the individual with a certain level of immunity.

In most cases primary tuberculous infection is asymptomatic and goes unnoticed. Its presence is indicated by tuberculin conversion: the tuberculin skin test reaction of an individual who previously had no significant reaction becomes significant in size 6 to 12 weeks after infection. Tuberculin conversion is the proof of recent infection and reflects the resulting immunity.

Practical point:

Infection of a healthy individual by the tubercle bacillus, or primary infection, is indicated by the appearance of a delayed-type hypersensitivity reaction to tuberculin caused by cell-mediated immunity occurring more than one month after first exposure to *M. tuberculosis*.

□ *Development of secondary foci*

Before immunity is established, bacilli from the primary infectious focus or from the nearest lymph node are transported and disseminated throughout the body by the lymph system and then via the bloodstream. Secondary foci containing a limited number of bacilli are thus constituted, particularly in the lymph nodes, serous membranes, meninges, bones, liver, kidneys and lungs. As soon as an immune response is mounted most of these foci spontaneously resolve. However, a number of bacilli may remain latent in the secondary foci for months or even years.

Different factors that can reduce the organism's system of defence can lead to reactivation of the bacilli and their multiplication in one or more of these foci. This

reactivation is the cause of clinical disease at extrapulmonary sites and of a proportion of cases of pulmonary tuberculosis — those due to endogenous reactivation. Extrapulmonary tuberculosis and the infrequent generalized tuberculosis (miliary with or without meningitis) do not constitute sources of infection.

□ *Pulmonary tuberculosis*

Pulmonary tuberculosis occurs in a previously infected individual when there are large quantities of bacilli and/or when there is immune deficiency, by one of the three following mechanisms:

- **infrequently, by progression of the primary focus during primary infection;**
- **by endogenous reactivation** of bacilli that have remained latent after primary infection. In the absence of treatment and of immune deficiency, this risk is estimated at 5–10% in the 10 years following primary infection, and 5% for the remainder of the individual's life-time;
- **by exogenous re-infection:** the bacilli causing these cases come from a new infection in a previously infected person.

The mechanism that comes into play depends on the density of the sources of infection (particularly smear-positive cases) in a community: in a country where the number of sources of infection is high, exogenous re-infection is more common; in countries where sources of infection are less frequent, endogenous reactivation is the most frequent cause of post-primary pulmonary tuberculosis.

Whichever mechanism is responsible, the immune reaction to primary infection is insufficient to prevent the multiplication of bacilli in a focus, which can then become the site of caseating necrosis. The resulting liquefaction and evacuation of caseous material via the bronchi leads to the formation of a cavity in the lung.

□ *Evolution of the disease and cycle of transmission*

The natural evolution of pulmonary tuberculosis in the absence of treatment explains how the disease perpetuates itself: 30% of patients are spontaneously cured by the body's defence mechanisms, 50% die within 5 years, and 20% continue to excrete bacilli and remain sources of infection for many years before dying.

Patients with extrapulmonary tuberculosis will either die or reach spontaneous cure, at times with crippling sequelae.

Practical point:

Individuals infected with the tubercle bacillus can develop tuberculosis disease at any time. Cases of pulmonary tuberculosis are highly contagious when they are smear-positive and represent potent sources of infection, thus completing the cycle of transmission.

❏ *Factors that modify the natural history of tuberculosis*

The natural history of the disease explains how it perpetuates itself: a smear-positive patient who is not treated can infect approximately 10 individuals per year, for an average duration of infectiousness of 2 years, before becoming non-infectious (due to spontaneous cure or death). A smear-positive patient can infect 20 people during his/her lifetime and create two new cases of tuberculosis, at least one of which will be infectious. As long as at least one new case of tuberculosis is created by each existing case, the disease is maintained in the community.

For an individual, the likelihood of getting the disease is directly related to the likelihood of becoming infected and the efficiency of the body's immune defence. The natural history of the disease can thus be modified by a number of factors.

- **Factors that increase the likelihood of becoming infected**

Factors that increase the risk of infection in a non-infected individual:

These are factors that increase the rate of transmission due to increases in the intensity and/or duration of exposure. Transmission typically occurs within the household of the patient with tuberculosis. It may be enhanced by overcrowding, in buildings that are poorly ventilated. This type of overcrowding occurs in the most underprivileged population groups: impoverished families living in crowded dwellings, prisoners, migrant workers accommodated in collective dormitories, or refugee or displaced populations living in inadequate conditions. These conditions are often associated with delays in diagnosis of patients with tuberculosis, increasing the length of time that their families are exposed to the bacilli.

Factors that accelerate progression from infection to disease:

These are factors that are likely to reduce the efficiency of the body's means of defence: malnutrition, conditions leading to immune deficiency such as HIV infection, diabetes, or long-term treatment with corticosteroids or immunosuppressive medications.

Among these risk factors, HIV infection plays a major role: it increases the probability of progression from infection to disease, and it increases the risk of reactivation of old tuberculosis. The risk of an HIV-positive subject developing tuberculosis disease is 5–8% per year.

Practical point:

The cumulative risk of tuberculosis disease is around 50% in the lifetime of an HIV-positive individual, whereas it is around 5–10% in non-HIV-infected individuals.

- **Factors that reduce the likelihood of becoming infected**

These are factors that interrupt the chain of transmission:

Reducing the number of sources of infection in the community. This is most effectively achieved through detection and treatment of smear-positive cases in a community, as this “dries up” the reservoir of infection.

Reducing the risk of infection among healthy individuals, by improving living conditions (reducing overcrowding, letting sun and air into dwellings) and nutrition.

Preventing the risk of disease in high-risk groups by BCG vaccination of non-infected children and treatment of latent tuberculous infection in individuals who have already become infected.

Practical point:

The diagnosis of new smear-positive cases and their cure through treatment constitutes the best prevention against tuberculosis. This leads to the progressive reduction of sources of infection in the community.

The immune response to tuberculosis

□ *Humoral immunity*

Immunity due to the formation of circulating antibodies plays a marginal role in tuberculosis, as the mycobacteria are resistant to the direct effect of antibodies and their products. However, the existence of these antibodies is the focus of research into new methods of serological diagnosis of tuberculosis.

□ *Cellular immunity*

After phagocytosis of tubercle bacilli by the macrophages, antigens are liberated from the bacilli. The antigens activate nonspecific lymphocytes, which become specific CD4 and CD8 lymphocytes. These specific lymphocytes are central to tuberculosis immunity.

Their fundamental role in tuberculosis control is demonstrated in studies of HIV-infected individuals. These individuals have a reduced number of specific circulating lymphocytes, in particular CD4 lymphocytes, which diminish as their disease develops. This is why they are more likely to develop tuberculosis following infection.

Practical implications

□ *BCG vaccination*

The basic immunological process explains the action of the BCG vaccination. The vaccine is prepared from live attenuated tubercle bacilli that have lost some of their virulence. The introduction of these bacilli into the body provokes the same immunological reactions as primary infection with tubercle bacilli, without leading

to disease. BCG vaccination confers partial immunity, essentially against the consequences of primary infection, and particularly against the acute forms of tuberculosis in children (disseminated tuberculosis and meningitis).

❑ *Tuberculin skin test*

Tuberculin is prepared from metabolic products of *M. tuberculosis* bacilli, and therefore contains a number of polyantigenic proteins. In infected subjects, intradermal injection of tuberculin provokes the liberation of lymphokines that cause a delayed-type hypersensitivity reaction, demonstrated by the appearance 24–72 hours later of a localized infiltration of inflammatory cells into the skin, causing a swelling at the site of injection.

The delayed-type hypersensitivity reaction induced by microbial antigens of *M. tuberculosis* is also induced by BCG bacilli, and by certain environmental mycobacteria.

The tuberculin skin test reaction is used:

- **In individuals**, to diagnose tuberculous infection. A significant reaction indicates that the subject has been infected by mycobacteria at some stage. It does not provide proof of tuberculosis disease.
- **In the community**, surveys using the tuberculin skin test in a representative sample of non-BCG-vaccinated children determine the proportion of infected subjects in the sample. This proportion provides an indication of the rate of infection in this community, from which the annual risk of tuberculosis infection (ARI) can be calculated.

❑ *Serological tests for tuberculosis*

Serological tests attempt to demonstrate the presence of circulating antibodies, using mycobacterial antigens. The recognition of antigens by the antibodies present in infected individuals could aid in the diagnosis of disease at certain extrapulmonary sites for which diagnosis by bacteriology or histology is difficult. However, these costly tests are not yet sufficiently sensitive or specific to be of routine practical use.

Conclusion

Tuberculosis is an infectious disease with a very slow cycle of transmission from one person to another. Infection by the tubercle bacillus leads to a delayed-type hypersensitivity reaction that can be measured by the tuberculin skin test.

After primary infection, partial immunity to tuberculosis develops. This immunity is primarily cellular, via the specific T lymphocytes.

This immunity is not sufficient to prevent development of the disease in cases with high numbers of bacilli or immune deficiency.

References

Daniel TM, Ellner JJ. Cultivation of *Mycobacterium tuberculosis* for research purposes. In: Bloom BR, ed. *Tuberculosis: pathogenesis, protection and control*. Washington, DC, American Society for Microbiology, 1994:75–102.

Marchal G. La réponse immunitaire au cours de la tuberculose. [The immune response in tuberculosis.] *Annales de l'Institut Pasteur*, 1993, 4:216–224.

Marchal G. Pathophysiologie et immunologie de la tuberculose. [Pathophysiology and immunology of tuberculosis.] *Revue des Maladies Respiratoires*, 1997, 14:5S19–5S26.

Reynolds HY. Integrated host defense against infections. In: Crystal RG, West JB, eds. *The lung: scientific foundation*. New York, Raven Press, 1991:1899–1911.

Styblo K, Meijer J, Sutherland I. The transmission of tubercle bacilli. *Bulletin of the International Union Against Tuberculosis*, 1969, 42:3–104.

Appendix 1: Performing and reading the tuberculin skin test

The recommended tuberculin test is standardized:

- **The most commonly used purified tuberculins:**

- PPD-RT 23 tuberculin from Statens Serum Institut, Copenhagen (PPD: purified protein derivative) in solution form. An intradermal injection of 0.1 ml of solution corresponds to 2 international units of RT23.
- IP48 Pasteur is a purified lyophilized tuberculin that is delivered with its solvent and must be reconstituted immediately prior to use. Intradermal injection of 0.1 ml of the reconstituted solution corresponds to 10 units of IP48 tuberculin, equivalent to 2 units of RT23.

- **Required materials:**

- a fine (5/10) short (1 cm) intradermal needle, with a short bevel.
- a syringe graduated in 0.01 ml with an airtight plunger.

- **Injection technique:**

- 0.1 ml of tuberculin solution must be injected intradermally, about a third of the way down on the volar aspect of the forearm, at a distance from any other scarring (such as BCG).
- If the intradermal injection has been performed correctly, the product should be injected with difficulty and a rounded white wheal should form around the point of the needle, giving an “orange peel” aspect. If a wheal does not appear, this means that the needle is not inside the dermis: the needle should be withdrawn and the injection repeated elsewhere.

- **Test reading:**

- The test is read 48 to 72 hours after the injection; this involves identifying the margins of induration of the skin reaction and measuring its transverse diameter.

On examination the site of injection can have different aspects:

- either the skin is normal,
- or the skin is raised by a wheal with a reddish centre. This wheal is sometimes surrounded by a large reddish aureole or covered with a number of vesicles.

The test result must be measured with precision: the site is palpated and the transverse margins of the induration (and not the redness) are marked with a pen. Next the transverse diameter of the induration is measured using a transparent ruler. **The test result is always expressed in mm.**

- **Interpretation of the result**

A tuberculin reaction of ≥ 10 mm is significant, indicating that the individual has most likely been infected. A reaction of < 10 mm is non significant, and the

individual is likely not to have been infected. In infected subjects, the reaction size can nevertheless be non significant due to malnutrition, severe disease, a viral infection in HIV positive patients, treatment with corticosteroids or immunosuppressants, advanced age, or if the test was performed during the early stages of infection.

TUBERCULOSIS BACTERIOLOGY

Tuberculosis is an infectious disease caused by multiplication of bacilli belonging to the genus *Mycobacterium*. The principal bacterium responsible for the disease is *Mycobacterium tuberculosis* (the Koch bacillus), which was isolated by Robert Koch in 1882. *Mycobacterium africanum* is a variety that sometimes appears in West Africa and is often resistant to thioacetazone. *Mycobacterium bovis* is responsible for tuberculosis in domestic or wild cattle. It can be transmitted, although rarely, to humans in milk that is not pasteurized or boiled.

These three species of bacilli are **tuberculous mycobacteria** and constitute the “tuberculosis complex”.

Non-tuberculous or atypical mycobacteria are often non-pathogenic, but they can sometimes cause clinical manifestations (in the lungs, bones, lymph nodes or skin) that simulate those of tuberculosis. Infection due to opportunistic mycobacteria is most often observed in countries with a low prevalence of tuberculosis and among immunosuppressed patients.

Characteristics of tubercle bacilli

Tubercle bacilli are aerobic, with lipid-rich walls and a slow rate of growth (they take 20 hours on average to double in number). The lungs, dark and oxygen rich, at a temperature of 37 °C, provide an ideal environment for the bacilli to replicate. Tubercle bacilli are rapidly destroyed in the ambient environment by ultraviolet rays (sunlight).

It is difficult to stain the bacilli with stains commonly used for other bacteriological examinations. They require special stains that can penetrate the wax-rich wall of the bacillus.

Sampling for diagnosis

For bacteriological examination, the quality of the samples sent to the laboratory is of fundamental importance.

For pulmonary tuberculosis: the specimen that should be collected for examination is sputum obtained from the patient after coughing (more rarely the sample is obtained by gastric aspiration or bronchoscopy). As sputum can be contaminated by other bacteria, it must be collected in clean sputum containers (non-sterile) that can be firmly sealed. All sputum samples that are not examined at the centre where they are collected must be stored and transported following strict guidelines (Appendix 2).

For extrapulmonary tuberculosis: fluid from serous effusion, cerebrospinal fluid (CSF) or biopsied fragments can be sent to the laboratory for culture. All sampling must be performed in strictly sterile conditions so that culture can be performed directly without prior decontamination. Samples must never be placed in formol, which kills the bacilli.

The main bacteriological techniques

□ *Microscopy*

A smear of a selected part of a submitted specimen is made on a slide, then examined by microscope after staining (Appendix 3).

- **Staining methods**

There are several staining methods used for the tubercle bacillus; it is important for the method or methods used to be standardized for each country. The stains that are the most effective are hot Ziehl-Neelsen (ZN) staining and auramine staining.

Ziehl-Neelsen staining

The smear is covered with carbol fuchsin, and then heated. The smear is then destained successively using sulfuric acid and alcohol. All of the smears must be almost totally destained, and then restained with methylene blue. The bacilli are stained red by the fuchsin and are resistant to the acid and alcohol, hence the name **acid-fast bacilli** (AFB).

Destaining by the successive application of acid and alcohol can also be done using only 25% sulfuric acid; however, it should be applied several times until the smear is completely destained. This is the method recommended by the IUATLD, as it is less delicate and does not require alcohol (which is not always available in some countries).

On microscopic examination of the stained smear, the tubercle bacilli look like fine, red, slightly curved rods that are more or less granular, isolated, in pairs or in groups, and stand out clearly against the blue background (Appendix 4).

Fluorescent auramine staining

The fuchsin is replaced by auramine; the bacilli fix the fluorescent stain and retain it after the acid and alcohol staining.

- **Reading by microscopy**

After Ziehl-Neelsen staining

The stained smear is examined using a binocular microscope with an immersion lens (magnification $\times 100$). The number of AFB per 100 fields (about one length and one width of a slide) are counted. This technique is simple, rapid and fairly inexpensive.

After auramine staining

The stained smear is examined by fluorescence microscopy with a dry lens of low magnification ($\times 25$ or 40). This microscope has an ultraviolet lamp to enable the fluorescent bacilli to be seen: they are clearly visible in the form of greenish-yellow fluorescent rods.

The sensitivity and specificity of examination by fluorescence microscopy are comparable to those of microscopy after ZN staining. The main advantage is the

ease and rapidity of reading: on the same slide surface, the results of 10 minutes' reading by optic microscope are obtained in 2 minutes on fluorescence microscopy.

As this technique requires more costly equipment (the microscope itself, and the lamps, which need to be replaced frequently — on average after 200 hours of use), it is cost-effective only if more than 30 slides are examined each day. A constant electricity supply and trained technicians are also indispensable.

- **How to record the results**

After Ziehl-Neelsen staining

The number of bacilli present in a patient's sputum is in direct relation to the degree of infectiousness. For this reason the result must be recorded in a quantitative fashion. The following method proposed by the IUATLD should be used:

Reading method for smears stained by Ziehl-Neelsen (immersion lens $\times 100$)

NUMBER OF AFB	CODE
No AFB per 100 immersion fields	0
1–9 AFB per 100 immersion fields	exact number of AFB
10–99 AFB per 100 immersion fields	+
1–10 AFB per field	++
More than 10 AFB per field	+++

After auramine staining

On fluorescence staining, the smaller the lens the larger the surface examined. This is why the same reading method cannot be used as after ZN staining. The following method, proposed by J. Grosset (Hôpital Pitié-Salpêtrière, Paris), is often used:

Reading method for smears stained by auramine (dry lens $\times 25$)^a

NUMBER OF AFB	CODE
No AFB on the slide	0
1–10 AFB on the slide	doubtful (use Ziehl-Neelsen)
Fewer than 1 AFB per field but more than 10 on the slide	+
1–9 AFB per field	++
10–99 AFB per field	+++
More than 100 AFB per field	++++

^a To compare the number of bacilli on a slide read on fluorescence microscopy with a reading on ZN stain, it is easiest to restain the slide with ZN and re-read it.

- **Sensitivity**

The sample examined must contain at least 10 000 bacilli per ml in order to be positive on microscopy. Such a high number of bacilli is found only in the lesions of patients with cavitory pulmonary tuberculosis.

Practical point:

The most infectious tuberculosis patients can be detected rapidly using microscopy. This is the key examination in the diagnosis of pulmonary tuberculosis.

All forms of extrapulmonary tuberculosis (except sometimes renal tuberculosis) are usually poor in bacilli, as the conditions in these sites do not encourage the replication of bacilli. For this reason they are rarely detected on smear examination. In the case of renal tuberculosis, microscopic examination of urine samples after centrifugation can sometimes lead to the identification of bacilli.

□ *Classic culture methods*

Culture of a pathological specimen suspected of containing bacilli is the most rigorous method of diagnosing tuberculosis. The specificity of this test is much higher, as each live bacillus forms colonies on culture.

The equipment and running costs for performing culture are much higher than those for microscopy; culture also necessitates a high level of training of laboratory technicians.

- **Method**

Decontamination of samples

Most pathological specimens, except those that are obtained from closed lesions (serous membranes, joints, samples obtained from surgery), are contaminated by other bacteria. In order to destroy these bacteria, which can contaminate the culture media, it is important to decontaminate the sample with basic antiseptics, which kill the contaminants much more rapidly than the mycobacteria. Decontamination also homogenizes the specimen.

Centrifugation and neutralization

The specimens are then centrifuged, the supernatant is discarded and the sediment is neutralized using a mild acid.

Inoculation

The centrifuged sediment is inoculated into at least two tubes containing a specific culture medium, usually Löwenstein-Jensen medium (a solid egg-enriched medium).

In the case of closed lesions (or during surgery), samples must be obtained in strictly sterile conditions and should be inoculated directly on the culture medium without decontamination.

Incubation

The inoculated tubes are placed in an incubator at 37 °C for 4–12 weeks. As tuberculous mycobacteria grow very slowly (an average period of doubling of 13–20 hours), colonies will be visible to the naked eye after at least 3 weeks' incubation.

- **Examination**

When growth has occurred on culture, large, rounded, buff-coloured “cauliflower-like” colonies are visible to the naked eye on the surface of the culture medium; they have a dry, rough surface, and are isolated or confluent, depending on the number of bacilli present in the original sample (Appendix 4).

- **Identification**

When colonies appear, they must be identified according to criteria based on their macroscopic aspect (rough colonies) and by their response to biochemical tests: *M. tuberculosis* colonies have a thermolabile catalase activity (positive at 22 °C, destroyed by heat at 68 °C), and a nitrate reductase activity, and they accumulate nicotinic acid or niacin, which can be demonstrated by the niacin test. In other cases another mycobacterium must be identified (*M. bovis*, BCG or atypical mycobacteria).

Criteria for identification of mycobacteria

MYCOBACTERIA	ASPECT OF COLONIES	NIACIN	NITRATE	CATALASE 22°	CATALASE 68°
Tuberculous	R	+	+	+	–
Bovis	S	–	–	+	–
BCG	R	–	–	+	+
Atypical	V	V	V	+	+

R = rough; S = smooth; V = variable.

- **Recording the results**

The number of colonies present in the culture tubes is in direct relation to the number of bacilli in the lesions. This is why the colonies are counted and the results are expressed as the number of colonies per tube, except if their number is so high

that they are confluent (in this case the result will be expressed as innumerable confluent colonies). As in the case of microscopy the following reading code can be adopted:

Code for reading cultures

NUMBER OF COLONIES	READING CODE
Fewer than 10 colonies	+
10–100 colonies	++
More than 100 colonies	+++
Innumerable	Innumerable

Practical point:

As culture is a complicated, relatively costly technique, which is slow to yield results (1–2 months after sampling), it is not suitable for rapid identification of the most potent sources of infection.

Culture should be used only for paucibacillary tuberculosis patients who are not easily diagnosed by microscopy, such as smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis.

- **Comparative results of microscopy and culture**

When a single sputum sample is obtained from patients with pulmonary tuberculosis, 66% are positive on smear microscopy after Ziehl-Neelsen staining, while 93% are positive on culture. However, the results of microscopy improve as the number of samples examined per patient increases.

NUMBER OF SAMPLES	SMEAR-POSITIVE ZIEHL-NEELSEN (%)	CULTURE-POSITIVE (%)
1	66	93
2	76	97
3	84	99
4	85	100

Andrews RH, Radhakrishna S. A comparison of two methods of sputum collection in the diagnosis of pulmonary tuberculosis. *Tubercle*, 1959, 40:155–162.

Practical point:

The yield of sputum smear microscopy increases with the number of examinations performed; it is therefore necessary to examine at least three successive sputum samples from a patient suspected of pulmonary tuberculosis in order to confirm the diagnosis of tuberculosis.

□ *Other culture methods*

Two much more delicate and costly methods are used in some laboratories to compensate for the slow growth of the tubercle bacillus:

- **culture on solid agar-based medium (Middlebrook medium):** the cultures are examined after 3–4 weeks (instead of 4–6 weeks using the classic method).
- **culture on liquid medium:** using culture on radioactive (**Bactec**) or non-radioactive (**MGIT**) media, the bacilli can be detected in 8–14 days.

□ *Molecular genetics or PCR*

To detect *M. tuberculosis* a multitude of nucleotide sequences of a single copy of a target sequence of the bacillus can be obtained in a few hours using a genome amplification technique. Specific probes are then used to identify the different mycobacteria. This technique is known as the polymerase chain reaction (PCR).

PCR can detect and identify the presence of *M. tuberculosis* in a pathological specimen within 24 to 48 hours. However, it is of poor sensitivity compared with culture (80% on average), and its specificity is from 97–98%. This delicate technique, which requires sophisticated, costly equipment, is limited to research.

Practical point:

Smear microscopy and the classic method of culture on solid media are currently the most efficient methods of tuberculosis diagnosis.

□ *Susceptibility testing*

Susceptibility tests are used to determine the susceptibility or resistance of a patient's bacillary strain to the different anti-tuberculosis drugs.

These tests are delicate because of the presence of resistant mutant bacilli in the susceptible strains. **In a wild susceptible bacillary strain** (which has never been in contact with anti-tuberculosis drugs) from a case with cavitary pulmonary tuberculosis, the majority of bacilli are susceptible, but some rare bacilli are resistant to the different anti-tuberculosis drugs: these are **resistant mutants**. These bacilli appear in a susceptible strain, without having been in contact with an anti-tuberculosis drug, because of chromosomal mutation as soon as the bacillary

population is very large. The pulmonary cavities are the only tuberculosis lesions that are sufficiently rich in bacilli for these mutations to occur.

This phenomenon of mutation is:

- Spontaneous: mutation occurs in a bacillary strain without the strain's having come into contact with anti-tuberculosis drugs.
- Rare and specific: in a population of 10^8 bacilli, the probability of finding resistant bacilli varies depending on the anti-tuberculosis drug: a single mutant resistant to rifampicin, 10^3 to isoniazid, 10^3 to streptomycin, 10^4 to pyrazinamide.
- Hereditary: this mutation is transmitted to all the bacilli that result from the multiplication of the resistant mutant.

On the other hand, when a **strain is resistant to an anti-tuberculosis drug** most of the bacilli are resistant to this drug, and the rest of the strain is composed of susceptible bacilli and some mutants resistant to the other drugs.

Therefore, when a patient presents with a strain that is resistant to an anti-tuberculosis drug, the whole bacillary population will contain a very high proportion of resistant bacilli. To determine the resistance of a strain to anti-tuberculosis drugs, the classic method used is the "proportion method", based on the **determination of a sufficiently high proportion of colonies of resistant bacilli** in the entire bacillary population, in order to confirm the resistance of the strain.

There are two types of susceptibility testing:

- **indirect susceptibility testing**, performed after obtaining colonies in culture before testing; the results are available only 2 to 3 months after sampling.
- **direct susceptibility testing**, performed directly on the sample if it is rich in bacilli (i.e. if the smear made from the sample is strongly positive). In this case the results are available in 4–6 weeks.

These tests should be performed only in laboratories where this delicate technique is commonly used and where internal and external quality controls are conducted to confirm its reliability.

Susceptibility testing is unnecessary in the treatment of the majority of patients, except in certain individual cases. Its main role is in the conduct of nationwide studies in the epidemiological surveillance of tuberculosis.

Practical point:

Susceptibility testing is a delicate, expensive technique which is slow to yield results: 4 to 6 weeks after inoculation of the culture, i.e. 2–3 months after the sample has been obtained and treatment has commenced. It is not used in routine practice for deciding on treatment.

Conclusion

Microscopy and culture are currently the two methods most widely used to confirm the diagnosis of tuberculosis. The more sophisticated techniques, particularly molecular biology, are inefficient and have no place in patient management in countries with a high prevalence of tuberculosis.

For pulmonary tuberculosis, the recommended method of examination is microscopy. A series of three samples (at times two or three series) is necessary. For suspect cases who are not confirmed by smear microscopy, at least three cultures should be performed when a laboratory capable of performing culture is available.

For extrapulmonary tuberculosis, smear microscopy is usually negative. The diagnosis may be confirmed by culture of a pathological sample or by histological examination of a biopsy of the affected tissue or organ.

References

- Enarson DA et al. *Management of tuberculosis: a guide for low-income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
- Gangadharam PRJ. Drug resistance in tuberculosis. In: Reichmann LB, Hershfield ES, eds. *Tuberculosis: a comprehensive international approach*. New York, Marcel Dekker, 1993:293–328.
- Grosset J. Bacteriology of tuberculosis. In: Reichmann LB, Hershfield ES, eds. *Tuberculosis: a comprehensive international approach*. New York, Marcel Dekker, 1993:49–74.
- Grosset J. Place des examens microbiologiques et anatomopathologiques dans la décision diagnostic et thérapeutiques. [Smear, culture and pathological changes for the diagnosis and treatment of tuberculosis.] *Medecine et Maladies Infectieuses*, 1995, 25 (3):327–333.
- Kubica GP, Wayne LG. *The mycobacteria: a source book*. New York, Marcel Dekker, 1984:133–175.
- Rieder HL et al. *The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network: minimum requirements, role and operation in a low-income country*. Paris, International Union Against Tuberculosis and Lung Disease, 1998.
- Roberts GD, Koneman EW, Kim YK. Mycobacterium. In: Balows et al., eds. *Manual of clinical microbiology*. 5th ed. Washington, DC, American Society for Microbiology, 1991:304–339.

Appendix 2: Collection, storage and transport of sputum samples

Collection

- Sputum must be collected in the open air or in a well-ventilated room reserved for this purpose, as far as possible from other people.

Trained health personnel must:

- explain to the patient how to cough to bring up sputum from as deep as possible in the lungs.
- open the sputum container, stand behind the patient and ask him/her to expectorate with his/her mouth close to the sputum container.
- check the quality and quantity of sputum collected (2–3 ml of sputum containing solid particles).
- close the sputum container securely.
- wash their hands with soap and water before giving a new container to the patient to be returned to the health centre the next day with a new sputum sample.
- ensure that the patient has understood how to collect a sputum sample the next morning and how to close the container securely.

Storage and transport of sputum samples

If the sputum samples are not examined at the health centre, they should be sent to a laboratory on a daily basis or at least once or twice weekly. For storage and transport of the samples, special transport boxes are used that can each hold 10–20 containers. The following rules must be followed:

- Each sputum container must be clearly identified by a label with the patient's family name, first name and register number **on the side** of the container.
- The transport box with the sputum containers should be kept as cool as possible. If the samples are to be cultured they should be refrigerated at +4 °C.
- A list of the patients' names and information should be sent with the transport box.

NB: If desired, fixed smears can be sent instead of sputum samples: smears that are performed and fixed at the health centre can be sent to the microscopy laboratory for reading. However, results currently obtained in countries that use this method are not very encouraging.

Appendix 3: Preparation of smears and Ziehl-Neelsen staining

● **Labelling the slides**

- Take a new slide; using a diamond-pointed stylus, engrave the identification number of the sputum specimen at the end of each slide, referring to the accompanying list of samples.
- Prepare one slide per sample in this way (do not prepare more than 10–12 sputum samples at a time)

● **Preparation of smears**

- Take each slide by the end where the number is engraved, and place it on the slide-holder with the engraved end towards you
- Take the sputum container that corresponds to the number of the slide, open it and place the container to the right of the slide rack with its lid next to it
- Hold the metal loop over the flame until red-hot and leave it to cool
- Take a small portion of sputum, selecting purulent particles if present
- Spread the smear as thinly as possible (2 cm × 1 cm) on the slide
- Place the slide on the dryer
- Sterilise the metal loop over the flame before taking the next sputum container
- Prepare the other slides in the same way

● **Drying**

- Let the smear dry in the air for at least 15 minutes (15–30 minutes). Do **not** use the burner to dry the smear

● **Fixation**

- Take each slide by the engraved end using forceps, with the smear uppermost
- Pass the slide three times (for 3–5 seconds) through the flame of the Bunsen burner or spirit lamp
- Put the slide back on the clean dryer

● **Staining**

- Place the slides on the slide-rack with the smears uppermost, ensuring that the edges do not touch
- Cover the slides with Ziehl-Neelsen carbol fuchsin. The fuchsin should be filtered directly onto the slides through filter paper placed in a funnel
- With a wad of cotton wool soaked in methylated spirits fixed to the end of a metal rod, heat the slides very gently from underneath until they begin to steam. The stain must never boil or dry on the slide
- Leave the warm stain for 3 minutes
- Repeat the heating of the stain twice

- **Destaining¹**

- Rinse each slide separately in running tap water until the excess stain is washed away
- Replace all of the slides on the slide-rack and cover each slide with the sulfuric acid
- Leave for 3 minutes
- Rinse in running water
- Cover in 70° alcohol
- Leave for 5 minutes
- Rinse again in running water
- Destain again with the acid until almost all of the stain has disappeared
- Rinse each slide again under running water

- **Counter-staining**

- Replace the destained slides on the slide-rack and recover the smears with 0.3% methylene blue for 1 minute
- Rinse each slide in running water and leave to dry in the open air

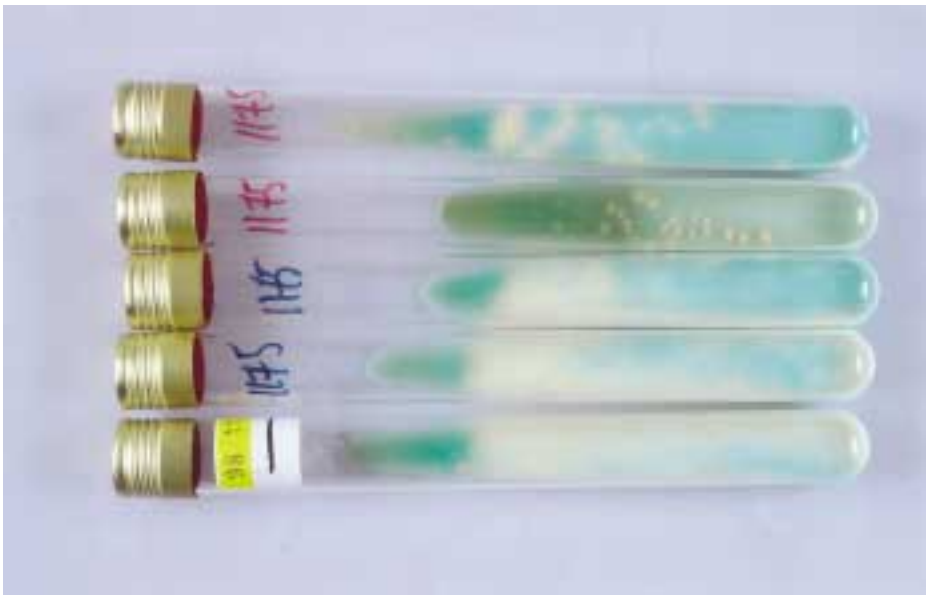
¹ Destaining of the smears can also be done using only 25% sulfuric acid several times until the smear is completely destained (IUATLD Tuberculosis Guide)

Appendix 4:

Photograph of tubercle bacilli on microscopy after Ziehl-Neelsen staining



Photograph of cultures of Mycobacterium tuberculosis





TUBERCULOSIS HISTOLOGY

Multiplication of tubercle bacilli in any site of the human body causes a specific type of inflammation, with formation of a characteristic granuloma. Anatomic pathology involves examining tissue for suspect TB. Tissue samples may be obtained either by biopsy from a patient or at autopsy.

Histology consists of **macroscopic examination** of lesions that suggest the presence of tuberculosis if the technician has access to all or a large part of the affected organ (lymph node or kidney), and **microscopic examination** of a sample.

Histology is an aid to diagnosis when bacteriological techniques cannot be applied. It is especially useful for extrapulmonary tuberculosis. It is helpful to consider histological examination and bacteriological techniques as complementary.

Types of samples

□ *Aspiration of the lymph nodes*

Affected peripheral lymph nodes, particularly cervical nodes, can be aspirated. Aspiration should be performed at the upper pole of the node.

□ *Biopsy of the serous membranes*

Effusions of the serous membranes can be aspirated. However, the effusions are much less useful for diagnosis than histology or, even better, culture of the biopsy specimen.

□ *Tissue biopsy*

● **Without surgery**

- **The serous membranes:** biopsy of the pleura (with an Abrams or Castelain needle) and the pericardium is performed closed. As a result the fragments are not always sampled from the site of the lesions. In contrast, when biopsy of the peritoneum is performed during laparoscopy, samples can be taken directly from a suspect lesion. Whatever serous membrane is affected, several fragments should be sampled during a single biopsy.
- **The skin:** skin biopsy.
- **The reproductive organs:** biopsy of the endometrium by curettage.
- **Different organs after endoscopy:** bronchial biopsy during bronchoscopy, pleural biopsy using thoracoscopy, gastric biopsy during endoscopy, or liver biopsy during laparoscopy. As these biopsies are performed under direct observation, fragments of suspect lesions can be sampled using biopsy forceps.

- **During surgery**

A surgical intervention can be performed to confirm the diagnosis by sampling of a deep or superficial lymph node, a bone fragment or part of an organ. During the surgical intervention a sample can sometimes be examined immediately in order to decide on the next step.

- **Post mortem**

After death from an unknown cause, tissue samples taken at autopsy can be analysed.

Methods

□ *Cytological techniques*

- **Material sampled by biopsy of tissue specimens**

After biopsy of tissues such as lymph nodes, a smear is made by spreading the sample on a slide. The smear is then air-dried and stained with May-Grünwald-Giemsa.

- **Aspirated fluid**

The fluid, taken from a test tube, should be centrifuged at 2000 cycles/minute. A smear is made of the centrifuged sediment, which is then stained as described. In general, smear examinations of aspirated fluid have a lower diagnostic yield than smears of tissue.

□ *Bacteriological and histological techniques for biopsied samples*

These techniques are only possible if there is at least one tissue fragment in the specimen.

□ *Bacteriological techniques*

Bacteriological examination is always more definitive than histological techniques and must take priority, where possible, where specimens are limited and bacteriological services are available. It is very important, where such services are available, that surgeons be reminded not to place the suspect specimens in fixing agents such as formal, as these prevent any cultures from being obtained.

- **Biopsied samples**

A biopsied fragment is placed in a tube containing saline and sent to the mycobacteriology laboratory for culture.

- **Aspirated material**

The serous fluid or material obtained by aspiration of a lymph node can also benefit from culture in a mycobacteriology laboratory.

□ *Histological techniques*

Whatever type of specimen is available, the following steps should be followed to prepare it for histological examination:

- **Fix the specimen:**

As soon as it has been obtained, the biopsied fragment should be placed, in a quantity of fixing agent equal to at least 10 times the volume of the fragment (formol diluted to 10% or Bouin's fluid).

- **Prepare the sample for examination:**

The sample is dehydrated, then placed in paraffin and cut with a microtome. Slants are then treated with haematoxylin and eosin stains for histological examination. Other slants are stained using Ziehl-Neelsen or auramine, then examined for tuberculous bacilli.

Practical point:

On biopsy, at least two fragments are collected: one is put into saline and sent to the mycobacteriology laboratory for culture, while the other is put into a fixing agent for histology.

Macroscopic aspects

Caseum, or necrotizing granulomata, is specific to tuberculosis. If it is recent, it has a yellowish white, cheesy texture; on ageing it becomes greyish and chalky. When caseating material is obtained (from aspiration of an abscess or fistulation of a lymph node), tuberculosis is the first diagnosis that comes to mind. Sometimes the granuloma softens, liquefies and drains away, leaving a cavity.

Various types of macroscopic lesions are symptomatic of tuberculosis. Certain lesions can be observed on clinical examination of a patient:

- **Ulcerations** on the surface of the skin or the mucous membranes are irregularly draining sinuses with raised edges, containing necrotizing granuloma.
- **Fistulas and sinuses** form in the absence of natural drainage (adenitis, cold abscess).

Other lesions can be observed on endoscopy (laparoscopy, fibroscopy, thoracoscopy, coelioscopy):

- **Isolated nodules** present as disseminated whitish or yellowish granuloma. These granuloma can be of different sizes: from miliary granulation of less than 1 mm diameter to tuberculoma which can reach up to 20 mm in diameter.
- **Diffuse lesions** may be gelatinous, and are grey or yellow in colour.

On examination of a sample excised during surgery or autopsy any of these lesions can be observed. Dissection of the sample (lung, kidney) can sometimes reveal **tuberculous cavities**, which present in the form of **cavities filled or covered with caseating granuloma**. These types of lesions are most characteristic of tuberculosis.

Several types of macroscopic lesion are generally present on a single excised sample. Nevertheless, however clear the diagnosis seems to be, the examination must be completed by microscopic examination of tissue segments after specific staining.

Microscopic aspects

The involvement of an organ by tuberculosis is associated with an inflammatory reaction at the affected site. The inflammation occurs in three successive stages that can be simultaneous — acute, subacute and chronic — and that have different histological aspects.

□ *The acute phase*

Infection by the tubercle bacillus first leads to a rapid, nonspecific inflammatory reaction manifested by **exudative lesions** that are not particularly specific to tuberculosis. The focus of the inflammation is the site of a sero-fibrous exudate with numerous macrophages in the centre.

At this stage the bacillus can be observed at the centre of this site of inflammation.

□ *The subacute phase*

Lysis of the bacilli liberates the phospholipids from their capsule, provoking a specific tissue reaction and the formation of follicles, "**Koëster follicles**" (Appendix 5). Two kinds of follicular lesions can be observed:

- **The epithelioid giant cell follicle**

A rounded focus containing:

- **numerous epithelioid cells**. These are monocytes with an egg-shaped centre, abundant cytoplasm and indistinct cytoplasmic edges.
- **several Langhans giant cells**, generally situated at the centre of the follicle. These are large cells with abundant cytoplasm, indistinct edges and multiple centres arranged in the shape of a crown or a horseshoe. Langhans cells are caused by the fusion of epithelioid cells. Epithelioid cells and Langhans cells are

created from the metamorphosis of monocytes under the action of lymphokines.

- **and a peripheral crown of lymphocytes.**

This follicle does not contain necrosis and is not specific to tuberculosis. It is common to “granulomata”: tuberculous leprosy, sarcoidosis and connective tissue diseases.

- **The necrotizing granuloma**

The epithelioid giant cell follicle presents with **central caseating necrosis**. This lesion is very specific to tuberculosis.

Caseating necrosis is a fine-grained, homogeneous, eosinophilic necrosis.

□ *The chronic phase*

The fibrous follicle: the tuberculous follicle gradually develops into a fibrous follicle. Collagenous fibres invade the tuberculous focus, which is enclosed in a fibrous shell with fibroblasts and lymphocytes, forming a fibro-caseating follicle that is then transformed into a fully fibrous follicle. This follicle **can become entirely calcified**.

Isolated or clustered follicles of varying types and sizes can be observed. There are usually a number of visible lesions at the different acute, subacute or chronic stages.

Practical point:

Of all of these lesions, only follicular lesions with necrotizing granulomas are sufficiently specific to confirm the diagnosis of tuberculosis, as is detection of bacilli on histological samples after appropriate staining.

Conclusion

Although bacteriology remains the key examination for confirming the diagnosis of tuberculosis, histology does play an important role, particularly for confirming the diagnosis of extrapulmonary forms.

Combining histological techniques with bacteriology increases the yield of histology. Bacteriological culture of tissue fragments (or, less usefully, fluid) sampled at the same time as those obtained for histological examination can enhance the confirmation of diagnosis of extrapulmonary tuberculosis.

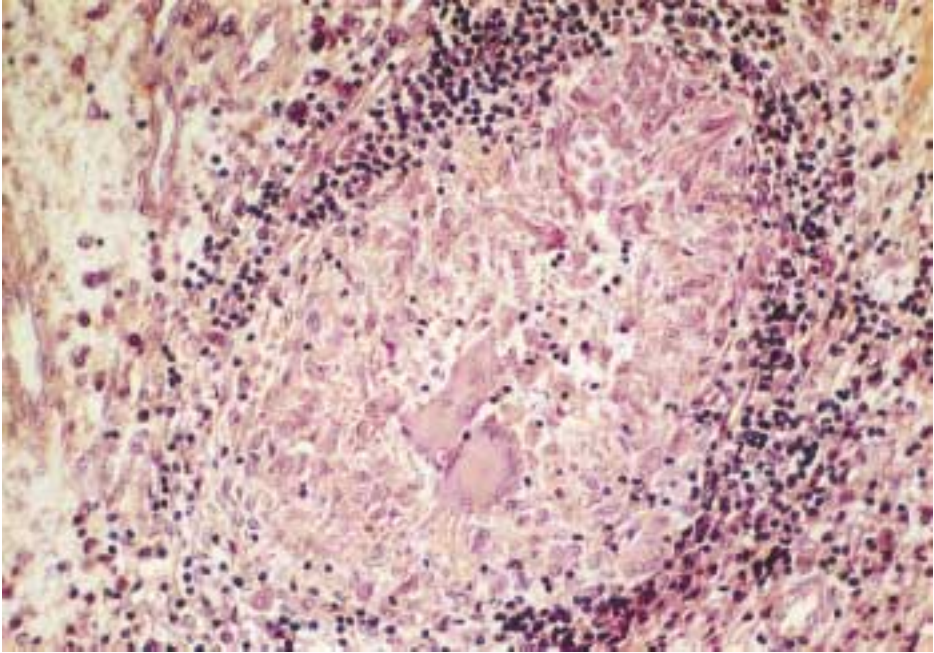
References

Glassroth J. Diagnosis of tuberculosis. In: Reichmann LB, Hershfield ES, eds. *Tuberculosis: a comprehensive international approach*. New York, Marcel Dekker, 1993:149–162.

Grosset J. Place des examens microbiologiques et anatomopathologiques dans la décision diagnostic et thérapeutiques. [Smear, culture and pathological changes for the diagnosis and treatment of tuberculosis.] *Medecine et Maladies Infectieuses*, 1995, 25 (3):327–333.

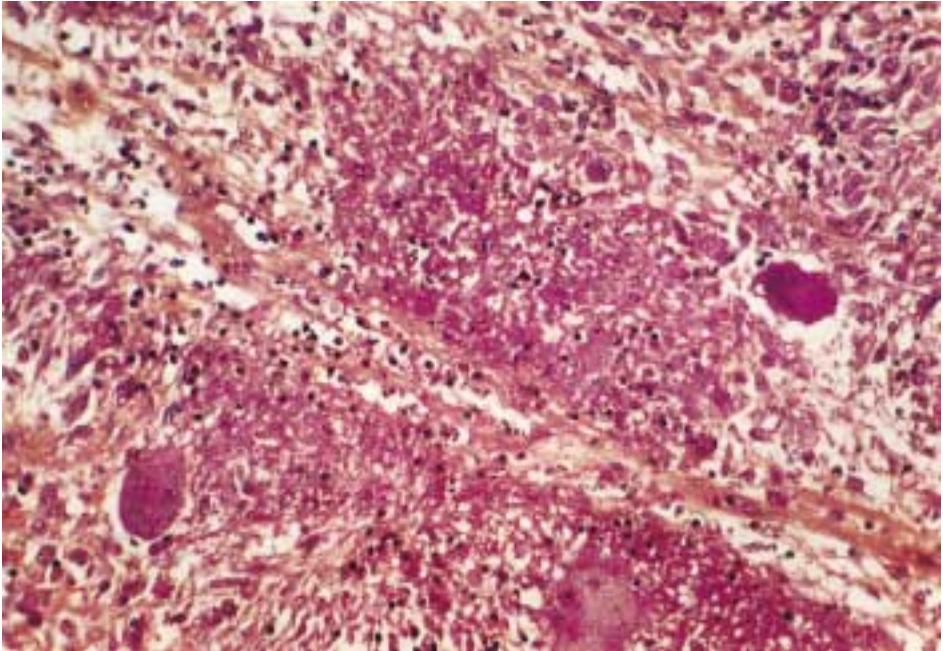
Appendix 5: Photographs of the Koëster follicle

Epithelioid giant cell follicle (without central caseating necrosis)



The follicle is surrounded by a crown of lymphocytes; in the centre are two giant cells and a cluster of epithelioid cells.

Caseating follicle (with central caseating necrosis)



The caseating necrosis can be seen in the centre of the photo; at the exterior two giant cells and epithelioid cells can be seen.

CHAPTER 2

TUBERCULOSIS IN THE INDIVIDUAL PATIENT

PULMONARY TUBERCULOSIS IN ADULTS

The most frequent form of presentation of tuberculosis is disease that affects the lungs (pulmonary tuberculosis), while less frequent forms may affect any part of the body (extra-pulmonary tuberculosis) or present as acute disseminated tuberculosis.

What are the clinical signs suggestive of pulmonary tuberculosis?

The onset of the disease is often insidious; symptoms often develop slowly, over several weeks:

Chest symptoms are often nonspecific, and can mimic virtually any respiratory condition: cough is almost always present, with sputum production, possibly chest pain and/or dyspnoea as accompanying symptoms. Less commonly, haemoptysis may occur; this alarming symptom frequently causes the patient to seek help immediately.

Systemic symptoms — fever in the evening (on average 38°C), heavy night sweats, loss of appetite, loss of weight and a general sense of malaise — are nonspecific but frequently accompany chest symptoms. If they continue they often prompt the patient to seek attention.

What is the differential diagnosis?

More than 95% of patients who present with chronic cough do not have tuberculosis; it is therefore very important to differentiate other respiratory conditions (acute or chronic) from tuberculosis. The duration of symptoms is a key indicator for differentiating symptoms related to tuberculosis from those of other conditions.

□ *The symptoms started less than 3 weeks ago*

These are more commonly indicative of acute respiratory infections, although tuberculosis remains a possibility. A history of an epidemic of acute respiratory illness in the community is especially important in such cases.

Diagnostic evaluation may reveal the following:

- inflammatory conditions of the respiratory tract, such as sore throat or acute bronchitis
- acute bacterial pneumonia, with pain in the side, high fever and evidence of pulmonary consolidation

- interstitial pneumonia, generally viral, with fever and dyspnoea
- more rarely, a lung abscess with fever and abundant purulent sputum

With appropriate treatment, including appropriate antibiotics (where indicated), symptoms will disappear within 1–2 weeks.

□ *The symptoms have been present for more than 3 weeks*

They can be more probably due to tuberculosis. However, symptoms that have been present for a very long time (several months or years), with a recent exacerbation that has prompted the consultation, suggest a chronic respiratory condition, although tuberculosis remains a possibility:

- **Bronchiectasis** with episodes of acute infection (a complication of previous tuberculosis or other respiratory infection). Abundant mucopurulent sputum and bacteriological examinations that are consistently negative for tuberculosis are characteristic of this condition.
- **Chronic bronchitis or chronic obstructive pulmonary disease:** the patient has had cough and sputum production each winter for at least 2 years. Seasonal episodes caused by acute infection are common. Gradually worsening breathlessness on effort is a symptom that may worry the patient. A history of tobacco smoking in individuals aged over 50 years or exposure to smoke from wood-fired cooking or heating in an unventilated room supports this diagnosis.
- **Asthma** may present with chronic symptoms. Episodic breathlessness, often occurring at night, and wheezing, alternating with periods of absence of symptoms, is suggestive of asthma. When the patient presents with such symptoms, peak flow measurement can demonstrate the presence of airflow obstruction that may be relieved by treatment with aerosol bronchodilators (such as salbutamol).

Other, less common conditions should also be considered in such cases:

- **Mitral stenosis** may present with episodes of breathlessness, accompanied by repeated light haemoptysis. Presence of the characteristic diastolic murmur can identify this condition.
- **Heart failure** with breathlessness, disseminated pulmonary râles and oedema in the legs.
- **Lung cancer** in men aged over 50 years with a long history of tobacco smoking presenting with cough, haemoptysis and sometimes persistent chest pain.
- **Pneumoconiosis** in the case of long-term exposure to mineral dusts.

The duration of symptoms in tuberculosis cases is shorter than that of chronic conditions and longer than that of acute conditions.

Practical point:

If, after interview and clinical examination, there is no evidence of another cardio-pulmonary condition in a patient who presents with cough lasting for more than 3 weeks, pulmonary tuberculosis should be suspected. Bacteriological examinations must then be performed, starting with smear microscopy for acid-fast bacilli.

What are the key radiographic features of pulmonary tuberculosis?

Pulmonary tuberculosis in adults can present with a wide variety of radiographic features. Chest radiography is not a method of diagnosis. When it is available, it can be used to screen patients with respiratory symptoms to identify features that might be caused by tuberculosis, or that are consistent with other diseases, or to demonstrate the absence of abnormality.

❑ *Certain radiographic abnormalities are consistent with tuberculosis:*

- **Nodules** are round shadows (or “densities”) with clearly defined borders; their size varies from a micronodule (less than 3 mm in diameter), to a nodule (more than 3 mm and less than 1 cm in diameter), to a round shadow (more than 1 cm in diameter);
- **Patchy shadows**, or infiltrations, have irregular borders that are not as clearly defined. They are of varying size, sometimes extending to large parts of the lungs.
- **Cavities are the most characteristic sign of tuberculosis.** A cavity is an area of lucency with a fairly thick wall (more than 1 mm), in which an area of bronchial drainage, demonstrated by opaque parallel lines, may be evident at the pole closest to the hilum of the lung. Cavities sometimes contain liquid at the base (liquefied caseous material), evident as an “air fluid level”.

In tuberculosis, a wide variety of abnormalities may be present on the same film. In films taken at least 2 weeks apart, changes in the abnormalities can be detected: growth of the cavities, confluence and spread of the nodules, or the formation of a cavity inside a patchy shadow. This kind of evolution of the radiographic features suggests that the tuberculosis is clinically active.

When the tuberculosis has progressed over several months, the destruction of the lung parenchyma and gradual fibrosis lead to retraction of the neighbouring structures: the trachea may be displaced, the hilum may become elevated, the diaphragm may be pulled upward and the cardiac silhouette may change shape and place.

Lesions due to tuberculosis can be unilateral or bilateral; they are most frequently observed in the upper zones of the radiograph. The extent of the abnormalities may vary from a minimal lesion (an area less than the size of a single intercostal space), to far advanced lesions, with extensive involvement of both lungs.

□ *Some radiographs show tuberculosis sequelae*

Pulmonary tuberculosis lesions may have various types of sequelae:

- nodules that are fully or partially calcified
- stellate abnormalities
- fibrous retraction
- fine-walled bullae/cavities

In some cases the retraction may be extensive, and may affect a whole lobe or even a whole lung.

No matter how experienced a person is in reading chest radiographs (Appendices 1 and 2), it is impossible to be certain of a diagnosis of active tuberculosis on X-ray, as a number of other bacterial conditions (such as pneumonia or abscess) or non-bacterial processes (fungal diseases, carcinoma, sarcoidosis or pneumoconiosis) can produce similar images.

Practical points:

- **Pulmonary tuberculosis cannot be diagnosed with certainty by radiography alone.**
- **If a radiograph is suggestive of tuberculosis, bacteriological examinations must be requested.**
- **If a radiograph shows cavities but bacteriological examination is negative, the diagnosis of a condition other than active tuberculosis needs to be considered.**

How to diagnose pulmonary tuberculosis

The diagnosis of pulmonary tuberculosis in adults relies on bacteriological examination of sputum samples.

Bacteriological diagnosis of tuberculosis depends on the number of samples examined and the time of day the sample is collected (Appendices 3 and 4).

For all tuberculosis suspects, three sputum samples are recommended to be collected over two days: two samples are collected on the spot during consultation on two consecutive days and a third is collected by the patient at home on the morning of the second day, before coming to the consultation. These samples must be examined by microscopy, and, if possible, cultured.

If all three examinations are negative but the chest radiograph shows signs consistent with tuberculosis, the patient should receive a course of broad-spectrum antibiotics. Two weeks later, if the symptoms continue despite treatment, a new

series of three samples should be collected and examined by microscopy, and, if possible, culture. If all microscopic examinations are negative it is necessary to wait for the results of the culture, if this has been performed, or to refer the patient to a more experienced physician for confirmation of tuberculosis or the establishment of another diagnosis. A trial course of anti-tuberculosis treatment must **never** be prescribed to establish the diagnosis of tuberculosis.

Pulmonary tuberculosis almost never presents an immediate, life-threatening danger. In almost all cases, there is sufficient time to properly investigate the case with bacteriology prior to proceeding with treatment.

Criteria for the diagnosis of pulmonary tuberculosis

Smear-positive cases:

- At least two positive smears, or
- One positive smear and radiographic abnormalities compatible with pulmonary tuberculosis, or
- One positive smear and one positive culture

Smear-negative cases

- At least three negative smears and one or more positive cultures, or
- At least two series of negative smears from samples taken at least 2 weeks apart, with persisting radiographic abnormalities compatible with active tuberculosis, not improved with treatment using broad-spectrum antibiotics for at least 1 week.

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

What are the most common complications of pulmonary tuberculosis?

□ *Complications may be the first indication of tuberculosis, or may occur as the disease develops:*

Haemoptysis can be light, moderate or extensive. Massive haemoptysis, caused by the erosion of an arterial wall, is a rare but dramatic complication that can result in sudden death.

Pneumothorax, caused by rupture of a cavity into the pleural space, is a serious complication. Bacilli from the cavity can infect the pleural space, leading to pyopneumothorax. In the latter event, pleural drainage may be required in addition to anti-tuberculosis treatment.

Contiguous pleurisy can accompany active pulmonary tuberculosis.

□ *Some complications may occur in patients successfully treated for tuberculosis who subsequently present with sequelae:*

Bronchiectasis: repeated acute pulmonary infection and haemoptysis are the most common manifestations. It should not be confused with recurrence of tuberculosis disease, which must always be confirmed by bacteriological examination.

Chronic respiratory failure may occur in patients who have previously had extensive tuberculosis, in whom large parts of the lung have been destroyed.

Pneumothorax may result from rupture of a bulla in association with lung scars; this type of pneumothorax does not lead to infection of the pleura. It is usually benign, and can usually be relieved within 48 hours with simple medical treatment.

Aspergilloma, due to infection by *Aspergillus fulmigatus* of a healed cavity, may present with haemoptysis and often requires surgical excision.

Conclusion

Pulmonary tuberculosis should always be considered in adults presenting with symptoms of the respiratory tract (cough and expectoration of sputum) lasting for more than three weeks.

In countries with a high prevalence of tuberculosis, the majority of cases of pulmonary tuberculosis in adults are sputum smear-positive.

The diagnosis of tuberculosis in adults is therefore based on microscopy of sputum smears.

References

- Crofton J, Horne N, Miller F. Clinical tuberculosis. London, Macmillan Education, 1992.*
- Enarson DA et al. Management of tuberculosis: a guide for low-income countries, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.*
- Toman K. Tuberculosis case-finding and chemotherapy: questions and answers. Geneva, World Health Organization, 1979 [New edition in preparation].*

Appendix 1: International Union Against Tuberculosis and Lung Disease international study on classification of respiratory tuberculosis

Indices of disagreement between different readers according to questions asked below.

Is the film abnormal?	34%
Calcification in lung?	42%
Non-calcified abnormality, probably tuberculous?	37%
Cavity present?	28%
Abnormality in lung, probably not tuberculous?	45%
Abnormality in lymph nodes?	60%
Need for medical action?	31%

Nyboe J. Results of the international study on x-ray classification.
Bulletin of the International Union against Tuberculosis, 1968, 41:115–124.

Appendix 2: Study performed by the Japanese Anti-Tuberculosis Association, 1970

Observer error: under-reading and over-reading of chest radiophotographs

EXPERIENCE	NO. OF READERS	UNDER-READING (%)	OVER-READING (%)
Averag, all readers	192	21.8	19.5
a) By years of experience			
- 1–4 years	37	28	18
- 5–9 years	37	19	19
- ≥10 years	88	18	17
b) By the number of films read annually			
- 1000–5000	43	22	17
- 5000–20 000	48	24	18
- >20 000	41	15	15

The results given by doctors with less than 1 year of experience or who read fewer than 1000 X-rays a year were excluded from the detailed analyses a) and b).

Nakamura K et al. *Kekkaku* 1970; 45: 221.

Appendix 3: Comparison of the results of microscopy and culture in sputum examination

(among 348 tuberculosis patients diagnosed at the chemotherapy centre of Chennai)

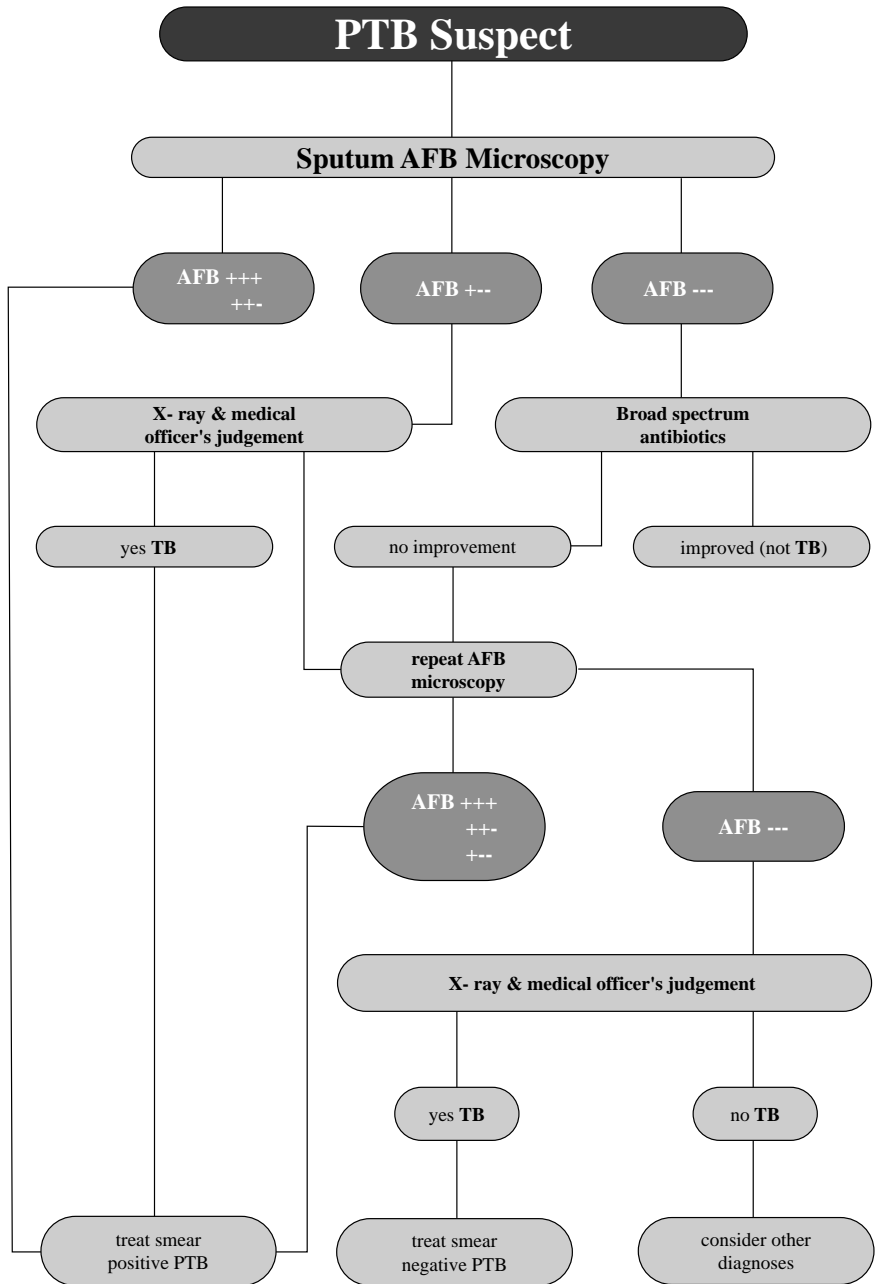
NUMBER OF SAMPLES PER PATIENT	TYPE AND COMBINATION OF SAMPLES	SMEAR-POSITIVE (%)	CULTURE-POSITIVE (%)	POSITIVE RESULT ON MICROSCOPY AND/OR CULTURE
1	<ul style="list-style-type: none"> ● “on-the-spot” ● “early morning” 	66	90	93
2	<ul style="list-style-type: none"> ● 2 “on-the-spot” ● 1 “on-the-spot” and 1 “early morning” 	76	94	
3	<ul style="list-style-type: none"> ● 2 “early morning” ● 2 “on-the-spot” and 1 “early morning” 	81	96	97
	<ul style="list-style-type: none"> ● 1 “on-the-spot” and 2 “early morning” 	83	97	
4	<ul style="list-style-type: none"> ● 2 “on-the-spot” and 1 “early morning” 	84	98	99
	<ul style="list-style-type: none"> ● 1 “on-the-spot” and 2 “early morning” 	84	99	
4	<ul style="list-style-type: none"> ● 2 “on-the-spot” and 2 “early morning” 	85	99	100
	<ul style="list-style-type: none"> ● 2 “early morning” 	84	99	

Andrews RH, Radhakrishna S. A comparison of two methods of sputum collection in the diagnosis of pulmonary tuberculosis.

Tubercle, 1959, 40:155–162.

Appendix 4: Management plan for tuberculosis suspects in an out-patient centre

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).





EXTRAPULMONARY TUBERCULOSIS

Tuberculosis that affects any organ outside the pulmonary parenchyma is designated extrapulmonary tuberculosis. In addition to all the sites of the body outside the chest affected by tuberculosis that are clearly extrapulmonary, certain forms of tuberculosis occurring in sites that are fully or partially within the chest are also considered extrapulmonary:

Pleural tuberculosis and tuberculosis of the hilar or mediastinal lymph nodes are classified as extrapulmonary, provided there are no discernible lung parenchymal abnormalities.

Disseminated tuberculosis (often accompanied by “miliary” shadows on chest radiograph) is a form of the disease that affects many sites in the body simultaneously and is not limited to the lungs.

How to diagnose acute severe forms of tuberculosis

Disseminated (miliary) tuberculosis and **tuberculous meningitis** are acute, severe forms of tuberculosis caused by the haematogenous spread of the bacilli, often occurring soon after primary infection. They occur most often in children and young adults. Unlike pulmonary tuberculosis, these acute forms are highly fatal. When such forms of the disease are suspected, treatment should be commenced immediately without waiting for bacteriological proof of diagnosis.

□ *The diagnosis of disseminated tuberculosis is based on the following:*

- **Clinical signs:** general deterioration, high fever and dyspnoea. Clinical signs that other organs may be affected include: pleural effusion, digestive problems, hepatosplenomegaly and sometimes meningeal signs.
- **Characteristic chest radiograph:** a “miliary” pattern may be seen on a good quality anterior radiograph: extensive, tiny (1–2 mm) nodules resembling millet seeds, all the same size and spread symmetrically over both lungs.
- **Smear microscopy of sputum from cases with disseminated (miliary) tuberculosis is usually negative**, as the disease is paucibacillary.

□ *The diagnosis of tuberculous meningitis is based on the following:*

- **Clinical signs:** nonspecific, progressive deterioration of the patient’s general state and mood, high temperature;
- **Meningeal signs**, with characteristic nuchal rigidity;
- **Paralysis of the oculomotor nerve**, leading to strabism and/or ptosis (drooping eyelids) and sometimes convulsions.

□ *Clinical characteristics suggestive of disseminated tuberculosis or tuberculous meningitis*

- **The tuberculin skin test** is usually negative
- **Fundusoscopic examination** may show the characteristic tuberculous lesions (choroidal tubercles) that signal haematogenous dissemination of the tubercle bacilli. Round, slightly raised yellow or whitish lesions of 1–3 mm in diameter are clearly distinguishable from the vasculature on the retina. Ophthalmological examination can reveal papillary oedema, indicating intracranial hypertension, which is a contraindication for lumbar puncture.
- **Cerebrospinal fluid (CSF) obtained by lumbar puncture** should be examined even if there are no clear meningeal signs. If meningitis is present, the CSF is clear, and pressure is elevated, with high levels of protein (>1 g/l) and lymphocytes (30–300/mm³).

Examination of three specimens of cerebrospinal fluid after centrifugation may demonstrate acid-fast bacilli.

If there are other clinical signs of dissemination, additional evidence of tuberculosis may be obtained by histological and bacteriological examination of hepatic or pleural biopsy.

Practical point:

When acute disseminated (miliary) tuberculosis and/or tuberculous meningitis is suspected, examination of the retina and the cerebrospinal fluid (provided that there are no contraindications for lumbar puncture) are recommended.

Because disseminated tuberculosis is such a deadly disease, a rapid clinical decision is required and treatment must be commenced immediately, without waiting for the culture results. The following conditions should be excluded beforehand:

In the case of isolated acute miliary disease, the other rare causes of acute, febrile miliary disease: viral, staphylococcal or carcinomatous disease;

In the case of meningitis, other forms of meningitis with clear CSF: inadequately treated bacterial meningitis, viral meningitis, or more rarely, in HIV-infected patients, cryptococcal meningitis.

Results of CSF examination in adults

MENINGITIS ETIOLOGY	CELLS	PROTEIN	MICROSCOPY
Tuberculous meningitis	30–300/mm ³ lymphocytes	0.6–2 g	Presence of AFB (rare)
Inadequately treated bacterial meningitis	Impaired polymorphonuclear cells	>0.6 g	Presence of bacteria after Gram staining (rare)
Viral meningitis	Lymphocytes >300/mm ³	<0.50 g	Negative
Cryptococcal meningitis	High polymorphonuclear lymphocytes	High	Presence of parasites after India ink staining

Practical point:

When clinical examination suggests the presence of acute disseminated tuberculosis, treatment must be started immediately, without waiting for the results of bacteriological examinations.

How to diagnose other forms of extrapulmonary tuberculosis

The other forms of extrapulmonary tuberculosis are not as life-threatening as disseminated tuberculosis. However, if they are not diagnosed and treated promptly they can lead to complications and severe sequelae: deficit of a vital function (respiratory, cardiac, hepatic or renal), important neurological deficits (due to compression of the spinal cord) or sterility (genital tuberculosis).

□ *Pleural tuberculosis*

- **Tuberculosis of pleura secondary to pulmonary tuberculosis** is evidenced by serous effusion or pyopneumothorax. Its tuberculous etiology is confirmed by a diagnosis of pulmonary tuberculosis as its cause, or by demonstrating the presence of tubercle bacilli in the pleural cavity.
- **Primary tuberculous pleurisy** occurs within the first months after primary infection, and is not accompanied by active pulmonary tuberculosis. The effusion is usually unilateral, more often on the right than on the left. Pleural biopsy yields a yellow liquid, an exudate showing a protein level of more than 30 g/l and clear lymphocytosis (80–100% lymphocytes). The tuberculin skin test may be negative at the time of diagnosis but becomes positive subsequently. Because the number of bacilli present is relatively small, acid-fast bacilli are usually not seen on microscopy of centrifuged specimens of pleural fluid; however, culture may be positive. If a biopsy of the pleura can be done, two

specimens are collected — one for histological examination, and the other for culture, in which case the diagnosis of tuberculosis can be confirmed in more than 70% of cases.

❑ *Tuberculous lymphadenitis*

Tuberculous lymphadenitis most frequently affects the lymph nodes in the neck. This form of tuberculosis, which occurs relatively early after primary infection with *Mycobacterium tuberculosis*, often affects young people in countries with a high prevalence of tuberculosis. Adenopathy usually occurs in a single lymph node or chain. At first the enlarged lymph nodes are small, firm and painless; they then increase in size, become fluctuant and may suppurate and drain in a chronic fistula. Within several months a permanent, irregular, dark red scar appears.

The tuberculin skin test is usually significant. Diagnosis may be confirmed by aspiration or biopsy of the most enlarged lymph node.

- **If the lymph node is suppurating or fistulated**, the diagnosis is fairly straightforward: the macroscopic aspect of the caseous pus is characteristic. Microscopy and culture of the pus can confirm the diagnosis in the majority of cases. The only differential diagnoses to be ruled out are acute suppurating lymphadenitis or secondary spread of infection from a local bacterial infection (for example, from dental caries).
- **If the lymph node is firm**, AFB may be found on microscopic examination of a smear taken from material removed by aspiration, or from the surface of a sectioned node that has been surgically removed. By excision of the node histology can be performed and a fragment can be sent for culture, allowing the tuberculous etiology of the lymph node to be confirmed in most cases.

The clinical aspects of the lymph nodes, their localization and in particular laboratory examination can distinguish tuberculous lymphadenopathy from other causes:

- malignant disease (lymphoma, metastatic carcinoma)
- sarcoidosis, generally accompanied by a negative tuberculin skin test
- HIV infection in populations with a high prevalence of HIV. In this case generalized persistent lymphadenopathy has the following characteristics: lymph nodes more than 1 cm in diameter, at least two extra-inguinal foci, and evolution over more than 3 months.

❑ *Tuberculosis of the abdomen*

- **Peritoneal tuberculosis** is manifested by general clinical signs and nonspecific abdominal symptoms:
 - It may present with **ascites**, with no signs of portal hypertension. Aspiration yields a yellow fluid that is rich in protein and lymphocytes. After aspiration, ultrasound shows liver and spleen of normal size, and sometimes retroperitoneal lymph nodes. If possible, laparoscopy will show the presence

of necrotising granulomata on the peritoneal surface, and histology will confirm the diagnosis of tuberculosis.

- It may result from the evolution of **retroperitoneal** and **mesenteric** tuberculous lymphadenitis. When lymph nodes in the peritoneum rupture, caseous nodules are formed with some adherence to the intestinal loops. This may cause episodes of obstruction or masses in the abdomen that resemble a tumour. In most cases the tuberculin test is significant. The diagnosis can only be confirmed after exploratory laparoscopy or surgery, based on macroscopic examination and bacteriological and histological examination of the samples.
- **Intestinal tuberculosis** is rare: it usually occurs in the ileo-caecal area, although it can affect the oesophagus, the stomach and the duodenum. It often presents with intestinal obstruction, fistula formation or an abdominal mass. Clinical and many pathological features are similar to those of regional enteritis (Crohn disease).
- **Anorectal tuberculosis** presents with anorectal fissure, abscess or fistula. It is most frequently seen in patients who suffer at the same time from pulmonary tuberculosis, particularly those with advanced and cavitary disease.

□ *Tuberculosis of the bones and joints*

● **Tuberculosis of the spine, or Pott disease**

This can be a severe form of tuberculosis when there are neurological sequelae. It is seen both in children, usually within 3 years following primary infection, and in adults. In many cases more than one intervertebral disc space is involved. As the disease develops, the vertebral body adjacent to the disc space is affected, an abscess is formed and spreads either forward towards the mediastinum or the retroperitoneal space, to the vertebral body with compression of the spinal chord, or back along the vertebral column, eventually appearing as a subcutaneous “cold” abscess. Collapse of adjacent vertebral bodies affected by tuberculosis may lead to angulated kyphosis. Thrombosis of the anterior spinal artery caused by the inflammation may lead to transverse myelitis and paralysis.

Involvement of the cervical vertebrae may signal its presence by pain in the neck and shoulders. It may lead to rigidity of the neck, a cervical cold abscess behind the sternomastoid muscle, and more rarely neurological signs leading to progressive tetraplegia.

Involvement of the dorsal vertebrae is indicated by localised back pain, deformity of the spine, and in extreme cases an angulated kyphosis (gibbus): the chief risk is spinal chord compression and paraplegia. In lower back lesions the abscess can appear behind the trunk.

Involvement of the lumbar vertebrae is indicated by lower back pain. The abscess can drain along the psoas muscle towards the inguinal area or towards the spine. A large draining abscess in the inguinal region (a “cold” abscess) is indicative of tuberculosis of the spine.

Symptoms of vertebral tuberculosis are:

- back pain
- referred pain radiating out from the site of origin (cervico-brachial, intercostal, crural and sciatic). This pain may be relieved at rest in the early stages of the disease.

Physical examination is nonspecific until complications (gibbus, cold abscess or neurological signs) appear.

As the lesions progress, they appear on X-ray. Postero-anterior and lateral images of the whole of the spine and images centred on the lesions should be taken. The lateral radiographs allow assessment of the vertebrae and discs. Initial changes are subtle, with narrowing of the disc space; later manifestations include involvement of adjacent vertebrae, wedge-shaped collapse and angulation. Radiographs can be supplemented by computed tomography in specialised services.

Two types of lesions can be seen:

Vertebral, cavity in a vertebral body, erosion of one or more vertebral surface with or without compression and cuneiform aspect

Disk damage, with compression and disappearance of the intervertebral space

When abscesses are large, they can appear:

In the neck, on the lateral image in the form of a shadow forcing the oesophagus forward

In the thorax, on the anterior image in the form of a rocket or a bird's nest, evocative of an aortic aneurysm or malignant mediastinal lymphadenopathy.

The diagnosis of Pott's disease is generally based on clinical and radiographic signs. Differential diagnosis includes (at early stages) degenerative disc disease, and other types of infectious spondylitis (staphylococcosis or brucellosis); and cancerous vertebral metastases which are more likely to start by affecting the vertebral bodies. When an abscess can be accessed for biopsy, culture of the pus allows tuberculosis to be confirmed.

● Tuberculosis of the joints

Tuberculosis of the joints primarily affects the large joints (hips, knees, shoulders and elbows) but can affect any joint, including those of the fingers and the small bones of the feet. Whatever the site, it is usually monoarticular arthritis (affecting one of the joints) which presents first as limitation in movement, then painless swelling of the joint after the creation of an abscess, but without redness or heat. Progressive localized wasting of muscles and almost complete functional destruction of the joint will ensue if diagnosis is delayed. Late manifestations typical of tuberculosis are draining sinuses from the joints, destruction of the joint and chronic disability.

Simple X-rays of the joint will show the bone lesions of the epiphyses with loss of bone shadowing. Clinical characteristics are generally sufficient for differentiating between the chronic appearance of osteo-articular tuberculosis and acute septic

arthritis. More difficult, at the early stages, is the differentiation from chronic degenerative joint disease (osteoarthritis).

- **Tuberculosis of other bones**

Tuberculosis of the long bones is clinically and radiographically similar to chronic osteomyelitis with fistula.

Tuberculosis of the flat bones (skull and ribs) is indicated by the appearance of cold abscesses.

□ *Tuberculosis of the genitourinary tract*

- **Renal tuberculosis**

As it usually occurs many years after primary infection, renal tuberculosis is rare in children. It is generally unilateral, beginning in the outer part of one kidney, then destroying kidney tissue, leading to the formation of cavities. When it affects the ureters, it can lead to obstruction, causing hydronephrosis and total renal destruction. It can affect the bladder, causing tuberculous cystitis. If both ureters or the bladder are affected, it can cause chronic renal failure due to obstruction. In men it can expand to the prostate, seminal vesicles and epididymus.

The clinical signs include pain in the kidney that is dull or acute (similar to renal colic), haematuria and pyuria, and frequent and painful micturition. Patients presenting with “sterile pyuria” (urine containing white blood cells but failing to grow ordinary bacteria on culture) should be considered to have tuberculosis until proven otherwise. Smear examination of sediment after centrifugation of urine samples can sometimes reveal acid-fast bacilli, but the result may be false-positive due to the presence of saprophytic mycobacteria, *Mycobacterium smegmatis*. Only culture of the sediment after centrifugation of early morning urine samples collected on 3 consecutive days can confirm the diagnosis of tuberculosis. Renal ultrasound and especially intravenous pyelography help to locate the site and extent of the lesions.

- **Genital tuberculosis**

In women, tuberculosis can affect the endometrium and the fallopian tubes. The patient often presents with pelvic pain and menstrual irregularity. Clinical investigation can reveal abdominal masses due to the formation of abscesses in the fallopian tubes.

Pelvic X-ray will show deformation of the uterus, often with synechiae and stenosis of the tubes, which can cause sterility or ectopic pregnancy. These anatomical lesions do not give any indication of whether the tuberculosis is active or old.

The diagnosis of genital tuberculosis in women is based on culture of menstrual blood, or cultures or histology of biopsy specimens of the endometrium. Peritoneoscopy can aid in locating and aspirating an abscess of the fallopian tubes and tuberculosis is confirmed on culture of the pus.

In men, the disease usually manifests itself by epididymitis, which swells and becomes hard and craggy, sensitive to the touch, but not painful (unlike acute non-tuberculous infection). This lesion can break down into an abscess involving the skin. The epididymitis can cause swelling of a testicle which is difficult to distinguish from testicular cancer in young men. The prostate and the seminal vesicles may also be enlarged; in 50% of cases, the kidney is also involved.

❑ *Tuberculosis of the pericardium*

Tuberculosis of the pericardium is an infrequent form of tuberculosis of the serous membranes; it is nevertheless more frequent among HIV-infected individuals. The clinical symptoms are those associated with pericardial effusion (progressively worsening dyspnoea, paradoxical rapid pulse, low blood pressure, quiet heart beat, high fever, general listlessness). X-ray of the chest may show an image typical of pericardial effusion: a large heart shadow with immobile, symmetrical margins or a “teapot image”. If it is not treated adequately, pericarditis may evolve towards constriction over the following months. Restrictive pericarditis is accompanied by signs of peripheral stasis (hepatomegaly, ascites, oedema of the legs), reduced heart sounds, and on X-ray the heart shadow may be reduced in size (“small heart”), with an immobile margin.

❑ *Rarer forms of extrapulmonary tuberculosis*

Tuberculosis of the upper airways (mouth, tonsils and larynx) may occur in association with pulmonary tuberculosis or tuberculosis of the skin.

Tuberculosis of other extrapulmonary sites (eye, inner ear, brain, spinal cord, liver and spleen, breast, thyroid, adrenal gland) should be investigated at a specialized hospital.

Conclusion

Most forms of extrapulmonary tuberculosis are paucibacillary, and it is therefore much more difficult to confirm the diagnosis by demonstration of bacilli on microscopy. However, culture can be performed if a biopsy is taken or an exudate (from the pleura, peritoneum, pericardium or CSF) or caseating material (from a lymph node or cold abscess) is sampled.

Extrapulmonary tuberculosis is often situated deep in the body; however, culture and histology of tissue samples obtained by biopsy or surgery can confirm the diagnosis of tuberculosis in the majority of cases.

If there is no access to a laboratory where culture or histology can be performed, the diagnosis is based on strong supportive evidence (clinical, biological and radiological) which is used to decide on what treatment to give.

References

Crofton J, Horne N, Miller F. Clinical tuberculosis. London, Macmillan, 1992.

Martini M. La tuberculose ostéo-articulaire. [Osteo-articular tuberculosis.] Berlin, Springer-Verlag, 1987.



SPECIFIC ASPECTS OF CHILDHOOD TUBERCULOSIS

Tuberculosis in children is difficult to diagnose, even in its pulmonary form; children rarely produce sputum, so sputum smear examination can therefore not be used to obtain bacteriological proof, which is the cornerstone of diagnosis in adults. It is therefore diagnosed using a systematic approach whereby a number of clinical signs are interpreted.

Infants and children may be infected within the family circle. There are two key factors in diagnosing tuberculosis in children:

- identification of an infectious adult close to the child;
- loss of weight or failure to thrive.

Tuberculosis is diagnosed in children either during a contact-tracing visit where all individuals living in contact with a case of infectious tuberculosis are systematically screened, or during a consultation when the child presents with symptoms.

Tuberculosis disease presents in various clinical forms:

- primary pulmonary tuberculosis;
- acute disseminated tuberculosis: meningitis and miliary tuberculosis;
- post-primary pulmonary tuberculosis;
- extrapulmonary tuberculosis.

Primary pulmonary tuberculosis

Primary pulmonary tuberculosis occurs most often in children less than 5 years of age.

- **Primary infection is asymptomatic** in the majority of cases, and goes unnoticed. This is termed infection and must be distinguished from disease.
- **In 10% of cases primary infection has clinical manifestations** and presents with certain symptoms and radiographic abnormalities.
- **Generalized symptoms** are often subtle: slight fever, loss of weight, apathy and listlessness can attract the attention of the parents. Sometimes the symptoms are more obvious (e.g. a high fever of 39–40 °C and profound lethargy), and alert the parents to the fact that something is wrong.
- **Mucocutaneous manifestations**, although infrequent, are highly characteristic: **Erythema nodosum** appears in the form of painful nodules on the shins, sometimes on the backs of the arms and rarely on the front, in two to three bursts. They are painful, red, raised lesions that may turn purple and take on the appearance of a bruise; **Phlyctenular conjunctivitis** begins with generalized pain and irritation in one eye accompanied by watering and photophobia. On examination, grey or yellow

lesions can be observed where the cornea joins the white of the eye; a number of blood vessels enter the lesions, giving an appearance of vascular engorgement of the conjunctiva. Each lesion persists for about a week, then disappears, to be replaced by others. In severe cases the cornea may ulcerate.

- **Radiological signs** of primary pulmonary tuberculosis are characteristic. On postero-anterior and lateral radiography, the following may be observed:
 - **typical primary complex**, the most frequent manifestation, consists of a small area of infiltration at any location in the lung parenchyma, accompanied by unilateral mediastinal lymphadenopathy. The infiltration forms when the bacilli are first inhaled (as a defence reaction around the location at which the bacilli first deposit); it is characteristically small (3 to 10 mm in diameter). This nodular shadow is sometimes surrounded by a lighter, less dense shadow with irregular edges. On lateral X-ray, mediastinal lymphadenopathy appears as a rounded or oval latero-tracheal or hilar shadow.
 - in some cases, **isolated mediastinal lymphadenopathy** may occur without any visible changes in the pulmonary parenchyma;
 - occasionally, primary infection lesions may present as **segmental (or lobar) consolidation associated with mediastinal lymphadenopathy**. This is shadowing of a discrete area (usually right middle lobe, or lingula on the left), with clear margins and no bronchial markings, caused by compression of the (usually) middle lobe bronchus. It can mask the infiltration and even part of the causal lymphadenopathy.

Practical point:

The presence of a mediastinal abnormality with a positive tuberculin skin reaction establishes the diagnosis of primary tuberculosis in an unvaccinated child, particularly if living in the same household as a person with active pulmonary tuberculosis.

In a BCG-vaccinated child with a mediastinal abnormality, a diagnosis of primary tuberculosis must be distinguished from radiographic abnormalities associated with a hypertrophied thymus in children aged under 2 years, and from lymphoma in older children.

The course of primary tuberculosis is usually benign, whether or not the child is treated, and most children recover completely without sequelae. They may, however, subsequently develop active tuberculosis (reactivate) after a period of quiescence.

Local complications of primary tuberculosis, while unusual, are well recognized:

Fistulation of the lymph node into the bronchi: the lymph node swells and erodes into the bronchus (usually between the 4th and 7th month of development). This can be a serious event for small infants, where the caseous

material can create acute bronchial obstruction; in older children it usually causes cough;

The formation of a primary tuberculous cavity at the site of infiltration is a more unusual complication.

In both cases the child is usually incapable of producing sputum, but if a sample of bronchial or gastric aspiration is obtained, **acid-fast bacilli can be recovered from smear microscopy**.

Delayed local complications can result from the sequelae. Without treatment, lymphadenopathy can compress a lobar or segmental bronchus, creating breathing difficulties. **Bronchiectasis** may develop in the poorly ventilated area of the lung, creating bronchial superinfections and repeated episodes of haemoptysis. The most characteristic feature of this type of sequelae is “**hilar disease**” or “right middle lobe syndrome”: atelectasis, hilar calcification and recurrent haemoptysis. Antero-posterior and lateral X-ray will show systematic, very dense retractile shadowing, with concave edges, with some clear images and hilar calcifications in the centre.

Acute forms of tuberculosis

These are early complications of primary infection (within 2–10 months). Caused by the dissemination of bacilli from the primary infection through the bloodstream, they can occur at all ages, but do so most often in very young children (<2 years of age), particularly if they have not been vaccinated with BCG. They are serious, and are often fatal if diagnosed late.

□ *Tuberculous meningitis*

Clinical signs of tuberculous meningitis are often very subtle in children, particularly in those aged under 5 years. Initial indications may be simply a lack of interest in playing, irritation, complaints about headache and vomiting. Still later, changes in state of consciousness, strabismus, and possibly nuchal rigidity should indicate signs of meningeal tuberculosis. Lumbar puncture should be performed rapidly. The diagnosis is obvious at a later stage, with the infant in fetal position, photophobia and extreme nuchal rigidity; in the final stage the child is in a coma, prostrate and stiff-legged. When the disease progresses to such an advanced stage, there is almost no chance of cure; even if the child survives, there are major neurological sequelae, such as paralysis, deafness or blindness.

Chest radiography may be normal or it may show a pattern characteristic of primary disease or miliary tuberculosis.

Funduscopy examination is difficult to perform in children, but may show characteristic choroidal tubercles.

Lumbar puncture is the key investigation: CSF is clear or opalescent, pressure is elevated, there are plenty of lymphocytes, and the glucose level is low. Protein is elevated (0.6–2 g/l): the higher the level, the worse the prognosis.

Bacteriological examination of CSF (microscopy and especially culture), preferably of three different samples collected after lumbar puncture, will aid in identifying tubercle bacilli in the majority of cases, but well after the decision has been made to treat.

Treatment must be instituted immediately if the disease is strongly suspected, without waiting for the final results of the CSF culture (if this examination is available for a posteriori confirmation) or the TST result, which is often negative.

Practical point:

High protein levels with an elevated lymphocyte count in clear cerebrospinal fluid is sufficient evidence to begin treatment for tuberculosis, especially in a child less than 5 years of age who has not been BCG-vaccinated and/or who is in contact with a case of pulmonary tuberculosis.

If the evidence of tuberculosis is not sufficiently convincing, it is still wise to begin treatment for tuberculosis unless there is other evidence to confirm another etiology of meningitis. Differential diagnoses to consider among the most common forms of meningitis with clear CSF in children are:

- inadequately treated bacterial meningitis;
- meningococcal meningitis;
- viral meningitis;
- meningeal reactions ('meningismus') during the course of other infections in children

Criteria for differential diagnosis of clear CSF meningitis in children

ETIOLOGIES	CLINICAL SIGNS	PROTEIN (G/L)	NUMBER OF CELLS IN CSF	BACTERIOLOGY
Tuberculous	Gradual commencement 1 to 2 weeks	0.6–2	Lymphocytes 30–300/mm ³	Smear-negative, culture-positive in 90% of cases
Viral	1 to 2 days (mumps or other viral infection)	0.2–0.3	Lymphocytes 200–1000/mm ³	Negative
Inadequately treated bacterial	Attenuated meningeal syndrome	>0.8	Impaired polynuclear cells	Sometimes bacteria (smear and culture)
Meningococcus	Rhinopharyngitis Herpes Purpura	0.4–0.5	Impaired polynuclear cells: 200– 500/mm ³	Intra — and extracellular meningococcus
'Meningismus' during infection	Crude meningeal syndrome	0.2–0.3	Fewer than 10/mm ³	Absence of bacteria

From: Anane T, Grangaud JP. La tuberculose de l'enfant, encore aujourd'hui. In: Chaulet P et al. *L'enfant en milieu tropical [Children in the tropics]*. Paris, Revue du Centre International de l'enfance, 1992, 196–197:37.

□ Acute miliary tuberculosis

This condition often occurs within the first weeks after primary infection; it appears as a severe generalized condition similar to typhoid fever, with high fever plateauing at 39–40°C, torpor, vomiting and diarrhoea. Unlike typhoid fever, there are no rose spots on the abdomen or splenomegaly, and the pulse is elevated (there is no dissociation between the pulse and the temperature), which enables this diagnosis to be eliminated. On the other hand, there are respiratory abnormalities: dyspnoea, cyanosis and occasional respiratory distress.

A good quality postero-anterior chest radiograph often demonstrates the miliary pattern of small nodules, all the same size, throughout the pulmonary parenchyma. There may be other signs such as mediastinal lymphadenopathy or confluence of the nodules.

In children, there is always widespread dissemination of the granulomas in other organs. Evidence may be found in the retina or in the cerebrospinal fluid, even when there is no other sign of abnormality.

The presence of a significant tuberculin reaction is strong supportive evidence of the diagnosis, but in many cases the test shows no significant reaction.

The diagnosis rests on strong clinical suspicion and treatment must be commenced urgently, once other causes of childhood acute febrile miliary disease have been ruled out (such as viral illness or staphylococcal infection). If treatment is delayed, the prognosis may be badly affected, as many children have accompanying meningitis.

Practical point:

When a child presents with acute febrile illness with miliary X-ray images, treatment for tuberculosis should be given unless there is evidence of a viral or staphylococcal infection. This is particularly the case if the child has not been BCG-vaccinated and/or if there has been contact with a case of pulmonary tuberculosis.

Post-primary pulmonary tuberculosis

This type of tuberculosis, a delayed result of primary infection, usually occurs in adults but may appear in children (especially older children and adolescents), particularly in the presence of malnutrition.

The clinical picture is similar to that of pulmonary tuberculosis in the adult (see preceding section). Confirmation of the diagnosis of tuberculosis can be made in 50–80% of cases if smear and culture facilities are available. For older children capable of expectorating on effort, sputum samples should be collected as for adults; for all other children gastric aspiration may be performed.

If sputum smears are negative and cultures are not available, the investigation should proceed as in adults. The following represent supportive evidence:

- history of contact with a case of pulmonary tuberculosis.
- significant reaction to the tuberculin skin test
- absence of elevated white cell count in the blood
- absence of clinical and/or radiological improvement after treatment with a broad-spectrum antibiotic

Unlike the acute forms, where treatment must be given promptly, this type of tuberculosis does not represent an emergency, and the physician can take the time to exclude the other definitive diagnoses, particularly acute respiratory infections, before proceeding to treatment.

Extrapulmonary tuberculosis

Extrapulmonary tuberculosis is caused by haematogenous spread of bacilli following primary infection. In children, the most serious forms are disseminated (miliary) tuberculosis and tuberculous meningitis; the most common forms are tuberculosis of the lymph nodes, the bones and the serous membranes.

Tuberculous lymphadenitis is the most common form, accounting for up to 50% of extrapulmonary cases in children.

Tuberculosis of the spine or joints is the second most common form of childhood EPTB, and may occur within the first few years following primary infection.

Tuberculosis of the serous membranes: tuberculous pleurisy and peritonitis are rare in small children, although frequent in adolescents. Peritonitis with ascites is relatively more common, particularly in girls aged 10–14 years. Localized forms in the pelvis, or pelvioperitonitis, can cause sterility due to obstruction of the fallopian tubes.

Criteria for the diagnosis of childhood tuberculosis

CATEGORIES	SUPPORTIVE EVIDENCE	DIAGNOSTIC CONFIRMATION
Primary pulmonary tuberculosis	Mediastinal lymphadenopathy with or without infiltration TS-positive	Positive sputum culture (rare, only if there is fistulization of the lymphadenitis into the bronchi)
Post-primary pulmonary tuberculosis	Pulmonary infiltration affecting upper zones with cavities	AFB on smear and culture of sputa/gastric aspiration
Tuberculous meningitis	Meningeal syndrome, strabismus, sometimes miliary pattern and choroid tubercles Clear CSF: high protein levels and lymphocytosis	Positive CSF culture
Miliary tuberculosis	General deterioration Typical miliary image Signs of dissemination (choroid tubercles, meningitis)	Culture (pleural fluid, CSF, etc.) or biopsy of another lesion (liver, pleura, etc.)
Other tuberculosis	X-ray and clinical signs TST positive Cytochemical examination of effusions (high protein level and lymphocytosis)	Positive culture (of sero-fibrinous effusion or pus) Tissue biopsy (culture and histology)

Adapted from Ait-Khaled et al. Childhood tuberculosis, still with us. In: Chaulet P, ed. *Children in the Tropics*. Paris, International Children's Centre, 1992, 196–197:37.

Conclusion

Diagnosis of tuberculosis in children requires a rational analysis of a number of key elements, including clinical signs and symptoms that vary depending on the site of involvement, the existence of an index case, reaction to the tuberculin skin test, occasional isolation of bacilli or specific histological changes.

In most cases, tuberculosis in children is a mild disease and may heal on its own without treatment. There is, however, a substantial risk of developing of the disease returning in the future. In a minority of cases, children present with disseminated tuberculosis, which is often fatal or, if treatment is not applied rapidly, may leave devastating complications.

References

Aït-Khaled N et al. Childhood tuberculosis, still with us. In: Chaulet P, ed. Children in the tropics. Paris, International Children's Centre, 1992:196-197.

Crofton J, Horne N, Miller F. Clinical tuberculosis. London, Macmillan, 1992.

TUBERCULOSIS AND HIV INFECTION

HIV infection is the most powerful risk factor that increases the likelihood of development of tuberculosis in a person previously infected with *Mycobacterium tuberculosis*. HIV-associated tuberculosis is included in the current international AIDS definition. This is why the specific clinical aspects of tuberculosis should be recognized, particularly in populations with a high proportion of adults aged between 15 and 49 years with HIV and tuberculosis co-infection.

Diagnosis

The circumstances of diagnosis are variable: tuberculosis may occur in individuals infected with HIV, while at other times it may be diagnosed in individuals whose HIV status is unknown; it is thus frequently the sentinel event that indicates HIV infection.

The patient is known to be HIV-infected

The infection is known, either because the HIV test is known to be positive, or because certain clinical signs are present that are strongly indicative of the presence of AIDS:

- cachexia or loss of weight of more than 10 kg;
- chronic diarrhoea, with or without prolonged fever, of more than 1 month's duration;
- cough of over 1 month duration;
- generalized pruritic dermatitis;
- oral or oesophageal thrush causing pain on swallowing;
- chronic progressive or disseminated herpes simplex;
- a history of herpes zoster (shingles);
- generalized bilateral lymphadenopathy of more than 3 months' duration;
- burning sensations in the feet suggestive of peripheral neuropathy;
- severe neurological problems without known association with a condition other than AIDS.
- **Other signs characteristic of AIDS** such as Kaposi sarcoma or cryptococcal meningitis.

Cough for more than a month and recurrent pneumonia may be associated with other complications of HIV infection. Nevertheless, if a person presenting with AIDS-related signs or HIV seropositivity has persistent cough, investigations should systematically be made to check for the presence of tuberculosis.

❑ *Tuberculosis is the first sign of HIV infection*

Pulmonary or extrapulmonary tuberculosis can be the sentinel event that indicates HIV infection. In countries with a high prevalence, HIV may be suspected in the following situations:

- in individuals at risk (drug-dependent individuals, patients who have undergone unmonitored blood transfusion, individuals treated for sexually transmitted diseases);
- in patients **on anti-tuberculosis treatment who lose weight** or who develop clinical signs of AIDS.

Clinical aspects

The clinical features of tuberculosis are closely related to the level of immune deficiency of the HIV-infected patient. As the CD4 lymphocyte level drops, the appearance of tuberculosis changes from the typical, localized forms to the atypical, disseminated forms.

❑ *Pulmonary tuberculosis*

At an early stage of immune deficiency, when the number of CD4 lymphocytes is greater than $200/\text{mm}^3$, the clinical and radiographic features of pulmonary tuberculosis are similar to those in patients without HIV infection, with a predominance of smear-positive patients (75–85%). In countries with a high prevalence of tuberculosis, tuberculosis is often a very early complication of HIV infection and often occurs when the level of cellular immunity is relatively high. It thus has the same aspects as among HIV-negative individuals.

At an advanced stage of immune deficiency, when the number of CD4 lymphocytes is less than $200/\text{mm}^3$, other symptoms appear and pulmonary tuberculosis presents in atypical forms, such as interstitial or miliary tuberculosis without cavitation, associated with mediastinal lymphadenopathy and/or pleurisy.

MANIFESTATIONS	IMMUNE DEFICIENCY	
	EARLY STAGE ($>200\text{CD}_4/\text{MM}^3$)	ADVANCED STAGE ($<200\text{CD}_4/\text{MM}^3$)
Clinical	Pulmonary tuberculosis	Severe pulmonary tuberculosis
Radiological	Involvement of the upper lobes Cavities	Interstitial involvement, miliary disease, lymphadenopathy, pleurisy Absence of cavities
Bacteriological	Smears usually positive	Smears usually negative Negative TST

As recurrent pneumonia due to other pathogens frequently occurs in HIV-infected patients, it should be kept in mind that seropositive patients with respiratory symptoms and abnormalities on chest X-ray should not always be assumed to have tuberculosis, and that the diagnosis of pulmonary tuberculosis should be based on criteria as rigorous as those for seronegative patients.

□ *Extrapulmonary tuberculosis*

Extrapulmonary tuberculosis is more common in HIV-positive individuals, especially those at an advanced stage of immune deficiency:

- **Tuberculous lymphadenitis**

The tuberculous etiology of this disease should be clearly established, and should not be confused with AIDS-related persistent disseminated lymphadenitis.

- **Tuberculosis of the serous membranes**

All exudates (pleurisy, ascites, pericarditis) should be treated as tuberculous effusions when they occur in an HIV-positive individual.

- **Tuberculous meningitis**

When CSF meningitis with a clear CSF occurs in an HIV-positive patient, tuberculous meningitis should be suspected immediately, after exclusion of cryptococcal meningitis.

Course of tuberculosis

The course of tuberculosis under treatment in HIV-positive patients is similar to that observed in HIV-negative patients, if standardised short-course chemotherapy is applied. However, side-effects are more frequent. Thioacetazone should **never** be

given, because of the high risk of severe intolerance manifested by generalized skin toxicity.

The outcome of treatment is affected by a high fatality rate, due in most cases to AIDS-related complications.

Conclusions

Tuberculosis is a common complication of HIV infection. It can be the first sign of infection or it can occur in a subject known to be HIV-infected. Patients with HIV or AIDS who present with signs compatible with tuberculosis should undergo the same rigorous investigations as HIV-negative patients.

The standardized chemotherapy regimens used for treating tuberculosis are as effective among HIV-positive as among HIV-negative patients; however, the fatality rate is higher among HIV-positive patients because of AIDS-related complications.

References

De Cock KM et al. Tuberculosis and HIV infection in sub-Saharan Africa. Journal of the American Medical Association, 1992, 268:1581-1587.

Guidelines for the clinical management of HIV infection in adults. *Geneva, World Health Organization, 1991 (document WHO/GPA/AIDS/HCS/91.6).*

Harries A et al. Tuberculosis and HIV: a clinical manual. Geneva, World Health Organization, 1996 (document WHO/TB/96.200).

TREATMENT

The appropriate treatment of tuberculosis is chemotherapy consisting of a combination of several anti-tuberculosis drugs. The duration of treatment has decreased considerably since 1960: initially given for 24 months, it now lasts for 6–8 months and is known as “short-course chemotherapy”.

Key (first-line) anti-tuberculosis drugs

There are five key anti-tuberculosis drugs (Appendix 5)

- isoniazid
- rifampicin
- pyrazinamide
- streptomycin
- ethambutol

The use of any of these drugs as single preparations leads to the selection of naturally resistant strains that normally make up the bacterial populations. This is why several anti-tuberculosis drugs must be given together in order to achieve cure in a patient with tuberculosis.

Action of the various first-line anti-tuberculosis drugs

Anti-tuberculosis drugs act on different bacillary populations in a patient with tuberculosis:

Metabolically active bacilli that replicate constantly and rapidly. These populations are found principally inside lung cavities.

Slowly-replicating bacilli, situated inside the macrophages. Their multiplication is slowed down by the lack of oxygen and the acid pH of the macrophage cytoplasm.

Dormant or persistent bacilli, which replicate in the tissues **very slowly and episodically,** are metabolically inactive. However, they are still alive, and can start to multiply once again as soon as the immune defence system weakens.

The actions of the different drugs vary depending on their bactericidal or sterilizing effect on these various bacillary populations.

The two most effective bactericidal drugs are **isoniazid (H)** and **rifampicin (R)**, which act not only against the metabolically active bacteria that multiply constantly and rapidly, but also against the semi-dormant bacilli that multiply slowly in the macrophages. Another advantage of rifampicin is that it acts at a very early stage of bacillary multiplication.

Two other bactericidal anti-tuberculosis drugs of medium efficacy and complementary action are **pyrazinamide (Z)**, which destroys intracellular bacteria that live in an acid environment, and **streptomycin (S)**, which is active only against extracellular bacteria as it cannot penetrate the cell membrane.

Two other bacteriostatic antibiotics, which are much less effective, are **ethambutol (E)** and **thioacetazone (T)**. They are used in conjunction with powerful bactericidal drugs to prevent the emergence of resistant bacilli.

Other antibiotics of low efficacy are not used in short-course chemotherapy. These include ethionamide, kanamycin, capreomycin, the quinolones, cycloserine and *p*-amino salicylic acid (PAS).

The only medications that destroy persistent bacilli and have a **sterilizing action** are **rifampicin** and **pyrazinamide**. These medications are always used in short-course chemotherapy.

Practical point:

Short-course chemotherapy consists of the association of at least the three most active drugs: isoniazid, rifampicin and pyrazinamide.

Dosages of the key anti-tuberculosis drugs

The key anti-tuberculosis drugs recommended by the WHO and the IUATLD for short-course chemotherapy are presented in the table.

Dosages of the essential anti-tuberculosis drugs

KEY ANTI-TUBERCULOSIS DRUGS	RECOMMENDED DOSE, MG/KG (RANGE)			
	MODE OF ACTION	DAILY	INTERMITTENT	
			THREE TIMES WEEKLY	TWICE-WEEKLY ^a
Isoniazid (H)	Bactericidal	5 (4–6)	10 (8–12)	15 (13–17)
Rifampicin (R)	Bactericidal	10 (8–12)	10 (8–12)	10 (8–12)
Pyrazinamide (Z)	Bactericidal	25 (20–30)	35 (30–40)	50 (40–60)
Streptomycin (S)	Bactericidal	15 (12–18)	15 (12–18)	15 (12–18)
Ethambutol (E)	Bacteriostatic	15 (15–20)	30 (25–35)	45 (40–50)
Thioacetazone (T)	Bacteriostatic	2.5	N/A	N/A

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

^a WHO does not generally recommend twice-weekly treatment regimens, as the risk of failure is higher if a patient misses one of the two weekly appointments.

Choice of treatment regimen

The choice of a treatment regimen is based on its effectiveness and its ability to prevent the emergence of resistant strains.

□ Preventing the emergence of resistance

● Combining anti-tuberculosis drugs

The success of chemotherapy is limited by the selection of naturally occurring resistant bacteria that are present in all large populations (at least 10^6 to 10^8) of *Mycobacterium tuberculosis*. Such high numbers of bacilli are always found in cavitory pulmonary tuberculosis. If such a patient is treated with a single medication (monotherapy), the majority of the bacilli are killed, leaving the mutant bacteria that are resistant to that drug to multiply, thus causing the bacterial population to be dominated by the strain of bacilli that is resistant to the drug. This is how **acquired resistance** to a specific drug is caused. If further treatment is given to this patient by adding just one more medication to the one previously given (to which the bacteria are resistant), the mutant bacteria resistant to this second drug are further selected, to form a population resistant to both of the anti-tuberculosis drugs used. Acquired resistance is thus an immediate consequence of inadequate therapy, and resistance to multiple drugs results from a series of errors.

If a patient whose disease is caused by a strain that is resistant to a drug infects another person, the strain of bacilli in this new patient will have the same pattern of resistance even though the patient has never received the drug in question. If a patient carrying a strain that is resistant to several drugs infects another person, the strain of bacilli in this new patient will have the same pattern of resistance even though the patient has never received any of the drugs in question. This is termed **primary resistance**.

Practical point:

Treatment of tuberculosis is always based on multidrug chemotherapy, which is the only way of preventing the emergence of resistant bacteria.

● Using different regimens depending on the treatment history

In patients who have never been previously treated for as much as one month, the recommended treatment regimens for “new” patients should be capable of curing even the few who may have primary resistance to isoniazid and/or streptomycin. This is why the recommended short-course chemotherapy regimen contains a combination of four drugs during the initial phase: isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin). This treatment regimen has the advantage of massively reducing the bacillary population, thus making the survival of resistant bacilli highly unlikely.

In previously treated patients who need re-treatment, a higher proportion will have acquired resistance to several of the drugs; the recommended re-treatment regimen

therefore consists of five medications given concurrently during the initial phase of treatment and at least three during the continuation phase.

Patients with active TB after a re-treatment are chronic cases. A large proportion of them have strains resistant to several drugs including rifampicin and isoniazid (multidrug resistant cases).

If the patient presents for treatment with bacteria that are already resistant to both isoniazid and rifampicin (multidrug-resistance, MDR-TB), such bacteria are unlikely to be killed even by the recommended regimen for re-treatment. As noted previously, multidrug resistance is usually caused by careless use of anti-tuberculosis drugs for treatment of patients with the result that bacteria with resistance to these highly potent drugs are selected. That is why it is always recommended, when rifampicin is to be used for patients with a high bacterial population (smear-positive patients), that it should always be used together with a minimum of three other medications in the initial intensive phase; it is recommended to be used in a fixed-dose combination of proven bioavailability, and always administered under direct observation.

Patients who return with active pulmonary tuberculosis after re-treatment are known as **chronic patients**. A high proportion are likely to have bacteria that are resistant to several drugs, including at least isoniazid and rifampicin: these cases are known as having MDR-TB. Such patients are difficult to cure; treatment regimens combining other, less effective, drugs are given for up to 2 years.

Practical point:

Correct application of standardized treatment regimens for primary and re-treatment cases and very careful use of the key medications are the optimal method of preventing the emergence of multidrug-resistant pulmonary tuberculosis cases.

□ *Determining the treatment categories*

In order to establish treatment priorities, WHO recommends that tuberculosis patients should be classified into four categories:

Category I: consists mainly of new, smear-positive tuberculosis cases, but includes new smear-negative cases with extensive parenchymal lesions, and new cases with severe extrapulmonary tuberculosis (disseminated, meningeal, pericardial, peritoneal, bilateral pleural, spinal, intestinal and genito-urinary). A new case is defined as a patient who has never previously been treated for tuberculosis or who has received treatment for less than one month.

Category II: smear-positive cases who have already received treatment for at least one month in the past who need to receive re-treatment. Among these patients three groups can be distinguished:

“Relapses” — patients who have been treated and declared cured, but whose smear examinations are once again positive. “Failures” — patients whose smear examinations have remained positive or have once again become positive five or more months after starting treatment. “Return after interruption” — patients who return to the health centre smear-positive after interrupting treatment for more than two consecutive months.

Category III: new cases of smear-negative pulmonary or extrapulmonary tuberculosis (excluding those with severe forms, included in Category I) who have never previously been treated for as much as one month in the past.

Category IV: chronic cases defined as smear-positive cases of pulmonary tuberculosis who have already received a supervised re-treatment regimen.

□ *Choosing standardized treatment regimens by treatment category*

All of the recommended treatment regimens consist of an initial intensive phase, which rapidly reduces the bacterial population, and a continuation phase, which destroys those bacteria that remain.

For cases of pulmonary tuberculosis with large bacterial populations (smear-positive patients), the initial intensive phase consists of at least four drugs. The continuation phase is given for 4 months if the two most bactericidal drugs, isoniazid and rifampicin, are used, and for 6 months if isoniazid and a bacteriostatic drug are used.

The efficacy of the regimens recommended based on this information has been demonstrated by clinical trials, and their high cost-effectiveness has been demonstrated in national tuberculosis programmes in different countries.

Each National Tuberculosis Programme must choose the standardized treatment regimen, from among those recommended by WHO, that is best suited to the resources of the programme and the development of local health services, as well as the professional capacities of the health personnel at peripheral level.

Individualizing the choice of treatment regimen is not wise in the case of patients who have already received inadequate treatment for tuberculosis. The standardized regimen recommended for Category II patients is the best and safest treatment to give to those patients who have not already received it in its entirety and under direct supervision, regardless of what regimen they have received previously.

In the case of individual failures or relapses (smear-positive) occurring after supervised application of the standardized re-treatment regimen, it is possible in certain circumstances to prescribe a standardized third-line regimen: this involves a daily combination of three minor drugs that the patient has never taken (e.g. ethionamide, kanamycin or capreomycin and a quinolone) with supplemented pyrazinamide for at least 3 months until smear conversion, followed by two drugs (generally ethionamide and a quinolone) daily for 18 months. However, this kind

of regimen is not always available, due to its high cost. It is also very lengthy and has substantially more side-effects, thus necessitating individual management by an experienced specialist, and even then it is very difficult to obtain a success rate of even 70%.

Treatment schedules recommended by tuberculosis case or treatment category

TREATMENT CATEGORY	TUBERCULOSIS CASE	RECOMMENDED TREATMENT SCHEDULE	
		INITIAL PHASE	CONTINUATION PHASE
1	- New case of smear-positive PTB - Severe forms of smear-negative PTB - Severe extra-pulmonary tuberculosis	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE or 6 TH 4 HR 4 H ₃ R ₃
2	- Smear-positive pulmonary tuberculosis: relapse failure return after interruption	2 SHRZE/1 HRZE 2 SHRZE/1 HRZE	5 H ₃ R ₃ E ₃ 5 HRE
3	- Smear-negative PTB - Less severe extrapulmonary tuberculosis	2 HRZ 2 HRZ 2 HRZ	6 HE or 6 TH 4 HR 4 H ₃ R ₃
4	Smear-positive pulmonary tuberculosis after re-treatment	Combinations of second-line drugs reserved for used by the reference centres	

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

The medications are indicated by capital letters; numbers preceding the letters indicate the duration of treatment in months; numbers in subscript indicate the number of times per week the medications are given; when the letters are without subscripts, the medications are given daily; e.g. 2 EHRZ/4 H₃R₃: daily administration of ethambutol, isoniazid, rifampicin and pyrazinamide for 2 months, followed by isoniazid and rifampicin three times weekly for 4 months. T = thioacetazone.

Patient management

Management of a patient involves a number of actions on which the success of the treatment depends.

□ *Performing an assessment before starting treatment*

Before starting to treat a patient, a clinical assessment is necessary for the correct treatment regimen to be chosen. This involves the following steps:

- **Specify the type of tuberculosis**

A proper diagnosis includes an initial classification of the patient according to the site(s) and severity of the disease and any bacteriological test results.

- **Obtain information on any previous treatment**

The patient interview must focus carefully on information concerning previous tuberculosis treatment. If there is any doubt, the interview should be recommended; patients should be asked whether they received a treatment card from another health service. If the patient has already been treated, it is essential to identify what drugs have already been given: primary treatment (failure, relapse after cure, or return after interruption of treatment) or re-treatment.

- **Identify possible factors that might complicate the disease or the treatment**

- It is important to know whether female patients are pregnant or taking oral contraceptives.
- Any known concomitant illnesses need to be identified, particularly diabetes mellitus, chronic nephropathy, AIDS and epilepsy.
- Conditions unknown to the patient, such as diabetes mellitus, kidney failure and liver failure, should be investigated wherever there is an indication; in populations where there is a high prevalence of HIV, patients should be advised to undergo HIV testing wherever possible.

□ *Prescribing and monitoring chemotherapy*

- **Prescribing chemotherapy**

After clinical assessment, a **standardized treatment regimen** corresponding to the treatment category recommended by the National Tuberculosis Programme should be prescribed.

Rarely, the standardized regimen will need to be adapted, but this should be done according to the recommendations of the National Tuberculosis Programme:

Pregnant women: streptomycin must never be given to pregnant women because of the risk of ototoxicity in the fetus. All other anti-tuberculosis medications are safe to use during pregnancy.

Women who are breastfeeding: breastfeeding women should follow a complete course of chemotherapy even while breastfeeding their infants. The infants should receive isoniazid prophylaxis for 6 months, and should then be BCG-vaccinated.

Women on oral contraception: because of the interaction of rifampicin with oral contraceptive medications, there is a risk that the effect of the contraception will be impaired. The patient should be recommended a higher dosage (50 µg) or to use another form of contraception.

Chronic liver disease: PZA is contraindicated; recommended regimens are 2 SHRE/4 HR or 2 SHE/10 HE.

Renal failure: isoniazid, rifampicin and pyrazinamide are almost entirely eliminated by the bile or transformed into non-toxic compounds; they can therefore be prescribed at normal doses even in cases of severe renal failure — pyridoxine should nevertheless be prescribed to avoid peripheral neuropathy. Streptomycin and ethambutol are excreted by the kidneys and will need to be given at reduced doses (if these drugs are indispensable) as long as kidney function is monitored. Although thioacetazone is partially eliminated by the kidneys, it should not be prescribed, as its toxicity level is very close to the therapeutic level. The safest regimen in case of renal failure is 2 HRZ/4 RH.

Patients who are HIV-infected or who have AIDS: thioacetazone should **never** be used in any patient known to be HIV-infected. For those patients receiving antiretrovirals, particularly protease inhibitors (indonavir, saquinavir), it is better to interrupt these drugs until cure of tuberculosis, because of the risk of interaction with rifampicin.

- **Ensuring patient compliance**

Rifampicin was the last effective anti-tuberculosis drug to be discovered (in 1966), and everything possible must be done to avoid the emergence of resistance to this drug. It is therefore of the utmost importance that every dose of rifampicin should be given under the surveillance of health personnel who must ensure that the patient swallows all of the drugs prescribed. This is called “directly observed treatment” (DOT). Treatment must therefore be organized in consultation with the patient so that DOT can be guaranteed, on an out-patient basis if possible, and if not, in hospital during the initial phase.

Rifampicin should always be given in the form of fixed-dose combinations of proven bioavailability in order to minimize the risk of development of resistance.

Hospitalization is necessary only if the patient is severely ill or has complications (such as massive haemoptysis or pneumothorax).

Health education of the patients and their families is very important, and must be repeated every time patients come into contact with health staff, in order to encourage them to comply with treatment. In addition, patients should be encouraged to interact with one another, often facilitated by the daily visits to the health facility for DOT. This form of health education is by far the most effective, even more so than that given by health professionals.

- **Monitoring the efficacy of treatment with bacteriological examinations**

In the case of pulmonary tuberculosis, the efficacy of treatment is measured by examination of sputum smears performed at the following stages of treatment:

At the end of the initial phase sputum conversion is observed in most cases. If the patient is still smear-positive the initial phase should be prolonged by 1 month.

At the end of the 4th month for 6-month regimens, and at the end of the 5th month for 8-month regimens.

During the last month (at the 6th or 8th month, depending on the regimen).

These smear examinations confirm the success or failure of the treatment.

In the case of extrapulmonary tuberculosis, follow-up is essentially clinical. A specialized opinion is sometimes necessary.

- **Identifying and managing side-effects of anti-tuberculosis drugs**

The identification of side-effects is first of all clinical. Patients should be informed about any possible side-effects and encouraged to report any symptoms that seem unusual during treatment. They should be warned that their urine may take on a reddish or orange colour caused by the rifampicin and that this has no biological significance.

Anti-tuberculosis drugs are generally well tolerated. There are a number of minor side-effects that do not necessitate interruption of treatment but that should be identified and managed so that patients do not stop treatment of their own accord.

Major side-effects are rare, but treatment must be stopped as soon as they occur, either because they can be fatal or because they may lead to functional impairment.

Side-effects by symptom

SIDE-EFFECT	DRUG RESPONSIBLE	MANAGEMENT
Minor: - Pain in the joints - Burning sensations in the feet - Anorexia, nausea, abdominal pain	Pyrazinamide Isoniazid Rifampicin	Aspirin Pyridoxine 100 mg/day Take with food
Major: - Itching, skin reaction - Deafness or dizziness - Jaundice - Visual impairment - Purpura, shock, acute kidney failure	- Thioacetazone or streptomycin - Rifampicin or isoniazid Streptomycin Isoniazid, rifampicin, pyrazinamide Ethambutol Rifampicin	Stop and do not give again (replace by ethambutol) Stop, then reintroduce with desensitization Stop and do not give again (replace by ethambutol) Stop until the jaundice disappears Stop and do not give again Stop and do not give again

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

It is easy to identify a side-effect when it is specific: thus purpura (rifampicin), vestibular problems (streptomycin), or the appearance of a scotoma in the field of vision (ethambutol) can immediately incriminate the drug in question, so it can be stopped immediately and a replacement drug selected.

The problem is more complicated when a major side-effect occurs for which a number of drugs could be responsible, such as a skin reaction or jaundice (Appendix 6).

Practical point

Patients experiencing severe side-effects of medications should be referred to a physician experienced in the management of tuberculosis

❑ *Deciding on other treatment measures*

Apart from chemotherapy, which is necessary for treating all cases of tuberculosis, adjunctive therapy is indicated for certain sites.

- **Treatment with corticosteroids**

The addition of corticosteroids at a dose of 0.5 mg/kg per day for 3 to 6 weeks has been shown to have an impact in the following cases:

Tuberculous meningitis of moderate severity, in order to improve neurological outcome and reduce fatality;

Tuberculous pericarditis, in order to reduce the need for surgical intervention and reduce fatality.

In pulmonary tuberculosis, tuberculous pleurisy and primary tuberculosis with lymphadenopathy, while treatment with corticosteroids may have short-term effects on symptoms and signs, has no long-term benefits.

- **Surgical treatment**

Surgical treatment in patients with drug susceptible tuberculosis is virtually restricted to treatment of complications. Surgery has no role in primary treatment of tuberculosis.

- *Screening and management of contacts*

Those who live in the same household as a person with pulmonary tuberculosis should be examined for evidence of tuberculous infection and disease. In children aged less than 5 years, those who are apparently healthy should receive a 6-month course of daily isoniazid chemoprophylaxis at 5 mg/kg per day, whatever their BCG status. All individuals with respiratory or extrapulmonary symptoms indicative of tuberculosis should undergo diagnostic examination and, if shown to have tuberculosis, given treatment.

Conclusion

The success of tuberculosis treatment depends above all on the application of the standardised treatment regimens selected by the National Tuberculosis Programmes in accordance with the regimens recommended by WHO and IUATLD.

It also depends on appropriate management, particularly by ensuring patient compliance with treatment and direct observation of the ingestion of each dose, at least during the initial phase of treatment.

References

- Crofton J, Chaulet P, Maher D. Guidelines for the management of drug resistant tuberculosis. Geneva, World Health Organization, 1996 (document WHO/TB/96.210).*
- Crofton J, Horne N, Miller F. Clinical tuberculosis. London, Macmillan, 1992.*
- Enarson DA et al. Management of tuberculosis: a guide for low-income countries. 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.*
- Guidelines for surveillance of drug resistance in tuberculosis. Geneva, World Health Organization, 1994 (document WHO/TB/94.178).*
- Harries A et al. Tuberculosis and HIV: a clinical manual. Geneva, World Health Organization, 1996 (document WHO/TB/96.200).*
- Horne NW. Modern drug treatment of tuberculosis. 7th ed. London, Chest Heart and Stroke Association, 1990.*
- Maher D et al. Treatment of tuberculosis: guidelines for national programmes. 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).*
- Toman K. Tuberculosis case-finding and chemotherapy: questions and answers. Geneva, World Health Organization, 1979 [New edition in preparation].*

Appendix 5: Presentation of the essential anti-tuberculosis drugs

DRUG	FORM/DOSAGE	
Single preparations		
Isoniazid	Tablets	100 mg; 300 mg
Rifampicin	Capsules or tablets	150 mg; 300 mg
Pyrazinamide	Tablets	400 mg; 500 mg
Ethambutol	Tablets	100 mg; 400 mg
Streptomycin	Powder for injection	1 g streptomycin dissolved in 5 ml water
Fixed-dose combinations		
<ul style="list-style-type: none"> Daily use 		
Thioacetazone + isoniazid	Tablets	50 mg + 100 mg 150 mg + 300 mg
Ethambutol + isoniazid	Tablets	400 mg + 150 mg
Rifampicin + isoniazid	Tablets	150 mg + 75 mg 300 mg + 150 mg
Rifampicin + isoniazid + pyrazinamide	Tablets	150 mg + 75 mg + 400 mg
<ul style="list-style-type: none"> For intermittent use (3 times per week) 		
Rifampicin + isoniazid	Tablets	150 mg + 150 mg
Rifampicin + isoniazid + pyrazinamide	Tablets	150 mg + 150 mg + 500 mg

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Appendix 6: What to do in the case of jaundice or a skin reaction during treatment

What to do in the case of jaundice

If a diagnosis of drug-induced hepatitis is made after exclusion of other possible causes of jaundice, all medications should be stopped. Isoniazid, rifampicin and pyrazinamide are the most frequent causes. The two drugs that are the least toxic for the liver (streptomycin and ethambutol) should be given until the jaundice has disappeared. The usual treatment can then be cautiously recommenced, one drug at a time, with the incriminating drugs given at their lowest effective dose.

What to do in the case of skin reaction

Most anti-tuberculosis drugs can provoke an itchy allergic skin reaction, with or without rash. The following steps should be taken:

- exclude another cause: in particular, look for scabies;
- stop the treatment;
- look for the incriminating drug.

⇒ If the treatment contains thioacetazone:

Stop the drug immediately and never give it again. The itching may be the sign of a serious skin reaction. Immediate interruption of treatment could stop the skin reaction or reduce its gravity. The occurrence of a severe reaction is evidenced by exfoliative dermatitis or bullous epidermal necrolysis, involvement of the mucous membranes and hypotension. The prognosis is serious; treatment with corticosteroids is recommended (60 mg/day of prednisone or 100–200 mg/day of hydrocortisone if the patient cannot swallow).

If tuberculosis is not too far advanced, treatment should be stopped for 3–4 weeks until resolution of the skin reaction. The initial treatment regimen can then be recommenced, replacing the thioacetazone by ethambutol.

If the tuberculosis is very advanced and prolonged interruption of treatment might lead to the death of the patient, at least two anti-tuberculosis drugs can be reintroduced as soon as the skin reaction begins to improve. The full drug regimen (without thioacetazone) can be recommenced after the skin reaction is healed.

In HIV-positive patients, skin reactions to thioacetazone are more common and more severe. In countries where HIV is frequent, it is preferable not to use regimens containing thioacetazone. Thioacetazone should **never** be given again to a patient who has reacted to this drug or is known to be HIV-positive.

⇒ If the treatment does not contain thioacetazone:

Severe skin reactions are rare, and each of the drugs used can cause skin reactions.

In the case of mild itching, continue the treatment and administer antihistamines with the treatment. If the itching disappears continue the anti-tuberculosis treatment.

In case of skin reaction, treatment must be stopped until it disappears. Afterwards it is necessary to identify the responsible drug: for this purpose drugs are reintroduced one after the other, starting with those least likely to have produced the reaction. A method for reintroduction of the drugs is indicated below:

Reintroducing anti-tuberculosis drugs after side-effects

DRUG	CAUSE OF THE REACTION	CHALLENGE DOSES		
		DAY 1	DAY 2	DAY 3
Isoniazid	The least probable	50 mg	300 mg	300 mg
Rifampicin		75 mg	300 mg	Full dose
Pyrazinamide		250 mg	1 g	Full dose
Ethambutol		100 mg	500 mg	Full dose
Streptomycin	The most probable	125 mg	500 mg	Full dose

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Each drug is given at gradually increasing dosages over 3 days, from a weak dose to the full dose, so that when the incriminating drug is reintroduced the side-effect will occur as soon as the weak dose is administered but much less severely than with the full dose. As soon as a drug is well supported it is administered at full dosage and the next drug is reintroduced following the same procedure. If the drug responsible is pyrazinamide, ethambutol or streptomycin, a treatment regimen is reintroduced that replaces this drug with another if possible. In the rarer cases where rifampicin or isoniazid is the cause of the reaction, desensitizing is possible, except if the patient is HIV-positive due to the extreme toxicity.



PREVENTION

The best measure for primary prevention of tuberculosis is treatment of infectious cases. Primary prevention can be promoted through good public health practice to reduce the chances of infection in institutions by adequate ventilation and isolation of infectious patients. Prevention of disease in already infected persons (secondary prevention) involves two technical measures of unequal efficacy: BCG vaccination and prescription of chemoprophylaxis for groups at risk.

Main groups at risk

“Groups at risk” are population groups whose risk of contracting tuberculosis is 5–10 times higher than that of the general population, either because they have a greater risk of being infected, or because they have a greater likelihood of progressing to disease once infected.

□ *Groups most exposed to sources of infection*

- **The family circle of index cases**

Subjects living in contact with smear-positive cases have a risk that is directly proportional to their contact with the patient. The greatest risk is observed in individuals who live in the same household as a smear-positive pulmonary tuberculosis case.

- **Health institutions**

Immunosuppressed individuals hospitalized at the same time as untreated or drug-resistant tuberculosis patients, and health personnel working in tuberculosis services or in bacteriology laboratories where cultures are carried out, are more exposed to sources of infection than the general population.

□ *Groups with lowered immunity*

This group mainly consists of individuals who are HIV-positive or who have AIDS.

Other diseases (such as silicosis, lymphoma, diabetes) and immunosuppressive treatment, in particular among organ transplant patients, provoke a lowering of immunity that is much less significant.

Drug dependence and alcoholism favour reduction in defences.

□ *Underprivileged and marginalized groups*

Individuals in precarious situations, those who are homeless, those who live in poor areas of big cities and prisoners often experience overcrowded living conditions that increase the intensity of exposure to tubercle bacilli excreted when someone in the environment has tuberculosis. HIV infection may also be higher in underprivileged population groups.

❑ *Migrants and refugees from countries with a high prevalence of tuberculosis*

Migrants and refugees also constitute a group at risk of developing tuberculosis not only because they are often poor, but mainly because they usually come from countries with a high prevalence of tuberculosis, as the risk of developing tuberculosis is linked to the probability of having been infected by *Mycobacterium tuberculosis* before immigrating. Thus a high proportion of tuberculosis cases in industrialized countries (sometimes more than 50%) occurs in immigrants.

❑ *Individuals with extensive sequelae of untreated tuberculosis*

These individuals have a higher risk of recurrence of tuberculosis through reactivation of bacilli that have remained latent after their disease has become quiescent. This is principally the case if they have had inadequate or no treatment for their previous episode of tuberculosis.

Measures of prevention

❑ *Treatment of smear-positive pulmonary tuberculosis*

Detection and treatment of sources of infection are still the best methods of tuberculosis prevention. To improve this means of prevention, it is essential to improve access to health care for the population in general and for groups at risk in particular (improve equity). It is also important for health practitioners to maintain a high level of awareness of the possibility of tuberculosis.

❑ *Treatment of latent tuberculous infection (preventive chemotherapy)*

Treatment of latent tuberculous infection (preventive chemotherapy) prevents disease from appearing in infected individuals. It is targeted mainly at contacts aged less than 5 years living in the same household as a newly identified case of pulmonary tuberculosis. Depending on the situation, preventive chemotherapy may be extended to other groups at risk. The regimen consists of isoniazid given at doses of 5 mg/kg for 6 months.

❑ *Measures that reduce the risk of nosocomial infection*

Smear-positive cases are virtually no longer infectious 2 weeks after commencing treatment, provided that the bacteria they harbour are susceptible to the medications used for treatment. Where patients are multidrug-resistant, they have a high risk of infecting those around them and, where this is likely to occur, very careful precautions must be taken to isolate such patients from those at risk of becoming infected by contact with them.

Measures that can be applied to lower the risk of exposure in health institutions vary according to available resources. They should be based on the following principles:

- increasing the ventilation of rooms where tuberculosis patients are hospitalized and letting as much sun into them as possible;
- absolutely ensuring that no tuberculosis patients are admitted to the same wards where AIDS cases (or those suspected of having AIDS) are hospitalized;
- taking particular care to ensure that there is adequate ventilation in mycobacteriology laboratories undertaking culture of *Mycobacterium tuberculosis* and in areas where patients cough, such as the bronchoscopy suite. When sputum specimens are collected, it is best to ask the patient to produce the specimen in the open air.

□ BCG vaccination

BCG vaccine consists of live bovine tubercle bacilli whose virulence has been attenuated by multiple passages through glycerinated potato. The bacilli of the vaccine are therefore alive, but have lost some of their virulence. When these bacilli are injected into the body the development of protective immunity is stimulated, and the person's means of defence is increased without causing disease.

● Who should be vaccinated?

After BCG vaccination, when the bacilli penetrate the body, the heightened defences of the vaccinated person are able to destroy them earlier. BCG vaccination is used in an attempt to prevent the development of disease in persons who become infected with *Mycobacterium tuberculosis*, and in high prevalence countries, where children are exposed at a very early age to the risk of infection, it should be administered as soon as possible after birth, as part of the Expanded Programme on Immunization (EPI).

If a child is not vaccinated at birth, BCG should be administered as soon as possible. When a child has contact with the health services for any reason it is important to check that the vaccination has been given correctly, as stipulated in the EPI; if not, the child should be vaccinated as soon as possible. In many countries a certificate of vaccination is required on starting school, thus allowing any omissions to be identified at the age of 6 years through the school medical system.

● How is the vaccine prepared?

The vaccine is available in dry, lyophilized powder that is sensitive to heat (the cold chain should never be interrupted, and the vaccine must be kept in a refrigerator or freezer) and to light (the vaccines are delivered in coloured vials or with a black paper or aluminium sleeve, which should be placed around the vial during the vaccination session). The vial with the powder is accompanied by another vial containing a solvent that must be used cold (it should be refrigerated for at least 24 hours before use).

Once the solvent has been added to the powder, the mixture must be kept in the refrigerator and used within 3 or 4 hours. The vaccine is prepared using a 5-ml sterile syringe and a long, large-calibre needle.

- **How do you vaccinate?**

To administer the vaccine, a 1-ml syringe and an intradermal needle are required. The vaccination is performed as follows:

- the skin must be disinfected on the front of the left upper arm or any other part of the arm (it is useful to use the same vaccination site in each country so that it is easy to detect the vaccination scar);
- the required dose is drawn into the syringe (0.05 ml for newborns and children aged up to one year, 0.1 ml for children aged over one year);
- the injection *must* be given intradermally (if the needle goes beyond the dermis, the needle should be withdrawn and inserted at an adjacent spot); if the injection is done subcutaneously local complications can occur; injection of the dose should raise a wheal, and the skin takes on an “orange peel” aspect;
- after injection, the arm should be wiped and left open to the air for several minutes.

- **Can BCG be given with other vaccines?**

BCG is the first vaccination on the EPI schedule, which should be followed in each country. If, by chance, it is not given according to schedule, it can be given later, at the same time as another vaccination. It is possible to give several vaccines at the same time, but at different sites, as each vaccination retains the same efficacy with the same results as if they were given separately. WHO has made the following recommendations:

At birth, on the same day as the BCG vaccination is given, the newborn should be given a dose of oral polio vaccine;

After 2 months, the first vaccination against diphtheria, pertussis and tetanus and poliomyelitis can be given at the same time as BCG;

After 9 months, BCG vaccination can be given at the same time as the measles vaccine.

- **How does the vaccination site develop?**

The weal from the vaccination disappears within half an hour. After 3 or 4 weeks, a small red induration appears, which swells to 6–8 mm in diameter and can persist for one or two months; it may ulcerate and ooze serous fluid. This stops after 2 to 8 weeks, a scab forms and later a scar develops which is round, lightly depressed, and approximately half a centimetre in diameter. The child’s parents and the health personnel should be informed that this process of scar formation is normal, and that the vaccination site should not be cleaned with any product.

- **What are the possible complications?**

It is unusual for complications to occur if the vaccination is given correctly. In about one in 1000 children lymphadenopathy may develop in the axilla or inside

the elbow, which may become fluctuant and fistulize. Treatment consists of an incision to drain the node, and application of dry dressings until scarring. It will heal within several days or weeks.

Occasionally, particularly during a mass vaccination campaign, an unusually high number of local complications is reported and can take on the aspect of an “epidemic”. This may have happened due to various factors:

Errors made by a new member of the health staff who has not been adequately trained, and who makes injections that are too deep, who gives newborns 0.1 ml instead of 0.05 ml, or who prepares the vaccine incorrectly before injection (insufficient volume of solvent, solution insufficiently well mixed).

Vaccines that contain an excessive amount of live bacilli: this was the case with certain vaccines commercialized in the 1980s.

- **Who should not be given BCG?**

Infants who have congenital or acquired immune deficiency should not be given BCG as they may develop severe complications such as osteitis or disseminated BCG (this occurs in less than one case in a million, and is usually associated with immune deficiency).

If the infant has AIDS, BCG is contraindicated; however, infants who are HIV-seropositive should be BCG-vaccinated, as the risk of tuberculosis in such infants is greater than the risk of complications from the vaccine. Infants born to HIV-positive mothers should also be vaccinated, unless they present symptoms of AIDS.

- **How do you determine that the vaccine has been correctly given?**

If the child has a typical vaccination scar, it can be assumed that the vaccination has been given. It is not necessary to check each child for successful vaccination. Verification of whether BCG vaccination has been performed correctly can be done by a tuberculin survey: if a tuberculin skin test is performed, around 90% of children will show a significant induration in the year following vaccination.

- **What quality and duration of protection is conferred by BCG?**

There has been a great deal of discussion about the efficacy of BCG vaccination ever since its first use. Controlled trials with different methodologies have shown different levels of protection (from 20% to 60%). It is now agreed that BCG gives protection against the acute forms of tuberculosis in childhood: disseminated disease and tuberculous meningitis.

Practical point:

In countries with a high prevalence of tuberculosis, all newborns should be given BCG vaccination as part of the Expanded Programme on Immunization (EPI).

BCG vaccination does not protect children from *Mycobacterium tuberculosis* infection, but from its immediate consequences. The main effect of BCG is to prevent the dissemination of the bacilli after infection. It therefore prevents the occurrence of acute disseminated forms of tuberculosis that are often fatal. BCG has little impact on reducing the number of adult infectious cases in the population.

The protective effect of BCG lasts for 10 to 15 years, but revaccination has no proven benefit. To reduce the number of infectious cases, it is much more important to give adequate treatment to all patients who constitute sources of infection, i.e. cases of smear-positive tuberculosis.

Studies on the efficacy of BCG

DATE AND PLACE OF THE STUDY	AGE OF THE POPULATION	VACCINE USED	RESULTS
Israel 1956–1979	0–12 years	Glaxo	Efficacy by age and sex 24% for pulmonary tuberculosis 64% for extrapulmonary tuberculosis
Boksburg Hospital, South Africa 1972–1976	0–4 years	Tokyo	Efficacy > 60% for all forms; 100% for tuberculous meningitis
Manitoba, Canada 1979–1983	0–14 years	Connaught	Efficacy > 60% for all forms 73% for bacteriologically confirmed cases
Rangoon Hospital, Myanmar (Burma) 1982	0–4 years	Tokyo half-dose	Efficacy 38% for all forms; 52% for tuberculous meningitis; 80% for disseminated forms
Lomé, Togo	0–6 years	Glaxo	Efficacy 61.5%. Higher for severe forms and in children aged under 6 years

Source: Milstein JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety.

Bulletin of the World Health Organization, 1990, 68:93–108.

Conclusion

Among the various methods of preventing tuberculosis, the most effective is the identification and effective treatment of patients with infectious pulmonary tuberculosis.

It is important to pay careful attention to adequate ventilation in institutions where tuberculosis patients may be encountered, in order to prevent infection of those in contact with tuberculosis patients. Isolation of infectious tuberculosis patients (especially where there is an increased possibility that the patient may have multidrug-resistant tuberculosis) is important to prevent infection.

Treatment of latent tuberculous infection has limited, individual indications, and applies above all to children aged under 5 years living in close contact with a source of infection. It should be extended to other groups only if compliance and surveillance can be ensured.

BCG vaccination is of proven efficacy in protecting small children against severe, acute forms of tuberculosis. Vaccination policies vary according to the epidemiology of each country.

References

Ait-Khaled N et al. Childhood tuberculosis, still with us. In: Chaulet P, ed. Children in the tropics. Paris, International Children's Centre, 1992:192-197.

International Union Against Tuberculosis and Lung Disease. Criteria for the discontinuation of vaccination programmes using BCG in countries with a low prevalence of tuberculosis. Tubercle and Lung Disease, 1994, 75:79-80.

Milstien JB. Module 5: Tuberculosis. Geneva, World Health Organization, 1993 (document WHO/EPI/GEN/93.15; The Immunological Basis for Immunization Series).

Ten Dam HG. BCG vaccination. In: Reichman LB, Hershfield ES, eds. Tuberculosis: a comprehensive international approach. New York, Marcel Dekker, 1993:251-274.



CHAPTER 3

TUBERCULOSIS AS IT AFFECTS THE COMMUNITY

EPIDEMIOLOGY OF TUBERCULOSIS

The extent of tuberculosis and its evolution over time defines its epidemiology. Epidemiology provides the basis for public health practice needed to control the disease. Various epidemiological indices are employed that differ in complexity.

Mortality

The number of deaths caused by the disease has traditionally defined the extent of the tuberculosis epidemic. **Mortality is expressed as the number of tuberculosis deaths per unit of population (usually 100000) and per unit of time (usually per year).** However, this information is not reliably collected in most countries where tuberculosis is common.

According to WHO's estimations, more than 1.9 million deaths due to tuberculosis occurred worldwide in 1997 (Table 1): more than 1 million in South-East Asia, fewer than 42000 in industrialised countries, with the other cases distributed in the other regions of the world.

Tuberculosis is the cause of an estimated 2.8% of deaths in the world in all age groups — and 26% of avoidable deaths in developing countries.

Practical point:

Tuberculosis kills more young people and adults than any other infectious disease; someone dies of tuberculosis every 10 seconds.

Morbidity

Tuberculosis morbidity is expressed by two main indices: prevalence and incidence.

□ *Disease prevalence*

The prevalence of a disease is **the number of cases of disease present in the community at any given point in time per unit of population (usually 100000).**

Prevalence can be determined only by surveys conducted on representative samples of the general population. These surveys are costly and difficult, but have been conducted in certain countries to monitor the epidemiological trend of tuberculosis.

*Table 1: Epidemiological variables and parameters of tuberculosis***Variables or indicators:**

- **Mortality rate:** the number of deaths due to tuberculosis per 100 000 population per year
- **Morbidity rate:**
 - Prevalence: the number of cases at a given moment per 100 000 population
 - Annual incidence: the number of new cases in one year per 100 000 population
- **Infection**
 - Prevalence: the percentage of the population infected at a given moment
 - Annual incidence or ARI: the percentage of the population newly infected in one year

Parameters (defined by surveys conducted before the HIV epidemic) that link the variables in the absence of treatment, during the natural course of the disease.

- **a smear-positive case remains infectious for an average of 2 years** (in the absence of treatment, during the natural course of the disease, the prevalence is estimated to be twice the incidence)
- **in one year, 25% of untreated cases die — this is the case-fatality rate:** the annual number of deaths is four times lower than the prevalence and two times lower than the incidence

All of these parameters are affected by the application of National Tuberculosis Programmes, and especially chemotherapy.

The impact of the HIV epidemic

- All of the parameters are affected by the HIV epidemic
- **The risk of developing tuberculosis is 10 times higher in an HIV-positive individual** than in a seronegative individual living in the same conditions
- **The case-fatality rate is higher for HIV-positive tuberculosis patients** than for HIV-negative patients

□ *Disease incidence*

Incidence is expressed by **the number of cases of a disease newly occurring over a specific period of time (usually one year) per unit of population (usually 100 000)**.

An estimation of incidence is obtained from notifications of new cases. The estimation is inexact because not all cases that occur during the year are diagnosed, and those that are diagnosed are not always notified. The incidence of tuberculosis cannot be accurately estimated by notification of cases; in general estimations of incidence based on notified cases is lower than the real incidence, as only 30–60% of cases are notified in many countries.

The number of new cases notified (i.e. all cases of tuberculosis put on treatment for tuberculosis) is expressed per 100 000 population, according to the estimated population for the year in question. The notified cases are usually specified by type (i.e. pulmonary tuberculosis, smear-positive or smear-negative, extrapulmonary).

The incidence of tuberculosis can also be predicted from estimates of the incidence of tuberculous infection. This is reliable only in regions that do not have a high incidence of HIV.

WHO estimated that there were 7.96 million new cases worldwide in 1997, more than half of which were infectious (Table 2). The majority of cases (95%) were thought to occur in the poorest countries.

Practical point:

95% of individuals with tuberculosis live in the poorest countries: because of the poor health coverage of the population, only a proportion of these patients are detected and treated.

● **In countries with high income**

These countries have an average income of US\$ 6000 per person per year. The average annual incidence of tuberculosis in industrialized countries is 30 per 100 000 population, ranging from 5 to 50 per 100 000. The majority of these countries have an incidence of less than 20 per 100 000 per year. Until the 1980s, tuberculosis rates were gradually declining in these countries. The first, so-called “natural”, decline occurred coincident with a rise in living standards of the population before the chemotherapy era; it then accelerated with the discovery of specific anti-tuberculosis drugs and approached levels that were close to the elimination of tuberculosis in some countries that had implemented effective control programmes. The reversal of this declining trend was noted as early as 1979 in big cities in the USA, with the greatest increases recorded in New York City. This increase mainly involved individuals aged under 45, African-Americans, Hispanics and immigrants from Asia and the Pacific. The overall increase in the USA was halted in 1993.

This increase in notification rate in the USA was accompanied by an increase in mortality, particularly in those aged 20–49 years, in states with large urban

populations where there were a high proportion of both HIV-infected and poor or homeless individuals. This phenomenon was also observed in a number of European countries, particularly in the big cities.

This increase in tuberculosis notification rate was associated with the dismantling of general health services — including tuberculosis control services — for poor people, with migration of populations from countries with a high tuberculosis burden and, to a lesser extent, with the appearance of HIV infection.

Practical point:

The recent increase in tuberculosis in high-income countries is due principally to the dismantling of tuberculosis control services and to migration of people from countries with a high tuberculosis burden, to social exclusion of disadvantaged groups, and, to a lesser extent, to the emergence of the HIV epidemic.

- **In countries with low and intermediate income**

Low-income countries have under US\$ 600 income per person per year; intermediate countries have an income between US\$ 600 and US\$ 6000 per year. Tuberculosis incidence cannot be based only on the incidence of notified cases, which in general is lower than real incidence because only 30–60% of TB cases are diagnosed and reported.

According to WHO estimates, in 1997 (Table 2) nearly 3 million cases occurred in South-East Asia, i.e. more than 40% of all global cases.

Table 2: Estimation of the number of cases and deaths due to tuberculosis in 1997

REGIONS	TUBERCULOSIS INCIDENCE		MORTALITY	
	CASES OF TUBERCULOSIS	RATE ^a	DEATHS	RATE ^a
South-East Asia	2 948 000	202	705 000	48
Africa	1 586 000	259	540 000	88
Eastern Mediterranean	615 000	129	141 000	30
Western Pacific	1 962 000	120	355 000	22
America ^b	411 000	52	66 000	8
Europe	440 000	51	64 000	7
Total	7 962 000	136	1 871 000	32

Source: Dye C et al. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. *Journal of the American Medical Association*, 1999, 282:677–686.

^a Incidence and mortality rates per 100 000 population.

^b Including USA and Canada.

In each region the rate of new cases of tuberculosis differs from one country to another, depending not only on the density and geographical distribution of the population, but also on the quality and extent of the National Tuberculosis Programme.

The highest estimated annual incidence of new cases is in Africa (259/100 000), closely followed by South-East Asia (202/100 000); the lowest incidence in the group of low income countries is in the Americas (without Canada and USA, 79 per 100 000). The lowest incidence of new cases of tuberculosis among the WHO regions is in Europe, with 51 cases per 100 000.

□ *Age distribution of tuberculosis*

- **In countries with a high population growth**

Tuberculosis affects mainly young, economically active adults, and thus has huge economic, social and familial repercussions. Furthermore this age group, which also corresponds to a period of sexual activity, is most exposed to the risk of HIV infection, which explains the increase in the number of tuberculosis cases in certain high TB prevalence countries heavily affected by the HIV epidemic.

Practical point:

In the poorest countries, demographic growth, rapid urbanization, the absence or recent creation of as yet ineffective National Tuberculosis Programmes, and the emergence of the HIV epidemic, are reasons for the increases in the incidence of tuberculosis.

- **In countries with a low population growth**

The age groups that are the most affected by tuberculosis are adults aged over 55 years, as infection by the tubercle bacillus in these countries was more common when these individuals were young. The greater risk of having been infected by the tubercle bacillus in their youth emerges as disease many years later. Young adults in these communities are much less exposed to the risk of infection and have little disease.

In these countries tuberculosis is a much rarer manifestation of HIV infection than in countries with a high prevalence of tuberculosis, as young HIV-positive adults are rarely co-infected with tuberculosis and the number of sources of tuberculosis infection in the community is much lower.

□ *Sex distribution*

While females often predominate among tuberculosis cases in those under 20 years of age, there is a predominance of males among all notified tuberculosis cases and among those dying from tuberculosis in most countries. Among women, tuberculosis kills more women than any cause of maternal mortality.

Tuberculous infection

Individuals who have been infected at any time with the tubercle bacillus carry the infection throughout their life time, even though they show no signs or symptoms of the disease.

□ *Prevalence of infection*

In 1997, WHO estimated that more than 1.9 billion people were infected by the tubercle bacillus, i.e. approximately one-third of the world's population. The proportion of infected subjects in the population, all ages combined, varies by country. This rate is highest, among WHO regions, in the Western Pacific (44% of the population), and lowest in the Eastern Mediterranean (19%). Of all individuals infected world wide, 25% are in South-East Asia, 22% in China, 22% in Europe, North America, Japan, Australia and New Zealand, 10% in Africa, 10% in the Western Pacific, 7% in Latin America and 3% in the Eastern Mediterranean.

However, it is the age distribution of the population infected by tuberculosis that is the most important factor: **the impact of the HIV epidemic and the likelihood of developing active tuberculosis among those already infected are higher in younger infected populations.**

□ *Incidence of infection*

● **Annual risk of infection (ARI)**

The ARI is the **proportion of individuals over the course of one year who are newly infected by the tubercle bacillus.** The ARI can be estimated from the results of tuberculin surveys conducted in a representative sample of non-BCG-vaccinated schoolchildren.

By comparing the results of two tuberculin surveys performed several years apart, in the same region and applying the same methodology, the evolution of the risk of infection (and therefore the trend in tuberculosis) can be measured when the reference population is stable.

● **Rate and evolution of the ARI**

From a rate of 5–10% in wealthy countries in the 1920s and 1930s, the ARI began to decrease by 4–5% per year before the introduction of specific anti-tuberculosis drugs (this was a natural decrease, probably due to improved living standards), and then from 14–18% per year due to the effectiveness of anti-tuberculosis treatment and the quality of the National Tuberculosis Programmes.

However, an estimation of the ARI in developing countries performed for the years 1985–1990 (Table 3) shows that the ARI has remained relatively high in these countries, particularly in certain areas of Africa or Asia, where it was over 2%.

Using the ARI, three groups of countries can be distinguished:

- countries with low tuberculosis prevalence: ARI <0.2%
- countries with moderate tuberculosis prevalence: ARI 0.2%–1%
- countries with high tuberculosis prevalence: ARI >1%

Practical point:

By calculating the ARI, the burden of tuberculosis can be estimated and its evolution over time can be followed.

Impact of HIV infection

□ *Dual HIV and tuberculosis infection*

According to estimations made in 1997 by UNAIDS, 15.3 million people are co-infected by HIV and tuberculosis: 11.7 million of these are in sub-Saharan Africa. The magnitude of HIV infection in sub-Saharan African countries can be estimated by the prevalence of HIV infection in tuberculosis patients, which ranges from 20% to 67% depending on the country.

Table 3: Estimation of the annual risk of tuberculosis infection and its trend in developing countries

REGION	ESTIMATION OF THE ANNUAL RISK OF INFECTION (%)	ESTIMATION OF THE ANNUAL DROP IN RISK (%)
Sub-Saharan Africa	1.5–2.5	1–2
North Africa and Eastern Mediterranean	0.5–1.5	5–6
South America	0.5–1.5	2–5
Central America and the Caribbean	0.5–1.5	1–3
South–East Asia and Western Pacific	1–2.25	1–3

Source: Murray CJ, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1990, 65:6–26.

□ *Impact on morbidity*

Individuals with HIV and tuberculosis co-infection have a much greater risk of developing active tuberculosis disease than the general population.

In countries with high tuberculosis prevalence, tuberculosis is an early manifestation of HIV infection and presents in the majority of cases as smear-positive pulmonary tuberculosis. Extra pulmonary tuberculosis, particularly tuberculosis pleurisy, lymphadenitis and pericardial tuberculosis, is more common in HIV-positive individuals.

Studies conducted in the Democratic Republic of the Congo (ex-Zaire) and Rwanda have shown that the annual risk of developing active tuberculosis disease for co-infected patients is on average 10% (between 5% and 15%).

In countries with high numbers of co-infected patients, there has been an increase in the overall number of tuberculosis cases because HIV infection occurs in the age groups in which the majority of individuals already have tuberculous infection.

In countries with low tuberculosis prevalence, tuberculosis is not the principal opportunistic infection observed, as HIV infection occurs in population groups that have not previously been infected by the tubercle bacillus.

□ *Impact on mortality*

Tuberculosis that occurs in AIDS- and HIV-positive patients can be cured using the treatment regimens prescribed for all tuberculosis patients. However, the proportion of patients who die while on treatment is higher, but this is often due to conditions unrelated to tuberculosis.

Estimation of the burden of tuberculosis in 2000

In 1999 the WHO published an estimation of the size of the problem that would be posed by tuberculosis in 2000. If efforts were not made to improve and expand tuberculosis control programmes, in 2000 more than 8.2 million cases were expected to occur world wide, of whom 10% or more would be attributable to the HIV epidemic; 2 million deaths due to tuberculosis were foreseen for 2000. Estimations of the geographic distribution of the incidence of tuberculosis and TB/HIV infection are given in Appendices 1 and 2. Sub-Saharan Africa and South-East Asia were expected to be most affected by this increase in cases.

Conclusion

In order to reverse these trends it is of utmost importance to implement and/or reinforce National Tuberculosis Programmes for many years to come.

As early as 1986, the IUATLD demonstrated that correct application of *short-course chemotherapy*, along with a recording and reporting system for the diagnosis and follow-up of the patients treated, could result in cure rates of as much as 80% in National Tuberculosis Programmes.

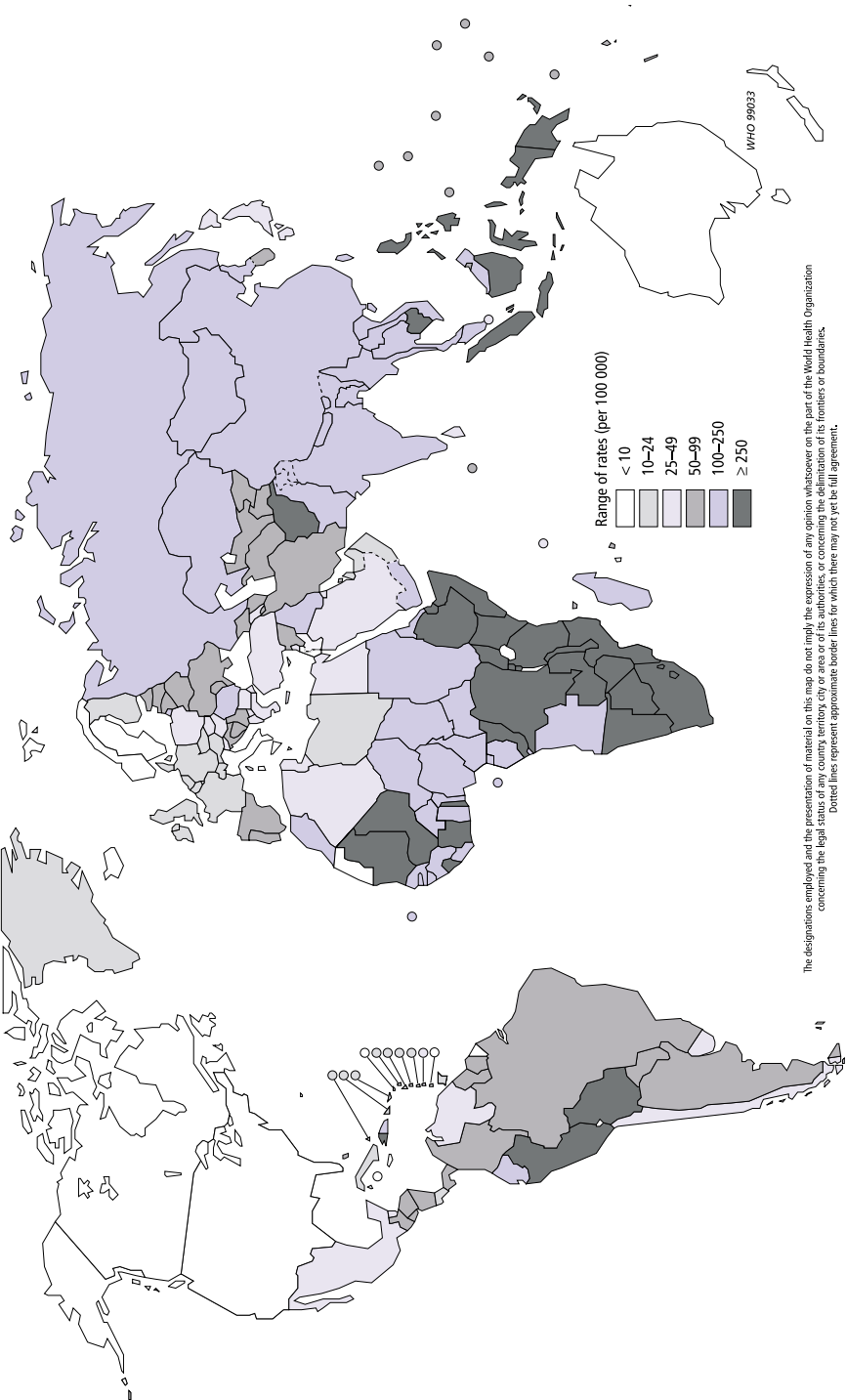
This is why the strategy currently recommended by the WHO and the IUATLD is the application of modern National Tuberculosis Programmes founded on the detection and cure of infectious cases using standardised short-course chemotherapy in which the ingestion of the medications is directly observed, at least during the initial phase of treatment.

References

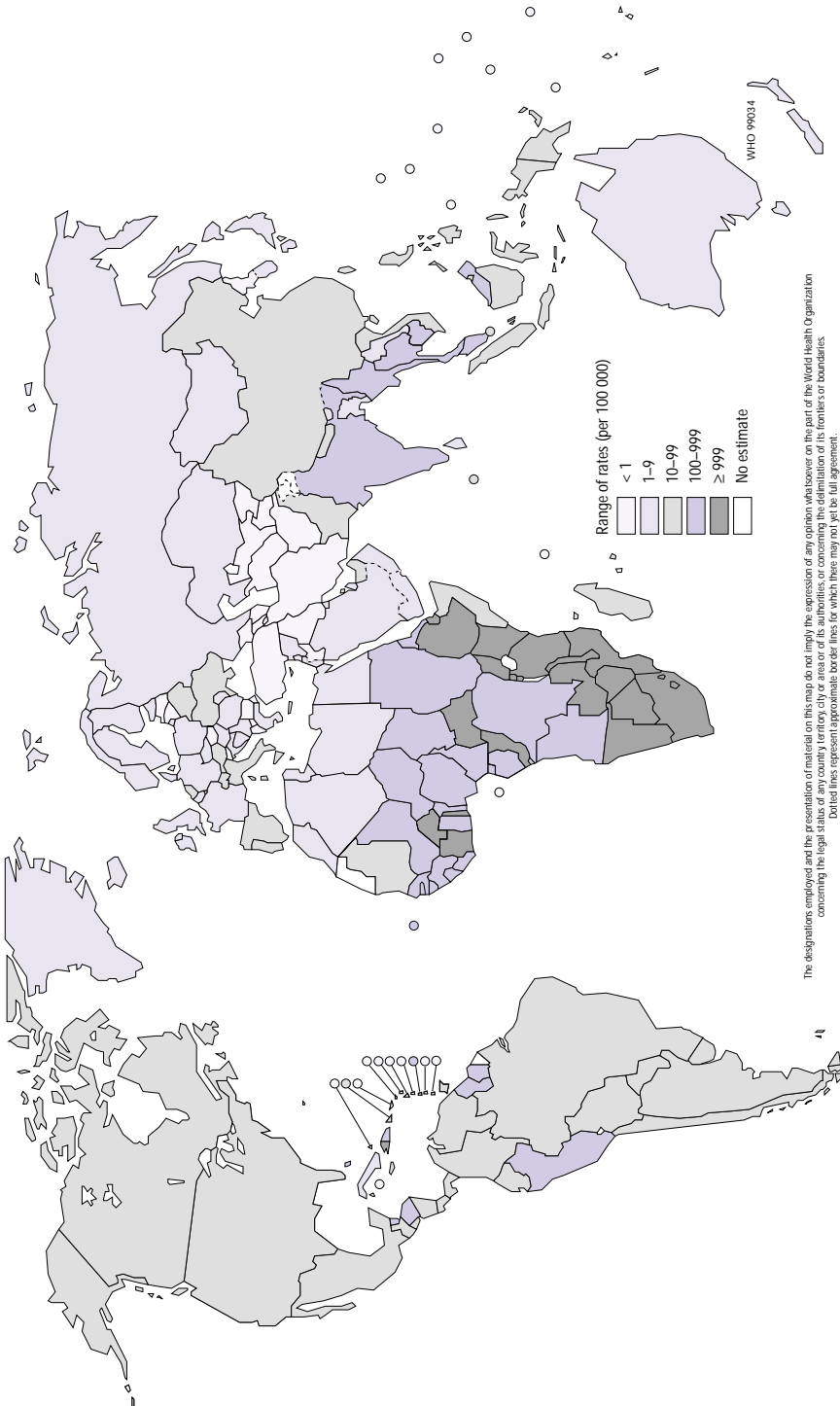
- Dye C et al. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. *Journal of the American Medical Association*, 1999; 282:677-686.
- Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. *Bulletin of the World Health Organization*, 1994; 72:213-220.
- Framework for effective tuberculosis control*. Geneva, World Health Organization, 1994 (document WHO/TB/94.179).
- Grzybowski S. The natural history of tuberculosis. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1991, 66:209-211.
- Murray CJ, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1990, 65:6-26.
- Raviglione MC et al. Tuberculosis and HIV: current status in Africa. *AIDS*, 1997, 11 (Suppl B): S115-S123.
- Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *Journal of the American Medical Association*, 1995, 273: 220-226.
- Riley RL. Transmission and environmental control of tuberculosis. In: Reichman LB, Hershfield ES, eds. *Tuberculosis: a comprehensive international approach*. New York, Marcel Dekker, 1993:123-138.
- Styblo K, Sutherland I. Epidemiological indices for planning, surveillance and evaluation of tuberculosis programmes. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1974, 49:49-55.

Appendix 1: Estimation of the rate of incidence of tuberculosis worldwide in 1997 (WHO report 1999, p 157)

1. Estimated TB incidence rates, 1997



Appendix 2: Estimation of the rate of TB/HIV co-infection in 1997
(WHO report 1999, p 158)





NATIONAL TUBERCULOSIS PROGRAMME PRINCIPLES

The overall objective of global tuberculosis control is to reduce deaths due to the disease, to lower the occurrence of the disease itself, and finally to drastically reduce the transmission of infection. To achieve this objective, WHO has:

- adopted a new strategy for tuberculosis control;
- defined specific objectives for tuberculosis control;
- announced a series of measures to be implemented by those countries wishing to put in place an efficient tuberculosis programme.

What is the new WHO strategy?

The strategy is based on **one absolute priority**: to ensure that all sputum smear-positive tuberculosis patients complete a full course of standardized short-course treatment with direct observation of treatment during at least the initial phase. This gives the greatest certainty of cure of infectious patients and is the most likely intervention to prevent transmission of the bacillus. The cure of smear-positive cases is currently the best available means of preventing tuberculosis.

BCG vaccination has virtually no impact on the transmission of tuberculosis, as its preventive effect on the infectious forms of tuberculosis is limited. Nevertheless, as it is effective in preventing serious and life-threatening forms of tuberculosis in infants and young children, BCG vaccination continues to be recommended in countries where tuberculosis is common. BCG vaccination is applied as part of the Expanded Programme on Immunization.

Practical point:

The global strategy for tuberculosis control prioritizes the detection of smear-positive cases and appropriate and effective treatment using short-course chemotherapy, which should be directly observed at least during the initial phase.

What are the specific objectives of tuberculosis control?

At a global level, the specific objectives established by WHO are:

- **To cure 85% of smear-positive cases diagnosed**
- **To diagnose at least 70% of cases in the community**

These objectives highlight the priority given to curing cases that are the most potent sources of transmission. In a National Tuberculosis Programme (NTP), this main objective should be reached before expanding case-finding.

Expansion of case-finding before good treatment results are achieved will have disastrous consequences: the number of chronic infectious cases will increase, and if

standardized treatment is not strictly applied the number of resistant cases will also increase.

On the other hand, obtaining a high cure rate is proof that the programme is functioning effectively. Improvements in case-finding will thus occur naturally in the programme as the coverage of health services to the population grows and the population is drawn to a health service that is capable of curing its patients.

Practical point:

Curing patients is the best method of gradually enhancing case-finding and of preventing transmission of infection.

What are the components of effective tuberculosis control?

Because the specific objectives and priorities are clearly established, a programme can only be implemented if the means necessary for its application are permanently available throughout the country and if its evaluation is guaranteed. The success of a programme depends on five public health principles:

❑ *Political commitment by the government*

This is reflected by an explicit statement of tuberculosis as a priority within the health services of the country and a designated budget directed to its control.

This must be guaranteed by concrete measures, i.e. allocation of **sufficient long-term financial resources** for the programme to be extended to cover the whole of the territory. For the programme to be implemented throughout the country:

- tuberculosis control must constitute **a permanent activity of the health system** and should be integrated into the existing health infrastructure;
- the technical direction of the programme should be entrusted to a central unit composed of **a permanent team dedicated to the management of tuberculosis control.**

This team has a number of responsibilities:

- to develop, launch, supervise and evaluate the essential activities of the NTP.
- to maintain communication with tuberculosis specialists locally and internationally in order to keep up to date with the tuberculosis situation, and to ensure that education about the NTP is given in universities and nursing schools.

❑ *Diagnosis and monitoring based on bacteriology with a system of quality assurance*

Tuberculosis case-finding is undertaken mainly by examining sputum samples from individuals who present to the health services with symptoms suggestive of

tuberculosis. The sputum smear examination confirms the diagnosis of the majority of cases of pulmonary tuberculosis, who are the main sources of infection. The results of sputum smear examination guides treatment and monitors its progress.

Effective primary health services and a quality controlled network of microscopy laboratories are the two conditions for the success of case-finding in the community.

❑ *Treatment using short-course chemotherapy*

The following technical measures will cure the majority of patients diagnosed:

- Patients should be treated with standardized **short-course chemotherapy** including rifampicin at least during the initial phase, with treatment managed in such a way as to ensure cure. Short-course chemotherapy must be given to at least all those with confirmed smear-positive tuberculosis.
- The chemotherapy regimens should be **standardized, and according to the treatment history of the patient**, so as to prevent the emergence of resistant strains. Primary treatment regimens are selected on the basis of each country's resources from the regimens recommended by WHO and IUATLD for new cases; patients previously treated for tuberculosis for as long as one month should always receive the 8-month re-treatment regimen.
- Specific procedures should be rigorously respected in order to ensure the **protection of rifampicin and compliance with treatment**: treatment should be directly observed by the health personnel at all times that rifampicin is administered, and patient management should be organized in such a way as to prevent defaulting from treatment.
- Other measures, in the form of regulations aimed at protecting rifampicin, are the responsibility of the health authorities: use of rifampicin in fixed-dose combinations of proven bioavailability, use of at least three other medications in association with rifampicin during the initial intensive phase of treatment of smear-positive patients, prohibition of sales of rifampicin on the private market and of its use for treating other conditions.

❑ *Uninterrupted supplies of drugs*

Anti-tuberculosis drugs should be included in the **list of essential drugs used in the country**, and drug ordering must be the direct responsibility of the head of the NTP.

- Drug ordering should be based on **the number of cases recorded during previous calendar periods, ensuring that there is always a "buffer" stock available to ensure that there is no interruption of supplies**. A 3-month reserve stock should be maintained at basic and intermediate levels, and a 6-month stock at central level.
- Planning for drug ordering must be done in such a way as to **avoid running out of stock**, as delivery can take a minimum of 6 months.

□ *Regular evaluation of the programme's activities using a permanent recording and reporting system*

The recording and reporting system should make it possible to obtain appropriate and precise information on the activities of the programme. This is of fundamental importance for managing the programme and evaluating the different activities, so as to be able to maintain or improve their quality. It consists of the following:

- **A notification register of all tuberculosis cases** put on treatment in the basic management unit, in which all patient characteristics and their outcome up to the end of treatment are recorded.
- **Quarterly reports** on the notification of cases and on the outcome of patient cohorts after treatment for each management unit within the country, which are sent to the central level.

Public health activities (including those for tuberculosis control) can remain efficient and appropriate only if there is continuous evaluation based on routine outcome-based reporting of the activities of the programme.

How to implement a programme

The success of a programme depends on the implementation of a number of activities:

- Preparation of a **programme manual** which sets out the technical and operational measures of the programme, including the case definitions and precise instructions for the diagnosis and treatment of patients.
- Preparation of a **programme development plan** consisting of budget details, sources of funding and the different areas of responsibility. This plan is finalized after a preliminary study has been conducted in a pilot area, and includes both long-term (5-year) and short-term (annual) components.
- **Creation of a reference laboratory** responsible for organizing a laboratory network, training microscopists and implementing quality assurance of diagnostic procedures.
- Development of a **laboratory network** of technicians trained in tuberculosis diagnosis. The network must cover the whole country and should comprise, on average, one multipurpose laboratory capable of performing tuberculosis microscopy for each population unit of, on average, 100 000 inhabitants in rural areas and 300 000 in urban areas.
- Creation, within the existing health structures, of **services that can identify tuberculosis suspects, directly observe treatment of diagnosed cases and educate patients and their families.**
- Implementation of a **training plan** for the different health personnel involved in patient management: doctors, nurses in charge of treatment supervision, and microscopists.
- Implementation of a **plan for supportive visits (supervision)** of NTP activities from the inception of the programme, at intermediate level and at basic

management level. These supervisory visits are an integral part of the training plan.

How to structure the services

The tuberculosis control activities must be integrated into the country's general health services, with prioritization of tasks according to the level of intervention in the health structure.

□ *The peripheral level: the basic management unit (district)*

- **The health organization of the basic management unit**

The basic unit of management of tuberculosis control is determined by the population served (a population of 100 000 on average). The anti-tuberculosis activities should be integrated into the other health activities of the district. They are part of the “minimum package of health activities” applied at this level.

Practical point:

The basic management unit (district) is the geographical, demographic, administrative and technical entity that enables the health authorities to organize and sustain primary health care and anti-tuberculosis activities.

The district covers a population of on average 50 000 to 150 000, and has one hospital and several health units out-patient clinics, dispensaries, health centres, and health posts.

At the district level the principal anti-tuberculosis activities performed on a permanent basis are targeted at identifying tuberculosis patients, particularly the sources of infection, and providing treatment. The application of BCG vaccination is organized by the teams responsible for the Expanded Programme on Immunization.

The activities of the NTP are carried out by personnel at every level of the health service. Their activities are coordinated and monitored by personnel within the basic management units whose task it is to ensure that patients are correctly diagnosed and receive proper treatment.

Practical point:

The main condition for the implementation of an NTP at district level is the existence of a “basic management unit” responsible for coordinating the tuberculosis control activities within the health services in the geographical area. It is managed by the “district tuberculosis coordinator”.

- **The basic management unit**

The basic management unit is situated in such a way that it can serve as a reference for all of the health institutions serving the population unit.

It is generally located in the main urban centre (in the hospital or in a referral centre).

- **Organization of the basic management unit**

The key elements of the basic management unit are:

- **a designated unit coordinator** who is trained and empowered to ensure the quality of diagnosis and treatment of all patients within all health services within the geographical area served by the unit.
- **a microscopy laboratory** with staff who are trained and monitored. **The laboratory register** kept at this level contains information on all of the examinations requested and their results.
- **a system to record essential information of all patients in the area:** individual patient files, the tuberculosis register, quarterly reports on case notification, patient outcome and drug ordering.

The quarterly reports are based on the tuberculosis register.

Practical point:

The information systematically collected and evaluated at the basic management unit empowers the personnel to effectively implement tuberculosis control activities, provides transparency in accounting for resources consumed and enables the personnel to ensure political commitment to tuberculosis control.

The different tasks of the staff of the tuberculosis control centre should be defined:

- **The role of the microscopist** is to examine the sputum samples of tuberculosis suspects, to report these results to the staff caring for the patient and to the unit coordinator and to ensure that samples of the examinations are reviewed to assure their quality.
- **The role of the unit coordinator (often a nurse)** is to oversee and organize the ongoing application of the national guidelines on case-finding and treatment. This person **is responsible for the supervision of the staff who provide directly observed treatment.** The coordinator also takes responsibility for planning activities, drug ordering and regular activity reports.
- **The role of the physician (or medical assistant)**, is to review all cases in which the diagnosis presents a challenge (especially smear negative and extrapulmonary cases), advise on the management of complications and adverse events and support the coordinator in discussions with other health services personnel.

- **The other institutions in the health service**

The health staff of all health service institutions participate in the tuberculosis control activities, particularly in case-finding:

- **At the community level**, serving a population of around 1000, the community health worker encourages people with long-term respiratory symptoms to present to the closest out-patient clinic.
- **At the village level**, covering a population of around 5000, the nurse identifies tuberculosis suspects who need to be sent to a health centre.
- **At the first level health centre**, covering a population of around 25 000, a physician, medical assistant or nurse (depending on the health services) manages patients and prescribes treatment. **This person will be more effective in tuberculosis control if he or she can respond appropriately to patients presenting symptoms of common respiratory conditions**, such as acute respiratory infection, asthma and chronic bronchitis. Pulmonary tuberculosis suspects can thus be identified at the most peripheral level of the health services, and care of tuberculosis patients and the management of contacts can be carried out in collaboration with the unit coordinator.

Practical point:

Tuberculosis control activities occupy only part of the working hours of any health worker: they can therefore be integrated naturally into the activities of the basic health services.

□ *The intermediate level*

The intermediate level is a geographical entity that covers 8 to 10 basic units. The clinician responsible for tuberculosis control at the intermediate level is the point of reference for the basic management units. The regional hospital can generally perform X-rays, microscopy and sometimes culture.

The clinician responsible for the NTP at intermediate level has a number of responsibilities:

- Coordination and supervision of the tuberculosis control activities of the basic management units, liaison with the central level, evaluation at intermediate level, training or retraining of health staff in coordination with the central level.
- Development of an intermediate level laboratory which must be able to provide training and quality control for the microscopists within the region as soon as possible, in coordination with the reference laboratory.
- Coordination with the other national programmes, particularly those dealing with leprosy, acute respiratory infection and AIDS.

□ *The central level*

At the central level, a number of structures are involved in the programme:

- **The central unit**, which is attached to the Ministry of Health, is directed by the manager of the programme and plans the activities and budget of the programme at the national level. It is responsible for ensuring the delivery of

supplies of medications and laboratory reagents to the basic management units, receiving and collating their quarterly reports, coordinating the tuberculosis control activities, training and supervision, and evaluating the programme's activities at national level. It provides the basic management units with technical support, and carries out operational research with the aim of enhancing the programme's performance.

- **The national reference laboratory** organizes the training, supervision and **quality control** of all of the microscopists working in the NTP, and ensures the ongoing reliability of the microscopy network, starting with quality control of the regional laboratories. The national reference laboratory must be able to perform cultures for diagnosis and susceptibility testing for epidemiological surveillance as soon as possible after it is established.
- **The university hospitals** see patients referred by the intermediate level. The specialists who practise here help to develop and apply the technical guidelines of the NTP and participate in the tasks of training and supervising health personnel.

Conclusion

Tuberculosis control must be integrated into the country's health system, in accordance with the technical guidelines defined by the central unit of the National Tuberculosis Programme.

The main activities of the programme (case-finding and treatment of patients) should be standardized and published in the NTP manual. The programme must be evaluated and supervised on a regular basis, and should have national coverage; it should always adhere to the basic principles of tuberculosis control.

The encouraging results in high prevalence countries that have implemented such programmes in the past 10 years are proof of their relevance.

References

Enarson DA et al. *Management of tuberculosis: a guide for low income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

Framework for effective tuberculosis control. Geneva, World Health Organization, 1994 (document WHO/TB/94.179).

Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Managing tuberculosis at district level: a training course. Geneva, World Health Organization, 1994.

Tuberculosis as an integral part of primary health care. Geneva, World Health Organization, 1988.

ORGANIZATION OF TREATMENT

The basic management unit, generally located in the main urban centre of the district, is responsible for organizing the treatment of all of the tuberculosis patients in the area. Organization of patient treatment requires the application of adapted organizational measures so as to ensure that treatment is directly observed at least during the initial phase and that patients comply with their treatment until cure.

□ *How to choose the place of treatment*

Tuberculosis can be cured only if the drugs are taken regularly. The choice of the place of treatment depends on two factors: the **state of the patient**, and the ability of the health staff to **provide treatment to patients**.

During the initial phase of treatment

During the initial phase of treatment, which always contains rifampicin, the patient must take the drugs in front of the health worker who is responsible for verifying that the patient **swallows all of the prescribed drugs every day**.

- If the patient lives, or can be housed, near a basic management unit, he or she can attend every morning to take the drugs.
- If the patient lives near a health post with staff who are trained and acknowledged to be capable by the district coordinator, treatment can be entrusted to this health post, but the follow-up of the patient must continue to be done by the basic management unit and systematic and regular visits must be made to the health post by the unit coordinator.
- If directly observed treatment can not be provided on an out-patient basis, or if the state of the patient requires it, the patient should be hospitalized during the whole of the initial phase of treatment.

Nevertheless, the application of outpatient-based directly observed treatment is not always easy:

- **In urban areas**, especially in big cities, there are often too few health care institutions, or they are poorly distributed and are not always able to provide correct patient management. These difficulties are further enhanced in some countries by the HIV epidemic and the rapid increase in the numbers of patients needing to be cared for by each centre.
- **In rural areas** the distances that patients need to travel in order to reach a basic management unit are sometimes too long or difficult (remote areas, bad weather, lack of transport or transport too costly for the patient).

Patients for whom directly observed treatment cannot be provided on an outpatient basis must be hospitalized throughout the initial phase of treatment. Hospitalization is a costly way of providing treatment, and alternative local solutions have already been identified in many countries: short-term renting of a room in the city, or accommodation in a shelter created for this purpose.

Systematic hospitalization of patients during the initial phase of treatment is neither possible (due to the lack of hospital beds), nor reasonable (it does not improve the chances of cure, nor does it reduce the risks of infection). It is furthermore extremely costly, not only for the health centres but also for the patients and their families.

During the continuation phase:

When the continuation phase of the treatment regimen does not contain rifampicin, in the majority of cases treatment is “self-administered”: a supply of drugs in fixed-dose combinations is given to the patient at regular intervals, and the patient is given the responsibility to take the drugs correctly every day. The interval between visits for drug supply is variable, and is set jointly by the health worker and the patient, depending on the ease of access to the health centre (usually monthly).

For tuberculosis patients who are in a precarious situation (homeless) and those who are drug users, alcoholics or who have behavioural problems, the organization of follow-up must aim at reducing the lack of compliance common in these population groups: for example, a fully supervised intermittent treatment can be selected if it is thought that the patient will comply with it more easily, and health staff should try to make themselves more available to these patients than others in case of problems, in order to identify solutions with the patients.

Practical point:

In order to avoid the emergence of strains that are resistant to both to isoniazid and rifampicin, all rifampicin-containing treatment should be taken under the direct observation of a health worker.

□ *Indications for hospitalization for medical reasons*

In the majority of cases it is unnecessary to hospitalize tuberculosis patients, either to achieve cure, or to avoid infecting the patient’s family. Only a few days after beginning adequate treatment tuberculosis patients are no longer infectious, provided that their bacilli are susceptible to the major medications used in their treatment; if members of their families are infected they will have been infected before the patient began treatment.

This is why tuberculosis patients need to be hospitalized only in the following situations:

- Severe deterioration of the patient’s general state, making outpatient treatment difficult or impossible;
- Tuberculosis-related complications: massive haemoptysis, pneumothorax;
- Complications associated with treatment: major side-effects such as jaundice, purpura or severe allergic skin reaction;

- Severe concomitant disease necessitating hospital care and specific surveillance, such as unstable or complicated diabetes, kidney failure, or stomach ulcer.

The period of hospitalization varies depending on the cause; it often lasts less than 2 weeks, and the patient can be discharged as soon as the reasons for hospitalization have resolved.

How to improve treatment compliance

Organizational measures are aimed at providing management of patients until cure. The two main obstacles that need to be overcome are the length of treatment (several months) and the constraints related to directly observed treatment.

In order to improve compliance, it is necessary to:

□ *Enhance patients' access to the health services*

The treatment centre (different from management unit, which is administrative) responsible for treatment and surveillance is usually located in the main centre of population. The population covered varies between 50 000 and 150 000.

In cases where there are transport problems that prevent patients from attending the treatment centre regularly, other health institutions that can provide directly observed treatment are identified by the coordinator.

Patients are registered by the treatment unit, then entrusted to the health facility closest to their homes for their drug intake to be directly observed. The patients (or their sputum samples, if a system of sputum transport is organized) are sent to the control centre at previously defined stages of their treatment for bacteriological tests, and at the end of treatment in order for cure to be confirmed and the patient's final status to be correctly recorded by the basic management unit. Where this is done, the unit coordinator must regularly visit the treatment centres.

□ *Improve the organization of the treatment centres*

The centres should be open not only every day, but also all day, including during lunch breaks, which will allow patients who work to attend for treatment. The choice of opening hours should be made according to the hours that best suit the patients, and the patients' appointments should be planned in such a way as to reduce unnecessary waiting.

□ *Communicate with the patient*

Health education is an ongoing process that allows health staff and other patients to inform patients about their illness and its treatment, and to respond to any questions that might be asked by patients and their families. It should aid in creating an immediate rapport with the patient. The first interview with the patient is often the key to how treatment progresses. Following this first contact, every encounter with the health staff should be seen as an opportunity to strengthen

communication and to improve the health education of the patients and their families.

● **What is the most important information?**

- * Pulmonary tuberculosis is a serious disease that can nevertheless be completely cured when treatment is taken correctly.
- * The treatment must be taken for at least 2 months in the presence of a health worker. The patient should not see this obligation as a punishment but as a necessity in order to ensure correct treatment, as well as an opportunity for daily contact with the health personnel in order to ask questions or resolve any problems that may occur.
- * Pulmonary tuberculosis is infectious before it is treated, but it is no longer so after the second week of treatment if the drugs have been taken correctly by the patient.
- * Treatment efficacy is monitored during appointments, by clinical examination and above all by bacteriological examinations in the case of pulmonary tuberculosis.
- * Children aged under 5 years living in the same household as a patient with pulmonary tuberculosis must be brought to the control centre to receive preventive therapy or treatment if they have tuberculosis.
- * The other members of the household should present to the nearest health facility or the tuberculosis control centre for examination.

It is nevertheless difficult for the patient to assimilate all of the information during the first interview: this is why all of the health personnel, and particularly the treatment supervisor, must be trained to give the information repeatedly and to respond to the questions that the patient will inevitably ask. Moreover, it is valuable to encourage interaction among patients as they visit the health facility, as this type of communication is often much more effective than contact with the health personnel alone.

● **What are the most common questions asked by patients or their families?**

The questions are most often about infection, but they are expressed in different ways:

- * Can the patient eat with his or her family as before?
- * Can the patient continue to live normally with his or her spouse?
- * Can the patient continue to work?

All responses should be clear: the patient can live normally in the community as long as treatment is strictly adhered to. These responses also aid in encouraging not only the patients, but also their families, to continue to take their treatment regularly and to attend follow-up appointments until cure.

A strong personal bond between the health staff and their patients, and also their families, is thus created and reinforced over time. This relationship will aid in identifying the problems of patients who default and in together finding a solution

which will enable them to continue to take their treatment regularly: e.g. changes in intervals between drug delivery, transfer of a patient to another treatment centre that is closer to the patient's workplace, or temporarily to another centre during a holiday.

This health education should also aid in enhancing the image of tuberculosis, which is still heavily stigmatized in some communities.

□ *Organize treatment follow-up*

Whatever regimen is given and wherever it is given, treatment must be monitored during follow-up visits.

- **Schedule regular appointments**

These dates are scheduled from the beginning of treatment. During these appointments bacteriological tests are performed for all pulmonary tuberculosis patients: at the end of the initial phase, at the 5th or 6th month, and during the last month of treatment. At the same time patients also undergo a clinical evaluation to check for any side-effects, compliance with treatment, reasons for non-compliance among defaulting patients and reinforcement of health education.

- **See the patients when they request a consultation**

If a problem occurs, the patient should be seen by a physician: the problem can be resolved if it is medical (side-effects, concomitant disease, a complication of the disease), but it can also be social (preventing the patient from attending the health centre regularly), and every effort should be made to resolve the problem.

- **Trace any patients who default**

Regular attendance should be strictly monitored and patient follow-up must be organized:

- * **During the initial phase**, patients should be contacted immediately if they miss their daily appointment for directly observed treatment.
- * **During the continuation phase** as soon as a patient has missed a scheduled visit.

The methods of tracing patients differ from one centre or one country to the next: it can be done by letter, telephone, home visits, or even visits by a neighbour being treated at the same centre. All available means need to be put into action when a patient misses a scheduled visit. The longer the absence, the less likelihood there is of finding the patient.

When the patient is found, treatment is based on the duration of treatment already received and the patient's bacteriological status on returning to the centre. It is essential to try and uncover the reasons why the patient has defaulted so as to be able to remedy the problem and prevent it from happening again.

Practical point:

Most reasons for defaulting from treatment are related to the inability of health workers to identify the difficulties experienced by the patient in following the treatment regimen regularly and to resolve the problem appropriately.

How to evaluate patient management

The evaluation of patient treatment is an activity that is essential to the organization of treatment. It serves as the basis for ordering drug supplies, and the results of treatment allow any problems that occur in patient management to be identified. Once these problems are identified, ways of improving the organization of patient treatment can be found.

The recording and reporting system

- **The treatment card (Appendix 3)**

All of the elements necessary for managing the patient are recorded on this card:

Personal information: age, sex, family status

Patient number

Patient's full address and address of a contact person, so as to be able to trace the patient if there are problems of compliance.

Type of disease (pulmonary or extrapulmonary)

Type of case: new, failure, relapse, transfer, return after default

Treatment regimen prescribed

Follow-up (appointment dates, weight, bacteriological tests)

Drug administration schedule: this should be updated daily by the health workers during the initial phase by ticking the correct box at each directly observed ingestion of drugs, and at each appointment when the treatment is self-administered.

Every morning, before the clinic opens, the treatment supervisor should prepare the patient cards for all of the patients who have appointments scheduled for that day. At the end of the day it is therefore very easy to check all those who have missed their appointments and to contact them the next day if they have still not turned up.

- **The Tuberculosis Register (Appendix 4)**

This is the cornerstone of the NTPs information system. Every tuberculosis patient put on treatment in the unit is recorded with an individual number. Information

concerning the patient — civil status, initial condition and treatment prescribed — is recorded on the day the patient is put on treatment. The results of the follow-up bacteriological examinations during the course of treatment as well as the treatment outcome are also recorded. For pulmonary tuberculosis patients who have completed treatment, the outcome of treatment is established by periodic smear examinations. Treatment outcome should be recorded as one of the six following categories:

Cured: at least two negative examinations (one after the end of the initial intensive phase of treatment and another during the last month of treatment).

Treatment completed: the patient has received a full course of treatment but has not undergone the necessary bacteriological examinations.

Failure: still positive, or positive once again after the 5th month of treatment.

Died: whatever the cause of death.

Transferred out: the patient has been transferred to another health centre while on treatment but the final outcome of the treatment is not known at the centre where the patient was registered. Where the final outcome is known, this should be recorded, rather than “transferred out”.

Defaulted: the patient has not turned up to collect drugs for more than 2 months since the last visit.

● Reports

These enable the staff at the health centre to evaluate their own activities. The reports should be sent to the intermediate and central levels for the NTP to be evaluated on a national level. All reports should be compiled at the level of the basic management unit and this should always be the “unit of reporting” for all official statistics.

The quarterly report on tuberculosis case-finding

This is based on the information recorded in the register. It provides information on the exact number of tuberculosis patients put on treatment by the health centre each quarter and the quality of the diagnosis (the number of cases of smear-negative pulmonary tuberculosis).

The quarterly report on the results of treatment for pulmonary tuberculosis cases

This is also based on the information recorded in the register, and provides the treatment results of the cohort of patients put on treatment during the quarter ending 15 months previously. This allows sufficient time for the patient to have completed treatment and for all information to be collected (for example, on patients transferred out for treatment). Any patient who has not completed treatment by this time or for whom information is unknown should be recorded as “defaulted”.

A (quarterly) patient cohort is defined by the series of all tuberculosis patients consecutively recorded in the tuberculosis register during a specified quarter. Reports are completed separately for those groups with the same initial disease status (new cases of smear-positive pulmonary tuberculosis, relapses, failures, etc) and who are receiving the same treatment regimen.

- **Quarterly ordering of treatment supplies**

Drug orders are based on the quarterly report on case-finding from the previous quarter.

- *What training is useful for health staff?*

Staff employed in the health centres should receive training on at least the following:

- **Current scientific knowledge** about tuberculosis, the treatment regimens used by the NTP, and the side-effects of the drugs used.
- **Training in communication**, so that they can provide patient education and optimise compliance with treatment. This aspect of training is extremely important, as it can change the health worker's attitude toward the patient.
- **Training in keeping the tuberculosis registers up to date.**

The manager of the health centre should ensure that all of the tasks related to patient management are performed satisfactorily by the health staff (Table 4), as well as carrying out other specific duties (Table 5).

Table 4: Principal tasks of the health personnel in organizing the treatment of a tuberculosis patient

1. Select the regimen according to the patient's diagnostic category
2. Calculate the doses according to the patient's weight
3. Use fixed-dose combinations whenever possible
4. Organize directly observed treatment at least during the initial phase
5. Provide a patient card and update it each time drugs are given
6. Record the case in the tuberculosis register
7. Communicate with the patient and provide health education
8. Organize patient follow-up
9. For pulmonary tuberculosis patients, organize follow-up bacteriological tests
10. Record the results of bacteriological tests in the register
11. Trace patients who miss appointments
12. Record the patient's outcome in the register at the end of treatment

Table 5: Specific tasks of the unit coordinator in the treatment of tuberculosis patients

1. Prepare the quarterly reports at the end of each quarter
2. Prepare the drug order forms
3. Ensure that each member of the health staff applies the guidelines of the National Tuberculosis Programme
4. Train and supervise the personnel responsible for treatment of tuberculosis patients

Conclusion

The organization of tuberculosis treatment is the key to a programme's success. The uninterrupted availability of drugs and rigorous organization of treatment delivery will ensure patients' compliance with treatment. Through the regular updating of the tuberculosis register the activities of the district tuberculosis centre can be evaluated regularly, and any improvements can be made.

References

Enarson DA et al. *Management of tuberculosis: a guide for low income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

Framework for effective tuberculosis control. Geneva, World Health Organization, 1994 (document WHO/TB/94.179).

Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Managing tuberculosis at district level: a training course. Geneva, World Health Organization, 1994.

Appendix 3: Treatment card

Enarson DA et al. Management of tuberculosis: a guide for low-income countries, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

TUBERCULOSIS PROGRAMME

TUBERCULOSIS TREATMENT CARD

District TB No. _____

Name: _____
 Address: _____
 Treatment centre _____ Age _____ Sex (check one): M [] F []
 Date _____

Disease site (check one):

Pulmonary [] Extrapulmonary [] Site (specify) _____

Category of patient (check one):

New [] Treatment after failure []
 Relapse [] Treatment after default []
 Transfer in [] Other [] (specify) _____

I. INITIAL INTENSIVE PHASE

Prescribed regimen and number of tablets:

STH		RHZE		SRHZE
{T}	S	{RH}	Z E	{RH} S Z E

{T}=thioacetazone/isoniazid; S=streptomycin; {RH}=rifampicin/isoniazid; E=ethambutol; Z=pyrazinamide

Month	Date / Lab no.	Smear result	Weight (kg)	Date of next appointment
0				
2				
5				
7				
>7				

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
Month																															

Enter X on day when medications were swallowed under direct observation.

(Please turn over)

II. CONTINUATION PHASE

regimen and number of tablets:

new cases (daily)

(2S(T_H)/10(T_H)-10 months;
2(R_H)/E/6(T_H)-6 months)

Day Month	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																		
	Re-treatment 3 times a week (5 months)																	{RH}	E	H																													

Enter X on day of supervised administration or when medications are collected. Draw a horizontal line through the days to indicate number of days' supply given.

Remarks:

Appendix 4: Tuberculosis register

Enarson DA et al. Management of tuberculosis: a guide for low-income countries, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

TUBERCULOSIS PROGRAMME										TUBERCULOSIS				
Date registered	Unit TB No.	Name in full	Sex M/F	Age	Address in full	Treatment Unit	Treatment start date	Regimen ^a	Disease site P/EP	Category of patient ^a				
										New/Relapse	Treatment after failure	Treatment after default	Transfer in	Other

^a **New case:** HRZE = 6-month or STH = 12-month
^b **Re-treatment:** SHRZE
P = pulmonary
EP = extrapulmonary
New: never previously treated for as much as 1 month
Relapse: previously treated, declared cured, returns smear positive
Treatment after failure: positive 5 or more months after starting treatment, commenced on re-treatment.
Treatment after default: returned smear positive after leaving treatment for 2 months or more, commenced on re-treatment.
Transfer in: registered and started treatment in another unit.

REGISTER

FORM 4

Year _____

Before treatment Result Lab no.date	Results of smear examination according to duration of treatment						Result of treatment* and date of result (check one)				Remarks	
	2 months	5 months	7 months	11 months	Smear result at completion:		Not done	Positive	Died	Defaulted		Transferred
Result Lab no.date	Result Lab no.date	Result Lab no.date	Result Lab no.date	Result Lab no.date	Result Lab no.date	Result Lab no.date	Negative	Positive				

*Smear negative (cured): negative smear at last month of treatment and on one previous occasion
 Smear not done (completed): completed treatment, but sputum examination insufficient (not done) for classification as smear negative.
 Smear positive (fault): positive smear at 5 months or later during treatment, confirmed by a second positive smear.
 Died: died from any cause while on treatment.
 Defaulted: failed to collect medications for more than 2 months after date last seen.
 Transferred: sent to another unit for continuation of treatment and result of treatment is unknown.



ORGANIZATION OF CASE-FINDING

The organization of tuberculosis case-finding should enable the sources of infection in the community (i.e. those with pulmonary tuberculosis) to be identified. The most effective method is passive case-finding, which consists of identifying pulmonary tuberculosis patients from among those who present to the health services of their own accord.

What is the main objective of case-finding?

The main objective of case-finding is to identify smear-positive pulmonary tuberculosis patients, who are the most potent sources of infection. These patients are found among adults (individuals aged over 15 years), as tuberculosis in children is rarely smear-positive and smear-negative patients rarely transmit disease, even if they are positive on culture.

Frequency of tuberculosis among contacts according to the bacteriological status of the index case

BACTERIOLOGICAL STATUS INDEX CASE OF THE		CONTACTS		
SMEAR	CULTURE	TOTAL	NUMBER OF CASES OF PULMONARY TUBERCULOSIS	PERCENTAGE (%)
Positive	Positive	1043	115	11
Negative	Positive	636	6	1
Negative	Negative	575	6	1

From: Shaw JB, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. *American Review of Tuberculosis and Pulmonary Diseases*, 1954, 69:724–732.

How to identify smear-positive pulmonary tuberculosis cases

Pulmonary tuberculosis cases frequently have non-specific symptoms that can suggest a number of chronic respiratory conditions. Tuberculosis is relatively rare compared with acute respiratory infection and chronic lung disease, which are the most common respiratory conditions presenting to the health services. In high prevalence countries, for every 100 to 200 tuberculosis patients put on treatment in an area of 100 000 population, on average 20 000 to 30 000 patients present to the health services with acute respiratory infection and 2500 to 5000 with asthma or another chronic lung condition.

The diagnostic approach must therefore enable health staff to identify the 100 or 200 new cases of pulmonary tuberculosis among the 30 000 to 35 000 patients who present to the services every year with respiratory symptoms.

It is for this reason that tuberculosis case-finding should be part of a comprehensive approach to the diagnosis and management of chronic respiratory conditions; the ability of the health staff to efficiently identify pulmonary tuberculosis patients will be enhanced by an understanding of the differential diagnosis of chronic respiratory conditions.

The system used to evaluate patients presenting with symptoms suggestive of tuberculosis (suspects) is often likened to a **funnel** with a series of filters that identify smear-positive cases among symptomatic individuals:

- The top of the funnel represents all adult patients presenting to the health care services. This number depends on the accessibility of the health services and the degree of confidence in the health system.
- The first filter is the clinical examination: among patients presenting with general symptoms, the staff working at the primary level of the health services must identify those with respiratory symptoms. On average 10–15% of adults presenting to the general health services have respiratory symptoms.
- The second filter is also a clinical examination: this distinguishes patients who have symptoms of less than 3 weeks' duration, who most probably have acute respiratory infection. Among those with longer duration of symptoms are not only tuberculosis patients but also patients with chronic lung disease. Of all patients presenting to the health services with respiratory symptoms, 10–25% have a long-term or chronic condition. Tuberculosis patients most frequently have symptoms of at least 3 weeks (distinguishing them from those with acute respiratory infection) but usually of less than one year (distinguishing them from those with asthma or other chronic lung conditions). These patients are termed “tuberculosis suspects”.
- The third, bacteriological, filter is indispensable, as it is the only means by which the most potent sources of infection can be identified. At least three smear microscopy examinations are performed to detect tuberculosis in all those individuals designated “tuberculosis suspects” after passing through the previous filters.

The role of radiography

- Chest radiography is not widely used in high prevalence countries, as X-ray facilities are frequently not available in the primary health services and the skills required to correctly interpret them are not present at that level. Furthermore, chest radiography is not necessary for detecting smear-positive patients; it is useful mainly for diagnosing pulmonary tuberculosis in patients whose smear examinations are negative.
- ⇒ **If radiography is not available, those patients with negative smears who have had respiratory symptoms for more than 3 weeks and less than one year (tuberculosis suspects) and who do not respond to symptomatic treatment (antibiotics, bronchodilators) may have smear negative pulmonary tuberculosis and may be considered for treatment, if so judged by a clinician;**
- ⇒ **If radiography is available, all those smear-negative patients considered as “tuberculosis suspects” who have an abnormal X-ray suggestive of tuberculosis**

and do not respond to symptomatic treatment may be considered for tuberculosis treatment as smear-negative cases, should the clinician judge them to be eligible.

In practice, the efficiency of case-finding depends on the quality of the filters. If the filters do not function well, the diagnosis of tuberculosis cannot be certain:

- Patients are sometimes put on treatment for tuberculosis based on simple clinical signs: weakness, weight loss and cough. This is particularly problematic in countries with a high prevalence of HIV infection, where many patients with conditions other than tuberculosis present with these symptoms.
- Patients are put on treatment for tuberculosis based on an abnormal X-ray without bacteriological proof of tuberculosis.
- When such poor practice occurs, it often results in the deterioration of the bacteriological filter, the only filter that is truly indispensable, with microscopists feeling increasingly marginalized and unnecessary. It is the patients who suffer, as their management is inappropriate.

Practice point:

The efficiency of the microscopy laboratory is based on the quality of patient selection: the rate of positive smears among examined samples increases the motivation and competence of microscopists.

How to organize the collection of sputum samples

When tuberculosis suspects are identified, bacteriological examination of their sputum is necessary. These examinations are performed in the multipurpose laboratory of the basic management unit where there are trained and quality controlled microscopists. The microscopists are responsible each year for diagnosing the 100 to 200 infectious tuberculosis cases in the area served. They are also responsible for the regular bacteriological follow-up of patients during treatment. The sputum specimens must reach the laboratory in good condition.

For each tuberculosis suspect, three sputum specimens should be collected. One specimen is collected on the spot on the day of the consultation, the second is produced at the patient's home the next day on waking (a sputum container with a tightly fitting lid is provided for this purpose), and the third specimen is collected at the laboratory on the same day. As the quality of the sputum specimen is important, the patient should be shown how to produce an adequate sample on coughing. Great care must be taken during this demonstration and when the patient is producing the actual specimens to ensure that there is adequate ventilation to prevent dangerous exposure to a potentially infectious patient. For this reason, it is often wise to undertake this procedure out of doors in the fresh air.

If the tuberculosis suspect lives near the centre, or can travel to it easily, the specimens are collected in the presence of the laboratory technician. If the patient

is detected at a centre that is a long way from the laboratory and transport of the samples to the laboratory is organized once or twice a week, applying the recommended procedures of conservation and transport, sputum collection can be done at the community health centre. If there is no organization of transport of sputum samples, all tuberculosis suspects should be referred to the laboratory at the basic unit of management.

How to diagnose other cases of pulmonary tuberculosis

As the other types of pulmonary tuberculosis are not such potent sources of infection, they constitute a lower priority for case-finding; furthermore, incorrect treatment of patients in this category who do not actually have tuberculosis poses a risk for the whole of the NTP. Strict guidelines should therefore be applied to ensure that the proportion of smear-negative patients is under 25% of the total number of pulmonary tuberculosis cases.

Smear-negative pulmonary tuberculosis has been defined by the WHO as:

- cases presenting with tuberculosis symptoms who are AFB negative on at least six smear examinations and whose X-rays (examined by a physician) show abnormalities suspicious of progressive tuberculosis leading to the decision to put the patient on a full course of anti-tuberculosis treatment; or
- a case whose diagnosis is based on positive culture even though the smear examinations are negative.

This definition implies:

- the need for X-ray, which should be read by a competent physician able to accurately evaluate abnormal images that indicate not only tuberculosis but also its progress;
- a medical decision to give a full course of anti-tuberculosis treatment, which does *not* include therapeutic trial; or
- a result of culture examination, which is not part of routine practice.

The decision to treat a case as a patient with smear-negative pulmonary tuberculosis should therefore be taken at health centres where these rules can be applied, i.e. where X-ray and a qualified doctor are available.

What type of information system should be used?

The recording and reporting system is the basis of any evaluation of tuberculosis control. All requests for testing are made using a printed form, and each sample is identified by a number which is recorded on each sputum container and every sputum smear examined. Every examination is recorded, with its number, in the **laboratory register**. All other useful information is recorded in this register, particularly if the examination is performed for the purposes of case-finding or treatment follow-up.

Conclusion

Tuberculosis case-finding is directed by symptoms, and is based essentially on microscopic examination of the sputum smears of tuberculosis suspects presenting with long-term respiratory symptoms.

The effectiveness of case-finding depends above all on the reliability of the microscopy network, which must be capable of diagnosing smear-positive pulmonary tuberculosis cases in each basic management unit. Quality control and retraining of microscopists and their continued motivation should be one of the main priorities of the National Tuberculosis Programme.

All health services must participate in case-finding in the provision of other aspects of health care by identifying tuberculosis suspects, as symptomatic patients may present at any level of the health service.

The identification of tuberculosis cases is all the more efficient if the health staff are competent in the management of other respiratory conditions.

References

Enarson DA et al. *Management of tuberculosis: a guide for low- income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Managing tuberculosis at district level: a training course. Geneva, World Health Organization, 1994.

Tuberculosis as an integral part of primary health care. Geneva, World Health Organization, 1998.



PREVENTION OF TUBERCULOSIS AND TUBERCULOUS INFECTION

Organization of preventive activities other than case management of tuberculosis patients differs from one country to the next, as it depends not only on the tuberculosis epidemiology and the resources of each country, but also on the success of the programme and the development of the health structures.

How to organize prevention in the community

□ *Improving access to care for high-risk groups*

Accessibility of the health system for the entire population is a prerequisite for any community health action. Patients with tuberculosis often belong to the most disadvantaged population groups that have the most difficulty in accessing health care. Every effort must be made to improve the accessibility of care for these population groups, by:

- providing free tuberculosis treatment;
- decentralizing health services to make them more accessible for marginalized groups (in the poorest urban areas), in centres for drug-dependent individuals or alcoholics, in prisons, and in psychiatric services.

□ *Prescribing treatment for latent tuberculous infection*

Treatment of latent tuberculous infection (preventive chemotherapy) consists of daily isoniazid given in doses of 5 mg/kg body weight for 6 months.

● **For individuals in contact with a tuberculosis patient**

Preventive chemotherapy is prescribed for individuals who are (or may be) newly infected (tuberculous infection) and who do not have disease (tuberculosis). Infection can be identified by tuberculin testing in non-BCG-vaccinated individuals.

In high prevalence countries, the tuberculin test is generally not available; the IUATLD therefore recommends prescribing treatment for all apparently healthy children aged under 5 years living in the same household as a newly diagnosed case of smear-positive tuberculosis, whether or not the child has been BCG-vaccinated (see the section on contact examination below).

● **For HIV-infected individuals**

Controlled clinical trials have confirmed the efficacy of preventive chemotherapy in these individuals in lowering the risk of tuberculosis. However, this individual care approach is difficult to apply at public health level in countries with a high prevalence of tuberculosis.

Practical point:

In NTPs in countries with a high prevalence of tuberculosis, treatment of latent tuberculous infection should be routinely given to all apparently healthy children aged under 5 years living in the same household as a newly diagnosed case of smear-positive tuberculosis.

□ *BCG vaccination*

BCG is the most widely used vaccine in the world; in the 172 countries where BCG vaccination is practised, 85% of newborns were vaccinated in 1993, with the average vaccination coverage ranging from 62% in Africa to 92% in South-East Asia and the Western Pacific.

The protection conferred by BCG when it is administered correctly at birth acts mainly on the severe extrapulmonary forms in children; it is currently estimated at between 60% and 90%.

● **WHO recommendations**

In the light of the results of various studies on BCG and the analysis of the different vaccination policies worldwide, WHO made the following recommendations in 1995:

- BCG vaccination should be included in national vaccination programmes.
- In countries with a high prevalence of tuberculosis, BCG vaccination should be administered to infants as soon as possible after birth, and in any case before the age of 1 year.
- In areas where tuberculin testing is used to decide whether individuals should be revaccinated, this practice should be stopped.
- In individuals who are BCG-vaccinated, revaccination is not recommended, and there is no scientific justification for this practice. Multiple revaccination is never recommended.

● **The impact of HIV infection on vaccination strategies**

As BCG is a live vaccine whose mechanism depends on cellular immunity, the risks related to vaccination and its benefits in terms of protection of the child should be taken into account in determining the vaccination strategy.

Practical point:

For countries with a high prevalence of tuberculosis, BCG vaccination is currently recommended for all children, even if their mothers are HIV-infected, except if they show clinical signs of AIDS.

How to organize prevention within the health structure

After 2 weeks of effective treatment, tuberculosis patients are generally no longer infectious, except in rare cases of multidrug-resistant tuberculosis (defined as

resistance to at least isoniazid and rifampicin). Steps must be taken to reduce the risk of nosocomial infection depending on the resources of each country. Policies describing simple measures that should be taken must be developed by each National Tuberculosis Programme:

- treat the majority of patients on an outpatient basis as soon as they are diagnosed;
- avoid, as much as possible, all contact between tuberculosis patients and those patients who are known or suspected to be HIV-positive or have AIDS; they should never be hospitalized in the same wards as tuberculosis patients;
- provide personal protective equipment for health personnel (solid cloth masks) dealing with patients with respiratory symptoms who cough (sputum collection, bronchoscopy, dental treatment);
- follow good practice for ventilation and personal protection in microbiology laboratories, particularly those that undertake culture of *Mycobacterium tuberculosis*.

How to organize prevention among those in contact with a patient

The organization of contact tracing is more difficult than passive case-finding of symptomatic individuals. However, in terms of health education it is extremely important, as it reinforces confidence in a health structure that cares about the health of whole families.

The individuals in closest contact with a case of tuberculosis are usually those who live in the same household. In high prevalence countries, there are often several families living together. This can be a serious challenge to an overburdened health structure, particularly if the NTP has not achieved the main objective of tuberculosis control, which is to cure at least 85% of diagnosed cases. When a health structure decides to organize systematic contact evaluation, this can be performed in the following way:

□ *Identify any contacts*

A full list of the contacts of each case of pulmonary tuberculosis should be made, using a “social” register that is separate from the treatment register. Preferably all of these individuals (and definitely all children aged under age 5 years) should then be invited to visit the centre for examination.

□ *Management of contacts*

● **Children in contact with a pulmonary tuberculosis case**

All children should undergo clinical examination, and those among them identified as tuberculosis suspects should undergo further testing. Children diagnosed with tuberculosis should receive a full course of treatment; all other children aged under 5 years who have been exposed to a smear-positive case should receive treatment for latent tuberculous infection whether or not they have been BCG-vaccinated.

- **Adult contacts**

Adults in contact with a pulmonary tuberculosis case should be examined, and tuberculosis suspects should be asked for three sputum samples for bacteriological examination (microscopy and, if possible, culture).

Systematic case-finding among contacts beyond individuals living in the same household is not feasible in many low-income countries. For example, case-finding in the workplace or in schools is difficult, costly and inefficient.

This is why it is preferable to educate the entire population about tuberculosis symptoms and to improve access to health care.

Practice point:

Within the NTP, centres that do not achieve a cure rate of at least 85% among the tuberculosis patients that they manage should limit contact evaluation to the two following measures:

- **request all contacts with symptoms to present for examination at the centre closest to their homes so that any cases can be diagnosed and treated;**
- **give isoniazid chemotherapy to all asymptomatic children aged under 5 years who have been in contact with a smear-positive case in the same household.**

Conclusion

Case-finding based on symptoms and treatment of patients are the principal means of preventing the transmission of tuberculosis in the community. For NTPs in high prevalence countries, the following preventive measures should be applied: BCG vaccination of children at birth, improved access to health care for high-risk groups, and prescription of preventive chemotherapy for all asymptomatic children aged under 5 years who are in contact with a newly diagnosed case of smear-positive pulmonary tuberculosis.

References

Enarson DA, Trébuçq A. Dépistage des individus et des groupes à risque: spécificité de la stratégie de dépistage de la prise en charge, du suivi. [Individual and high-risk group screening: characteristics of screening strategy, case-management and follow-up.] *Médecine et Maladies infectieuses*, 1995, 25:421–427.

Global Tuberculosis Programme and Global Programme on Vaccines. Statement on BCG revaccination for the prevention of tuberculosis. *Weekly Epidemiological Record*, 1995, 32:229–231.

Lévy-Bruhl D, Guérin N. Les stratégies vaccinales par le BCG dans les pays européens. [BCG vaccine strategies in European countries.] *Santé Publique*, 1995, 7:283–291.

Maher D et al. *Treatment of tuberculosis. guidelines for national programmes*. 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

EVALUATION OF A NATIONAL TUBERCULOSIS PROGRAMME

Each National Tuberculosis Programme should establish objectives for its activities, keeping in mind the ultimate goals of reducing deaths, disease and infection. Evaluation of the programme's activities provides an indication of how well these objectives have been achieved. The evaluation is based on the records kept in each district; evaluation is always made by "cohort analysis" which signifies that all patients recorded in a register within a specified calendar quarter are accounted for within the analysis (no patients are "conveniently" left out).

How to evaluate case-finding

□ *In each basic management unit*

By keeping the tuberculosis register up to date, the main case-finding indicators can be determined for each unit, each year:

- **The total of all newly notified cases**, corresponding to all patients recorded in the register at the time of commencing treatment.
- **Classification of smear-positive pulmonary tuberculosis cases by their status at the time of notification:** new cases, relapses, failures, return to treatment after default.

When the programme is poorly run there will be a high rate of previously treated patients, as the patients are not cured. As the NTP becomes better organized, the proportion of re-treatment cases will fall and most patients will be new cases.

- **Classification of new pulmonary tuberculosis cases by bacteriological status:** smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis. By this means it can be ensured that cases are properly diagnosed.
- **Site of disease:** pulmonary tuberculosis, extrapulmonary tuberculosis. Depending on the country, extrapulmonary tuberculosis represents 15–35% of all tuberculosis cases. This figure varies depending not only on the situation, but also on the technical ability to diagnose extrapulmonary tuberculosis.
- **The age and sex distribution of smear-positive pulmonary tuberculosis cases** provides an indication of the age groups mainly affected by the disease and its evolution over time.
- **The notification rate of new smear-positive tuberculosis cases per 100000 population** (based on annual estimates of population size).

The indicators used for new cases can also be used for newly notified relapses.

All of the information necessary for performing these evaluations is noted in the Tuberculosis Case Notification Register if it is properly kept up to date. This why it is so important to keep the register correctly and to train the health staff to update it.

□ *At the national level*

Quarterly case-finding reports are prepared by each basic management unit and kept at a national level. This centralization allows case-finding to be reviewed at intermediate and national levels for each of the basic management units. The rate of notified smear-positive pulmonary tuberculosis can thus be determined at national and intermediate levels as well as at the level of the basic management unit.

How to evaluate the results of treatment

□ *At the level of the basic management unit*

The treatment outcome of diagnosed patients is evaluated by cohort analysis. This analysis is based on the information recorded in the tuberculosis register. Certain indicators enable the progress of the NTP towards the global objective of a cure rate of 85% to be measured. They also highlight any weaknesses in the organisation of treatment, which can then be remedied. We will illustrate this analysis using the example of new smear-positive cases of pulmonary tuberculosis.

An early indication of treatment efficiency is provided by the rate of smear conversion: this is the proportion of smear-positive cases with negative smears at the end of the second month of short-course chemotherapy (or at the end of the third month in the case of re-treatment cases) out of all smear-positive cases registered for treatment.

Quarterly reports are completed separately for the various types of case (new smear-positive and re-treatment smear-positive cases; new smear-negative and extra-pulmonary cases are not usually evaluated). The treatment outcome of the cohort enables the following rates to be determined for a specified quarter. All outcomes can be determined for smear-positive cases; cure and failure cannot be considered outcomes where new smear-negative cases are evaluated.

- **Cured**

This is the proportion of smear-positive cases who have completed treatment and who have at least two negative sputum smear tests (one of these during the last month of treatment), out of all new smear-positive cases registered for treatment.

- **Completed treatment**

This is the proportion of cases who have completed treatment, but for whom cure is not confirmed by two bacteriological examinations, out of the total number of cases registered for treatment.

If this rate is high, the health centre should do its best to provide proof of cure by bacteriologically testing patients who have completed treatment, most of whom are likely to have been cured.

The success rate is obtained by adding together the cure rate and the completed treatment rate.

- **Failure**

This is the proportion of smear-positive cases who remain or revert to being smear-positive 5 months or later after commencing the course of treatment, out of the total number of smear-positive cases registered for treatment. In a well-functioning NTP the failure rate should be lower than 5%.

- **Defaulted**

This is the proportion of cases who have interrupted their treatment for 2 or more months, out of the total number of new smear-positive cases registered for treatment. This rate clearly reflects the quality of the organization of a tuberculosis control centre, and should be less than 10% in an efficient NTP. When this rate is too high (more than 15%), the causes should be analysed and corrective measures should be taken.

- **Transferred out**

This is the proportion of cases who have been transferred to another district (or to another province) during the course of treatment, out of the total number of cases registered for treatment, and whose results of treatment are unknown. Where results are obtained from the centre where the patient continued treatment, these results should be entered for the patient instead of “transferred out”.

Practical point:

Indicators of treatment outcome are useful to guide implementation and identify problems to be solved. Targets should be action-oriented, thus emphasis should be placed particularly on the proportion of cases who have defaulted or been transferred out.

□ *At intermediate and national level*

The cohort analyses are sent to the intermediate and national levels, thus allowing the NTP to be analysed by basic management unit, intermediate level and for the whole country, for surveillance purposes and to improve the programme. This analysis should aid, for example, in making the decision to improve patient management: closer supervision of certain basic units, creation of new treatment centres, and retraining of health staff. Cohort analysis performed on a regular basis allows the progress of the NTP to be measured over time.

What are the other ways of analysing the success of an NTP?

□ *Quality control of microscopists*

Quality control is organized at national or intermediate level, and permits ongoing evaluation of each district's microscopists. It also identifies those laboratory technicians who need retraining or training and those who need to be replaced. It usually consists of re-reading of a sample of sputum slides prepared for routine diagnosis.

❑ *Drug resistance surveillance*

Surveillance of drug resistance over time gives a clear indication of the quality of treatment: when a programme is first set up the rates of acquired and primary resistance may be high, due to the lack of organized treatment in the past. If standardized regimens are consistently applied and patient treatment is organized correctly, these rates will gradually decrease over time, thus providing proof of the effectiveness of the programme. Surveillance of primary resistance, particularly resistance to isoniazid and rifampicin, may be implemented by the reference laboratory when sufficient technical and human resources are available to ensure that basic operations are functioning efficiently. This is the second phase in the development of the reference laboratory once the microscopy network has been set up and quality control has been implemented.

❑ *Surveillance of HIV seroprevalence*

HIV surveillance should be performed in order to better plan, manage and evaluate the NTP. This provides a clearer analysis of the programme's results, as it can explain, for example, a sudden increase in case numbers and/or an excess death rate recorded for tuberculosis cases (as has been observed in many sub-Saharan African countries and in big cities in industrialized countries); it can also help NTP managers to anticipate problems that may arise in organizing the management of a greater number of patients, and to find solutions.

What are the advantages of the evaluation?

❑ *At the epidemiological level*

When an NTP is well organized, routine case notification provides an important epidemiological indicator; the number of smear-positive cases notified and the evaluation of drug resistance allows the size of the tuberculosis problem at national level and its evolution over time to be evaluated.

❑ *At the programme management level*

Evaluation is an essential management tool, not only for the analysis of results, but also for the management of the NTP, particularly for guiding implementation, ordering drugs and laboratory reagents, training of health staff, identifying problems in service delivery and eventually the expansion of the health structures involved in the NTP. Targets should be established to identify parts of the programme that are not functioning well. The targets selected should be action-oriented (they should be things that you can do something about) for example, the proportion of cases that default from treatment. Routine evaluation is required not simply for surveillance purposes but is necessary for efficient management of the programme. That is why regular collation of essential information must remain a part of the routine operations of a programme and not be compromised or minimized due to pressures from other agencies. The responsibility for maintenance of this management tool rests with the manager of the National Tuberculosis Programme.

Conclusion

The ongoing evaluation of programme activities depends principally on the regular upkeep of the tuberculosis register.

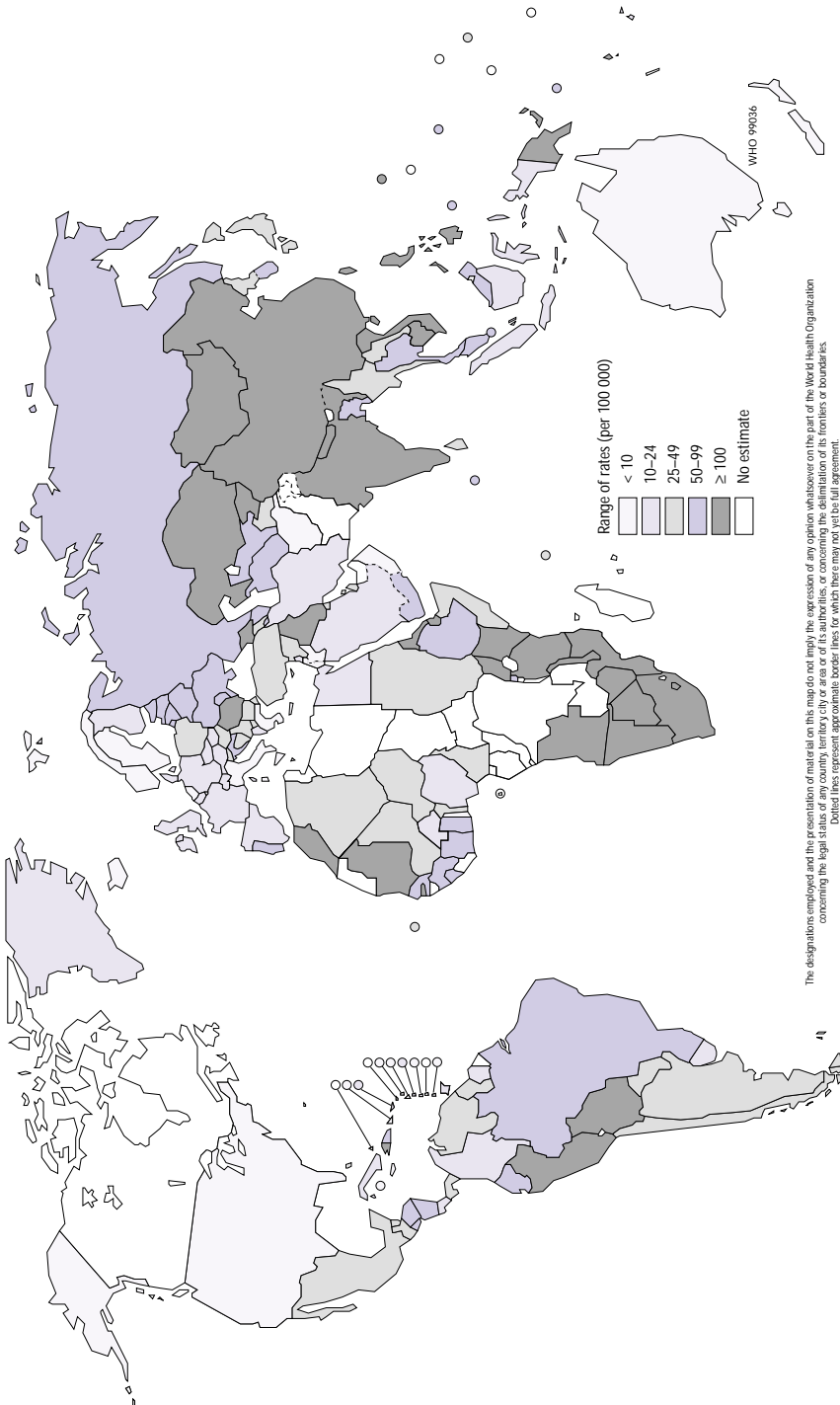
The regular updating of the registers and the quality of the quarterly reports are checked during the regular supervisory visits organized by the central and/or intermediate level. Review of the reports at the national level allows the NTP to be evaluated in its entirety, thus enabling the central unit to manage and make improvements to the NTP.

An evaluation is conducted each year by the WHO (Appendix 5) based on the data provided by the NTP of each country.

References

- Enarson DA et al. *Management of tuberculosis: a guide for low-income countries*. 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
- Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*. 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Appendix 5: Notification rate of tuberculosis cases worldwide in 1997 (WHO report 1999, p 160)



CONCLUSION

Tuberculosis must be one of the principal preoccupations of public health, as it potentially affects the entire community, appears at every level of the health service and has major economic implications. This is why it is essential for all those involved in tuberculosis control to be capable of assuming responsibility in both medical and social domains.

The medical students of today are the physicians of tomorrow. They will play a central role in leading the health teams who will operate National Tuberculosis Programmes in the years to come.

The future of these programmes depends on their professional competence. We hope that this manual will help them to acquire the medical skills that society requires of the “physicians of the future”.

