FRAMEWORK TOWARDS

TB ELIMINATION

IN LOW-INCIDENCE COUNTRIES

World Health Organization

Framework towards tuberculosis elimination in low-incidence countries

World Health Organization

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Contents

Abbreviations

BCG   bacillus Calmette-Guérin
ECDC   European Centre for Disease Prevention and Control
LTBI   latent tuberculosis infection
MDR   multidrug-resistant
TB   tuberculosis
USAID   United States Agency for International Development
US CDC   United States Centers for Disease Control and Prevention
XDR   extensively drug-resistant

Preface

On 19 May 2014, the World Health Assembly approved WHO's post-2015 global tuberculosis (TB) strategy, with the ambitious targets of reducing the numbers of deaths due to TB by 95% and the incidence rate of TB by 90% by 2035 as compared with 2015. The new global strategy is the result of 2 years of wide consultation with governments, nongovernmental organizations, civil society and other stakeholders. Built on three pillars, it emphasizes, among its four fundamental principles, the importance of adaptation of the approach according to context-specific situations.

In view of the progress made in several low-incidence countries, WHO joined forces with the European Respiratory Society and other partners to adapt the global strategy to provide a framework for TB elimination in these countries. Preparation of the framework included setting up a "writing committee" of world-wide experts and a workshop and conference held in Rome on 4–5 July 2014. Representatives from over 30 low-incidence countries and experts from various institutions convened to review the draft document and to discuss its finalization. The product is now available, and our two organizations are proud to promote it and disseminate it widely.

The framework, which represents an adaptation of the new global TB strategy to low-incidence (usually high-resource) settings, outlines eight priority action areas that can be considered the key interventions for accelerating progress towards pre-elimination and, ultimately, elimination of TB. The aim of this document is to provide strategic direction to governments and their partners for an intensified, well-structured effort to rapidly reduce the burden of TB in countries that have the capacity to eliminate the disease in the foreseeable future.

It is the hope of all of us involved in this effort that the document be transformed into an operational plan of action. The risks for not pursuing the actions highlighted in the framework are high, since unattended tuberculosis epidemics and outbreaks are costly, not only in terms of human suffering but also economically, as observed in the recent past.

WHO, the European Respiratory Society and the other partners involved stand ready to support governments and their partners in implementing the Framework, in the hope that its principles will be applied with intensity, persistence and assertiveness until the last case of TB is cured.

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Executive Summary

This Framework offers a coherent approach for eliminating tuberculosis (TB) in low-incidence countries. It is designed to guide national policy-makers and those responsible for technical aspects of the national TB response in accelerating efforts towards elimination. The document will also be informative for public health surveillance officers, practitioners and nongovernmental and civil society partners working on national TB care and prevention and serving the populations most vulnerable to TB.

The World Health Assembly approved WHO's post-2015 global TB strategy in May 2014. The long-term vision of the strategy is a world free of TB and the strategy goal is to end the global TB epidemic by 2035, defined as a global incidence of fewer than 100 cases per million population. This will require a 95% reduction in the number of deaths due to TB and a 90% reduction in the incidence of TB.

The strategy emphasizes global collaboration and national adaptation, based on the nature of the local epidemic and health system context. This framework provides an adaptation of that global strategy for low-incidence countries; those which have already reached a TB incidence of less than 100 per million. For the global incidence to reach <100 per million, and in order to progress further towards "pre-elimination" of TB (defined as <10 TB case per million), and elimination of TB as a public health problem (<1 TB case per million population) the current low-incidence countries need to progress further to even lower levels. Therefore, with the same vision, this framework provides further targets and modified strategy for this subset of countries.

In describing the Framework and how it can be pursued, the document builds on available evidence, best practices in low-incidence countries and expert consultation. It makes reference to existing WHO guidelines and policy documents and should be helpful for updating national plans and guidelines.

Pre-elimination of TB can be reached in low-incidence countries by 2035, while elimination should be possible by 2050 or before, with the introduction of new tools such as a hoped-for new vaccine. This trajectory is highly ambitious but feasible. Rapid progression towards pre-elimination and elimination will require accelerated annual decreases in TB incidence, with intensified effort domestically and globally.

The response must be multisectoral. Further progress towards elimination will require better access to high-quality diagnosis and care and more effective TB prevention, including addressing the social determinants of TB, with special attention to groups at the highest risk for TB.

While there have been encouraging examples of significant progress in TB control, there have also been set-backs and threats, including increasing development and spread of drug resistance, financial and social crises and diminishing government support for TB care and control. An additional threat is the sad state of funding for research on TB, which has resulted in a meagre pipeline of new technologies for TB diagnosis, treatment and prevention.

Owing to increasing globalization and population mobility, significant progress will be possible in low-incidence countries only if TB care and prevention are scaled up dramatically in countries with high and moderate incidence. This interdependency calls for concerted action and close collaboration among countries with high and low incidences of TB.

The epidemiology of TB in most low-incidence countries is characterized by: a low rate of transmission in the general population; occasional outbreaks; most cases of active TB due to reactivation of latent TB infection (LTBI); a high concentration of the disease in certain at-risk groups (including poor and homeless people, migrants, prisoners, ethnic minorities, people living with HIV infection or with other diseases, people with harmful alcohol use, users of illicit drugs and other marginalized groups); and challenges posed by cross-border migration.

Common challenges to the health system in low-incidence countries are diminishing political commitment, diminishing clinical and diagnostic expertise and diminishing general awareness of TB as TB incidence falls. The tailored response to these challenges is grouped into eight priority actions:

1. Ensure political commitment, funding and stewardship for planning and essential services of high quality.
2. Address the most vulnerable and hard-to-reach groups.
3. Address special needs of migrants and cross-border issues.
4. Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups, and provide appropriate treatment.
5. Optimize the prevention and care of drug-resistant TB.
6. Ensure continued surveillance, programme monitoring and evaluation and case-based data management.
7. Invest in research and new tools.
8. Support global TB prevention, care and control.

This document first provides the rationale for the Framework, outlines the approach used to develop it and gives definitions of important terms. The epidemiological basis for TB elimination in low-incidence countries and the specific challenges for TB care and prevention in those countries are summarized, followed by a detailed description of each of the eight priority actions, including illustrative case studies based on experience in countries. Finally, approaches to engaging national and international partners in TB care and prevention are discussed.

1 Background and aims

Tuberculosis (TB) is a major global public health problem that affects millions of people around the globe, predominantly in low- and middle-income countries *(1)*. It is also a persistent health threat in high-income countries, especially among the poorest, most vulnerable segments of the population *(2–4)*. In a globalized world, TB is a shared problem for all countries. Drug-resistant forms of TB are a particularly grave global issue that respects no borders, as further spread and amplification of drug resistance could undo all previous TB control efforts, rendering the disease yet again incurable *(5–8)*.

In times of increasing population mobility, TB will never be completely, sustainably eliminated in any country until it is eliminated globally. This interdependence calls for joint, intensified TB prevention and care in all countries. TB elimination in low-incidence countries, most of which are among the wealthiest in the world, will require both tailored actions in those countries and contributions to TB care and prevention in the poorest countries of the world (Fig. 1).

Further progress towards elimination will depend on better access to high-quality TB services, especially for the most vulnerable groups, and on reducing vulnerability by addressing the social determinants of TB (Fig. 1). These activities must be underpinned by strong health care governance, greater activity of the public health structures for TB care and prevention and relevant investment in high-quality surveillance and translational, clinical and operational research.

Fig. 1. Four dimensions of TB elimination in low-incidence countries
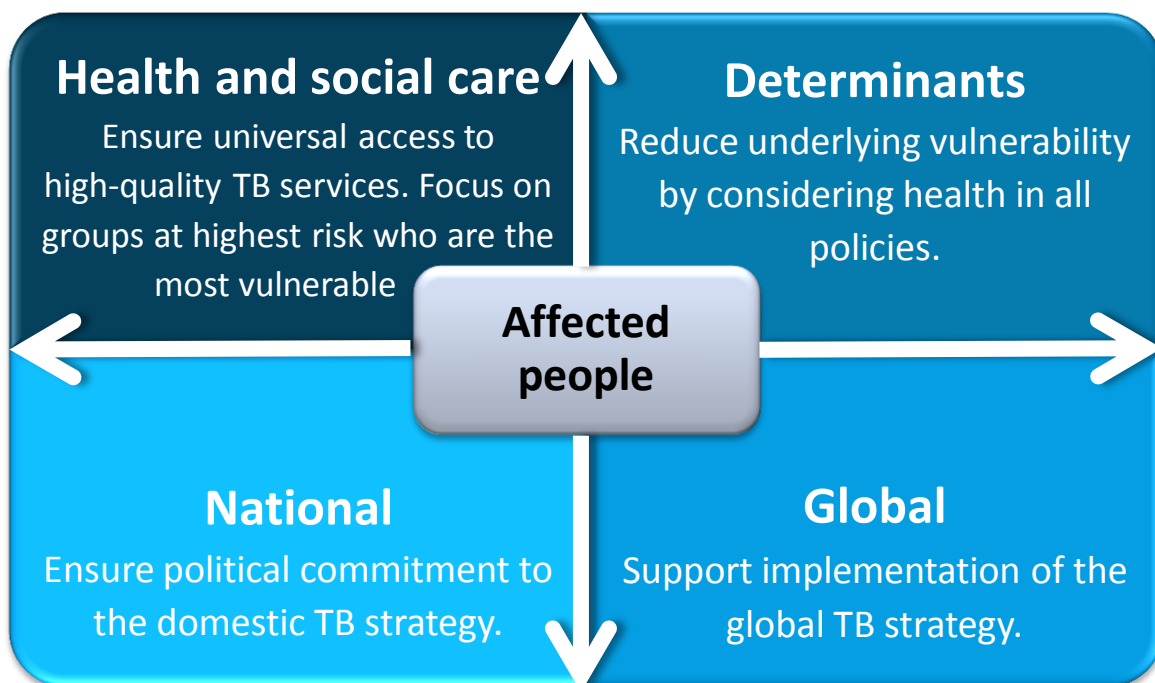
WHO has issued a new global TB strategy, which was approved by the World Health Assembly in May 2014 *(9)*. The vision, goal, targets, pillars and components of the strategy are summarized in Box 1. The new strategy includes a target of reducing the global incidence of TB by 90% between

2015 and 2035. This translates to a reduction from about 1000 to < 100 cases per million population globally. Thus, 20 years from now, the global average incidence rate would be the same as the average TB rates today in the member states of the Organisation for Economic Co-operation and Development. In order to reach this low global average, both high-incidence and low-incidence countries must intensify their efforts to prevent TB. The lowest-burden countries that today have an incidence of < 100 cases per million population must progress to pre-elimination (< 10 cases per million population) and move to elimination of TB as a public health problem (< 1 case per million population).

Box 1. The post-2015 global TB strategy

POST-2015 GLOBAL TUBERCULOSIS STRATEGY FRAMEWORK	
VISION	**A world free of tuberculosis** – zero deaths, disease and suffering due to tuberculosis
GOAL	**End the global tuberculosis epidemic**
MILESTONES FOR 2025	– 75% reduction in tuberculosis deaths (compared with 2015); – 50% reduction in tuberculosis incidence rate (compared with 2015) (less than 55 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis
TARGETS FOR 2035	– 95% reduction in tuberculosis deaths (compared with 2015) – 90% reduction in tuberculosis incidence rate (compared with 2015) (less than 10 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION
 A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
 B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support
 C. Collaborative tuberculosis/HIV activities, and management of co-morbidities
 D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS
 A. Political commitment with adequate resources for tuberculosis care and prevention
 B. Engagement of communities, civil society organizations, and public and private care providers
 C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
 D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

3. INTENSIFIED RESEARCH AND INNOVATION
 A. Discovery, development and rapid uptake of new tools, interventions and strategies
 B. Research to optimize implementation and impact, and promote innovations

The global TB strategy rests on four fundamental principles that should guide all countries, regardless of their TB burden: (i) government stewardship and accountability, with monitoring and evaluation; (ii) strong coalitions with civil society organizations and communities; (iii) protection and promotion of human rights, ethics and equity; and (iv) adaptation of the strategy at country level, with global collaboration. The approaches proposed in this Framework reflect these principles. The fourth principle—adaptation of the strategy—is of particular relevance for this document.

Adaption of the global TB strategy to country level will involve setting priorities and operationalization based on the local epidemiology and health system. The epidemiology of TB in most low-incidence countries is characterized by: a low rate of transmission in the general population; occasional outbreaks; most TB cases due to progression of latent infection; a high TB burden in certain high-risk groups; a significant contribution of cross-border migration; and changes in the age distribution, with more cases among the elderly, at least in the non-foreign-born population. These challenges require tailored responses, including improving access to effective prevention and care for high-risk groups, containment of local outbreaks and identification and management of LTBI *(10–22)*. Universal health coverage as well as broad strategies for TB prevention that include addressing the underlying determinants are important in all settings, but the priorities depend on the local context *(14–16)*.

A framework for TB control and elimination in European countries with a low incidence was prepared over 20 years ago *(17)* and was updated 10 years later *(10)*. The European Centre for Disease Prevention and Control (ECDC) *(18)*, the US Centres for Disease Control and Prevention (US CDC) *(19,20)* and other national and international agencies *(4)* have prepared similar frameworks and related standards *(21,22)*. Together, they cover most of the intervention options discussed in this document. The aim of the Framework is to consolidate previous national and regional frameworks with updated approaches and new tools and to harmonize them with the structure and principles of the global TB strategy. The goal is a common global framework for TB elimination in low-incidence countries.

This Framework is meant to guide national policy-makers and those responsible for technical aspects of the national TB response in achieving the proposed interim targets and actions for accelerated movement towards elimination, including the amendment or suppression of factors that prevent the expected decrease. The document will also be instrumental and informative for public health surveillance officers, practitioners and nongovernmental and civil society partners working on national TB care and prevention and serving the populations most vulnerable to TB.

2 Methods

2.1   Preparation of the Framework

The basis for this Framework is the global TB strategy, which was approved by the World Health Assembly in May 2014 *(9)*. It builds on the epidemiological analyses, health system assessments and strategic considerations that underpin the global strategy. Furthermore, the Framework is grounded in existing WHO guidelines for TB care, prevention and control.[1] It does not contain any new recommendations on the diagnosis, treatment or prevention of TB but proposes adaptations of the existing recommendations and priorities for the epidemiological and health system conditions that are common in low-incidence countries.

WHO policy documents and guidelines and published literature were reviewed, and additional references were identified by experts in the field. A first draft was prepared by the WHO Global TB Programme, and a writing group consisting of 17 experts in the field was established (Annex 1), which reviewed the draft at a meeting in April 2014. They then revised the draft and added text and specific case studies. Definitions and the eight priority action areas were agreed upon during the meeting.

The writing group revised the document several more times before it was discussed by the WHO TB Strategic and Technical Advisory Group in June 2014. It was then circulated it to 30 country representatives and 26 representatives of research institutions and technical agencies and nongovernmental and civil society organizations that were invited to a global consultation in Rome, Italy, on 4–5 July 2014. Participants were asked to review the document and submit comments and suggestions, and group sessions were organized, corresponding to eight priority action areas, in order to obtain further input. The final document was reviewed by all contributors (Annex 1). Declaration of Interest forms were filled in by all contributors. People with links to or receiving grants from companies producing tools related to the priority actions acted as observers and did not contribute to preparation of the Framework.

Information on TB epidemiology and health systems in the Framework was derived from four sources: WHO's global TB database *(23)*, a published survey of TB policies in the countries of the European Union *(4)*, other published research and a survey conducted in all countries represented at the global consultation on elements of TB epidemiology that are not routinely reported to WHO but are available in national surveillance data sets (to various extents) and on existing policy and practice in TB care and control.

Preparation of the Framework was coordinated and funded by WHO and the European Respiratory Society.

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[1] WHO guidelines and policy documents on TB can be found at: http://who.int/tb/publications/en/.

2.2   Definitions of low incidence, pre-elimination and elimination

In this Framework, low-incidence countries are defined as those with a TB notification rate of < 100 TB cases (all forms) per 1 million population and year. This definition was proposed previously *(17)*, while others have suggested different thresholds, such as < 200 per million *(10)* and < 160 per million *(24)*. The threshold of < 100 per million is the same as the target global incidence rate for 2035, which corresponds to the goal of the global TB strategy to "End the global tuberculosis epidemic". The principles and proposed actions of the Framework are relevant not only for countries that meet this low-incidence criterion but also for countries that are approaching the low-incidence threshold.

"Pre-elimination" is defined as < 10 notified TB cases (all forms) per million population and year, as proposed by Clancy et al. in 1991 *(17)*. "Elimination of TB as a public health problem" is defined as < 1 notified TB case (all forms) per million population and year. In the WHO European Region, TB elimination was previously defined as < 1 sputum smear-positive case per million and thus focused on the most infectious TB cases *(25)*. The ECDC has, however, proposed the above definition, which includes all forms of TB *(18)*. Similarly, the US CDC defines elimination in the USA as < 1 case of TB, all forms, per million population *(18,19)*.

In the above definitions, the TB notification rate is used rather than the estimated incidence, as both the health systems and TB surveillance systems in low-incidence countries are generally of high quality and the gap between the rate of notification of new cases and relapses and the true incidence rate is therefore small *(1)*. Nevertheless, TB notification rates should always be evaluated in the context of the quality of the coverage of the TB surveillance system and, specifically, the likelihood of significant under-detection or under-reporting of TB. WHO guidance is available for this purpose *(26)*.

3 Prospects and challenges for TB elimination in low-incidence countries

This section covers the prospects for reaching pre-elimination and elimination in low-incidence countries in the coming decades on the basis of an analysis of current TB incidence rates and projections. Common characteristics of TB epidemiology and related challenges for TB elimination in low-incidence settings are discussed.

3.1 Incidence rates, trends and projections

With the exception of a few very small countries and territories, none is approaching TB elimination, while a few are getting close to pre-elimination (Table 1). In the world's richest countries (high-income countries of the Organisation for Economic Co-operation and Development[2]), the average TB incidence is currently about 130 per million population and year, i.e. more than 100 times the elimination target.

Table 1 summarizes the TB burden, recent trends and future projections for 31 countries and two territories with populations > 300 000 with TB notification rates of < 100 per million in 2012[3]. All but six had a downward incidence trend between 2000 and 2012; four countries have seen increases, and two have seen no change. With the current rate of change, only four would reach pre-elimination by 2035, none would reach TB elimination by 2035, and only one would reach elimination by 2050. In order to reach TB elimination by 2035, the required average annual rate of decrease from 2015 onwards will be 12–18%, with a mean of 16%, i.e. much higher than the decrease most of these countries have experienced in the recent past (Fig. 2). The average annual rate of decrease required to achieve elimination in 2050 is 7–11% (Fig. 3).

The task of achieving TB elimination in the coming decades may thus seem daunting, even in countries with the lowest incidence in the world. TB rates are, however, already at pre-elimination levels and are getting closer to the elimination target in the non-foreign-born populations of some countries, especially in the youngest generations *(27)* (Table 1, Fig. 4). Very low TB rates have been achieved in the vast majority of the non-foreign-born populations of several countries through a combination of near-universal access to high-quality TB diagnosis and treatment (without incurring

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[2] Countries are aggregated into those in which the 2009 gross national income per capita was 12 196 US dollars or more.

[3] The countries and territories with populations < 300 000 are: Anguilla, Antigua and Barbuda, Bonaire, Saint Eustatius and Saba, Bermuda, Barbados, Cook Islands,Curacao, Dominica, Grenada, Saint Kitts and Nevis, Saint Lucia, Montserrat, Niue, Sint Maarten (Dutch part), British Virgin Islands

catastrophic costs for the families affected) and general socioeconomic development, with improved nutrition and living and working conditions *(28)*.

From these observations we can deduce that TB elimination is possible, in principle, with current tools, provided that the factors that have effectively prevented TB are present for all people. The projections presented above indicate, however, that it will take many decades to achieve elimination, even with full scaling-up of current technologies for TB diagnosis, treatment and prevention, combined with conducive social development. The prospect of such progress in low-incidence countries is closely associated with the prospects for improved TB care and prevention globally.

Table 1. TB burden trends and projections in low-incidence countries

Country or territory	Population (million)	Estimated TB mortality rate, 2012 (per million)[a]	Estimated TB incidence rate, 2012 (per million)	TB notification rate, 2012 (per million)[b]	Percent notified TB cases that are foreign-born, 2012[b]	Annual rate of change in incidence 2000-2012[c]	Projected incidence in 2035 (per million) if 90% reduction in 2015-2035	Required annual rate of decline to reach elimination by 2035	Required annual rate of decline to reach elimination by 2050
Australia	23.1	1.9	64	57	87%	0.8%	6.5	-18%	-11%
Austria	8.5	4.2	79	73	49%	-6.1%	6.6	-19%	-12%
Bahamas	0.4	3.7	110	86	0%	-6.9%	9.0	-20%	-12%
Belgium	11.1	5.9	93	89	53%	-3.3%	8.4	-20%	-12%
Canada	34.8	1.9	50	48	64%	-2.2%	4.7	-17%	-10%
Costa Rica	4.6	8.0	119	99	15%	-4.1%	10.5	-21%	-13%
Cuba	11.3	3.3	93	65	2%	-2.1%	8.7	-20%	-12%
Cyprus	1.1	2.0	64	79	74%	4.8%	7.4	-18%	-11%
Czech Republic	10.7	3.5	59	56	17%	-8.6%	4.6	-18%	-11%
Denmark	5.6	4.0	70	61	61%	-3.8%	6.3	-18%	-11%
Finland	5.4	2.9	62	48	29%	-4.7%	5.4	-18%	-11%
France	63.9	4.6	89	74	56%	-2.7%	8.2	-20%	-12%
Germany	82.8	3.5	53	49	48%	-6.6%	4.4	-17%	-10%
Greece	11.1	6.9	48	47	38%	-3.9%	4.3	-17%	-10%
Iceland	0.3	2.7	40	31	82%	-0.3%	4.0	-16%	-10%
Ireland	4.6	3.9	83	75	44%	-3.1%	7.5	-19%	-12%
Israel	7.6	2.3	58	62	90%	-4.6%	5.0	-18%	-11%
Italy	60.9	4.3	62	51	58%	-2.5%	5.7	-18%	-11%
Jamaica	2.8	2.2	65	33	n.a.	0.0%	6.5	-18%	-11%
Jordan	7.0	5.3	58	47	29%	-2.5%	5.4	-18%	-11%
Luxembourg	0.5	4.2	73	86	71%	-3.5%	6.5	-20%	-12%
Malta	0.4	3.7	101	98	85%	7.6%	12.6	-19%	-11%
Netherlands	16.7	1.7	62	55	73%	-3.8%	5.6	-18%	-11%
New Zealand	4.5	1.0	74	66	76%	-3.8%	6.6	-19%	-11%
Norway	5.0	1.4	76	69	85%	1.3%	7.9	-19%	-11%
Puerto Rico	3.7	2.3	22	19	13%	-7.9%	1.7	-13%	-8%
Slovakia	5.5	6.3	77	59	1%	-9.1%	5.8	-19%	-11%
Slovenia	2.1	9.7	84	65	35%	-8.1%	6.6	-19%	-12%
Sweden	9.5	1.4	68	62	85%	2.5%	7.4	-18%	-11%
Switzerland	8.0	2.2	67	52	75%	-3.2%	6.1	-18%	-11%
United Arab Emirates	9.2	1.0	17	9	n.a	-11.9%	1.2	-12%	-7%
United States of America	318.0	1.4	36	32	63%	-5.0%	3.1	-16%	-9%
West Bank and Gaza Strip	4.2	2.3	76	8	n.a.	-4.8%	6.6	-19%	-11%
Unweighted average		*4.02*	*68*	*66*	*54%*	*-3%*	*6.3*	*-18%*	*-11%*

a. From WHO global TB database (http://who.int/tb/country/data/download/en/)
b. From WHO global TB database, updated with data from countries responding to the survey
c. Annual rates of change where estimated based on estimated incidence rates as the slope of a linear regression model using log-transformed rates

Fig. 2. Observed and required annual rates of change to reach TB elimination by 2035 in low-incidence countries and territories with > 300 000 population
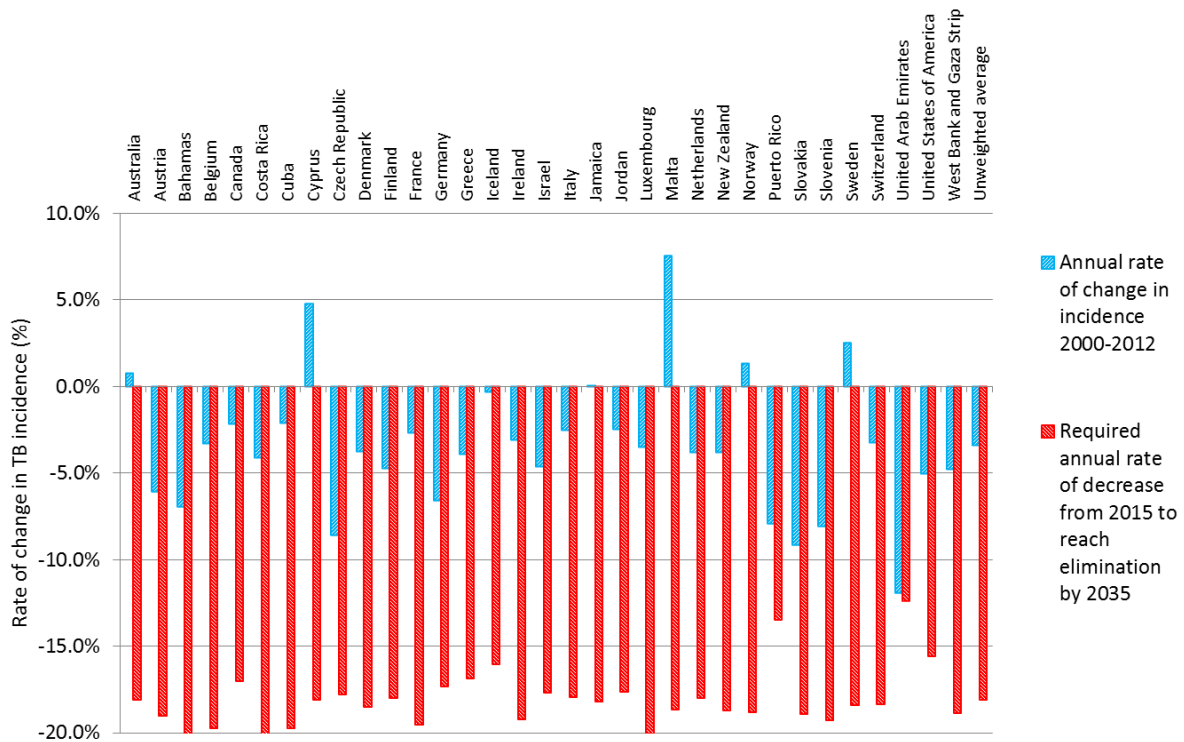
Fig. 3. Observed and required annual rates of change to reach TB elimination by 2050 in low-incidence countries and territories with > 300 000 population
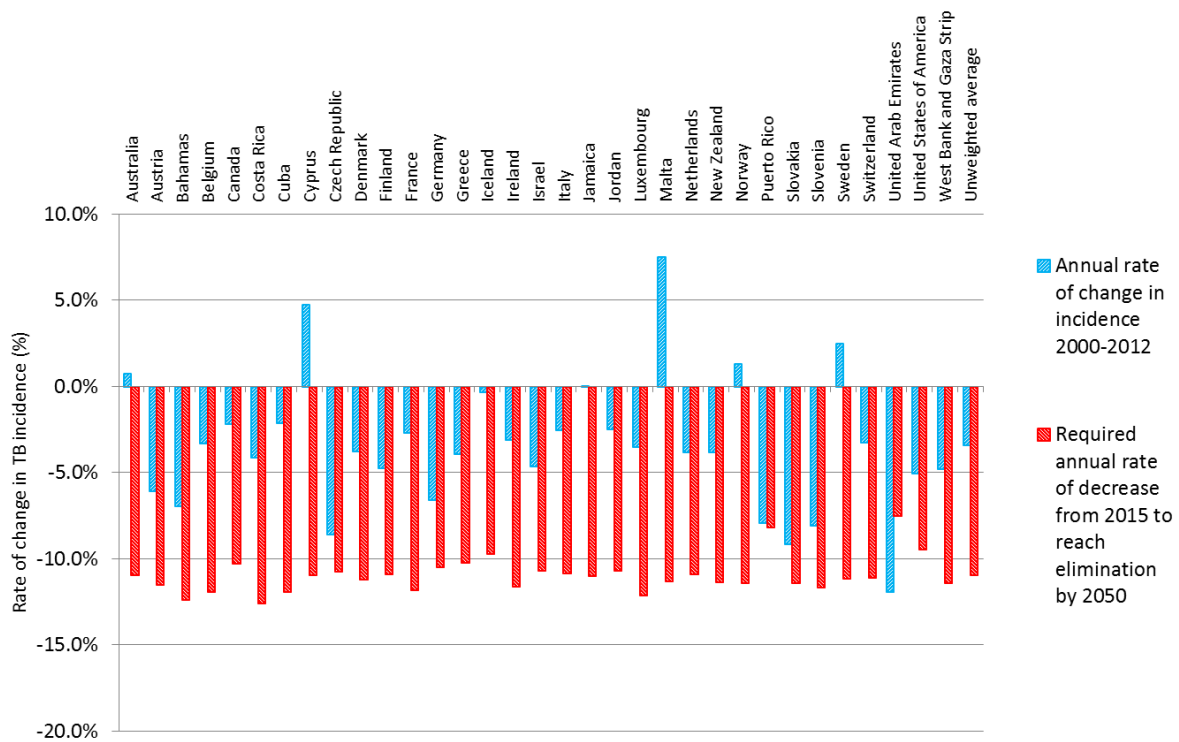
Fig. 4. TB notification rates in foreign-born and non-foreign-born populations and proportions of TB cases that are foreign-born people in low-incidence countries with > 300 000 populations in 2012. The inserted numbers are the notification rates per 100 000 in non-foreign-born populations.
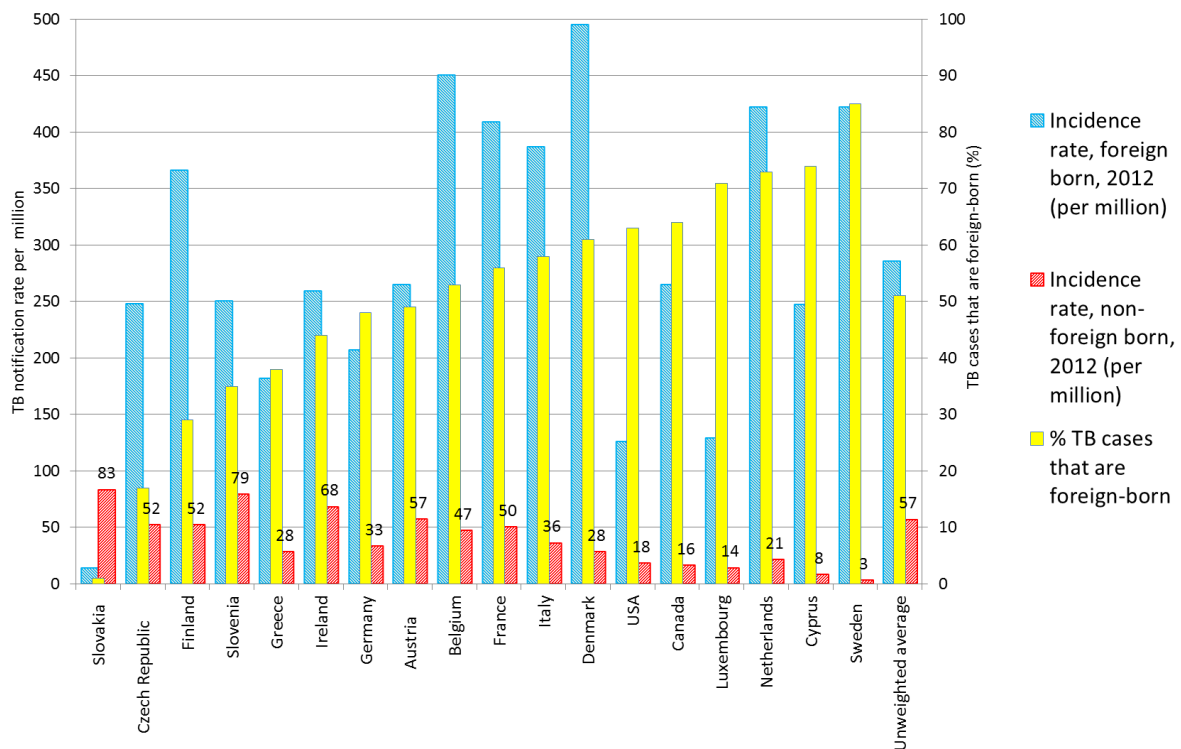
The global TB strategy has the ambitious target of a 90% reduction in TB incidence between 2015 and 2035 *(9)*. Such a reduction would bring all but two low-incidence countries to pre-elimination levels, but none to elimination by 2035 (Fig. 5). An important underlying assumption of the 90% reduction target is that new tools for prevention, detection and treatment will become available at the latest around 2025, allowing further acceleration of the decrease *(9)*. Even if this is achieved, most low-incidence countries can reasonably have pre-elimination as a goal for 2035, while a later date is needed for elimination. The low-incidence countries vary considerably in their current epidemiological situation and in their prospects for reaching elimination, and different targets and milestones must be defined for each country.

Fig. 5. Projected notification rates in low-incidence countries and territories in 2035 if there is a decrease of 90% between 2015 and 2035
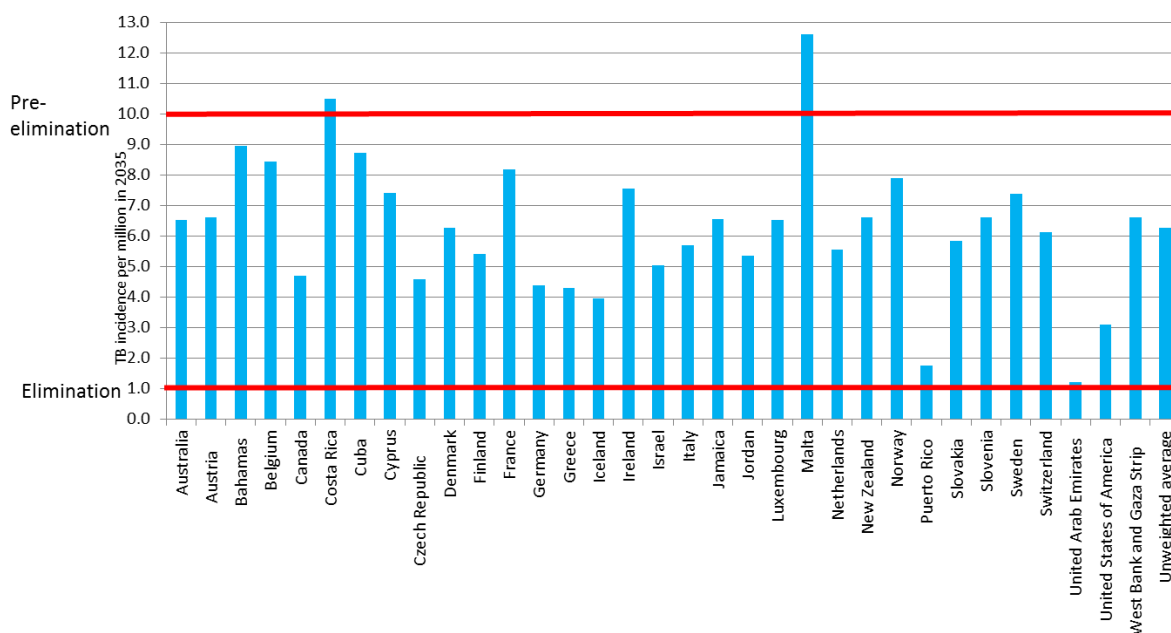
The above projections are based on the optimistic assumption that the current trends will continue in a favourable direction, and then accelerate. While aspiring for this, it is critical to consider the threats that can lead to deceleration and even to reversed trends and to prepare strategies to mitigate or prevent such threats. Elimination of TB—not to mention eradication—is an old dream of mankind and has been foreseen repeatedly since the end of the nineteenth century. The identification of *Mycobacterium tuberculosis* by Koch, introduction of bacillus Calmette-Guérin (BCG) vaccine, the large decreases in incidence and mortality observed during the twentieth century through improved socioeconomic conditions and the advent of antibiotics gave hope for elimination within the near future *(29)*. Time and several unexpected events (like the emergence and spread of HIV, the increase in the prevalence of multi-drug-resistant (MDR) TB, economic crises, the dismantling of TB control programmes, war, civil unrest and the increase in migratory movements between parts of the world with widely different incidence rates) have postponed realization of the dream. Elimination must still be the aim, but the strategies to reach it must take into account all the obstacles to be overcome *(9,14,18,20,22,28,30)*.

3.2   Special challenges for TB care and prevention in low-incidence countries

3.2.1   Concentration in vulnerable groups

As TB incidence falls, TB becomes concentrated in certain vulnerable groups, such as the poor, the homeless, migrants, people living with HIV/AIDS, people with harmful alcohol use, illicit drug users, prisoners and other marginalized groups, which often overlap. The factors that make these groups vulnerable operate through two principal pathways: increased risks for exposure and infection and an increased risk for progression from infection to active disease *(14,28,31-37)*. The former is closely linked to the sociodemographic mechanisms that determine the risk for interaction with a person with infectious TB and the conduciveness for transmission in the environment in which exposure

occurs. Crowded, poorly ventilated living and working conditions, incarceration and homelessness are examples of factors mediated fully or partly through this pathway *(28,32)*. Furthermore, poor access to health care can mean delayed diagnosis and prolonged infectiousness. Deficient infection control in health care settings is also a risk factor for transmission, including between drug-resistant cases with prolonged infectiousness and health care workers, fellow patients and visitors.

The second pathway is a range of factors that influence host defence, including medical conditions and therapeutic interventions that impair the immune system. HIV infection *(14)*, silicosis, undernutrition *(33)*, diabetes *(34)*, smoking *(35)* and alcohol use disorders *(36)* are examples of risk factors that fully or largely operate through this pathway. Poverty and low socioeconomic status are important underlying determinants of many factors in both pathways, and there are often synergistic effects of several concurrent risk factors *(28,37)*.

Mapping risk factors and risk groups helps in targeting efforts to improve access to TB services. It also helps to identify the underlying factors that must be addressed to improve TB prevention. The relative importance of the different factors varies by country. Strong risk factors like HIV infection, incarceration, homelessness and being a migrant from a high-incidence country are important in many countries, whereas less powerful but more common risk factors, such as diabetes mellitus, smoking and alcohol abuse, are important risk factors at the population level in others *(14)*. To better prevent TB, action should be taken against both powerful but less common risk factors and weaker but more prevalent factors. The public health and social interventions required to reduce the prevalence of these risk factors and the underlying vulnerability of the population to TB rest mainly with stakeholders beyond national TB and other disease control programmes and should be part of a broader health-in-all policies framework *(14,28,37)*.

Many vulnerable groups have greater risks not only for TB but also for not accessing diagnosis and treatment and for not adhering to TB treatment. The most marginalized people, such as the homeless, undocumented migrants and illicit drug users, have the greatest difficulty in accessing and adhering to care *(28,32,38)*. Treatment success rates are low in many low-incidence countries, and death rates are high in several of these countries *(1)*. The reasons for suboptimal outcomes vary but include: a high proportion of elderly people with TB; a high prevalence of comorbid conditions that hamper treatment response, such as HIV infection, diabetes, harmful alcohol use and drug dependence; late diagnosis in people with poor access to health care; and migrants moving between countries. Poor treatment adherence can be due to social vulnerability, drug abuse problems, mental illness or a combination of these.

Assessments of social situations and of the presence of comorbid conditions are therefore important for guiding tailored, comprehensive care and social support. Special efforts are needed for people with MDR or extensively drug-resistant (XDR) TB, who have particularly low treatment success rates *(39–43)*. These situations require engagement with social services or civil society organizations with links and expertise in providing services for vulnerable groups. It also requires integration of continuous support from local health authorities and chains of care with services such as HIV/AIDS care and treatment and mental health and substance abuse teams.

In some low-incidence countries, indigenous populations (e.g. Aboriginal people or First Nations) and certain ethnic minorities (e.g. Roma) have TB incidence rates that are much higher even than those in the general population in high-incidence countries. This can be due to a combination of higher exposure to TB risk factors, poor access to health care and possibly genetic factors *(44)*. Immigrants

from high-incidence countries may belong to the most vulnerable groups in their destination country, depending on their reason for migrating, their migration status and the conditions of migration *(45)*.

TB incidence rates are higher in urban than in rural areas in many low-incidence countries *(46–49)* because of higher population density as well as the congregation of certain vulnerable groups. The rates of homelessness and drug and alcohol abuse are often highest in large cities. Migrants, and in particular refugees, tend to settle in metropolitan areas and often live in crowded conditions. Health services are sometimes more fragmented in urban areas, and real access, especially for vulnerable groups, may be worse than in rural areas, despite the higher density of health services in urban areas. The risks for propagation of drug-resistant disease thus abound in cities. Urbanization in itself may not be the critical factor, but special attention must be paid to several phenomena associated with urbanization, and specific urban TB control efforts might be warranted for both TB determinants and access to TB services *(46)*.

3.2.2   Low transmission rates and increasing importance of progression from latent infection

TB transmission rates are often low in low-incidence countries *(50)*, although not negligible *(51)*. The majority of incident TB cases are generated by re-activation of LTBI acquired abroad or domestically in the past *(48,52–54)*. The diagnosis and management of LTBI in high-risk groups is therefore more important in low-incidence countries than in high-burden countries with generalized epidemics and high transmission rates *(11)*.

When domestic transmission does occur, it is often in the form of limited outbreaks, such as within a household, in health care facilities or in congregate settings such as prisons or shelters, and more occasionally in bars or schools *(55–57)*. The prevalence of both LTBI and active TB is high in household contacts, even in low-incidence countries. Contact investigation and outbreak management are essential elements of TB control in low-incidence setting and should be carried out rigorously on the basis of real-time disease surveillance *(58–61)*.

The risk for progression from LTBI to active disease is highest for people with recent infection, such as TB contacts (especially children under 5 years of age) and other recent converters, and for people with impaired immunity due to immunosuppressive conditions or treatments, such as HIV infection or treatment with TNF-α inhibitors *(56,57,59,62–65)*.

Chemoprophylaxis reduces the risk for progression to active TB disease by about 60% or more for individuals at high risk *(66)*. The efficacy of LTBI screening and chemoprophylaxis has, however, yet to be demonstrated at population level. Chemoprophylaxis for 6 months with isoniazid is associated with a small risk (0.4%) of hepatotoxicity, on rare occasions with a fatal outcome *(66)*, and this risk may be greater than the potential benefit for people with a low risk for progression. A 4-month rifampicin regimen is associated with significantly fewer serious adverse events (mainly hepatotoxicity) than isoniazid *(67)*. Recently, a regimen of 3 months' intermittent treatment with rifapentine and isoniazid showed similar efficacy, a lower rate of permanent drug discontinuation owing to an adverse event and lower rates of investigator-assessed drug-related hepatotoxicity *(68)*. Further post-marketing surveillance is required to confirm this. While there is some evidence of the efficacy of chemoprophylaxis for children exposed to MDR TB *(69)*, the benefit of such treatment has as yet to be evaluated in randomized controlled trials.

Risk–benefit evaluations are thus important for all risk groups. With currently available treatment options, only people at the highest risk for progression should be considered for prophylactic

treatment. Currently, no test can accurately predict that risk *(70)*. An additional challenge is that adherence to chemoprophylaxis is often poor *(71)*, although in some settings completion rates of 80% have been achieved *(72)*.

3.2.3 Cross-border migration

Global migration of populations has increased dramatically in recent decades due to the changing global economy, war, civil unrest, socioeconomic inequality and ease of travel. People moving across borders bring with them their individual health profiles, which affect disease burden, health access and health-seeking behaviour. Modern migration serves as a bridge across countries and regions with different disease patterns and other socioeconomic factors that influence the receiving destinations. Vulnerable populations, such as migrants, are often at increased risk for illness because of the poor conditions in which they travel and then work and live. While few countries collect sufficiently disaggregated data on migrants' health, population movement generally renders migrants more vulnerable to health risks and exposes them to potential hazards and greater stress *(73)*.

While traditionally viewed as a unidirectional phenomenon, human migration has become increasingly circular and complex, indicating the need to move beyond narrow unilateral approaches to migration to the linkage of effective public health interventions in source countries with measures in receiving states *(74)*. To this end, the Sixty-first World Health Assembly in 2008 called on countries to address migrant health issues in a more integrated, harmonized manner *(75)*.

In many low-incidence countries, trends in TB incidence are driven largely by migration dynamics *(13,76–81)*. With a few exceptions, the TB incidence rates in the foreign-born population are several times higher than those in the non-foreign-born population (Table 1, Fig. 4). The rates of TB in some migrant groups often correspond to those of their countries of origin *(82,83)*. TB in foreign-born people represents, on average, more than 50% of all TB cases in low-incidence countries, but this proportion varies widely, from 0% to 90% (Table 1, Fig, 4).

Migrants, depending on their country of origin and the conditions of their migration, may have an increased risk for having acquired TB in their country of origin as well as a high risk for reactivation due to socioeconomic vulnerability, which may be augmented by stressful migration conditions *(12,84)*. Some migrant subgroups may also have a higher risk for not completing treatment once started *(85)*. Stigmatizing immigration practices, such as restrictions on travel, work and residence abroad if active or non-active TB is detected, including deportation, are obstacles to timely, free access to early TB detection and care *(12)*.

TB is primarily transmitted within migrant communities, with limited evidence of transmission from migrant groups to host country populations *(86–90)*.

People may migrate during TB treatment or may migrate to access TB care of perceived better quality, particularly if they suffer from forms that are difficult to treat (M/XDR-TB) *(12,91)*. This creates challenges for treatment follow-up, continuity of care, contact investigation, outbreak management and surveillance. Insufficient coordination of TB care services across borders can reduce the quality of care and result in continued transmission and inadequate TB surveillance. To be truly effective in alleviating this problem and achieving the goals of TB elimination, direct investment in global TB control and broader strategies after arrival, including free access to

3.2.4 Shifting age distribution

The elderly are a key group in some low-incidence countries, as they often have a higher TB incidence than younger individuals. This is both because they have had higher cumulative exposure (especially in countries that had high infection rates in the past) and because of an elevated risk for progression to active disease in cases of age-related impaired immunity, e.g. due to comorbid conditions such as immunocompromising diseases, nutritional deficiencies or treatments *(93,94)*.

The populations in many settings with a low TB burden have aged rapidly over the past decades, and the burden of TB has shifted towards the oldest age groups, at least in the non-foreign-born population (Fig. 6) *(95)*; however, this is not seen consistently. For example, in the United States, the percentage of cases in people over 65 years has been steady during the past 20 years, while the incidence rate among the elderly has dropped dramatically *(96)*. The importance of TB in the elderly depends largely on the exposure of different birth cohorts and therefore varies with past TB trends in different settings and over time.

Immigrants tend to be younger than the non-foreign-born population, thus maintaining the lower average age of TB patients. As the incidence of TB is highest immediately after migration (because of the higher likelihood of recent infection than in people who migrated in a more distant past), TB rates are often higher in young than in elderly migrants (Fig. 6). Ageing cohorts of migrants from high-TB burden countries in the future may nevertheless contribute to a further shift towards a dominance of TB among the elderly in low-incidence countries if TB transmission in high-burden settings drops further, leading to a lower prevalence of LTBI in future young migrants.

Fig. 6. Age- and sex-specific TB incidence in foreign-born and non-foreign-born populations. Pooled data from 2004 in European Union countries that reported population data by age group, sex and geographic origin (Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Netherlands, Norway, Slovenia, Sweden, Switzerland, United Kingdom)
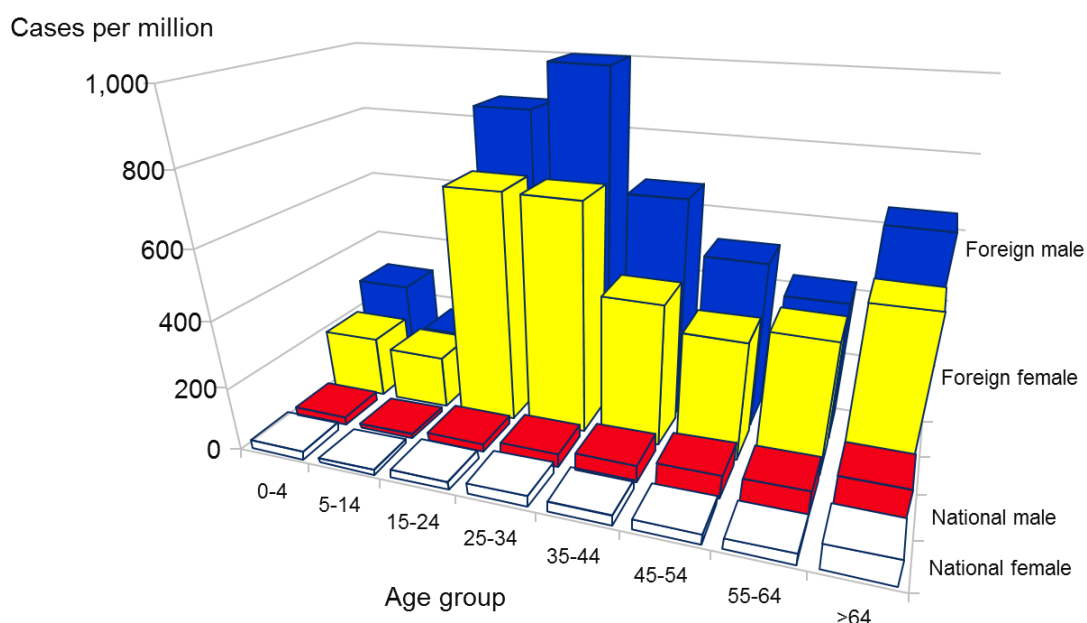
Attention must be paid to ensuring early TB diagnosis in the elderly, especially as the TB symptoms may be masked by other, more common conditions *(97)*. The elderly are at increased risk for missed diagnosis or death *(98–100)*. Systematic TB screening has been done as a part of general health check-ups in some settings where the TB incidence among the elderly is still very high, such as Japan *(101)*.

Treatment of active TB in the elderly presents special challenges because of comorbid conditions and general age-related vulnerability. Side-effects of TB medicines and other complications are also more common, warranting close clinical monitoring. While the elderly have higher risks for both LTBI and progression to active disease than younger people, chemoprophylaxis is problematic, as the risk for severe side-effects increases with age *(66)*.

3.2.5   Securing sustained political commitment for universal access and effective TB service planning and delivery

Most low-incidence countries have relatively well-financed health systems, with a comparatively high proportion of gross domestic product spent on health care (average in 2012, 9%) and a dominance of public over private financing of health care services (average in 2012, 72% public of all health care expenditure) (Table 2). TB diagnosis and treatment are nominally free of charge in almost all low-incidence countries. Despite these favourable basic conditions, several challenges remain.

Even where access is universal on paper and even if there are no direct costs for patients to access TB care, there may be other important barriers to access and adherence, including those linked to marginalization, language, stigma and discrimination, especially among some indigenous populations and among ethnic minorities and displaced and migrant populations. Patient-centred, culturally sensitive, holistic care that ensures optimal management of both TB and comorbid conditions while providing social support and social protection is required *(105)*.

Table 2. Health system context and TB service delivery in 22 low-incidence countries that responded to a survey

NA, not available or no answer
[a] Patient pays 25%
[b] Nominal fee of 1.50 € on each medication dispensed
[c] Diagnosis is covered by health insurance, but patients must pay the first 350 € of health care costs.

Country	Health expenditure, total (% of gross domestic product)	Health expenditure, public (% of total health expenditure)	National TB programme (Yes/No)	Central unit (Yes/No)	TB control and elimination plan (Yes/No)	Specific targets for TB control and elimination (Yes/No)	Specific TB budget (Yes/No)	Laboratory external quality assessment system (Yes/No)	Individual case-based electronic database (Yes/No)	Directly observed treatment (all or selected patients/ No policy)	Free TB diagnosis (Yes if TB is confirmed/Yes for all tested/Yes with other criteria/No)	Free TB treatment (Yes/No)	Special incentive/enabler for some or all TB patients (Yes/No)
Australia	9%	68%	No	No	Yes	Yes	No	Yes	Yes	Selected	Yes (all tested)	Yes	No
Austria	9%	76%	NA	NA	NA	NA	NA	NA	NA	Selected	NA	NA	NA
Belgium	11%	76%	No	No	No	No	Yes	Yes	Yes	Selected	Yes (all tested)	Yes	No
Canada	11%	70%	No	No	Yes	Yes	No	Yes	No	Selected	Yes (all tested)	Yes	No
Cuba	10%	95%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	All	Yes (all tested)	Yes	Yes
Cyprus	7%	43%	No	No	No	No	No	Yes	Yes	All	Yes (if confirmed)	Yes	No
Czech Republic	7%	84%	No	No	No	No	No	Yes	Yes	Selected	Yes (all tested)	Yes	No
Denmark	11%	85%	No	No	No	No	No	Yes	Yes	Selected	Yes (all tested)	Yes	No
Finland	9%	75%	Yes	No	Yes	No	No	Yes	Yes	Selected	Yes (all tested)	Yes	No
France	12%	77%	Yes	Yes	Yes	No	Yes	Yes	Yes	Selected	Yes (all tested)	Yes	No
Germany	11%	76%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Selected	Yes (all tested)	Yes	No
Greece	11%	61%	No	No	No	No	No	Yes	Yes	NA	Yes (other)	No[a]	No
Ireland	9%	70%	No	No	No	No	No	Yes	Yes	Selected	Yes (all tested)	No[b]	No
Israel	8%	62%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Selected	Yes (all tested)	Yes	Yes
Malta	9%	66%	Yes	Yes	Yes	Yes	No	Yes	Yes	Selected	Yes (all tested)	Yes	Yes
Netherlands	12%	86%	No	No	Yes	No	Yes	No	Yes	Selected	Yes, other criteria[c]	Yes	Yes
Norway	9%	86%	No	Yes	No	No	No	Yes	Yes	Selected	Yes (all tested)	Yes	Yes
Slovakia	9%	64%	Yes	Yes	Yes	No	Yes	Yes	Yes	Selected	Yes (all tested)	Yes	No
Slovenia	9%	73%	No	No	Yes	Yes	No	Yes	Yes	NA	Yes (all tested)	Yes	No
Sweden	9%	81%	No	No	No	No	No	Yes	Yes	No	Yes (all tested)	Yes	No
Switzerland	11%	65%	Yes	Yes	Yes	No	Yes	Yes	Yes	Selected	No	No	Yes
USA	18%	46%	Yes	Yes	Yes	Yes	Yes	No	Yes	Selected	Yes (all tested)	Yes	Yes

Outreach services, such as through mobile teams, may be necessary to reach certain risk groups. Low-incidence countries have to various extents implemented screening and delivery strategies for specific risk groups, but few have data on the contribution of such screening to yield and case detection (Table 3) *(4)*.

The special challenges in low-incidence countries require a bold health system response. Yet, it is often difficult to maintain political commitment for TB care and prevention when the TB incidence has decreased to low levels, especially when the disease is concentrated in marginalized groups. This can lead to diminishing visibility in clinical care as well as among the public and among policy-makers. Maintaining coherent stewardship of the national TB response is often a major challenge. Of the

low-incidence countries that completed the survey on their TB situation, less than half have a national TB programme, a central unit responsible for national TB care and prevention, or TB-specific funding, while 60% had a TB elimination plan (Table 2). Of the low-incidence countries in Europe previously surveyed *(4)*, only 55% reported having a defined national TB programme, 64% a national plan that included TB elimination and 45% a specific budget for TB activities.

Surveillance, forecasting, planning and budgeting are essential elements of TB care and prevention *(106)*. A central unit that coordinates such tasks and at least one centre that sustains clinical excellence are critical in settings where TB detection and management become rare events for clinicians and public health officers. In addition, defined advisory bodies or committees and professional networks can support national efforts.

For proper surveillance, it is essential that mandatory notification be embedded in proper public health laws with full respect for human rights and ethical principles. TB notification is mandatory in all low-incidence countries, although significant underreporting has been identified in capture–recapture studies in some settings *(107–109)*. Most low-incidence countries have case-based electronic TB surveillance (Table 2); however, regular supervision is performed in only 61% of European countries, and only 39% have a monitoring and evaluation plan *(4)*.

Table 3. **Screening strategies in 22 low-incidence countries that responded to a survey**

Country	Household contact investigation		Immigrant screening		Ethnic minority or indigenous population screening		Screening of people living with HIV/AIDS		Prison screening		Screening of health care workers	
	Policy (Yes/ No)	Percentage of all TB cases detected with this strategy	Policy (Yes/ No)	Percentage of all TB cases detected with this strategy	Policy (Yes/ No)	Percentage of all TB cases detected with this strategy	Policy (Yes/ No)	Percentage of all TB cases detected with this strategy	Policy (Yes/ No)	Percentage of all detected TB cases with this strategy	Policy (Yes/ No)	Percentage of all detected TB cases with this strategy
Australia	Yes	NA	Yes	0.0	No	NA	Yes	NA	No	NA	No	NA
Austria	Yes	NA	Yes	NA	No	NA	No	NA	Yes	NA	Yes	NA
Belgium	Yes	5.3	Yes	4.4	NA	NA	No	NA	Yes	NA	Yes	0.9
Canada	Yes	NA	Yes	4.5	No	NA	No	NA	Yes	NA	No	NA
Cuba	Yes	2.0	Yes	NA	No	NA	Yes	3.5	NA	NA	Yes	NA
Cyprus	Yes	NA	Yes	NA	No	NA	Yes	1.4	No	NA	Yes	0.0
Czech Republic	Yes	4.6	No	NA	No	NA	Yes	NA	Yes	NA	No	NA
Denmark	Yes	NA	Yes	NA	No	NA	Yes	NA	No	NA	No	NA
Finland	Yes	NA	Yes	NA	No	NA	No	NA	Yes	NA	No	NA
France	Yes	6.0	Yes	6.0	No	NA	Yes	NA	Yes	1.1	Yes	NA
Germany	Yes	6.8	Yes	17.0	No	NA	No	NA	Yes	14.0	Yes	NA
Greece	NA	NA	No	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ireland	Yes	6.1	Yes	0.3	No	NA	Yes	28.0	Yes	0.8	Yes	4.0
Israel	Yes	NA	Yes	NA	No	NA	Yes	NA	No	NA	Yes	NA
Malta	Yes	2.4	Yes	45	No	NA	Yes	NA	No	0.0	Yes	NA
Netherlands	Yes	7.0	Yes	6.0	No	NA	Yes	NA	Yes	1.8	Yes	0.2
Norway	Yes	2.0	Yes	17.0	No	NA	Yes	NA	Yes	NA	No	0.0
Slovakia	Yes	7.8	Yes	0.0	Yes	6.7	Yes	0.0	Yes	6.4	Yes	0.3
Slovenia	Yes	7.0	No	NA	No	NA	No	1.0	No	NA	No	0.7
Sweden	Yes	NA	Yes	NA	No	NA	No	NA	Yes	NA	No	NA
Switzerland	Yes	NA	Yes	3.0	No	NA	Yes	NA	No	NA	No	NA
USA	Yes	4.0	Yes	1.9	No	NA	Yes	NA	Yes	NA	Yes	0.4

NA, not available or no answer

In several low-incidence countries, programme approaches are or have been de-prioritized. Dropping crucial elements such as surveillance, forecasting, strategic planning, guideline development, quality control, inclusion of TB in medical curricula and resource mobilization can have deleterious effects on TB care and prevention. Underfunding or dismantling of TB control units has deflected attention from TB control, and a surge in TB rates requires massive re-investment *(110,111)*. In recent years, stock-outs of TB medicines *(112)*, loss of clinical expertise and diminishing proficiency in TB testing in laboratories have been reported and linked to weakened TB surveillance and planning *(113,114)*. In all low-incidence countries, it is essential to ensure that, as the TB burden falls, clinical experience and public awareness of TB do not diminish and to recognize that stronger efforts will be required to maintain political commitment for TB care and prevention.

Countries must find an appropriate balance between integration and ensuring the necessary TB-specific planning and service delivery and also between decentralization and safeguarding centres of excellence. Service integration and interdisciplinary collaboration across health and social sectors, including nongovernmental and civil society organizations, is crucial to ensure access, streamlined services and proper social support *(12,28,102,103,106)*. Integration should not deflect focus from essential TB-specific diagnosis, treatment and surveillance functions.

4 Adaptation of the global TB strategy in low-incidence countries: principles and actions

4.1 Adapting the principles

The aim of this adaptation of the global strategy to low-incidence settings is to accelerate movement towards TB elimination. It builds on the same four principles of the global strategy and should be applied in the context of the eight priority action areas proposed below. The four principles are:

1. *Government stewardship and accountability, with monitoring and evaluation:* In low-incidence settings, as discussed above, some distinct actions must be taken by government in its stewardship function. Action must be taken not only by public health authorities but also by other authorities, with clear roles and accountability, including reinforcement and adaptation of monitoring and evaluation approaches, such as cross-border collaboration.

2. *Strong coalition with civil society organizations and communities:* Reaching vulnerable and marginalized populations that carry the greatest TB burden in low-incidence settings requires new approaches to building coalitions with civil society organizations and the communities most severely affected. A coalition approach can both increase expression of the demand for TB prevention and care and ensure engagement in the formulation of plans and intervention strategies and their evaluation.

3. *Protection and promotion of human rights, ethics and equity:* Many of the people and groups most at risk for exposure to TB, infection, disease and poor outcomes face challenges in the protection and promotion of their human rights in general and in their right to health specifically. The approach to TB elimination must be based on human rights. This will include addressing issues of nondiscrimination, the availability, accessibility, acceptability and quality of interventions, privacy and confidentiality, participation, and accountability. A number of related ethical issues arise in the design and implementation of TB prevention and care interventions. Underlying inequities must also be addressed in the TB response within and beyond the health sector, such as in economic and social circumstances and related social determinants of disease and in access to health care. Another concern to be addressed is that accessing formal health services may disclose the irregular status of some immigrants and have legal implications.

4. *Adaptation of the strategy and targets at country level, with global collaboration:* As noted above, this Framework itself is an expression of the principle of adaptation of the global strategy to the country and local context. Global collaboration is a fundamental element of the Framework, as many of the challenges, including migration, building political commitment to TB elimination and ensuring a robust research portfolio, necessitate global collaboration.

4.2   Eight priority action areas in low-incidence countries

Table 4 summarizes eight priority action areas for countries moving towards pre-elimination and elimination, in line with the challenges discussed above. The table also shows the relevant principles and components of the global TB strategy for each action area, which are further elaborated below. Priorities for interventions and target groups should be based on an assessment of the epidemiology and health system in each setting, guided by an analysis of surveillance data and other research. Critically, such analyses should establish the distribution of TB in the population, the specific barriers to access of different groups, the health system capacity and barriers to and the availability and quality of TB-specific interventions and functions.

Table 4. Adaptation of the global TB strategy to low-incidence countries

Priority action area	Essential elements	Global strategy pillars and components
1. Ensure political commitment, funding and stewardship for planning and essential services of high quality.	Political commitment and financing (plans, targets and leadership) Advocacy from civil society, communities and other stakeholders Central coordination, management and staffing for TB elimination, including training, laboratory capacity, drug forecasting and management, and surveillance Partnerships among ministries, sectors and stakeholders	1a–d 2a–d
2. Address the most vulnerable and hard-to-reach groups.	Mapping of TB-risk groups, including all groups with elevated TB incidence and hard-to-reach groups Analysing and addressing barriers to access and adherence Social support and protection Addressing underlying social determinants	1a–d 2 b–d
3. Address special needs of migrants and cross-border issues.	Undertaking epidemiological assessment and proper surveillance Ensuring access to culturally sensitive health services Social support Establishment of cross-border collaboration Consider selective screening (pre- and/or post-entry) Address social determinants	1a-d 2b–d
4. Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups, and provide appropriate treatment.	Contact investigation Outbreak management Consideration and prioritization of other screening activities on the basis of mapping of risk groups and assessing benefits, risks and costs Monitoring for effectiveness of screening programmes and policies	1a+d
5. Optimize the prevention and care of drug-resistant TB.	Universal rapid drug-susceptibility testing Optimized treatment, care, support and social protection Drug regulation and management	1a–d 2a–d 3a–b
6. Ensure continued surveillance, programme monitoring and evaluation and case based-data management.	Enforcing compulsory notification Establishing an electronic case-based TB registry Implementing a core set of indicators for surveillance and monitoring of evaluation Use of molecular epidemiology tools when needed Linkage and integration with other surveillance systems A monitoring and evaluation framework Regular monitoring of implementation, with periodic evaluation and impact assessment	2a–c
7. Invest in research and new tools.	Mobilization of financial resources for TB research Influencing the research agenda of main institutions Support for national and international capacity-building for research	3a–b
8. Support global TB prevention, care and control.	Contribution and mobilization of financial resources Promotion of global TB advocacy and visibility Contributions to global TB surveillance, monitoring and evaluation Support for bilateral and multilateral collaboration and technical assistance	1–3

4.2.1 Ensure political commitment, funding and stewardship for planning and essential services of high quality.

Central coordination of TB care and prevention under government stewardship is essential in all countries to ensure a national strategic plan for TB elimination that is embedded in national health and social sector plans and to guarantee equitable access to high-quality TB services within universal health coverage schemes and related social protection benefits *(106)*.

Countries vary substantially in the structure of government, the degree of centralization or decentralization of authority and the nature of planning mechanisms. No matter the system, planning and target-setting in public health governance and administration can drive what gets done at national and local level as well as the resources assigned for the response.

In order to frame planning of elimination, baseline assessments are needed, and special commissions of leaders should be constituted to set a clear course towards TB elimination, as opposed to routine planning for service delivery. Operational and impact target-setting, including adoption of the proposed pre-elimination target of < 10 cases per million population, should be considered. Detailed operational planning and milestones, such as for 5-year periods, can then be pursued. Regular reporting and public dissemination of results and of lessons learnt through a range of mechanisms should be stimulated and financed.

Baseline assessments of TB elimination activities, planning and target-setting will lead to better definition of the interventions that require financing, those that are currently well resourced and where gaps exist. In most low-incidence settings, several authorities have budgetary responsibility for TB prevention, care, surveillance, research and global control funding. Therefore, mapping the needs and gaps is not easy; but it is necessary. Well-targeted financing can then drive changes in practice, performance and impact.

In countries where universal health coverage is not yet achieved, public health authorities should ensure that TB care of high quality and the associated social protection are available for all patients, regardless of their ability to pay for services. Health care systems in most low-incidence countries are relatively well resourced, and both public and private health care should have access to the best TB tests available for all in need and provide optimal, comprehensive management of TB (see Annex 2 for details).

Political commitment is also required for essential regulatory approaches, including a law on infectious diseases that is effectively implemented and enforced for both public and private health providers. Specific regulations are required for: vital registration; mandatory TB case notification and monitoring of treatment outcome; registration, importation, manufacture, prescribing and dispensing of TB tests and medicines; and infection control in health care services and other settings where the risk for disease transmission is high *(9)*.

Periodic meetings should be held between those responsible for domestic TB control and research and the leaders who finance and support global TB control in order to determine the full national impact of the response. Establishment of an advisory body that includes the relevant authorities, members of professional societies, researchers and civil society to review routine performance of national activities annually and progress towards targets should be considered. In some countries, this may best be done by an overarching body that addresses communicable diseases, if it regularly and substantively addresses TB.

National planning and advisory bodies for TB elimination are likely to be insufficient and ineffective without strong, active involvement of civil society organizations, affected vulnerable communities or patient organizations, and other stakeholders external to government. These partners can pursue independent efforts complementary to those of government in building the awareness of the public and of political authorities of the needs of people affected by TB. These partners may receive resources from government to perform these functions and mobilize additional resources. They therefore can better design responses, build accountability of national efforts and support their implementation. Their competence includes the ability to reach out effectively to vulnerable groups, mobilize communities, channel information, help to create demand for care, frame effective delivery models and address underlying determinants of TB.

Partnership should also extend to local health and social service officials, public health practitioners, implementing partners and researchers. The involvement of prison health services, occupational health departments, immigration authorities, special health and social services for vulnerable groups, including the homeless, indigenous populations and ethnic minorities at risk, and social services that cater for vulnerable groups such as the homeless, should be considered in effective planning and execution of TB screening, care and prevention in high-risk groups. TB care and prevention in large cities may require special initiatives with municipal authorities. Joint reports and information materials for these authorities and their constituencies can be valuable.

The size and capacity required for a central coordination team, the necessity for specialized units for TB diagnosis and treatment and the appropriate level of centralization or decentralization of services depend on the size of the country as well as on its TB burden and distribution. In all settings, certain functions must be filled either by fully TB-dedicated coordinating staff or by staff with sufficient time within multiple roles to ensure high-quality performance.

- Well-functioning chains of care, with strong referral, notification and information mechanisms between primary care, hospitals and specialist services—public and private—are necessary for effective, early TB diagnosis, care and surveillance.
- Human resource planning, capacity strengthening, basic and continuous medical education and targeted information campaigns on TB strategies and policies should be ensured at all levels of care, in all relevant specialist services and in both the public and the private sector.
- A high-quality network of laboratory services, validated by proficiency testing and other quality control and improvement mechanisms, should be available to all medical providers for early, accurate diagnosis.
- An uninterrupted, quality-controlled supply of drugs and diagnostic tests should be available, based on forecasting, with drug management capability and a strategy for rational drug use.
- High-quality data should be collected and analysed, and all levels of the health system should have capacity for surveillance and programme monitoring and evaluation.

The incidence of and mortality from TB began decreasing in the United States before widespread use of effective chemotherapy. National statistics showed a steady decrease in the number of incident cases of TB, from 83 304 cases reported in 1953 to 22 201 in 1985 *(119)*. As the number of cases of TB decreased, however, the public health infrastructure for control also decreased, as categorical Federal funding ended and local funding was shifted to other priorities. The number of reported incident cases increased from 22 768 in 1986 to 26 673 in 1992. This increase coincided with the onset of the HIV epidemic, increased nosocomial and institutional transmission of *M. tuberculosis* and increased numbers of cases in foreign-born people who had immigrated from countries with high rates of TB *(120)*. After the resurgence of TB, Federal resources for TB prevention and control were substantially increased and were directed to improving surveillance, increasing the capacity of public health laboratories, improving infection control and increasing the number of TB patients treated with directly observed therapy. As a result, the incidence steadily decreased between 1993 and 2013; in 2013, a historical low of 9588 incident cases of TB was reported in the United States *(121)*.

The responsibility for TB control and prevention in the United States rests with the public health system through Federal, state, county and local public health agencies. Programmes conducted by these agencies have been critical to the progress in TB control, and it was the deterioration of those programmes after the loss of categorical Federal funding that contributed to the resurgence of TB in 1985–1992 *(122–125)*. The current roles and responsibilities of Federal agencies (e.g. US CDC, National Institutes of Health) and jurisdictional public health agencies (e.g. state, county, local) are delineated in *Controlling tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America (126)*.

Paradoxically, the success and progress towards TB elimination have again created challenges. Maintenance of funding for TB programmes has again become less of a priority, as some policy-makers and the general public no longer view TB as a problem. An unstable supply of TB drugs is a consequence of a shrinking market. Clinicians are less familiar with TB, leading to delays in diagnosis that fuel outbreaks. These challenges will have to be overcome if TB elimination is to be achieved in the United States.

Case study 2. Ensuring political commitment for comprehensive TB care and prevention in a low-incidence, middle-income country: the case of Cuba

Cuba is one of very few middle-income countries that have achieved low-incidence TB. This was made possible by maintaining TB care and prevention high on the public health and broader political agenda, implementing both high-quality TB-specific interventions and ensuring action on social determinants of health. Cuba has a universal free-of-charge, integral health system, into which the national TB programme is fully integrated *(127)*. Political commitment for TB care and prevention has been reinforced continually at national and municipality levels.

Novel polices for improving TB control have been introduced into the TB control programme *(128,129)*. TB contacts and high-risk groups are screened systematically, with susceptibility testing for *M. tuberculosis* strains isolated from active TB cases. Cases of TB–HIV are managed comprehensively: all TB patients receive an HIV test, and all people living with HIV/AIDS are followed, treated with highly active antiretroviral therapy and tested for TB. Preventive treatment is recommended for eligible people with a high risk for TB. BCG vaccine is still administered to newborn children. Compulsory notification of TB cases was introduced by law in 1960, as an element of the communicable disease reporting system.

Civil society organizations (e.g. student associations, patient coalitions, the Cuban Women's Federation, the Cuban Hygiene and Epidemiology Society) support TB control actions *(130)*. The entire Cuban population has full access to employment, education, social security, sports, cultural centres and other social needs, regardless of their religious or political beliefs, sex, age or disability. People with active TB who work receive their full salary from the Social Security Board of the Labour Ministry throughout treatment *(131,132)*.

Research is an integral component of the national TB control strategy *(133)*. Strategies for improving implementation, for scaling-up TB control measures and for monitoring and evaluating effectiveness have been developed through operational research.

Case study 3. A central unit and coordination between regions in Italy are required

Italy is composed of 21 regions, each of which is responsible for developing a regional TB control plan consistent with the national guidelines, issued regularly by a national ad hoc committee nominated by the Ministry of Health. Among the main recommendations of the guidelines is that physicians notify both TB cases and treatment outcomes according to the legal framework in force and prescribe standard anti-TB regimens. The requirements included in the legal framework are consistent with ECDC surveillance requirements and WHO guidelines.

The regions have all prepared plans (some of which work well), although they differ significantly in several core components relevant for TB elimination. For example, not all regional programmes include recommendations for diagnosis and treatment of LTBI, and, when such recommendations are included, they are not always consistent in terms of strategies for diagnosing and treating LTBI. There is no national plan for the transport of samples of at least all drug-resistant strains collected from regional reference laboratories to central laboratories for second-line drug-susceptibility testing and molecular epidemiology, although ad hoc research projects have provided some irregular funding for part of this activity. Some core activities are performed on a voluntary basis by Governmental and nongovernmental institutions.

A central unit responsible for the main functions necessary for TB control and elimination (surveillance, prevention, diagnosis and treatment) is lacking. At present, the surveillance function (at the Ministry of Health) and the laboratory coordinating function (at the Istituto Superiore di Sanità) exist. In the past, a national TB committee was nominated for 1 year by the Ministry of Health for special needs (e.g. when the national TB guidelines were issued), but it was not funded, and each participant required funding from his or her institution.

Because of this lack of central capacity to deal with all components of TB control and elimination and the lack of communication between a central unit or authority and the regions, the country has systematic difficulties in providing complete national notification and treatment outcome reports to the ECDC to be included in European Union reporting. A few regions are often late in reporting. The lessons learnt from recent outbreaks further emphasize the lack of preparedness to coordinate clinical and public health services, contact tracing in particular, and to manage relations with the media at different levels.

4.2.2 Address the most vulnerable and hard-to-reach groups.

TB risk groups are all those with an elevated incidence. Hard-to-reach groups are those whose socioeconomic conditions or lifestyle makes it difficult to recognize TB symptoms, access health services, self-administer treatment and attend regular health care appointments. Mapping of TB risk populations and their socioeconomic conditions is necessary in order to:

- design interventions to improve access,
- tailor treatment and social protection interventions for TB-affected people and households and
- plan activities to diminish the underlying TB risk factors.

Adaptation of services to the special needs of the most vulnerable groups is essential in all countries. Regulation based on human rights to promote access to TB services for all is crucial. Hard-to-reach groups at increased risk for TB and for poor access to health care must be locally defined. These groups can include homeless people (including marginally housed people and populations in deprived areas), prison inmates, illicit drug users, people with alcohol use disorders, destitute migrants and some indigenous populations and ethnic minorities. These groups may lack proper documentation and may not be covered by social health insurance or national health services.

Specific training of social and medical staff in contact with groups at high risk to improve their awareness of TB should be considered, in order to decrease diagnostic delay and the duration of the infectious period of cases that may remain undetected in the absence of proper examination.

Beyond ensuring a correct diagnosis and prescribing the correct treatment, a conducive environment must be in place for full adherence to treatment, especially by vulnerable and marginalized groups that may face severe barriers to treatment adherence. A patient-centred care and support approach that is sensitive and responsive to patients' needs is crucial *(134)*. Although supportive treatment supervision is essential, it must be carried out in a context-specific, patient-sensitive manner. Some people may benefit from directly observed treatment. Often more important than supervision is identifying and addressing factors that may lead to treatment interruption and poor treatment response. Enabling interventions include removing financial barriers for treatment completion; making services user-friendly (e.g. decentralization, conducive opening hours, appropriate staff attitude, addressing language barriers); increasing awareness; alleviating stigma and discrimination; and addressing comorbid conditions. Offering a guarantee of non-deportation from the country of arrival to migrants throughout TB treatment might also improve the relationships between carers and patients and foster adherence to treatment *(12)*.

The adverse social and economic effects of TB and its treatment can make vulnerable people more vulnerable. Accessible, free TB services and appropriate social protection systems are required to prevent the catastrophic economic burden represented by the direct and indirect costs of TB. The adverse social consequences may include stigma and social isolation, interruption of studies, loss of employment, loss of housing and deportation. The negative consequences often extend to the families of people ill with TB.

Social protection policies should cover all vulnerable and hard-to-reach groups and include: schemes for compensating the financial burden, such as sickness insurance, disability pension, social welfare payments, other cash transfers, housing support, vouchers or food packages; legislation to protect people with TB from discrimination, such as deportation, expulsion from workplaces or housing, educational or health institutions, transport systems or housing; and instruments to protect and promote human rights, including addressing stigma and discrimination, with attention to gender, ethnicity and protection of vulnerable groups. This requires a multisectoral approach, to ensure that

existing social protection schemes are sufficient for TB patients and to ensure the eligibility of all those in need. Patient support might extend beyond health facilities to patients' families.

Health care staff should be trained to help patients navigate and access social protection schemes. Planning and implementation should involve both government social services and nongovernmental and civil society organizations, including formal and informal community leaders and health providers. The engagement of social services is crucial for TB awareness, for improving access to and the outreach of TB diagnosis and treatment and for delivering culturally sensitive services. Moreover, the involvement of social services is essential in designing and delivering social support and social protection.

Social interventions should address not only people already ill with TB but also people and communities at risk, through a "health-in-all-policies" approach *(28,37)*. Poverty alleviation reduces the risk for TB transmission and the risk for progression from infection to disease. It also helps to improve access to health services and adherence to the recommended treatment. Prevention can also be enhanced by addressing the direct risk factors for TB, including smoking and harmful use of alcohol and drugs, and by promoting a healthy diet *(14,28)*.

Case study 4. Find&Treat: taking TB control to the streets of London

The rates of TB in London are among the highest in western Europe and, as in many big cities, the epidemic in concentrated in vulnerable and socially excluded populations. Find&Treat is a specialist outreach team that takes TB control to the most affected communities, finds cases of active TB early and supports patients in completing treatment and being cured. The team includes former TB patients, who work as peer advocates *(135)*, specialist nurses, social and outreach workers, radiographers and expert technicians. Since 2005, Find&Treat has established a network of over 200 front-line partner health and social care services to tackle TB among homeless people, drug and alcohol users, vulnerable migrants and people who have been in prison. TB in these groups is characterized by delayed diagnosis, infectiousness, drug resistance, non-adherence, onward transmission and poor treatment outcomes, including loss to follow up and preventable death *(31)*.

Find&Treat spans the TB pathway from detection to cure. A mobile digital X-ray unit is used to screen almost 10 000 high-risk people in London every year and to manage outbreaks of TB nationally. In addition, the team supports TB services in London and beyond to manage over 300 of the most socially complex cases every year. Through a comprehensive package of health and social care to address the lifestyle factors that put people at increased risk for TB, 84% of the patients found by the mobile digital X-ray unit have successfully completed treatment. For many patients, TB has been a positive story, which enabled them to break cycles of addiction and homelessness. The team also locates patients who disengaged from services before completing a full course of treatment and provides training to raise awareness and tackle stigma and misinformation.

The work of Find&Treat indicates that the people they support are at high risk for multiple health problems and that their journey through the health system can often be hard to navigate. In addition to a very high burden of LTBI, which can be treated to prevent active disease, these populations have high rates of undetected co-infection with hepatitis C and B viruses and HIV. National TB guidelines recommend screening for these other important public health infections at the same time as mobile chest radiology *(136)*. Find&Treat is currently working with Public Health England to extend its work nationally and to incorporate screening for other infections and essential vaccinations. Both the National Institute for Health and Care Excellence and Public Health England have independently evaluated the service and found that it is highly cost-effective and potentially cost-saving *(137)*.

Case study 5. Improving TB control among indigenous peoples in Canada

Between February 2011 and March 2012, the Public Health Agency of Canada, through the National Lung Health Framework, provided 805 000 Canadian dollars in funding to the Taima TB project based in Iqaluit in the northern territory of Nunavut, Canada. The aim of Taima TB was to create greater awareness of TB among Inuit living in Iqaluit and to test a novel approach to the screening and treatment of LTBI in neighbourhoods in which the residents were at high risk for active TB disease. The project was carried out in three phases: an awareness campaign, a door-to-door campaign and a treatment phase. It was led by a team of researchers from the Ottawa Hospital Research Institute and members of the community who served as TB champions. Partners included the Government of Nunavut and organizations representing indigenous peoples.

The awareness campaign, conducted over 4 months, took a multifaceted approach tailored to the cultural and linguistic characteristics of the community. Feedback from focus group participants indicated that the strategies used to promote TB awareness were effective and well received by community members. In fact, community engagement was cited as the most successful aspect of the project in the performance measurement report submitted to the Public Health Agency of Canada.

During the door-to-door campaign, a TB nurse and a TB champion visited 440 people over 6 months, 300 of whom were screened for LTBI in their homes with both a tuberculin skin test and interferon-γ release assays. As a direct result of the campaign, 42 new cases of previously undiagnosed latent TB were identified. Thirty patients participating in the Taima TB project completed a full course of treatment for LTBI and took 100% of their expected doses of isoniazid within 12 months. In addition, the research team identified five cases of active TB earlier than they would have been reported in the existing programme.

Although the project was considered a success overall, it met a number of challenges. For example, the financial resources provided, while adequate for the timeframe of the project, did not allow for sustainability in the longer term. More human resources were needed for the door-to-door campaign and to ensure that medication was delivered to patients in an efficient, timely manner.

In 2012, the Canadian Institutes of Health Research awarded two grants to build on the lessons learnt from the Taima TB project: one to expand the awareness campaign to two communities in Nunavut and a second to evaluate the state-of-the-art TB diagnostic equipment purchased by the Government of Nunavut and installed at the Qikiqtani General Hospital in Iqaluit.

4.2.3   Address special needs of migrants and cross-border issues.

Epidemiological assessments should be conducted to explore whether TB in migrants is a priority and to assess which groups are at high risk for TB. For this, proper surveillance is required, which should include disaggregated data on migrant groups and related variables.

The essential activity is to ensure that health care services are accessible to all migrants and delivered in a patient-centred, culturally sensitive manner, including activities to overcome language and other barriers.

Political commitment across borders (including implementation of a framework for cross-border collaboration) and national legislation should guarantee the functionality of and access to TB services (prevention, infection control, contact management, diagnosis, treatment and psychosocial support) with no financial burden for all migrants regardless of their status, including undocumented migrants and migrants without full residence status *(12)*. It is important to establish cross-border referral systems, with contact tracing and information sharing, to ensure continuity of care for migrants and to enhance harmonization of treatment protocols across borders along migration corridors. For migrants with TB, the right to complete treatment in the country in which the diagnosis was made should be ensured, or schemes should be put in place to ensure that patients who move during treatment can continue treatment while minimizing the public health risk.

Migrant communities should be empowered through social mobilization and health communications. Medical and administrative personnel should be sensitized to the health profiles and special needs of migrants in order to build cultural competence. TB diagnosis, treatment and care for migrants should be integrated within general health services, while other efforts may be required to reach migrants in centres for refugees and asylum seekers, situations of displacement and other special settings, such as shelters for undocumented migrants.

On the basis of epidemiological assessment, countries may consider systematic screening for active TB in migrants, either before migration, at the point of arrival or after arrival. This should be accompanied by careful evaluation of the outcome of screening and appropriate referral to a treatment programme. Screening of migrants for TB should follow established ethical principles for screening for infectious diseases and be based on human rights. It is particularly important to safeguard against stigma, discrimination and deportation *(138)*. More research is needed to evaluate the effectiveness and cost-effectiveness of different screening approaches for different types of migrants, taking into account the health system, the patient and societal perspectives *(138)*. As systematic screening of migrants does not exclude the possibility of later occurrence of TB, continuous access to health care is important, whatever the screening system in place.

LTBI screening and treatment are important elements of contact investigation and outbreak management, for migrants as well as others. See section 4.2.4. for discussion on contact investigation, outbreak management and other aspects of LTBI screening and management.

Pre-migration screening, if done, may require investment in diagnostic and treatment facilities in the countries of departure. Such capacity-strengthening should ensure that the benefits are shared with the national TB programme in the country in which screening is done, and good links must be established with the country's surveillance system.

Bold intersectoral policies and systems are required to address the underlying vulnerability of migrants that increases the risk for TB and for poor access to health services. Policy coherence and shared solutions should be sought between health and non-health sectors, such as immigration authorities, social services and the labour sector. Special social protection measures may be required for migrants with or at risk for TB.

Case study 6: Integrating medical anthropology and other social sciences into a TB programme: the case of Ethiopian immigrants to Israel

Israel is a country of immigration, with some 90% of new TB cases in people born abroad *(139,140)*. The Israeli health care system has established new, unique methods of health care delivery to achieve maximum adherence of patients of various cultural backgrounds. The new Israeli TB programme (launched in 1997) *(141)* thus emphasizes the unique needs of immigrants from countries highly endemic for TB such as Ethiopia and adaptation of Israeli health care providers and workers to this population *(105)*.

The complexity and dynamic nature of the concepts related to health and well-being in this immigrant population were studied to identify the range of social problems affecting the patients, in order to achieve therapeutic goals. With TB as an example of a multifaceted public health issue, social science tools were used in the national TB programme to define the sociocultural, economic and political aspects related to TB and their interplay. Social sciences were also helpful in identifying pitfalls in the existing TB control programme and in indicating concrete solutions for overcoming them. Specifically, the research illustrated the gap between the Ethiopian concepts of health cosmology, death and well-being and western medical concepts and terminology. It showed that, partly because of this gap, patients found it difficult to commit to the TB treatment offered. A new set of health-related terms and vocabulary were therefore created to be incorporated into the Ethiopian health lexicon and enable better communication of a different health concept and not solely to translate medical jargon *(105)*. Later, a group of community health workers of Ethiopian origin was constituted to address the needs of the Ethiopian TB patients, their families and other health care staff serving this population and acting as a cultural mediator. These community health workers work at district health offices and TB centres. Their work goes above and beyond linguistic translation and involves long-term empowerment of patients. This multidisciplinary approach was incorporated into the Israeli TB control programme with several other essential components (e.g. directly observed treatment for all TB patients, regardless of their country of origin and throughout treatment, pre- and post- arrival screening of high-risk migrants and active case finding *(13,141,142)*.

When there is political and institutional commitment to combat TB and the organizational infrastructure is in place, it is fully appropriate to address cultural factors and any concomitant cultural barriers in order to achieve successful treatment. In such a context, applying social science tools within a national TB programme can provide useful insight and contribute to the success of the programme.

Case study 7. The Immigration and Refugee Health Working Group: experience in the United Kingdom

In 2005, migration experts from Australia, Canada, New Zealand, the United Kingdom and the USA formed the Immigration and Refugee Health Working Group, initially to address common concerns in respect of pre-migration processing of refugees. They have discussed uniform global migration standards for public health screening, specifically for TB, in order to create consistency among doctors in the 164 countries undertaking this work ("panel physicians") to meet the public health standards of the receiving countries while achieving the highest levels of efficiency and care for migrants. Shared international protocols and standards allow participating countries to pool resources for better quality, consistency, oversight, ethical pricing and treatment of migrants. Collaboration also allows the countries to negotiate volume discounts for diagnostic supplies for panel sites throughout the world and to share valuable data on migrants for WHO and national TB control programmes.

With protocols to strengthen screening algorithms and implementation of rigorous diagnostic and treatment programmes, many panel physician sites now have outstanding surveillance capacity, state-of-the-art TB laboratories capable of sputum smear, culture, drug susceptibility testing, interferon-γ release assay and standardized tuberculin skin testing and programme staff trained in directly observed treatment. The convergence of the growing capacity of panel sites and the development of uniform international standards on migration and TB represent a unique, unprecedented opportunity to improve TB control locally while contributing to TB elimination globally. The outcomes of panel physician pre-entry TB screening programmes in Australia, the United Kingdom and the USA, comprising 2.5 million clients screened annually, are used to assess the effectiveness by country of origin and treatment outcome, including, in some countries, LTBI screening for populations < 15 years of age.

Over the past few years, panel physicians for the different countries (many of them shared) have diagnosed large numbers of cases of TB among millions of clients. For example, in 2010–2013, Australia found 1694 cases in medical examinations of 1 652 669 applicants; between 2006 and 2012, the United Kingdom identified 578 cases of active TB at 696 000 medical examinations performed; and, in 2012, more than 1100 of nearly 500 000 visa applicants undertaking medical examinations for the USA offshore were found to have TB, approximately 60% of which cases were smear-negative but culture-positive. The largest panel group, the International Organization for Migration, identified 1170 cases of active TB among 368 238 people screened in several countries between 2010 and 2012, for a prevalence rate of 318 per 100 000 population.

In the United Kingdom, as in many low-incidence countries, TB disproportionately affects migrants from high-prevalence countries. Based partly on the experiences of the screening programmes of Australia, Canada and the USA, pre-migration screening in the United Kingdom is therefore done with international partners. It is part of a package of interventions, which include pre-migration screening for active TB and national recommendations for post-arrival testing and treatment for latent TB and vigilance for active TB in settled migrants. After a pilot phase in collaboration with the International Organization for Migration, the United Kingdom now conducts screening in all eligible countries with a high burden of TB. Migrants who are found to have TB are issued a visa after they have successfully completed treatment. Pre-migration TB screening of targeted populations represents an opportunity to give the appropriate treatment to the individual and to follow up and manage close contacts, with a potentially positive impact on not only the receiving country but also the country of origin. The benefits to the country of origin include early diagnosis of cases to limit spread and building up the TB management infrastructure to support the national TB programme.

Case study 8. Cross-border coordination and referral in the Torres Strait, between Papua New Guinea and Australia

Papua New Guinea's Western Province, with a total population of 219 103 in 2011, is a coastal, south-western province that shares an international sea border with Australia's Torres Strait Islands. Given the historical sea and land use of the Torres Strait area by its indigenous residents, a treaty agreement between Papua New Guinea and Australia was signed in 1978 that, to date, allows residents of both countries to cross the border freely. While there is no provision for medical care in the agreement, casual cross-border migrants from Papua New Guinea have been seeking health services in Australia's Torres Strait Islands for many years. Cross-border movement in this region unavoidably poses some risk for the spread of communicable diseases. In 2011, it was decided that all TB patients (and those with other medical conditions) from Papua New Guinea receiving treatment in Torres Strait clinics were to be transferred home, and major efforts were made to build the capacity of the Western Province's health care system and its TB services. To ensure proper cross-border referral of patients, a clinical collaborative group of Australian and Papua New Guinean doctors was established, which held its first official meeting in Daru (Western Province) in February 2013. All Papua New Guinean patients who seek care in Torres Strait clinics are now referred home by e-mail and mobile communication between designated cross-border communications officers, with positive programme results thus far.

To date, this venture has been successful not only in decreasing the movement of people for TB care but also in building the capacity of TB services in this region of Papua New Guinea. The interventions funded by the Australian Government include support for more human resources, including funding senior TB physicians and TB programme coordinators; training community-based health workers and volunteers to oversee community-level TB treatment; construction of a new 22-bed TB and isolation ward at Daru General Hospital; laboratory support and provision of anti-TB drugs and medical treatment; and increasing outreach by the provision of a sea ambulance and two banana boats. Better community awareness and diagnosis have led to an increase in the diagnosis of TB in Western Province, the case notification rate having increased from 227 per 100 000 in 2012 to 262 per 100 000 in 2013. The rate of successful completion of treatment by new patients with infectious TB in the South Fly District of Western Province increased from 60% in 2012 to 72.5% in 2013. As a result of earlier detection and better treatment in this District, the rate of deaths among patients with drug-resistant TB decreased from 45% in 2011 to 3% in 2013.

4.2.4 Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups, and provide appropriate treatment.

Early detection of TB is essential in all settings. While active case finding and systematic screening for active TB in high-risk groups could contribute, the main priorities are correct identification of people who should be tested for TB among those actively seeking care and use of the appropriate diagnostic tools *(138,143)*.

It is essential that health care staff receive continuous education about TB and particularly those who provide health services to groups at risk for TB, such as migrant health services, prison health services and outreach health services for vulnerable groups. Sufficient knowledge about TB and its risk groups is nevertheless a basic requirement for all health care workers.

Systematic screening for active TB in high-risk groups can help protect people who are both at high risk for TB and have a high likelihood of severe consequences from a delayed TB diagnosis and treatment, such as people living with HIV/AIDS. It can help reduce TB transmission by early detection of TB among contacts and among people living in congregate settings, such as prisoners. By outreach, TB screening can improve access to TB care for marginalized groups such as the homeless *(138)*.

Contact investigation, including finding the sources of recently infected cases, e.g. small children, should be done routinely for each newly detected TB case, with due consideration to time and space, perhaps extending to community contacts *(22,59)*. This requires effective real-time TB surveillance. Systematic screening should also be routine in people living with HIV/AIDS and should be included in general health check-ups of people working in the mining industry and other occupations with exposure to silica *(138)*.

In TB outbreaks,[4] there are usually multiple sources within a given risk group, and screening may be considered for the whole group at risk. Real-time surveillance, with mapping of cases in space and in time, preferably supported by genotyping, is required to identify an outbreak in a community, health care facility *(144)*, correctional facility *(145)* or institution and in other settings or risk groups *(146,147)*.

Other high-risk groups not identified through contact investigation or outbreak management, such as migrants, prisoners, homeless people, certain ethnic minorities, the elderly and people with immunocompromising disorders or treatments, may be given priority for screening for active TB, depending on the local TB epidemiology and an assessment of benefits, risks and costs *(138)*.

General population screening or screening of groups other than those at very high risk should not be performed in low-incidence countries, as there is weak evidence for any epidemiological impact *(148)*, it can be very expensive, and it is associated with a high risk for false-positive TB diagnoses when the prevalence is low *(149)*.

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[4] A disease outbreak is the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season (WHO 2014: http://www.who.int/topics/disease_outbreaks/en/).

A national strategy for systematic screening for active TB in selected high-risk groups should include careful case-based surveillance to guide reprioritization and discontinuation of screening when the yield becomes low.

The general principles of screening for LTBI are a positive trade-off between benefits and harm for the individual and a decision to test is an intention to treat if the results are positive. For an individual who is latently infected to be eligible for this intervention, he or she must have a higher risk for progression to active TB, and the benefits of treatment should outweigh the risk of drug toxicity. WHO is in the process of finalizing guidelines on LTBI screening and treatment, and this Framework will be updated when the guidelines have been finalized.

Case study 9. Strategic approach to outbreak management, TB screening and LTBI in The Netherlands

The Netherlands notified 848 cases of TB in 2013 (notification rate, 5.0/100 000 population); 74% of the patients were foreign born (notification rate foreign born, 35/100 000 population). The strategic approach is targeted screening of high-risk populations with systematic monitoring, evaluation of the results and adjustment of policies and target groups on the basis of monitoring results. The policies described below have been the cornerstones of the Dutch TB control programme for the past two decades.

The first is contact investigation, which involves systematic evaluation of the contacts of known TB patients to identify active disease or LTBI. Contacts are examined according to the principle that an investigation is extended to casual contacts if the rate in close contacts is higher than the expected background prevalence in the specific population. In an evaluation of a 5-year contact investigation (2006–2010) involving 85% of all TB patients in the Netherlands, 55 976 contacts of 1675 culture-positive pulmonary TB patients (median, six contacts per smear-negative pulmonary TB and 20 contacts of smear-positive patients) were examined for active TB or LTBI. The yields were 255 (0.54%) and 2918 (6.1%) for all contacts, respectively; 6.4% of all notified TB cases in the Netherlands were identified by contact investigation during that period. The number required to screen for active TB was 93 for close contacts (inner circle), 423 for middle circle contacts and 2913 for outer circle contacts. For LTBI, the numbers required to screen were 12, 23 and 38 for these circles, respectively.

Well-defined risk groups with a TB incidence of more than 50 per 100 000 populations are screened systematically. Migrants, asylum-seekers and refugees from high-incidence countries are screened radiographically for active TB when they apply for a residence permit or request asylum. These migrants are also offered follow-up radiographic screening if they originate from a country with a TB incidence of > 200 per 100 000 population. An evaluation of 6 years of migrant screening (2005–2010) showed that entry screening identified TB in 108 of the 117 389 screened migrants (number required to screen, 1087) and in 309 of 58 477 screened asylum seekers (number required to screen, 189). A country-wide prisoner screening programme has been in place since the early 1990s with mobile X-ray units. The screening programme was scaled down in 2011 to include only prisoners with a high risk for TB (symptomatic, foreign-born, substance dependent) to increase efficiency. In 2012, 17 patients were identified, corresponding to a number required to screen of 1246.

Since 1993, universal DNA fingerprinting analysis of all *M. tuberculosis* strains has been instrumental for identifying the cause of TB outbreaks. Outbreak management at local level, e.g. screening the population at risk, has been shown to be effective for containing outbreaks and stopping transmission *(150)*.

The challenge in the Netherlands is to sustain effective, efficient TB control interventions and reduce the burden of disease in migrants, e.g. by screening for LTBI, which is currently being considered.

4.2.5　Optimize the prevention and care of drug-resistant TB.

In countries in which the TB incidence has been reduced to a low level, most of the TB caseload is found to be concentrated in patient groups at risk for poor treatment adherence. As more countries are destined to follow this trend after 2015, greater vigilance is clearly required for the emergence and transmission of drug-resistant strains. Nonetheless, the time-honoured principles of good TB control should continue to apply. First, the treatment of drug-susceptible disease must ensure that the resistance does not develop as a result of improper treatment. Secondly, if drug resistance emerges, infection control measures must be reinforced for all forms of TB. Thirdly, patients with drug-resistant TB should be started on appropriate treatment as soon as possible, and, fourthly, contact investigation should start promptly.

The likelihood with which patients with drug-resistant TB will be cured effectively and rendered uninfectious depends on early institution of appropriate treatment and patient support. It is therefore crucial that "test and treat" approaches allow for early identification not only of TB but also of the resistance patterns that determine the type of treatment required. This implies strengthening diagnostic capacity *(151)*.

In order to limit loss of information on TB and drug-resistant TB and improve the completeness of notification, diagnostic laboratory information systems should interoperate with other databases of electronic medical records and surveillance data and should be comprehensive, also incorporating information from the private health sector. Surveillance of drug resistance patterns requires comprehensive susceptibility testing of all identified TB cases. The quality of the data and the performance of the surveillance system should be ensured by tools developed for this purpose, such as the TB surveillance standards and benchmarks *(26)*.

Optimal patient support is particularly important for people with M/XDR TB, who have longer, more challenging treatment. Clinical management of patients with drug-resistant TB should include the possibility of calling on the expertise of specialists in various medical fields, including paediatrics, HIV/AIDS care, substance abuse treatment and surgery. Such services will ideally be provided through an expert committee.

A patient-centred approach that is sensitive and responsive to patients' needs requires multidisciplinary input *(21,22,134)*. Support measures beyond the treatment regimen must be individualized to each patient. Social networks should provide comprehensive care of patients with drug-resistant TB in both ambulatory and hospital care. Directly observed treatment can improve adherence to treatment, with measures to educate patients and their families. The cost of financial enablers or other incentives to patients and their carers may be smaller than the expected gains, particularly when TB control hinges upon a smaller number of cases completing their prescribed treatment.

Treatment and support must extend beyond cure to address any sequelae associated with TB. Access to comprehensive palliative and end-of-life care is essential, particularly for people with M/XDR-TB *(151-153)*.

Currently available treatment regimens for drug-resistant TB remain unsatisfactory in terms of duration, safety, effectiveness and cost *(7,41,154–157)*. New, safer, affordable, more effective medicines that would allow shorter treatment regimens that are easier to administer are key to

improving treatment outcomes *(157–160)*. Linkage with existing pharmacovigilance mechanisms will contribute to safer use and management of medicines and their side-effects.

Treatment practice must keep pace with emerging treatments, and rapid translation of scientific findings into treatment practice will be vital. Future regimens should be much shorter and safer than those in current use. More refined investigation of the patient factors and biomarkers of clinical monitoring that are most closely associated with response to therapy would allow better adjustment of treatment. Better research is required on preventive therapy of contacts of drug-resistant TB patients. Extension of current trials (such as on shorter MDR TB regimens) to low-incidence settings would be desirable.

The experience of the past few decades indicates that resistance will also develop to anti-TB medicines that have not yet been released onto the market or even discovered. Closer surveillance of drug resistance in the community will be required. The shrinking market for second-line drugs will require mechanisms to avoid a shortage of drugs throughout the country. Rational use of drugs, backed by properly enforced regulation, and measures to assist clinical decisions and guarantee the quality of drug formulations (prequalification or conformity to the requirements of stringent drug regulatory authorities) are expected to forestall the development of drug resistance but not to eliminate the risk *(161)*.

Case study 10. National Advisory Group on TB treatment in Finland

Currently, there are 20 hospital districts (excluding Åland Islands) in Finland, which organize and provide specialist medical services for the populations of their municipalities. All TB patients are tested for drug-susceptible TB; M/XDR TB treatment is decentralized and can be started and followed in every public hospital. The numbers of cases of MDR TB, XDR TB and TB–HIV are relatively low, even though Finland has borders with countries with high MDR TB burdens, such as the Russian Federation and the Baltic States. Nevertheless, a certain level of readiness is required. The quality and level of care for MDR TB patients is maintained by the availability of expertise for treatment through the National Advisory Group for TB treatment.

In 2006, the Ministry of Social Affairs and Health in Finland established a national TB programme prepared with an expert group of professionals dealing with TB, which was updated in 2013. One proposal was to form a national advisory group on TB treatment, which was started and funded (as it is continuously) by the Ministry of Health in 2007. The purposes of the Advisory Group are to acquire, maintain and develop knowledge on the treatment of difficult cases of TB, to monitor and give guidance to clinicians treating all cases of M/XDR TB and to give advice on TB–HIV co-infection, poly-resistant cases and other difficult-to-treat TB cases. The members of the Group include pulmonary physicians and infectious disease specialists responsible for TB treatment in every university hospital (Helsinki, Tampere, Oulu, Kuopio, Turku), three paediatricians with an infectious disease sub-speciality, a representative from the mycobacterial reference laboratory and other specialists who are consulted as required.

The Advisory Group meets three or four times a year to discuss every patient in follow-up, represented by the member of the Group responsible for that case. Special electronic follow-up cards are used on a secured Internet (extranet) forum designed for the Group. The physician responsible for treatment of a case can contact the local university hospital representative or the chair of the Group. Each case is presented to the whole Group, which follows it thereafter. The physician treating the patient can seek further advice from the Group between meetings at which the patient is assessed routinely. For urgent cases or problems, the Advisory Group uses the Internet forum for discussion.

The practice was initiated because there was concern in Finland that doctors treating TB did not have the necessary knowledge, particularly for treating drug-resistant TB, because of the low incidence of TB in Finland. It was necessary to train and strengthen a group of doctors in the field of special TB treatment, who could act as consultants for other doctors treating TB. It was also necessary to standardize the treatment and care of drug-resistant TB throughout the country.

The Advisory Group follows up the treatment of all M/XDR TB cases and has thus been able to standardize the treatment of TB and M/XDR-TB in Finland. The Group has been proved useful for responding to continuous questions. A WHO–ECDC country visit in 2010 showed that the initiative is effective. The knowledge and interest of the members of the group have increased greatly since 2007, so that physicians treating TB throughout the country can seek and receive expert help when required.

4.2.6 Ensure continued surveillance, programme monitoring and evaluation and case-based data management.

As TB caseloads are reduced, it will become more important not to miss any new patients, particularly those who are more likely to die, to infect others or to have drug-resistant TB. Public health activities must therefore be maintained by a framework of complementary measures, both regulatory and enabling, to promote adequate vigilance.

Notification of TB should be compulsory at all levels, and surveillance methods must evolve to address new realities. Surveillance systems must be more sensitive and also allow discrimination among the forms of the disease that require different prevention and care approaches. Core indicators should be identified in the context of the country, particularly to monitor transmission. The practice of recording data on individual TB patients should be maintained and strengthened *(162)*, and surveillance systems should ensure the completeness, timeliness, consistency and validity of data, with periodic assessment of standards and benchmarks *(26)*.

Those responsible for surveillance must keep abreast of advances in TB diagnostic techniques, the results of which are increasingly automatically generated, and of the information and communication technology required to capture and transmit data rapidly. Future surveillance should better exploit information technology, including linking patient data (demographic, clinical, geopositioning, vital statistics and socioeconomic data) with the DNA fingerprints of strains. These techniques should be applied in particular when the number of cases becomes smaller and outbreak investigation more crucial.

Special attention to TB rates in children *(163)*, disaggregation according to risk profile and monitoring of people receiving LTBI treatment can also help determine trends in transmission and incidence for assessing impact and refining interventions.

Fewer patients may make it more feasible to collect more variables more frequently, which will be useful not only for patients under treatment but also for studying risk factors and disease determinants. Due consideration should be given to extending the range of variables beyond those usually collected in TB surveillance.

Data on the location of patients' residences permit spatiotemporal studies of TB hotspots for targeted public health action *(164–166)*, which becomes more pertinent as an epidemic recedes and fewer cases become more concentrated in space and time. Unique identifiers and biometric data may help in tracing patients in settings where migration is common.

Information on drug-related harm will become more important when new medicines are used before the completion of phase-3 trials, and pharmacovigilance could be integrated routinely into a monitoring framework for TB *(167)*.

The future should see more streamlining in interoperable linkage of data across facilities and systems, such as hospitals, laboratories, mortality registers and patient management systems, to ensure that more comprehensive, timely information is made available to clinicians and public health practitioners. Links with other disease surveillance networks, such as for HIV infection and other comorbid conditions including diabetes and hepatitis, should be explored.

Case study 11. Electronic registers, harmonization and collaboration in Europe

In response to the resurgence of TB and other serious communicable diseases, the European Parliament strengthened surveillance in the European Union in the late 1990s *(168,169)*. Sharing of information on high-priority diseases was mandated for early warning. In 2002, the European Commission published case definitions for surveillance, which were subsequently revised; these measures were crucial for standardizing reporting *(170,171)*. These landmark decisions were preceded by strong public health advocacy, led by a number of committed professionals and national TB managers as part of a "Wolfheze workshops" movement *(25)*. Useful guidance documents issued by this group include recommendations on TB surveillance and the variables to be collected *(172)*, treatment outcome monitoring *(173)* and surveillance of drug resistance *(174)*.

Countries were encouraged to use case-based (individual) data on TB patients at national level. Over the years, the number of variables increased to include those for first-line drug resistance and treatment outcome. The number of countries reporting case-based data for European supranational surveillance increased from fewer than 20 in 1995 to 35 in 2005, when about 100 000 TB cases were being reported each year to EuroTB, the WHO Collaborating Centre based in Paris, which coordinated the European database from 1996 to 2007 *(175)*. In 2008, this function was handed over to the ECDC. These individual data still constitute an important knowledge base for TB surveillance in Europe and have allowed in-depth descriptions of trends and patterns of TB *(176,177)* and of the determinants of drug resistance and outcome *(178)*.

Case study 12. Collection of migration-related variables in Australia

While the TB case notification rate among native-born Australians has decreased since the 1960s, rates among foreign-born residents have risen continually, accounting for 90% of all TB cases in 2010. Against this backdrop and an upward trend in the number of MDR TB cases, Australia recognized the importance of collecting detailed data on TB in migrants in order to prepare tailored, evidence-based policies for migrant populations. The variables that are routinely collected include migrant type, country and region of origin and time since arrival. Data on time since arrival, for instance, led to the finding that the rates among foreign-born TB cases are highest within the first 2–3 years after arrival, and this finding influenced Australia's immigration policy of follow-up TB screening for 2 years after arrival among migrants who previously had active TB or who have diagnosed latent TB. Data disaggregation by both region of origin and time since arrival allowed even more detailed analyses. As shown in the figure below, the incidence of TB is highest just after arrival but varies substantially by region of origin *(179)*, and this insight has been used to revise Australia's TB screening policies.
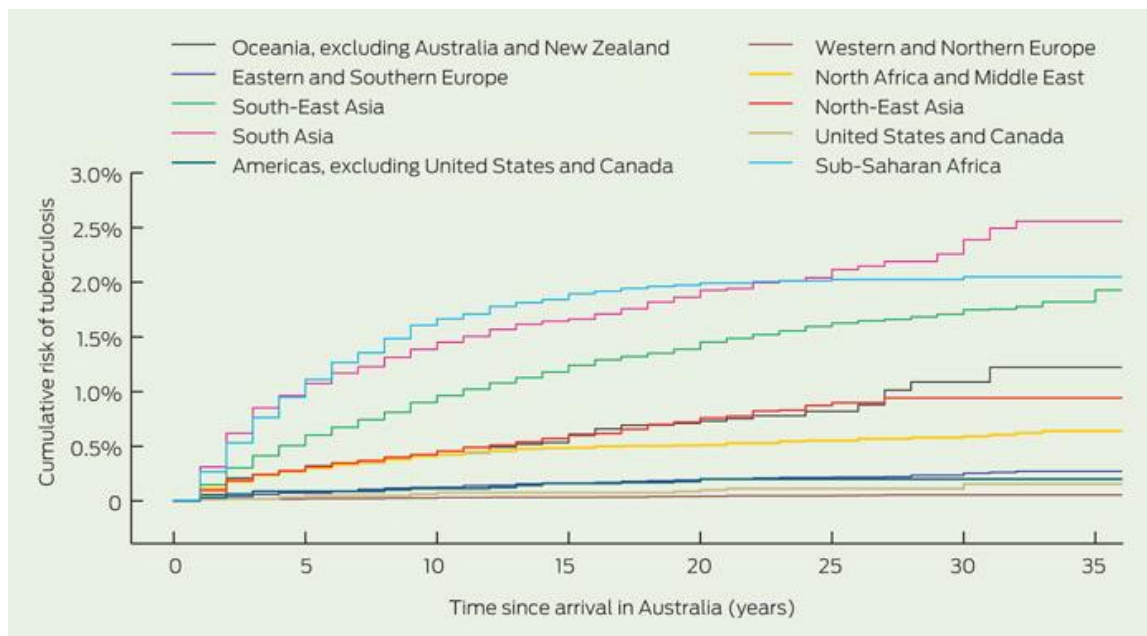
4.2.7 Invest in research and new tools.

With the currently available tools, TB elimination is not within sight in the near future. Revolutionary new technology and service delivery models are needed, which will require intensified research—from fundamental research on innovations for better diagnostics, medicines and vaccines to operational and health systems research to improve current programme performance and to introduce new strategies and interventions based on new tools. Low-incidence, high-income countries can contribute substantially to the required international financial and technical support, to collaboration for fundamental and clinical research on new tools and to epidemiological, social and operational research to improve uptake and ensure equitable access to new and existing technologies.

Of particular relevance for low-incidence countries is the development of better tools for screening high-risk groups for both latent infection and active TB. A rapid, accurate test for LTBI that could reliably predict the risk for progression to active disease, and a more effective, safer LTBI treatment regimen would greatly enhance the prospect of improving TB prevention through chemotherapy.

A new, effective vaccine could change the landscape of TB prevention *(180)*. More research and investment are required to address a series of major scientific challenges and to identify priorities for future TB vaccine research. An effective post-exposure vaccine to prevent the disease in latently infected individuals would be a huge advance towards TB elimination, which would be favourably complemented by the development of a safe pre-exposure vaccine to prevent *M. tuberculosis* infection at population level. As TB vaccine trials are expensive and lengthy, new clinical research strategies should be explored to provide answers about the pathophysiology of *M. tuberculosis* relevant to the development of new TB vaccines and about the safety, immunogenicity and potential clinical impact of candidate TB vaccines *(181)*.

MDR TB has been declared a public health crisis by WHO. Better, safer, shorter treatment for drug-resistant TB is urgently needed. The pipeline of new drugs has been extended substantially during the past decade *(182)*, and two novel drugs, bedaquiline and delamanid, have been approved for use in MDR TB treatment. Novel regimens including new or repurposed medicines and adjuvant and supportive therapy are being investigated *(183,184)*. In order for further progress to be made, investment is required in both research and capacity-building for conducting trials in accordance with international standards. Markers of treatment outcome should be developed to facilitate the conduct of clinical trials, and reliable, rapid, cost-effective diagnostics and markers of drug resistance are essential for diagnosing MDR TB and for early monitoring of the emergence of resistance *(185)*.

Fostering better, more relevant epidemiological, operational, health system and social science research will improve implementation and contribute to both national and global policies. For this purpose, good systems for research prioritization, planning and implementation must be in place at country level and internationally. Better strategies are required to identify and target interventions to high-risk groups with innovative tools. More research on social determinants of health, especially among high-risk groups (such as migrants, prisoners and homeless people) is essential.

A broad-based, concerted effort is required to improve research capacity, allocate appropriate resources and encourage stakeholders to work together. Capacity should be reinforced to conduct trials of new or improved drug regimens for drug-susceptible and drug-resistant TB and of new vaccines and to measure clinical and immunological outcomes. A prominent role should be assigned to research advocacy at national and international levels to support these activities. Countries

should consider investing in competitive thematic research grants and fellowships to encourage young cadres of scientists to become involved in the field.

4.2.8   Support global TB prevention, care and control.

In a globalized world, sustained national TB elimination cannot be achieved without a dramatic decrease in the global burden of TB. The interdependence between high- and low-income countries, where people move back and forth across borders, with different health profiles affecting disease burden and patterns, means that no country can now stand alone. Support for full implementation of the global TB strategy is therefore in the interest of low-incidence countries. Adopting, adapting and implementing the strategy, with full consideration for the key interventions, should, in itself, give significant support to global TB control.

Low-incidence countries might have to mobilize additional resources for comprehensive implementation of the global strategy in line with these interventions. Although many low-incidence countries have been contributing financially to global TB control efforts, these contributions must also be increased to implement the greatly enhanced interventions of the global strategy. Raising additional financial resources for both domestic and international TB care and prevention depends on TB remaining high on the international public health agenda. Active engagement and support from high-income, low-incidence countries to promote global TB advocacy could give the necessary visibility and sustained efforts essential for TB elimination.

Continuous monitoring will be required to measure progress and to ensure that implementation of the global TB strategy is on track. For this purpose, all countries should continue to participate in and benefit from global surveillance, monitoring and evaluation for TB prevention, care and control. Low-incidence countries can continue to support global efforts to control TB in various ways, besides contributing funding for TB care and prevention through bilateral and multinational mechanisms; these include participating in research consortia, contributing to guideline development, providing technical assistance, exchanging technology and strengthening research capacity.

The trends in TB rates in low-incidence countries are driven significantly by migration. Activities to address the continuity of care and the problem of TB among migrant and refugee populations could also benefit from close collaboration with national TB programmes and ministries of health in high-incidence countries along the lines described above.

Case study 13. International support through US CDC and the US Agency for International Development

US Government agencies work with the global TB community to combat TB. The US Agency for International Development (USAID) is a lead agency in international TB control and works with all the other US Government agencies involved to provide a coordinated approach to global TB control. USAID supports implementation and scaling-up of all components of the global TB strategy in bilateral programmes, in partnership with national TB control programmes. It also supports programmatically relevant operations research and late-stage clinical trials. USAID also works with the Office of the Global AIDS Coordinator at the Department of State, which leads the US Government response to TB–HIV co-infection as part of the President's Emergency Plan for AIDS Relief, coordinating the US Government agencies involved in the Emergency Plan.

The US CDC, an agency under the Department of Health and Human Services, leads domestic US Government TB control activities, provides technical support to international partners in epidemiology and surveillance (including of drug-resistant TB), laboratory strengthening and clinical and operational research to evaluate promising diagnostic and treatment strategies and ensures the efficient use of new approaches to TB care. The US CDC also funds the TB Clinical Trials Consortium and the TB Epidemiologic Studies Consortium to fill current gaps in understanding of TB diagnostics, treatment regimens, case detection and monitoring.

The National Institutes of Health, another agency of the Department of Health and Human Services, improves biomedical understanding of TB and conducts basic, applied and clinical research on both drug-sensitive and drug-resistant TB; it is also involved in developing new drugs, vaccines and diagnostics.

Global partnerships are an integral part of the US Government's approach to global TB control, and it participates in and provides support for several activities and initiatives. Engagement in the Stop TB Partnership is a critical element of the programme. USAID provides support to the Stop TB secretariat and is the leading bilateral donor to the Global Drug Facility. Both USAID and the US CDC are members of the Stop TB Partnership's coordinating board. USAID, the US CDC, the National Institutes of Health and the President's Emergency Plan for AIDS Relief participate in all the Stop TB Partnership's technical working groups relevant to the expertise of each agency. Regional partnerships are another important component of this approach, as they enable the US Government to support activities tailored to the characteristics of specific geographical areas. Through grants to regional institutions and regional initiatives, the US Government supports capacity-building, fosters cross-country collaboration and conducts international operations research and pilot activities. Examples include the establishment of centres of excellence for MDR TB that provide technical assistance and training to countries in their regions and bi-national partnerships to respond to cross-border TB control issues.

Case study 14. Canadian support to global TB control through TB REACH and the Global Drug Facility

TB REACH funds innovative projects to find and treat people with TB in some of the poorest, most vulnerable communities. Since 2010, 109 TB REACH projects in 44 countries have detected 210 000 additional TB cases, saved 105 lives and prevented 2.1 million new infections with innovative approaches. This initiative has served as an incubator for innovation. A number of successful projects have led to sustainable funding and scaling-up through domestic programmes, the Global Fund to Fight AIDS, Tuberculosis and Malaria and the US President's Emergency Plan for AIDS Relief. TB REACH also leveraged an additional 30 million US dollars in 2012 from UNITAID for distribution of a rapid diagnostic test, contributing to a significant reduction in the price of the test.

Canada also led in establishing the Global Drug Facility, committing more than 149.6 million Canadian dollars since its creation in 2001. This made Canada one of the largest single donor countries for first-line TB drugs. The Facility provides a unique package of services, including procurement of high-quality TB drugs and diagnostics at low cost and technical assistance to countries for drug management and monitoring of drug use. By the end of 2012, the Facility had delivered around 22 million first-line treatment courses and 100 000 second-line courses to more than 100 countries worldwide, at a cost of 155 million Canadian dollars.

To improve the availability of TB medicines, the Facility has helped standardize treatment regimens by promoting fixed-dose combinations of anti-TB medicines and kits containing all the medicines needed for full treatment of one patient, promoting worldwide the WHO recommendations on appropriate TB treatment. The Facility also supports improvement of drug management activities in countries. Although the mandate of the Facility does not make it responsible for medicines beyond the port of entry, in response to reports from partners that in-country drug management is weak, the Facility has used its monitoring missions to provide technical assistance in this area.

Case study 15: International support through the Global Fund

As a partnership organization that provides resources to low and middle-income countries in the response to AIDS, TB and malaria, the Global Fund works with governments, civil society, UN agencies, the private sector and affected communities. Its operational model is based on country ownership and performance-based funding. Since 2002, Global Fund has supported more than 1,000 programs in more than 140 countries with a total of US $ 30 billion signed for the three diseases. It is the main international financier for TB with a total of US$ 4.8 billion signed since 2002

The MDG target to halt and reverse the TB epidemic by 2015 has already been achieved with TB incidence declining at a rate of 2 percent per year. Worldwide, mortality from TB has fallen by 45 percent since 1990 and the world is on track to reach the global target of a 50 percent reduction by 2015. Access to TB care has been expanded substantially and between 1995 and 2012, 56 million people were successfully treated globally and 22 million lives saved. The Global Fund has played a crucial role in contributing to these global achievements.

Although the work of the Global Fund is mostly focused on high-incidence and high-prevalence TB countries, its successes create a significant spillover effect in low-incidence countries in diminishing the global pool of TB. As the analysis in this report has shown, in most low-incidence countries the rates of TB among the foreign-born populations are several times higher; this continues to sustain the incidence and significantly hampers TB elimination efforts in low-incidence settings. The collaborative and multi-sector approach adopted by the Global Fund, allows for value-added contribution and exemplifies the unique role the organization plays in creating a sustainable impact in the fight against TB across the world.

5 Engaging national and international partners

TB elimination is possible, but there are huge challenges ahead. Reinvigorated action will be required. Yet, as the TB burden falls, it will be even more challenging to keep TB on the public health agenda. The challenge is increased by financial crises, continuous health sector reforms, devolution of health care stewardship and, in some places, fragmentation of health services. In the future, it will be essential to ensure sufficient awareness, capacity and funding for TB prevention, care and research. Part of this agenda includes highlighting TB-specific needs, including non-negotiable central stewardship of TB surveillance and coordination. This will involve aligning TB care and prevention with broader health sector plans, while ensuring effective integration of services and synergistic partnerships. Many different partners can contribute. In this concluding section, possible roles for key partners engaged in national and international TB care and prevention are outlined.

5.1   Roles of national partners

TB elimination requires commitment and political leadership from national stakeholders, including a strong, sustained civil society movement to harness the collective force of voluntary local action. Involvement in and ownership of the national elimination plan by all stakeholders ensures that their needs and expectations are taken into account. The governance, leadership, funding and accountability arrangements required for success give national, regional and local governments a lead role. It is often difficult to secure such commitment in the face of declining rates, but the involvement of a wider partnership might help sway political and public health opinion to support an evidence-based national elimination plan that is funded and implemented. Ideally, national activities should be supported by a cross-cutting, multidisciplinary, multi-professional group that includes professional societies, academic institutions, civil society organizations, private sector health organizations and all government departments that might have role in TB elimination, including those responsible for housing, justice, immigration and social welfare. Ensuring that effective partnership arrangements are in place is even more critical in settings with devolved arrangements, where not all health facilities follow the guidelines and policies of the ministry of health. Professional societies might be able to advise on approaches to overcome potential difficulties in implementation. As the incidence of TB is strongly determined by a complex interplay of social, health care and wider societal factors, TB control must inevitably include social interventions, which require broad support to maximize their impact. Health professionals should form genuine partnerships with local community groups that provide a platform for the "voices" of patients. The trust and support of affected communities is important for early case presentation, engagement with treatment services and sustained commitment to address the wider social determinants of TB.

Only through a strong civil society movement can there be a multiplicative effect on the TB programme activities required for elimination. Such activities include increased capacity to deliver services and better access to care, especially by the poor and marginalized communities that are often disproportionately affected by TB. Involving community groups and patient organizations in the policy and design of health interventions is essential to ensure that services are accessible and relevant to the requirements of users. Nongovernmental and patient organizations might require support to build capacity to upgrade interventions and lead in specific programme areas. National authorities should recognize the value of sustained investment in the voluntary sector to create a

strong civil society movement. This can be achieved by building on established partnerships between health services and organizations working with TB-affected communities, such as homeless people, prisoners, people living with HIV and migrant communities.

5.2   Roles of international partners

When the rate of TB cases decreases to pre-elimination and elimination levels, countries may experience decreased government commitment and financial support and dwindling TB expertise among health professionals, resulting in less focus on TB policy and implementation and possibly less effective TB prevention, diagnosis and care. Under these circumstances, collaboration with other low-incidence countries, international organizations, technical partners and international professional associations will be more important to effectively and efficiently organize, implement and set the standards for the control and elimination of TB.

Full engagement of all those concerned with social welfare and migration is essential to ensure access to TB services for groups such as migrants refugees, prisoners and homeless people, who are the main sources of new TB patients in low-incidence countries. Intensified activities must be initiated beyond TB programmes and outside the health sector. Engagement of medical and pharmaceutical faculties and professional organizations can maintain interest in TB as a global infectious disease, and these partners can also play a role in drug and vaccine development, for which public–private collaboration should also be encouraged. International collaboration between research institutes and universities will foster more, better epidemiological research and modelling, which is required to identify the most (cost) effective approaches to worldwide elimination of TB.

Joining forces across national borders will bring together knowledge and expertise to develop common strategies in low-incidence countries and in populations moving to and through these countries, as exemplified in this document. In this way, countries' commitment to national and global TB control could be enhanced and monitored. Platforms for the exchange of experience, best practices and challenges will help countries to adjust their programmes and interventions to meet the demands of the changing epidemic. International organizations have facilitated these platforms in the past (e.g. the Wolfheze meetings in Europe) and will continue to do so. The guiding principle is to ensure country ownership and country-specific interventions, so that they can learn from each other while building unified mechanisms to address regional and cross-border problems compatibly. International organizations, technical partners and international professional associations have different but complementary roles in TB control, from international or regional TB policy development to TB surveillance, multinational operational research, the provision of professional training courses, facilitation of exchange visits and publication in scientific journals focused on TB control issues relevant to low-incidence settings. Research funding agencies should make funds available for research to rapidly fill the knowledge gaps that have hampered development of a vaccine and new drugs and diagnostics.

Collaboration and strong partnerships between national and international stakeholders beyond TB programmes and health sectors in low-incidence countries and their contribution to the global fight against TB will accelerate elimination of TB in both low- and high-incidence countries.

The mission of the European Respiratory Society is to promote respiratory health and to alleviate suffering from respiratory disease. It fulfils this goal by promoting research, education and advocacy. With over 20 000 members globally and the largest world conference on respiratory medicine (attended by more than 20 000 delegates every year), the Society has an integrated plan of research fellowships, grants and seminars and a comprehensive educational programme, part of which is dedicated to TB control and elimination.

The Society contributes to TB elimination by actively supporting numerous members worldwide and participants in annual meetings and courses and through its website (www.tbconsilium.org), which has a wealth of educational modules and interactive materials in the framework of its Presidential plan on TB *(2)*. Through the European Respiratory Society weekly newsletter, its members are informed about new documents and events related to TB elimination. Furthermore, the Society has a strong advocacy role through its Advocacy Committee and Brussels office (particularly at the level of the European Union) and through the European Lung Foundation, the public voice of the Society, which links patients and patient organizations, provides information and listens to and empowers patients. The Society also has an important strategic collaboration with the ECDC to eliminate TB in Europe.

The educational (*Breathe*) and scientific journals (including the *European Respiratory Journal* and the *European Respiratory Review*) of the Society are committed to publishing relevant contributions on TB elimination.

An important initiative launched in 2013 is the European Respiratory Society/WHO Tuberculosis Consilium *(186)*, the aim of which is to support clinicians in the daily management of difficult-to-treat cases of TB, including M/XDR TB. This electronic platform, accessible via the Society website, has been used by many clinicians in several countries to better manage individual cases or outbreaks. It operates, at present, in English, Portuguese, Russian and Spanish. The Society coordinates the forum for TB innovation, a think-tank to promote innovative approaches to TB elimination. Furthermore, it has promoted and organized a permanent multisectoral discussion on the rational introduction and responsible use of new TB tools *(187)*, which includes supranational agencies (such as WHO and ECDC), industry and other TB stakeholders. The Society also provides technical support and funding for TB-specific initiatives for eliminating TB, thus supporting and complementing the activities of WHO and other partners.

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Annex 1

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Annex 2

Adapting pillar 1 of the global TB strategy—integrated, patient-centred care and prevention—in low-incidence countries

Pillar 1a. Early diagnosis of tuberculosis, including universal drug susceptibility testing, and systematic screening of contacts and high-risk groups
Health care systems in all low-incidence countries are relatively well resourced and should have the capacity to use the best TB tests available for all in need. WHO-approved molecular tests, such as Xpert MTB/Rif, culture and phenotypic drug susceptibility testing, should be used routinely, in line with evidence-based practice *(1)*. Digital radiography is also generally available; it is an important tool for triaging and differential diagnosis, contributes to clinical TB diagnoses and is the preferred tool for screening for active pulmonary TB in groups at risk (see below) *(2)*.

Correct diagnosis of TB in children and of extrapulmonary TB often requires special clinical expertise and additional diagnostic capacity. Early and correct diagnosis of young children is particularly important since they are at increased risk of severe disease *(3-6)*. However, the diagnosis of TB in children is often challenging *(7)*. TB can affect any anatomical site. Clinical manifestations of extrapulmonary TB are not specific and may be similar to those of other infectious and noninfectious diseases such as malignancy; it is particularly common in people with HIV infection. Extrapulmonary TB and TB in children is generally paucibacillary, so that microbiological confirmation by microscopy, nucleic acid amplification testing and culture is more difficult than for pulmonary TB. Diagnosis of extrapulmonary TB may require a combination of imaging (e.g. plain radiography, computed tomography scanning, ultrasound) and noninvasive (e.g. urine collection) or invasive (e.g. biopsy) sampling of body fluids and tissues at the affected site for cytological or histopathological examination and microbiological testing *(8–10)*.

In low-incidence countries, effective, early identification of people who should be tested for TB is often a much greater challenge than diagnostic capacity. When the TB burden falls, clinical knowledge and attention to TB among clinicians naturally diminish, except among the few respiratory or infectious disease specialists who maintain a focus on TB. Therefore, in low-incidence countries, it is a challenge to ensure that health care staff are continually sensitized about TB. This is particularly critical for those who work with groups at risk for TB (e.g. migrant health services, prison health services and outreach health services for vulnerable groups). Sufficient knowledge about TB and its risk groups is nevertheless a basic requirement for all health care workers.

An important element of the risk group-focused approach in low-incidence countries is systematic screening for active TB in selected high-risk groups (which may be combined with LTBI screening, see below) *(2)*. This can help protect people who are both at high risk for TB and have a high likelihood of severe consequences from delayed TB diagnosis and treatment, such as people living with HIV/AIDS. It can help reduce TB transmission by routinely picking up TB early among contacts and among people living in congregate settings, such as prisoners. By outreach, TB screening can improve access to care for marginalized groups, such as homeless people. Contact investigation and outbreak management should be done routinely around each newly detected TB case and may be extended to community contacts *(11)*. This requires effective real-time TB surveillance. Systematic screening should also be done routinely for people living with HIV/AIDS and should be included in

general health check-ups of people working in the mining industry and other occupations with exposure to silica. Other high-risk groups (e.g. migrants, prisoners, homeless people, certain ethnic minorities, the elderly and selected clinical risk groups, such as people with immunocompromising disorders or treatments) should be given priority for screening, depending on the local TB epidemiology and an assessment of benefits, risks and costs *(2)*. General population screening (or screening of groups other than those at very high risk) should not be done in low-incidence countries, as there is weak evidence for an epidemiological impact *(12)*, it can be very expensive, and it is associated with a high risk for false-positive TB diagnoses when the prevalence is low *(2)*. A national strategy for systematic screening for active TB in selected high-risk groups should include careful case-based surveillance to guide reprioritization and discontinuation of screening when the yield becomes low.

Pillar 1b. Treatment of all people with TB, including drug-resistant TB, and patient support

Beyond prescribing the correct treatment, the main challenge is to ensure a conducive environment for full adherence to treatment, especially among the vulnerable and marginalized groups that may face severe barriers to treatment adherence. A patient-centred care and support approach that is sensitive and responsive to patients' needs is crucial *(13)*. Although supportive treatment supervision is essential, it must be carried out in a context-specific, patient-sensitive manner. Directly observed treatment can improve adherence to treatment, with supportive measures to educate patients and their families. Often more important than supervision itself is identifying and addressing the factors that can lead to treatment interruption and poor treatment response. Enabling interventions include removing financial barriers for treatment completion; making services user-friendly (e.g. decentralization, conducive opening hours, appropriate staff attitude, addressing language barriers, use of technology); increasing awareness; alleviating stigma and discrimination; and addressing comorbid conditions (see below).

Psychosocial and economic support (e.g. income replacement and other cash transfers, food, travel vouchers or reimbursement and housing support) are often needed, both for treatment adherence and to ensure financial risk protection, especially for the most vulnerable groups *(13)*. This should be done mainly through general social protection schemes and social services operating within or outside health facilities, which can be complemented by TB-specific social support interventions. In either case, health care staff must be trained to help patients navigate and access existing social protection schemes. Patient support should extend beyond health facilities to patients' homes, families, workplaces and communities (such as pharmacies). Nongovernmental and civil society organizations can play important roles in reaching out and delivering services.

For migrants with TB, the right to complete treatment in the country in which the diagnosis is made should be ensured, or schemes should be in place to ensure that patients who move involuntarily or voluntarily during treatment can continue their treatment. This will require cross-border coordination of services and surveillance systems.

Optimal patient support is particularly important for people with multi-drug resistant or extensively resistant TB (M/XDR TB), who have longer, more challenging treatments. The available treatment regimens for drug-resistant TB are unsatisfactory in terms of duration, safety, effectiveness and cost *(14,15)*. New, safer, affordable, more effective medicines that allow shorter treatment regimens that are easier to administer are key to improving treatment outcomes. Links with pharmacovigilance mechanisms will promote safer use and management of medicines and their side-effects. Measures should be taken to alleviate stigma and discrimination.

Treatment and support should extend beyond cure to address any sequelae associated with TB. Moreover, patients, especially those with M/XDR TB, should have access to comprehensive palliative and end-of-life care *(16)*.

Pillar 1c. Collaborative TB–HIV activities and management of comorbid conditions

Both TB-specific and general health outcomes can be improved by identifying and addressing important comorbid conditions that may reduce TB treatment adherence (e.g. alcohol and drug abuse, mental illness) *(17)* or weaken the treatment response (e.g. HIV *(18)*, undernutrition *(19)*, diabetes mellitus *(20)* and smoking *(21)*. Conversely, TB may worsen or complicate the management of other diseases *(22)*. Therefore, as a part of basic coordinated clinical management, people with diagnosed TB should be assessed routinely for relevant comorbid conditions. A holistic, integrated clinical care package is required to optimize health outcomes and could also increase the relevance and attractiveness of health services.

All TB patients should be tested for HIV, and those who are HIV-infected should receive antiretroviral treatment *(18)*. Other relevant comorbid conditions include several noncommunicable diseases and other conditions, including diabetes mellitus *(20)*, undernutrition *(19)*, silicosis, smoking *(21,23)*, harmful alcohol and drug use *(17)* and various immunocompromising disorders and treatments that are risk factors for TB. The local situation determines which comorbid conditions should be screened for systematically among people with active TB. At a minimum, all people with TB should be screened for diabetes mellitus *(20)* and have a basic nutritional assessment *(19)*. Information should be collected about smoking *(21)* and alcohol and drug use, and referral for appropriate management could be offered .

Pillar 1d. Preventive treatment of people at high risk and vaccination against TB

BCG vaccination can effectively reduce the risk of severe disseminated forms of TB and their sequelae in children *(24,25)*. However, the benefit of BCG vaccination diminishes with decreasing TB transmission rate *(26)*. Low-incidence countries should consider restricting BCG vaccination to neonates and infants in recognized high-risk groups or phasing out systematic BCG vaccination entirely, depending on the national TB epidemiology *(27)*.
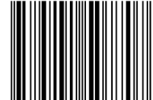
The general principles of screening for LTBI are a positive trade-off between benefits and harm for the individual and a decision to test is an intention to treat if the results are positive. For an individual who is latently infected to be eligible for this intervention, he or she must have a higher risk for progression to active TB, and the benefits of treatment should outweigh the risk of drug toxicity. WHO is finalizing guidelines on LTBI screening and treatment, and this Framework will be updated when the guidelines have been finalized.

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