GLOBAL TUBERCULOSIS REPORT 2018
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### Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>aDSM</td>
<td>active TB drug-safety monitoring and management</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>AMR</td>
<td>antimicrobial resistance</td>
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<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
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<tr>
<td>BCG</td>
<td>bacille Calmette-Guérin</td>
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<tr>
<td>BPaMZ</td>
<td>bedaquiline, pretomanid, moxifloxacin and pyrazinamide</td>
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<tr>
<td>BRICS</td>
<td>Brazil, Russian Federation, India, China and South Africa</td>
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<tr>
<td>CAD</td>
<td>computer-aided detection</td>
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<tr>
<td>CFR</td>
<td>case fatality ratio</td>
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<tr>
<td>CHOICE</td>
<td>CHOsing Interventions that are Cost-Effective (WHO)</td>
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<tr>
<td>CHW</td>
<td>community health worker</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CRS</td>
<td>creditor reporting system</td>
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<tr>
<td>CV</td>
<td>community volunteer</td>
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<tr>
<td>CXR</td>
<td>chest X-ray</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life-year</td>
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<td>DST</td>
<td>drug susceptibility testing</td>
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<td>EBA</td>
<td>early bactericidal activity</td>
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<td>EDCTP</td>
<td>European and Developing Countries Clinical Trial Partnership</td>
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<tr>
<td>EECA</td>
<td>Eastern Europe and Central Asia</td>
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<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
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<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
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<tr>
<td>GDP</td>
<td>gross domestic product</td>
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<td>GHCC</td>
<td>Global Health Cost Consortium</td>
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<tr>
<td>Global Fund</td>
<td>The Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>GPW</td>
<td>General Programme of Work (WHO)</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<tr>
<td>HBC</td>
<td>high-burden country</td>
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<tr>
<td>HDC</td>
<td>Health Data Collaborative</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HLM</td>
<td>high-level meeting</td>
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<tr>
<td>ICD-10</td>
<td>International classification of diseases (10th edition)</td>
</tr>
<tr>
<td>IER</td>
<td>Department of Information, Evidence and Research (WHO)</td>
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<tr>
<td>IGRA</td>
<td>interferon gamma release assay</td>
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<tr>
<td>IHME</td>
<td>Institute of Health Metrics and Evaluation</td>
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<td>ILO</td>
<td>International Labour Organization</td>
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<tr>
<td>LAM</td>
<td>lipoarabinomannan</td>
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<tr>
<td>LEAP</td>
<td>Livelihood Empowerment Against Poverty</td>
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<td>LF-LAM</td>
<td>lateral flow lipoarabinomannan assay</td>
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<td>LPA</td>
<td>line probe assay</td>
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<tr>
<td>LTBI</td>
<td>latent TB infection</td>
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<td>MAMS-TB</td>
<td>multi-arm, multi-stage TB</td>
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<tr>
<td>MBLA</td>
<td>molecular bacterial load assay</td>
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<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
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<tr>
<td>MDR</td>
<td>multidrug-resistant</td>
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<tr>
<td>MDR/RR-TB</td>
<td>multidrug-resistant TB or rifampicin-resistant TB</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>multidrug-resistant TB</td>
</tr>
<tr>
<td>M:F</td>
<td>male to female (ratio)</td>
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<tr>
<td>MIC</td>
<td>minimal inhibitory concentration</td>
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<tr>
<td>mRNA</td>
<td>messenger RNA</td>
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<tr>
<td>NACO</td>
<td>National AIDS Control Organization</td>
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<tr>
<td>NFC</td>
<td>near-field communication</td>
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<tr>
<td>NGO</td>
<td>nongovernmental organization</td>
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<td>NHI</td>
<td>national health insurance</td>
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<td>NHIF</td>
<td>National Health Insurance Fund</td>
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<td>NHI</td>
<td>National Institutes of Health</td>
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<tr>
<td>NTLD</td>
<td>National Tuberculosis, Leprosy and Lung Disease Programme</td>
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<tr>
<td>OEC</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PanACEA</td>
<td>Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PEPFAR</td>
<td>President’s Emergency Plan for AIDS Relief</td>
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<td>PLHIV</td>
<td>people living with HIV</td>
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<tr>
<td>PMDT</td>
<td>programmatic management of drug-resistant TB</td>
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<tr>
<td>P:N</td>
<td>prevalence to notification (ratio)</td>
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<tr>
<td>PPM</td>
<td>public–public and public–private mix</td>
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<td>ReSeqTB</td>
<td>Relational Sequencing TB Knowledgebase</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<tr>
<td>RNTCP</td>
<td>Revised National TB Control Programme</td>
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<td>RR</td>
<td>rifampicin-resistant</td>
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<tr>
<td>R-R-TB</td>
<td>rifampicin-resistant TB</td>
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<tr>
<td>RT-qPCR</td>
<td>reverse transcriptase quantitative PCR</td>
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<tr>
<td>SDG</td>
<td>Sustainable Development Goal</td>
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<tr>
<td>SHA</td>
<td>System of Health Accounts</td>
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<td>SRL</td>
<td>supranational reference laboratory</td>
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<td>SSI</td>
<td>Statens Serum Institut</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<td>TB Alliance</td>
<td>Global Alliance for TB Drug Development</td>
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<td>TBTC</td>
<td>TB Trial Consortium</td>
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<td>UN</td>
<td>United Nations</td>
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<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<td>US</td>
<td>United States</td>
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<td>USA</td>
<td>United States of America</td>
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<tr>
<td>USAID</td>
<td>US Agency for International Development</td>
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<tr>
<td>VR</td>
<td>vital registration</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WRD</td>
<td>WHO-recommended rapid diagnostic</td>
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<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant TB</td>
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**WHO European Region**


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**WHO Western Pacific Region**

The United Nations flag outside the Secretariat building of the United Nations, New York City, United States of America

Mike Segar / Reuters
Executive Summary

Context

On 26 September 2018, the United Nations (UN) will hold its first high-level meeting on tuberculosis (TB), at its headquarters in New York. The title of the meeting – United to End TB: An Urgent Global Response to a Global Epidemic – highlights the need for immediate action to accelerate progress towards the goal of ending the TB epidemic by 2030.

All Member States of WHO and the UN have committed to this goal, initially through their unanimous endorsement of WHO's End TB Strategy at the World Health Assembly in May 2014 and then their adoption of the UN Sustainable Development Goals (SDGs) in September 2015. Specific targets for 2030 set in the End TB Strategy are a 90% reduction in the absolute number of TB deaths and an 80% reduction in TB incidence (new cases per 100 000 population per year), compared with levels in 2015.

The UN high-level meeting follows the first WHO global ministerial conference on ending TB in the SDG era, which was held in November 2017 in the Russian Federation. The conference brought together over 1000 participants, including ministers of health and other leaders from 120 countries, and over 800 partners, including civil society. That conference resulted in the Moscow Declaration to End TB. At the World Health Assembly in May 2018, all WHO Member States committed to accelerate their actions to end TB, building on the Moscow Declaration.

In the months leading up to the UN high-level meeting, major country blocs have issued communiqués on the need for action on TB, including drug-resistant TB in the wider context of antimicrobial resistance (AMR). Examples include the G20, the G7, the BRICS group (Brazil, the Russian Federation, India, China and South Africa) and the Asia-Pacific Economic Cooperation (APEC). New commitments were made by ministers from countries in the WHO South-East Asia Region at the Delhi End TB Summit in March 2018 and by African leaders at a meeting of the African Union in July 2018.

This report

WHO has published a global TB report every year since 1997. This 2018 edition is published in the lead up to the UN high-level meeting on TB. It provides a comprehensive and up-to-date assessment of the TB epidemic, and of progress in the response to the epidemic, at global, regional and country levels. The report is based primarily on data reported annually to WHO by countries, and databases maintained by other UN agencies and the World Bank.

Latest status of the TB epidemic

Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS). Millions of people continue to fall sick with TB each year.

In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people and there were an additional 300 000 deaths from TB (range, 266 000–335 000) among HIV-positive people.

Globally, the best estimate is that 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017: 5.8 million men, 3.2 million women and 1.0 million children. There were cases in all countries and age groups, but overall 90% were adults (aged ≥15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These and 22 other countries in WHO’s list of 30 high TB burden countries accounted for 87% of the world’s cases. Only 6% of global cases were in the WHO European Region (3%) and WHO Region of the Americas (3%).

The severity of national epidemics varies widely among countries. In 2017, there were fewer than 10 new cases per 100 000 population in most high-income countries, 150–400 in most of the 30 high TB burden countries, and above 500 in a few countries including Mozambique, the Philippines and South Africa.

Drug-resistant TB continues to be a public health crisis. The best estimate is that, worldwide in 2017, 558 000 people (range, 483 000–639 000) developed TB that was resistant to rifampicin (RR-TB), the most effective first-line drug, and of these, 82% had multidrug-resistant TB (MDR-TB). Three countries accounted for almost half of the world’s cases of MDR/RR-TB: India (24%), China (13%) and the Russian Federation (10%).

Globally, 3.5% of new TB cases and 18% of previously
treated cases had MDR/RR-TB. The highest proportions (>50% in previously treated cases) are in countries of the former Soviet Union. Among cases of MDR-TB in 2017, 8.5% (95% confidence interval, 6.2–11%) were estimated to have extensively drug-resistant TB (XDR-TB). About 1.7 billion people, 23% of the world’s population, are estimated to have a latent TB infection, and are thus at risk of developing active TB disease during their lifetime.

Progress in reducing TB cases and deaths

The disease burden caused by TB is falling globally, in all WHO regions, and in most countries, but not fast enough to reach the first (2020) milestones of the End TB Strategy. By 2020, the TB incidence rate (new cases per 100,000 population per year) needs to be falling at 4–5% per year, and the proportion of people with TB who die from the disease (the case fatality ratio, CFR) needs to fall to 10%.

In 2017, the proportion of people with TB who died from the disease was 16%, down from 23% in 2000. Worldwide, the TB incidence rate is falling at about 2% per year. The fastest regional declines from 2013 to 2017 were in the WHO European Region (5% per year) and the WHO African Region (4% per year). In the same 5 years, particularly impressive reductions (4–8% per year) occurred in southern Africa (e.g. Eswatini, Lesotho, Namibia, South Africa, Zambia and Zimbabwe), following a peak in the HIV epidemic and the expansion of TB and HIV prevention and care; and in the Russian Federation (5% per year), following intensified efforts to reduce the burden of TB and scrutiny of progress from the highest political levels.

Globally, the absolute number of TB deaths among HIV-negative people has fallen by a best estimate of 29% since 2000, from 1.8 million in 2000 to 1.3 million in 2017, and by 5% since 2015 (the baseline year of the End TB Strategy). The number of TB deaths among HIV-positive people has fallen by 44% since 2000, from 534,000 in 2000 to 300,000 in 2017, and by 20% since 2015.

The TB mortality rate (i.e. TB deaths among HIV-negative people per 100,000 population per year) is falling at about 3% per year, and the overall reduction in the period 2000–2017 was 42%. Of the WHO regions, the fastest declines in the 5 years 2013–2017 were in the WHO European Region (11% per year) and the WHO South-East Asia Region (4% per year). High TB burden countries with rates of decline exceeding 6% per year in the 5 years 2013–2017 include the Russian Federation (13% per year), Ethiopia (12% per year), Sierra Leone (10% per year), Kenya (8% per year) and Viet Nam (8% per year).

TB diagnosis and treatment

Diagnosis and successful treatment of people with TB averts millions of deaths each year (an estimated 54 million over the period 2000–2017), but there are still large and persistent gaps in detection and treatment.

Worldwide in 2017, 6.4 million new cases of TB were officially notified to national authorities and then reported to WHO. This number has been increasing since 2013, following 4 years (2009–2012) in which 5.7–5.8 million new cases were reported annually, mainly due to increased reporting of detected cases by the private sector in India and, in 2017, an upturn in notifications in Indonesia.

The 6.4 million cases reported represented 64% of the estimated 10.0 million new cases that occurred in 2017. Ten countries accounted for 80% of the 3.6 million global gap, the top three being India (26%), Indonesia (11%) and Nigeria (9%). Gaps between the estimated number of new cases and the number actually reported are due to a mixture of underreporting of detected cases, and underdiagnosis (either because people do not access health care, or because they are not diagnosed when they do). Underestimation or overestimation of the total number of new cases is also possible. An informative example is Indonesia; in 2017, a national study found that although about 80% of new cases were detected, 41% of these cases were not reported. Actions to correct underreporting are being put in place.

There were 464,633 reported cases of TB among people living with HIV in 2017 (51% of the estimated 920,000 new cases in the same year), of whom 84% were on antiretroviral therapy. Most of the gaps in detection and treatment were in the WHO African Region, where the burden of HIV-associated TB is highest.

To support countries to close gaps in TB detection and treatment, in 2018 WHO, in collaboration with the Stop TB Partnership and the Global Fund to Fight AIDS, Tuberculosis and Malaria, launched an initiative called Find. Treat. All. The initiative includes a target of detecting and treating 40 million people with TB in the period 2018–2022.

The latest treatment outcome data for new cases show a global treatment success rate of 82% in 2016. This is a reduction from 86% in 2013 and 83% in 2015; in countries where notifications have increased, reporting of treatment outcomes has not kept pace.

Drug-resistant TB: diagnosis and treatment

Urgent action is required to improve the coverage and quality of diagnosis, treatment and care for people with drug-resistant TB.

Globally, 160,684 cases of MDR/RR-TB were detected and notified in 2017 (a small increase from 153,119
in 2016). Of these, a total of 139 114 people (87%) were enrolled on treatment with a second-line regimen, up from 129 689 in 2016 but still only 25% of the estimated 558 000 people who developed MDR/RR-TB in 2017. China and India alone accounted for 40% of the global gap; these and eight other countries accounted for 75%.

Treatment success remains low, at 55% globally. Examples of high burden countries in which better treatment success rates are being achieved include Bangladesh, Ethiopia, Kazakhstan, Myanmar and Viet Nam (all of which have rates above 70%).

Closing gaps in detection and treatment requires much higher coverage of drug susceptibility testing among people diagnosed with TB, reducing underdiagnosis of TB, models of care that make it easier to access and continue treatment, new diagnostics, and new medicines and treatment regimens with higher efficacy and better safety.

In July 2018, the latest evidence on treatment of drug-resistant TB was reviewed by an independent panel of experts convened by WHO. A rapid communication on key changes to recommendations for the treatment of drug-resistant TB has been issued by WHO, to be followed by the release of updated and consolidated WHO policy guidelines later in the year.

**TB prevention services**

The main health-care interventions to prevent new infections of *Mycobacterium tuberculosis* and their progression to TB disease are treatment of latent TB infection and vaccination of children with the bacille Calmette-Guérin (BCG) vaccine. TB preventive treatment for a latent TB infection is expanding, but most of those for whom it is strongly recommended are not yet accessing care, whereas coverage of BCG vaccination is high.

WHO has strongly recommended treatment for latent TB infection in two priority groups: people living with HIV, and children aged under 5 years who are household contacts of someone who has bacteriologically confirmed pulmonary TB.

The number of people living with HIV reported to have been started on preventive treatment was 958 559 in 2017. Of the 15 high TB/HIV burden countries that reported data, coverage ranged from 1% in Eswatini to 53% in South Africa. The number for children aged under 5 years reached 292 182 in 2017 – a threefold increase from 2015 but still only around 23% of the 1.3 million estimated to be eligible.

In countries with a high incidence of TB, WHO guidance issued in 2018 includes a new recommendation to consider testing and treatment for people aged 5 years or more who are household contacts of bacteriologically confirmed pulmonary TB cases. This substantially increases the potential number of people eligible for treatment.

WHO estimates that at least 30 million people will be eligible for TB preventive treatment between 2018 and 2022.

BCG vaccination should be provided as part of national childhood immunization programmes according to a country’s TB epidemiology. In 2017, 158 countries reported providing BCG vaccination, of which 120 reported coverage of at least 90%.

**Financing for TB prevention, diagnosis and treatment**

Funding for the provision of TB prevention, diagnostic and treatment services has more than doubled since 2006 but continues to fall short of what is needed.

In 119 low- and middle-income countries that reported data (and accounted for 97% of reported TB cases globally), funding reached US$ 6.9 billion in 2018. The amount available each year has been in the range US$ 6–7 billion since 2014, after increasing from US$ 3.3 billion in 2006. The Stop TB Partnership’s Global Plan to End TB 2016–2020 estimated that US$ 10.4 billion is required in these countries in 2018, leaving a gap of US$ 3.5 billion. Without an increase in funding, the annual gap will widen to US$ 5.4 billion in 2020 and to at least US$ 6.1 billion in 2022.

As in previous years, most of the funding (86%) available in 2018 is from domestic sources. However, this global aggregate figure is strongly influenced by BRICS, in which 96% (range 91–100%) of funding is from domestic sources. In India, domestic funding more than tripled between 2016 and 2018.

International donor funding (US$ 0.9 billion in 2018, a slight decrease from 2017) accounts for 39% of funding in the 25 high TB burden countries outside BRICS and for 57% of funding in low-income countries.

**Universal health coverage, social protection and social determinants**

The End TB Strategy milestones for 2020 and 2025 can only be achieved if TB diagnosis, treatment and prevention services are provided within the context of progress towards universal health coverage (UHC), and if there is multisectoral action to address the social and economic factors that drive TB epidemics.

TB incidence needs to be falling at 10% per year by 2025, and the proportion of people with TB who die from the disease needs to fall to 6.5% by 2025. Such levels have only been achieved in the context of UHC, combined with social and economic development that reduces known risk factors for TB infection and disease.

UHC means that everyone – irrespective of their living standards – receives the health services they need, and that using health services does not cause financial hardship. SDG Target 3.8 is to achieve UHC by 2030.
A 2017 WHO/World Bank report on UHC found that at least half of the world’s population lacks access to essential health services and almost 10% experience catastrophic expenditures on health. All of the 30 high TB burden countries need to increase service coverage and reduce levels of catastrophic expenditures to reach UHC, consistent with findings from surveys of costs faced by TB patients and their households.

WHO projections published in 2017 suggest that most middle-income countries could mobilize the funding needed to achieve UHC by 2030 from domestic resources, while this is unlikely in low-income countries.

This report features a TB-SDG monitoring framework that focuses attention on 14 indicators (from seven SDGs) that are associated with TB incidence. Monitoring of these indicators can be used to identify key influences on the TB epidemic at national level and inform the multisectoral actions required to end it.

Many new cases of TB are attributable to undernourishment, HIV infection, smoking, diabetes and alcohol use (five of the indicators featured in the TB-SDG framework). A recent modelling study shows that eliminating extreme poverty and providing social protection (both targets under SDG 1, and two other indicators in the TB-SDG framework) could substantially reduce TB incidence.

TB research and development

The SDG and End TB Strategy targets set for 2030 cannot be met without intensified research and development. Technological breakthroughs are needed by 2025, so that the annual decline in the global TB incidence rate can be accelerated to an average of 17% per year. Priorities include a vaccine to lower the risk of infection, a vaccine or new drug treatment to cut the risk of TB disease in the 1.7 billion people already latently infected, rapid diagnostics for use at the point of care and simpler, shorter drug regimens for treating TB disease.

The development pipelines are progressing, but slowly. Few diagnostic technologies emerged in 2017. There are 20 drugs, several treatment regimens and 12 vaccine candidates in clinical trials. Annual reports by Treatment Action Group published since 2006 show that funding for TB research and development has increased in recent years, peaking at US$ 724 million in 2016. However, this is only 36% of the estimated requirement of US$ 2 billion per year.

Actions needed to accelerate progress

Accelerating progress towards ending TB requires closing gaps in TB diagnosis, treatment and prevention within the context of progress towards UHC, multisectoral efforts to address the social and economic determinants and consequences of TB, intensified TB research and development, and strengthened accountability using a framework to track and review progress towards commitments and actions needed to end TB at global, regional and national levels. These are only possible with increased and sustained funding, including from domestic sources (especially in middle-income countries), international donors and public–private partnerships.

For countries where the burden of TB is already low, the focus should be on actions needed to eliminate TB, paying particular attention to vulnerable groups with the highest risk of infection and disease.

Conclusion

TB is an old disease that was once a death sentence. Effective drug treatments first became available in the 1940s, and in combination with social and economic development they allowed countries in western Europe, North America and some other parts of the world to reduce their burden of TB disease to very low levels.13 For most countries, however, the “end” of TB as an epidemic and major public health problem remains an aspiration rather than a reality. The UN high-level meeting on TB on 26 September 2018, with attendance of heads of state and other eminent people, provides a platform to step up the commitments and actions needed to end the global TB epidemic, by the SDG deadline of 2030.

1 The first milestones, for 2020, are a 35% reduction in TB deaths and a 20% reduction in TB incidence, compared with 2015. The SDG target of ending the TB epidemic is part of SDG Target 3.3, under the SDG health goal (SDG 3).
2 Here and throughout the report, “range” refers to the 95% uncertainty interval.
3 When an HIV-positive person dies from TB disease, the underlying cause is coded as HIV in the International classification of diseases system.
4 The other 22 countries are Angola, Brazil, Cambodia, Central African Republic, Congo, the Democratic People’s Republic of Korea, the Democratic Republic of the Congo, Ethiopia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Papua New Guinea, the Russian Federation, Sierra Leone, Thailand, the United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.
5 Defined as resistance to rifampicin and isoniazid.
6 Defined as MDR-TB plus resistance to at least one drug in the following two classes of medicines used in treatment of MDR-TB: fluoroquinolones and second-line injectable agents.
7 The absolute number has been around 10 million per year since 2000, and has fallen slowly since 2005.
8 The other seven countries are shown in Fig. 4.17 in the main report. http://www.who.int/tb/joint-initiative/en/
9 The other eight countries are shown in Fig. 4.21 in the main report.
10 The countries listed are those treating at least 500 MDR/RR-TB patients annually.
11 This figure is based on a recent extension of Global Plan projections, which indicate that at least US$ 13 billion will be required annually by 2022.
12 Around 10 or fewer new TB cases per 100 000 population per year and less than one TB death per 100 000 population per year.
UNITED TO END TUBERCULOSIS:
AN URGENT GLOBAL RESPONSE TO A GLOBAL EPIDEMIC
BOX 1.1

Basic facts about TB

TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB), but can also affect other sites (extrapulmonary TB). The disease is spread when people who are sick with pulmonary TB expel bacteria into the air, for example by coughing.

A relatively small proportion (5–10%) of the estimated 1.7 billion people infected with M. tuberculosis will develop TB disease during their lifetime. However, the probability of developing TB disease is much higher among people infected with HIV; it is also higher among people affected by risk factors such as undernutrition, diabetes, smoking and alcohol consumption.

Overall, about 90% of cases occur among adults, with more cases among men than women. The male:female ratio among adults is approximately 2:1.

Diagnostic tests for TB disease include:

- **Rapid molecular tests** – The only rapid test for diagnosis of TB currently recommended by WHO is the Xpert® MTB/RIF assay (Cepheid, USA). It can provide results within 2 hours, and was initially recommended (in 2010) for diagnosis of pulmonary TB in adults. Since 2013, it has also been recommended for use in children and to diagnose specific forms of extrapulmonary TB. The test has much higher accuracy than sputum smear microscopy.

- **Sputum smear microscopy** – Developed more than 100 years ago, this technique requires the examination of sputum samples using a microscope to determine the presence of bacteria.

- **Culture-based methods** – These form the current reference standard; they require more developed laboratory capacity and can take up to 12 weeks to provide results.

Globally, use of rapid molecular tests is increasing, and many countries are phasing out the use of smear microscopy for diagnostic purposes (although microscopy and culture remain necessary for treatment monitoring).

There are also tests for TB that is resistant to first-line and second-line anti-TB drugs. They include Xpert MTB/RIF, which simultaneously tests for TB and resistance to rifampicin (the most effective first-line anti-TB drug); rapid line probe assays (LPAs) that test for resistance to rifampicin and isoniazid (referred to as first-line LPAs); a rapid LPA that tests for resistance to fluoroquinolones and injectable anti-TB drugs (referred to as a second-line LPA); and sequencing technologies.

First-line LPAs were first recommended by WHO in 2008; the second-line LPA was first recommended in May 2016. Culture-based methods currently remain the reference standard for drug susceptibility testing.

Without treatment, the mortality rate from TB is high. Studies of the natural history of TB disease in the absence of treatment with anti-TB drugs (conducted before drug treatments became available) found that about 70% of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed, as did about 20% of people with culture-positive (but smear-negative) pulmonary TB.  

Effective drug treatments were first developed in the 1940s. The currently recommended treatment for cases of drug-susceptible TB is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. The Global TB Drug Facility supplies a complete 6-month course for about US$ 40 per person.

Treatment success rates of at least 85% for cases of drug-susceptible TB are regularly reported to WHO by its 194 Member States. Treatment for rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) is longer, and requires more expensive (≥ US$ 1000 per person) and more toxic drugs. The latest data reported to WHO show a treatment success rate for MDR-TB of 55%, globally.

There are 20 TB drugs in clinical trials, and combination regimens that include new compounds as well as other drugs are also being tested in clinical trials. The bacille Calmette-Guérin (BCG) vaccine, which was developed almost 100 years ago and has been shown to prevent severe forms of TB in children, is still widely used. However, there is currently no vaccine that is effective in preventing TB disease in adults, either before or after exposure to TB infection. There are 12 TB vaccines in Phase I, Phase II or Phase III trials.

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*b* Defined as resistance to isoniazid and rifampicin, the two most powerful anti-TB drugs.
Tuberculosis (TB) is an old disease – studies of human skeletons show that it has affected humans for thousands of years. The cause remained unknown until 24 March 1882, when Dr Robert Koch announced that he had discovered the bacillus Mycobacterium tuberculosis, an event that is now commemorated every year as World TB Day. The disease is spread when people who are sick with TB expel bacteria into the air, for example by coughing. Basic facts about TB are provided in Box 1.1.

In the late 1800s, cause-of-death data from national vital registration systems show that TB was one of the leading causes of death in some European countries. With social and economic development – such as improvements in incomes, housing and nutrition – numbers of TB cases and deaths started to decline in western Europe, North America and some other parts of the world around the turn of the 20th century, albeit slowly (1–2% per year). From the 1940s, the discovery, development and use of effective drug treatments substantially accelerated these trends, with national case rates (per 100,000 population) falling by up to 10% per year and mortality rates falling even faster. In countries that have experienced such reductions in disease burden, and now have only around 10 or fewer cases and less than 1 death per 100,000 population per year, TB is often regarded as a disease of the past.

For many countries, however, the “end” of TB as an epidemic and major public health problem is still a distant reality. This is despite the fact that, with a timely diagnosis and correct drug treatment, most people who develop the disease can be cured. Twenty-five years ago, in 1993, WHO declared TB a global health emergency. There has been major progress in subsequent years – more than 60 million people have been documented as treated and cured since 2000, and case and death rates have fallen steadily. Nevertheless, worldwide, around 10 million people still fall ill with the disease each year (more adults than children, and more men than women), and TB is one of the top 10 causes of death. It is also the leading cause of death from a single infectious agent, ranking above HIV/AIDS.

In 2014 and 2015, all Member States of WHO and the United Nations (UN) committed to ending the TB epidemic. They did this by unanimously endorsing WHO’s End TB Strategy at the World Health Assembly in May 2014, and by adopting the UN Sustainable Development Goals (SDGs) in September 2015. The End TB Strategy has the overall goal of ending the global TB epidemic, and it defines the targets (2030, 2035) and milestones (2020, 2025) for reductions in TB cases and deaths needed to achieve that goal. The SDGs include a target to end the TB epidemic by 2030.

In 2017 and 2018, efforts to step up political commitment to the fight against TB have intensified. The first global ministerial conference on TB was held in November 2017. The UN’s first high-level meeting (HLM) on TB, on 26 September 2018 at its headquarters in New York, includes heads of state. The title is United to End TB: An Urgent Global Response to a Global Epidemic. WHO has published a global TB report every since 1997. This 2018 edition is published in association with the UN HLM. It provides a comprehensive and up-to-date assessment of the TB epidemic, and of progress in the response, at global, regional and country levels. This is based primarily on data gathered by WHO from countries and territories in annual rounds of data collection, and databases maintained by other multilateral agencies.

The topics covered in the main chapters of the report are: global commitments to end TB and multisectoral accountability; estimates of TB disease burden 2000–2017; TB diagnosis and treatment; TB prevention services; financing for TB prevention, diagnosis and treatment; universal health coverage, social protection and social determinants of TB; and TB research and development.

The report’s annexes describe WHO’s online global TB database, present profiles for 30 high TB burden countries and WHO’s six regions, and contain data for key indicators for all countries, for the latest available year.
Primary school children in a village in northern Lao People's Democratic Republic

Hady nyah / Getty Images
Chapter 2. Global commitments to end TB and multisectoral accountability

From 2000 to 2015, global and national efforts to reduce the burden of tuberculosis (TB) disease were focused on achieving targets set within the context of the Millennium Development Goals (MDGs). The MDGs were established by the United Nations (UN) in 2000, and targets were set for 2015. Target 6c of MDG 6 was to “halt and reverse” TB incidence. The Stop TB Partnership, established in 2001, adopted this target and set two additional targets: to halve TB prevalence and TB mortality rates by 2015 compared with their levels in 1990. The global TB strategy developed by WHO for the decade 2006–2015, the Stop TB Strategy, had the overall goal of reaching all three of these targets. In October 2015, WHO published its assessment of whether the 2015 global TB targets for reductions in TB incidence, prevalence and mortality had been achieved.1

In 2016, the MDGs were succeeded by a new set of goals, known as the Sustainable Development Goals (SDGs). Adopted by the UN in September 2015 following 3 years of consultations, the SDG framework of goals, targets and indicators covers the period 2016–2030.2 Similarly, in 2012 WHO initiated work on a new global TB strategy, which was completed in 2014. The End TB Strategy was unanimously endorsed by all WHO Member States at the 2014 World Health Assembly, and covers the period 2016–2035.3 The SDGs and the End TB Strategy provide the framework for national and international efforts to end the TB epidemic during the period 2016–2030.

This chapter provides an overview of both the SDGs (Section 2.1) and the End TB Strategy (Section 2.2). It then describes the Moscow Declaration from the first global ministerial conference on ending TB (Section 2.3), which was held in November 2017 with the aim of accelerating progress towards targets set in the SDGs and End TB Strategy through a multisectoral response. The Moscow Declaration includes commitments by WHO Member States and calls to partner agencies, and has informed the first UN high-level meeting on TB at UN headquarters in New York in September 2018. In Section 2.3, specific attention is given to the development of a multisectoral accountability framework to accelerate progress towards ending TB, which was one of four topics featured in the declaration and which has been a major focus of work for WHO, in collaboration with WHO Member States and partner agencies, in 2018.

Given the multisectoral influences on the TB epidemic and the multisectoral actions needed to end it, WHO developed a TB-SDG monitoring framework in 2017.5 This is described and explained in Section 2.4. The framework is designed to focus attention on, and encourage analysis of, SDG targets and indicators that will influence the course of the TB epidemic, with findings then used to drive action. Analysis of the 14 indicators included in the framework is part of Chapter 7.6

At the 2018 World Health Assembly, Member States endorsed WHO’s General Programme of Work (GPW) for 2019–2023.7 The GPW is based on the foundation of SDG 3, the health goal of the SDGs, and it includes TB targets for 2023 that are consistent with those of the End TB Strategy. Section 2.5 describes the GPW’s three strategic goals and associated outcomes, and its targets for TB, highlighting how these goals, outcomes and targets link with the SDGs and the End TB Strategy.

For the first 5 years of the SDGs and End TB Strategy (2016–2020), WHO has defined three lists of high-burden countries (HBCs): for TB, TB/HIV and multidrug-resistant TB (MDR-TB). Particular attention is given to the countries in each of these lists throughout this report. For this reason, they are presented and explained in Section 2.6.

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4 The conference was titled “Ending TB in the Sustainable Development Era: a multisectoral response”.
6 In addition, Annex 2 shows the latest data and recent trends for each indicator for the 30 high TB burden countries. For other countries, the same data are available in country profiles that can be accessed online at www.who.int/tb/data.
7 See: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_4-en.pdf?ua=1
2.1 The Sustainable Development Goals

The 17 SDGs are shown in Box 2.1.

The consolidated goal for health is SDG 3, which is defined as “Ensure healthy lives and promote well-being for all at all ages”. Thirteen targets have been set for this goal (Box 2.2), and one of these targets, Target 3.3, explicitly mentions TB: “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases”. The language of “ending epidemics” is also now a prominent element of global health strategies developed by WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) for the post-2015 era, including the End TB Strategy (Section 2.2).

The TB indicator for Target 3.3 is the TB incidence rate (new TB cases per 100,000 population per year).

SDG 3 also includes a target (Target 3.8) related to universal health coverage (UHC) in which TB is explicitly mentioned. The WHO/World Bank definition of UHC is that all people receive the health services they need, while at the same time ensuring that the use of these services does not expose the user to financial hardship. Target 3.8 includes an indicator for the coverage of essential prevention, treatment and care interventions. This is a composite indicator based on the coverage of 16 so-called “tracer interventions”, one of which is TB treatment.

The SDGs include considerable emphasis on disaggregated analysis and reporting of data (as well as reporting for an entire country). Depending on the indicator, examples include disaggregation by age, sex, location and economic status (e.g., bottom 40%, or bottom versus top income quintiles). Some indicators also give particular attention to specific subpopulations, such as pregnant women, people with disabilities, victims of work injuries, and migrants.

In support of the requirement for disaggregation for many indicators, SDG 17 includes two targets and associated indicators under the subheading of “Data, monitoring and accountability” that specifically refer to disaggregated data and the mechanisms needed to generate such data (Table 2.1). Emphasis is also given to the importance of death registration within national vital registration systems, to allow for accurate tracking of causes of death (this is Part b of Indicator 17.19.2).

Strengthening national vital registration systems as the basis for direct measurement of the number of TB deaths is one of the five strategic areas of work of the WHO Global Task Force on TB Impact Measurement, as discussed in Chapter 3.

Disaggregation is intended to inform analysis of within-country inequalities and associated assessments of equity, with findings used to identify particular areas or subpopulations where progress is lagging and greater attention is needed. Such disaggregation is also an important consideration for the TB community, given the influence of sex, age, socioeconomic status and differential access to health care on the risks for and consequences of TB infection and disease. Chapter 3 and Chapter 4 of this report include analyses of TB data disaggregated by age and sex.

2.2 The End TB Strategy

The End TB Strategy “at a glance” is shown in Box 2.3.

The overall goal is to “End the global TB epidemic”, and there are three high-level, overarching indicators and related targets (for 2030 – linked to the SDGs – and for 2035) and milestones (for 2020 and 2025). The three indicators are:

- the number of TB deaths per year;
- the TB incidence rate (new cases per 100,000 population per year); and
- the percentage of TB-affected households that experience catastrophic costs as a result of TB disease.

The 2030 targets are a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate, compared with levels in 2015. The 2035 targets are a 95% reduction in TB deaths and a 90% reduction in the TB incidence rate, compared with levels in 2015. The most immediate milestones, set for 2020, are a 35% reduction in TB deaths and a 20% reduction in the TB incidence rate, compared with levels in 2015. The trajectories of TB incidence and TB deaths that are required to reach these milestones and targets are shown in Fig. 2.1. For the third indicator (the percentage of TB-affected households that experience catastrophic costs as a result of TB disease), the milestone for 2020 is zero, to be sustained thereafter.

The Stop TB Partnership has developed a Global Plan to End TB, 2016–2020, which focuses on the actions and funding needed to reach the 2020 milestones of the End TB Strategy. More details about this plan are provided in Chapter 6.

Progress towards UHC and actions to address health-related risk factors for TB (as well as broader social and economic determinants of TB) will be fundamental to achieving the targets and milestones for

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4 There are many different prevention and treatment interventions. SDG indicator 3.8.1 is based on the coverage of 16 interventions that have been selected as “tracers” for assessment of progress towards UHC for all interventions. Further details are provided in Chapter 7.
BOX 2.1

The Sustainable Development Goals

Goal 1. End poverty in all its forms everywhere
Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture
Goal 3. Ensure healthy lives and promote well-being for all at all ages
Goal 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
Goal 5. Achieve gender equality and empower all women and girls
Goal 6. Ensure availability and sustainable management of water and sanitation for all
Goal 7. Ensure access to affordable, reliable, sustainable and modern energy for all
Goal 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
Goal 9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
Goal 10. Reduce inequality within and among countries
Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable
Goal 12. Ensure sustainable consumption and production patterns
Goal 13. Take urgent action to combat climate change and its impacts*
Goal 14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development
Goal 15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
Goal 16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
Goal 17. Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development

* Acknowledging that the United Nations Framework Convention on Climate Change is the primary international, intergovernmental forum for negotiating the global response to climate change.
**BOX 2.2**

**Sustainable Development Goal 3 and its 13 targets**

**SDG 3: Ensure healthy lives and promote well-being for all at all ages**

**Targets**

3.1 By 2030, reduce the global maternal mortality ratio to less than 70 per 100 000 live births

3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases

3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being

3.5 Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol

3.6 By 2020, halve the number of global deaths and injuries from road traffic accidents

3.7 By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all

3.9 By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination

3.a Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate

3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all

3.c Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States

3.d Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks

**TRIPS, Trade-Related Aspects of Intellectual Property Rights**

reductions in TB cases and deaths, for two reasons. First, reaching the milestones for reductions in TB cases and deaths set for 2020 and 2025 requires the annual decline in the global TB incidence rate to accelerate from 1.5% per year in 2015 to 4–5% per year by 2020, and then to 10% per year by 2025. A decline of 10% per year is equivalent to the best-ever performance to date at national level (e.g. in countries in western Europe during the 1950s and 1960s), and has only been documented in the context of UHC combined with broader social and economic development. Second, the global proportion of people with TB who die from the disease (the case fatality ratio, or CFR) needs to be reduced to 10% by 2020 and then to 6.5% by 2025. A CFR of 6.5% is similar to the current level in many high-income countries, but is only possible if all those with TB disease can access high-quality treatment. Analysis of CFRs at global and national levels is included in Chapter 3.

The percentage of TB patients and their households facing catastrophic costs is a good tracer indicator for progress towards UHC as well as social protection. If UHC and social protection are in place, then people with TB should be able to access high-quality diagnosis and treatment without incurring catastrophic costs.¹

After 2025, reaching the 2030 and 2035 targets will require an unprecedented acceleration in the rate at ¹ This indicator, including results from recent national surveys to measure it, is discussed in more detail in Chapter 7.
TABLE 2.1
SDG 17, and targets and indicators related to data, monitoring and accountability

<table>
<thead>
<tr>
<th>TARGETS</th>
<th>INDICATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.18 By 2020, enhance capacity-building support to developing countries, including for least developed countries and small island developing States, to increase significantly the availability of high-quality, timely and reliable data disaggregated by income, gender, age, race, ethnicity, migratory status, disability, geographic location and other characteristics relevant in national contexts</td>
<td>17.18.1 Proportion of sustainable development indicators produced at the national level with full disaggregation when relevant to the target, in accordance with the Fundamental Principles of Official Statistics</td>
</tr>
<tr>
<td>17.19 By 2030, build on existing initiatives to develop measurements of progress on sustainable development that complement gross domestic product, and support statistical capacity-building in developing countries</td>
<td>17.19.2 Proportion of countries that (a) have conducted at least one population and housing census in the last 10 years; and (b) have achieved 100 per cent birth registration and 80 per cent death registration</td>
</tr>
</tbody>
</table>

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**BOX 2.3**

The End TB Strategy at a glance

<table>
<thead>
<tr>
<th>VISION</th>
<th>A WORLD FREE OF TB — zero deaths, disease and suffering due to TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOAL</td>
<td>END THE GLOBAL TB EPIDEMIC</td>
</tr>
</tbody>
</table>

**INDICATORS**

<table>
<thead>
<tr>
<th>MILESTONES</th>
<th>TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>2025</td>
</tr>
<tr>
<td>Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)</td>
<td>35%</td>
</tr>
<tr>
<td>Percentage reduction in the TB incidence rate (compared with 2015 baseline)</td>
<td>20%</td>
</tr>
<tr>
<td>Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown)</td>
<td>0%</td>
</tr>
</tbody>
</table>

**PRINCIPLES**

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

**PILLARS AND COMPONENTS**

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

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

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

* Targets linked to the Sustainable Development Goals (SDGs).
which TB incidence falls globally, to an average of 17% per year. Such an acceleration will depend on a technological breakthrough that can substantially reduce the risk of developing TB disease among the approximately 1.7 billion people (approximately one quarter of the world’s population) who are already infected with *Mycobacterium tuberculosis*. Examples include an effective post-exposure vaccine or a short, efficacious and safe treatment for latent TB infection. The latest status of the development pipelines for new TB diagnostics, drugs and vaccines is presented in Chapter 8.

To achieve the targets and milestones, the End TB Strategy has four underlying principles and three pillars. The four principles are government stewardship and accountability, with monitoring and evaluation; a strong coalition with civil society organizations and communities; protection and promotion of human rights, ethics and equity; and adaptation of the strategy and targets at country level, with global collaboration. The three pillars are integrated, patient-centred TB care and prevention; bold policies and supportive systems (including UHC, social protection, and action on TB determinants); and intensified research and innovation. The 10 components of the three pillars of the End TB Strategy are shown in Box 2.3.

WHO has defined 10 priority indicators for monitoring of progress in implementing the End TB Strategy. These are shown in Table 2.2. The table also indicates the particular chapter of this report in which available data for each indicator can be found.

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**Table 2.2**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator 1</td>
<td>The number of new smear-positive TB cases reported per 100,000 population.</td>
</tr>
<tr>
<td>Indicator 2</td>
<td>The number of new smear-negative TB cases reported per 100,000 population.</td>
</tr>
<tr>
<td>Indicator 3</td>
<td>The proportion of confirmed smear-positive TB cases with a second smear done within 3 months.</td>
</tr>
<tr>
<td>Indicator 4</td>
<td>The proportion of smear-negative TB cases with a diagnosis confirmed within 3 months.</td>
</tr>
<tr>
<td>Indicator 5</td>
<td>The proportion of confirmed smear-positive TB cases with a diagnosis confirmed within 3 months.</td>
</tr>
<tr>
<td>Indicator 6</td>
<td>The proportion of smear-negative TB cases with a diagnosis confirmed within 3 months.</td>
</tr>
<tr>
<td>Indicator 7</td>
<td>The proportion of smear-positive TB cases with treatment begun within 3 months.</td>
</tr>
<tr>
<td>Indicator 8</td>
<td>The proportion of smear-negative TB cases with treatment begun within 3 months.</td>
</tr>
<tr>
<td>Indicator 9</td>
<td>The proportion of smear-positive TB cases with treatment completed within 6 months.</td>
</tr>
<tr>
<td>Indicator 10</td>
<td>The proportion of smear-negative TB cases with treatment completed within 6 months.</td>
</tr>
</tbody>
</table>

Data for five of the 10 indicators cannot be captured routinely using the standard recording and reporting forms for paper-based systems that are included in the latest revision of WHO’s framework for TB case definitions and reporting. Collection of data on the costs faced by TB patients and their households, and assessment of whether these are catastrophic (Indicator 3 in Table 2.2) requires periodic surveys of a representative sample of TB patients; further details are provided in Chapter 7. For the other four indicators (Indicators 4, 5, 6 and 8 in Table 2.2), data may already be captured routinely in countries that have electronic case-based systems for recording and reporting of data; if this is not the case, these systems can be adapted to capture the information. Alternatively, countries can undertake periodic surveys of the medical records or patient cards of a random sample of TB patients. Further guidance is provided in the WHO operational guidance on the End TB Strategy.

---

2.3 The Moscow Declaration to end TB

The first global ministerial conference on ending TB was held in Moscow in November 2017. It was organized by WHO and the Ministry of Health of the Russian Federation, in recognition of the fact that investments and actions have been falling short of those needed to reach SDG and End TB Strategy targets and milestones.

---


**TABLE 2.2**

Top 10 indicators (not ranked) for monitoring implementation of the End TB Strategy at global and national levels, with recommended target levels that apply to all countries. The target level is for 2025 at the latest.

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>RECOMMENDED TARGET LEVEL</th>
<th>MAIN RATIONALE FOR INCLUSION IN TOP 10</th>
<th>MAIN METHOD OF MEASUREMENT, AND RELEVANT CHAPTER OF THIS REPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB treatment coverage</strong></td>
<td>≥90%</td>
<td>High-quality TB care is essential to prevent suffering and death from TB and to cut transmission.</td>
<td>Routinely collected notification data used in combination with estimate of TB incidence. Chapter 4</td>
</tr>
<tr>
<td><strong>TB treatment success rate</strong></td>
<td>≥90%</td>
<td>High coverage of appropriate treatment is a fundamental requirement for achieving the milestones and targets of the End TB Strategy.</td>
<td>Routinely collected data. Chapter 4</td>
</tr>
<tr>
<td>Percentage of TB-affected households that experience catastrophic costs due to TB*</td>
<td>0%</td>
<td>One of the End TB Strategy’s three high-level indicators; a key marker of financial risk protection (one of the two key elements of UHC) and social protection for TB-affected households.</td>
<td>National survey of notified TB patients. Chapter 7</td>
</tr>
<tr>
<td>Percentage of new and relapse TB patients tested using a WHO-recommended rapid diagnostic (WRD) at the time of diagnosis</td>
<td>≥90%</td>
<td>Accurate diagnosis is a fundamental component of TB care. Rapid molecular diagnostic tests help to ensure early detection and prompt treatment.</td>
<td>Routinely collected data (as part of case-based surveillance), or national survey of medical records or patient cards of TB patients. Chapter 4</td>
</tr>
<tr>
<td>Latent TB infection (LTBI) treatment coverage</td>
<td>≥90%</td>
<td>Treatment of LTBI is the main treatment intervention available to prevent development of active TB disease in those already infected with Mycobacterium tuberculosis.</td>
<td>Routinely collected data (as part of case-based surveillance), or national survey of medical records or patient cards of people living with HIV and TB patients. Chapter 5</td>
</tr>
<tr>
<td>Contact investigation coverage</td>
<td>≥90%</td>
<td>Contact tracing is a key component of TB prevention, especially in children.</td>
<td>As above for LTBI.</td>
</tr>
<tr>
<td>Drug-susceptibility testing (DST) coverage for TB patients</td>
<td>100%</td>
<td>Testing for drug susceptibility for WHO-recommended drugs is essential to provide the right treatment for every person diagnosed with TB.</td>
<td>Routinely collected data (as part of case-based surveillance), or national survey of medical records or patient cards of TB patients. Chapter 4</td>
</tr>
<tr>
<td>Treatment coverage, new TB drugs</td>
<td>≥90%</td>
<td>An indicator that is relevant to monitoring the adoption of innovations in all countries. The definition of which patients are eligible patients for treatment with new drugs may differ among countries.</td>
<td>As above for DST.</td>
</tr>
<tr>
<td>Documentation of HIV status among TB patients</td>
<td>100%</td>
<td>One of the core global indicators used to monitor collaborative TB/HIV activities. Documentation of HIV status is essential to provide the best care for HIV-positive TB patients, including antiretroviral therapy.</td>
<td>Routinely collected data for all TB patients. Chapter 4</td>
</tr>
<tr>
<td>Case fatality ratio (CFR)</td>
<td>≤5%</td>
<td>This is a key indicator for monitoring progress towards the 2020 and 2025 milestones. A CFR of 6% is required to achieve the 2025 global milestone for reductions in TB deaths and cases.</td>
<td>Mortality divided by incidence. In countries with a high-performance surveillance system, notifications approximate incidence. Chapter 3</td>
</tr>
</tbody>
</table>

* Catastrophic costs are provisionally defined as total costs that exceed 20% of annual household income.
The conference brought together over 1000 participants, including ministers of health and other leaders from 120 countries, and over 800 partners, including civil society.

The key outcome of the conference was the Moscow Declaration to End TB,\(^1\) which was adopted by almost 120 WHO Member States represented at the conference. The declaration was developed through consultations with partners and Member States, led by the Russian Federation.

The Declaration includes both commitments by Member States and calls for actions by global agencies and other partners in four key areas (Fig. 2.2).\(^2\)

- Advancing the TB response within the SDG agenda;
- Ensuring sufficient and sustainable financing;
- Pursuing science, research and innovation;
- Developing a multisectoral accountability framework.

At the World Health Assembly in May 2018, all Member States committed to accelerate their actions to end TB, building on the commitments of the Moscow Declaration. They also welcomed a draft version of a multisectoral accountability framework for TB, and supported its further development, adaptation and use (Box 2.4).

The topics of the Moscow Declaration are prominently featured in the UN high-level meeting on TB on 26 September 2018,\(^3\) which will seek further commitments from Heads of State. The title of the meeting was United to End TB: An Urgent Global Response to a Global Epidemic.

In the months leading up to the UN high-level meeting, ministers and heads of state of major country blocs have issued communiqués on the need for action on TB, including drug-resistant TB in the wider context of antimicrobial resistance (AMR). Examples include the G20; the G7; Brazil, the Russian Federation, India, China and South Africa (BRICS); and the Asia-Pacific Economic Cooperation (APEC). New commitments have also been made by ministers from countries in the WHO South-East Asia Region at the Delhi End TB Summit in March 2018 and by African leaders at a summit of the African Union in July 2018.

2. The SDG agenda and a multisectoral accountability framework for TB are discussed in this chapter. The topic of financing is covered in Chapter 6 and Chapter 7; research and development is the subject of Chapter 8.

### FIG. 2.2
The four outcome areas of the Moscow Declaration

2.4 A TB-SDG monitoring framework

Monitoring of TB-specific indicators is well established at global and national levels. For example, standardized monitoring of notifications of TB cases and their treatment outcomes at global and national levels has been in place since 1995, and WHO has been publishing annual estimates of TB incidence and mortality for more than a decade. In the era of the End TB Strategy and SDGs, such monitoring needs to be sustained, alongside continued efforts to strengthen notification and vital registration systems so that they can provide reliable data for direct measurement of TB incidence and TB deaths (see also Chapter 3), and monitoring of the newer priority indicators (five of those listed in Table 2.2 were introduced in the context of the End TB Strategy).

As explained in Section 2.2, achieving the End TB Strategy targets and milestones requires progress in reducing health-related risk factors for TB infection and disease, as well as broader social and economic determinants of TB infection and disease. As explained in Section 2.1, the SDG framework includes targets and indicators related to these risk factors and determinants, and the global ministerial conference on ending TB and the associated Moscow Declaration emphasized the need for a multisectoral approach and a multisectoral accountability framework (Section 2.3). In this context, TB monitoring needs to include analysis of selected SDG indicators that will influence the course of the TB epidemic, with findings used to inform the multisectoral actions needed to end the TB epidemic.

WHO developed a TB-SDG monitoring framework in 2017, based on previously published work that identified clear linkages between various SDG indicators and TB...
Developing a draft multisectoral accountability framework to accelerate progress to end TB

Background
The first WHO global ministerial conference on TB, titled “Ending TB in the Sustainable Development Era: a multisectoral response”, was held in Moscow in November 2017. The aim was to accelerate implementation of the End TB Strategy, in recognition of the fact that investments and actions have, to date, fallen short of those needed to reach SDG and End TB Strategy targets, and to inform the UN high-level meeting on TB in September 2018.

The Moscow Declaration to End TB includes both commitments by Member States and calls for actions by global agencies and other partners. It addresses four key areas for action, one of which is multisectoral accountability. Member States committed to “supporting the development of a multisectoral accountability framework” in advance of the UN HLM on TB, and called on WHO to develop such a framework, working in close cooperation with Member States and partners, for consideration by WHO’s governing bodies (i.e. the Executive Board and World Health Assembly). The rationale for such a framework is that strengthened accountability for the response to TB at national and global levels should contribute to faster progress towards the targets and milestones of the SDGs and End TB Strategy.

The Executive Board reiterated this request in its January 2018 meeting, in the form of a decision point. This included a specific request, addressed to the WHO Director-General, to develop a draft framework for consideration by Member States at the World Health Assembly in May 2018, and for presentation at the UN HLM on ending TB in September 2018.

Definitions and concepts
Accountability means being responsible (or answerable) for commitments made or actions taken.

An accountability framework defines who is accountable (e.g. an individual, organization or national government, or the global community), what commitments and actions they are accountable for, and how they will be held to account. Broadly, mechanisms for how specific entities are held to account fall into two major categories: monitoring and reporting, and review. A generic illustration of an accountability framework, represented as a cycle of components, is shown in Fig. B2.4.1.

Conceptually, commitments should be followed by the actions needed to keep or achieve them. Monitoring and reporting are then used to track progress related to commitments and actions. Review is used to assess the results from monitoring that are documented in reports and associated products, and to make recommendations for future actions. The cycle of action, monitoring and reporting, and review can be repeated many times. The results from monitoring and reporting, and the recommendations from reviews based on those results, should drive the next cycle of actions. Periodically, new commitments or reinforcement of commitments may be required, based on reviews of progress.

Accountability can be strengthened by reinforcing one or more of the four components of the framework. Examples include adding new actions or improving existing ones; increasing the quality and coverage of data and reports available to inform reviews of progress; elevating reviews to a higher level; improving review processes (e.g. by making them more independent, more transparent and with wider participation); and ensuring that the results of reviews have meaningful consequences for action. If each of the “actions – monitoring and reporting – review” components of the cycle is strong, progress towards commitments should be faster than if one or more of those components is weak.

Development process to date
WHO prepared a background document on the development of a multisectoral accountability framework in February 2018. The background document was used as the basis for consultations with Member States and other partners, including in a 2-day consultation held in March 2018. Consultations informed the development of a “draft multisectoral accountability framework to accelerate progress to end TB”, which was posted for public review in mid-April 2018. Input from this review, from Member States and partners, was used to produce an updated draft.

The draft multisectoral accountability framework for TB that was submitted for the consideration of the 2018 World Health Assembly is available online; a brief outline is provided here.

The framework has two major parts: global and regional levels; and national (including local) level. The four components of each part of the framework are the same as those in the generic framework shown in Fig. B2.4.1 — namely, commitments, actions, monitoring and reporting, and review.
The content of the framework is based on the following principles:

- The SDGs and the End TB Strategy, and associated political declarations form the foundation of the framework, as do existing monitoring and reporting systems, and associated best practices.
- Civil society, TB-affected communities and patient groups have a fundamental role to play in all aspects of accountability.
- It is not possible to be exhaustive in listing all elements of relevance under each of the four major components, especially at national level; hence, major examples are provided, using generic language.
- The national component of the framework requires adaptation. For example, there are differences between low and high TB burden countries, differences between countries that fund their TB responses entirely from domestic resources and those that rely on external resources for a large share of their total funding, and differences that relate to national administrative structures and legislative frameworks.

The global and regional part of the framework defines commitments, actions, monitoring and reporting processes, and review mechanisms that apply to all countries collectively or at regional level. The national part of the framework defines commitments, actions, monitoring and reporting processes, and review mechanisms that apply to individual countries, at national and local levels.

Discussions at the 2018 World Health Assembly and next steps

At the 2018 World Health Assembly, a resolution (EB142.R3) that included text on the UN HLM for TB and the multisectoral accountability framework was presented for consideration by Peru and the Russian Federation. With respect to the multisectoral accountability framework specifically, the resolution:

- welcomed the draft framework;
- requested the Secretariat to continue to develop it, working with Member States and partners;
- requested the Director-General of WHO to present the draft framework at the UN HLM on TB in September 2018; and
- requested that the Secretariat report on progress at the next World Health Assembly in 2019.

The resolution was unanimously endorsed by all Member States.

Next steps for WHO include the following:

1. Presentation of the draft framework by the WHO Director-General at the UN HLM on TB.
2. Further work on the framework, in consultation with Member States and partners. The first updates to the framework will be based on the content of the Political Declaration from the UN HLM on TB. There may be a need for additional consultations on the “review” component of the draft framework.
4. Provision of support to Member States that express interest in beginning to adapt and use the draft multisectoral accountability framework.


The others areas for action were advancing the response within the 2030 Agenda for Sustainable Development; ensuring sufficient and sustainable financing; and pursuing science, research and innovation.


This figure is derived from the unified accountability framework for women’s, children’s and adolescents’ health. That framework depicts the action–monitoring–review cycle in a circle, as here, for the global and country levels separately. The accountability framework for TB adds a component for “commitments” and highlights “monitoring and reporting” in its third component.


Developing a multisectoral accountability framework to accelerate progress to end TB. Document submitted to the 2018 World Health Assembly (A71/16.Add.1.)
incidence,\textsuperscript{1,2,3,4} and further analysis of the relationship between SDG indicators and TB incidence.\textsuperscript{5} The framework, which comprises 14 indicators under seven SDGs, is shown in Table 2.3.

For SDG 3, the seven indicators selected for monitoring are:

- coverage of essential health services;
- percentage of health expenditures that are out-of-pocket;
- health expenditure per capita;
- HIV prevalence;
- prevalence of smoking;
- prevalence of diabetes; and
- prevalence of alcohol use disorder.

For SDGs 1, 2, 7, 8, 10 and 11, the seven indicators selected for monitoring are:

- proportion of the population living below the international poverty line;
- proportion of the population covered by social protection floors or systems;
- prevalence of undernourishment;
- proportion of the population with primary reliance on clean fuels and technology;
- gross domestic product (GDP) per capita;
- Gini index for income inequality;\textsuperscript{6} and
- proportion of the urban population living in slums.

The rationale for the selection of these 14 indicators and data sources is provided in Table 2.3, with comments on whether it is relevant to collect data for TB patients specifically.

The framework includes only indicators for which a relationship with TB incidence could be established. It excludes:

- indicators that are sub-indicators of indicators that have already been included (e.g. sub-indicators related to UHC, under SDG 3); and
- indicators that are only remotely associated with TB risks, and that operate mainly through other SDGs (e.g. education under SDG 4, gender equality under SDG 5 and resilient infrastructure under SDG 9).

Importantly, collection and reporting of data for the 14 indicators shown in Table 2.3 does not require any additional data collection and reporting efforts by national TB programmes. Nor does it require data collection and reporting efforts that go beyond those to which countries have already committed in the context of the SDGs.

At the global level, the UN has established a monitoring system for SDG indicators, and countries are expected to report data on an annual basis via the appropriate UN agencies (including WHO). Therefore, analysis of the status of, and trends in, the 14 indicators related to TB will be based primarily on accessing the data held in the UN’s SDG database, as shown in Table 2.3.\textsuperscript{7} In some cases, the SDG indicator is not considered the best metric, and a better (but closely related) alternative has been identified and justified (five indicators under SDG 3, one under SDG 8 and one under SDG 10). In such cases, the data sources are either WHO, the Organisation for Economic Co-operation and Development (OECD), UNAIDS or the World Bank (also shown in Table 2.3).

The data for the indicators shown in Table 2.3 that will be available in the WHO, OECD, UN and World Bank databases will be for national populations. These data will not be available for TB patients specifically, with the exception of data on HIV prevalence, given that HIV status among TB patients has been routinely monitored as part of national TB surveillance for more than a decade. This is not a problem for monitoring of TB risk factors and determinants, since it is the population-level prevalence that influences population-level TB risks.

For a few of the indicators included in Table 2.3, collection of data for TB patients specifically could be considered. However, there is a clear risk of making routine TB surveillance far too complex, and this risk needs to be avoided. If the indicator is considered important enough to monitor among TB patients at country level, periodic surveys should be considered as an alternative to routine surveillance (in which data would be collected for all TB patients).

Analysis of the indicators in the TB-SDG monitoring framework for high TB burden countries is included in Chapter 7. The latest status and recent trends in each indicator are also shown for these countries on the second page of the country profiles in Annex 2 (this information is shown for other countries in profiles that are available online).\textsuperscript{8}


\textsuperscript{5} Monitoring and evaluation of TB in the context of the Sustainable Development Goals: Background Paper for WHO Ministerial Conference on ‘TB in the context of the Sustainable Development Goals’. Available on request.

\textsuperscript{6} The index can take values between 0 and 1, with 0 representing perfect equality and 1 representing perfect inequality.

\textsuperscript{7} Further details are provided in Annex 1.

\textsuperscript{8} http://www.who.int/tb/data/en/}
### TABLE 2.3A
TB-SDG monitoring framework: indicators to monitor within SDG 3

<table>
<thead>
<tr>
<th>SDG TARGETS FOR 2030</th>
<th>SDG INDICATORS</th>
<th>ALTERNATIVE INDICATORS TO MONITOR</th>
<th>RATIONALE</th>
<th>DATA SOURCE</th>
<th>COLLECT DATA FOR TB PATIENTS SPECIFICALLY?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3 End the epidemics of AIDS, TB, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases</td>
<td>3.3.1 Number of new HIV infections per 1000 uninfected population</td>
<td>HIV prevalence</td>
<td>HIV is a strong risk factor for development of TB disease and is associated with poorer treatment outcomes. HIV prevalence (rather than incidence) will be monitored because it is directly measured and those newly infected with HIV are at lower risk of developing TB compared with those who have been infected for more than 1 year.</td>
<td>UNAIDS</td>
<td>Yes, already routinely collected.</td>
</tr>
<tr>
<td></td>
<td>3.3.2 TB incidence per 100 000 population</td>
<td></td>
<td></td>
<td>WHO</td>
<td>NA</td>
</tr>
<tr>
<td>3.4 Reduce premature mortality by one third from non-communicable diseases and promote mental health and well-being</td>
<td>3.4.1 Mortality rate attributed to cardiovascular disease, cancer, diabetes or chronic respiratory disease</td>
<td>Prevalence of diabetes</td>
<td>Diabetes is a strong risk factor for development of TB disease, although a link with TB incidence at the national (as opposed to individual) level has been difficult to establish due to confounding. Diabetes prevalence is more relevant than mortality for TB since it directly influences the risk of developing TB.</td>
<td>WHO</td>
<td>Could be considered at country level, to inform planning of care for comorbidities.</td>
</tr>
<tr>
<td>3.5 Strengthen prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol</td>
<td>3.5.2 Alcohol consumption per capita per year (in litres of pure alcohol) among those aged ≥15 years (harmful level defined nationally)</td>
<td>Prevalence of alcohol use disorder</td>
<td>Alcohol use is a strong risk factor for TB disease and poorer treatment outcomes at the individual level, although a link with TB incidence at the national (as opposed to individual) level has been hard to establish due to confounding. The prevalence of alcohol use disorder is the most relevant indicator in the context of TB.</td>
<td>WHO</td>
<td>Could be considered at country level, to inform planning of care for comorbidities.</td>
</tr>
<tr>
<td>3.8 Achieve UHC, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all</td>
<td>3.8.1 Coverage of essential health services (defined as the average coverage of essential services based on tracer interventions that include reproductive, maternal, newborn and child health, infectious diseases, non-communicable diseases and service capacity and access, among the general and the most disadvantaged population).</td>
<td>NA</td>
<td>Achieving UHC is required to achieve the three high-level targets of the End TB Strategy for reductions in the TB incidence rate, the number of TB deaths and eliminating catastrophic costs for TB patients and their households. TB treatment coverage has been monitored for years and is one of the 16 tracer indicators that have been selected to measure SDG indicator 3.8.1. Health expenditure per capita is correlated with TB incidence.</td>
<td>WHO</td>
<td>To assess progress in elimination of catastrophic costs for TB patients and their households, periodic surveys of TB patients are recommended.</td>
</tr>
<tr>
<td></td>
<td>3.8.2 Proportion of population with large household expenditures on health as a share of total household expenditure or income</td>
<td>Percentage of health expenditures that are out-of-pocket</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Health expenditure per capita</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.a Strengthen implementation of the WHO Framework Convention on Tobacco Control</td>
<td>3.a.1 Age-standardized prevalence of current tobacco use among those aged ≥15 years (%)</td>
<td>Prevalence of smoking among those aged ≥15 years (%)</td>
<td>Smoking is a strong risk factor for TB disease at the individual level, although a link with TB incidence at the national (as opposed to individual) level has been difficult to establish due to confounding.</td>
<td>WHO</td>
<td>Could be considered (e.g. to inform access to smoking cessation interventions).</td>
</tr>
</tbody>
</table>
### TABLE 2.3B
TB-SDG monitoring framework: indicators to monitor beyond SDG 3

<table>
<thead>
<tr>
<th>SDG TARGETS FOR 2030</th>
<th>SDG INDICATORS</th>
<th>ALTERNATIVE INDICATORS TO MONITOR</th>
<th>RATIONALE</th>
<th>DATA SOURCE</th>
<th>COLLECT DATA FOR TB PATIENTS SPECIFICALLY?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Eradicate extreme poverty for all people everywhere</td>
<td>1.1.1 Proportion of population living below the international poverty line</td>
<td>NA</td>
<td>Poverty is a strong risk factor for TB, operating through several pathways. Reducing poverty should also facilitate prompt health-care seeking. Countries with higher levels of social protection have lower TB burden. Progress on both indicators will help to achieve the End TB Strategy target to eliminate catastrophic costs for TB patients and their households.</td>
<td>UN SDG database, World Bank</td>
<td>No</td>
</tr>
<tr>
<td>1.3 Nationally appropriate social protection systems and measures for all, including floors</td>
<td>1.3.1 Proportion of population covered by social protection floors/systems</td>
<td>NA</td>
<td>Could be considered (e.g. to facilitate access to social protection).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 End hunger and ensure access by all people to safe, nutritious and sufficient food year-round</td>
<td>2.1.1 Prevalence of undernourishment</td>
<td>NA</td>
<td>Under-nutrition weakens the body’s defence against infections and is a strong risk factor for TB at the national and individual level.</td>
<td>UN SDG database</td>
<td>Could be considered (e.g. to plan food support).</td>
</tr>
<tr>
<td>7.1 Ensure universal access to affordable, reliable, sustainable, and modern energy for all</td>
<td>7.1.2 Proportion of population with primary reliance on clean fuels and technology</td>
<td>NA</td>
<td>Indoor air pollution is a risk factor for TB at the individual level. There has been limited study of ambient air pollution but it is plausible that it is linked to TB incidence.</td>
<td>WHO</td>
<td>No</td>
</tr>
<tr>
<td>8.1 Sustain per capita growth with at least 7% growth in GDP per year in the least developed countries</td>
<td>8.1.1 Annual growth rate of real GDP per capita</td>
<td>GDP per capita</td>
<td>Historic trends in TB incidence are closely correlated with changes in the absolute level of GDP per capita (but not with the growth rate).</td>
<td>World Bank</td>
<td>No</td>
</tr>
<tr>
<td>10.1 Achieve and sustain income growth of the bottom 40% of the population at a rate higher than the national average</td>
<td>10.1.1 Growth rates of household expenditure or income per capita, overall and for the bottom 40% of the population</td>
<td>Gini index for income inequality</td>
<td>TB is a disease of poverty, and decreasing income inequalities combined with economic growth should have an effect on the TB epidemic.</td>
<td>World Bank, OECD</td>
<td>No</td>
</tr>
<tr>
<td>11.1 Ensure access for all to adequate, safe and affordable housing and basic services and upgrade slums</td>
<td>11.1.1 Proportion of urban population living in slums, informal settlements or inadequate housing</td>
<td>NA</td>
<td>Living in a slum is a risk factor for TB transmission due to its link with overcrowding. It is also a risk factor for developing TB disease, due to links with air pollution and under-nutrition.</td>
<td>UN SDG database</td>
<td>No</td>
</tr>
</tbody>
</table>
2.5 WHO’s General Programme of Work 2019–2023

WHO’s GPW for 2019–2023 was drafted in 2017; it was then revised following review by WHO’s Executive Board in January 2018, and a final version adopted by the World Health Assembly in May 2018. The thirteenth in a series of GPWs since WHO was founded in 1948, the current GPW sets out the organization’s strategic direction for the next 5 years.

The GPW for 2019–2023 is based on the foundation of the SDGs and is relevant to all countries: low-, middle- and high-income. In the context of SDG 3 in particular (Box 2.2), GPW 13 provides a vision that is rooted in Article 1 of WHO’s Constitution: “A world in which all people attain the highest possible standard of health and well-being”. GPW 13 also recognizes the influence of other SDGs on health, and the need for multisectoral approaches to address the social, economic and environmental determinants of health.

The GPW is structured around three strategic priorities and associated goals (Fig. 2.3). The three strategic priorities are UHC, addressing health emergencies and promoting healthier populations. The associated goals for 2023 are the so-called “triple billion goals”: that 1 billion more people are benefiting from UHC, 1 billion more people are better protected from health emergencies, and 1 billion more people are enjoying better health and well-being. WHO and the World Bank have estimated that only about half the world’s population had access to essential health services in 2015. Achieving all three goals depends on joint efforts by Member States, WHO and other partners.

The GPW goal related to UHC is directly linked to SDG Target 3.8 (Box 2.2). As explained in Section 2.2, progress towards this goal will be crucial to reaching End TB Strategy milestones and targets. Similarly, progress in TB prevention and care will contribute to the UHC target, with TB treatment being one of the tracer indicators for SDG Target 3.8 (Section 2.1, Table 2.3), and to more people enjoying better health and well-being. Protecting people from the public health threat posed by TB contributes to the health emergencies goal. At the same time, broader progress towards the goals related to health emergencies and better health and well-being contribute to progress towards End TB Strategy targets and milestones by positively influencing the determinants of TB included in the TB-SDG monitoring framework shown in Table 2.3.

GPW 13 includes 10 outcomes, one of which is based on the SDG 3 target related to ending epidemics. Outcome 5 is defined as “Accelerated elimination and eradication of high-impact communicable diseases”. Under this outcome, there are two targets for TB: that the number of TB deaths is reduced by at least 50% between 2018 and 2023, and that by 2023 there is at least 80% treatment coverage for people with drug-resistant TB.

Linked to the GPW, WHO’s Global TB Programme has also defined two other targets:

- 40 million people with TB are reached with care during the period 2018–2022, including 3.5 million children and 1.5 million people with drug-resistant TB;
- At least 30 million people are reached with TB prevention services during the period 2018–2022.

TB targets that have been aligned with the GPW are illustrated in Fig. 2.4. To catalyze global efforts to support the achievement of these targets, WHO, the Stop TB Partnership and the Global Fund to Fight AIDS, Tuberculosis and Malaria have launched a joint initiative, called “Find.Treat.All” (Box 2.5).

2.6 Lists of high-burden countries being used by WHO during the period 2016–2020

During the period 1998–2015, the concept of an HBC became familiar and widely used in the context of TB. In 2015, three HBC lists – for TB, TB/HIV and MDR-TB – were in use. The HBC list for TB (22 countries) had remained unchanged since 2002; also, the HBC lists for TB/HIV (41 countries) had not been updated since 2009, and those for MDR-TB (27 countries) had not been updated since 2008.
FIG. 2.4
Strategic priorities and targets for TB aligned with WHO’s General Programme of Work

Achieve universal access to TB prevention, treatment and care services

TARGETS
- At least 40 million people with TB reached with care in the period 2018–2022, including 3.5 million children and 1.5 million people with drug-resistant TB
- At least 30 million people reached with TB prevention services in the period 2018–2022
  - No TB-affected households facing catastrophic costs due to TB by 2020

Prevent TB as a public health threat and contribute to protecting populations from airborne infections

TARGET
- Increase treatment coverage for MDR-TB to 80% of estimated incidence by 2023

Protect populations and vulnerable groups from the social and economic impacts of TB infection and disease

TARGET
- Reduce TB deaths by 50% by 2023 compared with a baseline of 2018 (aligned to the End TB Strategy, but with baseline and target years that correspond to the GPW)

BOX 2.5
FIND. TREAT. ALL: a joint initiative to scale up the global response towards universal access to TB prevention and care, 2018–2022

Following the first global ministerial conference on TB in 2017 and in the advance of the UN high-level meeting on TB in 2018, WHO, the Stop TB Partnership, and The Global Fund to Fight AIDS, Tuberculosis and Malaria have launched a joint initiative to scale up the End TB response towards universal access to TB prevention and care. The initiative is for the five-year period 2018–2022.

The initiative includes a target to diagnose, treat and report 40 million people with TB, including 3.5 million children and 1.5 million people with drug-resistant-TB, between 2018 and 2022.

Achieving the targets will require the efforts of many stakeholders, including country leaders, government ministries, civil society and TB-affected communities, the private sector and global agencies. Global, regional and national responses will need to be transformed in terms of commitments, actions to accelerate access to prevention and care, and measurement of progress.

The initiative encompasses all countries, with priority given to the 30 high TB burden countries. It has become a flagship initiative at WHO.
With 2015 marking the end of the MDGs and a new era of SDGs, as well as the last year of the Stop TB Strategy before its replacement with the End TB Strategy, it was an ideal time to revisit these three HBC lists.

Following a wide consultation process, in 2015 WHO defined three HBC lists for the period 2016–2020: one for TB, one for MDR-TB and one for TB/HIV (Fig. 2.5, Table 2.4). Each list contains 30 countries (Table 2.4). These are defined as the top 20 countries in terms of the absolute number of estimated incident cases, plus the additional 10 countries with the most severe burden in terms of incidence rates per capita that do not already appear in the top 20 and that meet a minimum threshold in terms of their absolute numbers of incident cases (10 000 per year for TB, and 1000 per year for TB/HIV and MDR-TB). The lists were defined using the latest estimates of TB disease burden available in October 2015. Each list accounts for about 90% of the global burden, with most of this accounted for by the top 20 countries in each list.

There is overlap among the three lists, but 48 countries appear in at least one list. The 14 countries that are in all three lists (shown in the central diamond in Fig. 2.5) are Angola, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand and Zimbabwe.

The 30 high TB burden countries are given particular attention in the main body of this report. Where estimates of disease burden and assessment of progress in the response are for TB/HIV and MDR-TB specifically, the countries in the TB/HIV and MDR-TB lists, respectively, are given particular attention. Annex 2 contains a two-page profile for each of the 30 high TB burden countries; the annex has a clear demarcation between the 20 countries included on the basis of absolute numbers of incident cases and the 10 additional countries included on the basis of the incidence rate per capita. Country profiles for all countries (with the same content as those presented in Annex 2) are also available online.4

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2 As explained in the last row of Table 2.4, the three lists have a lifetime of 5 years, and the countries included in each list and the criteria used to define each list will be reviewed in June 2020.

3 These 14 countries accounted for 64% of the estimated global number of incident TB cases in 2017.

4 See: www.who.int/tb/data
### TABLE 2.4
The three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020

<table>
<thead>
<tr>
<th>LIST</th>
<th>THE 30 HIGH TB BURDEN COUNTRIES</th>
<th>THE 30 HIGH TB/HIV BURDEN COUNTRIES</th>
<th>THE 30 HIGH MDR-TB BURDEN COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose and target audience</td>
<td>To provide a focus for global action on TB in the countries where progress is most needed to achieve End TB Strategy and SDG targets and milestones, to help build and sustain national political commitment and funding in the countries with the highest burden in terms of absolute numbers or severity, and to promote global monitoring of progress in a well-defined set of countries.</td>
<td>To provide a focus for global action on HIV-associated TB in the countries where progress is most needed to achieve End TB Strategy, UNAIDS and SDG targets and milestones, to help build and sustain national political commitment and funding in the countries with the highest burden in terms of absolute numbers or severity, and to promote global monitoring of progress in a well-defined set of countries.</td>
<td>To provide a focus for global action on the MDR-TB crisis in the countries where progress is most needed to achieve End TB Strategy targets and milestones, to help build and sustain national political commitment and funding in the countries with the highest burden in terms of absolute numbers or severity, and to promote global monitoring of progress in a well-defined set of countries.</td>
</tr>
<tr>
<td>Definition</td>
<td>The 20 countries with the highest estimated numbers of incident TB cases, plus the top 10 countries with the highest estimated TB incidence rate that are not in the top 20 by absolute number (threshold, &gt;10,000 estimated incident TB cases per year).</td>
<td>The 20 countries with the highest estimated numbers of incident TB cases among people living with HIV, plus the top 10 countries with the highest estimated TB/HIV incidence rate that are not in the top 20 by absolute number (threshold, &gt;1000 estimated incident TB/HIV cases per year).</td>
<td>The 20 countries with the highest estimated numbers of incident MDR-TB cases, plus the top 10 countries with the highest estimated MDR-TB incidence rate that are not in the top 20 by absolute number (threshold, &gt;1000 estimated incident MDR-TB cases per year).</td>
</tr>
<tr>
<td>Countries in the list</td>
<td>The top 20 by estimated absolute number (in alphabetical order): Angola Bangladesh Brazil China DPR Korea DR Congo Ethiopia India Indonesia Kenya Mozambique Myanmar Nigeria Pakistan Philippines Russian Federation South Africa Thailand UR Tanzania Viet Nam</td>
<td>The additional 10 by estimated incidence rate per 100,000 population and with a minimum number of 10,000 cases per year (in alphabetical order): Cambodia Central African Republic Congo Lesotho Liberia Namibia Papua New Guinea Sierra Leone Zambia Zimbabwe</td>
<td>The additional 10 by estimated incidence rate per 100,000 population and with a minimum number of 1000 cases per year (in alphabetical order): Botswana Central African Republic Chad Congo Eswatini Ghana Guinea-Bissau Liberia Namibia Papua New Guinea</td>
</tr>
<tr>
<td>Share of global incidence in 2017 (%)</td>
<td>84%</td>
<td>2.9%</td>
<td>83%</td>
</tr>
<tr>
<td>Lifetime of list</td>
<td>5 years (review criteria and included countries in June 2020).</td>
<td>5 years (review criteria and included countries in June 2020).</td>
<td>5 years (review criteria and included countries in June 2020).</td>
</tr>
</tbody>
</table>
Transporting chest X-ray equipment during the 2016 national TB prevalence survey of the Philippines

Raldy Benavente / FACE Inc (Philippines)
Chapter 3. TB disease burden

**KEY FACTS AND MESSAGES**

Worldwide, tuberculosis (TB) is one of the top 10 causes of death, and the leading cause from a single infectious agent (above HIV/AIDS); millions of people continue to fall sick with the disease each year.

In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people, and there were an additional 300 000 deaths from TB (range, 266 000–335 000) among HIV-positive people. There were an estimated 10.0 million new cases of TB (range, 9.0–11.1 million), equivalent to 133 cases (range, 120–148) per 100 000 population.

TB affects all countries and all age groups, but overall the best estimates for 2017 were that 90% of cases were adults (aged ≥15 years), 64% were male, 9% were people living with HIV (72% of them in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Only 6% of cases were in the WHO European Region and the WHO Region of the Americas, each of which had 3% of cases.

The severity of national epidemics varies widely. In 2017, there were under 10 new cases per 100 000 population in most high-income countries, 150–400 in most of the 30 high TB burden countries, and above 500 in a few countries including Mozambique, the Philippines and South Africa.

Globally in 2017, there were an estimated 558 000 new cases (range, 483 000–639 000) of rifampicin-resistant TB (RR-TB), of which almost half were in three countries: India (24%), China (13%) and the Russian Federation (10%). Among RR-TB cases, an estimated 82% had multidrug-resistant TB (MDR-TB).

Globally, 3.5% of new TB cases and 18% of previously treated cases had MDR/RR-TB, with the highest proportions (>50% in previously treated cases) in countries of the former Soviet Union.

Globally, the absolute number of deaths from TB among HIV-negative people has been estimated to have fallen by 29% since 2000, from 534 000 in 2000 to 300 000 in 2017, and by 20% since 2015.

The TB mortality rate (TB deaths among HIV-negative people per 100 000 population per year) is falling at about 3% per year, and the best estimate for the overall reduction during 2000–2017 is 42%. The fastest regional declines in mortality rates in the 5-year period 2013–2017 were in the WHO European Region and WHO South-East Asia Region (11% and 4% per year, respectively).

Worldwide, TB incidence (new cases per 100 000 population per year) is falling at about 2% per year. The fastest regional declines from 2013 to 2017 were in the WHO European Region (5% per year) and WHO African Region (4% per year). In the same 5 years, particularly impressive reductions (4–8% per year) occurred in southern Africa (e.g. Eswatini [formerly Swaziland], Lesotho, Namibia, South Africa, Zambia, Zimbabwe) following a peak in the HIV epidemic, and the expansion of TB and HIV prevention and care, and in the Russian Federation (5% per year) following intensified efforts to reduce the burden of TB.

In 2017, the best estimate of the proportion of people with TB who died from the disease (the case fatality ratio, CFR) was 16%, down from 23% in 2000. The CFR needs to fall to 10% by 2020 to reach the first milestones of the End TB Strategy. There is considerable country variation in the CFR, from under 5% in a few countries to more than 20% in most countries in the WHO African Region, demonstrating large inequalities among countries in access to TB diagnosis and treatment.

National notification and vital registration systems need to be strengthened towards the goal of direct measurement of TB incidence and mortality in all countries. National TB prevalence surveys provide an interim approach to directly measuring the burden of TB disease in an important subset of high TB burden countries; 25 surveys were completed between 2007 and the end of 2017.

*When an HIV-positive person dies from TB disease, the underlying cause is classified as HIV in the international classification of diseases system (ICD-10).*
The burden of tuberculosis (TB) disease can be measured in terms of:
- **incidence** – the number of new and relapse cases of TB arising in a given time period, usually 1 year;
- **prevalence** – the number of cases of TB at a given point in time; and
- **mortality** – the number of deaths caused by TB in a given time period, usually 1 year.

Global targets and milestones for reductions in the burden of TB disease have been set as part of the Sustainable Development Goals (SDGs) and WHO’s End TB Strategy (Chapter 2). SDG 3 includes a target to end the global TB epidemic by 2030, with TB incidence (new and relapse cases per 100,000 population per year) defined as the indicator for measurement of progress. The 2030 targets set in the End TB Strategy are a 90% reduction in TB deaths and an 80% reduction in TB incidence, compared with levels in 2015. Targets for 2035 and milestones for 2020 and 2025 have also been defined (Table 3.1).

### TABLE 3.1
**Targets for percentage reductions in TB disease burden set in WHO’s End TB Strategy**

<table>
<thead>
<tr>
<th>INDICATORS</th>
<th>MILESTONES</th>
<th>TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in the absolute number of TB deaths per year (compared with 2015 baseline)</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>Percentage reduction in the TB incidence rate (new and relapse cases per 100,000 population per year) (compared with 2015 baseline)</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

This chapter has five major sections. Section 3.1 and Section 3.2 present the latest WHO estimates of TB incidence and mortality between 2000 and 2017, and highlight sources of data and actions needed to improve measurement of TB incidence and mortality. Section 3.3 focuses on the burden of drug-resistant TB, including progress in global surveillance of resistance to anti-TB drugs, and estimates of the incidence of multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB). Section 3.4 discusses national TB prevalence surveys. TB prevalence is not an indicator for which a global target has been set during the period 2016–2035. Nevertheless, in many countries, national TB prevalence surveys still provide the best method for estimating the burden of TB disease (including by age and sex) and for planning actions needed to reduce that burden. In addition, results from national TB prevalence surveys can inform estimates of TB incidence and mortality, and thus contribute to monitoring of progress towards SDG and End TB Strategy targets. Finally, Section 3.5 covers estimates of TB incidence and mortality, disaggregated by age and sex. This is in line with the increasing emphasis on the importance of within-country disaggregation of key indicators in the SDGs and the End TB Strategy (Chapter 2).

WHO updates its estimates of the burden of TB disease annually, using the latest available data and analytical methods. Since 2006, concerted efforts have been made to improve the available data and methods used, under the umbrella of the WHO Global Task Force on TB Impact Measurement (Box 3.1). A summary of the main updates to available data and methods since the 2017 global TB report is provided in Box 3.2. To put these updates in a broader context, comparisons of the annual updates made by WHO for TB are compared with those for HIV and malaria, as well as with estimates for TB that are updated annually by the Institute of Health Metrics and Evaluation (IHME) at the University of Washington, United States of America (USA), in Box 3.3.

#### 3.1 TB incidence

**3.1.1 Methods to estimate TB incidence**

TB incidence has never been measured at national level because this would require long-term studies among large cohorts (hundreds of thousands) of people, which would involve high costs and challenging logistics. However, notifications of TB cases provide a good proxy indication of TB incidence in countries that have high-performance surveillance systems (e.g. with little underreporting of diagnosed cases), and in which the quality of and access to health care means that few cases are not diagnosed.

The ultimate goal is to directly measure TB incidence from TB notifications in all countries. This requires a combination of strengthened surveillance, better quantification of underreporting (i.e. the number of cases that are missed by surveillance systems) and universal health coverage. A TB surveillance checklist developed by the WHO Global Task Force on TB Impact Measurement (Box 3.1) defines the standards that need to be met for

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2. This is in contrast to the period covered by the Stop TB Strategy (2006–2015), when the target was to halve prevalence by 2015 compared with a baseline of 1990.
3. The online technical appendix is available at www.who.int/tb/data.
4. The updates can affect the entire time series back to 2000. Therefore, estimates presented in this chapter for 2000–2016 supersede those of previous reports, and direct comparisons (e.g. between the 2016 estimates in this report and the 2016 estimates in the previous report) are not appropriate.
5. Inventory studies can be used to measure the number of cases that are diagnosed but not reported. For a guide to inventory studies, see World Health Organization. Assessing tuberculosis underreporting through inventory studies. Geneva: WHO; 2012 (http://www.who.int/tb/publications/inventory_studies/en/, accessed 15 August 2018).
The WHO Global Task Force on TB Impact Measurement

Establishment and progress made, 2006–2015

The WHO Global Task Force on TB Impact Measurement (hereafter referred to as the Task Force) was established in 2006 and is convened by the TB Monitoring and Evaluation unit of WHO’s Global TB Programme. Its original aim was to ensure that WHO’s assessment of whether 2015 targets set in the context of the Millennium Development Goals (MDGs) were achieved at global, regional and country levels was as rigorous, robust and consensus-based as possible. Three strategic areas of work were pursued:

- strengthening routine surveillance of TB cases (via national notification systems) and deaths (via national VR systems) in all countries;
- undertaking national TB prevalence surveys in 22 global focus countries; and
- periodically reviewing methods used to produce TB disease burden estimates.

Work on strengthened surveillance included the following:

- Development of a TB surveillance checklist of standards and benchmarks (with 10 core and three supplementary standards). This checklist can be used to systematically assess the extent to which a surveillance system meets the standards required for notification and VR data to provide a direct measurement of TB incidence and mortality, respectively. By the end of 2015, 38 countries including 16 high TB burden countries had used the checklist. The global status of progress in using the checklist by August 2018 is shown in Fig. 3.1.

- Electronic recording and reporting. Case-based electronic databases are the reference standard for recording and reporting TB surveillance data. A guide was produced in 2011, and efforts to introduce such systems were supported. The global status of progress in case-based electronic surveillance for TB by August 2018 is highlighted in Chapter 4.

- Development of a guide on inventory studies to measure underreporting of detected TB cases, and support such studies in priority countries. An inventory study can be used to quantify the number of cases that are detected but not reported to national surveillance systems, and can serve as a basis for improving estimates of TB incidence and addressing gaps in reporting. The global status of progress in implementation of inventory studies by August 2018 is shown in Fig. 3.1. An excellent recent example of a national inventory study, in Indonesia, is profiled in Chapter 4.

- Expanded use of data from VR systems and mortality surveys to produce estimates of the number of TB deaths, and contributions to wider efforts to promote VR systems. By 2015, VR data were used to produce estimates of TB mortality in 127 countries, up from three in 2008.

There was substantial success in the implementation of national TB prevalence surveys in the period 2007–2015, which has continued. Between 2007 and the end of 2015, a total of 23 countries completed a survey and a further two had done so by the end of 2017; this included 18 of the 22 global focus countries. A Task Force subgroup undertook a major review and update of methods between June 2008 and October 2009. A second thorough and comprehensive review was undertaken in 2015, with consensus reached on methods to be used for the 2015 targets assessment published in WHO’s 2015 global TB report.

Updated strategic areas of work, 2016–2020

In the context of a new era of SDGs and WHO’s End TB Strategy, the Task Force met in April 2016 to review and reshape its mandate and strategic areas of work for the post-2015 era. An updated mandate and five strategic areas of work for the period 2016–2020 were agreed.

The mandate was defined as follows:

- To ensure that assessments of progress towards End TB Strategy and SDG targets and milestones at global, regional and country levels are as rigorous, robust and consensus-based as possible.
- To guide, promote and support the analysis and use of TB data for policy, planning and programmatic action.

The five strategic areas of work are as follows:

1. Strengthening national notification systems for direct measurement of TB cases, including drug-resistant TB and HIV-associated TB specifically.
2. Strengthening national VR systems for direct measurement of TB deaths.
3. Priority studies to periodically measure TB disease burden, including:
   a. national TB prevalence surveys
   b. drug-resistance surveys
   c. mortality surveys
   d. surveys of costs faced by TB patients and their households.
4. Periodic review of methods used by WHO to estimate the burden of TB disease and latent TB infection.
5. Analysis and use of TB data at country level, including:
   a. disaggregated analyses (e.g. by age, sex and location) to assess inequalities and equity;
   b. projections of disease burden; and
   c. guidance, tools and capacity-building.

The SDG and End TB Strategy targets and milestones referred to in the mandate are the targets (2030, 2035) and milestones (2020, 2025) set for the three high-level indicators; that is, TB incidence, the number of TB deaths and the percentage of TB-affected households that face catastrophic costs as a result of TB disease (Chapter 2).

Strategic areas of work 1–3 are focused on direct measurement of TB disease burden (epidemiological and, in the case of cost surveys, economic). The underlying principle for the Task Force’s work since 2006 has been that estimates of the level of and trends in disease burden should be based on direct measurements from routine surveillance and surveys as much as possible (as opposed to indirect estimates based on modelling and expert opinion). However, strategic area of work 4 remains necessary because indirect estimates...
will be required until all countries have the surveillance systems or the periodic studies required to provide direct measurements. Strategic area of work 5 recognizes the importance of analysing and using TB data at country level (as well as generating data, as in strategic areas of work 1–3), including the disaggregated analyses that are now given much greater attention in the SDGs and End TB Strategy.

In the years up to 2020, the top priorities for the Task Force are strengthening of national notification and VR systems as the basis for direct measurement of TB incidence and TB mortality.

Further details about the work of the Task Force are available online, an up-to-date summary is provided in the latest brochure about its work.

Notification data to provide a direct measure of TB incidence. By August 2018, a total of 68 countries, including 26 of the 30 high TB burden countries (listed in Table 3.1) had completed the checklist, often in association with a national TB epidemiological review (Fig. 3.1).

Methods currently used by WHO to estimate TB incidence can be grouped into four major categories, as follows (Fig. 3.2):

- **Results from TB prevalence surveys.** Incidence is estimated using prevalence survey results and estimates of the duration of disease, with the latter derived from a model that accounts for the impact of HIV co-infection and antiretroviral therapy (ART) on the distribution of disease duration. This method is used for 22 countries, of which 22 have national survey data and one – India – has a survey in one state. The 23 countries accounted for 60% of the estimated global number of incident cases in 2017.

- **Notifications adjusted by a standard factor to account for underreporting, over-diagnosis and under-diagnosis.** This method is used for 144 countries that are all high-income countries except the Netherlands and the United Kingdom, plus selected middle-income countries with low levels of underreporting, including Brazil, China and the Russian Federation. For three countries (France, Republic of Korea and Turkey) the adjustment was country specific, based on results from studies of underreporting. These 144 countries accounted for 15% of the estimated global number of incident cases in 2017.

- **Results from national inventory studies that measured the level of underreporting of detected TB cases combined with capture–recapture analysis.** This method is used for six countries: Egypt, Indonesia (yielding best estimates that are lower but statistically consistent with those previously derived from the 2013–2014 national TB prevalence survey), Iraq, the Netherlands, the United Kingdom and Yemen. These countries accounted for 9% of the estimated global number of incident cases in 2017.

- **Case notification data combined with expert opinion about case-detection gaps.** Expert opinion, elicited through regional workshops or country missions, is used to estimate levels of underreporting, over-diagnosis and under-diagnosis. Trends are estimated through mortality data, surveys of the annual risk of infection or exponential interpolation using estimates of case-detection gaps for 3 years. In this report, this

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2. Estimation of prevalence from incidence is not straightforward. For example, it requires assumptions about the duration of disease for different categories of case, and since prevalence surveys focus on bacteriologically confirmed TB in adults, adjustments to include children and extrapulmonary TB are needed.
3. The national inventory study implemented in Indonesia in 2017 is the largest of its kind to date. Further details are provided in Box 3.2 and in Chapter 4, Box 4.4.
4. Capture-recapture modelling is possible if six assumptions are met: (i) all cases should be observable; (ii) the proportion of mismatches and matching failures in record-linkage is low, which typically requires a large sampling fraction; (iii) a closed population during the study period (typically 3–6 months); (iv) if S represents the number of case lists or data sources available, then at least three data sources should be available (S≥3) and their dependencies must be accounted for in the model design, while the full S-way interaction between sources is assumed null; (v) homogeneity of within-source observation probabilities across subpopulation groups, such as those defined by socioeconomic and demographic characteristics; (vi) consistent case definitions across data sources. Few high TB burden countries are expected to be able to implement inventory studies that will meet these 6 assumptions to a sufficient degree.
Box 3.2
Updates to estimates of TB disease burden in this report and anticipated updates

Updates in this report

1. Indonesia
Indonesia conducted a national inventory study to measure the underreporting of detected TB cases in the first quarter of 2017. Capture–recapture modelling based on three separate lists was then used to update incidence estimates, using methods set out in WHO guidance on inventory studies. The updated incidence estimates are consistent with those previously derived from the results of the national TB prevalence survey implemented in 2013–2014, but the best estimates are lower (about 15%) and also more precise (i.e. with narrower uncertainty intervals). Details are provided in Box 4.4 in Chapter 4.

Estimates of TB mortality in Indonesia are based on those published by the Institute of Health Metrics and Evaluation (IHME), University of Washington, USA (see below).

2. South Africa
Trends in TB incidence in South Africa have been revised for two major reasons. First, there is now a clear, consistent and sustained downward trend in TB case notifications, which is also evident in other countries of southern Africa and which can be explained by the high coverage of ART among people living with HIV (for further details, see Box 3.4). Second, the values of the ratio of notified to incident cases based on previously published trends, following further declines in notifications, are now implausible. For recent years, the revised estimates of TB incidence are lower than those previously published (e.g. the estimate for 2016 in this report is 21% lower than the estimate for 2016 published last year).

TB incidence will be reassessed when the results from the national TB prevalence survey 2018–2019 become available. Estimates of TB mortality in South Africa are based on those published by IHME (see next section).

3. Newly reported data and updated estimates from other agencies
New VR data were reported to WHO between mid-2017 and mid-2018. Several countries reported historical data that were previously missing, or made corrections to previously reported data. In total, 1949 country-year data points were retained for analysis. Updated estimates of HIV prevalence and mortality were obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS) in July 2018. (In most instances, any resulting changes to TB burden estimates were well within the uncertainty intervals of previously published estimates, and trends were generally consistent.

In 19 countries (shown in Fig. 3.10), estimates of TB mortality (HIV-negative) were based on estimates published by IHME. These estimates use data from national and sample VR systems, and verbal autopsy surveys. Estimates of TB mortality in South Africa are adjusted by IHME for miscoding of deaths caused by HIV and TB. IHME estimates used in this report were slightly adjusted from those published by IHME to fit WHO estimates of the total number of deaths (mortality envelope). The median country-year envelope ratio (WHO/IHME) was 1.01 (interquartile range: 0.92–1.09) among 319 data points.

4. Findings from national TB epidemiological reviews
Small adjustments to incidence trajectories were made for Belarus, Malawi, Thailand and Turkmenistan, based on findings from recent national TB epidemiological reviews.

5. Drug-resistant TB
The estimated incidence of rifampicin-resistant TB in 2017 is based on the following formula:

\[ I_r = \frac{I}{(1 - f_p)(1 - r) + r_p) + f_p} \]

where \( I \) is overall TB incidence, \( f_p \) is the incidence of rifampicin resistance, \( f \) is the cumulative risk for incident cases to receive a non-relapse retreatment (following failure or return after default), \( r \) is the proportion of relapses, \( r_p \) is the relative risk ratio in relapses compared with first episodes of TB, and \( p \) and \( p_r \) denote the proportion of rifampicin-resistant cases among previously untreated and previously treated patients, respectively.

Routine surveillance data for 2017 on levels of drug resistance were reported by 91 countries with continuous surveillance systems (i.e. routine diagnostic testing for drug resistance). New data from national surveys became available from seven countries since the publication of the 2017 global TB report: Eritrea, Eswatini, Indonesia, Lao People’s Democratic Republic, Sri Lanka, Togo and the United Republic of Tanzania.

Updates anticipated in the near future
Updates to estimates of disease burden are expected towards the end of 2018 or in 2019 for Eswatini, Mozambique, Myanmar Namibia, Nepal, South Africa and Viet Nam, following the completion of national TB prevalence surveys. Estimates of TB burden in India will be updated once results from a national TB prevalence survey planned for 2018–2019 become available.

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* http://aidsinfo.unaids.org

**BOX 3.3**

**WHO estimates for TB disease burden in the context of other estimates**

The latest global estimates published by WHO and IHME are similar. For example, the best estimate for TB incidence in 2016 in this report is 10.1 million (range, 9.0–11.1 million), whereas the most recent best estimate from IHME is 10.4 million.

The best estimate of the number of TB deaths among HIV-negative people in 2016 in this report is 1.3 million (range, 1.2–1.4 million), whereas the best estimate from IHME is 1.2 million. There is general consistency in mortality estimates in countries with VR systems and standard coding of causes of deaths of good quality, and in incidence estimates in countries with strong health-care and notification systems. Discrepancies are most apparent for countries where the underlying data are weaker, due to differences in the indirect estimation methods that are used.

When annual updates for TB are published by both WHO and IHME, entire time series (starting in 2000 for WHO, and 1990 for IHME) are updated. New information or refinements to methods used to produce estimates can result in changes to the estimates published for earlier years in previous publications. This is a normal part of disease burden estimation, and also occurs with disease burden estimates published for other diseases, such as HIV and malaria. For example, global estimates for 2015 for HIV, malaria and TB published by WHO, UNAIDS and IHME in consecutive years (2015 and 2016) by the same agency have been within about 2–8% of each other. Global estimates of TB disease burden in 2015 published by WHO in this and the previous two global TB reports are within 4–5% of each other.

Country-specific estimates of TB disease burden published by WHO are generally consistent from year to year. In WHO reports published in 2014–2017, updates that have been apparent at global level have been due to updates for three countries: Nigeria (2014 report, following results from the country’s first national TB prevalence survey in 2012); Indonesia (2015 report, following completion of a national TB prevalence survey in 2013–2014); and India (2016 report, following accumulating evidence from both survey and surveillance data).

As the availability and quality of data continue to improve, variability for the same year in consecutive reports will decrease and estimates published by WHO should converge with those published by other agencies. Ideally, estimates of TB incidence and mortality are based on national notification and vital registration systems that meet quality and coverage standards.

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3.1.2  Estimates of TB incidence in 2017

Globally in 2017, there were an estimated 10.0 million incident cases of TB (range, 9.0–11.1 million), equivalent to 133 cases (range, 120–148) per 100,000 population. Estimates of absolute numbers are shown in Table 3.2 and estimates of rates per capita are shown in Table 3.3.

Most of the estimated number of cases in 2017 occurred in the WHO South-East Asia Region (44%), the WHO African Region (25%) and the WHO Western Pacific Region (18%); smaller proportions of cases occurred in the WHO Eastern Mediterranean Region (7.7%), the WHO Region of the Americas (2.8%) and the WHO European Region (2.7%).

The 30 high TB burden countries accounted for 87% of all estimated incident cases worldwide, and eight of these countries accounted for two thirds of the global total: India (27%), China (9%), Indonesia (8%), and

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1 The online technical appendix is available at www.who.int/tb/data.
FIG. 3.1
Strengthening national TB surveillance (status in August 2018)

Countries in which a national TB epidemiological review has been undertaken since July 2012

Countries in which a checklist of standards and benchmarks has been completed since January 2013

Countries in which national inventory studies of the underreporting of detected TB cases have been implemented since 2000
### TABLE 3.2
Estimated epidemiological burden of TB in 2017 for 30 high TB burden countries, WHO regions and globally. Number in thousands.*

<table>
<thead>
<tr>
<th>High TB burden countries</th>
<th>POPULATION</th>
<th>HIV-NEGATIVE TB MORTALITY</th>
<th>HIV-POSITIVE TB MORTALITY</th>
<th>TOTAL TB INCIDENCE</th>
<th>HIV-POSITIVE TB INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST</td>
<td>INTERVAL</td>
<td>BEST</td>
<td>INTERVAL</td>
<td>BEST</td>
</tr>
<tr>
<td>Angola</td>
<td>30 000</td>
<td>20</td>
<td>12–31</td>
<td>7.8</td>
<td>3.9–13</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>165 000</td>
<td>59</td>
<td>38–85</td>
<td>0.17</td>
<td>0.09–0.29</td>
</tr>
<tr>
<td>Brazil</td>
<td>209 000</td>
<td>51</td>
<td>4.8–5.3</td>
<td>1.9</td>
<td>1.4–2.5</td>
</tr>
<tr>
<td>Cambodia</td>
<td>16 000</td>
<td>3.1</td>
<td>2.0–4.3</td>
<td>0.41</td>
<td>0.27–0.57</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>5 000</td>
<td>3.2</td>
<td>1.8–4.9</td>
<td>2.7</td>
<td>1.4–4.4</td>
</tr>
<tr>
<td>China</td>
<td>1 410 000</td>
<td>37</td>
<td>33–41</td>
<td>1.8</td>
<td>0.84–3.1</td>
</tr>
<tr>
<td>Congo</td>
<td>5 000</td>
<td>3.3</td>
<td>1.9–5.2</td>
<td>2.3</td>
<td>1.2–3.7</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>25 000</td>
<td>16</td>
<td>11–22</td>
<td>0.04</td>
<td>0.02–0.07</td>
</tr>
<tr>
<td>DR Congo</td>
<td>81 000</td>
<td>49</td>
<td>29–74</td>
<td>7.5</td>
<td>3.5–13</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>105 000</td>
<td>25</td>
<td>16–37</td>
<td>3.6</td>
<td>2.5–5.0</td>
</tr>
<tr>
<td>India*</td>
<td>1 340 000</td>
<td>410</td>
<td>381–441</td>
<td>11</td>
<td>6.5–16</td>
</tr>
<tr>
<td>Indonesia</td>
<td>264 000</td>
<td>107</td>
<td>100–114</td>
<td>9.4</td>
<td>5.0–15</td>
</tr>
<tr>
<td>Lesotho</td>
<td>2 000</td>
<td>1.0</td>
<td>0.55–1.7</td>
<td>4.6</td>
<td>2.9–6.7</td>
</tr>
<tr>
<td>Liberia</td>
<td>5 000</td>
<td>2.7</td>
<td>1.6–4.1</td>
<td>0.91</td>
<td>0.57–1.3</td>
</tr>
<tr>
<td>Mozambique*</td>
<td>30 000</td>
<td>22</td>
<td>13–33</td>
<td>27</td>
<td>17–39</td>
</tr>
<tr>
<td>Myanmar*</td>
<td>53 000</td>
<td>27</td>
<td>18–39</td>
<td>4.9</td>
<td>3.5–6.6</td>
</tr>
<tr>
<td>Namibia*</td>
<td>3 000</td>
<td>0.75</td>
<td>0.48–1.1</td>
<td>0.80</td>
<td>0.55–1.1</td>
</tr>
<tr>
<td>Nigeria</td>
<td>191 000</td>
<td>120</td>
<td>70–183</td>
<td>35</td>
<td>21–52</td>
</tr>
<tr>
<td>Pakistan</td>
<td>197 000</td>
<td>54</td>
<td>42–67</td>
<td>2.2</td>
<td>1.1–3.8</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>8 000</td>
<td>4.3</td>
<td>2.9–6.0</td>
<td>0.93</td>
<td>0.51–1.5</td>
</tr>
<tr>
<td>Philippines</td>
<td>105 000</td>
<td>26</td>
<td>23–31</td>
<td>0.38</td>
<td>&lt;0.01–3.3</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>144 000</td>
<td>10</td>
<td>9.4–12</td>
<td>1.7</td>
<td>0.85–2.8</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>8 000</td>
<td>3.0</td>
<td>1.8–4.5</td>
<td>0.78</td>
<td>0.49–1.1</td>
</tr>
<tr>
<td>South Africa*</td>
<td>57 000</td>
<td>22</td>
<td>20–24</td>
<td>56</td>
<td>39–77</td>
</tr>
<tr>
<td>Thailand</td>
<td>69 000</td>
<td>9.3</td>
<td>7.0–12</td>
<td>2.9</td>
<td>2.1–3.8</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>57 000</td>
<td>27</td>
<td>12–48</td>
<td>22</td>
<td>10–38</td>
</tr>
<tr>
<td>Viet Nam*</td>
<td>96 000</td>
<td>12</td>
<td>7.5–17</td>
<td>0.84</td>
<td>0.61–1.1</td>
</tr>
<tr>
<td>Zambia</td>
<td>17 000</td>
<td>5.0</td>
<td>2.9–7.7</td>
<td>13</td>
<td>8.2–19</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>17 000</td>
<td>2.0</td>
<td>1.3–2.9</td>
<td>6.3</td>
<td>4.5–8.5</td>
</tr>
<tr>
<td><strong>High TB burden countries</strong></td>
<td><strong>4 760 000</strong></td>
<td><strong>1 110</strong></td>
<td><strong>1 030–1 190</strong></td>
<td><strong>247</strong></td>
<td><strong>214–282</strong></td>
</tr>
</tbody>
</table>

* Numbers shown to two significant figures if under 100 and to three significant figures otherwise.  
* Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.  
* Estimates of TB incidence and mortality for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.  
* Estimates of TB incidence and mortality for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
### TABLE 3.3
Estimated epidemiological burden of TB in 2017 for 30 high TB burden countries, WHO regions and globally. Rates per 100 000 population.

<table>
<thead>
<tr>
<th></th>
<th>HIV-NEGATIVE TB MORTALITY</th>
<th>HIV-POSITIVE TB MORTALITY</th>
<th>TOTAL TB INCIDENCE</th>
<th>HIV PREVALENCE IN INCIDENT TB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>36</td>
<td>23–52</td>
<td>0.11</td>
<td>0.05–0.18</td>
</tr>
<tr>
<td>Brazil</td>
<td>2.4</td>
<td>2.3–2.5</td>
<td>0.91</td>
<td>0.67–1.2</td>
</tr>
<tr>
<td>Cambodia</td>
<td>19</td>
<td>13–27</td>
<td>2.6</td>
<td>1.7–3.6</td>
</tr>
<tr>
<td>China</td>
<td>2.6</td>
<td>2.4–2.9</td>
<td>0.13</td>
<td>0.08–0.22</td>
</tr>
<tr>
<td>Congo</td>
<td>63</td>
<td>36–98</td>
<td>43</td>
<td>22–71</td>
</tr>
<tr>
<td>DR Congo</td>
<td>63</td>
<td>43–86</td>
<td>0.17</td>
<td>0.09–0.28</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>24</td>
<td>15–35</td>
<td>3.5</td>
<td>2.4–4.8</td>
</tr>
<tr>
<td>Indiaa</td>
<td>31</td>
<td>28–33</td>
<td>0.79</td>
<td>0.48–1.2</td>
</tr>
<tr>
<td>Indonesia</td>
<td>40</td>
<td>38–43</td>
<td>3.6</td>
<td>1.9–5.8</td>
</tr>
<tr>
<td>Liberia</td>
<td>57</td>
<td>34–86</td>
<td>19</td>
<td>12–28</td>
</tr>
<tr>
<td>Myanmarc</td>
<td>51</td>
<td>33–73</td>
<td>9.2</td>
<td>6.6–12</td>
</tr>
<tr>
<td>Namibia</td>
<td>30</td>
<td>19–43</td>
<td>31</td>
<td>22–43</td>
</tr>
<tr>
<td>Nigeria</td>
<td>63</td>
<td>36–96</td>
<td>18</td>
<td>11–27</td>
</tr>
<tr>
<td>Pakistan</td>
<td>27</td>
<td>21–34</td>
<td>1.1</td>
<td>0.56–1.9</td>
</tr>
<tr>
<td>Philippines</td>
<td>25</td>
<td>22–29</td>
<td>0.36</td>
<td>&lt;0.01–3.1</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>7.3</td>
<td>6.6–8.0</td>
<td>1.2</td>
<td>0.59–1.9</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>39</td>
<td>23–59</td>
<td>10</td>
<td>6.5–15</td>
</tr>
<tr>
<td>South Africac</td>
<td>39</td>
<td>35–43</td>
<td>99</td>
<td>68–135</td>
</tr>
<tr>
<td>Thailand</td>
<td>13</td>
<td>10–17</td>
<td>4.2</td>
<td>3.1–5.6</td>
</tr>
<tr>
<td>Viet Namc</td>
<td>12</td>
<td>7.8–17</td>
<td>0.88</td>
<td>0.64–1.2</td>
</tr>
<tr>
<td>Zambia</td>
<td>30</td>
<td>17–45</td>
<td>76</td>
<td>48–110</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>12</td>
<td>7.7–17</td>
<td>38</td>
<td>27–51</td>
</tr>
<tr>
<td><strong>High TB burden countries</strong></td>
<td><strong>23</strong></td>
<td><strong>22–25</strong></td>
<td><strong>5.2</strong></td>
<td><strong>4.5–5.9</strong></td>
</tr>
<tr>
<td>The Americas</td>
<td>1.8</td>
<td>1.7–1.9</td>
<td>0.60</td>
<td>0.53–0.67</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>13</td>
<td>11–15</td>
<td>0.43</td>
<td>0.26–0.66</td>
</tr>
<tr>
<td>Europe</td>
<td>2.6</td>
<td>2.5–2.7</td>
<td>0.54</td>
<td>0.41–0.69</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>32</td>
<td>30–35</td>
<td>1.4</td>
<td>1.1–1.8</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>4.9</td>
<td>4.5–5.3</td>
<td>0.26</td>
<td>0.20–0.34</td>
</tr>
<tr>
<td><strong>GLOBAL</strong></td>
<td>17</td>
<td>16–18</td>
<td><strong>4.0</strong></td>
<td><strong>3.5–4.5</strong></td>
</tr>
</tbody>
</table>

a Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.

b Estimates of TB incidence and mortality for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.

c Estimates of TB incidence and mortality for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
FIG. 3.2
Main methods used to estimate TB incidence

- Capture-recapture
- Case notifications, expert opinion
- Case notifications, standard adjustment
- Prevalence survey
- No data
- Not applicable

FIG. 3.3
Estimated TB incidence in 2017, for countries with at least 100 000 incident cases

- South Africa
- Bangladesh
- Nigeria
- Indonesia
- Philippines
- Pakistan
- China
- India
Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%) (Fig. 3.3).

The severity of national TB epidemics in terms of the annual number of incident TB cases relative to population size (the incidence rate) varied widely among countries in 2017. There were under 10 incident cases per 100,000 population in most high-income countries, 150–400 in most of the 30 high TB burden countries (Fig. 3.4), and above 500 in a few countries including the Democratic People’s Republic of Korea, Lesotho, Mozambique, the Philippines and South Africa (Table 3.3).

An estimated 9% (range, 7.9–11%) of the incident TB cases in 2017 were among people living with HIV (Table 3.2, Table 3.3). The proportion of TB cases coinfected with HIV was highest in countries in the WHO African Region, exceeding 50% in parts of southern Africa (Fig. 3.5). The risk of developing TB in the 37 million people living with HIV was 20 times higher than the risk in the rest of the world population (range, 17–23), increasing with a decreasing prevalence of HIV in the general population.

Estimates of the incidence of zoonotic TB are shown in Table 3.4.

3.1.3 Estimated trends in TB incidence, 2000–2017

Consistent with previous global TB reports, the number of incident cases is falling slowly, in both absolute terms and per capita (Fig. 3.6, Fig. 3.7). Globally, the average rate of decline in the TB incidence rate was 1.5% per year in the period 2000–2017, and 1.8% between 2016 and 2017. This needs to accelerate to 4–5% per year by 2020 and to 10% per year by 2025, to achieve the milestones for reductions in cases and deaths set in the End TB Strategy (Chapter 2).

Trends are shown for the six WHO regions in Fig. 3.8 and for the 30 high TB burden countries in Fig. 3.9. The fastest declines in the 5-year period 2013–2017 were in the WHO European Region (on average, 5% per year). In the same period, particularly impressive reductions (4–8% per year) occurred in southern Africa (e.g. Eswatini [formerly Swaziland], Lesotho, Namibia, South Africa, Zambia and Zimbabwe) following a peak in the HIV epidemic and the expansion of TB and HIV prevention and care (Box 3.4), and in the Russian Federation (5% per year) following intensified efforts to reduce the burden of TB and scrutiny of progress from the highest political levels.

3.2 TB mortality

Deaths from TB among HIV-negative people are classified as TB deaths in the most recent version of the International classification of diseases (ICD-10). When

1 Time series of estimates for all countries are available online. Annex 1 explains how to access and download them.
FIG. 3.5
Estimated HIV prevalence in new and relapse TB cases, 2017

TABLE 3.4
Estimated incidence and mortality due to *M. bovis* TB. Best estimates (absolute numbers) are followed by the lower and upper bounds of the 95% uncertainty interval.²

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>INCIDENT CASES</th>
<th>DEATHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
</tr>
<tr>
<td>Africa</td>
<td>70 000</td>
<td>18 800–154 000</td>
</tr>
<tr>
<td>The Americas</td>
<td>821</td>
<td>222–1 800</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>7 660</td>
<td>1 980–17 100</td>
</tr>
<tr>
<td>Europe</td>
<td>1 150</td>
<td>308–2 550</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>44 900</td>
<td>11 500–100 000</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>18 000</td>
<td>4 740–40 000</td>
</tr>
<tr>
<td><strong>GLOBAL</strong></td>
<td><strong>142 000</strong></td>
<td><strong>70 600–239 000</strong></td>
</tr>
</tbody>
</table>

² Numbers shown to two significant figures if under 100 and to three significant figures otherwise.
an HIV-positive person dies from TB, the underlying cause is classified as HIV. For consistency with these international classifications, this section makes a clear distinction between TB deaths in HIV-negative people and TB deaths in HIV-positive people.

### 3.2.1 Methods to estimate TB mortality

TB mortality among HIV-negative people can be measured directly using data from national vital registration (VR) systems, provided that these systems have high coverage and that causes of death are accurately determined and coded according to ICD-10. Sample VR systems covering representative areas of the country (the approach used, for example, in China) provide an interim solution. Mortality surveys can also be used to estimate deaths caused by TB. In 2017, most countries with a high burden of TB lacked national or sample VR systems, and few had conducted mortality surveys. In the absence of VR systems or mortality surveys, TB mortality can be estimated as the product of TB incidence and the case fatality ratio (CFR), or through ecological modelling using mortality data from countries with VR systems.

TB mortality among HIV-positive people is hard to measure, even when VR systems are in place, because deaths among HIV-positive people are coded as HIV deaths, and contributory causes (e.g. TB) are often not reliably assessed and recorded. TB deaths among HIV-positive people were estimated as the product of TB incidence and the CFR, with the latter accounting for the protective effect of ART.

Until 2008, WHO estimates of TB mortality used VR or mortality survey data for only three countries. This was substantially improved to 89 countries in 2009, although most of the data were from countries in the WHO European Region and the WHO Region of the Americas, which accounted for less than 10% of the world's TB cases. For the current report, VR or mortality survey data were used for 127 countries (Fig. 3.10), which collectively
accounted for 57% of the estimated number of TB deaths (among HIV-negative people) globally in 2017. For 19 countries, analyses of VR data and resulting estimates of TB deaths published by the Institute of Health Metrics and Evaluation (IHME) at the University of Washington, USA, were used. The WHO African Region has the greatest need to introduce or strengthen VR systems in which causes of death are classified according to ICD-10.

Details about the methods used to produce estimates of TB mortality are provided in the online technical appendix.²

### 3.2.2 Estimates of TB mortality in 2017

Estimates of the absolute number of deaths caused by TB are shown globally, for the six WHO regions and for the 30 high TB burden countries, in Table 3.2. There were an estimated 1.3 million (range, 1.2–1.4 million) deaths from TB among HIV-negative people in 2017 and an additional 300 000 (range, 266 000–335 000) deaths from TB among HIV-positive people.

TB is the tenth leading cause of death worldwide, and since 2011 it has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS (Fig. 3.11, Fig. 3.12 and Fig. 3.13).³ Most of these deaths could be prevented with early diagnosis and appropriate treatment (Chapter 1). For example, among people whose TB was detected, reported and treated in 2016, the treatment success rate was 82% globally (Chapter 4); and in high-income countries with universal health coverage, the proportion of people who die from TB can be under 5% (Section 3.2.4).

About 82% of TB deaths among HIV-negative people occurred in the WHO African Region and the WHO South-East Asia Region in 2017; these regions accounted for 85% of the combined total of TB deaths in HIV-negative and HIV-positive people. India accounted for 32% of global TB deaths among HIV-negative people, and for 27% of the combined total TB deaths in HIV-negative and HIV-positive people.

Estimates of TB mortality rates (per 100 000 population) are shown globally, for the six WHO regions and for the 30 high TB burden countries, in Table 3.3. Globally, the number of TB deaths among HIV-negative people per 100 000 population was 17 (range, 16–18) in 2017, and 21 (range, 20–22) when TB deaths among HIV-positive people were included. There was considerable variation

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2. The online technical appendix is available at www.who.int/tb/data.
FIG. 3.9

Trends in estimated TB incidence in the 30 high TB burden countries, 2000–2017. TB incidence rates are shown in green and incidence rates of HIV-positive TB are shown in red. Shaded areas represent uncertainty intervals. The black lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.

* Estimates of TB incidence for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.

b Estimates of TB incidence for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
**BOX 3.4**

**Rapid decline in TB incidence in six countries in southern Africa**

In six countries in southern Africa, TB incidence is estimated to have fallen rapidly in the period 2010–2017, with average annual rates of decline of 18% in Eswatini, 10% in Zimbabwe, 8% in Botswana, 7% in Lesotho and South Africa, and 6% in Namibia. Such national rates of decline in TB incidence are among the fastest of recent decades. TB case notifications in all six countries have also declined in this period, at nearly the same average rates. 

Since the 1990s, TB incidence in southern Africa has been strongly driven by the HIV epidemic. In 2017, the estimated proportion of incident TB cases coinfected with HIV ranged from 36% in Namibia to 71% in Lesotho. The prevalence of HIV in the general population has remained relatively stable in all six countries since 2010 (ranging from 8% in Namibia to 17–19% in Eswatini). What has changed is that the coverage of HIV care in the general population and among new TB cases in people living with HIV has improved substantially.

In the general population, ART coverage among people living with HIV rapidly increased in the period 2010–2017, with improvements ranging from 24% to 61% in South Africa and from 30% to 84% in Zimbabwe (Fig. B3.4.1). In four of the six countries, ART coverage was above 80% of estimated prevalent HIV cases in 2017, a remarkable achievement. Trends in ART coverage among new TB cases coinfected with HIV followed similar trends and reached similar levels of coverage by 2017, with the exception of Botswana (34%).

The HIV pandemic has had a major impact on the health of people in southern Africa. HIV drove the annual national incidence of TB in the six featured countries to some of the highest rates ever globally (e.g. to over 1% of the population per year in Eswatini and Lesotho, and 0.9% of the population per year in South Africa in 2010). In 2010, the estimated TB incidence rate ratio (TB incidence among HIV-positive individuals divided by TB incidence in HIV-negative individuals) ranged from 10 in Botswana to 32 in Zimbabwe. Those relative risks nearly halved within 8 years, from 4.7 in Botswana to 18 in Zimbabwe in 2017.

The rapid increase in ART coverage among people living with HIV in all six countries led to a tremendous reduction in TB incidence rates over the past 8 years, confirming predictions made in 2010. Further reductions will require addressing other important determinants of TB (Chapter 7) and improving the coverage of preventive treatment (Chapter 5).

---

**FIG. B3.4.1**

Trends in TB incidence rates expressed as a percentage of the best estimate for 2010 (in red), overall ART coverage among people living with HIV (solid black line) and ART coverage among new TB cases coinfected with HIV (dashed line), in 6 selected countries in southern Africa, 2010–2017.
**FIG. 3.10**
Main methods used to estimate TB mortality in HIV-negative people

- Mortality is estimated as the product of TB incidence and the TB case fatality ratio. Further details are provided in the online technical appendix.

**FIG. 3.11**
Top causes of death worldwide in 2016. Deaths from TB among HIV-positive people are shown in grey.

- This is the latest year for which estimates for all causes are currently available. See WHO estimates, available at [http://apps.who.int/gho/portal/uhc-fp-cabinet-wraper-v2.jsp?id=1020201](http://apps.who.int/gho/portal/uhc-fp-cabinet-wraper-v2.jsp?id=1020201) (accessed 15 August 2018).

**FIG. 3.12**
Estimated number of deaths from HIV/AIDS and TB in 2017. Deaths from TB among HIV-positive people are shown in grey.

- For HIV/AIDS, the latest estimates of the number of deaths in 2017 that have been published by UNAIDS are available at [http://www.unaids.org/en/resources/publications/all](http://www.unaids.org/en/resources/publications/all) (accessed 15 August 2018). For TB, the estimates for 2017 are those published in this report.

- Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International classification of diseases.
among countries (Fig. 3.14), ranging from less than one TB death per 100 000 population in many high-income countries, to 40 or more deaths per 100 000 population in much of the WHO African Region and in four high TB burden countries in Asia (the Democratic People’s Republic of Korea, Indonesia, Myanmar and Papua New Guinea).

Estimates of the number of deaths caused by zoonotic TB are shown in Table 3.4.

3.2.3 Estimated trends in TB mortality, 2000–2017

Globally, the absolute number of deaths caused by TB among HIV-negative people has been falling since 2000, from a best estimate of 1.8 million in 2000 to 1.3 million in 2017 (Fig. 3.6), a reduction of 29%. The reduction since 2015 (the baseline year for milestones and targets set in the End TB Strategy, as shown in Table 3.1) was 5%. The TB mortality rate (TB deaths among HIV-negative people per 100 000 population per year) fell by 42% globally between 2000 and 2017 (Fig. 3.7), and by 3.2% between 2016 and 2017.

Mortality rates among HIV-negative people have been falling in all six WHO regions since 2000, but the rate of decline varies (Fig. 3.15). For example, in the 5-year period 2013–2017, the fastest average rates of decline were in the WHO European Region (11% per year) and the WHO South-East Asia Region (4.3% per year), and the slowest rate was in the WHO African Region (1.7% per year).

Trends also vary markedly among the 30 high TB burden countries (Fig. 3.16), ranging from substantial reductions (more than 50%) since 2000 (e.g. in Cambodia,
3.2.4 The case fatality ratio and across-country equity

The CFR is the proportion of people with TB who die from the disease; it can be approximated as the number of TB deaths divided by the number of new cases in the same year. The CFR allows assessment of variation in equity in terms of access to TB diagnosis and treatment among countries (because if everyone with TB had access to timely diagnosis and high-quality treatment, the CFR would be low in all countries). To achieve the milestones for reductions in TB deaths set for 2020 and 2025 in the End TB Strategy, the global CFR needs to fall to 10% by 2020 and to 6.5% by 2025 (Chapter 2).

In 2017, the global CFR (calculated as the combined number of TB deaths in HIV-negative people and HIV-positive people, divided by the total number of incident cases in both HIV-negative and HIV-positive people) was 16%, down from 23% in 2000. It varied widely among countries (Fig. 3.17), from under 5% in a few countries to more than 20% in most countries in the WHO African Region. Intensified efforts are required to reduce the CFR to 10% globally by 2020.

---

1 Time series of estimates for all countries are available online. Annex 1 explains how to access and download them.

2 The CFR was calculated based on the combined total of deaths in HIV-negative and HIV-positive people for the purpose of cross-country comparisons; in particular, to illustrate the high CFRs in African countries, which could be reduced by effective detection and care programmes. CFRs restricted to HIV-negative TB deaths and cases can also be calculated but are not shown here. At the subnational level, CFRs can also be restricted to HIV-negative TB deaths, depending on the country and its HIV burden.
FIG. 3.16
Trends in estimated TB mortality rates in the 30 high TB burden countries, 2000–2017. TB mortality rates in HIV-negative people are shown in blue and mortality rates of HIV-positive TB are shown in red. The black lines show observations from vital registration systems. Shaded areas represent uncertainty intervals.

a Estimates of TB mortality for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.

b Estimates of TB mortality for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
3.2.5 Estimated number of deaths averted by TB treatment, 2000–2017

The actual numbers of TB deaths (presented above) can be compared with the number of TB deaths that would have occurred in the absence of TB treatment, to estimate the number of deaths averted by TB interventions. The number of deaths that would have occurred each year in the absence of TB treatment (and without ART provided alongside TB treatment for HIV-positive cases) can be conservatively estimated as the number of estimated incident cases (Section 3.1) multiplied by the relevant estimated CFR for untreated TB. Estimates are conservative because they do not account for the impact of TB services or the availability of ART on the level of TB incidence, or for the indirect, downstream impact of these interventions on future levels of infections, cases and deaths.

Between 2000 and 2017, TB treatment alone averted an estimated 45 million deaths among HIV-negative people (Table 3.5). Among HIV-positive people, TB treatment supported by ART averted an additional 9 million deaths.

3.3 Drug-resistant TB

Drug-resistant TB remains a major public health concern in many countries. Three major categories are used for global surveillance and treatment. MDR-TB is TB that is resistant to both rifampicin and isoniazid, the two most powerful anti-TB drugs; it requires treatment with a second-line regimen. RR-TB also requires treatment with second-line drugs. With increasing use of Xpert® MTB/RIF for simultaneous detection of TB and resistance to rifampicin, a growing number of RR-TB cases (without further testing for isoniazid resistance) are being detected and notified (Chapter 4). Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to at least one drug in both of the two most important classes of medicines in an MDR-TB regimen: fluoroquinolones and second-line injectable agents (amikacin, capreomycin or kanamycin). Estimates of the disease burden caused by drug-resistant TB presented in this chapter focus on MDR/RR-TB.

3.3.1 Global surveillance of anti-TB drug resistance

Since the launch of the Global Project on Anti-tuberculosis Drug Resistance Surveillance in 1994, data on drug resistance have been systematically collected and analysed from 160 countries worldwide (82% of the 194 WHO Member States), which collectively have more than 97% of the world’s population and TB cases. This includes 91 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility testing (DST) of Mycobacterium tuberculosis isolates.
### TABLE 3.5
Cumulative number of deaths averted by TB and TB/HIV interventions 2000–2017 (in millions), globally and by WHO region

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>HIV-NEGATIVE PEOPLE</th>
<th>HIV-POSITIVE PEOPLE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
</tr>
<tr>
<td>Africa</td>
<td>5.5</td>
<td>4.5–6.4</td>
<td>6.0</td>
</tr>
<tr>
<td>The Americas</td>
<td>1.5</td>
<td>1.4–1.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>3.5</td>
<td>3.0–4.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Europe</td>
<td>1.9</td>
<td>1.7–2.1</td>
<td>0.21</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>20</td>
<td>16–24</td>
<td>1.9</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>13</td>
<td>11–14</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>GLOBAL</strong></td>
<td><strong>45</strong></td>
<td><strong>39–50</strong></td>
<td><strong>8.9</strong></td>
</tr>
</tbody>
</table>

*Numbers shown to two significant figures.

### FIG. 3.18
Data sources available to estimate levels of TB drug resistance

Source of data:
- Surveillance
- Survey
- No data
- Not applicable
obtained from all TB patients, and 69 countries that rely on epidemiological surveys of bacterial isolates collected from representative samples of patients (Fig. 3.18). Surveys conducted about every 5 years represent the most common approach to investigating the burden of drug resistance in resource-limited settings where routine DST is not accessible to all TB patients owing to lack of laboratory capacity or resources.

Progress towards achieving global coverage of drug-resistance surveillance data is shown in Fig. 3.19. Among the 30 high TB burden countries and the 30 high MDR-TB burden countries (which comprise a total of 40 countries, because of overlap between the two groups)\(^1\), 37 have data on levels of drug resistance. The three countries that have never conducted a drug-resistance survey are Angola, Congo and Liberia. Angola has initiated a national survey in 2018. Among the other 37 high TB burden or high MDR-TB burden countries, four countries (Brazil, Central African Republic, Democratic People’s Republic of Korea and Papua New Guinea) rely on drug-resistance surveillance data gathered from subnational areas only.

In 2016–2017, the first-ever national drug resistance surveys were completed in Eritrea, Indonesia and Lao People’s Democratic Republic, and repeat surveys were completed in Eswatini, Sri Lanka, Togo and the United Republic of Tanzania. In 2017–2018, drug-resistance surveys were ongoing in 12 countries, with the first nationwide surveys in five countries (Angola, Burundi, Haiti, Mali and Timor-Leste) and repeat surveys in seven countries (Bangladesh, Cambodia, Ethiopia, Malawi, the Philippines, Thailand and Turkmenistan).

3.3.2 Estimates of the disease burden caused by MDR/RR-TB

Globally in 2017, an estimated 3.5% (95% confidence interval [CI]: 2.5–4.7%) of new cases and 18% (95% CI: 6.3–34%) of previously treated cases had MDR/RR-TB (Table 3.6). The proportions of new and previously treated TB cases with MDR-TB were 82% (460 000 out of 560 000) (Table 3.6). The countries with the largest numbers of MDR/RR-TB cases (47% of the global total) were China, India and the Russian Federation (Fig. 3.22).

There were an estimated 558 000 (range, 483 000–639 000) incident cases of MDR/RR-TB in 2017. This is a slight downward revision from the best estimate published in the 2017 edition of the WHO global TB report, for reasons explained in Box 3.2. As before, however, the proportion of cases estimated to have MDR-TB was 82% (460 000 out of 560 000) (Table 3.6). The countries with the largest numbers of MDR/RR-TB cases (47% of the global total) were China, India and the Russian Federation (Fig. 3.22).

There were about 230 000 (range, 140 000–310 000) deaths from MDR/RR-TB in 2017, similar to the best estimate for 2016 that was published in the 2017 edition of the WHO global TB report.

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\(^1\) For a full list of the high TB burden and high MDR-TB burden countries, see Chapter 2.
Estimated incidence of MDR/RR-TB in 2017 for 30 high MDR-TB burden countries, WHO regions and globally

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated % of new cases with MDR/RR-TB</th>
<th>Estimated % of previously treated cases with MDR/RR-TB</th>
<th>Incidence of MDR/RR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best estimate</td>
<td>Uncertainty interval</td>
<td>Best estimate</td>
</tr>
<tr>
<td>Angola</td>
<td>2.5</td>
<td>1.1–4.3</td>
<td>14</td>
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<tr>
<td>Azerbaijan</td>
<td>12</td>
<td>11–14</td>
<td>28</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1.6</td>
<td>0.74–2.8</td>
<td>29</td>
</tr>
<tr>
<td>Belarus</td>
<td>38</td>
<td>36–41</td>
<td>67</td>
</tr>
<tr>
<td>China</td>
<td>7.1</td>
<td>5.6–8.7</td>
<td>24</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>2.2</td>
<td>0.82–4.2</td>
<td>16</td>
</tr>
<tr>
<td>DR Congo</td>
<td>2.2</td>
<td>1.0–3.5</td>
<td>9.6</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>2.7</td>
<td>1.6–4.1</td>
<td>14</td>
</tr>
<tr>
<td>India</td>
<td>2.8</td>
<td>2.0–3.5</td>
<td>12</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.4</td>
<td>1.8–3.3</td>
<td>13</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>26</td>
<td>25–28</td>
<td>44</td>
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<td>Kenya</td>
<td>1.3</td>
<td>0.74–2.0</td>
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<td>Kyrgyzstan</td>
<td>26</td>
<td>24–27</td>
<td>61</td>
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<td>3.4–7.2</td>
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<tr>
<td>Nigeria</td>
<td>4.3</td>
<td>3.2–5.5</td>
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</tr>
<tr>
<td>Pakistan</td>
<td>4.2</td>
<td>3.2–5.3</td>
<td>16</td>
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<tr>
<td>Papua New Guinea</td>
<td>3.4</td>
<td>1.7–5.0</td>
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</tr>
<tr>
<td>Peru</td>
<td>6.3</td>
<td>5.9–6.7</td>
<td>20</td>
</tr>
<tr>
<td>Philippines</td>
<td>2.6</td>
<td>1.9–3.4</td>
<td>28</td>
</tr>
<tr>
<td>Republic of Moldova</td>
<td>28</td>
<td>25–30</td>
<td>55</td>
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<td>Somalia</td>
<td>8.7</td>
<td>6.1–12</td>
<td>47</td>
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<td>South Africa</td>
<td>3.4</td>
<td>2.5–4.3</td>
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<td>Tajikistan</td>
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<td>19–22</td>
<td>24</td>
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<tr>
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<td>1.5–3.0</td>
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</tr>
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<td>58</td>
</tr>
<tr>
<td>Viet Nam</td>
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<td>2.8–5.7</td>
<td>17</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>4.6</td>
<td>3.0–6.2</td>
<td>14</td>
</tr>
</tbody>
</table>

MDR/RR HBCs: 3.8

Africa: 2.7

The Americas: 2.7

Eastern Mediterranean: 4.3

Europe: 17

South-East Asia: 2.7

Western Pacific: 5.0

GLOBAL: 3.5

Numbers shown to two significant figures if under 100 and to three significant figures otherwise.

Estimates are for the latest available year.

Rates are per 100,000 population.
**FIG. 3.20**
Percentage of new TB cases with MDR/RR-TB*

* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2002–2018.

**FIG. 3.21**
Percentage of previously treated TB cases with MDR/RR-TB*

* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2005–2018. The high percentages of previously treated TB cases with RR-TB in Belize, Guam and Sao Tomé and Principe refer to only a small number of notified cases (range: 1–8 notified previously treated TB cases).
**FIG. 3.22**
Estimated incidence of MDR/RR-TB in 2017, for countries with at least 1000 incident cases

Data compiled from surveys and continuous surveillance of drug resistance among TB patients also allow estimation of the number of MDR/RR-TB cases among notified TB patients with pulmonary TB. These are the MDR/RR-TB cases that could be detected if all notified patients were tested for drug resistance using WHO-recommended diagnostic tests. Globally in 2017, there were an estimated 330,000 (range, 310,000–350,000) MDR/RR-TB cases among notified TB patients.

### 3.3.3 Trends in drug resistance

Of the 40 countries with a high TB or MDR-TB burden (or both), only 22 have repeated a survey at least once to evaluate trends in drug resistance. Among these countries, 10 have at least 3 years of data: Belarus, Kazakhstan, Myanmar, Peru, Republic of Moldova, Russian Federation, Tajikistan, Thailand, Ukraine and Viet Nam. For these settings, **Fig. 3.23** shows trends in the number of new TB cases notified, the proportion of new TB cases with MDR, and per capita TB and MDR-TB rates. Based on these data, there is a slight trend for cases of MDR-TB to increase as a proportion of all TB cases in these countries, with the burden of MDR-TB either increasing faster or decreasing more slowly than the overall TB burden in each country.

### 3.3.4 Resistance to other anti-TB drugs

Data on resistance to all first-line anti-TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) was gathered from surveys conducted in six countries: Azerbaijan, Bangladesh, Belarus, Pakistan, South Africa and Ukraine. The average level of resistance to all first-line anti-TB drugs was 19% (95% CI: 18–20%) in new TB cases; in previously treated cases, the average was 43% (95% CI: 40–46%).

Data on levels of resistance to isoniazid without concurrent rifampicin resistance are available for 149 countries over the period 2003–2017. The proportions of TB patients resistant to isoniazid but susceptible to rifampicin in each country were weighted according to the number of new TB cases that were notified in the country, to generate a global average. The global averages of isoniazid resistance without concurrent rifampicin resistance were 7.1% (95% CI: 6.2–8.0%) in new TB cases and 7.9% (95% CI: 5.9–10%) in previously treated TB cases.

By the end of 2017, XDR-TB had been reported by 127 WHO Member States. Of these, 113 countries and five territories reported representative data from continuous surveillance or surveys regarding the proportion of MDR-TB cases that had XDR-TB. Combining their data, the average proportion of MDR-TB cases with XDR-TB was 8.5% (95% CI: 6.2–11%), an increase from the 6.2% in 2016 that was published in the 2017 edition of the WHO global TB report.

Among the 40 countries with a high TB or MDR-TB burden, 22 have surveillance data on resistance to second-line anti-TB drugs. The proportion of MDR/RR-TB...
FIG. 3.23
Trends in levels of drug resistance in selected high MDR-TB burden countries with at least three years of data. The blue line shows the number of new notified TB cases per 100,000 population. The red line shows the number of MDR-TB cases among new TB patients per 100,000 population.
cases with resistance to any fluoroquinolone for which testing was done – including ofloxacin, levofloxacin and moxifloxacin – was 22% (95% CI: 17–28%).

3.4 National TB prevalence surveys

The prevalence of TB disease is not an indicator in the SDGs or a high-level indicator of the End TB Strategy, and no global target has been set for the period 2016–2035.1 Furthermore, indirect estimates of prevalence suffer from considerable uncertainty, because they are derived from estimates of incidence and assumptions about disease duration. Hence, indirect estimates of TB prevalence (i.e. estimates that are not from a national TB prevalence survey) are not presented in this chapter.2 Nonetheless, in an important subset of countries with a large proportion of the world’s TB burden, national TB prevalence surveys continue to provide the best method for measuring the burden of TB disease (both in absolute terms and to assess trends when repeat surveys are done, and by age and sex). Findings can inform assessment of actions needed to reduce this burden as well as estimates of TB incidence (Fig. 3.2), thus contributing to the monitoring of progress towards SDG and End TB Strategy targets. The WHO Global Task Force on TB Impact Measurement has retained national TB prevalence surveys within its strategic areas of work for 2016–2020 (Box 3.1), and has defined the group of countries where they continue to be relevant as those with a relatively high burden of TB (about 150 incident cases per 100 000 population) that do not yet have health, national notification and VR systems of the quality and coverage required to provide reliable and routine direct measurements of the number of TB cases and deaths.3 The most recent example of a prevalence survey that has informed understanding of trends in TB disease burden, estimates of TB incidence and identification of actions required to reduce the burden of TB disease is the 2016 survey in the Philippines.4,5

1 This is in contrast to the era of the Millennium Development Goals (MDGs) and Stop TB Strategy, when one of the global targets for reductions in TB disease burden was to halve prevalence between 1990 and 2015.
2 WHO will continue to produce indirect estimates of TB prevalence. These can be provided upon request to tbdata@who.int.
3 In the Task Force’s April 2016 meeting, epidemiological criteria for conducting a survey were defined for two groups of countries: those that implemented a survey in 2009–2015 and in which a repeat survey could be considered; and those that have never conducted a survey. There were 24 countries in the first group and 33 in the second group. For any of these 57 countries, it was emphasized that feasibility criteria must also be considered. In particular, the prerequisites for conducting a survey defined in the WHO handbook on national TB prevalence surveys should be met. For further details on the meeting, see World Health Organization Global Task Force on TB Impact Measurement: Report of the sixth meeting of the full Task Force; 19–21 April 2016, Glion-sur-Montreux, Switzerland. Geneva: WHO; 2016 (http://www.who.int/tb/adv/adv_bodies/impact_measurement_taskforce/meetings/tf6_report.pdf?ua=1, accessed 8 August 2018).

FIG. 3.24


<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>2000</td>
</tr>
<tr>
<td>China</td>
<td>2001</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2002</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2003</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2004</td>
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<td>Eritrea</td>
<td>2005</td>
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<tr>
<td>Thailand</td>
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<tr>
<td>Philippines</td>
<td>2007</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>2007</td>
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<tr>
<td>Bangladesh</td>
<td>2008</td>
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<tr>
<td>Myanmar</td>
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<tr>
<td>China</td>
<td>2010</td>
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<tr>
<td>Cambodia</td>
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<td>Ethiopia</td>
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<td>Laos PDR</td>
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<td>Pakistan</td>
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<td>Gambia</td>
<td>2012</td>
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<tr>
<td>Nigeria</td>
<td>2012</td>
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<tr>
<td>Rwanda</td>
<td>2012</td>
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<tr>
<td>UR Tanzania</td>
<td>2012</td>
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<tr>
<td>Thailand</td>
<td>2012</td>
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<tr>
<td>Ghana</td>
<td>2013</td>
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<td>Malawi</td>
<td>2013</td>
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<td>Sudan</td>
<td>2013</td>
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<td>Indonesia</td>
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<td>Zambia</td>
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<td>Zimbabwe</td>
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<td>Bangladesh</td>
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<td>Kenya</td>
<td>2015</td>
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<td>Mongolia</td>
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<td>Uganda</td>
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<td>DPR Korea</td>
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<td>Philippines</td>
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<td>Mozambique</td>
<td>2017</td>
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<td>Myanmar</td>
<td>2017</td>
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<td>Namibia</td>
<td>2017</td>
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<tr>
<td>South Africa</td>
<td>2017</td>
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<tr>
<td>Viet Nam</td>
<td>2017</td>
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<td>Botswana</td>
<td>2018</td>
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<td>Eswatini</td>
<td>2018</td>
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<tr>
<td>Nepal</td>
<td>2018</td>
</tr>
<tr>
<td>India</td>
<td>2019</td>
</tr>
<tr>
<td>Lesotho</td>
<td>2019</td>
</tr>
</tbody>
</table>

6 The surveys in Bangladesh (2008) and Eritrea (2005) collected sputum samples from all individuals (aged ≥15 years), and did not use chest X-ray and/or a symptom questionnaire to screen individuals for sputum submission.
7 Field operations are ongoing as of August 2018.
8 Field operations are ongoing as of August 2018.
9 Field operations are ongoing as of August 2018.

Countries in which national prevalence surveys were implemented in 2000–2018 or are planned for 2019 are shown in Fig. 3.24 and Fig. 3.25. An unprecedented number of surveys were implemented in 2007–2015, a period in which the WHO Global Task Force on TB Impact Measurement defined national TB prevalence surveys in 22 global focus countries as one of its three strategic areas of work (Box 3.1). Between 2007 and the end of 2017, a total of 25 surveys that used the screening and diagnostic methods recommended in the second edition of the WHO handbook on prevalence surveys were completed. This included 13 surveys in Asian countries and 12 in African countries. No surveys were completed in 2017; however, in early 2018, field operations were completed in the first national survey in Namibia and a repeat survey in Viet Nam (following a first survey in 2007). It is expected that Myanmar will finish its repeat survey (following a first survey in 2009) in late 2018. As of August 2018, field operations were ongoing in five...
FIG. 3.25
Countries in which national population-based surveys of the prevalence of TB disease have been implemented using currently recommended screening and diagnostic methods since 2000 or are planned in the future (status in August 2018)

Screening methods include field chest X-ray; at least culture was used to confirm diagnosis. The most recent surveys in Bangladesh, Kenya, Namibia, Myanmar, Mozambique, Nepal, the Philippines and Viet Nam used both culture and Xpert MTB/RIF (or Xpert Ultra) to confirm diagnosis.

A country has submitted at least a draft survey protocol and a budget plan to the WHO Global Task Force on TB Impact Measurement.

Countries were implementing field operations in August 2018 or were undertaking data cleaning and analysis.

A survey was conducted in accordance with WHO recommendations as outlined in 'Tuberculosis prevalence surveys: a handbook (2011)' and at least a preliminary report has been published.

A repeat national survey is one in which participants were screened with chest X-ray, and (at least) culture was used to diagnose TB cases.

No survey planned
Survey planneda
Survey ongoingb
One survey completedc
≥1 repeat survey completedd
Not applicable

countries: Eswatini, Mozambique, Myanmar, Nepal and South Africa. Surveys in Botswana, India and Lesotho are planned in 2019 or 2020.

A comparison of estimates of TB prevalence before and after the implementation of a national survey is shown for 25 countries in Fig. 3.26. Post-survey prevalence estimates were almost always more precise (i.e. had narrower uncertainty intervals). For 18 countries, estimates were within the pre-survey uncertainty interval, whereas for the other seven countries the survey found a burden that was either significantly above (six countries) or below (one country) the burden that had been estimated in the absence of survey data.

The distribution of TB disease by age (in adults) and sex based on prevalence survey data is shown in Fig. 3.27 and Fig. 3.28. In Asia and some African countries (e.g. Ghana, Malawi, Rwanda, the United Republic of Tanzania and Zimbabwe), prevalence increases with age. However, in several African countries (e.g. Ethiopia, Gambia, Nigeria, Sudan, Uganda and Zambia), prevalence per 100 000 population peaks among those aged 35–54 years. The male to female (M:F) ratio of cases for the same set of surveys shows a systematically higher burden of TB disease among men, with ratios ranging from 1.2 (in Ethiopia) to 4.5 (in Viet Nam) for bacteriologically confirmed pulmonary TB. In most countries, the ratio was in the range 2–4.

The ratio of prevalence to notifications (P:N) can be used to assess detection and reporting gaps (Fig. 3.29a) and variation in these gaps by sex (Fig. 3.29b). The P:N ratios from surveys implemented in 2007–2017 suggest that women are accessing available diagnostic and treatment services more effectively than men. The higher disease burden in men, combined with larger gaps in detection and reporting, also suggests that there is a need for strategies to improve access to and use of health services among men.1

FIG. 3.26
Estimates of TB prevalence (all ages, all forms of TB) for 25 surveys, before (in blue) and after (in red) results from national TB prevalence surveys became available since 2007. Countries are ordered according to the before–after difference.

These data relate to the repeat prevalence survey conducted in 2016.
These data relate to the prevalence survey conducted in 2007.
These data relate to the prevalence survey conducted in 2015–2016.

FIG. 3.27
Age-specific prevalence rate ratio of bacteriologically confirmed TB in surveys implemented 2007–2017

Age-specific prevalence ratios were calculated using the prevalence of the 15–24 year age group as the baseline. Data in the presented age groups were not available for Gambia and Rwanda. Data are not shown for UR Tanzania because laboratory challenges during the survey meant that it was only possible to directly estimate the prevalence of smear-positive (as opposed to bacteriologically confirmed) TB.
These data relate to the prevalence survey conducted in 2007.
These data relate to the repeat prevalence survey conducted in 2016.
3.5 Estimates of TB incidence and mortality disaggregated by age and sex

This section presents estimates of TB incidence and TB mortality disaggregated by age and sex.

3.5.1 Methods to disaggregate estimates by age and sex

Estimates of TB incidence in children (aged <15 years) were based on case notifications, adjusted for under-diagnostics and underreporting1 and combined with estimates derived from dynamic modeling.2 Results for the 0–14 year age group (0–4 and 5–14 years) in each country were then further disaggregated using outputs from an established deterministic model,2 followed by disaggregation by sex using results from a meta-analysis of the M:F notification ratio. Estimates of TB incidence in adults were derived by first subtracting incidence in children from incidence in all ages. The estimate for adults was then disaggregated into six age groups (15–24, 25–34, 35–44, 45–54, 55–64 and ≥65 years) using data from national TB prevalence surveys implemented in 2007–2017 (Section 3.4). Country-specific distributions were used for countries that had implemented a survey; for other countries, the age distribution was predicted using prevalence survey data. Disaggregation by sex was based on actual M:F ratios for countries that had implemented surveys; for other countries, this disaggregation was based on regional M:F ratios from a systematic review and meta-analysis.3

TB mortality in children was estimated for the two age groups using a previously published approach derived from dynamic modelling,4 and then by sex, on the assumption that the pattern was the same as that for incidence. If available, data on TB deaths among adults were disaggregated for six age groups (15–24, 25–34, 35–44, 45–54, 55–64 and ≥65 years) using VR data. For countries whose mortality estimates were not based on VR data, a CFR was applied to the adult age- and sex-disaggregated incidence. This CFR accounted for differences between HIV-positive and HIV-negative TB cases, and for variation in HIV prevalence by age and sex.

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**FIG. 3.29a**
The prevalence to notification (P:N) ratio of adult TB cases in prevalence surveys implemented 2007–2017

**FIG. 3.29b**
The prevalence to notification (P:N) ratio by sex for adult TB cases in prevalence surveys implemented 2007–2017

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*The P:N ratio is for smear-positive TB, except for Uganda and Zimbabwe where it is based on bacteriologically confirmed TB. Prevalence estimates are from a cross-sectional survey, and therefore only represent one point in time. Notification data are from the main year of the survey (shown in Fig. 3.24).

* These data relate to the repeat prevalence survey conducted in 2016.

** These data relate to the prevalence survey conducted in 2015–2016.

*** These data relate to the prevalence survey conducted in 2007.
Details of the methods used are provided in the online technical appendix.\(^1\)

### 3.5.2 TB incidence disaggregated by age and sex

Estimates of TB incidence disaggregated by age and sex are shown in Fig. 3.30 (global), Fig. 3.31 (WHO regions) and Fig. 3.32 (30 high TB burden countries), and in Table 3.7. There were cases in all age groups but, overall, 90% were adults and 10% were children (aged <15 years). Globally, 64% of cases were among men and boys, and 36% were among women and girls.\(^2\) The higher shares of TB cases among men shown in Fig. 3.33, Fig. 3.34 and Fig. 3.35 are consistent with evidence from prevalence surveys, which show that TB disease affects men more than women (Fig. 3.28), and that gaps in case detection and reporting are higher among men (Fig. 3.29).

The M:F ratio of incident TB cases for all ages ranged from 1.3 in the WHO Eastern Mediterranean Region to 2.1 in the WHO Western Pacific Region. In children, the M:F ratio was close to 1.

### FIG. 3.30

Global estimates of TB incidence (black line) and case notifications disaggregated by age and sex (female in **red**; male in **green**), 2017

### FIG. 3.31

Regional estimates of TB incidence (black line) and case notifications disaggregated by age and sex (female in **red**; male in **green**), 2017

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\(^1\) The online technical appendix is available at www.who.int/tb/data.

\(^2\) Further breakdowns by HIV status are not possible, because data on the HIV status of TB cases by age and sex are not available.
FIG. 3.32
Estimates of TB incidence (black line) and case notifications disaggregated by age and sex (female in red, male in green), 2017, in the 30 high TB burden countries

- Age and sex disaggregated case notifications were not available.
- Estimates of TB incidence for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.
- No age and sex disaggregated case notifications from 15 years and above were available for Mozambique.
- Estimates of TB incidence for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.

* Numbers are rounded to the nearest 5,000 tuberculosis cases.

** Notes:**
- Angol
- Bangladesh
- Brazil
- Cambodia
- Central African Republic
- China
- Congo
- DPR Korea
- DR Congo
- Ethiopia
- India
- Indonesia
- Kenya
- Lesotho
- Liberia
- Mozambique
- Myanmar
- Namibia
- Nigeria
- Pakistan
- Papua New Guinea
- Philippines
- Russian Federation
- Sierra Leone
- South Africa
- Thailand
- UR Tanzania
- Viet Nam
- Zambia
- Zimbabwe

* a: Age and sex disaggregated case notifications were not available.
  b: Estimates of TB incidence for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.
  c: No age and sex disaggregated case notifications from 15 years and above were available for Mozambique.
  d: Estimates of TB incidence for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
### TABLE 3.7
Estimated number of TB cases (in thousands) in children and adults, globally and for WHO regions, 2017

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>TOTAL</th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
</tr>
<tr>
<td>Africa</td>
<td>2 480</td>
<td>2 210–2 760</td>
<td>1 540</td>
</tr>
<tr>
<td>Europe</td>
<td>273</td>
<td>236–313</td>
<td>177</td>
</tr>
<tr>
<td>S.-E. Asia</td>
<td>4 440</td>
<td>3 530–5 450</td>
<td>2 820</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1 800</td>
<td>1 490–2 130</td>
<td>1 220</td>
</tr>
<tr>
<td>GLOBAL</td>
<td>10 000</td>
<td>9 000–11 100</td>
<td>6 360</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>TOTAL 0–14 YEARS</th>
<th>MALE 0–14 YEARS</th>
<th>FEMALE 0–14 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
</tr>
<tr>
<td>The Americas</td>
<td>33</td>
<td>30–36</td>
<td>17</td>
</tr>
<tr>
<td>Europe</td>
<td>21</td>
<td>18–24</td>
<td>11</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>207</td>
<td>166–249</td>
<td>109</td>
</tr>
<tr>
<td>GLOBAL</td>
<td>1 010</td>
<td>888–1 120</td>
<td>529</td>
</tr>
</tbody>
</table>

* Numbers shown to two significant figures if under 100 and to three significant figures otherwise.

#### 3.5.3 TB mortality disaggregated by age and sex

Estimates of TB mortality in 2017 disaggregated by age and sex are shown in Fig. 3.33 (global), Fig. 3.34 (WHO regions) and Fig. 3.35 (30 high TB burden countries), and in Table 3.8. Estimates are shown for HIV-positive and HIV-negative people separately, given that the cause of TB deaths among HIV-positive people is classified as HIV in ICD-10 (see also Section 3.2).

Globally in 2017, 63% of the TB deaths among HIV-negative people were men and boys, and 37% were women and girls. Children (aged <15 years) accounted for 15% of total deaths, higher than their share of estimated cases, suggesting poorer access to diagnosis and treatment.

Globally in 2017, 57% of HIV-positive TB deaths were men and boys and 43% were women and girls. Children (aged <15 years) accounted for 10% of total deaths in HIV-positive people.
FIG. 3.33
Global distribution of TB mortality in HIV-negative people by age group and sex (female in red; male in green), 2017

* The total area represents global TB mortality and all rectangles are proportional to their share of total TB mortality.

FIG. 3.34
Regional distribution of TB mortality in HIV-negative people by age group and sex (female in red; male in green), 2017

* The total area represents TB mortality and all rectangles are proportional to their share of total TB mortality by region.
FIG. 3.35
Estimated distribution of TB mortality in HIV-negative people in the 30 high TB burden countries by age group and sex (female in red; male in green), 2017

* The total area represents TB mortality and all rectangles are proportional to their share of total TB mortality by country.

a Estimates of TB mortality for India are interim in nature, pending results from the national TB prevalence survey planned for 2019/2020.

b Estimates of TB mortality for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>HIV-NEGATIVE</th>
<th>HIV-POSITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOTAL  MALE 0–14 YEARS FEMALE 0–14 YEARS MALE ≥15 YEARS FEMALE ≥15 YEARS</td>
<td>TOTAL  MALE 0–14 YEARS FEMALE 0–14 YEARS MALE ≥15 YEARS FEMALE ≥15 YEARS</td>
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<tr>
<td></td>
<td>BEST ESTIMATE UNCERTAINTY INTERVAL  BEST ESTIMATE UNCERTAITY INTERVAL  BEST ESTIMATE UNCERTAINTY INTERVAL  BEST ESTIMATE UNCERTAINTY INTERVAL  BEST ESTIMATE UNCERTAITY INTERVAL  BEST ESTIMATE UNCERTAITY INTERVAL  BEST ESTIMATE UNCERTAITY INTERVAL  BEST ESTIMATE UNCERTAITY INTERVAL</td>
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</tr>
<tr>
<td>The Americas</td>
<td>18 17–19 2.0 1.8–2.3 1.7 1.5–1.9 9.6 8.6–11 4.6 4.1–5.1</td>
<td>6.0 5.3–6.7 0.25 0.21–0.29 0.21 0.18–0.24 4.1 3.5–4.8 1.4 1.2–1.6</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>89 75–104 7.8 5.7–9.8 6.5 4.8–8.3 41 30–53 33 24–42</td>
<td>3.0 1.8–4.5 0.11 0.04–0.17 0.09 0.03–0.15 2.0 0.71–3.3 0.78 0.28–1.3</td>
</tr>
<tr>
<td>Europe</td>
<td>24 23–25 2.4 2.2–2.6 2.3 2.1–2.4 13 12–14 6.1 5.6–6.5</td>
<td>5.0 3.8–6.4 0.07 0.05–0.09 0.06 0.04–0.08 3.7 2.5–5.0 1.1 0.77–1.5</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>638 598–679 41 37–45 35 32–38 363 328–398 199 180–218</td>
<td>28 22–36 0.68 0.45–0.91 0.58 0.39–0.78 20 13–26 7.4 4.9–9.9</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>92 85–100 21 18–24 17 15–20 37 31–43 17 15–20</td>
<td>5.0 3.8–6.4 0.22 0.15–0.30 0.18 0.12–0.24 3.6 2.4–4.8 1.1 0.70–1.4</td>
</tr>
</tbody>
</table>

* Numbers shown to two significant figures if under 100 and to three significant figures otherwise.
A health officer teaching patients about TB and multidrug-resistant TB detection and treatment in a hospital in Lima, Peru

WHO / Pan American Health Organization
Chapter 4. Diagnosis and treatment: TB, HIV-associated TB and drug-resistant TB

KEY FACTS AND MESSAGES

Globally in 2017, 6.7 million people with tuberculosis (TB) were notified to national TB programmes (NTPs) and reported to WHO. Of these, just over 6.4 million had an incident episode (new or relapse) of TB. The global number of new and relapse TB cases notified and the notification rate per 100,000 population have both been increasing since 2013, following 4 years (2009–2012) in which 5.7–5.8 million new cases were notified annually. This increase is mostly explained by increased notifications in India (+44% between 2013 and 2017) and Indonesia (+21% between 2016 and 2017).

In 2017, 30% (2.0 million) of the 6.6 million new and previously treated TB cases notified globally were reported to have been tested for resistance to rifampicin. Coverage was 24% for new TB patients and 70% for previously treated TB patients. Globally, 160,684 cases of multidrug-resistant TB and rifampicin-resistant TB (MDR/RR-TB) were notified in 2017 (up from 153,119 in 2016), and 139,114 cases were enrolled in treatment (up from 129,689 in 2016).

Globally in 2017, 60% of notified TB patients had a documented HIV test result, up from 58% in 2016 and representing a 23-fold increase since 2004. In the WHO African Region, where the burden of HIV-associated TB is highest, 86% of TB patients had a documented HIV test result. A total of 464,633 TB cases among HIV-positive people were reported; of these, 84% were on antiretroviral therapy (ART).

Despite increases in notifications of TB, progress in closing detection and treatment gaps is slow and large gaps remain. Globally in 2017, there was a gap of 3.6 million between notifications of new and relapse cases and the best estimate of the number of incident cases (10.0 million). Ten countries accounted for around 80% of this global gap, with India (26%), Indonesia (11%), Nigeria (9%) and the Philippines (7%) accounting for more than half of the global total.

Gaps between the estimated number of new cases and the number actually reported are due to a mixture of underreporting of detected cases, and underdiagnosis (either because people do not access health care or because they are not diagnosed when they do). An informative example is Indonesia. In 2017, a national study found that about 20% of new cases were not diagnosed; of the approximately 80% of new cases that were detected, 41% were not reported. Actions to correct underreporting are being put in place.

There are also large gaps in detection and treatment of MDR/RR-TB and HIV-associated TB. In 2017, the number of MDR/RR-TB cases started on treatment was only 25% of the estimated incidence of 558,000 cases, while the number of notified HIV-positive TB cases was only 51% of the estimated 920,000 new cases of TB among people living with HIV.

Ten countries accounted for 75% of the gap between enrolments in MDR-TB treatment in 2017 and the estimated number of incident MDR/RR-TB cases in 2017; two countries – China and India – accounted for 39% of the total gap. Most of the gaps in detection of HIV-positive TB cases and provision of ART in 2017 were accounted for by the WHO African Region.

The global male:female (M:F) ratio for notifications in 2017 was 1.7. Results from national TB prevalence surveys of adults show higher M:F ratios, indicating that notification data underestimate the share of the TB burden accounted for by men in some countries. Globally, children (aged <15 years) accounted for 7.1% of the new and relapse cases that were notified in 2017.

The WHO-recommended rapid diagnostic (WRD) test for detection of TB and rifampicin resistance currently available is the Xpert MTB/RIF® assay. Of the 48 countries in at least one of the lists of high burden countries, 32 had adopted national algorithms positioning the WRD as the initial diagnostic test for all people suspected of having pulmonary TB by the end of 2017.

The latest treatment outcome data show treatment success rates of 82% for TB (2016 cohort), 77% for HIV-associated TB (2016 cohort), 55% for MDR/RR-TB (2015 cohort) and 34% for extensively drug-resistant TB (XDR-TB) (2015 cohort). As part of efforts to improve outcomes for MDR/XDR-TB, 68 countries and territories reported that they had started using bedaquiline and 42 reported that they had started using delamanid by the end of 2017.
Prompt and accurate diagnosis of tuberculosis (TB), HIV-associated TB and drug-resistant TB, followed by provision of treatment in line with international standards, prevents deaths and limits ill-health among people who develop TB. It also prevents further transmission of infection to others. The 2020 and 2025 milestones for reductions in TB incidence and TB deaths set in the End TB Strategy (Chapter 2) require the case fatality ratio (i.e. the proportion of people with TB who die from the disease) to fall to 10% by 2020 and to 6.5% by 2025. The latter is only feasible if all people with TB are promptly diagnosed and effectively treated. Patient-centred care and prevention – backed by bold policies and supportive systems such as universal health coverage (UHC) and social protection – are Pillars 1 and 2 of the End TB Strategy (Box 4.1).

This chapter provides the latest national data reported to WHO on the diagnosis and treatment of TB, HIV-associated TB and drug-resistant TB. Section 4.1 presents and discusses data for 2017 on notifications of TB cases and associated coverage of diagnostic testing, as well as trends since 2000. It includes data on the contribution of community engagement and public–public and public–private mix (PPM) initiatives to case-finding efforts. Section 4.2 focuses on treatment coverage (and on detection and treatment gaps) for patients with TB, HIV-associated TB and drug-resistant TB, comparing numbers detected and treated with underlying estimates of disease burden. Section 4.3 provides the most recent data on treatment outcomes, for new and relapse TB patients, TB patients living with HIV and patients with multidrug-resistant TB and rifampicin-resistant TB (MDR/RR-TB), as well as global trends for these three groups between 2012 and 2016.

Throughout the chapter, data are presented at global, regional and country levels, giving particular attention to high burden countries (HBCs).1 Further country-specific details for all of the indicators covered in this chapter are provided in Annex 2 and Annex 4.

4.1 Case notifications and testing coverage

4.1.1 TB case notifications and bacteriological confirmation

In 2017, 6.7 million people with TB were notified to national TB programmes (NTPs) and reported to WHO (Table 4.1). Of these, 6.4 million had a new or relapse (incident) episode of TB (shown as the total of new and relapse cases), and an additional 260 000 had been previously diagnosed with TB but their treatment was changed to a retreatment regimen.

The number of new and relapse TB cases notified increased between 2000 and 2009, was then stable at around 5.7–5.8 million annually during 2009–2012, and has subsequently increased (Fig. 4.1).2 The increase since 2013 is mostly explained by a continuous increase in notifications in India (+44% between 2013 and 2017), following the introduction of a national policy of mandatory notification in 2012 and the rollout (also since 2012) of a nationwide web-based and case-based reporting system (called “Nikshay”) that facilitates reporting of detected cases by care providers in the public and private sectors. There was also an upturn in notifications in Indonesia in 2017 (an increase of 21% compared with 2016), for reasons discussed later in this chapter (Section 4.2).

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1 The three lists of HBCs for TB, HIV-associated TB and MDR-TB are explained in Chapter 2.

2 A similar pattern exists for case notification rates (new and relapse cases per 100 000 population per year). See Fig. 3.7 and Fig. 3.8 in Chapter 3.
The distribution of notified cases in 2017 by age and sex is shown globally and for WHO regions in Fig. 4.2. The global male:female (M:F) ratio for notifications was 1.7. In contrast, the M:F ratio in 25 national TB disease prevalence surveys of adults in African and Asian countries implemented in 2007–2017 was about 2.5 overall, and reached 4.5 in Viet Nam. This indicates that notification data understate the share of the TB burden accounted for by men in some countries (see Chapter 3 for further details). Children (aged <15 years) accounted for 7.1% of the new and relapse cases that were notified globally. In the WHO Eastern Mediterranean, South-East Asia and Western Pacific regions, the TB epidemic is a markedly ageing one, with a progressive increase in the notification rate with age, and a peak among those aged 65 years or over. Elsewhere, notification rates were highest among adults, most noticeably in the WHO African Region (in the 45–54 year age category) and the WHO European Region (in the 35–44 year age category). In several central and eastern European countries, as well as three high TB burden countries in Asia – China, Thailand and Viet Nam – less than 2% of notified cases

### TABLE 4.1
Notifications of TB, HIV-positive TB and MDR/RR-TB cases, globally and for WHO regions, 2017

<table>
<thead>
<tr>
<th>Region</th>
<th>TOTAL NOTIFIED</th>
<th>NEW AND RELAPSE</th>
<th>PULMONARY NEW AND RELAPSE</th>
<th>OF WHICH BACTERIOLOGICALLY CONFIRMED (%)</th>
<th>EXTRA-PULMONARY NEW AND RELAPSE (%)</th>
<th>HIV-POSITIVE NEW AND RELAPSE</th>
<th>MDR/RR-TB</th>
<th>XDR-TB</th>
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<td>14%</td>
<td>464 633</td>
<td>160 684</td>
<td>10 800</td>
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* New and relapse includes cases for which the treatment history is unknown. It excludes cases that have been re-registered as treatment after failure, as treatment after lost to follow up or as other previously treated (whose outcome after the most recent course of treatment is unknown or undocumented).
**FIG. 4.2**

New and relapse TB case notification rates by age and sex in 2017, globally and for WHO regions

- **Africa**
- **The Americas**
- **Eastern Mediterranean**
- **Europe**

![Bar charts showing TB case notification rates by age and sex for different regions.](image)

Countries not reporting cases in these categories are excluded. Cases included account for 89% of reported cases.

**FIG. 4.3**

Percentage of new and relapse TB cases that were children (aged <15), 2017

- **Infection by region:** Africa, The Americas, Eastern Mediterranean, South-East Asia, Western Pacific, Global

![Map of the world showing the percentage of TB cases among children.](image)

2016 data were used for 23 countries.

* Countries not reporting cases in these categories are excluded. Cases included account for 89% of reported cases.
were children (Fig. 4.3). Variation among countries in the child:adult and M:F ratios of cases may reflect real differences in epidemiology, differential access to or use of health-care services, or differential reporting practices.

Of the 5.5 million new and relapse pulmonary TB patients notified globally in 2017, 56% were bacteriologically confirmed. The remaining patients were diagnosed clinically; that is, based on symptoms, abnormalities on chest radiography or suggestive histology. The percentage of pulmonary cases with bacteriological confirmation worldwide has declined slightly since 2013 (Fig. 4.4), mainly reflecting trends in the WHO South-East Asia Region (67% to 59%) and the WHO Western Pacific Region (43% to 39%). There was an improvement in the WHO African Region (57% to 66%) and the WHO European Region (59% to 64%). Considerable variation in the percentage of new and relapse pulmonary TB patients that are bacteriologically confirmed is evident, even among countries with a similar epidemiological profile (Fig. 4.5).

Reasons for a low proportion of cases being bacteriologically confirmed should be assessed at country level, as should reductions over time. The microbiological detection of TB is critical for infection control because it allows patients to be correctly diagnosed and started on the most effective treatment regimen as early as possible. Most clinical features of TB and abnormalities on chest radiography or histology results generally associated with TB have low specificity, which may lead to false diagnoses of TB, and hence to people being enrolled in TB treatment unnecessarily.

Extrapulmonary TB represented 14% of the 6.4 million incident cases that were notified in 2017, ranging from 8% in the WHO Western Pacific Region to 24% in the WHO Eastern Mediterranean Region (Fig. 4.6 and Table 4.1).

Engagement of all care providers in the public and private sectors should be integral components of national TB strategies, and PPM initiatives have particular relevance to HBCs in Africa and Asia. The contribution of PPM to total notifications in countries that have reported PPM data for several years is shown in Box 4.2.

4.1.2 HIV testing for TB patients, detection of HIV-associated TB and screening for TB among people living with HIV

In 2017, 168 countries reported 3.8 million notified new and relapse TB patients with a documented HIV test result (a 4% increase from 2016), equivalent to 60% of notified TB cases. This represented a 23-fold increase in the number of people with TB tested for HIV since 2004, when WHO first asked countries to report data (Fig. 4.7). In 125 countries and territories, at least 75% of TB cases knew their HIV status (Fig. 4.8). Documentation of

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1 A bacteriologically confirmed case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-recommended rapid diagnostic test, such as Xpert MTB/RIF.
FIG. 4.5
Percentage of new and relapse pulmonary TB cases with bacteriological confirmation, 2017

* 2016 data were used for 18 countries.

FIG. 4.6
Percentage of extrapulmonary cases among new and relapse TB cases, 2017

* 2016 data were used for 18 countries.
**BOX 4.2**

**Trends in the contribution of public–private mix approaches to TB case notifications**

One of the major challenges in ensuring universal access to quality TB services is the lack of systematic engagement of all health-care providers, especially those in the private sector, which is where people with TB often seek care initially. In 2017, about 3.6 million of the estimated 10 million people with TB worldwide were either not reported or not diagnosed (see Section 4.2); many of these people are likely to have been treated by public and private providers who are not linked to the NTP. The quality of care provided in these settings is difficult to ascertain and may be substandard.

WHO policies and global and national TB strategies have long acknowledged the need to engage all care providers, through PPM approaches. PPM encompasses diverse collaborative strategies. Public–public mix refers to engagement by the NTP of public sector providers of TB care that are not under the direct purview of the NTP (e.g. public hospitals, public medical colleges, prisons or detention centres, military facilities, railways and public health insurance organizations). PPM refers to engagement by the NTP of private sector providers of TB care (e.g. private individual and institutional providers, the corporate or business sector, mission hospitals, nongovernmental organizations and faith-based organizations).

Many countries have made some progress in engaging non-NTP public providers and major non-profit facilities, especially those managed by faith-based organizations that have historically had close relationships with ministries of health. Gaps in engagement are typically more evident in the case of for-profit private providers.

Trends in the contribution of PPM to notifications in selected countries where PPM has been recognized as a priority and from which data have been reported to WHO for each year during 2012–2017 are shown in Fig. B4.2.1 and Fig. B4.2.2. The contribution of PPM to case notifications quantifies the engagement of different providers in the delivery of TB care, and the alignment of their TB management practices with national and international standards.

Countries that have prioritized PPM – such as Bangladesh, India, Indonesia, Kenya and Pakistan – clearly show an increasing trend in the contribution of public non-NTP or private sector engagement to TB case notifications. As electronic case notification systems and digital technologies begin to be set up and rolled out in countries (see also Box 4.3), including for PPM approaches, contributions to case notifications from the private sector and from the currently unengaged parts of the public sector will continue to increase.

Inventory studies that quantify the underreporting of detected TB cases in both public and private sectors can help to identify where further PPM efforts are needed. An excellent recent example, from Indonesia, is highlighted in Box 4.4.

Electronic systems for online reporting of a limited number of variables can facilitate more complete reporting of cases from the private sector. Recent examples include Bangladesh and Pakistan.

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**FIG. B4.2.1**

**Contribution of public–public mix to TB case notifications in eight countries, 2012–2017**

**FIG. B4.2.2**

**Contribution of public–private mix to TB case notifications in eight countries, 2012–2017**
**FIG. 4.7**
Percentage of new and relapse\(^a\) TB cases with documented HIV status, 2004–2017, globally and for WHO regions\(^b\)

- Africa
- The Americas
- Eastern Mediterranean
- Europe
- South-East Asia
- Western Pacific
- Global

\(^a\) The calculation is for all cases in years prior to 2015.

\(^b\) Countries were excluded if the number with documented HIV status was not reported to WHO.

**FIG. 4.8**
Percentage of new and relapse TB cases with documented HIV status, 2017\(^a\)

- 2016 data were used for 15 countries.
HIV status averaged 66% of TB patients in the 30 high TB/HIV burden countries, but varied considerably, from 13% in Congo to above 80% in 16 high TB/HIV burden countries in the WHO African Region. In the WHO African Region, which accounted for 72% of the global burden of HIV-associated TB in 2017 (Chapter 3), 86% of TB patients knew their HIV status.

Globally, 464,633 cases of TB among people living with HIV were notified in 2017 (Table 4.1), equivalent to 12% of TB patients with an HIV test result. The number notified was only 51% of the estimated number of incident cases among people living with HIV (Fig. 4.9), but an increase from 49% in 2016.

Overall, the percentage of TB patients testing HIV-positive has been falling globally since 2008. This decline is evident in all WHO regions with the exception of the WHO European Region, where the proportion of TB patients testing HIV-positive increased from 3% in 2008 to 13% in 2017.

Systematic symptom screening for TB among people living with HIV is recommended by WHO as an essential component of the HIV care package, together with linkage to diagnostic services, as necessary. In 2017, 92 countries reported annual data on the number of TB cases notified among those newly enrolled in HIV care (up from 90 countries in 2016). In total, 8% of the 1.5 million people who were reported to be newly enrolled in HIV care in 2017 were diagnosed with TB during the same year; data for the 17 high TB/HIV burden countries that reported data are shown in Table 4.2.

4.1.3 Rapid testing for TB
Increasing patient access to early and accurate diagnosis using a WHO-recommended rapid diagnostic (WRD) is one of the three main objectives of TB laboratory strengthening efforts under the End TB Strategy. As a first step towards reaching this objective, countries should adopt policies that include diagnostic algorithms in which a WRD is the initial diagnostic test for all people with signs or symptoms of TB. They should also adopt such policies as part of working towards the first indicator of the Framework of indicators and targets for laboratory strengthening under the End TB Strategy, which was launched in 2016. Such policies should be an especially high priority for the 48 countries included in one or more of the lists of high TB, TB/HIV and MDR-TB burden

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1 Although the national figure for China was 55%, in the counties defined as having a high burden of HIV-associated TB the figure was 87%.

2 See also Table 3.2 in Chapter 3 for the global estimate of TB incidence among people living with HIV. The best estimate was 920,000 cases in 2017 (9% of the total number of incident cases).

3 WRDs use molecular techniques to detect TB among people with signs or symptoms of TB. They include the XpertMTB/RIF® assay (Cepheid, United States) and the LoopampTM MTBC Detection Kit (Eiken Chemical Company Ltd, Japan).

countries; of these 48 countries, 32 reported having policies that included such an algorithm by the end of 2017 (Table 4.3). The second indicator of the framework is the percentage of new and relapse TB cases actually tested with a WRD as the initial diagnostic test. Of 190 reporting countries and territories, 133 indicated that their routine surveillance system captures the data required to monitor this indicator. Among the 48 HBCs, 12 countries reported that a WRD had been used as the initial diagnostic test for more than half of their notified TB cases.

The Xpert MTB/RIF® assay (Cepheid, United States) is currently the WRD used most frequently by countries worldwide; it simultaneously detects both TB and resistance to rifampicin. The assay is performed using the GeneXpert® platform, a modular testing device that can detect multiple diseases.1 Between 2010 (when the test was initially recommended by WHO) and 2017, a cumulative total of 9449 GeneXpert instruments, comprising 42 392 modules and 34.4 million cartridges, were procured by the public sector in 130 of 145 countries eligible for concessional pricing.

### 4.1.4 Drug susceptibility testing and detection of drug-resistant TB

Drug-resistant TB threatens global TB care and prevention, and it remains a major public health concern in many countries. Three categories are used for global surveillance and treatment: RR-TB, MDR-TB and extensively drug-resistant TB (XDR-TB). MDR-TB is TB that is resistant to both rifampicin and isoniazid, the two most powerful anti-TB drugs; it requires treatment with a second-line regimen. RR-TB also requires treatment with second-line drugs.2 With increasing use of Xpert MTB/RIF for simultaneous detection of TB and resistance to rifampicin, a growing number of RR-TB cases (without further testing for isoniazid resistance) are being detected and notified.3 XDR-TB is defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable agent (amikacin, capreomycin or kanamycin).

The End TB Strategy calls for universal access to drug susceptibility testing (DST).

### Drug susceptibility testing for first-line drugs and detection of MDR/RR-TB

**Fig. 4.10** shows progress in DST coverage since 2009, when WHO intensified efforts to track progress in the programmatic response to drug-resistant TB.4 In 2017, 2.0 million (30%) of the 6.7 million new and previously treated TB cases notified globally were tested for rifampicin resistance, with coverage of 24% for new TB patients and 70% for previously treated TB patients. These figures represent an improvement since 2015, when 12% of new and 53% of previously treated TB cases had a test result for rifampicin resistance. DST coverage increased in four of the six WHO regions between 2016 and 2017, with a high of 57% in the WHO European Region in 2017. DST coverage varied substantially between countries (even within the same region) and among the 30 high MDR-TB burden countries (Fig. 4.11).

Globally, 160 684 cases of MDR/RR-TB were detected and notified in 2017 (Table 4.1). This was a small increase from 153 119 in 2016 (Fig. 4.12), although aggregate global trends conceal faster progress in some countries (Fig. 4.13). Between 2016 and 2017, the number of reported MDR/RR-TB cases increased by more than 30% in six of the 30 high MDR-TB burden countries (Angola, Democratic People’s Republic of Korea, Indonesia, Nigeria, Somalia and Thailand).

The global number of MDR/RR-TB cases notified in 2017 was 29% of the estimated 558 000 incident cases in 2017 (Fig. 4.12; incidence estimates are discussed in more detail in Chapter 3) and 49% of the estimated 330 000 cases of MDR/RR-TB among notified TB cases. Closing these large detection gaps will require improvements in both overall TB detection (Section 4.2) and coverage of diagnostic DST. The latter requires further strengthening of laboratory capacity and wider uptake of new rapid diagnostics.

### Drug susceptibility testing for second-line drugs and detection of XDR-TB

Among MDR/RR-TB patients notified in 2017, 50% were tested for resistance to both fluoroquinolones and second-line injectable agents, a considerable increase from the 39% tested in 2016. Coverage varied widely among countries (Fig. 4.14). A total of 10 800 cases of XDR-TB were reported by 77 countries, (up from 8014 cases reported by 72 countries in 2016), with 88% of cases being from the WHO European and South-East Asia regions (Table 4.1). The five countries that reported the largest numbers of cases were Belarus (525), India (2650), the Russian Federation (3661), South Africa (747) and Ukraine (1097).

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3 Surveillance and survey data show that about 82% of RR-TB cases have MDR-TB. Further details are provided in Chapter 3.


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## TABLE 4.3
National policies and their implementation to increase access to rapid TB testing and universal DST, 2017

<table>
<thead>
<tr>
<th>Country</th>
<th>HIGH TB BURDEN</th>
<th>HIGH TB/HIV BURDEN</th>
<th>HIGH MDR-TB BURDEN</th>
<th>NATIONAL POLICY AND ALGORITHM INDICATE A WHO AS THE INITIAL DIAGNOSTIC TEST FOR ALL PEOPLE PRESUMED TO HAVE TB</th>
<th>PERCENTAGE OF NOTIFIED NEW AND RELAPSE TB CASES TESTED WITH A WHO AS THE INITIAL DIAGNOSTIC TEST</th>
<th>NATIONAL POLICY AND ALGORITHM INDICATE UNIVERSAL ACCESS TO DST</th>
<th>PERCENTAGE OF NOTIFIED BACTERIOLOGICALLY CONFIRMED TB CASES WITH DST RESULTS FOR RIFAMPICIN-RESISTANT TB</th>
<th>PERCENTAGE OF NOTIFIED RIFAMPICIN-RESISTANT TB CASES WITH DST RESULTS FOR FLUOROQUINOLONES AND SECOND-LINE INJECTABLE AGENTS</th>
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Blank cells indicate data not reported. — indicates value that cannot be calculated.

The 48 countries shown in the table are the countries that are in one or more of the three lists of high TB, TB/HIV and MDR-TB burden countries (see also Chapter 2, Figure 2.5 and Table 2.4).

Testing in cases with unknown previous treatment history is not included. The percentage may exceed 100% for several reasons, e.g. samples rather than cases are counted in the numerator; laboratory specimen results are not linked to the denominator data source when enumerated; or there is incomplete reporting of bacteriologically confirmed cases in the denominator. Bacteriologically confirmed extrapulmonary cases are not included in the denominator because they cannot be differentiated from clinically diagnosed ones in the way data are reported to WHO.
FIG. 4.10
Percentage of all TB cases tested for RR-TB, globally and for WHO regions, 2009–2017

Africa

The Americas

Eastern Mediterranean

Europe

South-East Asia

Western Pacific

Global

FIG. 4.11
Percentage of all TB cases tested for RR-TB, 2017

* 2016 data were used for 18 countries.
4.1.5 Electronic, case-based surveillance for TB

A growing number of countries are capturing data for notified TB cases in electronic case-based surveillance systems. These systems have several advantages compared with more traditional paper-based reporting of aggregated data, including enabling more timely access to data (up to “real-time”) and the availability of data at the level of individual patients up to national level. They also greatly facilitate data analysis (including by age, sex and location) to inform adaptation and targeting of response efforts, both geographically and for specific population groups. Further details, including of global efforts to support the adoption of case-based surveillance for TB, are provided in Box 4.3.

4.2 Treatment coverage

The Sustainable Development Goals (SDGs) include a target to “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all” (Chapter 2). One of the indicators for Target 3.8 of SDG 3 is the coverage of essential health services; this is a composite indicator based on 16 tracer indicators, one of which is TB treatment. Achieving UHC is a fundamental requirement for achieving the milestones and targets of the End TB Strategy; hence, priority indicators for monitoring progress in implementing the End TB Strategy include both TB treatment coverage and the percentage of TB patients and their households that face catastrophic costs as a result of TB disease (Chapter 2).

TB treatment coverage is defined as the number of new and relapse cases detected and treated in a given year, divided by the estimated number of incident TB cases in the same year, expressed as a percentage. In this section, numbers of notified new and relapse cases in 2017 are used as the numerator for the indicator, because these are the data that are available. However, as discussed further below, there are people with TB who are treated but not notified to national authorities (and in turn are not notified to WHO), and people who are notified but who may not be started on treatment.

ART is recommended for all HIV-positive TB patients, and a second-line MDR-TB treatment regimen is recommended for people with MDR/RR-TB. This section includes estimates of treatment coverage for these two interventions as well.

4.2.1 TB treatment coverage

Trends in notifications of new and relapse cases and estimated incidence are shown for the 30 high TB burden countries in Fig. 4.15. Estimates of TB treatment coverage in 2017 (calculated as notifications of new and relapse cases divided by estimated TB incidence) are shown globally, for WHO regions and the 30 high TB burden countries, in Fig. 4.16.

Globally, TB treatment coverage was 64% (range, 58–72%) in 2017, up from 53% (range, 46–64%) in 2010 and 35% (range, 30–43%) in 2000. Three WHO regions achieved levels above 75%: the WHO Region of the Americas, the WHO European Region and the WHO Western Pacific Region. High TB burden countries with high levels of treatment coverage in 2017 (>80%) included Brazil, China, Namibia, the Russian Federation and Viet Nam. The lowest levels, with best estimates of 50% or less, were in Central African Republic, Lesotho, Nigeria and the United Republic of Tanzania.

Globally in 2017, there was a gap of about 3.6 million cases between the 6.4 million new and relapse cases that were notified, and the estimated 10 million incident TB cases in the same year (Fig. 4.1). The global gap has been narrowing, especially in the WHO Eastern Mediterranean Region and the WHO Western Pacific Region, and to a lesser extent in the WHO South-East Asia Region. Ten countries account for 80% of the total estimated global gap between incidence and notifications (Fig. 4.17), with India (26%), Indonesia (11%), Nigeria (9%) and the Philippines (7%) accounting for more than half of the global total.

There are three main reasons for a gap between notifications and estimated incidence:

- Underreporting of detected TB cases. In many countries, levels of underreporting may be high; this is especially the case for those countries that lack policies on mandatory notification and other measures to ensure reporting of detected cases by all care providers and large private health sectors.
FIG. 4.13
Number of MDR/RR-TB cases detected (green) and enrolled on MDR-TB treatment (purple), 2009–2017, 30 high MDR-TB burden countries
**Underdiagnosis of people with TB.** Underdiagnosis can occur for reasons such as poor geographical and financial access to health care; lack of or limited symptoms that delay seeking of health care; failure to test for TB when people do present to health facilities; and diagnostic tests that are not sufficiently sensitive or specific to ensure accurate identification of all cases.

**Overestimation of the level of TB incidence.** In this report, estimates of TB incidence for 44 countries with 19% of the world’s estimated cases are based on expert opinion about levels of underreporting and underdiagnosis, as opposed to direct measurements from surveillance or survey data (Chapter 3). Also, the uncertainty intervals around the best estimates of TB incidence can be wide, and gaps may be lower or higher than the best estimates quoted in this section.

In some of the countries with the largest estimated gaps between notifications and TB incidence, there is already good evidence about the reasons for such gaps, and actions to address them are being taken or are planned.

An excellent recent example is Indonesia. The 2013–2014 national TB prevalence survey showed high levels of underreporting of detected TB cases, leading to recommendations such as a mandatory policy on notification (enacted in January 2017), and intensified engagement with public and private hospitals where many people with TB were being treated. The results from the national TB prevalence survey also led to a decision to implement a national inventory study to measure the level of underreporting of detected TB cases. This was implemented in the first quarter of 2017, and the study proved to be large and robust enough to allow the use of capture-recapture analysis to reassess estimates of incidence. The key study results were that 41% of detected cases were not reported to the national surveillance system, and that about 20% of incident cases were not diagnosed. In other words, although about 80% of incident cases were estimated to be detected, only 59% of these detected cases were officially reported. Based on capture-recapture analysis (see also Chapter 3).

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1. This confirmed earlier data on extensive sales of drugs in the private sector.


3. Capture-recapture modelling is possible if six assumptions are met: (i) all cases should be observable; (ii) the proportion of mismatches and matching failures in record-linkage is low, which typically requires a large sampling fraction; (iii) a closed population during the study period (typically 3–6 months); (iv) if S represents the number of case lists or data sources available, then at least three data sources should be available (S ≥ 3) and their dependencies must be accounted for in the model design, while the full S-way interaction between sources is assumed null; (v) homogeneity of within-source observation probabilities across subpopulation groups, such as those defined by socioeconomic and demographic characteristics; (vi) consistent case definitions across data sources. Few high TB burden countries are expected to be able to implement inventory studies that will meet these assumptions to a sufficient degree.
**BOX 4.3**

**National case-based electronic surveillance systems for TB: status of progress, global efforts to support expansion, broader context**

Case-based electronic surveillance systems for TB with national coverage have several advantages over more traditional paper-based reporting of aggregated data. For example, they enable more timely access to data (up to “real-time”) and the availability of data at the level of individual patients up to national level; also, they greatly facilitate data analysis (including by age, sex and location) to inform adaptation and targeting of response efforts, both geographically and for specific population groups.

WHO has promoted case-based electronic surveillance for TB for several years, with guidance issued in 2012. Status of progress in national case-based electronic surveillance for TB, August 2018

In August 2018, data on the type of TB surveillance system in place at national level were available for 206 countries (Fig. B4.3.1). Of these, 136 had a case-based surveillance system that covered all TB cases (both drug-susceptible and drug-resistant TB). These countries accounted for 67% of global TB notifications in 2017. A further 24 countries, mainly in the WHO African Region and the WHO South-East Asia Region, had a case-based surveillance system for all cases of drug-resistant TB. These countries are in a transition phase between aggregate paper-based reporting and case-based electronic surveillance. The initial prioritization of MDR-TB is explained by the additional complexity of monitoring treatment and treatment outcomes compared with drug-susceptible TB, which is much easier to manage with case-based surveillance; and by the fact that often the numbers of treatment centres and laboratories that need to be involved are smaller, making introduction more feasible from a logistics perspective. About half of the countries in the WHO African Region still have paper-based systems for recording and reporting of data.

**Global efforts to support further expansion of national case-based electronic surveillance for TB**

Building on the WHO guidance issued in 2012, WHO’s Global TB Programme has been working with other WHO departments and the University of Oslo to develop modules in the DHIS2 software for electronic management of data in both aggregated format (as an interim step for countries not yet ready to transition to case-based surveillance) and case-based data. Both modules are based on the WHO recording and reporting framework and both allow extensive data analysis at different levels of the health system. To facilitate the routine analysis and use of TB data, standard dashboards have been developed as part of these DHIS2 modules; these include graphs, tables and maps for core surveillance (e.g. notifications, coverage of testing for drug resistance and HIV, and treatment outcomes) indicators and data quality indicators (e.g. completeness and internal consistency), based on WHO guidance on analysis and use of TB data, and the WHO TB surveillance checklist of standards and benchmarks.

The modules were developed in DHIS2 because many countries are already using this software within their health information systems, it is open-source software with no license fees, and it is being supported by a wide range of technical and funding partners.

WHO and the University of Oslo have already supported six countries to implement, optimize and use their own TB module for aggregated data in DHIS2: Ghana, Guinea-Bissau, Liberia, Myanmar, Uganda and the United Republic of Tanzania. An additional 24 countries are being supported to use the DHIS2 module for aggregated data. By August 2018, aggregated data down to the regional or district level for at least five years had been compiled and stored in a DHIS2 TB platform developed by WHO for 44 countries (Fig. B4.3.2), with more limited data available for an additional four countries. These data can be easily transferred into national DHIS2 databases once these have been adopted and implemented.

**FIG. B4.3.1**

National TB surveillance systems in place in August 2018

Data source: WHO global TB database 2018, supplemented with information provided during WHO workshops on analysis and use of TB data and national TB epidemiological reviews.
A DHIS2 TB module for case-based data that enables electronic management of data for both drug-susceptible and drug-resistant TB in one system is currently in the pilot-testing phase in the Lao People’s Democratic Republic.

**Broader context: the WHO Global Task Force on TB Impact Measurement and the Health Data Collaborative**

Efforts to expand national case-based electronic surveillance systems for TB are part of wider efforts to support the strengthening of national health information systems, and the associated analysis and use of data.

Two of the five strategic areas of work of the WHO Global Task Force on TB Impact Measurement are strengthening national notification systems for direct measurement of TB incidence (within which one of the priorities is case-based electronic surveillance), and analysis and use of TB-relevant data at country level (for further details, see Box 3.1 in Chapter 3).

The Health Data Collaborative (HDC) is a joint effort of multiple global health partners to work alongside countries to improve the availability, quality and use of data for local decision-making and the tracking of progress towards the health-related SDGs. The Secretariat sits with the Department of Information, Evidence and Research (IER) at WHO headquarters. The role of the HDC is to build on existing efforts by establishing a network of working groups that will address specific technical issues and identify and fill technical gaps.

Under the umbrella of the HDC, WHO’s Global TB Programme is working with IER as well as the Global HIV and Hepatitis Programme, the Global Malaria Programme, the Department of Immunisation and the University of Oslo on a 3-year workplan (2017–2020). The workplan covers three major topics:

- Strengthening country health information systems (in general and for specific diseases). This includes support for the development and management of Health Management Information Systems (HMIS) and DHIS2 modules. Examples include WHO health data apps for DHIS2 (cross-cutting and disease specific), which include standard indicators, dashboards and outputs, and capacity-building for case-based surveillance.

- Strengthening analysis and use of the data generated by country information systems. Examples include a curriculum for routine analysis and use of health facility data (curriculum content on TB has already been developed), national epidemiological reviews, and national and regional workshops.

- Ensuring quality in the data generated by country health information systems and in the analysis and use of data. Examples include guidance documents and tools; reviews of plans and investments related to monitoring and evaluation; establishment of a pool of trained consultants, national professional officers and in-country staff and institutions to provide technical assistance; and peer review of the quality of tools, plans, investments and reviews.

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**FIG. B4.3.2**

Subnational, aggregated data stored in the DHIS2 platform developed by WHO (status in August 2018)

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a https://www.dhis2.org/overview


e https://tbhistoric.org

f https://tbhistoric.org

g https://www.healthdatacollaborative.org
**FIG. 4.15**
Case notification rates (new and relapse cases, all forms) (black) compared with estimated TB incidence rates (green), 2000–2017, 30 high TB burden countries. Shaded areas represent uncertainty bands.

- Estimates of TB incidence for India are interim, pending results from the national TB prevalence survey planned for 2019/2020.
- Estimates of TB incidence for Mozambique, Myanmar, Namibia, South Africa and Viet Nam will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.
estimates of incidence were revised to a best estimate of 842 000 cases (range, 767 000–919 000) in 2017 (less than the previous best estimate of around 1 million, although still consistent with the range that was estimated based on the prevalence survey).\textsuperscript{1} Actions are now being taken to correct the high level of underreporting, with results already evident from the notifications reported for the whole of 2017 (Fig. 4.15). A fuller description of the study, including methods, results and lessons learned, is provided in Box 4.4.

In India, multiple sources of evidence from surveys and surveillance have shown large underreporting of detected TB cases, especially in the private sector.\textsuperscript{2} Three examples of actions that have been taken to close reporting gaps are mandatory notification, a simplified national electronic reporting system that facilitates reporting of cases, and further efforts to engage all care providers through PPM schemes, all of which have already had an effect on notification trends (Section 4.1.1; Fig. 4.15).

A good example of a country where underdiagnosis is a major challenge is Nigeria. The 2012 prevalence survey in Nigeria found that 75% of the smear-positive cases detected had symptoms that met national screening criteria but had not been previously diagnosed, demonstrating high levels of underdiagnosis and a need to strengthen access to screening, diagnostic and treatment services of high quality.\textsuperscript{3}

In countries where underreporting is thought to exist, inventory studies in which electronic lists of notified cases are compared with electronic lists of TB cases detected by all care providers, ideally employing unique identifiers, can be used to quantify levels of underreporting.

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\textsuperscript{1} See also Box 3.2 in Chapter 3.


ing, as in Indonesia. Other high TB burden countries that have already implemented an inventory study are India, Kenya, Pakistan and Viet Nam. Four more are underway or being planned, in China, the Philippines, South Africa and the United Republic of Tanzania. When this type of study is done prospectively (as opposed to retrospectively, using electronic databases that are already available), the mapping of providers that is required at the beginning can subsequently help with efforts to engage all care providers, including in reporting (Box 4.4).

Examples of mechanisms to ensure reporting of all detected cases include linking reimbursement from health insurance schemes to notification of cases (as is done in the Philippines and the Republic of Korea) and linking the supply of first-line drugs to notification of cases (as is done in Brazil).

Recent national TB prevalence surveys have also shown that, in both Africa and Asia, detection and reporting gaps are systematically higher for men than for women (Chapter 3). This suggests that specific efforts are needed to improve access to TB diagnosis and treatment for men.

Systematic screening for active TB among specific populations can also help to ensure early diagnosis and reduce levels of underdiagnosis. WHO recommends such screening for contacts of bacteriologically confirmed cases, people living with HIV and people exposed to silica dust. Other individuals at risk should be considered for systematic screening based on an assessment of TB epidemiology in each setting. To date, there have been few assessments of the implementation and outcomes of systematic screening in countries that are currently introducing or scaling up systematic screening. However, this is expected to become a more prominent part of national programme monitoring and evaluation efforts in future. Engaging communities can also add value to efforts to improve case detection and patient support (Box 4.5).

2 Results from these studies have been used to inform estimates of TB incidence.

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**FIG. 4.17**
The ten countries with the largest gaps between notifications of new and relapse (incident) TB cases and the best estimates of TB incidence, 2017

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5 The data requested as part of WHO’s global monitoring focus on screening among people living with HIV and close contacts. Hence, the data requested in WHO’s annual round of global TB data collection focus on screening among people living with HIV and close contacts. These data are presented in Chapter 5.
BOX 4.4
The 2017 national TB inventory study in Indonesia: main results, lessons learned, policy and programmatic implications

Indonesia is a country with a large private health sector that is not yet firmly linked to the reporting network of the NTP. Furthermore, some of the secondary and tertiary level facilities of the public health sector do not have functioning and sustained reporting links with the NTP.

In 2016, a total of 360,565 TB cases were notified to national authorities, while the estimated TB incidence was 1,020,000 (95% confidence interval [CI]: 660,000–1,460,000). To address underreporting, a Health Ministerial Decree was enacted in 2017, making notification of TB mandatory nationwide.

A national TB inventory study was implemented in 2017 under the leadership of the NTP and the National Institute of Health Research and Development. The aim was to directly measure the level of underreporting of detected TB cases to the national TB surveillance system (SITT, System Informasi Tuberkolosis Terpadu) maintained by the NTP for the different types of health facilities, and to identify best-practice methods for addressing TB underreporting.

Methods and main results

The study methods from design through implementation, analysis and reporting of results followed the recommendations of the WHO Global Task Force on TB Impact Measurement.

The study employed a random, nationally representative sample of 23 districts (out of a total of 514) from across the country, using a sampling design with stratification by urban or rural status and three regions – Sumatera, Java/Bali and “other provinces” (Fig. B4.4.1). The 23 districts accounted for 10% of the national population of 260 million.

In each of the sampled districts, all health-care providers of TB services were mapped, starting from existing but outdated lists of health-care providers, which were then confirmed by study enumerators (Fig. B4.4.2). A total of 4,207 health-care providers were enumerated in the 23 districts, of which 1,687 were eligible (defined as a facility that reported having diagnosed or treated at least one TB patient in the previous 3 months). Of the eligible health-care providers, 99% participated in the study – a testament to the success of district-level workshops and meetings with all stakeholders. Pharmacies were not included in the sampling frame of the study.

During the study period (the first quarter of 2017), patient records for a total of 21,320 unique TB patients were detected overall. Of these, 13,211 unique TB patients were notified and registered in SITT. Probabilistic matching allowed linkage of records from the TB case lists, measuring their overlap and corresponding underreporting (Fig. B4.4.3).

The overall level of underreporting of detected TB cases (i.e. the proportion of detected cases not in SITT) was estimated to be 41% (95% CI: 36–46%), ranging from 15% (95% CI: 11–20%) underreporting by primary health-care “puskesmas” units which are part of the existing NTP network to 65% underreporting by hospitals to 96% underreporting by the combined category of general practitioners (GPs), clinics and laboratories. Patients with clinically diagnosed and extrapulmonary TB, as well as children, were more likely to be underreported (Table B4.4.1).

Incidence was estimated using capture–recapture modelling of the three TB case lists (SITT, study public and study private), according to recommendations (see also section 4.2.1). It was estimated that 18% (95% CI: 15–21%) of incident cases were not detected. The annual incidence rate for 2017 was estimated at 319 (95% CI: 290–349) per 100,000 population per year. This updated best estimate of TB incidence is lower but statistically consistent with the previously published estimate derived from the 2013/2014 prevalence survey (Fig. B4.4.4).

Study results and updated estimates were discussed and agreed upon in a national consensus meeting held in April 2018. The excellent participation rate of health-care providers, in addition to the consistency of key results through sensitivity analyses, show that the study was implemented to a high standard and has produced robust results.

During the course of 2017, the NTP already started to take corrective action to reduce underreporting. This led to a substantial increase in TB notifications in 2017 compared with 2016. While the measure of underreporting in the study during the first quarter of 2017 was 41%, in the subsequent three quarters of 2017 the NTP reduced this; the overall level of underreporting for 2017 was 36% (Fig. B4.4.5).
Lessons learned
The key lessons learned from the study were as follows:

1. TB underreporting in Indonesia up to the first quarter of 2017 was very high.
2. Out of incident TB cases missed from the TB surveillance system, two thirds were not reported and the remaining one third were not detected.
3. An up-to-date master list of health facilities (both for the public and private sectors) needs to be maintained for efficient monitoring of the effectiveness of the policy of mandatory case notification.
4. Record linkage should occur routinely (at least once a year) between the database of the NTP (SITT) and other databases of TB cases.
5. A unique identifier (e.g., health insurance number) strongly facilitates disease surveillance in general, and record linkage in particular.

6. More than 95% of TB cases identified during the study were treated using a drug regimen that was consistent with national TB guidelines, indicating that a high quality of TB care is provided by different types of health providers. The low level of drug resistance among TB cases found in the recent national survey of drug resistance (see Chapter 3) is consistent with this finding.

Policy and programmatic implications
The major implications of study results, some of which require high-level policy action, include the following:

1. All health-care providers need to be made aware that all TB cases must be reported. Previously, emphasis was given to reporting of pulmonary, bacteriologically confirmed cases.
2. Human resource capacity for data collection and management needs to be increased. Dedicated staff are required to work on data entry and reporting, especially...
FIG. B4.4.4
Trends in estimated rates of TB incidence and case notifications, 2000–2017. Updated time series of incidence rates for 2000–2017 are shown in blue, previous estimates for 2000–2016 that were based on the 2013–2014 national TB prevalence survey are shown in orange and case notifications are shown in black. Shaded areas represent uncertainty bands.

FIG. B4.4.5
TB incidence in Indonesia, 2017 broken down into those cases detected and notified, those detected and not notified (or underreported) and those not detected at all.

TABLE B4.4.1
Level of TB under-reporting (%) by type of health care provider, type of TB case, age, sex and strata, accounting for sampling design

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<th>MEAN PERCENTAGE (95% CONFIDENCE INTERVAL)</th>
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<td><strong>By type of health provider</strong></td>
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<td>Primary health care (“puskesmas”)</td>
<td>15 (11–20)</td>
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<tr>
<td>Non-primary health care</td>
<td>71 (61–79)</td>
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<tr>
<td>Hospital</td>
<td>62 (52–72)</td>
</tr>
<tr>
<td>Other</td>
<td>96 (92–98)</td>
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<tr>
<td><strong>By TB case type</strong></td>
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<tr>
<td>Bacteriologically confirmed</td>
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<td>Clinically diagnosed</td>
<td>55 (49–61)</td>
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<td><strong>By site of disease</strong></td>
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<tr>
<td>Pulmonary</td>
<td>38 (33–44)</td>
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<tr>
<td>Extra-pulmonary</td>
<td>58 (49–66)</td>
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<tr>
<td><strong>By age</strong></td>
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<tr>
<td>&lt;15 years</td>
<td>54 (44–64)</td>
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<tr>
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<tr>
<td>Male</td>
<td>41 (36–46)</td>
</tr>
<tr>
<td><strong>By strata</strong></td>
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<tr>
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<tr>
<td>Bali/Java</td>
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</tr>
<tr>
<td>Other</td>
<td>39 (28–51)</td>
</tr>
</tbody>
</table>

* Clinics, general practitioners, laboratories.

GP networks. The inventory study provided additional ideas for how to strengthen approaches to working with these care providers.

Conclusions and next steps
The 2017 national TB inventory study in Indonesia is the largest study of its kind ever conducted globally. It generated high-quality data, as well as important evidence with clear policy and programmatic implications.

Following official and wide dissemination of findings in April 2018, results are now being used to help to develop national and district level responses for further rollout. A study report is being finalized and results will be summarized in a paper for a peer-reviewed journal.

b When using population estimates from the Statistics Bureau, Indonesia – instead of population estimates from the United Nations Population Division – the estimated TB incidence rate is 322 (95% CI: 294–352) per 100 000 population per year.
c Further discussions were also held between WHO and the NTP during the drafting and finalization of this box.
BOX 4.5

Community contributions to TB notifications and treatment support

The WHO End TB Strategy calls for close collaboration with affected communities and civil society organizations in planning, implementation, and monitoring and evaluation.

Community-based TB activities include a wide range of activities that contribute to prevention, diagnosis, treatment and care, and can positively influence TB outcomes. They are delivered primarily by community health workers (CHWs) and community volunteers (CVs) who are drawn from within the community and are, therefore, both accessible and acceptable to community members.

In the current era of the SDGs and in the context of UHC, primary health care is receiving greater attention. An increasing number of countries are taking steps to absorb cadres of CHWs into the workforce of national health systems. This will help to strengthen community-based service delivery and also help to reach those who are otherwise unable to access health services.

In WHO’s 2018 round of global TB data collection, 61 countries reported data about the contribution of communities through CHWs or CVs to TB notifications or treatment support. This represents nearly a fivefold increase in reporting since 2013, when data were first collected on the two core indicators (contributions to new notifications and to treatment support) used to monitor community contributions to TB outcomes.

The contribution of community referrals to TB notifications was reported by 57 countries. The percentage of notified TB patients attributed to community referrals averaged 27% (ranging from less than 1% in Iran and Sri Lanka, to 100% in Bulgaria, Congo, Gabon, Haiti, Paraguay, and Sao Tome and Principe). The treatment success rates for people who benefited from any form of community treatment support could be calculated for 44 of these 57 countries. The average treatment success rate was 87%, ranging from 39% in Burkina Faso to 100% in Burundi, Honduras and Serbia.

In 2018, 112 countries were asked to report data on community contributions to TB care, of which 91 (81%) reported implementing community-based TB activities. In these 91 countries, the mean coverage of community-based TB activities was 74% of all basic management units.

FIG. B4.5.1
Percentage of basic management units in which there is community contribution to new case finding and/or to treatment adherence support, 2017

FIG. B4.5.2
Number of countries reporting on WHO community engagement indicators, 2013–2018

Data only requested from 111 countries.

4.2.2 Treatment coverage of ART for HIV-positive TB cases

WHO recommends ART for all HIV-positive TB patients within the first 8 weeks of starting TB treatment, and within two weeks in profoundly immunosuppressed HIV-positive TB patients with low CD4 counts less than 50. The number of notified HIV-positive TB patients on ART has grown in recent years (Fig. 4.18); it reached 377 040 in 2017, equivalent to 84% of the notified TB patients known to be HIV-positive (Table 4.1).¹ In the 30 high TB/HIV burden countries, overall, 85% of the TB patients known to be HIV-positive were on ART. Eight of these countries (Eswatini, Kenya, Malawi, Mozambique, Namibia, Papua New Guinea, Uganda and the United Republic of Tanzania) maintained coverage of at least 90% in both 2016 and 2017. In contrast, there were six high TB/HIV burden countries (Angola, Botswana, Brazil, Guinea-Bissau, Indonesia and Liberia) in which less than 50% of HIV-positive TB patients were started on ART in 2017. Cameroon, Chad and China did not report data on ART for TB patients for 2017.

ART treatment coverage for people with TB can also be assessed by comparing the number of HIV-positive TB patients on ART with the estimated number of HIV-positive incident TB cases (Fig. 4.19). This comparison revealed larger gaps. Globally in 2017, the number of HIV-positive TB patients on ART was 41% of the estimated global number of incident HIV-positive TB cases; this is lower than the global ART coverage of 59% among all people living with HIV in 2017. There was considerable variation among the high TB/HIV burden countries and, according to best estimates, only eight countries achieved ART coverage of more than 50% (Eswatini, Ethiopia, Malawi, Namibia, South Africa, Uganda, Zambia and Zimbabwe).

Improvements are still needed in the detection of active TB disease among HIV-positive people, the coverage of HIV testing among TB patients, and the enrolment of HIV-positive TB patients in ART. A recent example of efforts to address gaps in the cascade of care in India is provided in Box 4.6. An overview of progress and gaps in TB preventive treatment among people living with HIV is provided in Chapter 5.

4.2.3 Treatment coverage for MDR/RR-TB

Trends in the number of patients enrolled in MDR-TB treatment globally and in the 30 high MDR-TB countries since 2009 are shown in Fig. 4.12 and Fig. 4.13, respectively. The number of people enrolled in treatment globally was 139 114 in 2017, representing a more than fourfold increase since 2009 (when WHO first asked countries to report data) and up from 129 689 in 2016.

Between 2016 and 2017, there were notable increases in enrolments in the Democratic People’s Republic of Korea (from 814 to 1732), Indonesia (from 1879 to 3042) and Angola (from 334 to 534), and modest increases in several other high MDR-TB burden countries. However, the number of enrolments fell in nine high MDR-TB burden countries (Fig. 4.13).

Globally, the 139 114 patients starting second-line MDR-TB treatment in 2017 represented 25% of the 558 000 estimated MDR/RR-TB incident cases in 2017 (Fig. 4.20). The highest levels of treatment coverage among high MDR-TB burden countries were in Kazakhstan (82%) and South Africa (73%). Ten countries accounted for about 75% of the gap between enrolments in MDR-TB treatment in 2017 and the estimated number of incident MDR/RR-TB cases in 2017; and China and India accounted for 40% of the total gap (Fig. 4.21). Treatment coverage will not improve globally unless there is an intensification of efforts in the countries with the largest burden, particularly China, India and Indonesia.

The number of cases starting MDR-TB treatment in 2017 was equivalent to 87% of the 1 606 84 MDR/RR-TB patients notified in 2017 (Fig. 4.12). The figure exceeded 90% in 17 high MDR-TB burden countries (Fig. 4.13) and in the WHO European Region and the WHO Region of the Americas; however, it was much lower in the WHO African Region and the WHO Western Pacific Region.² Enrolments represented no more than 60% of the number of notified MDR/RR-TB cases in two high MDR-TB burden countries in 2017: China (45%) and Indonesia (60%). These low percentages show that progress in detection is outstripping the capacity to provide treatment; they may also reflect weaknesses in data collection systems. In these settings, the risk of transmission of drug-resistant TB is high, and efforts are needed to rapidly close gaps in enrolment and notification.

In many countries, one of the barriers to adequate access to treatment of drug-resistant TB is that the network for the programmatic management of drug-resistant TB (PMDT) is too centralized and too reliant on hospital-based models of care. Greater decentralization and more use of outpatient models of care are needed.

Globally, 8703 patients with XDR-TB were enrolled in treatment in 70 countries and territories, a small (2%) increase compared with 2016. In 20 of these countries, the number of XDR-TB cases enrolled in treatment was less than the number notified. Only one high MDR-TB burden country (Thailand) and three other countries (Algeria, Bhutan and Uganda) reported prescribing morphine to treat pain or terminal dyspnoea in patients for whom second-line TB treatment regimens did not work, suggesting that there are widespread unmet needs in terms of end-of-life care as well as inadequate data gathering on this issue.

¹ There may be discrepancies in data on provision of ART to HIV-positive TB patients that are reported by NTPs and national HIV programmes. These discrepancies have reduced in recent years and have mostly been resolved through follow-up and validation efforts.

² For data for WHO regions, see Annex 3.
**FIG. 4.18**
Number of new and relapse cases\(^a\) known to be HIV-positive (black) and number started on ART (blue) compared with estimated number of incident HIV-positive TB cases (red), 2004–2017, 30 high TB/HIV burden countries

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\(^a\) The calculation is for all cases in years prior to 2015.

\(^b\) Estimates of TB incidence for Eswatini, Mozambique, Myanmar, Namibia and South Africa will be reviewed after final results from their respective national TB prevalence surveys are available in 2019.

\(^c\) Estimates of TB incidence for India are interim in nature, pending results from the national TB prevalence survey planned for 2019/2020.
4.3 Treatment outcomes

This section summarizes the latest results of treatment for new and relapse cases of TB who started treatment on a first-line regimen in 2016 (including people with HIV-associated TB), and people detected with RR-TB, MDR-TB or XDR-TB who started a second-line MDR-TB regimen in 2015.1

4.3.1 Treatment outcomes for new and relapse TB patients

Data on treatment outcomes for new and relapse cases of TB in 2016 are shown for the world, the six WHO regions and the 30 high TB burden countries in Fig. 4.22. The global trend 2012–2016 is shown in Fig. 4.23. Globally, the treatment success rate for the 5.9 million new and relapse cases who were treated in the 2016 cohort was 82%. This is a reduction from 86% in 2013 and 83% in 2015; the main explanation is that in countries where notifications have increased (notably India), reporting of treatment outcomes has not kept pace with notifications. In India, treatment outcome data were not reported for 22% of cases notified in 2016. The absolute number of TB patients reported to have been successfully treated has risen substantially over the past 16 years, both globally and in all WHO regions (Fig. 4.24).

Among the six WHO regions, the highest treatment success rates in 2016 were in the WHO Eastern Mediterranean Region (92%) and the WHO Western Pacific Region (91%). The lowest rates (at 75%) were in the WHO South-East Asia Region (due to high proportions of unevaluated cases, especially in India), the WHO Region of the Americas (due to high levels of loss to follow-up and missing data) and the WHO European Region (due to high rates of treatment failure and death, influenced by the high frequency of MDR/RR-TB).
only nine of the 30 high TB burden countries reached or exceeded a 90% treatment success rate. However, in several high TB burden countries, the completeness of outcome reporting was low. In five countries (Angola, Brazil, Central African Republic, Liberia and Papua New Guinea), loss to follow-up exceeded 10%, and in four countries (Angola, Congo, India and Papua New Guinea), the treatment outcome was not documented for more than 10% of cases.

4.3.2 Treatment outcomes for new and relapse TB patients coinfected with HIV

A total of 124 countries reported treatment outcomes for the 2016 patient cohort disaggregated by HIV status; collectively, these countries accounted for 94% of the HIV-positive TB patients reported by NTPs in 2016. These 124 countries included 24 of the 30 high TB/HIV burden countries; no data were reported by Chad, Congo, the Democratic Republic of the Congo, Ethiopia, Liberia and Papua New Guinea (Fig. 4.25). Overall, the treatment success rate was 77%, an increase from 68% in 2012 (Fig. 4.23), although still worse than the level of 82% for all new and relapse TB patients.

FIG. B4.6.1 Cascade of TB case-finding among people living with HIV (PLHIV) attending antiretroviral therapy (ART) clinics, India, 2017

Fig. B4.6.1 depicts the next stages of the TB case-finding cascade. In 514,862 consultations, 65% of those attending ART centres in whom TB symptoms were identified were referred for TB diagnosis; of those, 85% underwent a TB diagnostic test, of whom 14% were found to have TB. These extensive nationwide efforts help to identify gaps in referral and diagnosis to prompt follow-up as necessary.

Capturing data for each step in the cascade can be challenging, unless a robust, integrated and preferably electronic, case-based recording and reporting system is in place that communicates the information across the programmes. In the absence of electronic recording and reporting systems, periodic patient record surveys of people attending HIV care is recommended, to evaluate the gaps in the TB case-finding continuum, which in turn helps to inform and improve programming, recording and reporting, and client follow-up.

For the past year, the Revised National TB Control Programme (RNTCP) and National AIDS Control Organization (NACO) in India have been capturing data to evaluate TB case-finding activities among people attending ART centres.

According to data reported by the RNTCP for 2017, an estimated 58% (n = 49,000 [95% CI: 21,000–84,000]) of people with HIV-associated TB were not reported to have reached TB care. Reasons for missing people with TB include poor access to services, weaknesses in service delivery, gaps in recording and reporting, and limited engagement of the private sector.

Identifying the size and nature of these gaps requires data about each part of the cascade of care, from initial evaluation for TB signs and symptoms to the start of treatment. For HIV-associated TB, analysis should also be conducted on the HIV care cascade among TB patients. Depending on the degree of integration between a country’s TB and HIV services and their respective monitoring and evaluation systems, the patient pathway for HIV-associated TB can be more complex to track, since there may be a need for referral from one programme to another. Close collaboration between the TB and HIV services is therefore critical for reducing loss to follow-up and preventable mortality. To strengthen integration, the Government of India has rolled out TB service delivery from all HIV clinics since December 2016.

Although reporting of HIV case-based data for the TB case-finding cascade has not yet been possible in India, the RNTCP and NACO have been able to report data based on clinic visits. People living with HIV made almost 11 million visits to ART centres in 2017. In 83% of these visits, the clinic attendees received an evaluation for TB. Of those who were evaluated, 6% had TB symptoms.

Only nine of the 30 high TB burden countries reached or exceeded a 90% treatment success rate. However, in several high TB burden countries, the completeness of outcome reporting was low. In five countries (Angola, Brazil, Central African Republic, Liberia and Papua New Guinea), loss to follow-up exceeded 10%, and in four countries (Angola, Congo, India and Papua New Guinea), the treatment outcome was not documented for more than 10% of cases.
FIG. 4.20
Estimated treatment coverage for MDR/RR-TB (patients started on treatment for MDR-TB as a percentage of the estimated incidence of MDR/RR-TB) in 2017, 30 high MDR-TB burden countries, WHO regions and globally

Globally, the proportion of HIV-positive TB patients who died during treatment was 11%, similar to previous years and about three times the level among all new and relapse cases (4%). In the WHO regions, the relative difference was smallest in the WHO African Region (9% versus 5%) and highest in the WHO Eastern Mediterranean Region (14% versus 2%). In the WHO Region of the Americas and the WHO European Region, the proportion of HIV-positive TB patients who died was 20% and 22%, respectively.

Reasons for comparatively poor outcomes for HIV-positive TB patients include late detection of HIV-associated TB and MDR-TB, and delays in starting ART or TB treatment. To reduce excessive TB mortality in people who are HIV-positive, WHO recommends routine HIV testing among presumptive and diagnosed TB cases, TB screening among people living with HIV, early ART, improved infection control and provision of TB preventive treatment. Options that could help to ensure earlier diagnosis and reduce mortality include strategic placement of WHO-recommended rapid molecular TB diagnostics such as Xpert MTB/RIF within HIV care settings, and uptake of the lateral flow urine lipoarabinomannan assay (LF-LAM) for seriously ill people living with HIV.

4.3.3 Treatment outcomes for TB patients with MDR/RR-TB and XDR-TB

A total of 144 countries and territories reported treatment outcomes for people started on MDR-TB treatment in 2015. The number of cases reported in annual cohorts has steadily increased over time, reaching 114,180 cases globally in the 2015 cohort. Overall, the proportion of MDR/RR-TB patients in the 2015 cohort who successfully completed treatment (i.e. cured or treatment completed) was 55%; in 8% the treatment failed, 15% died, 14% were lost to follow-up and for 7% there was no outcome information (Fig. 4.26).

Globally, treatment success has increased slightly in recent years (Fig. 4.23). In the 2015 cohort, the treatment success rate was highest in the WHO Eastern Mediterranean Region (62%) and was lowest in the WHO

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1 This is the latest year for which data on treatment outcomes for drug-resistant TB have been reported to WHO. There is a longer lag time for reporting of data due to the longer duration of treatment for drug-resistant TB.
South-East Asia Region (50%). In contrast, treatment failure was highest in the WHO European Region (12%), and the death rate was highest in the WHO African Region (20%). Loss to follow-up was highest in the WHO Region of the Americas (26%), while the WHO Western Pacific Region had the highest percentage of cases without outcome data (17%).

Among the 30 high MDR-TB burden countries, 15 had MDR/RR-TB cohorts in 2015 with more than 1000 cases; among these, only Kazakhstan and Myanmar reported treatment success of more than 75%. Treatment success was less than 50% in China, India, Indonesia, Mozambique, the Republic of Moldova and Zimbabwe. This was due to high rates of death and loss to follow-up in India (20% and 19%) and Indonesia (16% and 31%), high rates of loss to follow-up or missing data about treatment outcome in China (13% and 32%), a high death rate and missing data about treatment outcome in Mozambique (26% and 13%) and Zimbabwe (17% and 32%), and high rates of loss to follow-up and failure in the Republic of Moldova (20% and 18%).

Among 8399 patients started on treatment for XDR-TB in 2015, in 49 countries and territories for which outcomes were reported, 34% completed treatment successfully, 26% died, treatment failed for 19%, and 21% were lost to follow-up or their treatment outcome was not evaluated. India, the Russian Federation and Ukraine accounted for 74% of the 2015 XDR-TB cohort. Among seven countries with XDR-TB cohorts of more than 100 individuals, mortality was highest in India and Uzbekistan (42% and 41%).

Although improving in some countries, the treatment success rate for MDR/RR-TB globally remains unacceptably low. The wider use of more effective MDR-TB treatment regimens designed on the basis of the latest available evidence, and the use of more patient-centred models of care, are expected to help improve this situation. New guidance related to the treatment of drug-resistant TB was recently reviewed by a WHO Guidelines Development Group, and WHO will issue updated guidance later in 2018 (Box 4.7).

By the end of 2017, 62 countries, mostly in Africa and Asia, reported having used shorter MDR-TB regimens (Fig. 4.27). These regimens have been reported to achieve high treatment success rates (87–90%) in selected MDR/RR-TB patients. By the end of 2017, 68 countries reported having imported or started using bedaquiline, and 42 countries had used delamanid (Fig. 4.28 and Fig. 4.29). Most (79%) of the patients treated with bedaquiline were reported by two countries: the Russian Federation and South Africa.

With the introduction of new drugs and regimens, there is a need for active TB drug-safety monitoring and management (aDSM). aDSM is defined as the active and systematic clinical and laboratory assessment of

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**FIG. 4.21**

The ten countries with the largest gaps between the number of patients started on treatment for MDR-TB and the best estimates of MDR/RR-TB incidence, 2017

*The ten countries ranked in order of the size of the gap between the number of patients started on MDR-TB treatment and the best estimate of MDR/RR-TB incidence in 2017 are India, China, Russian Federation, Pakistan, Nigeria, the Philippines, Indonesia, Ukraine, Myanmar and Mozambique.*
FIG. 4.22
Treatment outcomes for new and relapse TB cases in 2016, 30 high TB burden countries, WHO regions and globally

FIG. 4.23
Treatment outcomes for new and relapse TB cases, new and relapse HIV-positive TB cases, and MDR/RR-TB cases, 2012–2016 globally

* Treatment outcomes are for new cases only.

* MDR/RR-TB annual treatment cohorts are reported one year later than other TB cohorts.
BOX 4.7

WHO revises its guidance on the treatment of MDR/RR-TB

Since WHO last issued MDR/RR-TB treatment guidelines in 2016, new patient data have emerged. These include final results from the first-ever Phase III randomized controlled trials of delamanid and the 9-month shorter MDR-TB regimen.

In 2018, WHO convened a Guideline Development Group (GDG) to advise on the revision of its guidance. The scope of the new guidelines covered the use of the shorter MDR-TB regimen, the composition and duration of longer MDR-TB regimens, and the use of culture to monitor treatment response in these regimens. Before a meeting of the GDG in July 2018, WHO issued a public call for individual patient data from trials, as well as observational studies and programmatic cohorts. Systematic reviews and meta-analyses were undertaken using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, in accordance with WHO’s requirements for the formulation of evidence-based health policy.

Based on the latest evidence, the GDG recommended significant changes to the design of longer MDR-TB treatment regimens. The listing of medicines to choose from as first priority include three that have shown the most advantageous balance between effectiveness and toxicity: later generation fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline and linezolid. The regimen is completed with other agents, in order of relative potency. Unlike the previous algorithms, the systematic inclusion of injectable medicines is no longer required, and all-oral longer regimens are now an option for many patients, subject to individual need. Some of the older TB medicines, such as the injectable agents kanamycin and capreomycin, are no longer recommended for use.

As a result of these modifications, and as global access to the most effective agents in longer regimens improves, the role of the shorter MDR-TB treatment regimen in programmatic TB care is destined to change.

All patients on longer and shorter MDR-TB regimens should receive appropriate counselling and be informed of their options before enrolment on treatment. DSM for all patients enrolled in treatment is essential.

The full guidelines will be released in late 2018, along with revised decision aids and practical advice (e.g. drug dosage schedules for adults and children) in an update of the WHO MDR-TB implementation manual.


**FIG. 4.24**

Treatment outcomes for new and relapse TB cases absolute numbers), 2000–2016, globally and for WHO regions
FIG. 4.25
Treatment outcomes for new and relapse HIV-positive TB cases in 2016, 30 high TB/HIV burden countries, WHO regions and globally

FIG. 4.26
Treatment outcomes for MDR/RR-TB cases started on treatment in 2015, 30 high MDR-TB burden countries, WHO regions and globally

<table>
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<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentage of cohort (%)

Treatment success  Failure  Died  Lost to follow-up  Not evaluated  No data reported

* These countries reported less than 500 MDR/RR-TB cases who started second line TB treatment in 2015.

patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.1 In 2017, 16 of the 30 high MDR-TB burden countries reported data on adverse events collected from their TB information systems.

**FIG. 4.27**
Countries that had used shorter MDR-TB treatment regimens by the end of 2017

**FIG. 4.28**
Countries that had used bedaquiline for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of 2017
FIG. 4.29
Countries that had used delamanid for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of 2017
A young TB patient waits with his mother to see a doctor at a clinic in New Delhi, India

Gary Hampton / WHO and Vital Strategies
Chapter 5. TB prevention services

KEY FACTS AND MESSAGES

Prevention of new infections of Mycobacterium tuberculosis and their progression to tuberculosis (TB) disease is critical to reduce the burden of disease and death caused by TB, and to achieve the End TB Strategy targets set for 2030 and 2035.

Current health interventions for TB prevention are treatment of latent TB infection (LTBI), prevention of transmission of M. tuberculosis through infection prevention and control, and vaccination of children with the bacille Calmette-Guérin (BCG) vaccine.

WHO guidelines published before 2018 identified four priority groups in which testing and treatment for LTBI was strongly recommended: people living with HIV (all countries), children aged under 5 years who are household contacts of bacteriologically confirmed pulmonary TB cases (all countries), people aged five years or more who are household contacts of pulmonary TB cases (upper middle-income and high-income countries with a low incidence of TB) and clinical risk groups (upper middle-income and high-income countries with a low incidence of TB). Updated guidance published in 2018 includes an additional recommendation to consider testing and treatment for people aged 5 years or more who are household contacts of bacteriologically confirmed pulmonary TB cases in countries with a high incidence of TB; it also expands the recommendation for clinical risk groups to all countries.

Globally in 2017, 67 countries reported initiating TB preventive treatment for a total of 958 559 people living with HIV; this included 640 201 people who were newly enrolled in HIV care, in 60 countries. South Africa accounted for 39% of the total.

Of the 30 high TB/HIV burden countries, 15 reported providing TB preventive treatment to people newly enrolled in HIV care in 2017, up from 11 in 2016. Coverage ranged from 1% in Eswatini (formerly Swaziland) to 53% in South Africa. Overall, in the 59 countries for which it could be calculated, coverage was 36%.

There were an estimated 1.3 million children aged under 5 years who were household contacts of bacteriologically confirmed pulmonary TB cases and thus eligible for treatment according to WHO recommendations. The number of children in this age group reported to have been started on TB preventive treatment increased to 292 182 in 2017, up 79% from 163 720 in 2016, and a more than three-fold increase from 87 242 in 2015, but was still only 23% of those estimated to be eligible.

Improvements to routine surveillance are needed to capture complete and reliable data on the provision of TB preventive treatment.

The ratio of the TB notification rate among health-care workers to the TB notification rate in the general adult population is a good indicator of the impact of TB infection prevention and control in health facilities. In 2017, a total of 929 999 health-care workers from 65 countries were reported with TB; China accounted for 35% of these cases. In six countries (Brunel Darussalam, Colombia, Dominican Republic, Honduras, Paraguay and Zimbabwe), the number of TB cases per 100 000 health-care workers was more than double the notification rate in the general adult population.

BCG vaccination should be provided as part of national childhood immunization programmes according to a country's TB epidemiology. In 2017, 158 countries reported providing BCG vaccination as a standard part of these programmes, of which 120 reported coverage of at least 90%, up from 111 countries in 2016.
Prevention of new infections of *Mycobacterium tuberculosis* and their progression to tuberculosis (TB) disease is critical to reduce the burden of disease and death caused by TB, and to achieve the End TB Strategy targets set for 2030 and 2035. The targets of an 80% reduction in TB incidence from the 2015 level by 2030, and of a 90% reduction by 2035, will require a historically unprecedented acceleration in the rate at which TB incidence falls after 2025 (Chapter 2). This accelerated rate (an average of 17% per year between 2025 and 2035) is possible only if the probability of progression from latent TB infection (LTBI) to active TB disease among the approximately 1.7 billion people already infected worldwide is substantially reduced. Health-care interventions that could help to cut the risk of progression from LTBI to active TB disease include more effective drug treatments for LTBI, and development of a vaccine to prevent reactivation of LTBI in adults. Action on the broader determinants of TB could also cut the risk; these are discussed further in Chapter 7.

Currently, three major categories of health interventions are available for TB prevention:
- treatment of LTBI;
- prevention of transmission of *M. tuberculosis* through infection prevention and control; and
- vaccination of children with the bacille Calmette-Guérin (BCG) vaccine.

The three main sections of this chapter present and discuss progress in provision of these services. Particular attention is given to the 30 high TB burden countries and the 30 high TB/HIV burden countries (Chapter 2).

### 5.1 Treatment of latent TB infection

LTBI is defined as a state of persistent immune response to *M. tuberculosis* without clinically manifested evidence of active TB disease.

WHO guidelines published before 2018 identified four priority groups in which testing and treatment for LTBI was strongly recommended: people living with HIV (all countries); children aged under 5 years who are household contacts of bacteriologically confirmed pulmonary TB cases (all countries); people aged 5 years or more who are household contacts of pulmonary TB cases (upper middle-income and high-income countries with a low incidence of TB); and clinical risk groups (upper middle-income and high-income countries with a low incidence of TB). Updated guidance published in 2018 includes an additional recommendation to consider testing and treatment for people aged 5 years or more who are household contacts of bacteriologically confirmed pulmonary TB cases in countries with a high incidence of TB; it also expands the recommendation for clinical risk groups to all countries. Further details, including estimates of the number of people eligible for treatment based on the updated guidance, are provided in Box 5.1.

Data on the provision of TB preventive treatment for people living with HIV (specifically, those newly enrolled in HIV care) have been collected annually by WHO for more than a decade, and for children aged under 5 years since 2016. In 2018, data for people aged 5 years or more were requested for the first time. The rest of this section presents and discusses the available data for these three priority groups.

Data for clinical risk groups – such as patients starting anti-tumour necrosis factor (TNF) therapy and those preparing for organ transplantation – are currently not requested as part of WHO’s annual rounds of global TB data collection. Countries are nevertheless encouraged to monitor treatment initiation and completion, either routinely or through special surveys.

Routine collection of data about TB preventive treatment remains challenging. To facilitate faster, systematic and more complete data collection, WHO has developed a mobile phone application (app) which can be adapted at country level to record and report case-based data on TB preventive treatment.

#### 5.1.1 People living with HIV

Trends in the annual number of people living with HIV provided with TB preventive treatment 2005–2017 are shown in Fig. 5.1. Globally, the number was low until 2009; it then grew substantially to reach 932,663 in 2014, and has subsequently levelled off. The number in 2017

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8. The indicator focuses on people newly enrolled in HIV care to help monitor trends in the programmatic management of LTBI. However, all people living with HIV should be regularly assessed for TB disease, and be offered preventive TB treatment if they are eligible for it.
WHO issued updated and consolidated guidelines for the programmatic management of LTBI in 2018. The document brings together guidance that was previously available in separate guidelines; it also includes updates to previous guidance. Recommendations in the guidelines are based on the probability of progression to active TB disease in specific risk groups, the level and distribution of TB disease burden, the availability of resources, the likelihood of a broad public health impact, and the relative benefits and risks of treatment provision. The guiding principle is that individual benefits should outweigh risks.

The 2018 guidelines define three priority groups in which testing and treatment for LTBI is strongly recommended, in all countries:

- people living with HIV;
- infants and children aged under 5 years who are household contacts of bacteriologically confirmed pulmonary TB cases; and
- clinical risk groups, including patients initiating anti-TNF treatment, receiving dialysis, or preparing for organ or haematological transplantation, and those with silicosis.

In low-incidence settings, treatment for LTBI is also strongly recommended for HIV-negative people aged 5 years or more who are household contacts of bacteriologically confirmed pulmonary TB cases.

In high-incidence settings, the guidelines recommend considering testing and treatment for LTBI for HIV-negative people aged 5 years or more who are contacts of bacteriologically confirmed pulmonary TB patients, taking into account resource availability and health system capacity. Compared with earlier guidance, this conditional recommendation substantially increases the potential number of people eligible for treatment.

Active TB disease should always be ruled out by screening for symptoms before prescribing preventive treatment. Chest radiography may also be considered for ruling out active TB disease among people living with HIV who are on ART, and among HIV-negative household contacts aged 5 years or more. The guidelines recommend testing for LTBI using either a tuberculin skin test or interferon-gamma release assay, in all countries. Lack of access to chest radiography, tuberculin skin testing, or interferon-gamma release assay should not be a barrier to initiation of treatment of LTBI.

The guidelines include four options for treatment of LTBI, including new shorter drug regimens:

- A weekly dose of rifapentine and isoniazid for 3 months.
- A daily dose of rifampicin plus isoniazid daily for 3 months.
- A daily dose of 3–4 months of rifampicin.
- A daily dose of isoniazid for at least six months.

Shorter regimens are expected to help patients to adhere to and complete treatment.

Based on the updated guidance, WHO estimates that at least 30 million people would be eligible for TB preventive treatment between 2018 and 2022. This represents an enormous increase compared with the numbers reported to have received TB preventive treatment in 2017 (Section 5.1).

### BOX 5.1

Updated WHO guidance on the programmatic management of latent TB infection issued in 2018, and associated estimates of the number of people eligible for TB preventive treatment from 2018–2022

1 These 67 countries accounted for 72% of the estimated number of TB cases among people living with HIV in 2017.

2 Countries have regularly reported challenges in capturing data on TB preventive treatment among people newly enrolled in HIV care. In 2018, if countries could not report data for this group, they were asked to provide data on the number of people currently enrolled in HIV care who were started on TB preventive treatment.

As in previous years, South Africa accounted for the largest share (39%) of the global total. Large absolute increases in numbers compared with 2016 were reported in Nigeria (+29,000) and India (+10,000). For three of the 30 countries with a high burden of HIV-associated TB – Angola, Namibia and Papua New Guinea – data were reported for the first time in at least 4 years.

Despite progress in some countries, much remains to be done. For example, only 15 of the 30 high TB/HIV...
burden countries reported some provision of TB preventive treatment to people living with HIV in 2017. Coverage among those newly enrolled in HIV care varied from 1% in Eswatini (formerly Swaziland) to 53% in South Africa (Table 5.1). Overall, in the 59 countries for which it could be calculated, coverage was 36%.

Gaps in the provision of TB preventive treatment to people living with HIV for selected high TB burden countries or high TB/HIV burden countries are illustrated in Fig. 5.2.

5.1.2 Children aged under 5 years who are household contacts of TB cases

There were 189 countries that reported at least one notified bacteriologically confirmed pulmonary TB case in 2017, of which 138 (73%) reported data about the number of household contacts aged under 5 years who were started on TB preventive treatment. Among these 138 countries, 124 reported that at least one child was started on preventive treatment in 2017 (up from 110 countries in 2016). This included 28 of the 38 high TB or high TB/HIV burden countries (Table 5.1) – an increase from 20 countries in 2016. Of these countries, data were reported to WHO for the first time by Botswana, Congo, Eswatini, Ethiopia, South Africa, Thailand and Zambia.

A total of 292,182 children aged under 5 years were reported to have been initiated on TB preventive treatment in 2017, an increase of 79% from 163,720 in 2016 and a more than three-fold increase from 87,242 in 2015. The largest numbers were reported by the WHO African Region (47% of the global total; 32 countries) and the WHO South-East Asia Region (25% of the global total; 9 countries). In the 28 high TB and TB/HIV burden countries that reported data, 199,630 children started TB preventive treatment (68% of the global total). At country level, India reported the largest number (38,745), followed by South Africa (32,104) (Table 5.1).

Globally, the 292,182 children started on treatment in the 28 high TB and TB/HIV burden countries that reported data represented 18% of the 1.1 million children estimated to be eligible for treatment. Higher levels of coverage were estimated for 20 countries in the WHO European Region (of which 13 reached coverage of ≥75%), followed by 23 countries in the WHO Region of the Americas (of which 13 reached coverage of ≥75%) and 16 countries in the Eastern Mediterranean Region (of which 9 reached coverage of ≥75%) (Fig 5.3). The 199,630 children started on treatment in the 28 high TB and TB/HIV burden countries that reported data represented 18% of the 1.1 million children estimated to be eligible for treatment.

**FIG. 5.1**
Provision of TB preventive treatment to people newly enrolled in HIV care, a 2005–2017

<table>
<thead>
<tr>
<th>Year</th>
<th>Global</th>
<th>Rest of Africa</th>
<th>South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>250</td>
<td>250</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>2011</td>
<td>750</td>
<td>750</td>
<td>750</td>
</tr>
<tr>
<td>2013</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>2015</td>
<td>1250</td>
<td>1250</td>
<td>1250</td>
</tr>
<tr>
<td>2017</td>
<td>1500</td>
<td>1500</td>
<td>1500</td>
</tr>
</tbody>
</table>

a For seven countries, data are for people currently enrolled in HIV care: Congo, Ecuador, Grenada, Kenya, Mozambique, Nepal and Ukraine.
TABLE 5.1
TB preventive treatment for people living with HIV and children under 5 years of age who were household contacts of a bacteriologically confirmed pulmonary TB case, high TB or TB/HIV burden countries, 2017

<table>
<thead>
<tr>
<th>Country</th>
<th>Treatment People Living with HIV Newly Enrolled in Care</th>
<th>People Living with HIV Newly Enrolled in Care Started on TB Preventive Treatment</th>
<th>Estimated Number of Child Contacts Under 5 Years of Age Eligible for TB Preventive Treatment</th>
<th>Children Under 5 Years of Age Started on TB Preventive Treatment</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>22 137</td>
<td>2 842</td>
<td>24 800 (22 600–27 000)</td>
<td>11 394</td>
<td>21</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>54 400</td>
<td>781</td>
<td>(711–850)</td>
<td>556</td>
<td>**</td>
</tr>
<tr>
<td>Botswana</td>
<td>54 400</td>
<td>2 860</td>
<td>(1 850–3 860)</td>
<td>2 410</td>
<td>44</td>
</tr>
<tr>
<td>Cambodia</td>
<td>3 582</td>
<td>754</td>
<td>5 540 (5 040–6 030)</td>
<td>89</td>
<td>0.86</td>
</tr>
<tr>
<td>Cameroon</td>
<td>10 300</td>
<td>2 860</td>
<td>(9 400–11 200)</td>
<td>89</td>
<td>(0.79–0.95)</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>8 180</td>
<td>0</td>
<td>3 500 (3 190–3 810)</td>
<td>89</td>
<td>4.1</td>
</tr>
<tr>
<td>Chad</td>
<td>4 520</td>
<td>4 520</td>
<td>(4 110–4 920)</td>
<td>89</td>
<td>(6.8–8.2)</td>
</tr>
<tr>
<td>China</td>
<td>10 400</td>
<td>1 380</td>
<td>(6 710–14 000)</td>
<td>89</td>
<td>(9.9–12)</td>
</tr>
<tr>
<td>Congo</td>
<td>1 380</td>
<td>2 860</td>
<td>(2 190–2 620)</td>
<td>98</td>
<td>(3.7–4.5)</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>9 450</td>
<td>2 860</td>
<td>(8 610–10 300)</td>
<td>11 984</td>
<td>**</td>
</tr>
<tr>
<td>DR Congo</td>
<td>84 400</td>
<td>17 801</td>
<td>(76 900–92 000)</td>
<td>13 045</td>
<td>(14–17)</td>
</tr>
<tr>
<td>Eswatini</td>
<td>23 271</td>
<td>23 271</td>
<td>(20 900–25 500)</td>
<td>1 693</td>
<td>31</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>39 126</td>
<td>23 271</td>
<td>(20 900–25 500)</td>
<td>1 693</td>
<td>31</td>
</tr>
<tr>
<td>Ghana</td>
<td>1 380</td>
<td>2 860</td>
<td>(1 380–3 810)</td>
<td>89</td>
<td>(3.7–4.5)</td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>2 060</td>
<td>2 060</td>
<td>(1 880–2 250)</td>
<td>394</td>
<td>18</td>
</tr>
<tr>
<td>India</td>
<td>173 174</td>
<td>173 174</td>
<td>(163 000–183 000)</td>
<td>34 400</td>
<td>10</td>
</tr>
<tr>
<td>Indonesia</td>
<td>49 215</td>
<td>7 681</td>
<td>(65 200–77 900)</td>
<td>6 080</td>
<td>**</td>
</tr>
<tr>
<td>Kenya</td>
<td>155 377</td>
<td>155 377</td>
<td>(134 000–176 000)</td>
<td>24 900</td>
<td>26</td>
</tr>
<tr>
<td>Lesotho</td>
<td>1 760</td>
<td>1 760</td>
<td>(1 610–1 920)</td>
<td>133</td>
<td>5.8</td>
</tr>
<tr>
<td>Liberia</td>
<td>2 300</td>
<td>2 300</td>
<td>(2 100–2 510)</td>
<td>133</td>
<td>5.8</td>
</tr>
<tr>
<td>Malawi</td>
<td>168 972</td>
<td>168 972</td>
<td>(154 000–183 000)</td>
<td>3 068</td>
<td>**</td>
</tr>
<tr>
<td>Mozambique</td>
<td>23 271</td>
<td>23 271</td>
<td>(20 900–25 500)</td>
<td>1 693</td>
<td>31</td>
</tr>
<tr>
<td>Myanmar</td>
<td>37 402</td>
<td>37 402</td>
<td>(33 000–41 000)</td>
<td>337</td>
<td>2.1</td>
</tr>
<tr>
<td>Namibia</td>
<td>21 213</td>
<td>21 213</td>
<td>(18 800–23 600)</td>
<td>1 069</td>
<td>31</td>
</tr>
<tr>
<td>Nigeria</td>
<td>232 822</td>
<td>91 873</td>
<td>(76 800–106 200)</td>
<td>7 610</td>
<td>(7.6–8.2)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>107 000</td>
<td>107 000</td>
<td>(97 100–116 000)</td>
<td>10 258</td>
<td>**</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>3 788</td>
<td>3 788</td>
<td>(3 550–4 020)</td>
<td>2 430</td>
<td>(2–2.1)</td>
</tr>
<tr>
<td>Philippines</td>
<td>6 755</td>
<td>6 755</td>
<td>(6 200–7 300)</td>
<td>6 473</td>
<td>**</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>16 868</td>
<td>16 868</td>
<td>(15 000–18 600)</td>
<td>10 356</td>
<td>**</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>23 693</td>
<td>5 323</td>
<td>(4 900–5 730)</td>
<td>7 690</td>
<td>(7–8)</td>
</tr>
<tr>
<td>South Africa</td>
<td>710 083</td>
<td>710 083</td>
<td>(670 000–750 000)</td>
<td>32 104</td>
<td>79</td>
</tr>
<tr>
<td>Thailand</td>
<td>5 510</td>
<td>5 510</td>
<td>(5 020–6 000)</td>
<td>278</td>
<td>5.0</td>
</tr>
<tr>
<td>Uganda</td>
<td>20 700</td>
<td>20 700</td>
<td>(18 900–22 500)</td>
<td>1 307</td>
<td>6.4</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>21 000</td>
<td>21 000</td>
<td>(19 100–22 800)</td>
<td>7 303</td>
<td>35</td>
</tr>
<tr>
<td>VietNam</td>
<td>14 509</td>
<td>14 509</td>
<td>(12 200–16 800)</td>
<td>4 128</td>
<td>26</td>
</tr>
<tr>
<td>Zambia</td>
<td>234 586</td>
<td>42 961</td>
<td>(39 600–46 300)</td>
<td>4 044</td>
<td>3.8</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>164 963</td>
<td>164 963</td>
<td>(150 000–180 000)</td>
<td>7 610</td>
<td>(6–6.5)</td>
</tr>
</tbody>
</table>

Blank cells indicate data not reported.

1 Estimates are shown to three significant figures.
2 Reasons for higher than expected coverage might be that the numerator did not exclude non-household contacts or children of five years and older.
3 Coverage was not calculated because reported data on people living with HIV is for all enrolled in care, not just those newly enrolled in care.
4 Coverage was not calculated because the numerator included contacts aged 5 years or older (Botswana, DPR Korea and Nigeria), those who were non-household contacts of TB cases (Indonesia and the Russian Federation), or those household contacts of clinically diagnosed TB cases (Malawi and the Philippines), or the number of PLHIV on TB preventive treatment was provided for the period July–December 2017 only (Zimbabwe).
to be eligible for treatment in the 38 high TB or TB/HIV burden countries. The highest coverage levels (≥75%) in this group of countries were in Mozambique and South Africa (Fig 5.3 and Table 5.1).\(^1\)

5.1.3 Households contacts aged 5 years and older

In WHO’s 2018 round of global TB data collection, data on provision of TB preventive treatment to household contacts aged 5 years or more were requested for the first time. Of the 189 countries that reported at least one notified bacteriologically confirmed pulmonary TB case in 2017, 78 (41%) reported data about the number of household contacts aged 5 years or more who were started on TB preventive treatment. Of the 78 countries, 70 reported that at least one contact aged 5 years or more was started on preventive treatment. This included eight countries that are in the lists of high TB burden, high multidrug-resistant TB (MDR-TB) or high TB/HIV burden countries: Azerbaijan, Kazakhstan, Kyrgyzstan, Republic of Moldova, Tajikistan, Thailand, Ukraine and Uzbekistan.

A total of 103,344 household contacts aged 5 years or more were reported to have been initiated on TB preventive treatment in 2017. The largest numbers were reported by the WHO European Region (56,335, 55% of the global total) and the WHO Eastern Mediterranean Region (29,331, 28% of the global total). At country level, Afghanistan reported the largest number (22,939), followed by Ukraine (15,811) and Turkey (11,940).

5.2 TB infection prevention and control

TB infection prevention and control is one of the components of Pillar 2 of the End TB Strategy (Chapter 2); it is also one of the collaborative TB/HIV activities that falls under Pillar 1. The risk of TB transmission is high in health-care and other congregate settings. This puts health-care workers at greater risk of TB infection and disease, and nosocomial outbreaks of MDR-TB and extensively drug-resistant TB (XDR-TB) among people living with HIV have been documented in the literature.\(^2,3\)

TB infection prevention and control should be part of national infection prevention and control policy. In health-care facilities and congregate settings, a comprehensive set of infection control measures — comprising administrative, environmental and personal protection measures

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\(^1\) Annex 1 explains how to access data reported by other countries.


– should be implemented.\textsuperscript{1} Periodic assessment of TB infection prevention and control in health-care facilities is essential to ensure that appropriate measures are in place.\textsuperscript{2}

The risk of TB among health-care workers relative to the risk in the general adult population is one of the indicators recommended by WHO for measuring the impact of TB infection prevention and control activities in health-care facilities.\textsuperscript{3} If effective TB infection control measures are in place, the relative risk of TB in health-care workers compared with the general adult population should be close to one.

In 2017, 9,299 TB cases among health-care workers were reported from 65 countries; China accounted for 35% of these cases and Brazil for 11%. The notification rate among health-care workers could be calculated for 58 of the 65 countries; it ranged from zero to 685 cases per 100,000 health-care workers, with the highest rate observed in Mozambique.

The notification rate among the general adult population in each country was calculated based on the number of notified TB cases in adults and the estimated size of the adult population from the United Nations population division (2017 revision),\textsuperscript{4} restricted to those aged 15–64 for comparability with the health workforce. The ratios of the TB notification rate among health-care workers to the rate in the general adult population are shown in Fig. 5.4. The ratio was above two in four countries (Brunei Darussalam, Dominican Republic, Paraguay and Zimbabwe) and above three in Colombia and Honduras. The ratio was below one in four high TB burden countries: China, Namibia, Nigeria and Thailand.

5.3 TB vaccination

There is a clear need for a vaccine that is more effective than the BCG vaccine, in particular to reduce the risk of infection with \textit{M. tuberculosis} and the risk of progression from infection to active TB disease in adults. Although there are 12 new candidates in the pipeline, it is unlikely that a new TB vaccine will be available in the immediate future (Chapter 8). To promote the development of

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig54.png}
\caption{Notification rate ratio of TB among health-care workers compared with the adult population (15–65 years), 2017\textsuperscript{a}}
\end{figure}

\textsuperscript{a} Data from 3 countries were excluded where the number of health-care workers reported was less than 1000.


\textsuperscript{4} https://esa.un.org/unpd/wpp/
FIG. 5.5
BCG vaccination policy by country


FIG. 5.6
Coverage of BCG vaccination, 2017

The target population of BCG coverage varies depending on national policy, but is typically for the number of live births in the year of reporting.

vaccines with optimal effectiveness and suitability in low- and middle-income countries, in 2018 the WHO Preferred Product Characteristics for New Tuberculosis Vaccines was developed through a multi-stakeholder process led by WHO’s Initiative for Vaccine Research.  

BCG vaccination has been shown to prevent disseminated disease; this category includes TB meningitis and miliary TB, which are associated with high mortality in infants and young children. Currently, WHO recommends that, in countries with a high TB burden, a single dose of the BCG vaccine should be provided to all infants as soon as possible after birth as part of childhood immunization programmes. In countries with low TB incidence rates, provision of the BCG vaccine may be limited to neonates and infants in recognized high-risk groups, or to older children who are skin-test negative for TB infection.

Fig. 5.5 summarizes national policies on BCG vaccination. Among 180 countries for which data were collected, 154 recommended universal BCG vaccination; 20 reported having had a national BCG policy for everyone in the past, and the remaining six countries had policies of selective vaccination for at-risk individuals in high-risk groups.

The latest data on BCG coverage (for 2017) are shown in Fig. 5.6. In the 158 countries for which data are available, 120 reported coverage of at least 90%. Among the 30 high TB burden countries, coverage ranged from 53% in Nigeria to 99% in Bangladesh, Brazil, China, Mozambique, Thailand, the United Republic of Tanzania and Zambia; 21 reported coverage of at least 90%, up from 12 in 2016. In addition to Nigeria, coverage was below 80% in five other high TB burden countries: Central African Republic, Kenya, Lesotho, Papua New Guinea and South Africa.

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Volunteers sign in patients at a TB clinic in Dar es Salaam, United Republic of Tanzania

INTERFOTO / Alamy Stock Photo
Chapter 6. Financing for TB prevention, diagnosis and treatment

KEY FACTS AND MESSAGES

Financing for tuberculosis (TB) prevention, diagnosis and treatment continues to fall short of the amount needed and commitments from both domestic and international donor sources need to be stepped up.

The Stop TB Partnership’s Global Plan to End TB, 2016–2020⁴ (the Global Plan) estimates that, in low- and middle-income countries, US$ 10.4 billion is required in 2018, increasing to US$ 12.3 billion in 2020. Based on data reported to WHO by 119 low- and middle-income countries with 97% of the world’s notified TB cases, US$ 6.9 billion is available for TB prevention, diagnosis and treatment in 2018, representing a shortfall of US$ 3.5 billion.

The Global Plan estimates that an additional US$ 2 billion per year is needed for TB research and development.

Of the total of US$ 6.9 billion available in 119 low- and middle-income countries in 2018, US$ 4.8 billion is for drug-susceptible TB and US$ 2.0 billion is for MDR-TB; the remainder is for TB/HIV interventions or miscellaneous items.

Of the total of US$ 6.9 billion available in 119 low- and middle-income countries in 2018, US$ 6.0 billion (86%) is from domestic sources. However, this aggregate figure is strongly influenced by the BRICS group of countries (Brazil, the Russian Federation, India, China and South Africa).

BRICS accounted for 54% of the available funding for TB in 2018 (and 46% of the world’s TB cases), with 96% (range 91–100%) of the group’s funding coming from domestic sources. In other countries with a high TB burden, international donor funding remains crucial; for example, it accounted for 39% of the funding available in the 25 high TB burden countries outside BRICS (which have 40% of the world’s notified TB cases) and for 57% of the funding in low-income countries.

International donor funding reported by national TB programmes (NTPs) dropped to US$ 0.9 billion in 2018, falling far short of the US$ 2.6 billion annual requirement estimated in the Global Plan. The single largest source (74% of the total) of funding reported by NTPs is the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund).

International donor funding documented in the Organisation for Economic Co-operation and Development (OECD) creditor reporting system includes funding that flows through NTPs as well as other recipients. The total amount recorded in 2016 (the latest year for which data are available) was US$ 0.9 billion, of which 69% was from the Global Fund (the Fund’s contribution averaged 66% from 2006 to 2016). This was much less than funding for HIV (US$ 6.8 billion) and malaria (US$ 1.9 billion). To provide some context for these amounts, the latest estimates (for 2016) of the burden of disease in terms of disability-adjusted life years (DALYs) lost due to illness and death are 58 million for HIV/AIDS, 56 million for malaria and 44 million for TB.

The median cost per patient treated in 2017 was US$ 1224 for drug-susceptible TB and US$ 7141 for MDR-TB. The latter figure was lower than in previous years, following expanded use of a lower cost shortened treatment regimen that was first recommended by WHO in 2016.

Health financing data from national health accounts provide important insights into the current status of progress towards universal health coverage, as discussed in Chapter 7.

Progress in tuberculosis (TB) prevention, diagnosis and treatment requires adequate funding sustained over many years. WHO began annual monitoring of funding for TB in 2002, and has published findings in global TB reports and peer-reviewed publications.1

This chapter has four main sections. It starts with a summary of the most up-to-date estimates of the financial resources required to achieve the 2020 milestones of the End TB Strategy (Section 6.1). It then presents and discusses trends in funding for TB prevention, diagnosis and treatment by category of expenditure and source of funding for the period 2006–2018, both globally and for major country groupings (Section 6.2). More detailed country-specific data for 2018 are also presented for the 30 high TB burden countries. The third section analyses funding gaps reported by national TB programmes (NTPs) to WHO, with breakdowns by category of expenditure and country group (Section 6.3). The final section provides the latest estimates (for 2017) of the unit costs of treatment for drug-susceptible TB and multidrug-resistant TB (MDR-TB) (Section 6.4).

As highlighted in the previous three editions of the Global tuberculosis report2,3,4, analysis of health financing data can provide important insights into progress towards universal health coverage (UHC), which is necessary to achieve the End TB Strategy milestones set for 2020 and 2025 (Chapter 2). Measurement of costs faced by TB patients and their households is also required to assess progress towards one of the three high-level indicators of the End TB Strategy; that is, the percentage of TB patients and their households who face catastrophic costs as a result of TB disease. The 2020 milestone of zero set for this indicator requires progress towards UHC and social protection (included under Pillar 2 of the End TB Strategy). These two topics — analysis of health financing data, and measurement of costs faced by TB patients and their households — are discussed in Chapter 7.

Further country-specific data on TB financing can be found in finance profiles that are available online.5

6.1 Estimates of funding required to achieve the 2020 milestones of the End TB Strategy

The 2020 milestones of the End TB Strategy are a 35% reduction in TB deaths compared with deaths in 2015, a 20% reduction in the TB incidence rate compared with 2015, and that no TB patients and their households face catastrophic costs as a consequence of TB disease (Chapter 2). Estimates of the funding required to achieve these milestones have been set out in the Stop TB Partnership’s Global Plan to End TB, 2016–2020 (the Global Plan).2,3 Worldwide, the total amount required for implementation of TB prevention, diagnostic and treatment interventions is US$ 58 billion for the period 2016–2020, rising from US$ 9.5 billion for the year 2016 to US$ 14 billion for the year 2020. An additional US$ 9.0 billion is needed for global TB research and development in the same period.7

Of the US$ 58 billion required over the 5 years from 2016 to 2020 (excluding research and development), an estimated US$ 52 billion is required in low- and middle-income countries, growing from US$ 8.3 billion in 2016 to US$ 12 billion in 2020 (Fig. 6.1). In 2018, an estimated total of US$ 10.4 billion is required: US$ 7.7 billion (74%) for diagnosis and treatment of drug-susceptible TB, US$ 2.5 billion for drug-resistant TB5 and the remainder for TB/...
HIV interventions. The amount for TB/HIV interventions is comparatively small because it does not include the funding needed for antiretroviral therapy for HIV-positive TB patients; this figure is instead included in estimates of funding required for HIV, published by the Joint United Nations Programme on HIV/AIDS (UNAIDS). In 2018, in the context of preparations for the UN high-level meeting on TB, Global Plan projections of funding requirements were extended to 2022, suggesting that at least US$ 13 billion will be needed in 2022.

The Global Plan, estimates of the funding that could be mobilized from domestic and international donor sources were restricted to countries eligible to apply to the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund). For eligible countries, the funding required over 5 years amounted to US$ 29 billion. Of this total, it was estimated that about US$ 16 billion could be mobilized from domestic sources, and that the remainder (an average of US$ 2.6 billion per year) would need to be provided by international donors.

The Global Plan did not attempt to assess the broader investments required to increase the overall coverage and quality of health-care services or the funding required to remove financial barriers to accessing care. Such investments are needed for many essential preventive, treatment and care interventions, not only those related to TB. Progress on these fronts is critical, as reflected in Pillar 2 of the End TB Strategy. The costings in the Global Plan can thus be seen as the financial resources required for Pillars 1 and 3 of the End TB Strategy. Recent estimates of the funding required in low- and middle-income countries to make progress towards UHC by 2030 are presented and discussed in Chapter 7.

### 6.2 TB funding, overall and by category of expenditure and source of funding, 2006–2018

Data reported by NTPs to WHO since 2006 were used to analyse funding trends for 2006–2018 in 119 low- and middle-income countries (Fig. 6.2). These countries accounted for 97% of the global number of TB cases notified in 2017. The methods used to compile, review, validate and analyse financial data are summarized in Box 6.1.

In these 119 low- and middle-income countries, funding for TB prevention, diagnosis and treatment reached US$ 6.9 billion in 2018, an increase from US$ 6.2 billion...
**BOX 6.1**

Methods used to compile, review, validate and analyse financial data reported to WHO

**Overview**

WHO began monitoring government and international donor financing for TB in 2002. All data are stored in the WHO global TB database. The standard methods used to compile, review, validate and analyse these data have been described in detail elsewhere; however, this box provides a summary.

Each year, WHO asks NTPs in all low- and middle-income countries to report:

- the funding they estimate will be needed for TB prevention, diagnosis and treatment in their current fiscal year, by category of expenditure and source of funding; and
- expenditures for the most recently completed fiscal year, also by category of expenditure and source of funding.

In the 2018 round of global TB data collection, the fiscal years were 2018 (for funding needs) and 2017 (for expenditures). Categories of expenditure used to report TB budget and expenditure data have been kept consistent as far as possible, to enable monitoring of trends.

**Categories used for reporting of budgets and expenditures from 2002 to 2018**

The categories used for annual reporting of funding needs (current fiscal year) and expenditures (last fiscal year) by NTPs in low- and middle-income countries are summarized below.

1. Drug-susceptible TB
   - Laboratory infrastructure, equipment and supplies.
   - NTP staff at central and subnational levels (e.g. NTP managers and provincial or district TB coordinators).
   - First-line drugs.
   - Programme costs; for example, management and supervision activities, training, policy development, meetings, purchase of office equipment and vehicles, recording and reporting of notifications and treatment outcomes, advocacy and communication, public–private mix activities and community engagement.
   - Operational research, including surveys.
   - Patient support – this category was first introduced as a stand-alone category in 2015, to reflect the emphasis on financial and social protection in the End TB Strategy.

2. MDR-TB
   - Second-line drugs.
   - Programme costs specifically related to MDR-TB.

3. TB/HIV
   - Collaborative TB/HIV activities, including TB preventive treatment for people newly enrolled in HIV care. This category excludes any budget items that are financed by HIV programmes, such as antiretroviral therapy for TB patients living with HIV.

An “other” category is used to capture miscellaneous items that do not fit in one of the categories listed above.

**Sources of funding**

Low- and middle-income countries report on the breakdown of the total amount of available or committed funding by source, using four standard categories. These categories are domestic funding excluding loans; external loans, also considered domestic funding; the Global Fund; and grant financing from sources other than the Global Fund.

**High-income countries**

As in previous years, in 2018, all high-income countries were asked to report their funding requirements and expenditures in total, without any breakdown by category of expenditure or source of funding. However, of the 73 high-income countries, only seven reported expenditures and only 23 reported the amount of funding needed in 2018. Total TB funding trends for 2006–2018 are available for eight of the 73 high-income countries; however, those countries are not featured in this chapter given its focus on low- and middle-income countries.

**Average cost of drugs per patient (since 2014)**

Since 2014, an extra question about the average cost of drugs per patient treated has been asked, to allow reviewers to better assess the validity of budgets reported for first-line and second-line drugs, and to identify whether reported budgets include funding for buffer stocks.

**Use of general health services (2002–2018)**

Annually since 2002, all countries (irrespective of income level) have been asked to report on the use of inpatient and outpatient care for treatment of people with drug-susceptible TB and MDR-TB on a per-patient basis (i.e. the average number of days spent in hospital, and the average number of outpatient visits to a health facility). These data can be based on actual use of services (preferable where available), or on the expected use of services based on the typical approach used to deliver treatment (which may be defined in national policy documents and protocols). These data on health service use are then combined with other data to estimate the financial resources used for TB treatment that are not reflected in NTP-reported budgets and expenditures (further details are provided below).

**Data validation by WHO’s Global TB Programme**

The core methods used to review and validate data have remained consistent since 2002. They include the following:

- routine checks for plausibility and consistency, including validation checks that are built into the online reporting system – examples of validation checks are checks for implausibly large year-to-year changes (e.g. in total reported funding by source and by category of expenditure), or implausibly high or low values of funding for drugs relative to the number of TB patients (that differ substantially from prices quoted by the Global TB Drug Facility);
- discussions with country respondents to resolve queries; and
- triangulation with other data sources – these include estimates of unit costs from independent economic
evaluations (Box 6.3)\(^a\) and data extracted by the Global Fund from funding applications submitted to them (comprehensive budgets for national strategic plans for TB are an essential requirement for funding applications to the Global Fund); further details about the comparisons with other data sources are available from WHO upon request.

In review and validation of data, particular attention has always been given to the high TB burden countries.

In 2018, specific efforts to improve the quality of financial data reported to WHO included discussions with NTP staff during a workshop on TB budgeting; and individual and customized follow-up with in-country staff involved in the development of national strategic plans and reporting of financial data.

Except for the Russian Federation, China, South Africa in 2018 and Viet Nam in 2017, TB funding reported by NTPs in 2017 and 2018 did not include the financial costs associated with the inpatient and outpatient care required during TB treatment. Since many detailed costing studies in numerous countries show that these costs can account for a large share of the cost of treating someone with TB, WHO analyses of TB financing have always included estimates of the funding required for both inpatient and outpatient care. These costs have been estimated from a provider perspective only, and do not include the costs faced by TB patients and their households. Increasing attention is now being given to costs faced by TB patients and their households, as discussed in Chapter 7.

**Estimates of the costs of inpatient and outpatient care for patients with drug-susceptible TB or MDR-TB**

To estimate the funding used to provide inpatient and outpatient care for TB patients, WHO multiplies the number of outpatient visits and days of inpatient care per patient (reported by NTPs each year, as explained above) by the cost per bed day and per clinic visit available from the WHO CHOosing Interventions that are Cost-E\(^{ective}\) (WHO-CHOICE) database,\(^b\) and then by the reported number of TB patients notified or projected to be notified. These estimates are done separately for drug-susceptible TB and MDR-TB. In 2018, costs per bed day and per clinic visit were estimated using the CHOICE regression model and the latest data available from the World Bank. For two countries (India and Thailand), WHO-CHOICE estimates were replaced with estimates of unit costs obtained directly from national health account data, or from recent studies and discussions with experts supporting the costing of national strategic plans.

Where possible, estimates are compared with hospital and clinic expenditure data for drug-susceptible TB and MDR-TB that are being tracked through the System of Health Accounts (SHA).\(^c\) In 2018, SHA data were available for 27 countries for 1 or 2 years, including six high burden countries (Cambodia, the Democratic Republic of the Congo, Namibia, the Philippines, Sierra Leone and the United Republic of Tanzania).\(^d\) After review, the SHA data were used in preference to estimates based on the combination of reported use and WHO-CHOICE unit cost estimates. The WHO Health Governance and Financing Department has initiated a process to assess the validity of the latest results from the new SHA, including disease-specific results.

Expanded implementation of SHA and validation against existing disease-specific tracking systems may facilitate more comprehensive reporting of domestic funding for TB. In particular, it may facilitate reporting of the contributions from subnational administrative levels that are not always known or compiled at the national level. Although much of this contribution is probably for delivery of inpatient and outpatient care (which is included in current WHO estimates of domestic funding for TB, as explained above), reporting of funding from these levels (including TB-specific budgets) is a particular challenge in large countries with decentralized systems for TB treatment (e.g. Indonesia, Nigeria and South Africa).

**Estimates of the cost per patient treated for drug-susceptible TB and MDR-TB**

Since 2014, WHO has been reporting estimates of the costs per patient treated for drug-susceptible TB and MDR-TB. Costs are calculated separately for drug-susceptible TB and MDR-TB. In each case, the numerator is the total estimated cost of treatment, which has two main parts – the national expenditures reported by the NTP, and the costs associated with the use of health services for TB patients – with data validated as described above. Categories of expenditure considered as costs for MDR-TB were second-line drugs and all other inputs used or activities implemented for the programmatic management of MDR-TB. All other categories (except collaborative TB/HIV activities) were assumed to be for drug-susceptible TB. An exception was made for the Russian Federation, for which expenditures for staff and infrastructure were allocated by WHO to drug-susceptible TB (33%) and MDR-TB (67%), based on the proportion of bed days used for these two categories of patients.

Unit costs were then calculated as the sum of 2017 NTP expenditures and total costs for use of inpatient and outpatient care, divided by the reported number of patients treated. Again, this calculation was carried out separately for drug-susceptible TB and MDR-TB.

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in 2017 and more than double the US$ 3.4 billion that was available in 2006 (Fig. 6.3; all figures are in constant 2018 US dollars). Despite this growth in funding, amounts continue to fall short of what is needed. Moreover, the shortfall compared with the Global Plan estimate (Section 6.1) has widened over the past 2 years. This is consistent with the need to increase the coverage of diagnosis and treatment for MDR-TB, which currently falls far short of Global Plan targets both overall and in most countries with a high burden of MDR-TB (for details, see Chapter 4). It is also evident from the Global Plan estimates of funding required in future years: the annual funding required for MDR-TB will reach US$ 3.6 billion in 2020, substantially higher than the amount of US$ 2.0 billion available in 2018.

Overall, most funding during the period 2006–2017 has been provided from domestic sources, and this remains the case in 2018 (Fig. 6.5). In 2018, US$ 6.0 billion (86%) of the total funding of US$ 6.9 billion for TB is from domestic sources. However, aggregated figures for the 119 low- and middle-income countries are strongly influenced by BRICS, and they conceal substantial variation among countries in the share of funding from domestic and international sources (Fig. 6.6).

BRICS accounted for 54% of the available funding for MDR-TB in 2018, compared with 46% in 2017. This downturn after 2014 is explained by decreases in funding in the Russian Federation (2014–2016) and in South Africa (2013–2014 and 2017–2018). Funding for MDR-TB in other countries decreased from 2014 to 2017 and then increased in 2018 (Fig. 6.4).

Although the gap between the funding available in 2018 and the requirement of US$ 2.5 billion in 2018 estimated in the Global Plan is relatively small (US$ 0.5 billion), it has widened over the past 2 years. This is consistent with the need to increase the coverage of diagnosis and treatment for MDR-TB, which currently falls far short of Global Plan targets both overall and in most countries with a high burden of MDR-TB (for details, see Chapter 4). It is also evident from the Global Plan estimates of funding required in future years: the annual funding required for MDR-TB will reach US$ 3.6 billion in 2020, substantially higher than the amount of US$ 2.0 billion available in 2018.
TB in 2018 (and 46% of the world’s notified TB cases), with 96% (range 91–100%) of their funding coming from domestic sources. As highlighted in the 2017 Global tuberculosis report, in India there has been a particularly striking increase in the TB-specific budget and domestic funding for this budget since 2016 (Fig. 6.7). Between 2016 and 2018, domestic funding for the national budget for TB in India more than quadrupled, from US$ 110 million in 2016 to US$ 458 million in 2018.

Domestic funding also dominates in seven of the nine (not mutually exclusive) country groups shown in Fig. 6.6, ranging from 60% in Africa to 97% in upper-middle-income countries. In contrast, international donor funding continues to exceed funding from domestic sources in low-income countries (57% of the total in 2018). In the 25 high TB burden countries excluding BRICS, the share of funding from domestic sources increased to 61% in 2018, up from 55% in 2017. In this group, the countries with notable increases in funding from domestic sources between 2017 and 2018 were Cambodia, Indonesia, Lesotho, Papua New Guinea and Philippines.

International donor funding reported by NTPs to WHO amounted to US$ 0.9 billion in 2018, a slight decline compared with 2017. Of this amount, most (74%) was provided by the Global Fund.

The importance of international donor funding in high TB burden countries is particularly evident when considering only the TB-specific budgets included in national strategic plans for TB (Fig. 6.8, Table 6.1 and Table 6.2). In 17 of the 30 high TB burden countries, more than 50% of available funding for the TB-specific budgets included in national strategic plans for TB is from international donors in 2018.

Both Fig. 6.7 and Fig. 6.8 illustrate the potential to increase domestic funding in some high TB burden countries. In the group of nine low-income high TB burden countries, the proportion of the TB budget funded from domestic sources in 2018 ranges from 0% in Zimbabwe to 14% in Central African Republic. In the group of 15 lower-middle-income high TB burden countries, the proportion ranges from 3% in Pakistan to 79% in India. In the group of six upper-middle-income countries, the proportion ranges from 85% in Brazil to 100% in the Russian Federation.

Funding reported by NTPs to WHO does not capture all international donor funding for TB. For this reason, a complementary analysis based on donor reports to the Organisation for Economic Co-operation and Development (OECD) is provided in Box 6.2.

6.3 Funding gaps reported by national TB programmes, 2006–2018

Many NTPs reported a shortfall in the funding required for full implementation of their national strategic plans (Fig. 6.8, Fig. 6.9 and Table 6.2). Funding gaps (i.e. the difference between assessments by NTPs of funding needs for TB prevention, diagnosis and treatment, and the actual amount of funds mobilized) have increased, and in 2018 they amounted to a reported total of US$ 1.2 billion. This is almost a third of the gap of US$ 3.5 billion that exists between the US$ 10.4 billion estimated to be needed in low- and middle-income countries in 2018 according to the Global Plan (Section 6.1) and the US$ 6.9 billion available in 2018 (Section 6.2). The difference can be explained by the fact that, in many countries, national strategic plans for TB are less ambitious than the targets set in the Global Plan (Section 6.1).

Of the US$ 1.2 billion funding gap reported by NTPs in 2018, US$ 0.99 billion (80%) is for drug-susceptible TB and US$ 0.24 billion (20%) is for MDR-TB. Relative to total funding needs, the funding gap is larger for drug-susceptible TB than for MDR-TB.

Lower-middle-income countries account for the largest reported funding gap (US$ 826 million) in 2018.

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2 The list of 30 high TB burden countries being used by WHO during the period 2016–2020 is explained in Chapter 2. The countries are those listed in Fig. 6.8, Table 6.1 and Table 6.2.
3 These figures exclude domestic funding for inpatient and outpatient care during treatment. For further details for these countries, see the country profiles in Annex 2.
5 Donor funding is also provided to entities other than NTPs, including international and national organizations, both governmental and nongovernmental.
6 Out-of-pocket expenditures are also not included in the financing data reported by NTPs. These are discussed in more detail in Chapter 7.
<table>
<thead>
<tr>
<th>Country</th>
<th>TOTAL BUDGET IN NATIONAL STRATEGIC PLAN FOR TB</th>
<th>DS-TB</th>
<th>MDR-TB</th>
<th>TB/HIV</th>
<th>INPATIENT AND OUTPATIENT CARE (DS-TB)</th>
<th>INPATIENT AND OUTPATIENT CARE (MDR-TB)</th>
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</table>

Subtotals do not always add to the total due to rounding.

* No amounts for the additional resources required for inpatient and outpatient care are shown for China, the Russian Federation and South Africa because the NTP budgets reported by those countries include all budgets for inpatient and outpatient care.

* In the Russian Federation, the staff and infrastructure reported for TB care and control were allocated to DS-TB (33%) and MDR-TB (67%) by WHO based on the proportion of beddays used by DS-TB and MDR-TB patients.

* In 2018, the budget reported by Thailand was for the central level only.
TABLE 6.2
Reported budget in national strategic plans for TB, available funding for this budget from domestic and international donor sources and funding gap, 30 high TB burden countries, 2018 (current US$ millions)

<table>
<thead>
<tr>
<th>Country</th>
<th>Total budget in national strategic plan for TB</th>
<th>Domestic funding (A)</th>
<th>International donor funding (B)</th>
<th>Share of available funding (A+B) provided from domestic sources (%)</th>
<th>Share of available funding (A+B) provided by international donors (%)</th>
<th>Funding gap</th>
</tr>
</thead>
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<td>37</td>
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<td><strong>30 high TB burden countries</strong></td>
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<td><strong>3 052</strong></td>
<td><strong>670</strong></td>
<td><strong>82</strong></td>
<td><strong>18</strong></td>
<td><strong>1 073</strong></td>
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</table>

Subtotals do not always add to the total due to rounding.

* In 2018, the budget reported by Thailand was for the central level only.

** The funding gap reflects the anticipated gap for the year at the time a country reported data to WHO in the 2018 round of global TB data collection.
FIG. 6.6
Funding for TB prevention, diagnosis and treatment from domestic sources and international donors, 2006–2018, 9 country groups

a. BRICS

b. HBCs excluding BRICS

c. Rest of world\(^a\)

d. Low-income countries

e. Low-middle-income countries

f. Upper-middle-income countries

g. Africa

h. Asia\(^b\)

i. Other regions\(^c\)

*Rest of world includes 89 countries that are not in the list of 30 high TB burden countries.
*Asia includes the WHO regions of South-East Asia and the Western Pacific.
*Other regions consist of three WHO regions: the Eastern Mediterranean Region, the European Region, and the Region of the Americas.
FIG. 6.7
National budget for TB and sources of funding in India, 2006–2018

(Fig. 6.9). Compared with 2017, funding gaps increased in all country groupings.

In 2018, the largest funding gaps among low-income countries were for high TB burden countries: the Democratic People’s Republic of Korea (US$ 77 million), Ethiopia (US$ 52 million), the Democratic Republic of the Congo (US$ 37 million) and the United Republic of Tanzania (US$ 33 million) (Table 6.2). Funding gaps increased for upper-middle-income countries in 2018 (US$ 154 million). This increase is mostly explained by large funding gaps reported by China (US$ 67 million) and Guatemala (US$ 16 million).

Half of the total reported funding gap in 2018 is accounted for by countries in the WHO African Region (US$ 600 million), with Nigeria accounting for half of the region’s gap (US$ 312 million), followed by Ethiopia (US$ 52 million), Angola (US$ 37 million) and the Democratic Republic of the Congo (US$ 37 million). Most of the remaining gap was reported by countries in the WHO South-East Asia Region, primarily Indonesia (US$ 145 million) and the Democratic People’s Republic of Korea (US$ 77 million), and by countries in the WHO Western Pacific Region, primarily China (US$ 68 million) and the Philippines (US$ 66 million) (Fig. 6.9).

6.4 Unit costs of treatment for drug-susceptible TB and multidrug-resistant TB, 2017

The cost per patient treated in 2017 for drug-susceptible TB and MDR-TB was estimated for 113 countries and 85 countries, respectively.1 All 30 countries in the lists of high TB burden countries and high MDR-TB burden countries were included in the analyses.2 Unit cost estimates are shown in Fig. 6.10 and Fig. 6.11, and analytical methods are summarized in Box 6.1.

A recent global initiative to improve the availability and quality of unit cost data for TB is summarized in Box 6.3.

6.4.1 Drug-susceptible TB

The median cost per patient treated for drug-susceptible TB in 2017 was US$ 1224 (Fig. 6.10).3 In general, about 68% of this cost was accounted for by reported NTP expenditures, with the remainder being costs for inpatient and outpatient care. There was a positive relationship between the cost per patient treated and the gross domestic product (GDP) per capita, and a negative relationship with the size of the patient caseload (indicating economies of scale, e.g. in China and India). In 29 of the 30 high TB burden countries included in the analysis, the cost per patient treated for drug-susceptible TB was less than the GDP per capita; the exceptions were Sierra Leone and Namibia.

The cost per patient treated was typically higher in the 17 countries included from the WHO European Region. Countries in Eastern Europe and Central Asia (EECA) have relatively high costs due to extensive use of hospitalization for patients in the intensive phase of treatment, with hospital admissions averaging 56 days per person in 2017. High programme costs relative to a smaller pool of patients also help to explain comparatively high per-patient costs in some countries (e.g. in Bosnia and Herzegovina, and Macedonia). However, it is also evident that some EECA countries have markedly reduced the use of hospitalization and have changed the model of care for patients with drug-susceptible TB. From 2014 to 2017, 15 of the 17 EECA countries reduced the number of bed days per patient treated for drug-susceptible TB (see Box 6.1 for estimation method); the exceptions were Ukraine (12% increase) and Kyrgyzstan (10% increase).

6.4.2 Multidrug-resistant TB

For MDR-TB, the median cost per patient treated was US$ 7141 in 2017 (Fig. 6.11). As with drug-susceptible TB, the cost per patient treated was positively correlated with GDP per capita. New shortened regimens of 9–12 months cost about US$ 1000 per person. These regimens have been recommended since 2016 by WHO for patients (other than pregnant women) with rifampicin-resistant or MDR pulmonary TB who do not have resistance to second-line drugs.4 The uptake of such regimens has contributed to a decrease in the unit cost of treatment for MDR-TB in 2017.

1 Analysis for drug-susceptible TB was limited to countries that notified at least 100 TB cases in 2017. For MDR-TB, estimates were restricted to countries that reported at least 20 patients on second-line treatment for MDR-TB in 2017.
2 For further details about both lists, see Chapter 2.
3 Median values are cited rather than means because of extreme values for a few countries.
4 For further details about this recommendation, see Chapter 1.
Not all international donor funding that is provided for TB prevention, diagnosis and treatment is channelled through NTPs. The creditor reporting system (CRS) of the OECD is the most comprehensive source of information about international donor funding. Funding data (both commitments and disbursements) are provided by 31 multilateral donor organizations, the 26 countries that are members of the OECD’s Development Assistance Committee, and a further two non-committee members (Kuwait and the United Arab Emirates).

Disbursement data include both direct transfers to countries and the provision of goods and services, such as in-kind transfers or technical assistance. Data on gross disbursements for TB (code 12263: Tuberculosis control) received by non-OECD countries during 2006–2016 were analysed. Funding for TB that flows from one OECD member to an institution or government within the OECD, such as grants from the United States (US) National Institutes for Health flowing to the United Kingdom, is not captured in the CRS. Also, government contributions to multilateral organizations are not attributed to the government of origin, only to the multilateral organization.\(^b\)

Fig. B6.2.1 shows trends in international donor funding between 2006 and 2016, from four major sources as a total and by four major regions of the world. The total from all sources in 2016 was US$ 871 million, a big increase from US$ 221 million in 2006. In 2016, 69% of international donor funding was provided by the Global Fund. The second largest contributor was the US government (21%, US$ 179 million).\(^c\)

Given that about one third of the contributions to the Global Fund are from the US government, about 44% of international donor funding for TB globally originated from the US government in 2016.

From 2006 to 2016, the Global Fund was consistently the largest provider of international donor funding (with the share averaging 66% in this period). There was a marked drop between 2013 (US$ 710 million) and 2014 (US$ 398 million), a period in which a new funding model was introduced. This was followed by a recovery to US$ 483 million in 2015 and to US$ 603 million in 2016. Disbursements from the US government steadily increased from 2006 to 2014, peaking at US$ 253 million in 2014 before declining to US$ 179 million in 2016.\(^c\) The regional panels show that Africa and Asia receive the vast majority of international donor funding.

Fig. B6.2.2 shows the proportion and amounts of funding from 2006 to 2016 from individual countries to non-OECD countries, including their estimated funding for TB via contributions to the Global Fund. Over this period, 46% of this funding came from the United States of America. The next largest individual country contributors were France (10%), the United Kingdom (9.0%), Germany (6.2%), Japan (5.9%) and Canada (5.6%).
Funding amounts include bilateral funding as well as estimated funding for TB via contributions to the Global Fund (estimated based on the assumption that 18% of contributions are for TB). Data are shown for countries that provided at least US$ 50 million in the time period 2006–2016. All other countries are combined in the "Other countries" box.

FIG. B6.2.2

FIG. B6.2.3
International donor funding for TB, HIV and malaria, 2006–2016

This translates into US$ 119 of international donor financing per DALY lost for HIV, US$ 34 for malaria, and US$ 20 for TB.

a As opposed to commitments, which may not materialize.
b An important example is funding from the Global Fund to non-OECD countries, which is attributed to the Global Fund and not to the governments or other entities that contribute to the Global Fund.
c Disbursements from the US government captured in the OECD database are lower than official allocations.
### FIG. 6.8
Sources of funding and funding gaps for the TB-specific budgets included in national strategic plans for TB in 2018, 30 high TB burden countries

#### Low-income
- Central African Republic
- Ethiopia
- DPR Korea
- Mozambique
- UR Tanzania
- Liberia
- DR Congo
- Sierra Leone
- Zimbabwe

#### Lower-middle-income
- India
- Congo
- Papua New Guinea
- Philippines
- Indonesia
- Kenya
- Lesotho
- Zambia
- Bangladesh
- Cambodia
- Viet Nam
- Nigeria
- Angola
- Myanmar
- Pakistan

#### Upper-middle-income
- Russian Federation
- South Africa
- China
- Thailand
- Brazil
- Namibia

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Domestic funding</th>
<th>Global Fund</th>
<th>International donor funding (excluding Global Fund contributions)</th>
<th>Budget gap</th>
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<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>10-20</td>
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<td>90</td>
<td>0</td>
<td>10</td>
</tr>
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<td>20-30</td>
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<td>80</td>
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</tr>
<tr>
<td>30-40</td>
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<td>70</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>40-50</td>
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<td>60</td>
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</table>
BOX 6.3

The Unit Cost Study Repository of the Global Health Cost Consortium: a new resource to estimate the cost of TB and HIV interventions

Planning and financing for TB prevention, diagnosis and treatment requires reliable data on the costs of TB services. Reporting of TB expenditures has improved substantially in recent years, and can be combined with data on the costs of specific TB services to inform TB budgeting and improve the efficiency of TB programmes. However, cost studies are time-consuming, and funding is required to implement them.

It has been recognized for several years that there is a global scarcity of cost data for TB services, and that available data were also becoming out of date. Examples of gaps in data availability include the cost of implementing new diagnostics, shortened treatment regimens for MDR-TB, innovative ways of providing TB services (e.g. public–private mix) and interventions to improve the quality of TB care. Many high TB burden countries do not have data on the unit cost of each of the TB interventions being provided.

The Global Health Cost Consortium (GHCC) was established in 2016, with funding from the Bill & Melinda Gates Foundation, to help to address these gaps. The aim of the GHCC is to improve the resources available to estimate the costs of both TB and HIV interventions. To date, it has focused on two things: standards and methods for costing, and the development of a repository of unit cost data.

The Reference case for estimating the global health services and interventions provides a set of standardized principles and methods that can assist with both collecting and evaluating cost data. It also provides detailed costing guidelines and tools for costing TB services.

The Unit Cost Study Repository (UCSR) is a centralized source of costing data for TB and HIV interventions that is easily accessible to policy analysts, country officials and implementing organizations via an online application for desktop or mobile devices. It provides standardized unit cost data at the intervention and service output levels, with disaggregation of the unit cost available by input (e.g. personnel and capital) and for different categories of activity. An assessment of the quality of each estimate is included, based on the reference case publication.

As of July 2018, a total of 174 TB studies were included in the UCSR, based on a systematic review of costing studies implemented during the period 1990–2017 (Fig. B.6.3.1). Of these, 67 studies reported only costs incurred by patients, 60 reported provider costs, and 47 reported costs from a societal perspective (i.e. both patient and provider costs were considered). The interventions that were costed in each study varied. As collection of new data takes place and data producers share their data with the GHCC, the UCSR will be enriched and, ultimately, this resource will improve the cost data available for use by the TB community.

UCSR data will be used by WHO’s Global TB Programme to triangulate its estimates of the cost per patient treated for drug-susceptible TB and MDR-TB (Fig. 6.10 and Fig. 6.11); in particular, the unit cost estimates for inpatient stays and outpatient visits. Also, the Global TB Programme may use the UCSR data in preference to the data sources that are currently relied upon.

FIG. B6.3.1
Cost per patient treated for drug-susceptible TB or MDR-TB: current availability of unit cost data from independent costing studies, 1990–2017

FIG. 6.9
Reported funding gaps for TB by income group and by WHO region, 2006–2018

Total gap in 2018 = US$ 1.2 billion

Low-income countries
Lower-middle-income countries
Upper-middle-income countries

FIG. 6.10
Estimated cost per patient treated for drug-susceptible TB in 113 countries, 2017a

Limited to countries with at least 100 patients on first-line treatment in 2017.
FIG. 6.11
Estimated cost per patient treated for MDR-TB in 85 countries, 2017*

* Limited to countries with at least 20 patients on second-line treatment in 2017.
The Paraisópolis favela in São Paulo, Brazil, and the neighbouring district of Morumbi
Tuca Vieira
Chapter 7. Universal health coverage, social protection and social determinants

KEY FACTS AND MESSAGES

Achieving the tuberculosis (TB) targets and milestones of the End TB Strategy and the TB target set in the Sustainable Development Goals (SDGs) requires provision of TB care and prevention within the broader context of universal health coverage (UHC), and multisectoral action to address the social and economic determinants and consequences of TB.

UHC means that everyone – irrespective of their living standards or their particular disease or health needs – receives the health services they need, and that using health services does not cause financial hardship. SDG target 3.8 is to achieve UHC by 2030.

The SDGs include two indicators for monitoring progress towards UHC. The first is the coverage of essential health services, measured as an index (with values from 0 to 100). The second is the proportion of households in the general population that face catastrophic health expenditures, defined as household expenditures on health that exceed a certain percentage of total household expenditure or income; the denominator includes many households that did not use health services or had only very minor contact with the health system.

The latest estimates published by WHO and the World Bank suggest that at least half of the world’s population lacks access to essential health services and that annually around 800 million people – almost 10% of the world’s population – experience catastrophic expenditures on health. All high TB burden countries still face significant challenges to ensure both aspects of UHC.

In 2017, WHO published estimates of the resources needed to make progress towards UHC and reach other SDG-related health targets by 2030. These suggested that most middle-income countries could mobilize the required resources domestically, but that this is unlikely in low-income countries.

Social protection for people with TB and their households is part of Pillar 2 of the End TB Strategy, and social protection more broadly is an indicator under SDG 1. TB-specific social support is in place in some countries: examples include cash transfers, food packages and assistance with costs related to transport. There are also examples of TB patients being linked to more general social protection schemes.

Since 2016, considerable progress has been made in measuring costs faced by TB patients and their households. In national facility-based surveys completed to date, best estimates of the percentage of TB patients and their households facing direct and indirect costs that exceeded 20% of their annual household income ranged from 27% to 71%. Survey results should be used to help develop approaches to financing, service delivery and social protection that will reduce these costs. Examples of countries where this has been done in 2018 are Ghana and Kenya.

Many new cases of TB are attributable to undernourishment, HIV infection, smoking, diabetes and alcohol use. A recent modelling study also shows how poverty is an important underlying driver of national TB epidemics, and that eliminating extreme poverty and providing social protection (both targets under SDG 1) could substantially reduce TB incidence.
The End TB Strategy and the Sustainable Development Goals (SDGs) include a common aim: to end the global tuberculosis (TB) epidemic. Specific targets set in the End TB Strategy include a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate (new cases per 100,000 population per year) by 2030 compared with 2015; more immediate milestones for 2020 are reductions of 35% and 20%, respectively. As highlighted elsewhere in this report, in particular in Chapter 2, achieving these targets requires provision of TB care and prevention within the broader context of universal health coverage (UHC), multisectoral action to address the social and economic determinants and consequences of TB, and a technological breakthrough by 2025 so that incidence can fall much faster than it has done historically.

This chapter has four major sections. Section 7.1 provides an overview of the status of global progress towards UHC, and a summary of recent WHO estimates of the resources required for progress towards UHC and other SDG health targets during the period 2016–2030. Section 7.2 discusses the role of social protection in improving care and support to TB patients and their households, and what is known about the current status of such protection in high TB burden countries. Section 7.3 presents the status of progress in implementing national surveys of costs faced by TB patients and their households as of July 2018, and survey results from eight countries. It highlights the implications of such costs, including for approaches to TB service delivery, financing and social protection. Section 7.4 covers the broader determinants of TB, including analysis of 14 indicators (under seven SDGs) that are associated with TB incidence.

7.1 Global progress towards UHC

UHC means that everyone – irrespective of their living standards – receives the health services they need, and that using health services does not cause financial hardship.¹

The SDG targets are for 2030, and SDG Target 3.8 is defined as “Achieve UHC, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines” (Chapter 2).

Two SDG indicators have been defined to monitor progress towards SDG Target 3.8. The first (Indicator 3.8.1) is the coverage of essential health services; this is a composite index (with values from 0 to 100) based on 16 tracer indicators (one of which is TB treatment²). The second (Indicator 3.8.2) is the “proportion of the population with large household expenditures on health as a share of total household expenditure or income”. Large is defined using two thresholds: 10% and 25%. When these thresholds are surpassed, expenditures are classified as “catastrophic”. Since this measure is population-based, the denominator includes many people who did not use health services or had only very minor contact with the health system.

The WHO/World Bank report on tracking progress towards UHC, published in December 2017, was the first to publish data on the two SDG indicators for UHC.³ Key findings from the report are summarized here.

7.1.1 Coverage of essential health services

The value of the UHC service coverage index in 2015, by country, is shown in Fig. 7.1. There was a great deal of variation among countries, with values ranging from a low of 22 in Somalia to 80 or above, and a median value of 65. The highest values were in high-income countries in Asia, Europe and North America. The lowest values were predominantly in countries in the WHO African Region; other countries with values below 40 were Afghanistan and Yemen. Overall, at least half of the world’s population lacked access to essential health services in 2015.

7.1.2 Financial protection

The estimated proportion of the general population facing catastrophic health spending, using the cut-off of more than 10% of household expenditure or income, is shown in Fig. 7.2. Compared with the service coverage index, there is more geographical variability in this indicator, including within regions.

Countries with the highest levels of catastrophic spending on health (≥15% of the general population facing catastrophic spending on health) include the countries that rank first (India) and second (China) in terms of their total number of TB cases, most countries in Latin America and several countries in the WHO African Region.

Countries with the lowest levels (0–3%) include a mix of high-income, middle-income and low-income countries. It is important to highlight that some countries may have low levels of measured spending on health because people do not access health care at all, or because capacity to spend household resources on health is very low. One example is Mozambique, for which the value of the service coverage index was 42 while the estimated proportion of households facing catastrophic expenditures on health was 1.2% (based on data for 2008).

Globally, WHO and the World Bank estimated that, in


² The indicator used in the WHO/World Bank report is “effective TB treatment coverage”. It was calculated as treatment coverage multiplied by the treatment success rate, to capture a “quality” dimension of care. This differs from the definition of “treatment coverage” in the list of priority End TB Strategy indicators (see Chapter 2).


⁴ For Indicator 3.8.2, estimates in the report are based primarily on the cut-off of 10% of total household income.
**FIG. 7.1**
UHC service coverage index by country, 2015

Source: WHO Universal Health Coverage data portal.

**FIG. 7.2**
Percentage of the general population facing catastrophic health expenditures, a latest available year of data b

a Defined as ≥10% of total household income or household consumption.
2010, a total of 808 million people (12% of the world’s population) incurred catastrophic expenditures on health.

7.1.3 Status of the two UHC indicators in the 30 high TB burden countries

The status of the two SDG indicators for UHC (3.8.1 and 3.8.2) in the 30 high TB burden countries, stratified by income group, is shown in Table 7.1. There is a general trend for the service coverage index to improve with income, but the level of catastrophic health spending varies considerably within each income band. The countries with the highest service coverage index (above 70) are (in descending order) Brazil, China, Thailand and Viet Nam. The countries with the worst (highest) values for levels of catastrophic spending on health were middle-income countries (for example Brazil, India and Nigeria), while those with the lowest values (<2%) included both low-income countries and several middle-income countries. As explained above, some countries may have low values for the percentage of the population facing catastrophic expenditures on health because people do not access health care at all, or because capacity to spend household resources on health is very low.

7.1.4 UHC financing prospects, 2016–2030

In 2017, WHO published estimates of the resources needed during the period 2016–2030 to make progress towards UHC and to reach other SDG-related health targets, and compared these with projected total health expenditures in the same time period. Referred to in shorthand as the WHO SDG Health Price Tag, the estimates are for 67 low- and middle-income countries that account for 75% of the world’s population, and they focus on the additional (or incremental) resources needed compared with levels in 2014. Two scenarios were considered for resource needs (termed “ambitious” and “progress”), and two scenarios (referred to as “moderate” and “optimistic”) were also considered for total health expenditures.

Key findings included the following:

- In the “ambitious” scenario for resource needs (based on achievement of the 2030 SDG targets), the additional investment (compared with 2014) required per year grew from US$ 134 billion in 2016 to US$ 371 billion (equivalent to an extra US$ 58 per person) in 2030.
- Most of the increased investment required (75% of the total) was for expanding and strengthening the health workforce and health services infrastructure

1 Income groups are based on the classification of 2018 for consistency with Chapter 6 of this report. However, estimates of the incidence of catastrophic health spending in the WHO/World Bank report, on monitoring UHC, are for earlier years.


Further analyses based on the WHO SDG Health Price Tag, focusing on comparisons of total (as opposed to incremental) investment needs with projections of total health expenditures, are shown in Fig. 7.3 and Fig. 7.4. These illustrate the same key messages in terms of the extent to which the resources needed to achieve UHC and other SDG-related health targets can be mobilized in low- and middle-income countries. In addition, they indicate that, by 2030, total average health spending would need to increase to US$ 112 per capita in low-income countries, US$ 146 per capita in lower-middle-income countries and US$ 536 per capita in upper-middle-income countries (Fig. 7.4). Total funding needs as a percentage of gross domestic product (GDP) would rise from 5.6% in 2014 to 7.5% by 2030 across all 67 countries (data not shown), with a much greater increase needed in low-income countries (from an average of 6% in 2014 to around 12% by 2024).

7.2 Social protection in the context of the TB response

Social protection refers to an integrated set of policies and programmes that provide support to those in need. Major elements include:

- social assistance programmes;
- social insurance schemes; and
- labour market interventions, for example to facilitate access to employment and development of skills.

Social protection floors are a basic minimum set of policies and programmes that provide a safety net in the
### TABLE 7.1
**UHC service coverage indicator (SDG 3.8.1) and percentage of general population facing catastrophic health expenditures (SDG 3.8.2),<sup>a</sup> 30 high TB burden countries, stratified by income group<sup>b</sup>**

<table>
<thead>
<tr>
<th>Country</th>
<th>Service Coverage Index</th>
<th>Catastrophic Health Expenditure&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW INCOME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>39</td>
<td>0.82</td>
</tr>
<tr>
<td>Mozambique</td>
<td>42</td>
<td>1.2</td>
</tr>
<tr>
<td>DR Congo</td>
<td>40</td>
<td>5.8</td>
</tr>
<tr>
<td>Liberia</td>
<td>34</td>
<td>7.9</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>39</td>
<td>9.9</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>DPR Korea</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td><strong>LOWER–MIDDLE INCOME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>56</td>
<td>0.29</td>
</tr>
<tr>
<td>Pakistan</td>
<td>40</td>
<td>1.0</td>
</tr>
<tr>
<td>Lesotho</td>
<td>45</td>
<td>1.8</td>
</tr>
<tr>
<td>Congo</td>
<td>38</td>
<td>2.0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>49</td>
<td>3.6</td>
</tr>
<tr>
<td>Kenya</td>
<td>57</td>
<td>5.8</td>
</tr>
<tr>
<td>Philippines</td>
<td>58</td>
<td>6.3</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>73</td>
<td>9.8</td>
</tr>
<tr>
<td>Angola</td>
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<td>12</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>India</td>
<td>55</td>
<td>17</td>
</tr>
<tr>
<td>Nigeria</td>
<td>39</td>
<td>25</td>
</tr>
<tr>
<td>Myanmar</td>
<td>60</td>
<td>—</td>
</tr>
<tr>
<td>Cambodia</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>41</td>
<td>—</td>
</tr>
<tr>
<td><strong>UPPER–MIDDLE INCOME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>67</td>
<td>1.4</td>
</tr>
<tr>
<td>Thailand</td>
<td>75</td>
<td>3.4</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>63</td>
<td>4.9</td>
</tr>
<tr>
<td>China</td>
<td>76</td>
<td>18</td>
</tr>
<tr>
<td>Brazil</td>
<td>77</td>
<td>26</td>
</tr>
<tr>
<td>Namibia</td>
<td>59</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data of UHC service coverage are from 2015, and data of catastrophic health expenditures cover the period 2002–2015.

<sup>b</sup> Countries are listed within each income group (as per 2018 World Bank classification) according to the level of catastrophic health expenditure (from lowest to highest).

<sup>c</sup> Defined as ≥ 10% of total household income or household consumption.

The latest available year for data on “catastrophic health expenditures” ranges from 2008 to 2015 for 16 of the 30 countries; this time period is consistent with the years of data used for joint analysis of service coverage and catastrophic expenditures in the WHO/World Bank report on UHC monitoring (http://apps.who.int/iris/bitstream/handle/10665/259817/9789241513555-eng.pdf, accessed 21 June 2018). For 7 countries, however, the values shown in the table are for earlier years: China (2007), DR Congo (2004), Ethiopia (2004), Kenya (2005), Lesotho (2002), Liberia (2007) and Sierra Leone (2003). No data are available for Cambodia, Central African Republic, DPR Korea, Myanmar, Namibia, Papua New Guinea and Zimbabwe. Data can be obtained from the WHO Global Health Observatory: http://apps.who.int/gho/portal/uhc-fp-cabinet-wrapper-v2.jsp?id=1020201 (accessed 15 August 2018).
event of unforeseen shocks. Although this is protective, the aim of comprehensive social protection is for poverty reduction, and sustainable and inclusive economic growth.

Social protection is an indicator under SDG 1, which is “End poverty in all its forms everywhere”. SDG Target 1.3 is to “Implement nationally appropriate social protection systems and measures for all, including floors, and by 2030 achieve substantial coverage of the poor and the vulnerable”.

Poverty and TB are intricately linked. People with TB can face severe direct and indirect financial and economic costs that affect their ability to access care and complete treatment, while poverty is a well-recognized risk factor for TB. As such, social protection for people with TB and their households is part of Pillar 2 of the End TB Strategy (Chapter 2).

The 2016 and 2017 editions of the Global tuberculosis report and the 2015 WHO guide to implementing the

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End TB Strategy\(^1\) explained core principles related to social protection in the context of TB. They also provided country examples of steps being taken to establish and/or strengthen social protection systems in general, including social assistance schemes of particular relevance to TB-affected households and communities.

The need for expanded policy and legal frameworks, financing and programme strengthening to ensure that support is available on a systematic and sustainable basis was highlighted. In addition, examples were provided of social support in the context of TB treatment services, such as transport, vouchers, food packages, and psychosocial support, and cash-transfer schemes (including those in which TB patients are linked to general schemes). Documentation on social protection for TB patients is increasing.

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### TABLE 7.2
Social protection policy and cash transfer schemes in 30 high TB burden countries

<table>
<thead>
<tr>
<th>STRATEGY/POLICY(^a)</th>
<th>REGISTRY(^b)</th>
<th>POOR AND VULNERABLE</th>
<th>DISABLED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bangladesh</td>
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<td></td>
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<tr>
<td>Brazil</td>
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<tr>
<td>Cambodia</td>
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<td>Central African Republic</td>
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<tr>
<td>China</td>
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<tr>
<td>DR Congo</td>
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<td>Congo</td>
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<td>DPR Korea</td>
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<td>Ethiopia</td>
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<td>India</td>
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<td>Lesotho</td>
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<td>Liberia</td>
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<td>Mozambique</td>
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<td>Namibia</td>
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<td>Pakistan</td>
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<td>Papua New Guinea</td>
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<tr>
<td>Russian Federation</td>
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<tr>
<td>Sierra Leone</td>
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<td>South Africa</td>
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<td>Thailand</td>
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<td>UR Tanzania</td>
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<td>Viet Nam</td>
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<tr>
<td>Zimbabwe</td>
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</tbody>
</table>

\(^a\) Strategy/policy indicates whether a national strategy, and/or policy/legislative framework for social protection was identified.

\(^b\) Registry indicates whether a social and/or beneficiary registry system for social assistance programmes is in place.

Targeting indicates whether there are any identified non-contributory cash transfer schemes specifically for poor and vulnerable groups and the disabled. Poor and vulnerable groups include transfers to individuals and households based on socio-economic criteria and may include children, the elderly, poor people with disabilities, and those facing food insecurity; disabled refers to persons having a disability regardless of socio-economic status.

A summary of the elements of social protection of particular relevance to TB patients and their households that are in place in the 30 high TB burden countries is provided in Table 7.2, using information compiled by WHO’s Global TB Programme in 2017 and 2018. The focus is on three major elements of social protection schemes that may be of substantial relevance to efforts to improve social protection for TB patients and households. These are: the existence of overall policy, strategy or legislative frameworks; a register of target populations or beneficiaries; and some level of coverage of cash transfers for specific poor or vulnerable populations or disabled persons. Of the 30 countries, 26 have a policy document, strategy or relevant legislation for social protection, and most have some form of cash transfer system.

Data on coverage levels of cash transfers are not easy to obtain, but available data suggest that coverage in many of the 30 high TB burden countries remains low and fragmented. More positively, India is an example of a country that took major steps in 2017–2018 to expand TB-specific cash transfers and linkages to broader nutrition schemes.

Stakeholder workshops to discuss the results from national surveys of costs faced by TB patients and their households (Section 7.3) provide an opportunity to discuss how to improve social protection for people with TB, for example through improved models of care, direct social support and better linkage to social services and other forms of social protection.

7.3 National surveys of costs faced by TB patients and their households (TB patient cost surveys)

One of the three high-level targets of the End TB Strategy is that no TB patients or their households should face costs due to TB that are catastrophic (Chapter 2). Monitoring of progress towards this target can also inform monitoring of progress towards UHC. The distinction between the indicator of catastrophic total costs due to TB disease and the broader indicator of catastrophic spending on health (Section 7.1.2) is explained in Box 7.1.

In 2015, WHO established a standardized protocol1 for conducting a national survey to assess the direct and indirect costs incurred by TB patients and their households (TB patient cost surveys). Based on experience in pathfinding countries that conducted the first surveys, the protocol was refined and expanded into a handbook in 2017.2

TB patient cost surveys have two primary objectives:

- to document the magnitude and main drivers of different types of costs incurred by TB patients (and their households), in order to guide policies to reduce financial barriers to accessing care and minimize the adverse socioeconomic impact of TB; and
- to determine the baseline and periodically measure the percentage of TB patients (and their households) treated in the NTP network who incur catastrophic total costs due to TB.

In the context of these surveys, catastrophic costs for TB patients and their households have been defined as direct medical and non-medical costs plus income losses that sum to 20% or more of household income.

WHO recommends conducting a baseline survey by 2020 at the latest, especially in high TB burden countries.

7.3.1 Global progress in implementation of surveys

The status of progress in implementing survey planning and implementation is shown in Fig. 7.5. By July 2018, 11 countries had completed national surveys:3 China (2016), Fiji (2017), Ghana (2016), Kenya (2017), Mongolia (2017), Myanmar (2015), Nigeria (2017), the Philippines (2016), Republic of Moldova (2016), Timor-Leste (2017) and Viet Nam (2016).4

In July 2018, surveys were underway in four countries: India, Sudan, Uganda and Zimbabwe. There are 13 countries in which surveys are scheduled to start in 2018 or in 2019: Brazil, Burkina Faso, Colombia, Dominican Republic, the Democratic Republic of the Congo, Ethiopia, Indonesia, Lao People’s Democratic Republic, Papua New Guinea, Romania, Solomon Islands, South Africa, and the United Republic of Tanzania.

The main survey results for eight countries are shown in Fig. 7.6. The number in the centre of the circle shows the best estimate of the percentage of TB patients and their households that faced catastrophic costs, and the outer ring shows the distribution of costs using three major cost categories.

The percentage of TB-affected households that experienced total costs that were catastrophic ranged from 27% (95% confidence interval [CI]: 21–32%) in Kenya to 71% (95% CI: 68–73) in Nigeria.

The distribution of costs varied among countries. Nonetheless, it is evident that – despite the widespread norm of “free TB care” policies – the direct medical costs faced by TB-affected households can be high, and such costs accounted for a large proportion of total costs in some countries (e.g. in Mongolia and Myanmar). Minimizing direct medical costs borne by TB patients should be a high priority for NTPs and ministries of health.

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3 Defined as having completed survey field work, analysis of data, and documentation of results (e.g. in a report).

4 The year indicates the year in which data collection was done.
**BOX 7.1**

The difference between “catastrophic total costs” for TB patients and their households, and the SDG indicator of catastrophic expenditures on health

It is important to distinguish between the indicator of “catastrophic spending on health” used within the SDG monitoring framework (SDG 3.8.2) and the indicator of “catastrophic total costs due to TB”.

The former is a population-based indicator that measures the share of the population incurring “catastrophic spending” on health, with a threshold defined as exceeding 10% and 25% of a household’s total consumption expenditure or income. Health expenditures are defined as direct expenditures on medical care. The denominator of the SDG indicator includes many people who had no contact with the health system and thus had zero expenditures on health.

The TB-specific indicator incorporates not only direct medical payments for diagnosis and treatment, but also direct non-medical payments (e.g. for transportation and lodging) and indirect costs (e.g. lost income). In addition, the TB-specific indicator is restricted to a particular population: diagnosed TB patients who are users of health services that are part of NTP networks.

As a consequence of these differences, the percentage of TB patients facing costs that are large in relation to their household expenditure or income is expected to be much higher than the percentage of the general population facing catastrophic expenditures on health. The two indicators should not be compared directly.

**FIG. 7.5**

National surveys of costs faced by TB patients and their households since 2016: progress and plans (as of July 2018)
The surveys also show that actions to eliminate the indirect costs of care and to reduce income losses are needed. The combined cost of transportation, food, nutritional supplements and other non-medical expenditures (“direct non-medical costs”) accounted for the largest share of total costs in Fiji, Ghana, Nigeria, the Philippines and Viet Nam. Income losses associated with loss of employment or time lost while seeking or staying in care accounted for the largest single share of total costs in Mongolia, Myanmar and Timor-Leste.

All cost categories are influenced by the model of care, such as the extent to which hospitalization or outpatient care are relied upon, and the frequency with which attendance at health facilities is requested.

### FIG. 7.6
Results from selected national surveys of costs faced by TB patients and their households, implemented 2015–2018. The number in the centre of the circle is the best estimate of the percentage of TB patients and their households that experienced total costs that were above 20% of their annual income (i.e. catastrophic total costs). The outer ring shows the distribution of costs in three major categories. The number of TB patients included in each survey is shown after the country name.

- Fiji (n=224)
  - Direct non-medical costs: 40%
  - Income loss: 35%
  - Direct medical costs: 27%
- Ghana (n=691)
  - Direct non-medical costs: 64%
  - Income loss: 63%
  - Direct medical costs: 27%
- Kenya (n=1335)
  - Direct non-medical costs: 27%
  - Income loss: 35%
  - Direct medical costs: 38%
- Mongolia (n=810)
  - Direct non-medical costs: 68%
  - Income loss: 71%
  - Direct medical costs: 6%
- Myanmar (n=965)
  - Direct non-medical costs: 60%
  - Income loss: 65%
  - Direct medical costs: 7%
- Nigeria (n=1190)
  - Direct non-medical costs: 67%
  - Income loss: 71%
  - Direct medical costs: 6%
- Philippines (n=1880)
  - Direct non-medical costs: 35%
  - Income loss: 47%
  - Direct medical costs: 18%
- Viet Nam (n=735)
  - Direct non-medical costs: 63%
  - Income loss: 63%
  - Direct medical costs: 13%

### 7.3.2 Policy and strategy implications of survey results
Results from TB patient cost surveys can inform policy and strategy in two major ways. First, costs can be mitigated by improving approaches to TB service delivery and financing, such as removal of user fees and the introduction of more patient-centred models of care. Second, any costs that remain after the optimization of health-care delivery can be mitigated by improved social protection measures, in collaboration with stakeholders across the social sector. Survey results should be used to stimulate the engagement of multisectoral partners and to facilitate policy discussion on both topics.

A multi-stakeholder consultation can be an effective way to initiate discussions about survey results and the actions needed in response. An early example was a multisectoral meeting in Viet Nam in March 2017, which was used to disseminate findings and formulate a joint action plan with the country’s Ministry of Labour and Social Affairs. Similar dissemination and stakeholder consultations have subsequently been held in Myanmar (2017), Kenya (July 2018) and Ghana (August 2018), resulting in multisectoral action to improve social support to TB patients and their households. The two most recent examples, in Ghana and Kenya, are described in more detail in Box 7.2.

### 7.4 Addressing broader determinants of the TB epidemic
The influence of various social and economic determinants on the TB epidemic has long been recognized. In the late 1800s, cause-of-death data from national vital registration systems show that TB was one of the leading causes of death in some European countries. With social and economic development – such as improvements in incomes, housing and nutrition – numbers of TB cases and deaths started to decline in western Europe, North America and some other parts of the world around the turn of the 20th century, albeit slowly (1–2% per year).\(^1\)\(^2\) From the 1940s, the discovery, development and use of effective drug treatments substantially accelerated these trends, with national case rates (new cases per 100 000 population per year) falling by up to 10% per year and mortality rates falling even faster. The fastest historic declines in western Europe occurred during the 1950s and 1960s, in the context of UHC, rapid social and economic development and the availability of effective drug treatments.

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BOX 7.2
National surveys of costs faced by TB patients and their households in Ghana and Kenya: results and policy translation

Ghana

Ghana is a lower-middle-income country in which there has been economic growth for more than two decades and reductions in the proportion of the population living in poverty. However, social and health inequalities persist. Several social protection programmes have been implemented, and a National Health Insurance Scheme (NHIS) was introduced through an Act of Parliament in 2003. In 2017, active membership of the NHIS was estimated at 40% of the national population.

In 2016, the NTP worked with the London School of Hygiene and Tropical Medicine to conduct the first national survey of costs faced by TB patients and their households, according to the guidance in the WHO handbook on TB patient cost surveys. Ghana was the first country in Africa to implement such a survey.

The cross-sectional survey involved 691 patients with either drug-susceptible or multidrug-resistant (MDR) TB who were receiving treatment in health facilities in the public sector, across 25 clusters. The questionnaire included questions on costs, time losses, coping measures and asset ownership. Total costs were expressed as a percentage of annual household income; if total costs exceeded 20% of household income, the household was classified as “experiencing catastrophic total costs”.

The median cost that patients incurred per TB episode was US$ 455, equivalent to about 25% of the average annual household income reported by survey participants. The share was significantly higher for MDR-TB patients. Non-medical costs (and particularly food) and lost income accounted for the largest share of the total cost, while medical costs accounted for less than 20%. Overall, 64% (95% CI: 61–68%) of TB-affected households, and 73% (95% CI: 61–82%) of households of patients with MDR-TB experienced total costs that were catastrophic. People with MDR-TB were pushed significantly further above the threshold for catastrophic costs than those with drug-susceptible TB.

The survey also found that TB-affected households were more likely than the general population to be poor at the time of diagnosis (46% versus 24%), and that the costs associated with TB care increased the proportion of TB-affected households living below the poverty line (from 46% to 60%). More than half (52%) of all patients were unable to pay for TB treatment from their existing income sources, and had to rely on savings, borrowing or sale of assets.

Among survey participants, 45% were enrolled in the NHIS at the time of diagnosis. A further 35% enrolled after diagnosis, and the remaining 20% were uninsured throughout. Only four patients (<1%) benefited from the Livelihood Empowerment Against Poverty (LEAP) programme, which provides conditional cash transfers to extremely poor households, with the aim of alleviating short-term poverty, and supporting long-term resiliency and human capacity development.

Shortly after the survey was completed, the NTP engaged key government agencies, to inform them about the findings and the need for multisectoral action to mitigate costs faced by TB patients and their households, including through social support. Subsequently, a stakeholders meeting was used to disseminate survey findings and launch a national action plan to reduce and compensate for costs faced by TB patients and their households. The meeting was attended by representatives from the National Health Insurance Authority; the Ministry of Gender, Children and Social Protection; the Ghana Health Service; the Ghana AIDS Commission; the Ministry of Monitoring and Evaluation; the National Development Planning Commission; representatives of TB patients and civil society; and local and international partners.

Key intervention areas identified in the action plan to reduce direct medical costs are the inclusion of TB patients as one of the groups exempt from paying the NHIS premium under the category of indigent people, and further decentralization of TB services through the establishment of closer linkages with the Community-Based Health Planning and Services strategy. Interventions to reduce indirect costs include the expansion of existing social protection interventions to include TB patients, including their enrolment in LEAP, by making TB one of the criteria for eligibility; and the design of a social support package targeting the specific needs of TB patients, such as nutritional support and transport vouchers.

Further details are available in a recent publication.

Kenya

In 2017, the Kenya National Tuberculosis, Leprosy and Lung Disease Programme (NTLD) conducted the country’s first national survey of costs faced by TB patients and their households. The NTLD survey included 1071 patients with drug-susceptible TB and 282 patients with drug-resistant TB.

The median cost was US$ 256 for those with drug-susceptible TB and US$ 1434 for those with drug-resistant TB. The median value for total household annual expenditure was US$ 2550. The overall proportion of TB-affected households that faced catastrophic costs was 27% (95% CI: 21–32%), but this proportion was three times higher for those affected by drug-resistant TB (86%; 95% CI: 79–94%). Direct non-medical costs, particularly expenses on food and nutritional supplements beyond the patient’s normal diet, were the largest cost driver, followed by productivity losses.

Significant predictors for experiencing catastrophic costs were being in a low income quintile, having no education, having a small household size, and drug-resistant TB. More than half (59%) of the patients in the survey were either severely or moderately malnourished, and only 14% were covered by the National Health Insurance Fund (NHIF) during their TB treatment.

Based on survey results, a stakeholder consultation was held in July 2018. This was used to disseminate survey findings and to discuss the actions needed to achieve the goal of eliminating catastrophic costs for TB patients and their households in Kenya. Government stakeholders represented at the consultation included the Ministry of Treasury and Planning, the Ministry of Devolution and ASAL (Arid and Semi Arid Lands), the Ministry of Labour and Social Protection, and the health committee of the national parliament. Also...
participating were representatives from the NHIF and civil society, and former TB patients.

Six priority actions were identified, as follows:

1. Addition of TB as an eligibility criterion for existing social protection programmes, particularly cash-transfer programmes and systematic identification of TB patients eligible for social protection.

2. Ensuring systematic assessment of nutritional status and associated counselling for all TB patients, with provision of food support according to need, including for malnourished children of TB-affected households.

3. Inclusion of TB care in the NHIF benefit package, and increased NHIF coverage among TB patients through fast-track, premium-free enrolment.

4. Development and implementation of policies and laws to eliminate discrimination and ensure job security for TB patients, in collaboration with national authorities in the labour sector.

5. Engagement of all care providers in the provision of timely and quality-assured TB care, to reduce delays in accessing diagnosis and treatment.

6. Establishment of a high-level multi-stakeholder coordinating mechanism and forum for the implementation of the End TB Strategy.

During the consultation, the representative of the health committee of the national parliament pledged high-level political support to ensure implementation of the policy changes needed to eliminate catastrophic costs for TB-affected households in Kenya.

As explained in Chapter 2, WHO has developed a TB-SDG monitoring framework that focuses attention on 14 indicators (from seven SDGs) that are associated with TB incidence. Monitoring of these indicators can be used to identify key influences on the TB epidemic at national level and inform the multisectoral actions required to end the TB epidemic.

For SDG 3 (health), the seven indicators selected for TB-SDG monitoring are:

- proportion of the population living below the international poverty line;
- proportion of the population covered by social protection floors or systems;
- prevalence of undernourishment;
- proportion of the population with primary reliance on clean fuels and technology;
- GDP per capita;
- Gini index for income inequality;
- proportion of the urban population living in slums.

Collection and reporting of data for the 14 indicators does not require any additional data collection and reporting efforts by NTPs. Nor does it require data collection and reporting efforts that go beyond those to which countries have already committed in the context of the SDGs. Data are available from global databases, primarily those maintained by the United Nations (UN), WHO, the World Bank and the Joint United Nations Programme on HIV/AIDS (UNAIDS) (for further details, see Annex 1).

The most recent data for five of the seven SDG 3 indicators listed above are shown for the 30 high TB burden countries in Table 7.3. For all of the indicators shown, a lower level is more desirable.

For SDGs 1, 2, 7, 8, 10 and 11, the seven indicators selected for monitoring are:

- proportion of the population living below the international poverty line;
- proportion of the population covered by social protection floors or systems;
- prevalence of undernourishment;
- proportion of the population with primary reliance on clean fuels and technology;
- GDP per capita;
- Gini index for income inequality;
- proportion of the urban population living in slums.

The links between TB and poverty, social protection, the prevalence of undernutrition, diabetes, HIV, alcohol use, smoking, indoor air pollution and income per capita have been analysed, reviewed and summarized in recent publications (further details are provided in Chapter 2).¹ ²

As explained in Chapter 2, WHO has developed a TB-SDG monitoring framework that focuses attention on 14 indicators (from seven SDGs) that are associated with TB incidence. Monitoring of these indicators can be used to identify key influences on the TB epidemic at national level and inform the multisectoral actions required to end the TB epidemic.

For SDG 3 (health), the seven indicators selected for TB-SDG monitoring are:

- coverage of essential health services;
- percentage of total health expenditures that are out-of-pocket;
- health expenditure per capita;
- HIV prevalence;
- prevalence of smoking;
- prevalence of diabetes; and
- prevalence of alcohol use disorder.

For SDGs 1, 2, 7, 8, 10 and 11, the seven indicators selected for monitoring are:


3. The index can take values between 0 and 1, with 0 representing perfect equality and 1 representing perfect inequality.

4. Coverage of health services is not included because this indicator is covered in Section 7.1; health expenditure per capita is also not shown, but data are included in Annex 2.

5. GDP per capita is not included in Fig. 7.7 because it is the only indicator that is not measured on a scale of 0–100. However, the latest value and recent trends in this indicator are shown in the country profiles in Annex 2.
TABLE 7.3
Status of selected SDG 3 indicators, 30 high TB burden countries, latest available year

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>OUT-OF-POCKET HEALTH EXPENDITURE (% OF CURRENT HEALTH EXPENDITURE)</th>
<th>HIV PREVALENCE (% OF POPULATION AGED 15—49 YEARS)</th>
<th>SMOKING PREVALENCE (% OF POPULATION AGED ≥15 YEARS)</th>
<th>DIABETES PREVALENCE (% OF POPULATION AGED ≥18 YEARS)</th>
<th>ALCOHOL USE DISORDERS, 12 MONTH PREVALENCE (% OF POPULATION AGED ≥15 YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>33</td>
<td>1.9</td>
<td>—</td>
<td>8.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>72</td>
<td>0.1</td>
<td>44.7</td>
<td>10</td>
<td>9.3</td>
</tr>
<tr>
<td>Brazil</td>
<td>28</td>
<td>0.6</td>
<td>17.9</td>
<td>16.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Cambodia</td>
<td>59</td>
<td>0.6</td>
<td>33.7</td>
<td>2</td>
<td>7.4</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>40</td>
<td>4.0</td>
<td>—</td>
<td>8.0</td>
<td>7.6</td>
</tr>
<tr>
<td>China</td>
<td>32</td>
<td>—</td>
<td>48.4</td>
<td>1.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Congo</td>
<td>44</td>
<td>3.1</td>
<td>52.3</td>
<td>1.7</td>
<td>7.7</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DR Congo</td>
<td>37</td>
<td>0.7</td>
<td>—</td>
<td>—</td>
<td>6.2</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>38</td>
<td>1.1</td>
<td>8.5</td>
<td>0.4</td>
<td>5.8</td>
</tr>
<tr>
<td>India</td>
<td>65</td>
<td>0.3</td>
<td>20.6</td>
<td>1.9</td>
<td>9.1</td>
</tr>
<tr>
<td>Indonesia</td>
<td>48</td>
<td>0.4</td>
<td>76.1</td>
<td>2.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Kenya</td>
<td>33</td>
<td>5.4</td>
<td>20.4</td>
<td>1.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Lesotho</td>
<td>17</td>
<td>25</td>
<td>53.9</td>
<td>0.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Liberia</td>
<td>20</td>
<td>1.6</td>
<td>18.1</td>
<td>1.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Mozambique</td>
<td>6.8</td>
<td>12</td>
<td>29.1</td>
<td>6.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Myanmar</td>
<td>74</td>
<td>0.8</td>
<td>35.2</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Namibia</td>
<td>8.3</td>
<td>14</td>
<td>34.2</td>
<td>9.7</td>
<td>7.3</td>
</tr>
<tr>
<td>Nigeria</td>
<td>72</td>
<td>2.9</td>
<td>10.8</td>
<td>0.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Pakistan</td>
<td>66</td>
<td>0.1</td>
<td>36.7</td>
<td>2.8</td>
<td>13</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>5.8</td>
<td>0.9</td>
<td>48.8</td>
<td>23.5</td>
<td>15</td>
</tr>
<tr>
<td>Philippines</td>
<td>54</td>
<td>0.1</td>
<td>41</td>
<td>7.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>36</td>
<td>—</td>
<td>58.3</td>
<td>23.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>38</td>
<td>1.7</td>
<td>41.3</td>
<td>8.8</td>
<td>7.1</td>
</tr>
<tr>
<td>South Africa</td>
<td>7.7</td>
<td>19</td>
<td>33.2</td>
<td>8.1</td>
<td>9.7</td>
</tr>
<tr>
<td>Thailand</td>
<td>12</td>
<td>1.1</td>
<td>36.8</td>
<td>1.9</td>
<td>8.3</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>26</td>
<td>4.7</td>
<td>26.7</td>
<td>3.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>43</td>
<td>0.4</td>
<td>45.9</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>Zambia</td>
<td>28</td>
<td>12</td>
<td>24.7</td>
<td>3.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>26</td>
<td>14</td>
<td>30.7</td>
<td>1.6</td>
<td>6.5</td>
</tr>
</tbody>
</table>

— indicates data not available.

FIG. 7.7
Status of selected SDG indicators beyond SDG 3, 30 high TB burden countries, latest available year

Angola Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Bangladesh Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Brazil Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Cambodia Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Central African Republic Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

China Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Congo Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

DPR Korea Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

DR Congo Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Ethiopia Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

India Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Indonesia Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Kenya Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Lesotho Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Liberia Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Mozambique Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Myanmar Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Namibia Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Nigeria Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Pakistan Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Philippines Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Papua New Guinea Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Russian Federation Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Sierra Leone Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

South Africa Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Thailand Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

UR Tanzania Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Viet Nam Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Zambia Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Zimbabwe Not in slums
Clean fuel
Income equality
Despite
Nutrition
Social protection

Not in slums: Percentage of urban population not living in slums.
Income equality: An inverse Gini index is shown where 0 is perfect inequality and 100 is perfect equality.
Social protection: Percentage of population covered by social protection and labour programmes.
Not in poverty: Percentage of population covered by social protection and labour programmes.
Nutrition: Percentage of population not undernourished.
Clean fuels: Percentage of population with access to clean fuels and technologies for cooking.

* Red dot indicates that there are no data for the selected indicator.

of the hexagon (100) is the ideal value for each indicator. Therefore, better performance corresponds to a larger shaded-in region. To achieve this representation visually, the indicators “proportion of the urban population living in slums” and “proportion of the population living below the international poverty line” are inverted in Fig. 7.7. It should be highlighted that all indicator values in Fig. 7.7 are for the general population, as opposed to people with TB. Values for TB patients specifically (such as out-of-pocket expenditure and access to social protection) may differ from these general values.

Poverty is an underlying driver of national TB epidemics, influencing several of the other indicators associated with TB incidence. This is illustrated by a recent modelling study, which showed that eliminating extreme poverty and providing social protection (both targets under SDG 1) could substantially reduce TB incidence. The main results are summarized in Box 7.3.

Table 7.3 and Fig. 7.7 show that many high TB burden countries, especially those in the low-income category, still face significant challenges to achieve a range of TB-related SDG targets. Furthermore, values for poor populations and vulnerable groups most at risk of developing TB are likely to be worse than national averages.

**BOX 7.3**

**The impact of social protection and poverty elimination on global TB incidence: a modelling study**

SDG 1 is to end poverty in all its forms everywhere, and associated targets include eliminating extreme poverty and ensuring nationally appropriate social protection systems and measures for all (including floors). Achievement of SDG 1 is likely to affect the TB epidemic through a range of pathways, as illustrated in Fig. B7.3.1.

A recent study used data from the SDG data repository and the WHO global TB database for 192 countries to explore how achievement of SDG 1 could affect TB incidence. Analyses were used to assess the strength of the association between the SDG 1 targets and TB incidence, as a basis for defining a simplified framework for modelling in which SDG 1 indicators were linked to TB incidence.

It was estimated that ending extreme poverty could reduce global TB incidence by 33% by 2035 (95% confidence interval: 16–45%), while expanding social protection coverage could reduce incidence by 76% (45–90%) by 2035. Together, both pathways were estimated to be able to reduce TB incidence by 84% (55–95%). Full achievement of SDG 1 could thus have a substantial impact on the global burden of TB.

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FIG. 7.8
Estimated number of TB cases attributable to five risk factors, 30 high TB burden countries, 2017

### TABLE 7.4
TB cases attributable to selected risk factors, 2017

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RELATIVE RISK</th>
<th>EXPOSED (MILLIONS IN 2017)</th>
<th>GLOBAL POPULATION ATTRIBUTABLE FRACTION (%)</th>
<th>ATTRIBUTABLE TB CASES (MILLIONS IN 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undernourishment</td>
<td>3.1–3.3</td>
<td>734</td>
<td>18</td>
<td>1.9</td>
</tr>
<tr>
<td>HIV infection</td>
<td>20</td>
<td>36</td>
<td>8.7</td>
<td>0.88</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.6–2.5</td>
<td>1 047</td>
<td>7.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.3–4.3</td>
<td>460</td>
<td>7.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Harmful use of alcohol</td>
<td>1.9–4.6</td>
<td>407</td>
<td>4.7</td>
<td>0.49</td>
</tr>
</tbody>
</table>


Although it is typically not possible for NTPs to make progress on these issues alone, the UN high level meeting on TB in September 2018 (Chapter 1) and adaptation and use of the multisectoral accountability framework for TB developed in 2018 (Chapter 2) provide a basis for raising awareness and taking action on these issues.

Estimates of the number of incident TB cases attributable to five selected risk factors in 2017 are shown in **Table 7.4**. An estimated 1.9 million were attributable to undernourishment, 0.88 million to HIV infection, 0.83 million to smoking, 0.79 million to diabetes and 0.49 million to alcohol abuse. Applying the same method, country-specific estimates of the number of incident TB cases attributable to the five risk factors in the 30 high TB burden countries are shown in **Fig. 7.8**. This figure shows that although various factors (undernutrition, the prevalence of alcohol use disorder, diabetes, HIV and smoking) contribute to the TB epidemic in the 30 high TB burden countries, there is considerable variation among countries in the relative contribution of these factors, and thus also variation in which factors need to be prioritized as part of national efforts to reduce the burden of TB disease.
A handheld DNA sequencer being used in Madagascar to identify TB resistance in sputum samples

Institut Pasteur de Madagascar
Chapter 8. TB research and development

KEY FACTS AND MESSAGES

Tuberculosis (TB) research and development is essential to achieve the global TB targets set in the Sustainable Development Goals and the End TB Strategy. A major technological breakthrough is required by 2025, so that the rate at which TB incidence falls can be dramatically accelerated compared with historic levels, to an average of 17% per year between 2025 and 2035.

Priorities for TB research and development include a vaccine to lower the risk of infection, a vaccine or new drug treatment to cut the risk of TB disease in the 1.7 billion people already latently infected, rapid diagnostics for use at the point of care and simpler, shorter drug regimens for treating TB disease.

"Intensified research and innovation" is the third pillar of the End TB Strategy.

A substantial increase in investment in TB research and development is needed. Funding has increased in recent years and reached a peak of US$ 724 million in 2016, but this is only 36% of the estimated requirement of US$ 2 billion per year.

The diagnostic pipeline is relatively stagnant. A small number of technologies emerged in 2017–2018 and several have not demonstrated adequate performance in field evaluation studies. There is still no single rapid, accurate and robust TB diagnostic test suitable for use at the point of care.

There are 20 drugs in Phase I, II or III trials for the treatment of drug-susceptible TB, multidrug-resistant TB or latent TB infection. There are 11 new compounds (an increase of 3 since August 2017): contezolid, delpazolid, GSK-3036656, macoxizol, OPC-167832, pretomanid, Q203, SQ109, sutezolid, TBA-7371 and TBI-166. Two other drugs, bedaquiline and delamanid, have already received accelerated or conditional regulatory approval based on Phase IIb results. The seven repurposed drugs undergoing further testing are clofazimine, linezolid, levofloxacin, moxifloxacin, nitazoxanide, rifampicin (high dose) and rifapentine.

Various combination regimens with new or repurposed drugs are in Phase II or Phase III trials.

Twelve vaccine candidates are in clinical trials: four in Phase I, six in Phase II and two in Phase III. They include candidates to prevent the development of TB infection and disease, and candidates to help improve the outcomes of treatment for TB disease.

The global TB targets set in the Sustainable Development Goals (SDGs) and the End TB Strategy cannot be achieved without tuberculosis (TB) research and development. The SDG target is to “end the epidemic” by 2030; more specific targets for 2030 set in the End TB Strategy are a 90% reduction in TB deaths and an 80% reduction in TB incidence compared with levels in 2015, with targets for further reductions (95% and 90%, respectively) by 2035. Reaching these targets requires a major technological breakthrough by 2025, so that the rate at which TB incidence falls can be dramatically accelerated compared with historic levels, to an average of 17% per year from 2025–2035 (Chapter 2). Priorities for TB research and development include a vaccine to lower the risk of infection, a vaccine or new drug treatment to cut the risk of TB disease in the 1.7 billion people already latently infected, rapid diagnostics for use at the point of care and simpler and shorter drug regimens for treating TB disease.²³

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² Shortening treatment regimens as well as decreasing treatment toxicity are particularly high priorities for drug-resistant TB.
“Intensified research and innovation” is one of the three pillars of the WHO End TB Strategy. The two main components of this pillar are “discovery, development and rapid uptake of new tools, interventions and strategies” and “research to optimize implementation and impact, and promote innovations” (Chapter 2).

Technological breakthroughs and optimal use of available interventions require greater investment in TB research and development. The Stop TB Partnership’s “Global Plan to End TB 2016–2020” estimates that about US$ 2 billion per year is needed.1 To date, funding has not come close to this amount. In the 5 most recent years for which data have been published, annual funding was in the range of US$ 600–700 million, reaching a peak of US$ 724 million in 2016.2 This was equivalent to only about 40% of the amount required. Although TB accounts for nearly 2% of disability-adjusted life-years (DALYs) lost, it receives only 0.25% of the estimated US$ 265 billion spent on medical research annually,3 and less support than other global health threats such as HIV and malaria. Further details about recent funding for TB research and development are provided in Box 8.1.

Recognizing the need to accelerate efforts in TB research and development, “Pursuing science, research and innovation” was one of the four major topics of the Moscow Declaration to End TB. The commitments from Member States and the calls to partners included in the declaration are listed in Box 8.2. In April 2018, TB research and development was one of the topics prioritized for discussion at the first United Nations (UN) high-level meeting on TB in September 2018.4

This chapter is not intended as an exhaustive overview of current or recently completed TB research. As in previous global TB reports, it focuses on providing an overview of progress in the development of new TB diagnostics (Section 8.1), drugs (Section 8.2) and vaccines (Section 8.3), which account for most of the funding invested in TB research and development in recent years (Box 8.1). The status of the pipelines as of August 2018, based on recent publications as well as communications with the secretariats of the relevant working groups of the Stop TB Partnership and other stakeholders, is described and discussed. The last part of the chapter (Section 8.4) highlights how global and intercountry collaborations can help to expedite progress in TB research.

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**Box 8.1**

Global investments in TB research and development: a recent analysis

As part of preparations for the first Global Ministerial Conference on TB held in November 2017, recent investments in TB research and development were assessed.6

Key findings were as follows:

- A total of US$ 4.6 billion was invested from 2009–2016, mostly for development of new diagnostics, drugs and vaccines (61%). The rest was for basic research (21%), operational research (10%) and infrastructure or “unspecified” projects (8%).

- Most funding from 2009 to 2016 was from a few countries, led by the United States of America (USA, with US$ 1.8 billion), followed by the European Union and United Kingdom (US$ 269 million each). Contributions from other countries did not exceed US$ 62 million.

- The two largest funders were the US National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation. Combined, they accounted for 37% of total investments from 2005 to 2015.

- Spending by the pharmaceutical industry decreased considerably, following the withdrawal of several companies from the field and the maturation of clinical development programs for new TB drugs.

- Between 2011 and 2015, the top five recipients of funding were either product-development partnerships or research institutes and universities in the USA. Other recipients in the top 15 included the Medical Research Council (United Kingdom), the Foundation for Innovative New Diagnostics (FIND, Switzerland), the University of Cape Town (South Africa), the International Union Against Tuberculosis and Lung Disease (based in France) and the National Institute for Research in Tuberculosis (India).

- Insufficient investment in operational research has compromised the scale-up of new technologies and approaches, limiting their impact on the TB epidemic. Consistent with this finding, only 13% of all TB research publications in the past decade were related to operational or public health research.

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BOX 8.2
Commitments by Member States and calls to partners listed under the heading “Pursuing science, research and innovation” in the Moscow Declaration to End TB

Commitments by Member States

- Increasing national or regional capacity and funding, as needed, to urgently expand multidisciplinary TB research and innovation, and applied health research, by establishing and strengthening national TB research networks, including civil society and community-based mechanisms, considering TB research as a central element of national TB and research and development strategies, expanding existing networks to integrate TB research, and reducing research- and implementation-related regulatory impediments.

- Working, when relevant, across ministries, donors, the scientific community, the private sector, academia and other key stakeholders for the purpose of research:
  - for development and evaluation of rapid point-of-care diagnostics; new and more effective drugs; and shorter, high-quality and cost-effective treatment regimens for all forms of TB – including latent TB infection and drug-resistant TB – and; safe and effective TB vaccines by 2025; and
  - on environmental and social determinants of TB and effective interventions strategies.

- Improving, as appropriate, the coordination of research efforts nationally and globally, and ensuring that the emerging knowledge is promptly put into action, including by putting in place appropriate policy frameworks and implementing new medical technologies.

- Strengthening, as appropriate, surveillance systems, improving data collection and reporting at all levels, using innovative approaches and including surveillance in TB research agendas.

Calls to partner agencies

- WHO – in collaboration with global health and research partners and countries – to make further progress in enhancing cooperation and coordination of TB research and development, considering (where possible) drawing on existing research networks to integrate TB research, such as the new antimicrobial resistance (AMR) R&D collaboration hub proposed in the 2017 G20 Leaders’ Declaration, in particular, to facilitate rapid scale-up of innovative approaches and tools for TB prevention, diagnosis, treatment and care.

A TB resolution adopted at the World Health Assembly in May 2018 reinforced the Moscow Declaration’s call for the development of a global strategy for TB research and innovation, and requested WHO to develop such a strategy in collaboration with other stakeholders. The aim of the strategy is to accelerate progress in TB research and development, through strategic approaches such as fostering global collaborations, stimulating the development of innovative financing mechanisms for the most urgent priorities, promoting the sharing of data and information, and facilitating the rapid scale-up of new tools.


*b The BRICS countries are Brazil, Russian Federation, India, China and South Africa.


8.1 New diagnostics for TB

This section starts by providing an overview of the TB diagnostics pipeline, with particular attention to progress made in 2018. It then describes diagnostic tests, products and methods related to the detection of TB infection, disease and drug resistance that were reviewed by WHO in 2018, or that are scheduled for evaluation in 2019.

8.1.1 An overview of the diagnostics pipeline

Although the TB diagnostics pipeline appears robust, with several technologies in development, no new platform has emerged in 2018. Despite the promise from several manufacturers, there is still no single rapid, accurate and robust TB diagnostic test suitable for use at the point of care. This reflects serious underinvestment (especially in basic science), and persistent scientific and technical challenges that affect the development of new TB diagnostics.

An overview of the pipeline for TB diagnostics in August 2018 is shown in Fig. 8.1. The list of technologies is not necessarily complete, but does reflect technologies that have been documented in previous reports published by the Treatment Action Group1 and Unitaid. Technologies under development are primarily molecular-based; they include tests to detect TB for diagnosis and treatment monitoring, to detect drug resistance among confirmed TB cases, and to detect TB and drug resistance simultaneously in centralized high-throughput laboratories.

The pipeline remains largely unchanged from the one published in the 2017 edition of the global TB report,3 and highlights the urgent need for new technologies to minimize barriers to health-care access, ensure quality testing for difficult-to-diagnose groups, expand the spectrum of drug susceptibility testing (DST), and reduce the costs of diagnostic platforms and their maintenance.

The development of the Cepheid close-to-care platform – GeneXpert® Omni® (Omni) – continues to be delayed and is not expected to be available before 2019. Cepheid has developed an alternative to Omni – the GeneXpert® Edge® (Edge). The Edge is a single-module GeneXpert instrument connected to a tablet device for transfer of data; its specific features include an auxiliary battery that allows operation in more decentralized settings, at the same level as microscopy. The instrument is being developed to facilitate wider access to rapid molecular testing for TB and rifampicin resistance, and virology parameters for HIV and hepatitis C virus, for example. The Edge is expected to be available from November 2018.

The next-generation Xpert MTB/RIF Ultra (Ultra) cartridge has shown significantly better performance (increased sensitivity) than the current Xpert MTB/RIF cartridge in detecting Mycobacterium tuberculosis in specimens with low numbers of bacilli. This was particularly the case for smear-negative, culture-positive specimens (e.g. those from people living with HIV), extrapulmonary specimens (notably cerebrospinal fluid) and specimens from children.6

Despite the improved performance of the Ultra cartridge, as confirmed by WHO, the transition to this next-generation cartridge has been limited, in part, due to the short shelf-life of the cartridge. South Africa is the only high TB burden country currently using Ultra as the initial TB diagnostic test. WHO has commissioned an updated systematic review of the performance of Ultra for use in the diagnosis of pulmonary and extrapulmonary TB in adults and children, and expects to refine and update policy guidelines for the use of Ultra in 2019.

Two cartridge-based technologies being developed in China and India, respectively, are in the pipeline. These technologies have the potential to be used as an alternative to the GeneXpert platform in primary healthcare facilities. Both are similar to Xpert MTB/RIF in that they target the multicopy IS6110 and a single-copy gene target. Evidence about the performance of both technologies from well-designed validation studies is needed to enable WHO to review and assess their performance; ancillary solutions in areas such as maintenance and connectivity would also be needed to support roll-out.

The first of these two assays, the Truenat MTB assays® (Molbio Diagnostics, Bangalore, India), uses chip-based real-time polymerase chain reaction (PCR) for the detection of TB. A reflex assay has been developed to detect resistance to rifampicin in samples with positive results for M. tuberculosis. The Indian Council of Medical Research has recommended Truenat MTB to the Indian Central TB Division, based on local data. The Foundation for Innovative New Diagnostics (FIND) is planning a multicentre study of diagnostic accuracy at the level of peripheral microscopy centres, to assess the performance characteristics of the test in different epidemiological and geographical settings; the results will inform a WHO review.

Ustar Biotechnologies (China) has developed the EasyNAT TB® assay based on isothermal cross-priming amplification. The assay uses preloaded reagents in a single cartridge for integrated extraction, amplification and detection, using two separate chambers. Testing,

which is currently limited to detection of TB (drug resistance cannot be detected), can be performed by loading cartridges into a battery-operated device for testing two samples simultaneously.

### 8.1.2 Critical concentrations for phenotypic drug-susceptibility testing of medicines used in the treatment of drug-resistant TB

In May 2018, WHO and FIND released a technical report with updated laboratory parameters for DST of medicines used to treat drug-resistant TB. Culture-based phenotypic testing is the current reference method for DST of anti-TB medicines, and it relies on the testing of so-called critical concentrations of drugs, that is, the lowest concentration of an anti-TB medicine in vitro that will inhibit the growth of 99% of phenotypically wild-type strains of *M. tuberculosis*.

The report summarizes the current evidence used to determine critical concentrations in different culture media for performing DST for specific medicines used in the treatment of drug-resistant TB. Critical concentrations for the new and repurposed anti-TB agents bedaquiline, delamanid, linezolid and clofazimine are included, in addition to revised consensus critical concentrations for fluoroquinolones and second-line injectable agents.

### 8.1.3 TB diagnostic tests, products and methods that may be evaluated by WHO in 2019

In 2019, there may be sufficient data for WHO to reassess the critical concentrations to use when testing for resistance to isoniazid and rifampicin, and to determine the role of DNA-sequencing technologies in the diagnosis of drug-resistant TB. There may also be sufficient data to review the performance of the lateral flow lipoarabinomannan assay (LF-LAM), centralized high-throughput testing platforms, molecular sequencing as a reference standard for DST, and a new test for extensively drug-resistant TB (XDR-TB).

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1. The list of technologies is not necessarily complete, but does reflect technologies that have been documented in previous reports published by the Treatment Action Group and Unitaid.

2. XDR-TB is defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable.

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**Fig. 8.1**

An overview of progress in the development of TB diagnostics, August 2018

### TECHNOLOGIES IN DEVELOPMENT

<table>
<thead>
<tr>
<th>Molecular detection of TB and drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GenEndura TB/RIF ID, Epistem, UK</td>
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<tr>
<td>Xpert XDR-TB cartridge, Cepheid, USA</td>
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<tr>
<td>TruArray MDR-TB, Akkoni, USA</td>
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<tr>
<td>INFINITMTB Assay, AutoGenomics, USA</td>
</tr>
<tr>
<td>FluoroType XDR-TB assay, Hain Lifescience, Germany</td>
</tr>
<tr>
<td>MetiPro TB assay, Zeesan Biotech, China</td>
</tr>
<tr>
<td>QuantuMDx, POC, UK</td>
</tr>
</tbody>
</table>

**Tests for latent TB infection**

- Diaskin test, Generium, Russian Federation
- C-Tb test, Serum Institute of India, India

### TECHNOLOGIES ENDORSED BY WHO

<table>
<thead>
<tr>
<th>Molecular detection of TB and drug resistance</th>
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</thead>
<tbody>
<tr>
<td>Line probe assays for the detection of Mycobacterium tuberculosis (MTB), isoniazid and rifampicin resistance in acid-fast bacilli smear positive sputum or MTB cultures (FL-LPA), Hain Lifescience, Germany and Nipro, Japan</td>
</tr>
<tr>
<td>Line probe assays for the detection of resistance to fluoroquinolones and second-line injectable agents (SL-LPA), Hain Lifescience, Germany</td>
</tr>
<tr>
<td>TB LAMP for detection of TB, Eiken, Japan</td>
</tr>
</tbody>
</table>

### Nonmolecular technologies

- Interferon gamma release assay (IGRA) for the diagnosis of latent TB infection (LTBI) Oxford Immunotec, UK, Qiagen, USA

### Culture-based technologies

- Commercial liquid culture systems and rapid speciation
- Culture-based phenotypic DST using 1% critical proportion in LJ, 7H10, 7H11 media

### Microscopy

- Light and light-emitting diode microscopy (diagnosis and treatment monitoring)

### WHO POLICY UPDATES SCHEDULED FOR 2018/2019

- Molecular detection of TB and drug resistance
  - Molecular technologies for genotypic drug resistance testing (including sequencing technologies)
  - FluoroType MTBDR, Hain Lifescience, Germany
  - m2000 RealTime MTB System, Abbott, USA
  - BD Max MDR-TB, Becton Dickinson, USA
  - Roche cobas® MTB system, Roche Diagnostics, Basel, Switzerland

- Radiology
  - Computer aided detection (CAD)

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Critical concentrations for phenotypic drug-susceptibility testing of isoniazid and rifampicin

Anti-TB medicines such as isoniazid and the rifamycins (rifampicin, rifapentin and rifabutin) are essential for TB treatment. There is emerging evidence that some of the critical concentrations used to test for resistance to these medicines, established historically in solid culture media, may not necessarily apply to commercial liquid culture systems. Therefore, WHO has commissioned FIND to undertake a systematic review of available minimum inhibitory concentration data for phenotypically wild-type and non wild-type strains, including sequencing data for relevant resistance genes. The goal of the review is to evaluate the available evidence and, if indicated, to revise the critical concentrations used to test for resistance to these first-line anti-TB medicines on selected media.

Role of DNA-sequencing technologies

The successful diagnosis and treatment of drug-resistant TB depends upon universal access to accurate DST. Conventionally, the diagnosis of drug resistance in M. tuberculosis strains has relied heavily upon culture and DST in liquid or solid media in TB containment laboratories. Phenotypic results are only obtained after weeks to months of incubation, and establishing the stringent laboratory biosafety conditions required for these culture-based methods is a challenge.

Drug resistance in the Mycobacterium tuberculosis complex is mainly conferred through point mutations in specific gene targets in the bacterial genome. Given the challenges associated with performing phenotypic DST, molecular tests are increasingly being used to allow more rapid testing and thus earlier initiation of appropriate treatment for drug-resistant TB.

Rapid molecular tests such as Xpert MTB/RIF and line probe assays (LPAs) allow for the detection of a set of common resistance mutations in a few gene regions. However, for many drugs used in the treatment of drug-resistant TB, the mutations are spread over multiple gene regions. Moreover, not all mutations conferring resistance have been identified, and limited information is available for identifying the “high-confidence mutations” that would accurately predict clinical treatment outcomes.

An advantage of sequencing technologies, compared with the rapid molecular tests that are currently available, is that they are able to provide detailed information on resistance mutations for multiple gene regions. A first step that has been taken is to grade mutations according to the level of confidence in the association between resistance mutations and the conferred phenotypic drug resistance. FIND has recently completed a systematic review of the association between M. tuberculosis strains with specific mutations and minimal inhibitory concentrations data for drugs of interest. It is anticipated that WHO will be able to use this review to assess evidence about the accuracy of genotypic DST compared with current phenotypic reference standards, and to develop a related list of priority mutations (so-called high-confidence mutations), which could also be used to aid test development.

WHO and FIND are preparing a technical guide that summarizes the characteristics of available DNA-sequencing technologies, along with current knowledge of the genetic basis of TB drug resistance. This guide will provide a foundation for building additional knowledge related to the molecular basis of resistance, and will inform future WHO policy guidelines on the use and interpretation of DNA-sequencing technologies.

The Relational Sequencing TB Knowledgebase (ReSeqTB) is a global, clinical knowledge base that curates, standardizes and unifies genotypic and phenotypic DST data, along with metadata on drug-resistant TB. The database is regarded as a “living” knowledge base, in which sequencing, phenotypic and clinical outcome data for existing, repurposed and new TB drugs are continually gathered from countries and other stakeholders.

Lateral flow lipoarabinomannan assay

Tests based on the detection of the mycobacterial lipoarabinomannan (LAM) antigen in urine are available as potential point-of-care tests for TB. Urinary LAM assays are unsuitable for use as general screening tests for TB due to suboptimal sensitivity. However, compared with traditional diagnostic methods, they have demonstrated improved sensitivity for the diagnosis of TB among individuals coinfected with HIV, especially among patients with low CD4 counts.

The urine LAM strip-test (Determine®-TB Alere, USA) is currently recommended by WHO in HIV-positive adults with CD4 counts less than or equal to 100 cells/μL and with signs and symptoms of TB. Since 2015, new evidence has emerged that might justify the use of the test in a broader group of people living with HIV. WHO has initiated a review of the evidence and associated guidance, and a meeting to review the evidence is due to be held before the end of 2018.

Centralized high-throughput testing platforms

Several manufacturers have developed centralized testing PCR-based platforms suitable for high laboratory throughput. If sufficient evidence becomes available, the performance of these platforms could be assessed before the end of 2018. Examples of the platforms in development are the RealTime® platform, developed by Abbott; the FluoroType MTBDR®, launched by Hain

Lifescience in early 2017; and platforms being developed by Becton Dickinson and Roche.

WHO, in consultation with FIND, has developed a two-step evaluation process for this purpose. The first step includes verification of the accuracy of the assays in detecting \( M. \) tuberculosis as well as resistance to rifampicin and isoniazid, based on independent evaluation of a standardized panel of strains, conducted at one or more WHO TB supranational reference laboratories (SRLs). The second step is evaluation of the clinical validity of the assays, based on testing of the platforms in two or three national reference laboratories in high TB burden settings, and comparing results with the reference standards of culture, phenotypic DST and molecular sequencing, as well as with Xpert MTB/RIF.

**Tests for extensively drug-resistant TB**

Molecular LPAs for second-line anti-TB medicines are currently the only rapid molecular tests recommended by WHO for detecting whether patients with confirmed multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB have XDR-TB. However, LPAs require sophisticated laboratory infrastructure and equipment that is normally only available in centralized laboratories.

Cepheid is continuing to develop an XDR-TB cartridge to detect resistance to isoniazid, injectable agents and fluoroquinolones. If sufficient data become available, WHO will evaluate the XDR-TB cartridge using the same two-step approach described above for centralized high-throughput testing platforms.

**Computer-aided detection systems**

Chest radiography, or chest X-ray (CXR), is an important tool for TB triaging and screening, and is also a useful aid in the diagnosis of TB. A major limitation of CXR is that it requires experienced interpreters (usually radiologists or technicians) for interpreting the images. Even among trained readers, variation between readers is common, which further affects the accuracy of CXR. In many countries, few experienced CXR readers are available.

In recent years, computer-aided detection (CAD) systems have been developed that use digital technology to detect physiological and pathological conditions, including TB. These CAD systems incorporate computer algorithms that analyse a digital CXR and produce a standardized interpretation of the image. A score or report is generated that estimates the likelihood that the image is from an individual with active TB disease. CAD systems are trained on thousands of images, using machine-learning techniques. A research agenda to assess CAD systems is underway. FIND is establishing an archive of digital x-rays to assess the performance of commercially available CAD solutions. If sufficient data become available, WHO will evaluate the use of CAD systems for detecting TB in early 2019.

**Biomarkers for treatment monitoring**

DNA-based molecular diagnostic tools provide rapid results for the diagnosis of active TB disease. Tests such as the Xpert MTB/RIF assay have a sensitivity approaching that of culture, although they remain unsuitable for treatment monitoring because they detect dead bacilli.\(^2\)

St Andrew’s University, Scotland has developed a novel approach for real-time monitoring of a patient’s response to TB treatment. The Molecular Bacterial Load Assay (MBLA) is a real-time reverse transcriptase quantitative PCR (RT-qPCR) that uses 16S-ribosomal RNA (rRNA) targets to quantify the \( M. \) tuberculosis bacillary load over the course of treatment.

The 16S-rRNA targets are more abundant and stable than messenger RNA (mRNA), and yet are reduced during TB treatment, which makes this assay more sensitive for \( M. \) tuberculosis detection and monitoring of the response to treatment. Its ability to quantify a patient’s bacillary load of \( M. \) tuberculosis in real time, and avoid the challenges related to culture e.g. time to results and contamination concerns, gives MBLA the potential to eventually replace microscopy and culture as a test for treatment monitoring. To date, the assay has been evaluated in four high TB burden, low-resource settings in Africa.\(^3\)

The next crucial step is the development of a design-locked product that allows standardized evaluation. Laboratory-based studies of analytical sensitivity and stability need to be performed to further assess the limits of detection of the assay, and the correlation with currently recommended technologies for monitoring TB treatment response (especially culture). If the laboratory-based studies demonstrate good performance, clinical evaluation studies will be needed to assess the MBLA as a possible replacement for microscopy and culture monitoring during treatment.

### 8.2 New drugs and drug regimens to treat TB

The pipeline for new anti-TB drugs in August 2018 is shown in Fig. 8.2. The pipeline has expanded in recent months, and there are now 20 drugs in Phase I, II or III trials, compared with 17 in August 2017.\(^4\) There are

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11 new compounds (up by three since August 2017): contezolid, delpaзолiz, GSK-303656, maczoinone, OPC-167832, pretomanid, Q203, SQ109, sutezolid, TBA-7371 and TBI-166. Two other drugs (bedaquiline and delamanid) have already received accelerated or conditional regulatory approval based on Phase IIb trial results. Seven repurposed drugs are undergoing further testing: clofazimine, linezolid, levofloxacin, moxifloxacin, pyrazinamide for quinolone sensitive MDR-TB (MDR-END trial) and delamanid (OPTI-Q) for MDR-TB (TB PRACTECAL Phase 2/3 trial). Delamanid and linezolid, levofloxacin and pyrazinamide are also being used in trials of all-oral treatment regimens.

New TB regimens are also being tested. These are described in more detail in Section 8.2.1 and Section 8.2.2.

8.2.1 New compounds

Bedaquiline

WHO issued interim policy guidance on the use of bedaquiline for the treatment of adults with MDR-TB in 2013, based on Phase IIb trial results. The recommendation to use bedaquiline as part of longer MDR-TB treatment regimens was conditional upon proper patient selection, a regimen design following WHO recommendations, close monitoring of treatment, active TB drug safety monitoring and management, and informed consent according to local requirements. The recommendation was maintained following a review of data from observational studies in 2016. In 2018, additional data for patients treated with bedaquiline-containing regimens were analysed as part of a major update to WHO guidance on the treatment of drug-resistant TB.

The safety and efficacy of bedaquiline when used as part of short MDR-TB regimens (i.e. 6 and 9 months duration), compared with the updated current standard of care recommended by WHO (i.e. a shortened regimen) is being investigated in the second stage of the Phase III Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB (STREAM) trial. Recruitment started in March 2016, and the first results are expected in 2020. A study on the use of bedaquiline to treat children with MDR-TB is being implemented in the Philippines, the Russian Federation and South Africa. Bedaquiline is also being used in trials of all-oral treatment regimens (Section 8.2.3), and investigation of its use in the treatment of drug-susceptible TB has started.

Fig. 8.2

The global clinical development pipeline for new anti-TB drugs and regimens, August 2018

<table>
<thead>
<tr>
<th>Phase I*</th>
<th>Phase II*</th>
<th>Phase III*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contezolid (MRX-1)*</td>
<td>Delpaзолiz (LCB01-0371)</td>
<td>Bedaquiline (TMC-207)*</td>
</tr>
<tr>
<td>GSK-303656*</td>
<td>SQ109</td>
<td>Delamanid (OPC-67683)*</td>
</tr>
<tr>
<td>Maczoinone (PBTZ169)*</td>
<td>Sutezolid (PNU-100480)*</td>
<td>Pretomanid (PA-824)</td>
</tr>
<tr>
<td>OPC-167832</td>
<td>Linezolid dose-ranging</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Q203*</td>
<td>Nitazoxanide</td>
<td>High dose rifampicin for treatment of DS-TB</td>
</tr>
<tr>
<td>TBA-7371*</td>
<td>High dose rifampicin for DS-TB (PANACEA)</td>
<td>Rifapentine for treatment of DS-TB</td>
</tr>
<tr>
<td>TBI-166</td>
<td>Bedaquiline and delamanid (ACTG A5343 DELIBERATE trial)</td>
<td>Bedaquiline – Pretomanid – Linezolid (ZeNix TB trial)</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline – Pretomanid – Moxifloxacin – Pyrazinamide (BPamZ) regimen</td>
<td>Bedaquiline – Pretomanid – Linezolid (NIX-TB trial)</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline and pretomanid with existing and re-purposed anti-TB drugs for MDR-TB (TB PRACTECAL Phase 2/3 trial)</td>
<td>Bedaquiline with two optimised background regimens (oral, 9 months; with oral and injectables, 6 months) (STREAM trial)</td>
</tr>
<tr>
<td></td>
<td>Delamanid, linezolid, levofloxacin, and pyrazinamide for quinolone sensitive MDR-TB (MDR-END trial)</td>
<td>Bedaquiline – Linezolid – Levofloxacin with OBR for MDR-TB (NEtTrial)</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin with OBR for MDR-TB (OPTI-Q)</td>
<td>Bedaquiline and delamanid with various existing regimens for MDR-TB and XDR-TB (endTB trial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pretomanid – Moxifloxacin – Pyrazinamide regimen (ISTANDB trial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifapentine – Moxifloxacin for treatment of DS-TB (TB Trial Consortium Study 31/A5349)</td>
</tr>
</tbody>
</table>

* New drug compounds are listed first, followed by repurposed drugs and then by regimens.
* New chemical class.
* Optimized background regimen.

Source: Adapted from the Working Group on New TB Drugs pipeline. More information on these products and other ongoing projects can be found at http://www.newtbdrugs.org/pipeline.php

1 Most of the new compounds are being developed by not-for-profit organizations, academic institutions, small businesses or government agencies that lack the secure funding and resources available to major pharmaceutical companies. This makes the process of progression through trials and then registration more uncertain.


4 Further details are provided in Box 4.2 in Chapter 4.

Contezolid
MRX4, a prodrug\(^1\) of Contezolid (MRX-I), is in a Phase 1 trial in the USA. MRX-1 is an oxazolidinone antibiotic that is potent against Gram-positive pathogens. Orally administered MRX-1 has shown the same or better efficacy than linezolid in systemic and local-infection mouse models.

Delamanid
WHO issued interim policy guidance on the use of delamanid for the treatment of adults with MDR-TB in 2014, based on Phase IIb trial results.\(^2\) A conditional recommendation was made to use delamanid as part of longer MDR-TB treatment regimens for adults. The recommendation to use delamanid as part of longer MDR-TB treatment regimens was conditional upon proper patient selection, a regimen design following WHO recommendations, close monitoring of treatment, active TB drug safety monitoring and management, and informed consent according to local requirements. Following the release of results for children and adolescents treated for MDR-TB using delamanid in 2016, WHO’s guidance on the use of delamanid in adults was expanded to include patients aged 6–17 years.\(^3\)

In November 2017, final results from a Phase III trial assessing the safety and efficacy of delamanid as an addition to an optimized background regimen for adults with MDR-TB were reported to WHO by the manufacturer Otsuka Pharmaceutical, Japan. WHO conducted an expedited external expert review of the new data and issued a position statement in January 2018,\(^4\) which stated that the conditional guidance on delamanid remained valid, but that delamanid should only be added to a longer MDR-TB treatment regimen when the regimen cannot otherwise be composed according to WHO recommendations. In 2018, additional data from the Phase III trial were analysed by WHO alongside data from other studies of patients treated with delamanid-containing regimens as part of a major update to WHO guidance on the treatment of drug-resistant TB.\(^5\)

As with bedaquiline, delamanid is being used in trials of all-oral treatment regimens (Section 8.2.3). The use of delamanid in addition to an optimized background regimen to treat children less than 6 years old is also being investigated in other trials. Studies of its use in the prevention of drug-resistant TB among contacts of people with MDR-TB are planned.

Delpazolid (LCB01–0371)
Delpazolid is a new oxazolidinone developed by LegoChem BioSciences. It entered a Phase II trial in the Republic of Korea in 2017.

GSK-3036656
GSK-3036656 is a new oxaborole compound developed by GlaxoSmithKline. A Phase I trial started in March 2017.

Macozinone
Macozinone (formerly PBTZ169) is a benzothiazinone developed by Nearmedic Plus. A Phase I trial has been completed and a Phase II trial has been started in the Russian Federation. A Phase I study with a new formulation was started in 2018 in Switzerland.

OPC-167832
OPC-167832 is a carbostyril developed by Otsuka that is bactericidal against both growing and intracellular bacilli. A single ascending dose study has been completed. A multiple ascending dose and early bactericidal activity (EBA) study of OPC-167832 alone and in combination with delamanid is planned in 2018.

Pretomanid
Pretomanid is a nitroimidazole being developed by the Global Alliance for TB Drug Development (the TB Alliance). It is currently being tested as part of combination regimens for the treatment of both drug-susceptible and drug-resistant TB, including XDR-TB (Section 8.2.3).

Q203
Q203 is an imidazopyridine that has been developed by Qurient (Republic of Korea). Single doses of various sizes have been tested in Phase I trials, and a Phase II trial is planned.

SQ109
SQ109 is a new, small-molecule drug discovered by scientists at Sequella Inc. (USA) and the US National Institutes of Health (NIH). A Phase IIb/III trial in which the drug was added to a standard regimen for MDR-TB has been completed in seven clinical centres in the Russian Federation, and positive results in terms of safety, efficacy and tolerability were reported in a press release in March 2017. A Phase II trial in the USA is in the planning stages.

Sutezolid
Sutezolid (PNU-100480) is an oxazolidinone and an analogue of linezolid. Results from an EBA study presented...
in 2012 showed a significant reduction in colony-forming unit counts compared with the baseline level after 14 days of treatment. In January 2017, the Medicines Patent Pool announced that it had signed a licence with Johns Hopkins University to facilitate the clinical development of sutezolid in combination with other drugs. On World TB Day 2017, the TB Alliance and the Medicines Patent Pool announced a licensing agreement for the clinical development of sutezolid.

TBA-7371
TBA-7371 is an inhibitor of the enzyme DprE1, which is essential in the synthesis of components of mycobacterial cell walls. This inhibitor has been shown to be active against strains of M. tuberculosis resistant to known TB drugs. The TB Alliance is implementing a Phase I study in the USA.

TBI-166
TBI-166 was identified through a lead optimization effort by the TB Alliance in partnership with the Institute of Materia Medica, the Chinese Academy of Medical Sciences and the Peking Union Medical College in Beijing. This riminophenazine compound has improved physicochemical and pharmacokinetic properties (to avoid discoloration of skin), and has efficacy similar to clofazimine. A Phase I clinical trial started in January 2018 in China.

8.2.2 Approved drugs being tested for new purposes

Clofazimine
Clofazimine is a riminophenazine that is used to treat leprosy. Its use in MDR-TB treatment is being explored in preclinical models of TB infection, to better understand its anti-TB effects. Novartis, the company that manufactures the drug, has withdrawn support for Phase II trials; however, clofazimine continues to be tested as part of treatment regimens for MDR-TB in Phase III trials.

Levofoxacin
Levofoxacin is being tested in a Phase II study called Opti-Q, which is investigating the best dose of levofoxacin to use for treatment of MDR-TB in adults with smear- and culture-positive pulmonary TB. Four doses are being tested (11, 14, 17 and 20 mg/kg/day) as part of an optimized background regimen. Trial enrolment and follow-up (in Peru and South Africa) has been completed. Data analysis is underway.

Linezolid
Linezolid is a marketed oxazolidinone with potent activity against TB. It has been widely used in the treatment of drug-resistant TB, and there is good evidence that it improves culture conversion and cure rates when added to treatment regimens. Since the medicine has a narrow therapeutic window, and the optimal dosing strategy remains unknown, the TB Alliance has implemented a Phase II trial to evaluate the mycobactericidal activity, safety, tolerability and pharmacokinetics of five doses of linezolid in adults with pulmonary TB.

Moxifloxacin
Moxifloxacin is included in several trials of new regimens for treatment of both drug-susceptible and drug-resistant TB (Section 8.2.3).

Nitazoxanide
Nitazoxanide is an anti-parasitic drug. Its activity against M. tuberculosis is being tested in a Phase II trial in Haiti.

Rifampicin (high dose)
Findings from the multi-arm, multi-stage TB (MAMS-TB) trial of the Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA) were published in 2017.1 These showed that 35 mg/kg of rifampicin given over 12 weeks is safe, and shortens the time to stable culture conversion from 62 to 48 days. The other trial arms – which included various combinations of 10 mg/kg or 20 mg/kg of rifampicin, moxifloxacin and SQ109 – did not achieve significant improvements compared with the control arm. When all the data are taken into consideration, the trial suggests that a 35 mg/kg dose of rifampicin given for 12 weeks is likely to improve treatment outcomes. This trial is the first multi-arm adaptive trial design to be successfully implemented in multiple sites in countries with a high burden of TB. It may help to pave the way for accelerated testing of new TB treatment regimens at reduced cost.

Rifapentine
The effectiveness of rifapentine in the treatment of drug-susceptible TB is being studied in three trials. The TB Trial Consortium (TBTC) Study 31/ACTG A5349 is a Phase III trial that is investigating the use of rifapentine, with or without moxifloxacin, to shorten the treatment of drug-susceptible pulmonary TB to 4 months. TBTC Study 35, a Phase II study of the pharmacokinetics of new water-dispersible paediatric formulations of rifapentine, is scheduled to start at two sites in South Africa in 2018. TBTC Study 37 is a Phase III trial of the safety and efficacy of 6 weeks of daily rifapentine for the treatment of latent TB infection (LTBI) in HIV-negative people in settings with a low burden of TB. It is being compared with a locally available 3-4 month rifampicin-based regimen.

8.2.3 New regimens for the treatment of drug-susceptible or drug-resistant TB

New combinations of drugs are being tested in Phase II or Phase III trials.

**ACTG A5343 DELIBERATE**

The ACTG A5343 DELIBERATE trial is testing the bacteriological failure, relapse or clinical failure during a study protocol could not be shown. The external experts who reviewed the interim findings recommended that national TB programmes and other stakeholders should continue to use the shorter MDR-TB regimen under the same conditions as those recommended in WHO guidance issued in 2016. The final results from the STREAM Stage 1 trial were used to inform an update of WHO guidance on the treatment of MDR-TB in 2018.2

Following the release of preliminary results, WHO conducted an expedited review of data provided by the STREAM trial consortium. The analysis showed that a “favourable outcome” was slightly higher in patients treated with longer regimens than in patients on the shorter regimen; non-inferiority as defined by the study protocol could not be shown. The external experts who reviewed the interim findings recommended that national TB programmes and other stakeholders should continue to use the shorter MDR-TB regimen under the same conditions as those recommended in WHO guidance issued in 2016. The final results from the STREAM Stage 1 trial were used to inform an update of WHO guidance on the treatment of MDR-TB in 2018.4

**TB-PRACTECAL**

The TB-PRACTECAL trial is a Phase II/III trial to evaluate the safety and efficacy of 6-month regimens that contain bedaquiline, pretomanid and linezolid, with or without moxifloxacin or clofazimine, for the treatment of adults with MDR-TB or XDR-TB. Primary outcomes include 8-week culture conversion, and the development of unfavourable outcomes (treatment failure or recurrence, death, discontinuation or loss to follow-up during a 72-week follow-up period). It is being implemented by Médecins sans Frontières and other collaborators in Belarus, South Africa and Uzbekistan.

8.3 New vaccines to prevent TB

The bacille Calmette-Guérin (BCG) vaccine, first used in the 1920s, remains the only licensed vaccine for preventing TB. Despite high coverage of BCG vaccination as part of childhood immunization programmes (Chapter 5), the slow decline in TB incidence globally highlights the need for a much more effective vaccine that provides protection against all forms of TB in all age groups.

**STREAM**

The STREAM Stage 1 trial is comparing a 9-month regimen for MDR-TB with longer regimens of 18–24 months in Ethiopia, Mongolia, South Africa and Viet Nam. It is a Phase III trial for which enrolment and follow-up were completed in 2018.1

Follow the release of preliminary results, WHO conducted an expedited review of data provided by the STREAM trial consortium. The analysis showed that a “favourable outcome” was slightly higher in patients treated with longer regimens than in patients on the shorter regimen; non-inferiority as defined by the study protocol could not be shown. The external experts who reviewed the interim findings recommended that national TB programmes and other stakeholders should continue to use the shorter MDR-TB regimen under the same conditions as those recommended in WHO guidance issued in 2016. The final results from the STREAM Stage 1 trial were used to inform an update of WHO guidance on the treatment of MDR-TB in 2018.4
FIG. 8.3
The global development pipeline for new TB vaccines, August 2018

is shown in Fig. 8.3. There are 12 vaccines in Phase I, II or III trials. Their main characteristics are summarized below.

8.3.1 Phase I trials
There are four vaccine candidates in Phase I trials.

**Ad5 Ag85A**
Ad5 Ag85A is an adenovirus serotype 5 vector expressing Ag85A. It has been evaluated for safety and immunogenicity in both BCG-naive and previously BCG-immunized healthy volunteers in Canada. Overall, intramuscular administration was found to be safe, well tolerated and immunogenic in both trial groups, with more potent immunogenicity observed in volunteers who had been previously vaccinated with BCG. A safety and immunogenicity study of aerosol administration in BCG-vaccinated healthy volunteers has started.

**AEC/BC02**
AEC/BC02 is a freeze-dried recombinant vaccine expressing Ag85B and fusion protein ESAT6–CFP10. A Phase I study assessing safety and immunogenicity is underway in China, with sponsorship from Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.

**ChAdOx185A – MVA85A (ID/IM/Aerosol)**
ChAdOx185A is a simian adenovirus and MVA85A is a recombinant pox virus – both express antigen 85A. These candidates are being developed with the overall aim of generating a joint heterologous prime-boost regimen delivered through both systemic and mucosal routes.

A Phase I trial of intramuscular administration of ChAdOx185A in BCG-vaccinated adults in the United Kingdom, both alone and as part of a prime-boost strategy with MVA85A, has been completed. Phase I trials of aerosol administration of ChAdOx185A in BCG-vaccinated adults are scheduled to start in the third quarter of 2018. Two studies of aerosol administration of MVA85A in BCG-vaccinated individuals have been completed, and a further study in people with LTBI is being implemented.

**MTBVAC**
MTBVAC is a live strain of *M. tuberculosis*, attenuated via deletions of the *phoP* and *fadD26* genes. The primary target population is neonates (as a BCG replacement vaccine); the secondary target population is adolescents and adults (as a booster vaccine). A Phase Ib trial in neonates was completed in 2018. Phase IIa trials in both target populations will start in 2018.

8.3.2 Phase II and Phase III clinical trials
There are eight vaccines in Phase II or Phase III trials. Another vaccine (H4:IC31) was in development until recently, and for this reason it is also described below.

**DAR-901 booster**
DAR-901 is a whole-cell, heat-inactivated, nontuberculous mycobacterial vaccine booster. It represents a new scalable manufacturing method for SRL172, a candidate vaccine that showed efficacy among adults living with HIV in a Phase II/III trial in the United Republic of Tanzania. It is now being tested in a Phase Ib prevention of (established) infection trial among BCG-primed adolescents, also in the United Republic of Tanzania. The trial is scheduled for completion in 2019.

**H4:IC31**
H4:IC31 is a subunit vaccine that contains a fusion protein of Ag85B and TB10.4, formulated with IC31 adjuvant. A pre-proof-of-concept Phase II trial to evaluate prevention of (established) infection among IGRA-negative,
HIV-negative adolescents who had undergone neonatal BCG vaccination was recently completed in South Africa. The results showed that H4:IC31 induced increased immunogenicity specific to M. tuberculosis compared with placebo. However, statistical significance in preventing initial or sustained infection (measured using the QuantiFERON-TB Gold In-Tube test) was not shown. In the same study, a BCG revaccination arm showed a statistically significant reduction in the rate of sustained conversion compared with the placebo arm. Due to inadequate efficacy, further development and testing of the H4:IC31 candidate has been terminated. For this reason it is not shown in Fig. 8.3.

H56:IC31
H56:IC31 is an adjuvanted subunit vaccine that combines three M. tuberculosis antigens (Ag85B, ESAT-6 and Rv2608c) with the IC31<sup>©</sup> adjuvant, from Valneva Austria GmbH (Vienna Austria). Three Phase I or I/IIa trials of safety and immunogenicity have been completed. Two of these were in HIV-negative, BCG-vaccinated adults with and without LTBI, and without a history or any evidence of TB disease. The other was in HIV-negative pulmonary TB patients who had recently completed treatment. The trials showed that the vaccine had an acceptable safety profile and was immunogenic at all studied doses. Analysis of a Phase Ib trial evaluating the safety and immunogenicity of H4:IC31, H56:IC31 and BCG revaccination in adolescents is underway. In 2018, a Phase 2b trial assessing H56:IC31 for prevention of recurrence will be initiated in the United Republic of Tanzania and South Africa, co-sponsored by the Statens Serum Institut (SSI) and Aeras, with support from the European and Developing Countries Clinical Trial Partnership (EDCTP).

ID93 + GLA-SE
The ID93 + GLA-SE vaccine comprises four M. tuberculosis antigens associated with virulence (Rv2608, Rv3619 and Rv3620) or latency (Rv1813), and the adjuvant GLA-SE. A Phase IIa trial in HIV-negative TB patients that have recently completed treatment for pulmonary TB disease has been completed in South Africa, in preparation for a Phase Ib trial that will investigate the prevention of recurrence of disease in the same population. A Phase IIa trial in BCG-vaccinated healthy healthcare workers, to assess prevention of infection, is underway.

M72/AS01E
M72/AS01E is a subunit vaccine that pairs two M. tuberculosis antigens (32A and 39A) with an adjuvant (AS01E). It is being tested in a Phase Ib efficacy trial in HIV-negative adults infected with M. tuberculosis in Kenya, South Africa and Zambia. The primary end-point is the number of incident cases of active pulmonary TB disease not associated with HIV infection. Secondary end-points include safety and immunogenicity.

RUTI<sup>®</sup>
RUTI<sup>®</sup> is a non-live, polyantigenic vaccine based on cell-wall fragmented M. tuberculosis bacteria. It is intended as a therapeutic vaccine, to be used in conjunction with a short, intensive antibiotic treatment. A Phase I study in healthy volunteers and a Phase II study in people with LTBI have demonstrated a good safety profile, and found the vaccine to be immunogenic at all studied doses. The main target for RUTI is MDR-TB, and a Phase IIa study in patients with MDR-TB is being implemented.

TB/FLU-04L
TB/FLU-04L is a mucosal-vectored vaccine based on an attenuated replication-deficient influenza virus vector expressing antigens Ag85A and ESAT-6. It was designed as a prophylactic boost vaccine for infants, adolescents and adults. A Phase IIa trial in people with LTBI is being implemented.

Vaccae™
Vaccae™ vaccine is a specified lysate that has been licensed by the China Food and Drug Administration as an immunotherapeutic agent to help shorten TB treatment for patients with drug-susceptible TB. A Phase III trial to assess its efficacy and safety in preventing TB disease in people with LTBI has been completed, and data analysis is underway. It is the largest TB vaccine trial undertaken in the past decade, involving 10 000 people aged 15–65 years.

VPM1002
VPM1002 is a live recombinant vaccine. A Phase II trial is being implemented in South Africa to assess the safety and immunogenicity of the vaccine in HIV-exposed and unexposed neonates, and the preparations for a subsequent Phase III trial are underway. A Phase II/III trial for prevention of TB recurrence in adults is being implemented in India.

8.4 Research collaborations and partnerships to end TB
Stakeholders with a clear role to play in advancing TB research include national and local governments, private companies, academia, civil society and TB-affected communities, research institutions, universities, and funding agencies. The Global Action Framework for TB Research, published by WHO in 2015, was developed to facilitate research collaborations and partnerships. It has two main components: promoting TB research at a...
country level to find ways to address local barriers; and catalysing research at a global level through advocacy, knowledge sharing, research prioritization, collaboration and support to international networks for research and capacity-building.

One component of promoting research at the global level is the establishment of multicountry research networks. These can help to expedite innovation by fostering collaboration, leveraging resources and facilitating technology transfer, through public–private partnerships, north–south and south–south cooperation. Governments have an important role to play in strengthening such initiatives by creating policy frameworks that enable and promote research partnerships. At a G20 summit in 2017, heads of state called for the establishment of a collaborative hub for research and development “to maximize the impact of new and existing anti-microbial basic and clinical research initiatives as well as product development” for drug-resistant infections, including TB. A recent analysis of the authorship of research publications on TB between 2007 and 2016 suggested that north–south collaborations increased steadily during this period, while south–south collaborations were much less common. With growing scientific and economic capacity in low- and middle-income countries, the capacity of countries with a high burden of TB to contribute to research is expected to increase. This is particularly so for the BRICS countries (Brazil, Russian Federation, India, China and South Africa), which account for more than 40% of the global TB disease burden in terms of both TB incidence and TB deaths, and about 50% of the global burden of drug-resistant TB (Chapter 3). During the Global Ministerial Conference on TB in November 2017, the establishment of a BRICS TB research network was announced; further details are provided in Box 8.3.

**BOX 8.3**
The BRICS TB Research Network

In November 2017, the governments of Brazil, the Russian Federation, India, China and South Africa announced the establishment of a collaborative TB research network, the aim of which is to accelerate TB research and innovation through cooperation mechanisms.

The establishment of the network follows previous BRICS commitments to coordinated action related to the TB response. In the 2013 Delhi Communiqué, BRICS agreed to collaborate to develop “capacity and infrastructure to reduce the prevalence and incidence of TB through innovation for new drugs, vaccines, diagnostics and promotion of consortia of TB researchers to collaborate on clinical trials of drugs and vaccines”.

When BRICS ministers of health met in Brasilia in 2014, they agreed to cooperate on TB research and innovation, and they identified technology sharing, manufacturing capacity and TB financing as key priorities. In December 2016, they agreed to “the setting up of a BRICS network on TB research and creation of a research and development consortium on TB, HIV and malaria, including the possibility of international fund raising”.

The new network will include cooperation on TB research and innovation related to product development and validation, technology transfer, delivery of TB care and services, and capacity-building, based on the use of existing expertise and technological capacity within BRICS. Priority activities include leveraging domestic funds to support the development of common protocols and associated implementation of multicountry studies to accelerate the development of TB diagnostics, drugs and vaccines; and evaluating the epidemiological, clinical and economic impact of adopting innovative interventions at national level.

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