Tuberculosis elimination in the WHO European Region

Review of key actions, with a special focus on management of tuberculosis infection
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ABSTRACT
Recent guidance reports have been published at the global and European levels to support tuberculosis (TB) elimination and the management of TB infection. These warrant a review of the available reports and their implications for the WHO European Region. This publication aims to guide Member States in the Region to adequately implement TB infection management and the other core actions needed to meet the goals of the End TB Strategy and the related goals and targets of the Tuberculosis Action Plan for the WHO European Region 2016–2020, as well as to approach and sustain the TB elimination phase in both low- and intermediate-TB-incidence countries. The eight core actions recommended by WHO in *Towards tuberculosis elimination: an action framework for low-incidence countries* are reviewed and discussed in the light of the available evidence (and focusing on European experiences and needs) to inform European guidance. The publication aims to serve the policy-makers and professionals working on the national and regional TB response (such as TB specialists, pulmonologists, infectious disease specialists, primary health-care professionals, and other clinical and public health professionals), as well as health-care staff working in settings where TB infection and TB are managed.

KEYWORDS
TUBERCULOSIS INFECTION; TUBERCULOSIS PREVENTIVE TREATMENT (TPT) – SCREENING, DIAGNOSIS, TREATMENT; TUBERCULOSIS – TRANSMISSION, SCREENING, DIAGNOSIS, TREATMENT, EPIDEMIOLOGY, PREVENTION, CONTROL, AND ELIMINATION; TUBERCULOSIS, MULTIDRUG-RESISTANT – PREVENTION; ANTITUBERCULAR AGENTS TO MANAGE TPT; OCCUPATIONAL DISEASES – PREVENTION AND CONTROL; INFECTION CONTROL, WORKPLACE SAFETY
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Acknowledgments

This publication was developed by the WHO Regional Office for Europe and as part of the scientific activities of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, Italy and of the Global Tuberculosis Network (committees on impact evaluation, strategies and global health; Chair: Alberto G. Basteiro) and the WHO European Laboratory Initiative.

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WHO Regional Office for Europe would also like to thanks to the external peer reviewers provided their opinions as independent experts, based on their professional and technical experience, and their opinions are not necessarily those of their respective organizations, Member States or professional bodies. Neither the authors nor the peer reviewers declared any conflict of interest.

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>aDSM</td>
<td>active drug surveillance and monitoring</td>
</tr>
<tr>
<td>BCG</td>
<td>bacille Calmette-Guérin</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DST</td>
<td>drug-susceptibility testing</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>E-DETECT TB</td>
<td>Early Detection and Integrated Management of Tuberculosis in Europe (project)</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FAST</td>
<td>Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely and Treat effectively based on rapid drug-susceptibility testing (approach)</td>
</tr>
<tr>
<td>IGRA</td>
<td>interferon-gamma release assay</td>
</tr>
<tr>
<td>IL-6</td>
<td>interleukin 6</td>
</tr>
<tr>
<td>LTBI</td>
<td>latent tuberculosis infection</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
</tr>
<tr>
<td>M/XDR-TB</td>
<td>multidrug and extensively drug-resistant tuberculosis</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumour necrosis factor alpha</td>
</tr>
<tr>
<td>TPT</td>
<td>tuberculosis preventive treatment</td>
</tr>
<tr>
<td>TST</td>
<td>tuberculin skin test</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant tuberculosis</td>
</tr>
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</table>
Executive summary

Although recent reports have been published at the global and European levels to support tuberculosis (TB) elimination and the management of TB infection and TB preventive treatment (TPT), an evidence-based approach tailored to the WHO European Region has been lacking.

This publication aims to guide Member States in the Region to adequately implement TB infection management and the other core actions needed to meet the goals of the End TB Strategy and the related goals and targets of the Tuberculosis Action Plan for the WHO European Region 2016–2020, as well as to approach and sustain the TB elimination phase in both low- and intermediate-TB-incidence countries. The eight core actions recommended by WHO in *Towards tuberculosis elimination: an action framework for low-incidence countries* are reviewed and discussed, based on the available evidence (and focus on European experiences and needs).

The publication aims to target policy-makers and professionals dealing with TB (such as TB specialists, pulmonologists, infectious disease specialists, primary health-care professionals, and other clinical and public health professionals), as well as health staff working in settings where TPT and TB are managed from a public health perspective.

The publication reviews the following actions suggested by the above-mentioned TB elimination framework to discuss policy guidance, with a special focus on the WHO European Region, in the light of available evidence. These are to:

- ensure political commitment, funding and stewardship for planning and essential high-quality services;
- address the needs of the most vulnerable population groups;
- strengthen cross-border collaboration and cooperation and the specific needs of migrants;
- undertake screening for active TB and TB infection in TB contacts and selected high-risk groups and provide appropriate treatment;
- optimize the prevention and care of drug-resistant TB;
- ensure continued surveillance, programme monitoring and evaluation, and case-based data management;
- invest in research and new tools;
- support global TB prevention, care and control.

Relevant scientific reports published in English (including in the grey literature) were identified using the following keywords in the Google search engine: “tuberculosis”; “prevention”; “control”; “elimination”; “TB infection”; “screening”; “diagnosis”; “TPT” and “treatment”.

The following main policy considerations are derived from the present publication.

- TB eradication\(^1\) is not possible without new tools such as an effective vaccine because of the large TB infection reservoir from which future TB cases, including multidrug-resistant TB (MDR-TB) cases, will emerge, TB patients immigrating from outside the Region and the animal reservoir.

- TB elimination\(^2\) is epidemiologically plausible but at the current rate of treatment success it may take several decades to reach, even in low-incidence countries.

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1 Eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts.

2 TB elimination is defined as fewer than one TB case per million, representing a threshold low enough to ensure that TB will never emerge as a public health priority in the future.
• A comprehensive set of WHO and European Centre for Disease Prevention and Control (ECDC) guidelines published in 2018–2019 contains principles and interventions to support the implementation of priority actions to pursue TB elimination, along with epidemiological and operational indicators to guide the national implementation of priority actions.

• Surveys by the European Respiratory Society (ERS)/WHO/ECDC in 2013 and by the Early Detection and Integrated Management of Tuberculosis in Europe project (E-DETECT TB) in 2018 provide a regional overview of country preparedness to implement the actions necessary to pursue TB elimination.

• Government commitment, funding and stewardship are essential for TB elimination – an adequate legal framework can ensure implementation of core interventions, including: a costed national TB elimination plan; involvement and regulation of the private sector; approval of adequate prevention, diagnosis and treatment guidelines; and establishment of quality surveillance, diagnostic and treatment capacity.

• Social, economic and demographic factors contribute to TB transmission. Vulnerable, marginalized and hard-to-reach population groups who need special attention include people living in poverty, homeless people, migrants, people living with HIV, people who use substances and alcohol harmfully, prisoners, ethnic minorities and other marginalized groups, young children and elderly people.

• Specific indicators targeting at-risk groups are also useful for monitoring and evaluation. In particular, use of the ECDC-proposed indicator of TB in children as an indirect marker of transmission deserves special attention and standardized reporting.

• To respond to rapid changes in migration in the Region, efficient monitoring through improved surveillance (including molecular epidemiology) and Region-wide collaboration are needed to improve TB prevention and care. Transborder collaboration is important to tackle the needs of both vulnerable host populations and migrants. Universal, free-of-charge access to TB services without stigma is needed across the Region.

• Strong coordination and standardization of procedures across Member States are needed to strengthen TB control and make further progress towards TB elimination.

• WHO and ECDC guidelines consider appropriate TB infection management a top priority for TB elimination, particularly for population groups at the highest risks of TB infection and of progression from infection to disease, including people living with HIV, children aged under 5 years who are household contacts of pulmonary TB patients, people with clinical conditions such as silicosis and diseases requiring anti-tumour necrosis factor alpha (anti-TNF-α) treatment, and candidates for dialysis and organ or haematological transplantation. In low-incidence countries (such as in the European Union (EU)), additional at-risk groups should also undergo systematic TB infection testing and treatment, including HIV-negative children aged 5 years and over, and adolescents and adults who are household contacts of patients with bacteriologically confirmed pulmonary TB (strong recommendation); and migrants from endemic areas, prisoners, health-care workers, homeless people and people who use drugs (conditional recommendation). Additional at-risk groups may be considered depending on the TB epidemiology.

• ECDC/WHO-recommended regimens to treat TB infection include isoniazid for 6–9 months, rifampicin or isoniazid-rifampicin for 3–4 months, and the recently recommended regimen of isoniazid and rifapentine for three months. Unfortunately, the last regimen is unavailable in most European countries. Evidence is accumulating to support the gradual introduction of TPT with fluoroquinolone-based regimens for the contacts of MDR-TB patients.

• Experiences in different European countries show that successful TB infection screening and treatment of high-risk TB groups require adequate infrastructure and organization of services.
• Existing good practices in Europe show that establishing national TB infection registers for monitoring TB infection testing, yield and completion rates and for comparing the TPT cascade across countries is essential to pursue TB elimination.

• Actions to prevent TB infection by reducing TB transmission include: adoption of the FAST (Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely and Treat effectively based on rapid drug-susceptibility testing) approach; universal access to rapid molecular testing and high-quality drug-susceptibility testing (DST), along with chest radiography screening and surveillance of symptoms other than cough (such as loss of weight and fever, especially in children); a team approach to managing difficult-to-treat cases (TB consiliums); implementation of the 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (with full oral regimens and use of new drugs) and the 2017 WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care; active drug surveillance and monitoring (aDSM); and effective infection control practices and workplace safety practices (particularly in eastern Europe and central Asia).

• A comprehensive research effort to produce new vaccines, diagnostics and drugs/regimens, along with basic epidemiological, health systems and social research, is necessary to pursue TB elimination.

• Boosted pan-European collaboration, together with investment in bilateral/multilateral TB cooperation projects, is important to strengthen TB prevention and care and support TB elimination efforts, maintain a pool of experienced health staff with comprehensive EU-wide training and support the exchange of ideas and good practices among countries in the WHO European Region.

• TB national strategic plans should include activities for TB elimination and TB infection management and coordinate with national policies and roadmaps for health sector reform.

• A comprehensive approach based on the United Nations Sustainable Development Goals is essential for ending HIV, TB and viral hepatitis through intersectoral collaboration.
1 Introduction

1.1 Scope, purpose and target audience

WHO recently published evidence-based guidance at the global and European levels to support TB elimination and management of TB infection (1,2). This publication aims to adequately support the implementation of TB infection management by Member States in the WHO European Region, along with the other core actions recommended to meet the goals of the End TB Strategy (3) (and the related goals and targets of the Tuberculosis Action Plan for the WHO European Region 2016–2020, endorsed by the 65th session of the WHO Regional Committee for Europe in resolution EUR/RC65/R6 (4). The ultimate goal is to approach and sustain the TB elimination phase in both low- and intermediate-TB-incidence countries. The eight core actions recommended by Towards tuberculosis elimination: an action framework for low-incidence countries (2,5) are reviewed and discussed in the light of the available evidence, focusing on European experiences and needs.

The target readership of this publication includes policy-makers and professionals dealing with TB (such as TB specialists, pulmonologists, infectious disease specialists, primary health-care professionals, and other clinical and public health professionals), as well as health staff working in settings where TB infection and TB are managed as part of a public health approach, including centres dealing with occupational health, tobacco control, HIV care, and maternal and child health, as well as prisons.

1.2 Background

According to a recent WHO Regional Office for Europe analysis, implementation of the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region, 2011–2015 (6) has enabled 1 million patients to be cured, saved 26 million lives and averted 200 000 MDR-TB cases, while saving US$ 11 billion (7). Consistent strategies have recently been proposed to combat MDR-TB, TB/HIV coinfection and other major challenges in the Region, including infection control, workplace safety and prevention of transmission (8).

In 2018 WHO published consolidated and updated guidelines for TB infection management (1). In addition to other WHO guidance on TB (1,9–11), ECDC recently published a guidance report on TB infection management (12). In 2014 European low-TB-incidence countries participated in a global consultation in Rome that enabled WHO to publish Towards tuberculosis elimination: an action framework for low-incidence countries (2,5). The action framework identified eight priority actions to approach TB pre-elimination
globally: (i) ensure political commitment, funding and stewardship for planning and essential high-quality services; (ii) address the most vulnerable and hard-to-reach groups; (iii) address the special needs of migrants and cross-border issues; (iv) undertake screening for active TB and TB infection in TB contacts and selected high-risk groups, and provide appropriate treatment; (v) optimize the prevention and care of drug-resistant TB; (vi) ensure continued surveillance, programme monitoring and evaluation, and case-based data management; (vii) invest in research and new tools; and (viii) support global TB prevention, care and control (2,5). These actions need to be tailored to the specific needs of the WHO European Region.

A comprehensive effort is needed to improve TB diagnosis (by taking advantage of new rapid technologies) and treatment through a people-centred approach (as highlighted in the WHO Roadmap to implement the Tuberculosis Action Plan for the WHO European Region 2016–2020 (4,13)) in order to reach the ambitious targets set for the fight against TB in the Region. Member States are demanding further support and guidance to adequately improve TB infection management, as well as the other priority actions, and to approach TB elimination. In order to gather the most up-to-date evidence to provide decision-makers with relevant information for evidence-based policies, the WHO Regional Office for Europe developed this guidance report on TB elimination and the necessary priority actions in the Region, with a focus on TB infection management.

1.3 Aim
The present report aims to guide Member States in the WHO European Region to adequately implement TB infection management and other core actions needed to meet the goals of the End TB Strategy (3) (and the related goals and targets of the Tuberculosis Action Plan for the WHO European Region 2016–2020), as well as to approach and sustain the TB elimination phase in both low- and intermediate-TB-incidence countries. A decision was taken to include both the overall TB elimination perspective and the recommended necessary actions, with special focus on TB infection management (considered to be of core importance in Europe).

1.4 Methods and definitions
The scientific literature was extensively searched for coverage of the various topics presented in this guidance report. The report mainly relies on a narrative scientific literature review. However, given the policy-oriented structure, grey literature in English (including non-scientific journals and magazines) and reports from key international meetings and conferences were assessed to provide additional information with no time restrictions. The PubMed search engine was chosen to retrieve potential scientific articles using the following keywords in different combinations (strings): “tuberculosis”; “prevention”; “control”; “elimination”; “tuberculosis infection”; “TB infection”; “screening”; “diagnosis”; “TPT”; and “treatment”. Similar strings were adapted for searching Google and the websites of relevant conferences and meetings. Records were carefully assessed to retrieve potentially useful reports.

Information from countries presented in this report largely relies on reported programme implementation and policy data. The definitions used in this report are those included in the WHO report, Towards tuberculosis elimination: an action framework for low-incidence countries (2,5). Low-TB-incidence countries were defined as those with a TB notification rate of < 100 TB cases (all forms) per 1 million population per year. The report was written by a core writing committee of TB experts and revised by an external peer-review panel.
The WHO European Region’s caseload represents about 3.0% of the total global TB burden. In 2016 about 85% of incident TB cases occurred in the 18 high-priority countries. This indicates a high degree of heterogeneity in the Region regarding distribution of the TB disease burden. The average annual decline in the TB incidence rate was 4.3% during the 2007–2016 period and 4.4% between 2015 and 2016. Over the last 10 years, the TB incidence in the Region has decreased from 47 to 32 cases per 100 000 population, equivalent to 410 000 TB cases in 2007 and 290 000 in 2016 (14). This represents a decrease of the TB burden in the Region of about a third.

Yet, although the WHO European Region has the fastest rate of decline compared with the other WHO regions, there is a need for an even faster decline in TB incidence (of 90% between 2016 and 2035) if the Region is to meet the targets of the End TB Strategy by 2035 (3) and those of the Roadmap to implement the Tuberculosis Action Plan for the WHO European Region 2016–2020 (13).

Based on the TB notification rate, Member States in the WHO European Region can be classified into low- and intermediate-TB-incidence countries (summarized in Table 1; low-incidence threshold: 10 cases per 100 000 population or 100 cases per million) (15,16).

A considerable variation in mortality rates has been observed across the Region in recent years, ranging from less than one TB death per 100 000 population in western European countries to more than seven TB deaths per 100 000 population in four of the 18 high-priority countries (15). Together, the 18 high-priority countries account for over 90% of TB deaths in the Region.

Approximately one in five MDR-TB cases globally were estimated to have occurred in the WHO European Region. The alarmingly high MDR-TB rates in most eastern European and central Asian countries represent one of the main challenges in TB prevention and care in the Region. Nine out of 30 countries with the highest MDR-TB burden in the world are in the WHO European Region.

An increased HIV prevalence among incident TB cases was also observed in the WHO European Region, while the global average declined. This increase was mainly driven by the continuing upward trend in new HIV diagnoses in eastern and central Europe (in contrast to the declining rate of new diagnoses in western Europe) as a consequence of funding, legal or political barriers to the implementation of national HIV programmes. Otherwise, the HIV rate is declining in people without TB in western Europe (17). Indeed, while the rates of HIV testing, HIV treatment and viral suppression are growing in other HIV endemic regions, in some parts of eastern Europe and central Asia the number of people being tested for HIV is slowly increasing, even though the rates of HIV treatment and viral suppression remain among the lowest worldwide (14,18).

3 The 18 high-priority countries are Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.
## Table 1. Member States in the WHO European Region, classified by TB notification and estimated incidence rates

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Notification of incident TB cases*</th>
<th>TB incidence, best estimate (uncertainty interval)</th>
<th>Percentage of new TB cases with MDR/RR-TB, %</th>
<th>Best estimate¹ (uncertainty interval)</th>
<th>Percentage of previously treated TB cases with MDR/RR-TB, %</th>
<th>Best estimate¹ (uncertainty interval)</th>
<th>Incidence of MDR/RR-TB, best estimate (uncertainty interval)</th>
<th>n, in 1000s</th>
<th>Rate, per 100 000 population</th>
<th>n, in 1000s</th>
<th>Rate, per 100 000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries with a TB incidence of ≤ 10 cases per 100 000 population</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andorra</td>
<td>80</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01 (&lt;0.01–&lt;0.01)</td>
<td>1.5 (1.3–1.7)</td>
<td>0 (0–5)</td>
<td>12 (8–17)</td>
<td>0 (0–0)</td>
<td>0.01 (0–0.01)</td>
<td>0.00</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>8 700</td>
<td>0.56</td>
<td>0.64 (0.55–0.74)</td>
<td>7.3 (6.2–8.4)</td>
<td>2.3 (0.84–4.90)</td>
<td>18 (3.8–4.30)</td>
<td>18 (3.8–4.30)</td>
<td>0.019 (0.01–0.035)</td>
<td>0.22</td>
<td>0.1–0.40</td>
<td>0.1–0.40</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>1 100</td>
<td>0.92</td>
<td>1.1 (0.96–1.3)</td>
<td>9.8 (8.4–11)</td>
<td>1.6 (0.66–3.3)</td>
<td>8.8 (1.9–24)</td>
<td>8.8 (1.9–24)</td>
<td>0.029 (0.013–0.05)</td>
<td>0.25</td>
<td>0.12–0.43</td>
<td>0.12–0.43</td>
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<tr>
<td>Croatia</td>
<td>4 200</td>
<td>0.36</td>
<td>0.42 (0.36–0.49)</td>
<td>10.0 (8.7–12.0)</td>
<td>0 (0.01–0.01)</td>
<td>0 (0–16)</td>
<td>0 (0–16)</td>
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<td>0.02</td>
<td>0.01–0.03</td>
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<td>Cyprus</td>
<td>1 200</td>
<td>0.05</td>
<td>0.066 (0.056–0.076)</td>
<td>5.6 (4.8–6.4)</td>
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<td>0.02</td>
<td>0.01–0.06</td>
<td>0.01–0.06</td>
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</tr>
<tr>
<td>Czechia</td>
<td>11 000</td>
<td>0.5</td>
<td>0.57 (0.49–0.66)</td>
<td>5.4 (4.6–6.2)</td>
<td>2.2 (0.9–4.6)</td>
<td>12.0 (2.4–30.0)</td>
<td>12.0 (2.4–30.0)</td>
<td>0.017 (0.06–0.29)</td>
<td>0.16</td>
<td>0.06–0.29</td>
<td>0.06–0.29</td>
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<tr>
<td>Denmark</td>
<td>5 700</td>
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<td>5.1 (4.3–5.9)</td>
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<td>0 (0–21)</td>
<td>&lt; 0.01 (0.01–0.01)</td>
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<td>0.27 (0.23–0.31)</td>
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<td>3.0 (0.8–7.4)</td>
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<td>67.0 (9.4–99.0)</td>
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<td>2.2 (0.82–4.8)</td>
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<td>9.1 (0.23–41)</td>
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<td>8.1 (3.3–16)</td>
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<td>TB incidence, best estimate (uncertainty interval)</td>
<td>Percentage of new TB cases with MDR/RR-TB, %</td>
<td>Percentage of previously treated TB cases with MDR/RR-TB, %</td>
<td>Incidence of MDR/RR-TB, best estimate (uncertainty interval)</td>
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<td>n, in 1000s</td>
<td>Rate, per 100 000 population</td>
<td>Best estimate&lt;sup&gt;a&lt;/sup&gt; (uncertainty interval)</td>
<td>Best estimate&lt;sup&gt;b&lt;/sup&gt; (uncertainty interval)</td>
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<td>Rate, per 100 000 population</td>
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<td>12 (0–0)</td>
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<td>0.12 (0.1–0.14)</td>
<td>5.7 (0–3.9)</td>
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<td>0.56 (0.48–0.65)</td>
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<td>26 (9.1–51)</td>
<td>0.036 (0.017–0.062)</td>
<td>0.42</td>
<td>0.2–0.73</td>
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<td>United Kingdom</td>
<td>66 000</td>
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<td>5.9 (5.3–6.5)</td>
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<td>1.4 (0.93–2)</td>
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**Countries with a TB incidence of > 10 and ≤ 20 cases per 100 000 population**

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<th>Country</th>
<th>Population</th>
<th>Notification of incident TB cases*</th>
<th>TB incidence, best estimate (uncertainty interval)</th>
<th>Percentage of new TB cases with MDR/RR-TB, %</th>
<th>Percentage of previously treated TB cases with MDR/RR-TB, %</th>
<th>Incidence of MDR/RR-TB, best estimate (uncertainty interval)</th>
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<tbody>
<tr>
<td>Albania</td>
<td>2 900</td>
<td>0.5</td>
<td>0.58 (0.49–0.67)</td>
<td>20 (0.64–5.8)</td>
<td>6.7 (0.17–32)</td>
<td>0.017 (0.01–0.036)</td>
</tr>
<tr>
<td>Estonia</td>
<td>1 300</td>
<td>0.17</td>
<td>0.2 (0.17–0.23)</td>
<td>15 (0.14–29)</td>
<td>52 (0.046–0.1)</td>
<td>0.071 (0.046–0.1)</td>
</tr>
<tr>
<td>Malta</td>
<td>400</td>
<td>0.042</td>
<td>0.048 (0.041–0.056)</td>
<td>11 (0.96–13)</td>
<td>12 (0.8–17)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Montenegro</td>
<td>600</td>
<td>0.075</td>
<td>0.086 (0.074–0.1)</td>
<td>14 (0.12–16)</td>
<td>11 (0.28–48)</td>
<td>0 (0–0)</td>
</tr>
<tr>
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<td>0.22</td>
<td>0.27 (0.21–0.34)</td>
<td>13 (0.9–16)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Poland</td>
<td>38 000</td>
<td>5.5</td>
<td>6.4 (5.4–7.4)</td>
<td>17 (0.79–1.5)</td>
<td>3.9 (2.2–6.3)</td>
<td>0.1 (0.07–0.14)</td>
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<tr>
<td>Portugal</td>
<td>10 000</td>
<td>1.8</td>
<td>2 (1.7–2.3)</td>
<td>0.98 (0.51–1.7)</td>
<td>6.9 (2.8–14)</td>
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<tr>
<td>Serbia</td>
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<td>1.5</td>
<td>1.7 (1.4–1.9)</td>
<td>19 (0.49–2.2)</td>
<td>4.7 (1.3–11)</td>
<td>0.025 (0.011–0.046)</td>
</tr>
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<td>Turkey</td>
<td>81 000</td>
<td>12</td>
<td>14 (12–16)</td>
<td>17 (14–19)</td>
<td>3.3 (2.8–3.8)</td>
<td>0.6 (0.48–0.74)</td>
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</table>

**Countries with a TB incidence of > 20 cases per 100 000 population**

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<th>Notification of incident TB cases*</th>
<th>TB incidence, best estimate (uncertainty interval)</th>
<th>Percentage of new TB cases with MDR/RR-TB, %</th>
<th>Percentage of previously treated TB cases with MDR/RR-TB, %</th>
<th>Incidence of MDR/RR-TB, best estimate (uncertainty interval)</th>
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<td>Armenia</td>
<td>2 900</td>
<td>0.84</td>
<td>1.1 (0.8–1.3)</td>
<td>36 (27–45)</td>
<td>16 (12–20)</td>
<td>44 (35–54)</td>
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<tr>
<td>Azerbaijan</td>
<td>9 800</td>
<td>5.2</td>
<td>6.5 (5–8.3)</td>
<td>67 (51–84)</td>
<td>12 (11–14)</td>
<td>28 (27–30)</td>
</tr>
<tr>
<td>Belarus</td>
<td>9 500</td>
<td>2.8</td>
<td>3.5 (2.7–4.4)</td>
<td>37 (28–46)</td>
<td>38 (36–41)</td>
<td>67 (63–70)</td>
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<tr>
<td>Bosnia and Herzegovina</td>
<td>3 500</td>
<td>0.77</td>
<td>0.96 (0.73–1.2)</td>
<td>27 (21–35)</td>
<td>0 (0–0.97)</td>
<td>0 (0–8.2)</td>
</tr>
<tr>
<td>Country</td>
<td>Population</td>
<td>Notification of incident TB cases&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TB incidence, best estimate (uncertainty interval)</td>
<td>Percentage of new TB cases with MDR/RR-TB, %</td>
<td>Percentage of previously treated TB cases with MDR/RR-TB, %</td>
<td>Incidence of MDR/RR-TB, best estimate (uncertainty interval)</td>
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<td>Rate, per 100 000 population</td>
<td>Best estimate (uncertainty interval)</td>
<td>Best estimate (uncertainty interval)</td>
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<td>Rate, per 100 000 population</td>
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<td>60 (39–85)</td>
<td>32 (31–33)</td>
<td>67 (66–67)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>56 (36–82)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>39 (25–57)</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>8 900</td>
<td>5.9</td>
<td>7.5 (5.8–9.5)</td>
<td>85 (65–106)</td>
<td>20 (19–22)</td>
<td>23 (20–27)</td>
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<tr>
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<td></td>
<td></td>
<td>2.3 (1.6–3.1)</td>
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<td></td>
<td></td>
<td>26 (18–35)</td>
</tr>
<tr>
<td>Turkmenistan</td>
<td>5 800</td>
<td>2</td>
<td>2.5 (1.9–3.1)</td>
<td>43 (33–54)</td>
<td>14 (11–18)</td>
<td>38 (31–46)</td>
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<td></td>
<td>0.54 (0.37–0.73)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>9.4 (6.5–13)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>44 000</td>
<td>27</td>
<td>37 (24–53)</td>
<td>84 (54–119)</td>
<td>28 (27–29)</td>
<td>48 (47–49)</td>
</tr>
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<td></td>
<td>20 (13–30)</td>
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<td></td>
<td></td>
<td></td>
<td>46 (29–67)</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>32 000</td>
<td>17</td>
<td>23 (16–32)</td>
<td>73 (51–99)</td>
<td>15 (14–16)</td>
<td>57 (55–60)</td>
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<tr>
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<td></td>
<td></td>
<td>7.5 (4.7–11)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 (15–34)</td>
</tr>
<tr>
<td>Europe</td>
<td>920 000</td>
<td>220</td>
<td>273 (236–313)</td>
<td>30 (26–34)</td>
<td>17 (16–18)</td>
<td>53 (46–61)</td>
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<td>109 (86–136)</td>
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<td></td>
<td></td>
<td></td>
<td>12 (9.4–15)</td>
</tr>
<tr>
<td>Global</td>
<td>7 520 000</td>
<td>6 400</td>
<td>10 000 (9 000–11 100)</td>
<td>133 (120–48)</td>
<td>3.5 (2.5–4.7)</td>
<td>18 (6.3–34)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>558 (483–639)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>7.4 (6.4–8.5)</td>
</tr>
</tbody>
</table>

RR-TB: rifampicin-resistant tuberculosis.

<sup>a</sup> New and relapse cases include patients where the treatment history is unknown and exclude patients who have been re-registered as treatment after failure, treatment after loss to follow-up or other previously treated (whose outcome after the most recent course of treatment is unknown or undocumented).

<sup>b</sup> Best estimates are for the latest available year.

Sources: WHO (15,16).
The possibility to eliminate TB in Europe was discussed for the first time in operational terms within the Wolfheze initiative in 1990 (19–22). Initially conceived as an expert think-tank for low-TB-incidence countries with educational aims (for example, to involve promising young specialists in TB control), it became co-organized by the KNCV Tuberculosis Association, the biannual meeting of the WHO Regional Office for Europe and European TB surveillance focal points, latterly coordinated by ECDC (15–18).

The most widely accepted general definition of elimination of a communicable disease was approved at the Dahlem Workshop on the Eradication of Infectious Diseases in 1997 as “the reduction to zero of the incidence of a particular disease in a defined geographical area as a result of deliberate efforts”, while elimination of infection was defined as “the reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts” (21,23). Finally, eradication was defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent, as a result of deliberate efforts.

These definitions are generally considered inapplicable to TB (12) because of the high burden of TB infection: this large infection reservoir ensures the appearance of TB in cases for decades to come. Therefore, the concept of TB elimination involves identifying a threshold low enough to ensure the disease will no longer be a public health threat.

Until recently, the Wolfheze definition (less than one smear-positive case per million population) was considered valid in Europe. At the 2013 WHO/ERS global consultation in Rome on TB elimination in low-TB-incidence countries and in the 2014 WHO action framework (2,5), the definition was modified to “less than one case per million” to comply with the concept of eliminating all forms of TB (regardless of bacteriological confirmation).

Box 1 outlines the implications for policy on elimination of TB.

**Box 1. Implications for policy**

- In the absence of an immunizing vaccine, TB eradication in the WHO European Region is not feasible, at least in the medium term, owing to the intrinsic characteristics of the disease (a large TB infection reservoir from which future TB cases will emerge).
- However, TB elimination is epidemiologically plausible.
- TB elimination, defined as fewer than one TB case per million, is a threshold low enough to ensure that TB will never emerge as a public health priority in the future.
3.1 Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region, 2011–2015

The Consolidated Action Plan was developed through Region-wide consultations with representatives of the 53 European Member States, experts, patients and representatives of the affected communities to strengthen and intensify efforts to address the alarming regional problem of drug-resistant TB (6). It consists of six strategic directions and seven areas of intervention (coordinated with Health 2020 and other core publications in the Region) aiming to provide universal access to MDR-TB diagnosis and treatment.

The Consolidated Action Plan has guided Member States in the further development and integration of national MDR-TB response plans into their national TB and/or national health strategy plans (7), and also addresses the issues of TB infection and TB elimination.

3.2 Tuberculosis Action Plan for the WHO European Region 2016–2020

In accordance with The Global Plan to Stop TB 2006–2015 (24), the WHO Regional Office for Europe developed an ambitious strategy that was endorsed by the Sixty-seventh World Health Assembly in 2014 through World Health Assembly resolution WHA67.1 (25). As the ultimate success of the strategy will depend on the Member States and partners’ commitment to implement it, the resolution urges all Member States in Europe to adapt their use of the strategy to their national priorities and specificities and invites regional partners to support the strategy’s implementation.

The Tuberculosis Action Plan for the WHO European Region 2016–2020 was developed through a Region-wide participatory process. The overarching aim was to operationalize the global End TB Strategy (4) within the regional context, for its subsequent adaptation at national level according to each country’s priorities and specific needs. Importantly, in line with Health 2020 and other key regional health strategies and polices, this Action Plan sets regional goals and targets for TB and MDR-TB care and control by defining strategic directions. Activities to be carried out by the different stakeholders operating in the Region fall under three areas of interventions: integrated, people-centred care and prevention; bold policies and supportive systems; and intensified research and innovation. The Action Plan includes a monitoring framework; an analysis of strengths, weaknesses, opportunities and threats; an impact analysis; and a financial resource analysis (4).

3.3 Progressing towards TB elimination: ECDC, 2010

The Framework Action Plan to Fight Tuberculosis in the European Union was launched by ECDC in 2008 to provide guidance to Member States (26); it was aligned with the United Nations Millennium Development Goals and The Global Plan to Stop TB 2006–2015 (24). The long-term goal of the Framework Action Plan was to control and ultimately eliminate TB in EU and European Economic Area (EEA) countries by:

- increasing political and public awareness of TB as a public health issue in the EU;
- supporting and strengthening EU Member States’ efforts against TB in line with their national epidemiological situation and challenges;
- contributing to the prevention and care of TB in the EU by supporting the countries of origin of imported cases.
The 2010 report, *Progressing towards TB elimination: a follow-up to the Framework Action Plan to Fight Tuberculosis in the European Union*, included a monitoring framework in support of the Framework Action Plan (27). The objectives of the follow-up report were to provide: (i) an overview of the current strategic environment for TB control in the EU (focusing on childhood TB, TB in foreign-born individuals, multidrug and extensively drug-resistant TB (M/XDR-TB), TB/HIV co-infection and treatment outcome evaluation); and (ii) an outline of how this relates to the global situation. The overall purpose was to describe an epidemiological and strategic monitoring framework allowing the assessment of progress towards elimination of TB in the EU. For this, the 2010 ECDC follow-up report, *Progressing towards TB elimination: a follow-up to the Framework Action Plan to Fight Tuberculosis in the European Union*, proposed a number of core epidemiological and operational indicators and targets consistent with the existing indicators (at the global and regional levels) and the information collected and reported by Member States (27).

These core indicators are specifically related to the eight strategic areas of the Framework Action Plan (26) and aim to allow the assessment of progress of each of these areas: Area 1, TB control commitment, TB awareness and capacity of health systems; Area 2, surveillance; Area 3, laboratory services; Area 4, prompt, high-quality TB care for all; Area 5, M/XDR-TB; Area 6, TB/HIV co-infection; Area 7, new tools for TB control; and Area 8, build partnership and collaboration with countries (Table 2). The eight strategic areas of the Framework Action Plan are important because they were surveyed to assess country preparedness (28,29) and inspired the eight “priority actions” of the 2014 WHO report, *Towards tuberculosis elimination: an action framework for low-incidence countries* (2,5).

**TABLE 2. Epidemiological and operational indicators included in the 2010 ECDC report, *Progressing towards TB elimination***

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological indicator</strong></td>
<td></td>
</tr>
<tr>
<td>Trends in the case notification rate</td>
<td>A mean declining trend in case notification rate over the previous five years allowing for annual random variation, in a context where case-finding efforts remained constant or increased</td>
</tr>
<tr>
<td>Trends in the MDR-TB case notification rate</td>
<td>A mean declining trend in MDR-TB case notification rate over the previous five years allowing for annual random variation, in a context where MDR-TB case-finding efforts remained constant or increased</td>
</tr>
<tr>
<td>Trends in ratio of notification rates in children to adults</td>
<td>A mean declining trend in the ratio of the notification rate in children to that in adults over the previous 10 years, allowing for annual random variation</td>
</tr>
<tr>
<td>Trends in mean age of TB cases</td>
<td>An increasing trend in mean age of TB cases over the previous 10 years</td>
</tr>
<tr>
<td><strong>Operational indicator</strong></td>
<td></td>
</tr>
<tr>
<td>Availability of a national TB control plan</td>
<td>Member State: an up-to-date and endorsed national TB control plan is available EU: all Member States (100%) have an up-to-date and endorsed national TB control plan</td>
</tr>
<tr>
<td>Availability of guidelines for implementing the national TB control plan</td>
<td>Member State: up-to-date and endorsed TB guidelines are available EU: all Member States (100%) have up-to-date and endorsed TB guidelines</td>
</tr>
<tr>
<td>Percentage of national TB reference laboratories (adhering to ERLN-TB) achieving adequate performance in the external quality assurance scheme</td>
<td>Member State: a strategy within the national TB programme supporting the introduction and implementation of new tools for TB control is in place EU: all Member States (100%) have a strategy within the national TB programmes supporting the introduction and implementation of new tools for TB control</td>
</tr>
<tr>
<td>Availability of a strategy for introducing and implementing new tools for TB control</td>
<td>Member State: a strategy within the national TB programme supporting the introduction and implementation of new tools for TB control is in place EU: all Member States (100%) have a strategy within the national TB programmes supporting the introduction and implementation of new tools for TB control</td>
</tr>
</tbody>
</table>
### Indicator | Target
--- | ---
Percentage of new pulmonary TB cases confirmed by culture and percentage of cases tested by DST for first-line drugs | Member State: 80% of all new pulmonary TB cases are culture confirmed. 100% of the culture-confirmed cases should be tested by DST for first-line drugs. EU: 80% of all new pulmonary TB cases in the EU are culture confirmed. 100% of the culture-confirmed cases should be tested by DST for first-line drugs.

Percentage of Member States reporting treatment success rate | All Member States (100%) report treatment outcome monitoring to ECDC.

Treatment success rate | Member State: treatment success of 85% at 12 months for the complete cohort of new pulmonary culture-positive cases. Treatment success of 70% at 24 months for new pulmonary culture-positive pulmonary MDR-TB cases. EU: treatment success of 85% at 12 months for the complete cohort of new pulmonary culture-positive cases. Treatment success of 70% at 24 months for new pulmonary culture-positive pulmonary MDR-TB cases.

Percentage of TB patients for whom HIV status is known | Member State: HIV status is known for 100% of notified TB cases. EU: HIV status is known for 100% of TB cases.

**ERLN-TB**: European Reference Laboratory Network for TB.

Source: ECDC (27).

### 3.4 Towards tuberculosis elimination: an action framework for low-incidence countries

The action framework, jointly developed by WHO and ERS (5), starts with the End TB Strategy milestones (3) to develop the long-term vision of eliminating TB as a public health priority (defined as fewer than one case of TB per million population – to be reached by 2050) and involves passing through a pre-elimination phase (defined as fewer than 10 TB cases per million population) (2,5).

As having sound TB control activities (such as rapid diagnosis and effective treatment, contact tracing, and infection control/workplace safety) in place is not sufficient, countries need to implement additional actions to provide universal access to high-quality TB services (particularly for vulnerable groups) while tackling the social determinants leading to an increased risk of TB infection and TB. By building on previous national and regional frameworks (21,22,27,30–33), the action framework summarized the epidemiological basis for TB elimination in low-incidence countries (a low rate of transmission in the general population, occasional outbreaks, most TB cases generated from the progression of TB infection rather than local transmission, concentration in vulnerable/risk groups) and identified eight priority action areas (listed in section 1.2).

Section 5 of this guidance report will describe in detail ways to implement these priority action areas in both low- and intermediate-incidence countries.
3.5 Moscow Declaration to End TB, 2017

The Global Ministerial Conference on Ending TB in the Sustainable Development Era, held in Moscow, Russian Federation, on 16–17 November 2017, was a key event in promoting government commitment towards TB control and elimination (34).

The preamble to the Moscow Declaration to End TB emphasized the unprecedented ministerial commitment to end TB (35): “We, the Ministers of Health and from across Governments acknowledge that despite concerted efforts, TB, including its drug-resistant forms, causes more deaths than any other infectious disease worldwide and is a serious threat to global health security”.

The Conference called for action at the global and regional levels in four key areas: (i) making rapid progress towards universal health coverage by strengthening health systems and improving access to people-centred TB prevention and care, ensuring no one is left behind; (ii) mobilizing sufficient and sustainable financing through increased domestic and international investments to close gaps in implementation and research; (iii) advancing research and development of new tools to diagnose, treat and prevent TB; and (iv) building accountability through a framework to track and review progress on ending TB, including multisectoral approaches.

3.6 United Nations High-level Meeting on the Fight Against Tuberculosis, 2018

The way forward was launched at the United Nations General Assembly High-level Meeting on the Fight Against Tuberculosis held in New York, the United States of America on 26 September 2018 (36):

_We conclude with a commitment to act immediately on this Declaration in coordination with the WHO, and to engage with leaders and all relevant sectors of Government, United Nations agencies, bilateral and multilateral funding agencies and donors, academia, research organizations, scientific community, civil society and the private sector to prepare for and follow-up on the United Nations General Assembly High-level Meeting on Tuberculosis in 2018 in New York._

United Nations General Assembly resolution 73/3 (Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis (37)) was then adopted at the Seventy-third session of the United Nations General Assembly on 10 October 2018. The political declaration re-affirmed the agenda of the Sustainable Development Goals (38) and committed to “end the TB epidemic by 2030” while “re-focusing actions and investments” necessary “to treat successfully 40 million TB patients from 2018 to 2022 including 3.5 million children”. It further called for a “rapid scale-up of TB infection diagnosis and treatment” that, together with other interventions, will “make TB elimination possible” (37). Furthermore, the report commits:

_… to preventing tuberculosis for those most at risk of falling ill through the rapid scaling up of access to testing for tuberculosis infection, according to the domestic situation, and the provision of preventive treatment, with a focus on high-burden countries, so that at least 30 million people, including 4 million children under 5 years of age, 20 million other household contacts of people affected by tuberculosis, and 6 million people living with HIV, receive preventive treatment by 2022, and with the vision of reaching millions more._
4 Regional and country preparedness: European surveys and other experiences

4.1 The 2013 ERS/WHO/ECDC survey

Several reports provide evidence on the preparedness of European countries for TB prevention and care, with an occasional focus on TB elimination (28,29,39–41).

The first survey was performed by ECDC, ERS and WHO in 2013 and investigated country preparedness through a questionnaire investigating TB elimination activities among 38 national TB programme representatives of low-TB-incidence countries (defined there as fewer than 20 cases per 100,000 population) in the WHO European Region (28).

Of the 31 countries and territories providing a complete answer, 54.8% reported having a dedicated national TB programme, 64.5% having a national plan including TB elimination (with 41.9% including targets), 71% having guidelines, 45.2% having a specific budget for TB activities, and 74.2% having TB reference centres. All countries reported having a case-based electronic TB surveillance system, with 61.3% performing regular supervision, 38.7% having a monitoring and evaluation plan and 16.1% performing modelling. In three countries (9.7%), TB health services were free only for insured individuals. In 22 countries/territories (71%) not all anti-TB drugs were available, while 12 (38.7%) described having drug stock-outs. Although TB infection screening of high-risk groups was performed by most countries, only six (19.4%) provided completion rates for preventive treatment.

The authors concluded that not all of the elements identified as being essential for country preparedness to achieve TB elimination were available in the countries surveyed (28).

4.2 The 2018 E-DETECT survey

A second survey, undertaken as part of the E-DETECT TB project, was published in 2018 taking into account previous methodology and findings (29,42). The aim was to determine “how many European Union (EU) and European Economic Area (EEA) countries have national TB control plans/strategies, and what are the priority actions/populations and barriers to implementation”.

The response rate was 100% for the 31 EU/EEA countries surveyed through national TB correspondents. In all, 55% of countries reported to have a national TB strategy approved and under implementation, while five countries were still in a preparation phase. Most countries (74%) reported having a defined
organizational TB control structure with central coordination and 19% reported having a costed programme budget approved. Priority TB control actions included in the national plans were: (i) reaching vulnerable population groups (80%); (ii) screening for active TB in high-risk groups (63%); (iii) implementing electronic registers (60%); (iv) contact tracing and outbreak investigation (60%); and (v) tackling MDR-TB (60%). Of the priority populations identified, undocumented migrants were recognized as the top priority by 46% of countries. In response to questions on the perceived obstacles to implementation, the countries mentioned barriers related to: (i) care recipients (such as lack of TB knowledge or treatment seeking/adherence); (ii) care providers (for example, the need for specialist training of nurses and doctors); and (iii) the health system (funding, communication between health and social care systems). The study was considered adequate to inform the development of a planned TB strategy toolkit for Member States (29).

4.3 Country-specific efforts

A few published experiences of country-specific efforts are available, including in Europe for Cyprus and in other regions for Oman (in the Middle East) and Canada and the United States (in North America). Although these countries are not representative of the global situation (or of the situation in the WHO European Region) and the findings cannot be generalized to the European situation, they may provide interesting elements for discussion.

In all of these countries, the TB incidence is approaching the TB pre-elimination threshold, with TB rates among foreign-born and vulnerable populations largely exceeding the TB rate in members of the native population who are not in at-risk groups.

Relevant experiences are available on TB infection management in Europe and will be described in section 5.4.

4.3.1 The Cyprus experience

A recent study reported on the progress achieved by Cyprus towards TB elimination (39). Cyprus is a suitable country for modelling exercises because of its relatively small population (about 1 million) and free access to good-quality health services. Although Cyprus has no formal TB elimination plan, the country has implemented all eight priority actions (39).

The overall TB notification rate per million population decreased from 85 in 1980 to the historic minimum of 28 cases in 2002. Over the same period, the number of sputum smear-positive cases declined from 24 to 11 per million population. From 1996 to 2004 the TB notification rates (for all forms) declined progressively among native Cypriots from 31 to 6 cases per million population in 2004, then plateaued at around 7–8 cases per million population. Among foreign-born individuals, the notification rate for sputum smear-positive cases increased to 54 cases in total (9 cases per million population) in 2009.

The TB trends in Cyprus demonstrate that adequate TB control measures led to an annual average annual decline of 9.4% between 1997 and 2002 (from 46 to 20 cases in total). Although a mild increase in incidence was recently observed due to the contribution from the immigrant population, the TB elimination threshold has almost been met in the native population.
4.3.2 Oman, Canada and the United States

A similar national experience from Oman (43) was recently published. The study described the trajectory of Oman (one of the low-TB-incidence countries in the Gulf area) towards TB elimination between 2000 and 2016. The average overall decline of TB cases was −2% per year (and more rapid in the native population).

For native-born Omani people, the notification rate for sputum smear-positive cases and all TB cases was 28.4 and 78.2 per million population, respectively (and rates for foreign-born individuals were 49.8 and 77.5 cases per million population, respectively). Oman reported excellent treatment outcomes (88% success rate for the 2015 cohort) and a short treatment delay (half of the cases diagnosed within one month from the onset of symptoms).

In Canada, with approximately 1500 cases per year over the last decade, the TB incidence has remained rather stable at 5 cases per 100 000 population (44). Improving coordination among the different provincial TB programmes and developing federal anti-TB activities while setting clear goals and targets was recently underscored as a prerequisite to reach the TB elimination threshold. Furthermore, the involvement of migrants and indigenous communities was considered essential (45).

Since 1989 the United States has been pursuing the goal of TB elimination. After making substantial progress over the past two decades, the annual rate of TB cases notified in the United States has now levelled off and remains well above the elimination threshold. The essential role of TB infection management to reach TB elimination in the United States has been underlined recently (44,46).

In California (United States), 10 million of the 40 million residents are foreign-born (47). Of the approximately 2100 TB cases notified over the last five years (20–25% of the overall notifications in the United States), > 75% occurred among foreign-born people. The study concluded that a 14% annual decline in TB cases is needed to achieve TB elimination by 2040. Although the greatest annual decline observed was 11%, the decline observed over the last five years is three times lower than needed. At the present level of decline, TB elimination in California will take 100 years (47).

4.3.3 Latin America and the Caribbean

It is also useful to consider regional experience from Latin America and the Caribbean, where the TB incidence in several countries is above (or approaching) the low-TB-incidence threshold (48–50). Costa Rica, Cuba, Jamaica, Puerto Rico and English-speaking islands have an incidence of below 10 cases per 100 000 population, while Chile and Trinidad and Tobago have incidence rates of between 10 and 20 cases per 100 000 inhabitants.

Following a meeting in Santiago de Chile in July 2016 involving representatives of the Asociación Latinoamericana de Tórax (Latin American Association of the Thorax), ERS and the Pan American Health Organization/WHO, the Hoja de Ruta para la Eliminación de la Tuberculosis en Latinoamérica y el Caribe 2016–2025 (Roadmap for Tuberculosis Elimination in Latin America and the Caribbean) (49,50) was launched. It identified eight components and specific actions to achieve TB elimination in the WHO Region of the Americas and described the specific indicators necessary to measure the trajectory towards TB elimination.

Region-specific priorities were identified as strong political commitment, improved surveillance, active case-finding in at-risk groups, increased international collaboration, enhancement of existing programmes targeting big cities, improved access of the population to rapid testing, shorter treatments for TB infection, and improved availability of new drugs (bedaquiline and delamanid) (50).
Activating efficient research networks to collaborate with national TB research plans was also identified as a priority \((39,49–61)\). A clear difference with Europe is that these countries face much lower levels of immigration from endemic countries.

Box 2 highlights policy implications for country-specific efforts.

**BOX 2. Policy implications**

- A comprehensive set of WHO and ECDC reports is available to support implementation of the priority actions necessary to pursue TB elimination in the WHO European Region.
- The principles, recommended interventions and indicators are substantially consistent between the WHO and ECDC reports.
- These reports contain several epidemiological and operational indicators to guide the implementation of the priority actions at the national level.
- Two surveys (by ERS/WHO/ECDC in 2013 \((30)\) and E-DETECT in 2018 \((31)\)) provide a picture of the country preparedness to implement the actions necessary to pursue TB elimination in the WHO European Region.
The eight core priority actions to achieve TB elimination, as identified by WHO in *Towards tuberculosis elimination: an action framework for low-incidence countries* (originally defined as those with fewer than 10 cases per 100,000 population) (2,5) and captured by the Tuberculosis Action Plan for the WHO European Region 2016–2020, are discussed below in detail. Separate subsections discuss how each of the activities needs to be managed in intermediate-incidence countries (2,28,60). The descriptions are complemented by information provided in recent ECDC reports and other publications (26,27). Although efforts were made to impose a similar structure on each of the subsections, the heterogeneity of the topics made this difficult to achieve.

### 5.1 Ensure political commitment, funding and stewardship (Action 1)

It is well established that TB prevention and care as well as elimination cannot be reached in the absence of governmental commitment, funding and stewardship (62). Within this remit, an adequate legal framework allows the proper functioning of the core areas. For example, the involvement and regulation of the private sector (which is important in most European countries) is considered crucial within a multisectoral approach that includes the private health sector (63). Adequate involvement of the private sector ensures that TB patients are duly notified and clinically managed according to the guidelines in force (40). In particular, high-quality notification data and analysis of treatment outcomes (ideally also available for TB infection) can guide the public health response. The legal framework ensures the use of validated diagnostic algorithms and the rational use of drugs to prevent the selection of drug-resistant strains of *Mycobacterium tuberculosis*. This will be discussed in detail in the following subsections.

Funding and stewardship are core preconditions to achieve TB prevention and care and pursue TB elimination (2,5,35,63). Funding can be inadequate even in low-TB-incidence, high-income countries, particularly when vertical TB control programmes have been dismantled and TB services decentralized. Furthermore, the regionalization of health services (for example, peripheralization of TB control programmes at the subnational level, which is common in European countries) might complicate both the coordination and funding of core activities (2,5,64). Moreover, the declining TB incidence trend makes it increasingly difficult to keep TB high on the governmental agenda (64).
5. The Eight Priority Actions in Low- and Intermediate-TB-Incidence Countries

Both the 2017 WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era, held in Moscow, the Russian Federation, and the 2018 United Nations General Assembly High-level Meeting on the Fight Against Tuberculosis helped to place TB higher in the Member States’ agendas (34–37).

Surveys of national TB programmes provide evidence of the political commitment, funding and stewardship in Member States (28,29).

- According to the ERS/WHO/ECDC 2013 survey (28), of the 31 countries and territories surveyed, 17 (54.8%) reported having a national TB coordinating body or a dedicated national TB programme, 20 (64.5%) have a national plan that includes TB elimination, 22 (71%) have guidelines and 14 (45.2%) have only a specific budget for TB. As an indicator of government commitment and adaptation to a changing epidemiology, 23 (74.2%) countries/territories reported having TB reference centres.

- E-DETECT 2018 surveyed how TB programme coordination is managed in 31 countries (29). It found that three quarters of countries (23 out of 31) have a clearly defined organizational structure, with this structure being defined in the national TB control plan or strategy in about half of these countries. In 55% (n = 17) of the countries, TB control and prevention was coordinated centrally by a national TB control board, committee or other formal body. An important element is the availability of costed plans, which were available in six countries, with 17 of the remaining 25 countries having budgets for parts of a TB programme and/or for TB-related activities within their national, federal or municipal health-care systems. According to this survey, half of countries (n = 16) had conducted an impact assessment or other financial or health economic assessment of the likely impact of TB control.

Vaccination against TB is another responsibility of government health authorities. The E-DETECT survey provides useful and up-to-date information on this topic: 20 out of 30 countries had a strategy to provide and promote bacillus Calmette-Guérin (BCG) vaccination (documented in the national TB control plan or strategy of nine of the 20 countries) (29). Survey information was available on the proportions of BCG vaccination strategies, including universal BCG vaccination of infants (42.1%, eight out of 19 countries), high-risk infants (57.9%, 11 out of 19 countries) and high-risk adults (21.1%, four out of 19 countries). Ten countries did not have a BCG vaccination strategy. Of these, two countries vaccinated infants born to immigrant parents from high-TB-incidence countries and three provided selective vaccination for people in high-risk groups.

5.1.1 Application to intermediate-TB-incidence countries

The principles of this priority action are fully applicable to intermediate-incidence countries. It is important to emphasize that in these countries the national TB programme is usually more visible, so that there can be no doubts about who is doing what. Although more and more intermediate-TB-incidence countries are starting or planning a transition from a vertical to an integrated approach to TB, a strong central TB unit is generally maintained. The main issues that intermediate-TB-incidence countries need to consider are how to maintain strong coordination of the national TB programme while decentralizing and integrating prevention and care services. Another important priority for these countries is adapting the existing funding mechanisms for anti-TB activities to the WHO recommendations to focus on outpatient TB management (65,66).

From this perspective, refund mechanisms for outpatient care are needed to make this approach sustainable (66). Furthermore, a gradual shift from external funding (including from the Global Fund to Fight AIDS, Tuberculosis and Malaria) to internal funding is also needed. A commitment to improve infection control and workplace safety is also important for intermediate-incidence countries (8,67).
5.2 Address vulnerable and hard-to-reach groups (Action 2)

TB is a poverty-related disease that especially affects vulnerable and marginalized populations. Towards tuberculosis elimination: an action framework for low-incidence countries (2,5) clearly identifies and describes the most relevant vulnerable groups in Europe, including unemployed people, people with low incomes, homeless people, people living in conflict zones, migrants, people living with HIV, people who use substances and alcohol harmfully, prisoners and marginalized groups. These groups often overlap and have a higher risk of acquiring both TB infection and TB, along with limited access to health services and/or limited treatment adherence (22,30–32,68–75).

In Europe, some ethnic minority groups (such as Roma and natives of Greenland) have higher TB incidence rates than the general population (72). The congregation of different vulnerable groups as well as more fragmented health services explains why TB incidence is often higher in large cities than in small cities or rural settings (71,73,74,76,77). Elderly people and young children are also considered vulnerable populations (78–89).

Diagnosis of TB is often difficult in elderly people because their TB symptoms may be masked by other comorbidities (90) and in children because of nonspecific symptoms, the paucibacillary nature of the disease and the difficulty of interpreting chest radiographs (82–86,89). Treatment of active TB is also more challenging in elderly people (due to comorbidities, age-related vulnerability and more common adverse events) (2,5,40,91) and in children, for whom adequate experimental data and friendly-to-use drug formulations are lacking (92,93). TB control and elimination in these vulnerable groups requires an evaluation of effectiveness and cost–effectiveness of systematic TB screening in selected groups of elderly people (94,95) and consideration of selective BCG vaccination in children (2,5).

BCG has limited efficacy in preventing pulmonary TB but if administered early in life is effective in reducing the risk of severe disseminated forms of TB and their sequelae in children (96–98). However, the risk–benefit ratio of BCG vaccination becomes increasingly unfavourable as the TB transmission rate decreases (99–102).

The ECDC 2010 report, Progressing towards TB elimination: a follow-up to the Framework Action Plan to Fight Tuberculosis in the European Union, proposed that TB notification trends in children could be used as an indirect measure of transmission (27). The observed decline of TB notification rates in children aged under 15 years in the EU suggests reduced transmission, although some countries have higher paediatric notification rates (Bulgaria, Latvia, Lithuania and Romania).

Universal, free-of-charge access to TB services without stigma is a core principle for achieving TB elimination (103–107) because of: (i) individual human rights (that is, each human being has the right to a healthy life); and (ii) the specific features of the disease. In fact, the essential components of TB control (which is aimed at reducing transmission) are rapid diagnosis and the effective treatment of infectious cases. It is in the interests of the wider community to ensure that all individuals with signs and symptoms compatible with TB are diagnosed and treated in a timely manner (even in the absence of health insurance and independent of any other legal or residency requirement) (103–107).

This issue is clearly underlined in Towards tuberculosis elimination: an action framework for low-incidence countries (2,5):

Many of the individuals and groups most at risk of TB exposure, 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. A human-rights-based approach to pursuing TB elimination is necessary. This includes addressing issues of non-discrimination, availability, accessibility, acceptability and quality of interventions, privacy and confidentiality,
participation and accountability. There are a range of related ethical issues that arise in the design and implementation of TB prevention and care interventions. Underlying inequities also need to be addressed in the TB response within and beyond the health sector, such as inequity in economic and social circumstances and related social determinants of disease, and in access to health care. There is also a need to address the concerns derived from access to formal health services, which may disclose the irregular status of some migrants and have legal implications.

Many of the individuals and groups most at risk of TB exposure, 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. A human-rights-based approach to pursuing TB elimination is necessary. This

Several studies have demonstrated that the methods used and programme targets to screen vulnerable groups for TB and TB infection vary across Europe, with more focus remaining on active TB disease than on TB infection (28,108,109).

One of the challenges for TB control and elimination in Europe is the implementation of collaborative initiatives among the different countries. As this issue is particularly relevant for transborder migration, it will be described in section 5.3.

5.2.1 Application to intermediate-TB-incidence countries

The principles of this priority action are fully applicable to intermediate-incidence countries. The main issues are identifying which at-risk groups to screen among the vulnerable categories and choosing the screening methodology, which might need to be adapted for both low- and intermediate-TB-incidence countries.

5.3 Address the special needs of migrants and cross-border issues (Action 3)

Migration is currently a major issue, with obvious political, social, humanitarian and medical implications, as well as and implications for the media (30,103,104,107,110–121).

Several transborder migration patterns are relevant for the WHO European Region: (i) migration from another EU country (particularly Member States with the highest TB case notification rates – Bulgaria, Estonia, Latvia, Lithuania and Romania); (ii) migration from non-EU countries in the Region (such as Belarus, the Republic of Moldova, the Russian Federation, Turkey and Ukraine); and (iii) migration from the rest of the world (29). It is therefore important to understand how TB is transmitted between migrants and native populations in low-TB-incidence countries (27,111) as well as in intermediate-incidence countries.

Eight studies undertaken in the EU and one in the United States, and the results of molecular fingerprinting have demonstrated that cross-transmission between migrants and native populations is limited (111). The major impact of migration on TB in the Region is through reactivation of TB infection contracted outside Europe.

The global estimates for 2017 total 258 million international migrants, corresponding to approximately one migrant per 30 inhabitants of the world (122). If the 740 million people migrating within national borders are included, bringing the total to 1 billion, the proportion becomes one in every seven people worldwide (110). About 50% of international migrants are female, with 70% residing in high-income countries (7). Labour migrants represent more than 150 million people, an estimated 21 million are forced labour victims
and 30% are minors \(^{(110)}\). The overall estimates are 50 million irregular or undocumented migrants and 21.3 million refugees.

People migrating to escape extreme poverty, persecution, wars and other extreme situations usually have long, dangerous journeys by land, sea and/or air and face difficult situations when they eventually reach the port of entry of the host country \(^{(103,104,107,110,112–118)}\). TB is therefore an important disease in migrants because of the high rate of TB infection in those from high-burden countries and the large proportion of active TB cases due to reactivation \(^{(104,110,112)}\).

The available evidence indicates a pooled TB infection prevalence of about 45% based on the tuberculin skin test (TST; also known as the Mantoux test) but of only 25% based on the interferon-gamma release assay (IGRA) \(^{(123)}\); the latter finding is confirmed by data from the E-DETECT TB project for several European countries \(^{(124)}\).

5.3.1 Changing patterns of migration in Europe within the global scenario

Although globally south–north has been considered the predominant migration pattern, since 2015 south–south migration has reached a similar scale \(^{(110)}\). The top five countries currently contributing to migration are Bangladesh, China, India, Mexico and the Russian Federation, with all except Mexico being on the WHO high-TB-burden list \(^{(110)}\). More than half of international migrants live in low-TB-incidence countries, specifically in Australia, Canada, France, Germany, the Russian Federation, Saudi Arabia, Spain, the United Arab Emirates, the United Kingdom and the United States.

International migrants are the predominant population in which TB occurs in low-incidence countries, for example, 86% in Australia in 2014, 69% in the United States in 2016, 74% in the United Kingdom in 2016 and 90% in Sweden in 2016 \(^{(89,125)}\). In member countries of the Organisation for Economic Co-operation and Development, 52% (median value in 2013) of TB cases are diagnosed in foreign-born individuals \(^{(89,125)}\).

Fig. 1 provides summary information on the arrival of migrants and refugees to Europe by sea up to 25 February 2019. In the first two months of 2019, 8573 of the total of 10 958 reported arrivals were by sea, with an estimated 207 deaths (2%). The top three countries of origin (with the highest numbers of arrivals by sea and land) in 2018 were Guinea (11.3% of the arrivals), Morocco (11%) and the Syrian Arab Republic (9%). The top three initial destinations were Spain (because of the increase in arrivals via Gibraltar), Greece and Italy. Less information is available on the final destination, which is more relevant for TB control. Fig. 2 summarizes data from the United Nations Refugee Agency monthly by country. Table 3 shows how the overall number of migrant and refugee arrivals to Europe peaked in 2015 (at 1 032 400) and then decreased (to 373 700 in 2016, 185 100 in 2017 and 141 500 in 2018).

According to a European survey and policy report, several priorities have been identified to ensure adequate management of migrants and refugees, including improved surveillance, monitoring and evaluation, and operational research; universal access to prevention, diagnosis and treatment for TB and TB infection; and high-quality infection control (see also section 5.3.2) \(^{(103,104)}\).

5.3.2 Implications for TB control and elimination interventions

The particular living conditions experienced by migrants before, during and after travel (overcrowding and exposure to infectious cases) make them at a higher risk of TB infection (and potentially also for infected individuals to develop TB disease), as well as of being diagnosed later and interrupting treatment \(^{(110)}\). Several studies found that migrants have an increased risk of acquiring MDR-TB \(^{(110)}\).
5. The Eight Priority Actions in Low- and Intermediate-TB-Incidence Countries

**FIG. 1.** Refugee and migrant arrivals to Europe via the Mediterranean routes, January 2017–December 2018, monthly by country

**TABLE 3.** Refugee and migrant arrivals to Europe via the Mediterranean routes, January 2015–December 2018, yearly totals

<table>
<thead>
<tr>
<th>Year</th>
<th>Total arrivals</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>1,032,400</td>
</tr>
<tr>
<td>2016</td>
<td>373,700</td>
</tr>
<tr>
<td>2017</td>
<td>185,100</td>
</tr>
<tr>
<td>2018</td>
<td>141,500</td>
</tr>
</tbody>
</table>

Source: United Nations High Commissioner for Refugees (126).

Access to care can be difficult for migrants (particularly for undocumented migrants) due to problems such as stigma and fear of deportation, in addition to the costs and to language and cultural barriers (110). Migrants are often exposed to very difficult working environments, which further increase these risks. An example of this is South African miners who, due to their exposure to silica dust, have the highest rates of TB (3000–7000 TB cases per 100,000 miners, compared with the overall rate in South Africa of 981 cases per 100,000 general population in 2012) (110,127).

The WHO End TB Strategy recommends how to improve TB prevention, diagnosis and treatment among migrants (3) through several core interventions: adapting national TB programmes to migrants’ needs; collecting high-quality disaggregated data and ensuring adequate monitoring and evaluation of TB control/elimination strategies; ensuring the implementation of migrant-sensitive TB prevention and care services with culturally competent staff (to overcome language and other barriers) and cross-border
referral systems; supporting bold intersectoral policies and systems; ensuring coherence between health
and non-health sectors (such as implementing social interventions within and among countries); adopting
policies to facilitate universal access and social protection; eliminating discrimination and minimizing legal/
administrative barriers; keeping TB high on the agenda of agreements on migration with the public and
private sectors; implementing migrant-specific operational activities focused on social determinants; and
developing and implementing new tools.

One review describes the history and development of screening for TB and TB infection in the context of
migration (119). In particular, it discusses the screening strategies and diagnostic tests used over the 20th
century, outlines current practices and considers the future impact of new advances in screening. The
recent focus on the TB elimination strategy is further increasing the importance of diagnosing and treating
TB infection in migrant populations.

As a result of migration and the decreasing prevalence of TB among native populations, the proportion
of TB cases in foreign-born individuals has gradually increased across Europe, especially in low-incidence
countries. Countries have generally focused on two targeted interventions: (i) identifying people with active
TB before or soon after their arrival in the host country so as to detect prevalent TB cases; balanced with
(ii) diagnosing and treating TB infection to prevent TB reactivation and future cases of disease.

The first screening approach was implemented over a century ago. Passengers arriving by sea to the United
States were asked to climb a long, steep staircase while carrying their luggage, under the observation of
custom officers. Individuals who were smiling or laughing were screened for mental disorders (of which
syphilis was a common cause at the time) and those coughing were screened for TB
(119).

Today evidence is still lacking in many areas, including the best and cost-effective ways of screening for TB
and TB infection (whether before migration, at the port of entry or after reaching the host country) (2,5).
Importantly, screening should always be linked with follow-up or referral to a treatment programme, with
universal access to health services.

The initial screening of migrants for active TB usually combines clinical and radiological methods (128).
Some countries (heterogeneity is high) require individuals applying for permanent residence, temporary
workers and long-staying visitors, as well as asylum seekers, to undergo medical evaluation. Some
countries require all migrants, including asylum seekers, from high-incidence settings (the definition of
which varies) to undergo examination. The usual aim is to detect cases of active TB, not the possibility
of reactivation of TB infection in the future. In some countries, evaluations include both a physical
examination and laboratory investigation, complemented by chest radiography. Identifying individual
migrants in need of further investigation via scores and thresholds tailored to their country of origin has
significant advantages in terms of flexibility, cost and the burden of medical procedures on the screened
population (119).

Some countries screen migrants for TB upon arrival (129). In Europe screening before arrival is only performed
by the United Kingdom. Overall, screening before arrival is governed by different policies, although in
countries of origin with sociopolitical stability and trustworthy services, it might be easily implemented
in collaboration with local embassies (130–132). However, this approach cannot be used for migrants
who are escaping conflict or natural disaster, come from settings without appropriate administrative
structures or wish to avoid contact with legal authorities in their country of residence (for example,
irregular or undocumented persons or individuals escaping military service). Other countries require the
screening of resident foreign nationals, including labour migrants on (or after) arrival, and some may
impose residency conditions that include regular medical examinations or chest radiography. Radiological
findings compatible with or suggestive of pulmonary TB usually trigger more specific secondary screening investigations.

According to a recent study, the TB rate among pre-screened individuals ranged from 80 cases per 100,000 people for Australia (425 TB cases identified out of 530,801 people screened) to 230 per 100,000 people for the United States (1,450 TB cases identified out of 631,000 people screened) (89). On the negative side, if TB is diagnosed during visa processing, then a delay should be expected to allow the completion of TB or MDR-TB treatment.

Although approaches vary, screening might include diagnostic tests for TB infection (that is, by TST or, more recently, IGRA) and bacteriological examinations (sputum smear microscopy and culture and/or rapid genetic methods) (89, 119).

Currently WHO is (conditionally) recommending screening for both TB and TB infection among migrants from endemic countries who are living in low-TB-burden countries owing to concerns about implementation issues, as well as the low-quality evidence on the effectiveness and cost-effectiveness of available tools and of targeting at-risk groups. This will be discussed more extensively in section 5.4.

The 2013 ERS/WHO/ECDC survey found that TB care is not yet free for all patients in three out of 31 countries/territories (9.7%) (28). The public health importance of ensuring universal free access to TB diagnosis and treatment (including TB infection management) for all individuals, including migrants, with TB disease is internationally recognized (21, 30), particularly from a TB elimination perspective.

### 5.3.3 Application to intermediate-TB-incidence countries

The principles of this action are fully applicable to intermediate-incidence countries. As in section 5.2, the strategic approach to migrant and refugee screening needs to be tailored to the needs of both low- and intermediate-incidence countries.

However, migrants are often in transit through intermediate-incidence countries, which creates challenges in terms of TB detection and continuum of care. A transborder collaboration mechanism aimed at supporting both public health and clinical TB case management will be useful in addressing these (133). In the first quarter of 2020, the TB Consilium of the Global Tuberculosis Network activated a mechanism supporting transborder migration that focuses on both TB and TB infection (134).

Furthermore, the large number of individuals to be managed (sometimes settled in unofficial camps without adequate health services) and the reduced availability of resources poses additional challenges to intermediate-incidence countries (103, 104).

Box 3 highlights policy implications of Actions 1–3.
5.4 Manage TB infection and active TB (Action 4)

This section will mainly focus on TB infection management; however, some subsections (such as section 5.4.13 on screening migrants) discuss TB infection and TB together because of the difficulty in clearly dividing them.

WHO defines TB infection as a status characterized by the presence of an immune response to *M. tuberculosis* without clinical evidence of active TB (1,10,135). TB infection is estimated to affect approximately one third to one quarter of the total global population and forms the reservoir for the large majority of emerging active TB cases in low-incidence countries (1,10,135). The management of TB infection was discussed by WHO in dedicated guidelines for the first time in 2015 (it had been discussed previously in contact investigations).

**BOX 3. Policy implications (Actions 1–3)**

- The 2017 WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era, held in Moscow, the Russian Federation (34) and the United Nations General Assembly High-level Meeting on the Fight Against Tuberculosis in New York, the United States (36) confirmed the importance of government commitment, funding and stewardship in TB elimination. An adequate legal framework can ensure several core interventions, including: the implementation of costed national TB elimination plans; involvement and regulation of the private sector; approval of adequate prevention, diagnosis and treatment guidelines; and establishment of quality surveillance, diagnostic and treatment capacity.

- As social, economic and demographic factors contribute to TB, special attention needs to be paid to vulnerable and marginalized populations, including people on low incomes, homeless people, migrants, people living with HIV, people who use substances and alcohol harmfully, prisoners, ethnic minorities and other marginalized groups, as well as young children and elderly people.

- Specific indicators for vulnerable people and migrants are useful for monitoring and evaluation. In particular, use of the ECDC-proposed indicator of TB in children as an indirect marker of transmission deserves special attention and standardized reporting (12).

- Transborder collaboration activities are important to tackle the needs of migrants and other vulnerable populations (such as ensuring continuity of care; see section 5.3.3). In Europe, universal and free-of-charge access to TB services is needed without stigma.

- Migration flows are subject to rapid changes over time and need close monitoring through improved surveillance (including monitoring of plausible transmission events through molecular epidemiology), with European-wide collaboration and information exchange (103,104).

- Given the different approaches to TB infection and TB screening across Europe, strong coordination and increased standardization are necessary to strengthen TB prevention and care and progress further towards TB elimination.
and TB/HIV guidelines) (9) and is an integral part of Pillar 1 of the End TB Strategy (1,3,10,135). Importantly, as discussed in sections 3.3 and 3.4, the possibility of reducing the pool of infected individuals by treating TB infection and, therefore, of preventing future TB cases is a key element of TB elimination (2,5,21,22,28). The core steps for managing TB infection are diagnosis (which includes screening), preventive treatment, and monitoring and evaluation.

The evidence indicates that treating TB infection highly protects against reactivation (1,10). Therefore, public health will be improved if most infected individuals are diagnosed and treated and they adhere to and complete the recommended regimen (2,5,21,22,28). Studies performed among the indigenous (Inuit) populations of Alaska, Canada and Greenland between 1955 and 1974 demonstrated that the annual decline in TB incidence could increase from −8.7% to −17% with the aggressive diagnosis and treatment of TB infection (136).

As well as ensuring that eligible individuals benefit, the overall approach to TB infection testing and treatment should be organized from a programmatic perspective. This requires strong political commitment, adequate funding, and an effective monitoring and evaluation system. The recent WHO guidelines (1) consolidate existing publications and recommendations to provide universal guidance (Table 4).

The principle of TB infection management is that intention to test is intention to treat. Nevertheless, the decision to initiate treatment should consider the trade-off between efficacy and safety related to the underlying risk of activation and risk factors for toxicity (137).

5.4.1 The experience in European countries

Interesting data are available on TB infection management in several different European countries and are reported as an introduction to the specific sections on TB screening, diagnosis and treatment.

Persons with a high risk of exposure to TB (or of developing TB when infected) have received targeted diagnosis and treatment for TB infection and been monitored routinely in the Netherlands since 1993. A recent study describes the trends in specific groups as well as the diagnostic methods and treatment regimens used, and explores the determinants for treatment initiation, treatment completion and adverse events (138).

In total, 37 729 persons with TB infection were registered from 1993 to 2013, of whom 28 931 (77%) started TPT; of these, 82% completed the treatment and 8% interrupted due to adverse events. Two thirds of the notified cases were detected through contact investigations. In recent years, increasing numbers of people with immunosuppressive disorders, elderly people and foreign-born people have been notified owing to policy changes and the introduction of IGRAs. Children (96%) and immunosuppressed people (95%) were most likely to start TPT. Children (93%) were also more likely to complete TPT, with either rifampicin or rifampicin/isoniazid regimens (91% or 92%, respectively). These two patient groups were also 40% less likely to stop TPT due to adverse events.
TABLE 4. WHO recommendations for the management of TB infection

<table>
<thead>
<tr>
<th>At-risk populations</th>
<th>TB infection testing and treatment should be considered</th>
<th>TB infection testing and treatment may be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>People living with HIV:</strong></td>
<td>• all adults and adolescents living with HIV</td>
<td>HIV-negative children aged ≥ 5 years, adolescents and adults who are contacts in HBCs</td>
</tr>
<tr>
<td></td>
<td>• all infants and children living with HIV</td>
<td></td>
</tr>
<tr>
<td><strong>Contacts:</strong></td>
<td>• children aged &lt; 5 years, regardless of HIV status</td>
<td>Contacts of patients with MDR-TB</td>
</tr>
<tr>
<td></td>
<td>• adult and child contacts in LBCs</td>
<td>HIV-negative prisoners, health workers, migrants from HBCs; homeless persons, people who use illicit drugs, living in LBCs</td>
</tr>
<tr>
<td><strong>HIV-negative clinical risk groups:</strong></td>
<td>• patients on anti-TNF-α drugs, receiving dialysis, preparing for organ or haematological transplantation</td>
<td>Children living with HIV who have successfully completed treatment for TB</td>
</tr>
<tr>
<td></td>
<td>• patients with silicosis</td>
<td></td>
</tr>
</tbody>
</table>

**Ruling out TB**
Exclude active TB using clinical algorithms and TB investigations (according to national and WHO guidelines)

**Testing for TB infection**
Either the TST or IGRA can be used to diagnose TB infection

**Treating TB infection**
Daily isoniazid for 6–9 months
Daily rifampicin plus isoniazid for 3–4 months
Weekly rifapentine plus isoniazid for 3 months
Daily rifapentine plus isoniazid for 1 month
Daily rifampicin for 3–4 months
Daily levofloxacin for 6 months is possible for contacts of MDR-TB cases

HBC: high-burden country; LBC: low-burden country.

a Household contacts of bacteriologically confirmed active TB cases.
b May be 36 months or longer in eligible people living with HIV.

Source: WHO (1,137).

Under these operational conditions, TB infection management was estimated to reduce the risk of incident TB in the target population by 40–60% (138).

In Sweden, a consistently high completion rate for TPT in asylum seekers has been achieved since 2013 through implementing several people-centred interventions, including interpreter-assisted appointments and the use of short regimens (139).

Moreover, in a population of asylum seekers in Italy, the proportion of individuals completing the prescribed TB preventive treatment regimen was 47.9% (90 out of 191) (124).

These examples show that focusing on high-risk TB groups for TB infection screening and treatment can be successfully implemented if adequate infrastructure and organization of services are available.
5.4.2 Diagnostic testing for TB infection

Diagnosing TB infection is a challenge, not least because the scientific community has gradually come to consider TB as more of a continuum between infection and active disease rather than a clear dichotomous state of either TB infection or active TB. Moreover, the current diagnostic methodology cannot distinguish between individuals who have been infected with *M. tuberculosis* and continue to be infected from those who have cleared the infection. Individuals with TB infection are asymptomatic and all microbiological and molecular diagnostic assays are negative; therefore, TB infection diagnosis is based on tests that assess the adaptive immune response to *M. tuberculosis*.

Traditionally, testing for TB infection was based on the intradermal response to injection of a purified protein derivative of *M. tuberculosis*, as with the TST. The TST identifies an in vivo cell-mediated immune response to tuberculin following an intradermal injection of the purified protein derivative and the tested person has to return to the clinic after 48–72 hours to measure the TST reaction. As the purified protein derivative is a mixture of antigens, many of which are shared by *M. tuberculosis*, *Mycobacterium bovis*, the BCG vaccine strain and other environmental mycobacteria, the specificity of the TST is low. This is particularly relevant in populations from low- and intermediate-TB-incidence countries, such as those in Europe, some of which have a high coverage of BCG vaccination and infection with environmental mycobacteria.

An alternative diagnostic tool has been introduced based on the identification of antigens that elicit the production of interferon-gamma in a patient’s blood sample (which does not cross-react with *M. bovis*, the BCG vaccine or most non-tuberculous mycobacteria). Owing to the lack of response in BCG-vaccinated individuals, the IGRA is potentially a more specific test for TB infection (as it is unaffected by prior vaccination). Further developments led to commercial IGRA becoming available (140–142). The IGRA is based on the principle that the T cells of individuals infected with *M. tuberculosis* produce interferon-gamma when exposed to *M. tuberculosis*-specific antigens. The assumption is that such gamma-interferon production is indicative of TB infection. The two main commercial IGRA are the QuantiFERON-TB Gold Plus (Qiagen, Hilden, Germany) and the T-SPOT.TB test (Oxford Immunotec, United Kingdom). The QuantiFERON-TB Gold Plus measures gamma-interferon production in whole blood using an enzyme-linked immunosorbent assay; this test is a relatively new derivative based on the QuantiFERON Gold In-Tube but with TB-specific antigens that elicit CD4-positive and CD8-positive T-cell responses. T-SPOT.TB is based on an enzyme-linked immunospot method that determines the actual number of interferon-gamma-producing T cells.4

However, neither the TST nor the IGRA can tell you when infection actually took place or be used for diagnosing active TB or TB infections that may have been cleared by the body. Despite the progress achieved in this area, the available TB infection diagnostic tests still have suboptimal predictive capacity relating to the risk of reactivation.

5.4.3 Diagnostic policies for TB infection

Different guidelines have appeared over the last decade describing the tests to be used, interpretations and actions to be taken depending on the test results, the age of the individual, HIV status, and whether TB exposure was specific (for example, household- or health-care related) or more general (in individuals living in or travelling from low- or high-TB-incidence countries, for instance) (143–145).

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4 QuantiFERON-TB Gold is distributed by Qiagen (https://www.quantiferon.com/) and T-SPOT.TB is distributed by Oxford Immunotec (http://www.oxfordimmunotec.com).
A strong TST response following recent significant TB exposure(s) indicates that progression to active TB is more likely, thus offering the opportunity of chemoprophylaxis (TPT) to reduce the risk of developing TB. Recent studies have started to evaluate the probability of different IGRA responses and the subsequent likelihood of developing active TB (146).

The updated 2020 WHO TB guidance indicated that either the TST or IGRA can be used to test for TB infection (1), depending on the availability and affordability of the tests. Neither the TST nor the IGRA can be used to diagnose active TB disease nor for diagnosing adults suspected of having active TB. The WHO guidance also indicated that those people living with HIV who test positively for TB infection benefit more from preventive treatment compared with those with a negative TB infection test. Therefore, the global WHO guidance confirms earlier guidance that, where feasible, TB infection testing can be used to identify such individuals. The revised WHO guidance restated the previous guidance from 2011 that TB infection testing by either the TST or the IGRA is not a requirement for initiating preventive treatment for people living with HIV or for child household contacts aged under 5 years (144).

Based on evidence mainly from low-TB-incidence, high-income settings, ECDC concluded that both the TST and the IGRA are suitable, cost-effective diagnostic tools for TB infection (145).

5.4.4 Rationale for the recommendations, and when and how to detect TB infection in Europe

The evidence reviewed by both WHO and ECDC and the resulting recommendations related only to the use of the two commercially available IGRAs (QuantiFERON-TB Gold In-Tube and T-SPOT.TB). In its 2015 guidelines, WHO concluded that a comparison of TST and IGRA in the same population did not provide strong evidence that one test should be preferred over the other to predict progression to active TB disease (9,137). While the TST required significantly fewer resources than the IGRA and may be more familiar to practitioners in resource-constrained settings, recurrent global shortages of TST had reduced its use in scaling up the programmatic management of TB infection.

The preferences of exposed individuals and TB programmes are, however, affected by various factors, such as the need for venepuncture (which is not always easy, particularly in children), the higher cost of the IGRA and the requirement for a sophisticated laboratory infrastructure (for the IGRA, for example). The two clinic visits for TST (the second to read the test) and the need for an effective cold chain for the TST also carry a financial and programmatic burden. Therefore, operational difficulties should be considered in deciding which test to use. For these reasons, WHO recommended that the two tests should be considered equivalent options, with relatively similar advantages and disadvantages.

WHO guidance also noted that the performance of these tests is currently imperfect, which can lead to false-negative results, particularly for young children and immunocompromised individuals (such as people living with HIV). These tests were determined to be most useful and valuable for identifying recent conversion negative to positive test findings, particularly among the contacts of people with pulmonary TB, for whom TB preventive treatment would probably have the most benefit.

The value of IGRAs in the serial observation of TB patients and TB-infected individuals is less clear cut: studies in health-care workers tested serially in the United States showed that conversion from negative to positive test findings and reversion from positive to negative test findings are more commonly observed with the IGRA than the TST (147). This was particularly seen for cases where interferon-gamma values fell within the so-called grey zone. Therefore, WHO recommended that good clinical judgement (with tests repeated where necessary) must be used in interpreting the results of serial testing.
ECDC also created a mathematical model of TB transmission to estimate the contribution that TB infection screening and subsequent treatment for at-risk populations (such as people who inject drugs, homeless people, prisoners and migrants from high-TB-incidence countries) would have on reducing subsequent TB transmission (148). Application of the model to four EU countries (Czechia, the Netherlands, Portugal and Spain) indicated that screening (and subsequent treatment) for TB infection in certain at-risk groups (including people who inject drugs, homeless people and migrants) from high-TB-burden countries led to a decrease in pulmonary TB incidence. The model informed the assessment of the cost–effectiveness of selected TB infection screening and treatment strategies. Across all of the at-risk populations considered, the model showed that performing a TST and, if positive, an IGRA was the most cost-effective strategy for diagnosing TB infection. Analysis of cost–effectiveness suggested that TB infection screening of migrants at entry, prisoners and people who inject drugs/homeless people would be cost-effective in general. Moreover, TB infection screening and treatment of immunocompromised people would be cost-effective if they were part of a migrant population or of the native populations of European countries with a relatively high TB burden (that is, more than 50 incident cases per 100 000 population). The model also showed TB infection screening to be cost-effective for the close contacts of active pulmonary TB patients (148,149), consistent with national studies in low-TB-incidence countries such as the United Kingdom (115,150).

In arguably the largest head-to-head study of the TST (with stratification of the induration at 5, 10 and 15 mm cut-offs – designated TST-5, TST-10 and TST-15, respectively) and the two main IGRAs conducted in the United Kingdom between 2010 and 2015, 9610 adults (aged over 16 years) were recruited from 54 centres (including clinics and community settings). Participants were eligible if they were at a high risk of TB infection (that is, a recent contact of someone with active TB or a migrant who had arrived in the United Kingdom in the past five years from, or who frequently travelled to, a country with a high TB burden). Of this cohort, 4861 (50.6%) were contacts and 4749 (49.4%) were migrants. The participants were followed up for a median of 2.9 years (range, 21 days to 5.9 years). A total of 97 (1.0%) participants developed active TB (1.2% of the participants (77 out of 6380) with results for all three tests). In all tests, the annual incidence of TB was very low in those who tested negatively, ranging from 1.2 per 1000 person-years (95% confidence interval (CI): 0.6–2.0) for TST-5 to 1.9 per 1000 person-years (95% CI: 1.3–2.7) for QuantiFERON-TB Gold In-Tube. The annual TB incidence in participants with positive test results was highest for T-SPOT.TB (13.2 per 1000 person-years; 95% CI: 9.9–17.4), TST-15 (11.1 per 1000 person-years; 95% CI: 8.3–14.6) and QuantiFERON-TB Gold In-Tube (10.1 per 1000 person-years; 95% CI: 7.4–13.4). Positive results for these tests were significantly better predictors of progression compared with the TST-10 and TST-5 tests (for instance, the ratio of test positivity rates in those progressing to TB compared with those not progressing for T-SPOT.TB versus TST-5: 1:99 (95% CI: 1.68–2.34); P < 0·0001). Therefore, TST findings stratified by BCG vaccination status have a similar predictive value to those of the two commonly used IGRAs. The IGRA and TST-15 strategies gave a high proportion of negative test results, with low progression rates among these individuals, and correctly identified a high risk of progression in participants with positive test results, thus supporting their use in screening programmes (146).

ECDC described the key components for the implementation of programmatic management of TB infection (Table 5) and the target groups for prioritization for TB infection screening and treatment: people living with HIV; immunocompromised persons (patients on anti-TNF-α treatment, transplant patients, patients with end-stage renal disease or undergoing dialysis); patients with silicosis; people with pulmonary fibrotic lesions; and the contacts of infectious TB cases. Therefore, for diagnosing TB infection, both TST and IGRA or a combination can be used.
### Table 5. TB infection testing method by target group

<table>
<thead>
<tr>
<th>Target group</th>
<th>Preferred test</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children under 5 years of age</td>
<td>TST</td>
<td>Children’s immune system, difficulty of drawing blood, little data on the performance of IGRA in young children</td>
</tr>
<tr>
<td>Vulnerable and hard-to-reach populationsa</td>
<td>IGRA</td>
<td>No need for a second visit to read the test result</td>
</tr>
<tr>
<td>Immunocompromised patients (including people living with HIV)</td>
<td>Combination of TST and IGRA (parallel testing)b</td>
<td>TB infection tests are less sensitive in immunocompromised people; in order not to miss M. tuberculosis-infected people who may face significant adverse health effects due to TB, a more inclusive approach is advisable</td>
</tr>
<tr>
<td>Migrant populations</td>
<td>IGRA or TST acceptable (IGRA for large numbers)</td>
<td>No need for a second visit to read the IGRA result</td>
</tr>
<tr>
<td>BCG-vaccinated people</td>
<td>IGRA</td>
<td>TST may be affected by prior vaccination with BCG</td>
</tr>
</tbody>
</table>

* Adults, young people and children whose social circumstances or lifestyle, or those or their parents or carers, make it difficult to recognize TB symptoms, access health services, self-administer treatment and attend regular health-care appointments (151).
* After the initiation or antiretroviral treatment, repeated testing for TB infection may be considered for people living with HIV who are known to previously have negative TST or IGRA results (152).

Source: Rosales-Klintz et al. (153); table reproduced with permission from ECDC (12).

#### 5.4.5 Operational considerations for TB infection testing

TB incidence across Europe is classified as low to intermediate (15); ECDC (and ERS) guidance for testing for TB infection is based on this incidence range and the significant laboratory infrastructure available in much of the continent. Some of the key programmatic considerations for TB infection diagnosis based on the expert opinion of the ECDC ad hoc scientific panel are shown in Table 5 (153).

WHO global guidance considered issues around the practicability of TB infection diagnosis related to the availability and affordability of the TST and IGRA; therefore, the overall public health infrastructure required to implement the tests could determine which TB infection test is used.

The increased specificity of the IGRA compared with the TST is offset by the higher cost of the IGRA. Most of the increased specificity of the IGRA is due to previous BCG vaccination confounding TST results: IGRAstrs are unaffected by BCG vaccination, although some non-tuberculous mycobacterial infections cause false-positives in the IGRA. Even then, the WHO Expert Group noted that effects of previous BCG vaccination on the TST were dependent on the age at vaccination and the BCG strain used: when the BCG is given at birth it has a limited impact on TST specificity (154).

The results of the prospective cohort study of TST and the two main IGRAstrs conducted in the United Kingdom supports this (146). This study found that IGRA-based or BCG-stratified TST strategies were most suitable for screening for potential disease progression in high-risk groups. However, it noted that further work was needed to assess cost-effectiveness of each screening test in different countries.

ECDC guidance concluded that the methodologies used for evaluating cost-effectiveness were heterogeneous in terms of the outcome measures and definitions of cost-effective and willingness-to-pay thresholds (if reported) (145).
5.4.6 Evidence on the likelihood of progression from TB infection to active TB

There is no gold standard method for predicting in which individuals an infection will progress to active disease. A recent study using QuantiFERON-TB Gold Plus (which includes an additional antigen, TB2, that stimulates both CD4-positive and CD8-positive T cells) in contacts of TB patients argued that the new test has a stronger association with surrogate measures of TB exposure in adults screened for TB infection compared with QuantiFERON-TB Gold In-Tube (155).

WHO updated a previous systematic review to compare the predictive performance of IGRA and TST in identifying incident active TB in countries with a high TB incidence (156). Only head-to-head studies comparing TST with IGRA in the same population were included. Relative risk ratios for TB for people who tested positive and those who tested negative using the TST and IGRA were estimated. Five prospective cohort studies were identified, with a total of 7769 participants (three in South Africa and two in India) (157–160). The studies included people living with HIV, pregnant women, adolescents, health-care workers and household contacts. The pooled risk ratio estimate for TST was 1.49 (95% CI: 0.79–2.80) and for IGRA was 2.03 (95% CI: 1.18–3.50). Although the estimate was slightly higher for IGRA than for TST, the 95% CIs for the estimates for TST and IGRA overlapped, indicating that neither test was better than the other in predicting progression to active TB. Furthermore, there was limited evidence for the predictive utility of the tests in specific at-risk populations.

However, the WHO European Region comprises countries that have low or intermediate TB incidence (typically with migration from higher-TB-incidence countries). The review evidence underlying the current WHO guidelines for low- and intermediate-incidence countries has been published (1,10): the underlying studies evaluated TST versus a single IGRA in high-incidence countries and five studies compared the TST with the IGRA in low-incidence countries (146,161–164). Only two of these studies compared TST with each of the commercially available IGRA (146,164) (the other three studies only compared the TST with QuantiFERON-TB Gold In-Tube). The UK PREDICT TB study compared TST with both IGRA and included the largest number of TB-infected individuals and the largest number of patients progressing to active TB (146).

The UK PREDICT TB study (146) found the tests to have lower positive predictive values than those reported in most other studies and in other cohort studies (for example, see Harstad et al. (163) and Haldar et al. (165)). T-SPOT.TB (an IGRA) had a positive predictive value of 4.2% and the BCG-stratified TST, TST-15, had a positive predictive value of 3.5%, with the highest incident rate ratios: TB incidence in those with positive and negative results was 8.8 (95% CI: 5.5–14.2) for T-SPOT.TB and 7.1 (95% CI: 4.4–11.4) for TST-15.

Obviously, the positive predictive value for developing active TB partly depends on the TB incidence in the study population (that is, the positive predictive value is higher when the incidence is greater). The analysis of the TST stratified by BCG vaccination status found similar incident rate ratios to those found for both of the IGRA. This contrasts with the findings of the WHO guideline review, which concluded that use of TSTs (versus IGRA) gave a lower incident rate ratio for progression to active TB in low-incidence countries. The current analysis found that progression to active TB was higher among recently exposed participants compared with migrants, who had probably acquired the infection much earlier in another country.

Although the negative predictive values were similar for all tests, statistically significant differences in the prediction of progression to active TB were found between tests: a positive T-SPOT.TB result was a significantly better predictor than all other tests except the TST-15; and QuantiFERON-TB Gold In-Tube was a significantly better predictor than the TST-10. The review of WHO guidelines did not compare the performance of TST stratified by BCG vaccination status with IGRA. However, the PREDICT study showed for the first time that the TST with this stratification method had a similar performance to IGRA. The most recent WHO guidelines (for 2018) recommend either the TST or IGRA as equivalent alternatives without
considering previous BCG vaccination (1). However, the PREDICT results contradict this recommendation. Nevertheless, the decisions on which diagnostic strategy to use will also be influenced by practical healthcare infrastructure considerations.

5.4.7 Who benefits most from TB infection testing?

The group that benefits most from TB preventive treatment is people living with HIV (risk ratio: 0.68; 95% CI: 0.54–0.85) and the benefit is even higher for those with a positive TST (risk ratio: 0.38; 95% CI: 0.25–0.57) (1,9,91,135,166,167).

According to the available evidence, the risk of active TB given infection is higher in recent contacts (1), children aged below 5 years (168–170), people living with HIV (171,172) and individuals undergoing biological therapy (142,173–179). The TB infection prevalence, and therefore the TB incidence, is higher in migrants from high-TB-burden countries (103,104,114,180,181) and health-care workers (166,182–185), but the risk of disease in infected individuals is not necessarily higher in the absence of additional risk factors for progression.

The debate about which at-risk groups should be tested and treated is still ongoing. According to WHO, the primary targets (strong recommendation) are people living with HIV (regardless of their immunosuppression and antiretroviral therapy status), children under 5 years of age who are the household contacts of a pulmonary TB patient, and people with a clinical condition such as silicosis or a disease requiring anti-TNF-α treatment, dialysis or organ or haematological transplantation. In low-incidence countries (such as those in the EU), additional at-risk groups should also be considered for systematic TB infection testing and treatment: strong recommendation for HIV-negative children aged 5 years or over, and adolescents and adults who are household contacts of patients with bacteriologically confirmed pulmonary TB (10); and conditional recommendation for migrants from endemic areas, prisoners, health-care workers, homeless people and people who use illicit drugs (1,10). In countries where a high proportion of TB patients also have diabetes (for example, 30–40% of TB patients in Mexico have diabetes as a comorbidity), collaboration with diabetes clinics might provide an opportunity to manage TB infection in this risk group (Table 4) (58,59), although WHO does not recommend screening patients with diabetes for TB.

ECDC recently published a guidance report, *Programmatic management of latent tuberculosis infection in the European Union* (12), that identifies the key components for implementing the programmatic management of TB infection in the EU based on an assessment of the scientific evidence and the expert opinion of an ad hoc scientific panel (12,27,153). The target groups prioritized for TB infection screening and treatment in the report were: people living with HIV; immunocompromised persons (patients on anti-TNF-α treatment, patients preparing for organ or haematological transplantation, patients with end-stage renal diseases and/or preparing for dialysis); patients with silicosis; people with pulmonary fibrotic lesions; and the contacts of infectious pulmonary TB cases. Additional at-risk groups may be considered depending on the TB epidemiology.

5.4.8 Specific population groups to be tested for TB infection

5.4.8.1 People living with HIV

Despite the availability of antiretroviral drugs, TB remains the main cause of AIDS-related deaths at the global level (186). According to WHO 2017 data, HIV coinfected individuals have a 21 times higher probability of developing TB compared with non-infected individuals (15).
Several trials and meta-analyses have demonstrated the beneficial effect of isoniazid preventive therapy among persons living with HIV. The overall risk for TB in people living with HIV was reduced by 33% (relative effect (risk ratio): 0.67; 95% CI: 0.51–0.87) in a systematic review of 12 trials based on over 8500 individuals (166). Six months of isoniazid treatment reduced mortality by 37% after five years in western Africa (171). Due to the risk of reinfection in some settings, longer cycles of isoniazid preventive therapy (36 months or longer) are conditionally recommended by WHO, although Europe does not represent a target for this approach (1).

Although the evidence in children is weaker than in adults (187–189), in view of the increased risk of TB in children compared with adults, children living with HIV should be a priority for TPT.

### 5.4.8.2 Close contacts

A contact investigation of all children, adolescents and adults exposed to infectious (sputum smear-positive) cases is recommended in all low-TB-incidence countries, according to the stone-in-the-pond principle (190,191).

In a retrospective, population-based cohort study of close contacts of persons with infectious TB using casual contacts as the control (as a proxy for the general population), the TB incidence ratio ranged from 5.2 to 10.6 depending on the level of TST induration at baseline. In a systematic review and meta-analysis of TB infection in close contacts, the prevalence of TB infection was 51.4% (95% CI: 50.6–52.2) (192).

In countries with high incidence of TB, contact tracing, which was initially recommended only for children aged under 5 years, is increasingly also being performed for adult household contacts (1).

### 5.4.8.3 People with immunocompromising conditions

Although immunocompromising conditions are known, evidence covering this area is still suboptimal.

In a prospective cohort study of immunocompromised patients, the relative risk of progression (adjusted risk ratio) ranged between 8 and 41, depending on the baseline TST induration (193).

Because studies providing direct evidence of an increased risk of disease progression in other risk populations were unavailable, a series of systematic reviews was conducted to determine the incidence ratio for active TB in several candidate populations compared with year-adjusted national estimates derived from the WHO Global tuberculosis report 2013 (194). According to an unpublished WHO systematic review, recipients of anti-TNF-α drugs had a particularly high relative risk of incident TB (16.2; 95% CI: 14.6–18.0), similar to the findings of previous individual cohort analyses among people receiving TNF-α inhibitors.

Twenty years ago only a few anti-TNF-α agents (such as etanercept and infliximab) were available, but several (including adalimumab, certolizumab and golimumab) have been recently approved (174,175). TNF-α inhibition reduces granuloma activity, which boosts *M. tuberculosis* replication and, therefore, increases the risk of developing active TB (142,175–179). In the last 10 years, new and safer biological agents (but all with the potential to boost TB reactivation) have been introduced, including abatacept (cluster of differentiation 28 (CD28) inhibitor), rituximab (CD20 inhibitor) and tocilizumab (interleukin 6 (IL-6) inhibitor). No TB cases have been associated with the use of secukinumab (IL-17 inhibitor) or ustekinumab (IL12/IL-23 inhibitor) in patients with ankylosing spondylitis (175), and only sporadic cases have been reported with nivolumab, a novel inhibitor of the programmed death 1 (PD-1) checkpoint protein (195).
Candidates for organ or haematological transplantation are considered a priority group for TB infection testing (196). It is also important to emphasize that exposure to silica dust is associated with an increased risk of TB (197,198).

5.4.8.4 Health-care workers

Some health-care workers are at risk of acquiring TB infection and subsequent TB even in countries with a low TB incidence. The average annual risk of developing TB disease is estimated to be up to threefold higher for health-care workers who are infected with TB compared with the general population (182–185). Moreover, health-care workers are at a higher risk of developing MDR-TB: they are up to six times more likely to be hospitalized for MDR-TB compared with the population they care for. This is due to the difficulty of screening and treating this population for TB infection, as well as to other factors, such as delayed diagnosis, less effective treatment and longer contact periods with infectious patients, which together may increase the risk of transmission. Therefore, TB infection screening of health-care personnel is crucial for TB prevention and control in the workplace (10). The ECDC guidance report, Programmatic management of latent tuberculosis infection in the European Union (12), recommends targeting only health-care workers who work in settings with a high TB transmission risk or who have been identified in contact investigations.

5.4.8.5 Populations with indication for screening according to local epidemiology

There is evidence that systematic testing for and treating TB infection is beneficial for populations other than those already listed, but the extent of such benefits may vary significantly in different epidemiological settings: this is why WHO has issued conditional recommendations. Notably, screening is warranted if individuals belong to any of the recommended risk groups (such as close contacts and people living with HIV), although for these populations there are no screening indications per se.

Examples of such at-risk groups include prisoners (199) and people who use illicit drugs (200). For these populations, as well as for migrants from high- to low-TB-incidence countries, the advantages and disadvantages of screening (and treatment, if they have TB infection) depend on factors including the national legal framework and the political context (14).

5.4.9 Populations that should not be screened

WHO has issued recommendations against using diabetes, harmful alcohol use, tobacco smoking and underweight as indications for systematic TB infection testing and treatment. Persons with these known risk factors for progression to active disease should, of course, be screened if they have one of the indications for systematic screening discussed in section 5.4.8 (1,10).

A meta-analysis of observational studies (relative risk: 3.11; 95% CI: 2.27–4.26) and prospective cohorts (adjusted hazard ratio: 2.09; 95% CI: 1.10–3.95) have clearly demonstrated an increased risk of TB in patients with diabetes (80,201). Although the global number of diabetes-associated TB cases is large, the expected benefits of TPT for an individual with diabetes are marginal. Given the high and increasing global burden of diabetes, the number of persons belonging to this comorbidity group is huge: the costs of systematic TB infection screening would therefore be very large and no high-quality trials have shown that TPT benefits this specific group. Although the balance between benefits and potential harms is subject to debate, in countries facing a high prevalence of both conditions (in Mexico, about 25% of TB cases and 50% of MDR-TB cases have diabetes) this group needs special attention (15,202).

Other groups also need to be considered, for example persons receiving glucocorticoid therapy (203).
5.4.10 How to treat TB infection

Since 1957 TPT (also known as preventive chemotherapy or chemoprophylaxis) provided in the United States has consisted of isoniazid (204,205). A review published in 1970 of the available trials (206) demonstrated that isoniazid treatment ensures an overall protection of 60% against active TB. Guidelines for TPT have been developed over time. Initially, isoniazid monotherapy (at 300 mg a day) for 6–12 months was recommended, giving 54–90% protection (135,207–209). The efficacy of this regimen increases with a longer treatment duration. However, as the incremental benefit after nine months is small, the nine-month regimen is recommended in the United States (210), while many countries prefer the six-month regimen to enhance adherence.

The current availability of rifampicin and rifapentine, either alone or in combination with isoniazid, has enabled treatment regimens to be shortened while increasing completion rates and maintaining effectiveness and tolerability. A rifampicin-based regimen can be shortened to 3–4 months; it can be used to protect the contacts of isoniazid-resistant TB cases and as an alternative in the case of isoniazid hepatitis.

A meta-analysis performed in 2014 (211) and updated in 2017 (212) demonstrated that rifampicin gave similar protection to that offered by a six-month isoniazid regimen, but with a lower hepatotoxicity. A recent randomized clinical trial published in 2018 (213) comparing four months of rifampicin treatment with nine months of isoniazid treatment showed that both regimens were similarly protective, but that more patients completed the rifampicin regimen and the toxicity was also lower. Similarly, among children aged under 18 years, four months of rifampicin treatment had similar rates of safety and efficacy but a better rate of adherence compared with nine months of isoniazid treatment (214).

Three or four months of daily isoniazid plus rifampicin treatment is among the WHO-recommended regimens (1). Two meta-analyses revealed similar efficacy and toxicity for a six-month isoniazid regimen and a regimen of 3–4 months of isoniazid plus rifampicin (91,166). The same results have been confirmed in children (105,106,215,216).

The new WHO-recommended 3HP regimen (1) (now the most widely used in the United States) (210) of high-dose isoniazid and rifapentine (a maximum of 900 mg each) is administered once a week for 12 weeks under directly observed therapy (217). Original studies compared this regimen against the 6–9-month isoniazid reference regimen in individuals belonging to population groups at a high risk of active TB (close contacts, HIV-infected patients and patients with fibrotic changes detected by chest radiography). The results demonstrated a similar efficacy for both regimens but a higher rate of completion and fewer side-effects for the weekly regimen in all groups studied (217,218). Additional studies performed in children and pregnant women provided similar results (219,220).

However, duration of the protection conferred by the 3HP regimen is still unknown.

The new 2020 WHO guidelines also include the possibility of using a one-month daily regimen of rifapentine and isoniazid (1).

5.4.11 Exposure to MDR-TB patients

Some evidence is now available on the effectiveness of preventive treatment for the contacts of MDR-TB patients, including an unpublished systematic review used to develop the WHO guidelines (1), which identified only four studies with more than 20 participants, with only two of them reporting a comparison that was useful for decision-making (221,222). In the first study, 119 exposed individuals were enrolled and 104 contacts with TB infection initiated fluoroquinolone-based preventive treatment (with 93 (89%)
completing treatment): none of these developed active TB (223). In contrast, three of the 15 (20%) contacts who refused treatment developed MDR-TB (odds ratio: 0.02; 95% CI: 0.00–0.39). In the second study (224), confirmed or probable TB was observed in two out of 41 (5%) children receiving tailored preventive treatment and in 13 out of 64 (20%) children who did not (odds ratio: 0.20; 95% CI: 0.04–0.95).

Preventive therapy was provided using fluoroquinolones (such as levofloxacin and moxifloxacin) with or without other agents (like ethambutol and ethionamide). Neither study compared adverse events in patients and controls, although one of them reported no serious adverse events attributable to fluoroquinolone TPT (223,224). In fact, only 5.1% of participants discontinued treatment because of adverse events. Three cluster-randomized superiority clinical trials are ongoing and will inform future policies.

Interestingly, a recent Peruvian study suggests that TPT with isoniazid may provide protection against TB even for the contacts of isoniazid-resistant TB patients (Huang et al., unpublished observations) (225).

According to WHO recommendations, preventive treatment for MDR-TB contacts should be informed by the drug resistance profile of the source case and based on later-generation fluoroquinolones (such as levofloxacin for six months) (1). WHO-recommended TPT regimens are summarized in Table 4.

5.4.12 Which European countries are screening migrants for TB infection (and TB)?

According to the European study on screening among migrants described in previous sections, a legal obligation to screen for TB and/or TB infection is recognized in 21 of the 36 European countries evaluated (58.3%), with only 19 (52.7%) systematically screening for TB infection (and even fewer countries screening in a non-systematic manner) (104). The survey clearly demonstrated that screening approaches vary among countries, with the most commonly reported being chest radiography (27 countries, 75%), symptom-based questionnaires (21 countries, 58%) and bacteriological examinations (sputum testing by sputum smear microscopy, culture or polymerase chain reaction analysis (such as GeneXpert MTB/RIF assay); 18 countries, 50%). In 14 countries (38.8%), the TB incidence in the departure country was the trigger activating the TB/TB infection screening, although no threshold value was given.

5.4.13 Screening migrants for TB infection and TB

According to the 2016 European study, few countries have data on how migrants are screened, although the number of detected active cases is available from national TB registries, usually disaggregated by country of origin (104). More is known on active TB than on TB infection in this population because TB infection is normally not notifiable. In all, 22 countries (61.1%) have data on TB disease in migrants, although only eight (52.7%) are able to report treatment outcomes in this population. According to another recent study, the yield of screening for active TB varies across countries, from 66 cases per 100,000 migrants screened in the United Kingdom (both pre-entry and port-of-arrival screening) to 1174 cases per 100,000 migrants in Spain (community port-of-arrival screening). Screening coverage also varies among countries, but on average was above 74% (226).

The 2016 European survey found that 11 of the 36 countries (31%) have data on TPT in migrants, but only eight (22%) have information on the treatment completion rates (104). In 2015, one study reported that the yield of latent tuberculosis infection (LTBI) screening also varies across countries depending on the test used (28.2–42.5% for the TST and 17.4–29.0% for IGRAs (227)), while another reported the pooled LTBI prevalence to be about 45% for the TST and 25% for the IGRA (228). The screening coverage also varied among countries, but on average was above 47.7% (227).
The available European studies concluded that large heterogeneity still exists in screening policies and practices in the WHO European Region and that standardization of both the methods used and target groups would allow high-quality European-wide monitoring and evaluation (28,226,227). For this, a comprehensive set of indicators is necessary, including LTBI testing and treatment programme coverage, LTBI testing acceptance, IGRA test performance, LTBI treatment uptake, LTBI treatment completion and adverse events from LTBI treatment (28,89,226,227,229).

In the Netherlands between 2005 and 2010, 117,389 migrants were screened at entry for active TB, with the largest groups being from China (13%), Turkey (11%), India (8%), Morocco (6%) and Indonesia (5%). In total, 108 TB cases were detected through entry screening: 100 cases of pulmonary TB and eight of extrapulmonary TB (230). Confirmation of pulmonary TB in 84 patients and extrapulmonary TB in one patient was obtained by sputum smear culture. Six patients had MDR-TB. The prevalence of TB and pulmonary TB by entry screening was 92 cases per 100,000 migrants (95% CI: 75–109) and 85 cases per 100,000 migrants (95% CI: 68–102), respectively. The TB prevalence by screening was at least 50 cases per 100,000 migrants for most subgroups; exceptions were the 0–14-year age group and migrants from countries with a TB incidence of fewer than 50 cases per 100,000 population.

A systematic review comparing entry screening for active TB of regular migrants in several low-burden countries found the yield to vary between 101 and 139 cases per 100,000 persons screened. The prevalence was associated with the TB incidence in the country of origin of the migrants. In the United Kingdom, the former port-of-entry screening had a lower screening yield (29 cases per 100,000 migrants), while the current pre-entry screening programme had a prevalence of 92 bacteriologically confirmed TB cases per 100,000 individuals (128,129,231,232).

Studies have shown that TB incidence in migrant populations remains high after several years of residence in the host country (233,234), and that screening for TB infection and providing TPT to those infected is an effective and potentially cost-saving approach (150). In the National tuberculosis control plan 2016–2020 of the Netherlands (235), which aims to reduce the TB burden in the Netherlands by 25% by 2020, the main strategy is to supplement or replace radiographic screening with TB infection screening. TB infection screening will be introduced stepwise, prioritizing children and migrants from countries with a TB incidence of at least 200 cases per 100,000 population.

A recent systematic review identified 20 studies reporting on the coverage and yield of TB infection screening for migrants conducted in six EU/European Free Trade Association countries (Italy, the Netherlands, Norway, Spain, Switzerland and the United Kingdom) (114). The yield of screening was based on both the TST and IGRA in Italy, the Netherlands and Norway. Switzerland and the United Kingdom reported on IGRA testing only, while Spain reported on TST only. The coverage of TB infection screening was reported for three countries from six studies: the range was between 15.1% and 99.4%. The interquartile range of the yield of TB infection screening was 27.8–44.9% for the TST and 17.4–29.0% for the IGRA.

**5.4.14 Pre-entry screening and post-migration follow-up and their role in managing TB infection**

As discussed in sections 5.4.12 and 5.4.13, pre-entry screening aims to identify TB disease in individuals applying for a visa or entry permit to a host country (89,107,119,226). It is usually performed in high-TB-burden countries, but can occasionally be required for the citizens of low-incidence countries. One example might be an EU citizen entering (or in transit through) Canada under the visa exemption programme. If the
EU citizen declares having any previous contact with a TB patient, he or she must undergo (and pay for) pre-entry screening. A citizen from a high-TB-incidence country who applies for a visa to the United Kingdom or the United States would also have to undergo (and pay for) pre-entry screening.

The five members of the Immigration and Refugee Health Working Group (Australia, Canada, New Zealand, the United Kingdom and the United States) have similar TB pre-migration screening programmes established by current legislation (89). Although these countries screen for active TB, some of them also screen for TB infection: Australia and the United States screen for TB infection in children (Australia: 2–10 years of age; United States: 2–14 years of age) using the TST or IGRA if pre-entry screening is done in a country considered to have a high TB rate. TPT is then offered in the host country, but the TB infection status has no bearing on the visa application. Over 2 million individuals undergo pre-entry screening every year, although there is limited evidence for any impact other than detecting active cases before arrival and hence reducing the number of early incident cases in the host country (which means a financial saving for the host country, since the visa applicant pays for screening). However, there is proven impact on transmission in the host country (89,115,236–239).

The detection of TB infection or of minor radiographic abnormalities may also contribute to stigma and exacerbate underlying anxiety, which can undermine the validity of the screening process (89). Stigma is an important element to consider when discussing TB control and elimination.

Some countries have post-migration follow-up programmes for migrants at an increased risk of developing TB, consisting of single (United States) or multiple (Australia) medical follow-up visits (89). One review indicates that screening for active TB can be effective and cost-effective (or not) depending on the setting, target group and screening approach. The effectiveness and cost–effectiveness of TB infection screening as predicted by mathematical modelling are also highly dependent on the setting, with the best potential for good results if screening is restricted to high-risk groups and/or migrants from high-TB-burden countries. However, the effectiveness of modelling is highly dependent on the design and parameterization assumptions of the model (116).

5.4.15 Implications for TB elimination

Mathematical modelling suggests that TB elimination is plausible, although the time frame is very difficult to predict. Dye et al. described the potential major impact of preventive interventions by 2050 (240). In particular, the study findings suggest that very low incidence rates approaching the TB elimination threshold (one TB case per million population) can be reached only by combining rapid diagnosis and effective treatment for both active TB cases and TB infection, with TB infection requiring new, as-yet unavailable tools in order to be scalable (240).

Importantly, the positive impact of social protection and poverty reduction on TB incidence has been recently underlined (241,242). The contributions of a new vaccine, new shorter and better-tolerated regimens to manage TB and TB infection, and new point-of-care diagnostic tests have been carefully evaluated (53,54): TB infection diagnosis and treatment represent the most effective intervention by far for TB elimination.

The core issue is to what extent, based on national policies, TB infection diagnosis and treatment is performed to ensure the paradigm shift from an individual benefit to a public health impact. The results of a recent study are useful to understand this concept (61). TB infection management was surveyed in countries with a low or a high burden of TB, defined according to WHO criteria, and national policies were retrieved
and analysed. Original publications were obtained from 68 out of 113 low-burden countries and 30 out of 35 countries with the highest burdens of TB or HIV-associated TB. TB infection screening and treatment for people living with HIV was recommended in the guidelines of 29 (97%) high-burden and 54 (80%) low-burden countries. Screening of children aged under 5 years with a household TB contact was the policy of 25 (83%) high-burden and 28 (41%) low-burden countries. Most high-burden countries recommended symptom screening alone before treatment, whereas all low-burden countries recommended testing before treatment. The policies of some low-burden countries did not comply with WHO recommendations: nine (13%) recommended TB preventive treatment for people travelling to high-burden countries and 10 (15%) recommended the treatment for patients undergoing abdominal surgery. The study concluded that solid evidence was lacking on certain aspects of TB infection management, with huge intercountry variation.

As discussed in section 5.4, more is done to tackle TB infection in low-TB-incidence countries because more resources are generally available for managing fewer TB cases. However, much more information is generally available for TB than for TB infection. For example, few low-incidence countries have implemented an infectious disease register, although all have a TB register. Similarly, although all countries monitor TB treatment outcomes, very few can report national TPT completion rates. Furthermore, rifapentine is not yet registered in several countries.

Among the important challenges for countries approaching the TB pre-elimination phase are the development of new generation diagnostics (tests with a greater capacity to predict future disease) and safer, shorter treatment regimens (the 12-week regimen of weekly rifapentine/isoniazid or the ultra-short one-month regimen of daily rifapentine/isoniazid) (1).

5.4.16 Application to intermediate-TB-incidence countries

In theory the principles underlying this priority action are fully applicable to intermediate-incidence countries because they are consistent with WHO recommendations (1,10), although some of the implications need to be discussed at national level and a decision made by each country based on its own data and policies. All countries should screen and treat those population groups recommended by WHO. Screening and treatment of other groups need to be discussed at national level, with decisions taken at national level based on cost–effectiveness and feasibility criteria.

As discussed in section 5.3, the strategic approach to TB infection screening and management for migrants and refugees should be tailored to the needs of both low- and intermediate-incidence countries because of the potentially major burden on health services.

National algorithms need to be designed to balance the benefits and harms (and cost) of diagnosing and treating TB infection in additional at-risk groups.

However, intermediate-incidence countries need to ensure that their national guidelines are updated and/or consistent with WHO guidance (1) and applied adequately. This might require training and further government commitment to investing resources in the national TB programme.

Importantly, the registration of rifapentine (which is problematic in several countries in the WHO European Region) is a prerequisite to adopting the rifapentine-based TPT regimen.

Box 4 highlights policy implications of Action 4.

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5 Local studies might be needed to allow registration and there is not always a robust mechanism to pay for these.
**BOX 4. Policy implications (Action 4)**

- Appropriate TB infection management is a top priority to pursue TB elimination.
- The report summarizes current evidence and guidelines on which groups have the highest risk of TB infection and of progression from infection to disease.
- Recent WHO and ECDC reports provide comprehensive evidence-based guidance for European countries to implement the programmatic management of TB infection in Europe (1,12).
- Testing for TB infection can be done using the TST and/or IGRAs.
- According to the WHO consolidated guidelines on drug-resistant tuberculosis treatment, the primary targets are people living with HIV, children aged under 5 years who are household contacts of a pulmonary TB patient, and people with clinical conditions such as silicosis and diseases requiring anti-TNF-α treatment, dialysis and organ or haematological transplantation (243). In low-incidence countries (such as those in the EU), additional at-risk groups are recommended to undergo systematic TB infection testing and treatment: strong recommendation for HIV-negative children aged 5 years and over, and adolescents and adults who are household contacts of patients with bacteriologically confirmed pulmonary TB; and conditional recommendation for migrants from endemic areas, prisoners, health-care workers, homeless people and people who use illicit drugs.
- ECDC identified key components for implementing the programmatic management of TB infection in the EU (149). The target groups prioritized for TB infection screening and treatment are people living with HIV, immunocompromised persons (patients on anti-TNF-α treatment, preparing for organ or haematological transplantation, with end-stage renal diseases and/or preparing for dialysis); patients with silicosis; people with pulmonary fibrotic lesions; and contacts of infectious pulmonary TB cases. Additional at-risk groups may be considered depending on the TB epidemiology.
- The recommended regimens to treat TB infection include isoniazid for 6–9 months, rifampicin or isoniazid plus rifampicin for 3–4 months, and the recently recommended regimen of isoniazid and rifapentine for three months. Unfortunately, the last regimen is not available in most European countries.
- Experiences in the Netherlands and other European countries suggest that high-risk TB groups can be successfully targeted for TB infection screening and treatment if the infrastructure and organization of services are adequate.
- Cumulative evidence indicates that TPT for contacts of MDR-TB patients with fluoroquinolone-based regimens should be gradually introduced.

**5.5 Optimize prevention and care of MDR-TB (Action 5)**

MDR-TB is present in all European countries and particularly prevalent in former Soviet Union countries, where over 30% of new TB cases are caused by MDR-TB strains (15).

Treatment for M/XDR-TB is very long (for up to two years, versus six months for drug-susceptible TB) (244–247), clinically challenging (second-line anti-TB drugs are known to be more toxic than first-line drugs) and more expensive (the cost of treating one extensively drug-resistant TB (XDR-TB) patient might exceed €100 000 in Europe, while a regimen for drug-susceptible TB can cost less than €20) (248–250).
Incorrect treatment is the most important determinant of drug resistance, with factors ranging from the use of suboptimal-quality drugs to inadequately designed regimens (drug selection, dosage, duration) increasing the prevalence of drug resistance \(40,251–253\). Approaches to correctly control MDR-TB and prevent the further selection of resistant \(M.\ tuberculosis\) mutants include the correct management (rapid diagnosis and effective treatment) of existing drug-susceptible TB patients and M/XDR-TB patients (to prevent spread of resistant strains) \(254\). Therefore, the implementation of effective infection control practices in health-care facilities is of key importance in limiting transmission to health staff, patients and visitors, recognizing that the most dangerous TB cases are those that go undetected, including M/XDR-TB cases that are not recognized as such and are treated as drug-susceptible cases \(8,65,67,255\). Once detected, unequivocal de-isolation guidelines are necessary for M/XDR-TB cases (either in-hospital or in-house) \(255\).

Recent evidence suggests that the correct treatment is extremely effective in rapidly rendering the patient non-infectious \(8,65\). The current availability of reliable rapid diagnostic methods enables the drug-susceptibility/resistance pattern of the strain to be identified within a few hours, with the immediate design of an appropriate treatment \(8,52,53,67,105,256–258\). Unfortunately, the practice of treating new patients with the standard regimen (that is, treating blindly, as far as drug resistance is concerned) and considering drug DST only upon treatment failure is still common \(8,67,259\).

As ensuring treatment adherence is a core measure in preventing the emergence of drug resistance, adherence support measures need to be implemented using a people-centred approach \(105\). Countries that successfully reduce TB incidence to a low level usually observe that their TB (and MDR-TB) caseload becomes concentrated in patient groups at risk of poor treatment adherence and thus of acquired drug resistance \(2,5\). In several EU countries the prevalence of M/XDR-TB is higher in specific migrant subpopulations \(2,260–262\). Therefore, based on national epidemiological information, measures need to be implemented to ensure the adequate management of these cases. Good management for patients with drug-resistant TB should be based upon the expertise of clinicians specializing in paediatrics, HIV, psychiatry, substance abuse and surgery, among others. These services are ideally provided through an expert committee or consilium (a team of experts that recommend the best management of clinically complex and difficult-to-treat cases). National TB consilia need to be implemented and existing international resources utilized. For example, since October 2018 the Global TB Consilium of the Global Tuberculosis Network (which took over after the ERS/WHO TB Consilium stopped operating in July 2018) has provided free advice in several languages (English, Portuguese, Russian and Spanish) on the clinical management of difficult-to-treat TB cases within 48 hours and support for connecting clinicians in different countries to facilitate the transborder management of such cases. The service can be accessed via the World Association for Infectious Diseases and Immunological Disorders website \(263\) or by email (tbconsilium@gmail.com).

Treatment and support must be extended beyond cure to address any TB sequelae \(264,265\). Moreover, access to comprehensive palliative and end-of-life care is essential, particularly for people with XDR-TB that does not respond to any treatment \(266–268\).

As WHO recently changed the classification of drugs and the approach used to design an effective MDR-TB regimen (Table 5), all countries in the WHO European Region need to make efforts to apply the new guidelines \(105,243,246,248\). In particular, group A drugs (fluoroquinolones, bedaquiline and linezolid) should be prioritized in designing the regimen, complemented by group B and C drugs \(246\).

The shorter regimen can be considered for patients who meet the WHO indications (including proven susceptibility to fluoroquinolones and injectable agents), given the recent evidence that these will represent a minority of the existing MDR-TB patients in Europe \(104,242,245,269\).

TB infection management in the contacts of MDR-TB patients was discussed in section 5.4.11.

Although further research into safer, affordable and more effective medicines is urgently needed \(2,5\) existing pharmacovigilance mechanisms should be used (such as the WHO aDSM project) \(270,271\) and the rational use of drugs promoted \(272\).
In summary, national TB programmes in all European countries need to ensure that key interventions are in place for MDR-TB prevention and care, including: universal access to rapid molecular testing and high-quality DST; a team approach to managing difficult-to-treat cases (TB consiliums); and implementation of the 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (with full oral regimens and the use of new drugs with a people-centred approach) (243), aDSM and sound infection control practices.

5.5.1 Application to intermediate-TB-incidence countries

The principles of this priority action are fully applicable to intermediate-TB-incidence countries. Intermediate-incidence countries in Europe need to invest in infection control and workplace safety, as well as in high-quality (rapid) diagnostic testing for MDR-TB and adequate treatment. Rapid diagnostic methods are not yet universally accessible in all countries and a gap exists between the diagnosis and treatment of patients. Another priority for intermediate-incidence countries is access to second-line anti-TB drugs, as recommended in the 2018 WHO guidelines for drug-resistant TB (244,245). Particular focus is needed on group A drugs (fluoroquinolones, bedaquiline and linezolid), while second-line injectables (amikacin, according to the latest guidelines (244,245)) should be reserved for use in cases where no other options are available.

Registration of and access to WHO-recommended drugs and regimens are essential components of adequate treatment. A shift from a predominantly inpatient-based to an ambulatory model of care is recommended to minimize nosocomial transmission, achieve financial savings and promote the well-being of patients (8,67). To make this possible, health service funding schemes should no longer be based on bed occupancy because adequate remuneration of outpatient/ambulatory services is necessary (66,273).

5.6 Improve surveillance, monitoring and evaluation and case-based data management (Action 6)

The important role of surveillance in enabling the monitoring and evaluation of treatment outcomes and performance of TB programmes has been described by the directly observed therapy, short course (DOTS) strategy, and further emphasized in the End TB Strategy (3,15,20,59,60,62).

The current levels of technological development and accessibility indicate that surveillance systems based on computerized, real-time individual data are necessary in all European countries (60). Such systems enable the more precise and rapid monitoring and evaluation of programme performance at the regional and national levels, in addition to supporting improved clinical management of individual patients at the peripheral level. The need for comprehensive individual information is more stringent for MDR-TB cases because their management is more complicated (274). An adequate legal framework is necessary to implement and sustain a Europe-wide surveillance system (62), as discussed in section 5.1 on Action 1. The importance of adequately managing cross-border cases is described in section 5.3, while the role of national programme cooperation is discussed under Action 8 in section 5.8.

A recent ECDC report acknowledged that “monitoring and evaluation of the programmatic approach to TB infection management can pose a major challenge for a national TB control programme, but is important to tackle” (12,153,275). ECDC encourages “EU/EEA Member States to create or continue improving their LTBI [TB infection] surveillance systems, striving for data completeness and more accurate reporting of those eligible, tested and treated for LTBI [TB infection],” as well as for other actions relevant for TB elimination. These efforts will “contribute to quantify the country-specific cascade of care for LTBI [TB infection] and help identify areas for adaptation and improvement of programmatic management of LTBI [TB infection]” (275).
In addition, the ECDC report supports the following activities: establishment of a case-based registry of TB contacts identified during routine contact investigations; revision/development of data collection processes; definition of performance indicators; and implementation of regular programme monitoring, aligned with global and regional monitoring and evaluation frameworks (14,276).

As discussed in section 5.1, high-quality case notification and an analysis of treatment outcomes (ideally also for TB infection) will guide the public health response.

The experience from the Netherlands (section 5.4.1) demonstrates that it is possible to record whether a contact investigation was performed for each notified TB patient, how many contacts were eligible for screening, how many were screened and how many were identified as having TB or TB infection (138,230). In 2006–2010, 87% of contacts eligible for screening were screened for TB and 73% were screened for TB infection; of the latter, 7% tested positive for TB infection.

A positive feature of the TB infection register in the Netherlands is that it is integrated into the web-based TB surveillance system, which has an established reputation for completeness and reliability; however, TB infection notification is not mandatory (277). However, to enable the evaluation of programmatic TB infection management, the present system needs adjustments so as to properly distinguish the different clinical target groups, the reasons for not initiating TPT, and the occurrence and nature of adverse events. Furthermore, the surveillance system does not record TPT for vulnerable populations (child TB contacts and immunocompromised TB contacts) (138,230).

The End TB Strategy calls for increased efforts to evaluate the programmatic impact on the TB epidemic with the aim of monitoring the trajectory towards TB elimination in Europe.

### 5.6.1 Application to intermediate-TB-incidence countries

The principles of this priority action are fully applicable to intermediate-incidence countries. As discussed in sections 5.2–5.4, more information is needed on both TB and TB infection, particularly among vulnerable populations and at-risk groups, to guide public health actions.

### 5.7 Invest in research (Action 7)

Research at different levels is essential to close the evidence gaps discussed in sections 5.1–5.6. New vaccines, diagnostics and drugs/regimens are necessary to pursue TB elimination (2,5). However, operational research on how better to introduce and use new diagnostic and treatment weapons while improving specific aspects of the TB control and elimination programmes is equally relevant, as is fundamental epidemiological, health systems and social research. An important contribution in this direction is represented by the European Tuberculosis Research Initiative, launched by the WHO Regional Office for Europe in 2016 to advance TB research in the Region (278).

Therefore, it is important to implement country-specific, priority-oriented and funded national TB research plans.

### 5.7.1 Application to intermediate-TB-incidence countries

The principles of this priority action are fully applicable to intermediate-incidence countries.
5.8 Support global TB prevention, care and control (Action 8)

As summarized in WHO’s action framework for TB elimination in low-incidence countries and other reports (2,12), TB does not respect borders and international collaboration is necessary to achieve TB control and elimination. As discussed throughout this report, a major WHO achievement was the development and implementation of a framework allowing global data collection and publication of an annual TB global report, while creating a funding mechanism for TB control efforts in economically disadvantaged countries (the Global Fund). However, more still needs to be done to close the funding gap through improving collaboration among all stakeholders, including those in the private sector. Periodic reciprocal programmatic reviews (every five years, for instance) will contribute to accelerate the trajectory towards TB elimination. Investment in bilateral/multilateral TB cooperation projects is also important to maintain a pool of experienced human resources with comprehensive EU-wide training, as well as to exchange ideas and best practices between countries.

5.8.1 Application to intermediate-TB-incidence countries

The principles of this priority action are fully applicable to intermediate-incidence countries.

Box 5 highlights policy implications of Actions 5–8.

**BOX 5. Policy implications (Actions 5–8)**

- The available evidence calls for improvement in infection control practices in all countries, and particularly in eastern Europe and central Asia.

- The main recommended actions are adoption of the FAST approach (Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely and Treat effectively based on rapid drug-susceptibility testing); universal access to rapid molecular testing and high-quality DST; a team approach in managing difficult-to-treat cases (TB consilium); and implementation of the 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (with full oral regimens and use of new drugs) (243), aDSM and sound infection control practices.

- Existing good practices in Europe show the importance of establishing TB infection registers at national level to allow monitoring of the TPT completion rate and comparison of the TPT cascade across countries.

- New vaccines, diagnostics and drugs/regimens are necessary to pursue TB elimination, as well as fundamental epidemiological, health systems and social research.

- As TB does not respect borders, pan-European collaboration is necessary to strengthen TB control and pursue TB elimination in the WHO European Region, together with investment in bilateral/multilateral TB cooperation projects/programmes. This will also ensure the maintenance of a pool of experienced human resources with comprehensive training, as well as the exchange of ideas and best practices between countries.
Conclusions

This report, *Tuberculosis elimination in the WHO European Region*, which includes a review of the key actions and has a special focus on TB infection management, provides useful, comprehensive guidance on specific policy adaptations that are suitable for Member States in the WHO European Region. It will also enable implementation of the eight core actions described in the WHO report, *Towards tuberculosis elimination: an action framework for low-incidence countries*, as well as the recommendations and guidance provided in other relevant global and European reports (2,279). The report specifically focuses on the individual and public health management of TB infection (Action 4. Undertake screening for active TB and TB infection in TB contacts and selected high-risk groups, and provide appropriate treatment).

Other specific actions might need to be added as new evidence becomes available and/or based on country-specific needs in specific areas including human rights, prevention of stigma and engagement between nongovernmental organizations and affected communities.

The following main policy considerations for Member States in the WHO European Region are derived from the present report.

- TB eradication is not possible without new tools such as an effective vaccine because of the large TB infection reservoir from which future TB cases, including MDR-TB cases, will emerge, TB patients immigrating from outside the Region and the animal reservoir.

- TB elimination is epidemiologically plausible but at the current rate of treatment success may take several decades to reach, even in low-incidence countries.

- A comprehensive set of WHO and ECDC reports published in 2018–2020 (including (1,12,280)) contains principles and interventions to support the implementation of priority actions to pursue TB elimination, along with epidemiological and operational indicators to guide the national implementation of priority actions (27).

- Surveys by ERS/WHO/ECDC in 2013 (28) and E-DETECT in 2018 (29) provide a regional overview of country preparedness to implement the actions necessary to pursue TB elimination.

- Government commitment, funding and stewardship are essential for TB elimination – an adequate legal framework can ensure implementation of core interventions, including: a costed national TB elimination plan; involvement and regulation of the private sector; approval of adequate prevention, diagnosis and treatment guidelines; and establishment of quality surveillance, diagnostic and treatment capacity.
• Social, economic and demographic factors contribute to TB transmission. Vulnerable, marginalized and hard-to-reach population groups who need special attention include people living in poverty, homeless people, migrants, people living with HIV, people who use substances and alcohol harmfully, prisoners, ethnic minorities and other marginalized groups, young children and elderly people.

• Specific indicators targeting at-risk groups are also useful for monitoring and evaluation. In particular, the ECDC-proposed indicator of TB in children as an indirect marker of transmission deserves special attention and standardized reporting.

• To respond to rapid changes in migration in the Region, efficient monitoring through improved surveillance (including molecular epidemiology) and Region-wide collaboration are needed to improve TB prevention and care. Transborder collaboration is important to tackle the needs of both vulnerable host populations and migrants. Universal, free-of-charge access to TB services without stigma is needed across the Region.

• Strong coordination and standardization of procedures across Member States are needed to strengthen TB control and make further progress towards TB elimination.

• WHO and EDCD guidelines consider appropriate TB infection management a top priority for TB elimination (1,145), particularly for population groups at the highest risks of TB infection and of progression from infection to disease, including people living with HIV, children aged under 5 years who are household contacts of pulmonary TB patients, people with clinical conditions such as silicosis and diseases requiring anti-TNF-α treatment, and candidates for dialysis and organ or haematological transplantation. In low-incidence countries (such as those in the EU), additional at-risk groups should also undergo systematic TB infection testing and treatment, including HIV-negative children aged 5 years and over, and adolescents and adults who are household contacts of patients with bacteriologically confirmed pulmonary TB (strong recommendation); and migrants from endemic areas, prisoners, health-care workers, homeless people and people who use drugs (conditional recommendation). Additional at-risk groups may be considered depending on the TB epidemiology.

• EDCD/WHO-recommended regimens to treat TB infection include isoniazid for 6–9 months, rifampicin or isoniazid-rifampicin for 3–4 months, and the recently recommended regimen of isoniazid and rifapentine for three months. Unfortunately, the last regimen is unavailable in most European countries. Evidence is accumulating to support the gradual introduction of TPT with fluoroquinolone-based regimens for the contacts of MDR-TB patients.

• Experiences in different European countries show that successful TB infection screening and treatment of high-risk TB groups require adequate infrastructure and organization of services.

• Existing good practices in Europe show that establishing national TB infection registers for monitoring TB infection testing, yield and completion rates and for comparing the TPT cascade across countries is essential to pursue TB elimination.

• Actions to prevent TB infection by reducing TB transmission include: adoption of the FAST approach; universal access to rapid molecular testing and high-quality DST, along with chest radiography screening and surveillance of symptoms other than cough (such as loss of weight and fever, especially in children); a team approach to managing difficult-to-treat cases (TB consilia); implementation of the 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (with full oral regimens and use of new drugs) (243) and the 2017 WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care.
(244); aDSM; and effective infection control practices and workplace safety practices (particularly in eastern Europe and central Asia).

- A comprehensive research effort to produce new vaccines, diagnostics and drugs/regimens, along with basic epidemiological, health systems and social research, is necessary to pursue TB elimination.

- Boosted pan-European collaboration, together with investment in bilateral/multilateral TB cooperation projects, is important to strengthen TB prevention and care and support TB elimination efforts, maintain a pool of experienced health staff with comprehensive EU-wide training and support the exchange of ideas and good practices among countries in the WHO European Region.

- TB national strategic plans should include activities for TB elimination and TB infection management and coordinate with national policies and roadmaps for health sector reform.

- A comprehensive approach based on the United Nations Sustainable Development Goals (38) is essential for ending HIV, TB and viral hepatitis through intersectoral collaboration.
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