



# The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era

Katherine Floyd, Philippe Glaziou, Alimuddin Zumla, Mario Raviglione

Tuberculosis is the number one cause of death from infectious disease globally and drug-resistant forms of the disease are a major risk to global health security. On the occasion of World Tuberculosis Day (March 24, 2018), we provide an up-to-date review of the status of the tuberculosis epidemic, recommended diagnostics, drug treatments and vaccines, progress in delivery of care and prevention, progress in research and development, and actions needed to accelerate progress. This Review is presented in the context of the UN Sustainable Development Goals and WHO's End TB Strategy, which share the aim of ending the global tuberculosis epidemic. In 2016, globally there were an estimated 10·4 million new cases of tuberculosis, and 600 000 new cases with resistance to rifampicin (the most powerful first-line drug). All countries and age groups are affected by tuberculosis, but most cases (90%) in 2016 were in adults, and almost two-thirds were accounted for by seven countries: India, Indonesia, China, Philippines, Pakistan, South Africa, and Nigeria. The sex ratio (male to female) was 1·9 and 10% of patients with newly diagnosed tuberculosis were also HIV-positive. There were 1·7 million deaths from tuberculosis in 2016, including 0·4 million deaths among people co-infected with HIV (officially classified as deaths caused by HIV/AIDS). Progress in care and prevention means that the global mortality rate (deaths per 100 000 people per year) is decreasing by 3·4% per year and incidence (new cases per 100 000 people per year) is decreasing by 1·9% per year. From 2000 to 2016, the annual global number of tuberculosis deaths decreased by 24% and the mortality rate declined by 37%. Worldwide, an estimated 53 million deaths were averted through successful treatment. Nonetheless, major gaps in care and prevention remain. For example, the 6·3 million new cases of tuberculosis reported globally in 2016 represented only 61% of the estimated incidence; only one in five of the estimated number of people with drug-resistant tuberculosis was enrolled in treatment. Pipelines for new diagnostics, drugs, and vaccines are progressing, but slowly. Actions needed to accelerate progress towards global milestones and targets for reductions in the burden of tuberculosis disease set for 2020, 2025, 2030, and 2035 include closing coverage gaps in testing, reporting of cases, and overall access to health care, especially in countries that account for the largest share of the global gap; multisectoral efforts to reduce prevalence of major risk factors for infection and disease; and increased investment in research and development.

## Introduction

Every year, World Tuberculosis Day marks the announcement by Dr Robert Koch on March 24, 1882, that he had identified *Mycobacterium tuberculosis* as the cause of the disease.<sup>1</sup> At that time, cause of death data from national vital registration systems in European countries and Japan show tuberculosis mortality rates of more than 100 per 100 000 people per year. With no drug treatment available, about 70% of people with sputum smear-positive pulmonary tuberculosis could be expected to die within 10 years, and about 40% of people with all clinical forms of tuberculosis disease could be expected to die overall.<sup>2</sup> Studies of human skeletons show that tuberculosis has affected humans for thousands of years.<sup>3</sup>

A slow decline in tuberculosis incidence and mortality started around the turn of the twentieth century; from the 1940s the combination of social and economic development and discovery, development, and use of effective drug treatments resulted in rapid declines in the number of cases and deaths in western Europe, Japan, North America, and other parts of the world,<sup>4,5</sup> to the extent that tuberculosis is often regarded as a disease of the past. However, for many countries this idea has remained a distant reality. Tuberculosis was declared a global health emergency by WHO in 1993<sup>6</sup> and despite

major progress in subsequent years and the fact that tuberculosis can usually be cured with the right treatment regimen, in the second decade of the 21st century this disease remains the top cause of death from an infectious disease globally.<sup>7</sup> Intensified national and global efforts are needed to reduce this burden and achieve the ambitious global targets and milestones set for 2016–35.

In November, 2017, WHO and the Government of Russia hosted the first global ministerial conference on tuberculosis,<sup>8</sup> which will be followed by the first session for heads of state to discuss tuberculosis at the UN General Assembly in September, 2018.<sup>8</sup> Almost exactly halfway between these two unprecedented events and on the occasion of World Tuberculosis Day 2018, this article provides an up-to-date review of global strategy and targets for tuberculosis, the status of the epidemic, recommended diagnostics, drug treatments and vaccines, progress in delivery of care and prevention, progress in research and development, and actions needed to accelerate progress towards the goal of ending the global tuberculosis epidemic.

Our Review draws extensively on the 2017 edition of WHO's global tuberculosis report,<sup>7</sup> complemented by information from other publications and documents from the global ministerial conference, and follows

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Global TB Programme, WHO, Geneva, Switzerland (K Floyd PhD, P Glaziou MD, M Raviglione\*); Centre for Clinical Microbiology, Division of Infection and Immunity, University College London, and National Institute for Health Research Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK (Prof Sir A Zumla FRCP); and UNZA-UCLMS Research and Training Programme, Lusaka, Zambia (Prof Sir A Zumla)

\*Dr Raviglione retired in November, 2017

Correspondence to: Professor Sir Alimuddin Zumla, Division of Infection and Immunity, University College London, and National Institute for Health Research Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London WC1E 6BT, UK  
a.zumla@ucl.ac.uk

## Key messages

- Tuberculosis is one of the top causes of ill-health and death worldwide and the leading cause of death from an infectious disease. The UN Sustainable Development Goals (SDGs) and WHO's End TB Strategy include ambitious global targets for enormous reductions in this burden, including a 90% reduction in deaths and an 80% reduction in incidence between 2015 and 2030.
- The latest WHO estimates show important global progress between 2000 and 2016: the number of deaths fell 24%, the mortality rate (deaths per 100 000 people per year) declined by 37%, incidence (new cases per 100 000 people per year) decreased at an average rate of 1.4% per year, and 53 million deaths were averted through successful treatment.
- The pipelines for new diagnostics, drugs, treatment regimens, and vaccines are progressing, but slowly. Several new diagnostics have emerged from the research pipeline in recent years, and 17 drugs, several new treatment regimens, and 12 vaccine candidates are in clinical trials.
- The pace of progress is not fast enough to reach the SDG and End TB Strategy targets and intensified efforts are needed at national and global levels. Gaps in testing of tuberculosis cases for HIV and drug susceptibility, reporting of detected cases to national authorities, and overall access to health care must be closed, broader underlying social and economic determinants of infection and disease should be addressed, and investments in research and development increased.
- Commitments made in the Declaration from the Global Ministerial Conference on Tuberculosis in November, 2017, and the upcoming United Nations General Assembly (UNGA) high-level meeting on tuberculosis in New York in September, 2018, provide hope that the intensified efforts required to put countries (and the world) on the path to achieving the targets set for 2030 can be galvanised.

DOTS strategy (until 2005), followed by the Stop TB Strategy (2006–15), which had the overall goal of reaching all three targets.<sup>12</sup> WHO's assessment of whether the 2015 tuberculosis targets were achieved at global, regional, and country levels was published in October, 2015.<sup>13</sup>

In 2016, the MDGs were succeeded by the Sustainable Development Goals (SDGs). The SDGs were adopted by the UN in September, 2015, and cover the period 2016–30.<sup>14</sup> WHO developed a post-2015 global tuberculosis strategy between 2012 and 2014—the End TB Strategy—which was endorsed by all WHO Member States in 2014 and applies for the period 2016–35.<sup>15,16</sup>

The aim of both the SDGs and the End TB Strategy is to end the global tuberculosis epidemic. This is expressed as the goal of the End TB Strategy, and is part of Target 3.3 in the SDGs, which also includes ending the epidemics of HIV, malaria, and neglected tropical diseases.<sup>17</sup> The tuberculosis indicator for Target 3.3 is incidence per 100 000 population per year. Tuberculosis is also part of an indicator that will be used to assess progress towards the SDG target of achieving universal health coverage (Target 3.8). The WHO and World Bank definition of universal health coverage is that all people receive the health services they need, while ensuring that use of these services does not expose the user to financial hardship.<sup>18</sup> An indicator for Target 3.8 is the coverage of 16 essential prevention, treatment, and care interventions, one of which is tuberculosis treatment.

The End TB Strategy includes quantitative targets (for 2030 and 2035) and milestones (for 2020 and 2025) for three high-level indicators (table 1). These indicators are tuberculosis incidence (new cases per 100 000 people per year), the number of tuberculosis deaths, and the percentage of tuberculosis patients and their households that face catastrophic costs due to the disease. For 2030, the targets are to reduce the annual number of tuberculosis deaths by 90% and to reduce tuberculosis incidence by 80%, compared with 2015. For the third indicator, a milestone of zero households facing catastrophic costs due to tuberculosis is set for 2020, to be sustained thereafter. The trajectories of tuberculosis incidence and numbers of deaths required to achieve the milestones and targets are shown in figure 1.

To achieve the 2020 and 2025 milestones, the global rate of decline in tuberculosis incidence must accelerate from 1.5% per year (in 2015) to 4–5% per year by 2020 (similar to what is being achieved in some high tuberculosis burden countries),<sup>7</sup> and to 10% per year by 2025 (emulating the fastest national declines of the past).<sup>4,5</sup> The proportion of people with tuberculosis who die from disease must be reduced from 17% (in 2015) to 10% by 2020, and to 6.5% by 2025 (comparable to numbers in high-income countries).<sup>7</sup> Such reductions require provision of diagnostic and treatment services within the context of broader progress towards universal health coverage, so that all those in need can access care by 2025, and multisectoral efforts to reduce prevalence of major

	Milestones		Targets	
	2020	2025	2030	2035
Reduction in absolute number of tuberculosis deaths compared with 2015 baseline	35%	75%	90%	95%
Reduction in tuberculosis incidence (new cases per 100 000 people per year) compared with 2015 baseline	20%	50%	80%	90%
Tuberculosis-affected households experiencing catastrophic costs due to disease (level in 2015 unknown)	0	0	0	0

Table 1: Targets and milestones set in WHO's End TB Strategy

similar reviews published by *The Lancet* in 2010<sup>9</sup> and 2012.<sup>10</sup>

### Global End TB Strategy and Sustainable Development Goal targets

From 2000 to 2015, national and global efforts to reduce the burden of tuberculosis were focused on achieving targets set within the context of the Millennium Development Goals (MDGs). Established by the UN in 2000, MDG target 6C was to halt and reverse tuberculosis incidence (defined as the number of new cases per 100 000 population per year).<sup>11</sup> The Stop TB Partnership set two additional targets—to reduce tuberculosis prevalence and mortality by 50% by 2015, compared with numbers in 1990. The global tuberculosis strategies recommended by WHO between 2000 and 2015 were the

risk factors for infection and disease, including poverty, undernutrition, housing quality, HIV infection, diabetes, and smoking. Achieving the targets set for 2030 and 2035 depends on technological breakthroughs by 2025, such as the development of a vaccine capable of preventing disease in adults so that incidence can decline at much faster rates (on average, 17% per year) in the period 2025–35. These requirements provide the rationale for the three pillars of the End TB Strategy: integrated, patient-centred tuberculosis care and prevention, bold policies and supportive systems (including universal health coverage, social protection, and action on determinants), and intensified research and innovation.<sup>16</sup>

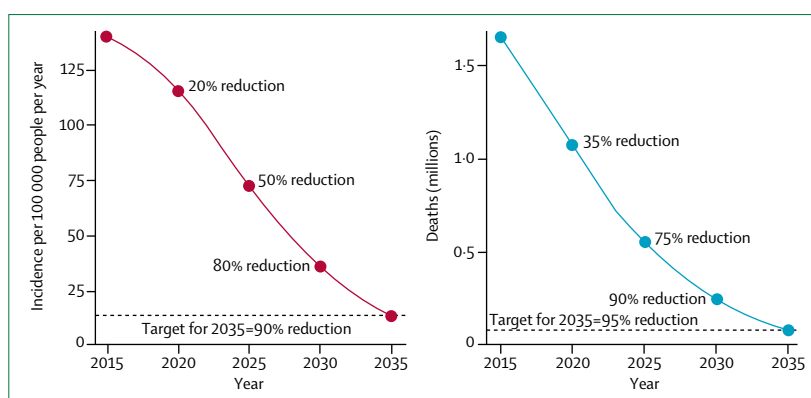
## Status of the tuberculosis epidemic

### Tuberculosis incidence and deaths

Global estimates of tuberculosis incidence and the number of tuberculosis deaths in the period 2000–16 are shown in figure 2. In 2016, there were an estimated 10.4 million (95% uncertainty interval 8.8–12.2 million) new (incident) cases, a number that has been relatively stable since 2000. Of these, 1 million (10%) were HIV-positive. Relative to the population, the number of incident cases (per 100 000 people per year) has been falling slowly, by 1.4% per year in 2000–16 and 1.9% in 2015–16. The number of tuberculosis deaths has also been falling, from a best estimate of 1.7 million in 2000 to 1.3 million in 2016 among people who were HIV-negative (a reduction of 24%), and from 0.5 million to 0.4 million among people who were HIV-positive (officially, these deaths are classified as caused by HIV/AIDS).<sup>19</sup> Between 2015 and 2016, the tuberculosis mortality rate (deaths per 100 000 people per year) among people who were HIV-negative decreased by 3.4% per year (4% when deaths among people who were HIV-positive were included), and decreased by 37% between 2000 and 2016.

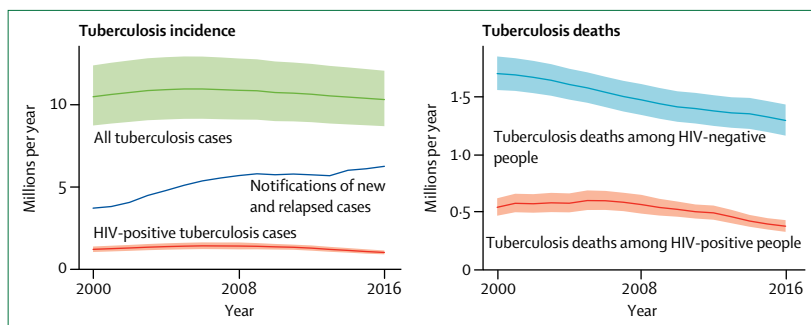
Regionally, the fastest declines in tuberculosis incidence were in the WHO European region (4.6% from 2015 to 2016). Since 2010, reductions of at least 4% per year are estimated to have occurred in several countries with a high burden of tuberculosis, including Ethiopia, Kenya, Lesotho, Namibia, Russia, Tanzania, Zambia, and Zimbabwe. From 2010 to 2016, the fastest declines in mortality were in the European (6% per year) and western Pacific (4.6% per year) regions.

Tuberculosis is found in every country in the world, but 18 countries had more than 100 000 new cases in 2016 (figure 3). Of these, seven accounted for 64% of the global total: India (27%), Indonesia (10%), China (9%), Philippines (5%), Pakistan (5%), South Africa (4%), and Nigeria (4%). Three WHO regions accounted for 87% of cases: southeast Asia (45%), Africa (25%), and the western Pacific (17%). The European region and the Americas each accounted for 3% of the total, with the remaining 7% in the eastern Mediterranean region. Of the estimated 1 million new tuberculosis cases among people who were



**Figure 1: Projected incidence and mortality curves required to reach the End TB Strategy targets and milestones, 2015–35**

Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

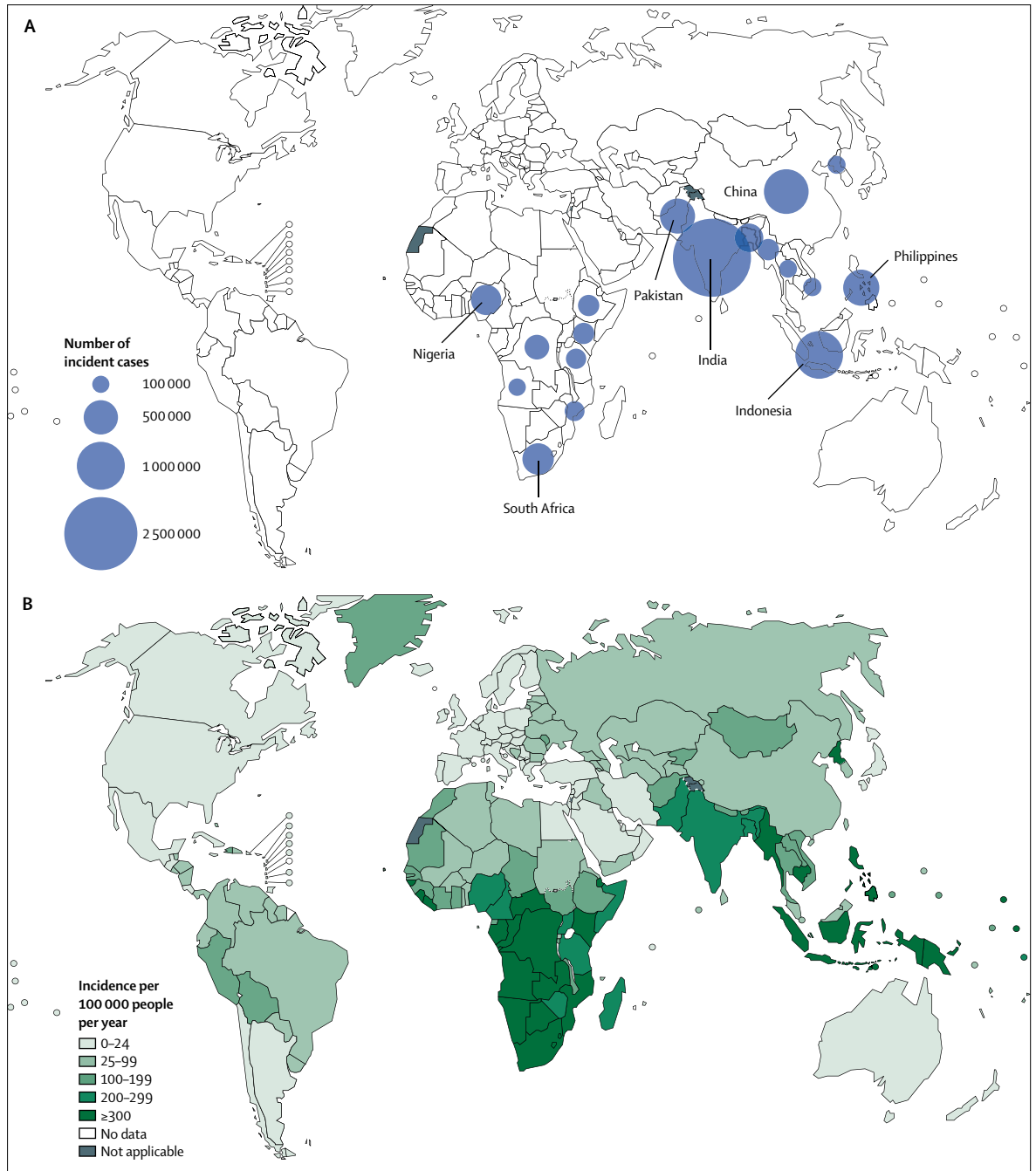


**Figure 2: Global trends in the estimated incidence of tuberculosis and tuberculosis deaths, 2000–16**

Shaded areas around each line represent uncertainty intervals. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

HIV-positive in 2016, 74% were in the African region. The number of incident cases relative to population size varied widely, from less than 10 per 100 000 people in most high-income countries to more than 500 per 100 000 in Kiribati, Lesotho, Mozambique, North Korea, Philippines, and South Africa (figure 3). Tuberculosis affects men, women, and children in all age groups (figure 4), but most cases are in adults (90%) and in men (65%).

Although the number of deaths due to tuberculosis is declining globally (figure 2), it remains one of the top ten causes of death worldwide (figure 5). In 2015, the last year for which WHO has published estimates for all causes of death, tuberculosis ranked as the ninth cause of death worldwide. From 2012 to 2016, it was the number one cause of death from a single infectious agent, ranking above HIV/AIDS. In 2016, about 82% of tuberculosis deaths among people who were HIV-negative were in the WHO regions of Africa and southeast Asia, as were 85% of the combined total of deaths among people who were HIV-negative and people who were HIV-positive. India alone accounted for 33% of global tuberculosis deaths among people who were HIV-negative, and for 26% of the combined total deaths in HIV-negative and HIV-positive people.



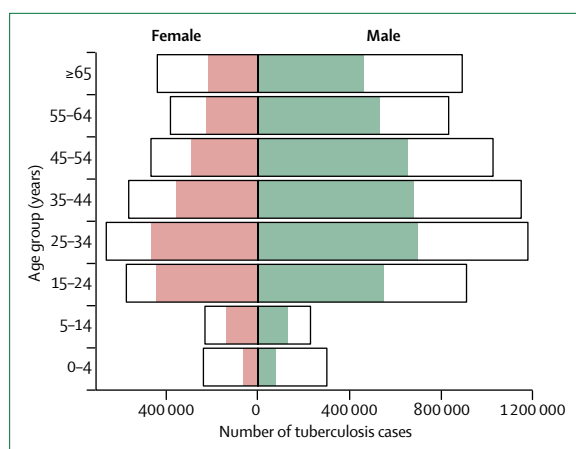
**Figure 3: Estimated tuberculosis incidence by country, 2016**  
 (A) Absolute numbers, for countries with at least 100 000 incident cases. (B) Per 100 000 people per year. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

The proportion of people with tuberculosis who die from the disease (approximated as the estimated numbers of deaths in a given year divided by the estimated number of incident cases in the same year) was 16% globally in 2016. However, this number varied widely between countries (figure 6), from less than 5% in some (including most countries in western Europe

[not the UK], Australia, and New Zealand) to more than 20% in most African countries, illustrating large inequities in access to diagnosis and treatment.

**Drug-resistant tuberculosis**

Drug-resistant tuberculosis has been found in every country in which it has been measured (figure 7). Globally



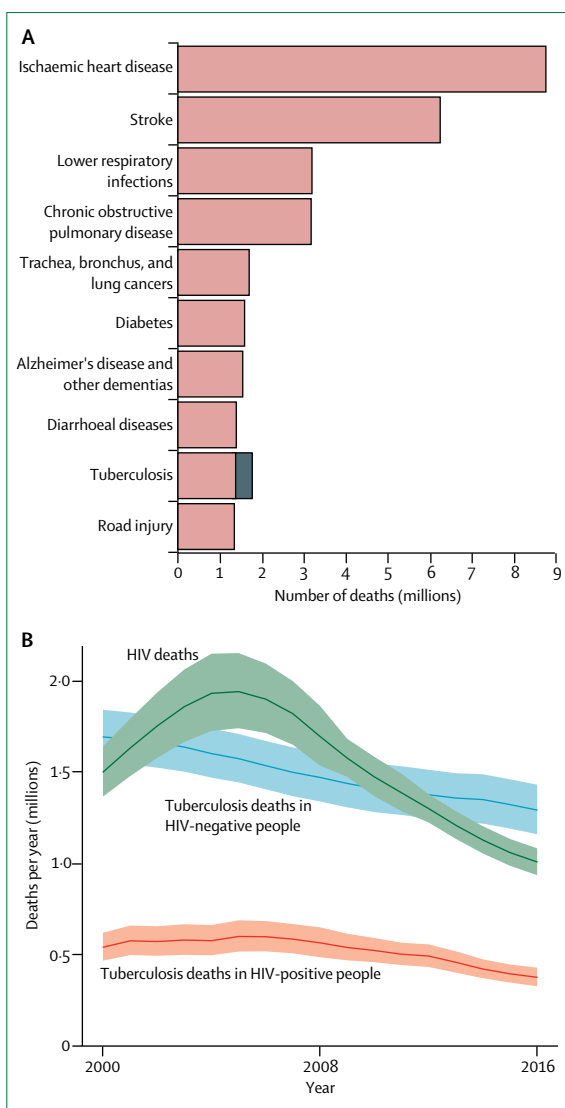
**Figure 4: Global distribution of incident tuberculosis cases by age and sex, 2016** Bars show estimated incidence. Red and green shaded portions show the number of incident cases that were officially reported to WHO in 2016, for female cases (red) and male cases (green). Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

in 2016, an estimated 4·1% of newly infected patients and 19% of previously treated patients had rifampicin-resistant tuberculosis and thus required treatment with second-line drugs. Worldwide, an estimated 600 000 people developed rifampicin-resistant tuberculosis in 2016; this number included 490 000 (82%) people with multidrug-resistant tuberculosis (ie, resistance to at least rifampicin and isoniazid). 45 countries had at least 1000 incident cases of rifampicin-resistant tuberculosis in 2016 (figure 7), and three countries accounted for almost half of the global total: India (25%), China (12%), and Russia (10%).

#### Improvements in data

Tracking the tuberculosis epidemic in terms of numbers of cases and deaths is best done using data from national systems for notification of diseases and vital registration that meet quality and coverage standards.<sup>20</sup> Periodic surveys of tuberculosis prevalence and mortality provide an interim solution for directly measuring the burden of disease. The WHO Global Task Force on TB Impact Measurement has provided guidance and support on these topics since 2006, with strategic areas of work focused on strengthening routine surveillance in all countries and periodic surveys of prevalence of disease in a specific subset of countries, as well as regular review of the data and analytical methods used to produce estimates of disease burden.<sup>7,21</sup>

There is some way to go before all countries have robust surveillance systems or repeat survey data, but there has been considerable progress in recent years.<sup>7,22</sup> In 2016, WHO estimates of tuberculosis incidence were based on direct measurements from national surveys of tuberculosis prevalence for 24 countries that accounted for 68% of the global burden, and on routine notification data (with a standard adjustment to allow for



**Figure 5: Tuberculosis deaths in context**

(A) Top ten causes of death worldwide in 2015. The grey section of the tuberculosis bar shows the estimated number of deaths among people who were HIV-positive; these are officially classed as deaths caused by HIV. (B) Trends in deaths caused by tuberculosis and HIV/AIDS, 2000–16. The shaded areas around each line represent uncertainty intervals. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

under-reporting and underdiagnosis) for 134 countries with 15% of the global burden. During 2007–16, 25 national prevalence surveys (13 in Asia and 12 in Africa) were completed using methods recommended by WHO,<sup>23</sup> compared with only a handful of such surveys in the previous decade (all of which were in Asia). In 2016, WHO estimates of tuberculosis deaths were based on national vital registration, with coding of cause of death, for 129 countries that collectively accounted for 57% of estimated tuberculosis deaths (for 18 countries, WHO used estimates produced by the Institute of Health Metrics and Evaluation [IHME]). Data on drug resistance



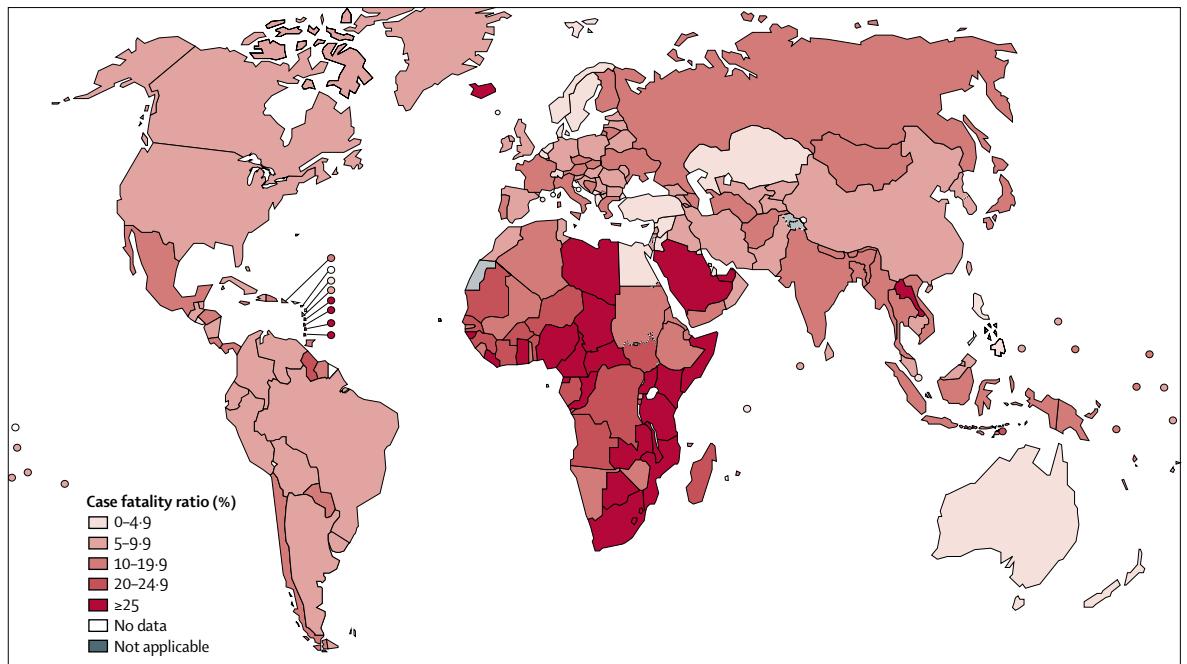


Figure 6: Estimates of the case fatality ratio for tuberculosis, 2016

were available for 160 countries (based on routine diagnostic testing in 90 countries and nationally representative survey data from 70 countries) that accounted for more than 99% of tuberculosis cases globally. About 200 countries report case notification data to WHO each year, with close to 100% of global notifications disaggregated by age and sex since 2013 (up from less than 50% in 2005).

Further required improvements include closing gaps in notification of detected cases (these gaps might be especially large in countries in which many tuberculosis patients seek care in the private sector or in public hospitals that are not linked to the reporting systems of national tuberculosis programmes), systematic and representative audits of data quality, and establishment or strengthening of national vital registration systems with coding of causes of death according to international standards.

With continued improvements to the availability and quality of data, estimates of the burden of tuberculosis disease will also improve, and those published by WHO should converge with estimates produced by other agencies. To date, the other entity publishing estimates of the burden of tuberculosis is IHME, as part of the Global Burden of Disease project.<sup>24</sup> Globally, estimates for 2016 are very similar; IHME estimated there were 1.2 million tuberculosis deaths among people who were HIV-negative in 2016 (compared with the WHO estimate of 1.3 million), and the incidence estimates were the same (10.4 million). General consistency exists for mortality estimates in countries with vital registration systems and good quality standard coding of causes of death, and in incidence

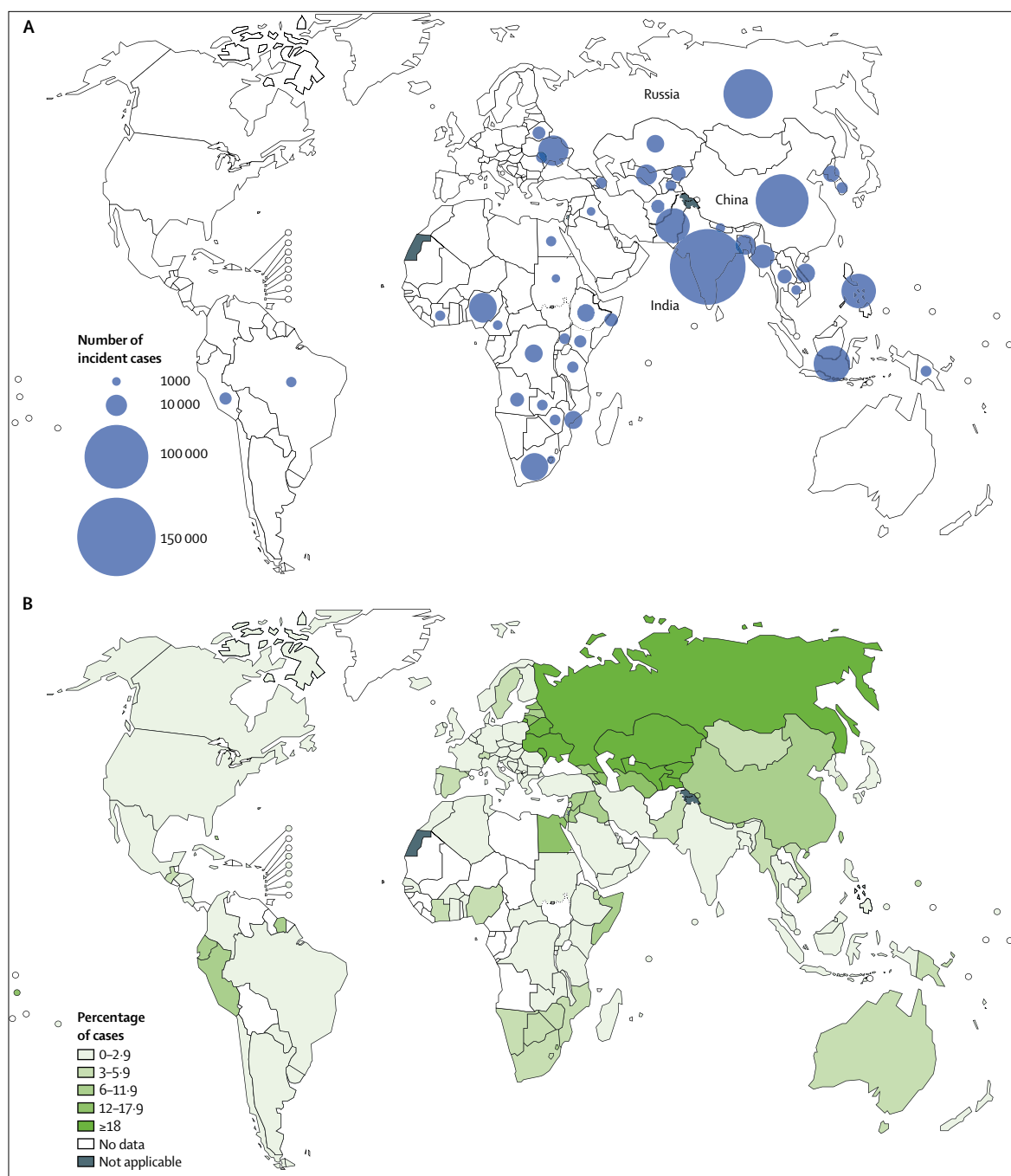
estimates in countries with strong health-care and notification systems. Discrepancies are most apparent for countries in which the underlying data are weaker because of differences in the indirect estimation methods used.

#### Latent tuberculosis infection

Estimates of latent tuberculosis infection burden were recently updated.<sup>25</sup> Globally, 23% (uncertainty interval 20–26) of the world's population was estimated to be infected with *M tuberculosis* in 2014, equivalent to 1.7 billion people.<sup>25</sup> Of these, 80% were in the WHO regions of southeast Asia, the western Pacific, and Africa. The lifetime risk of developing disease if infected is 5–15%.<sup>26</sup> In high burden settings, recent transmission probably accounts for most new cases of tuberculosis disease. By contrast, in some low burden countries, reactivation of previous infections can account for about 80% of new cases of disease.<sup>27</sup>

#### Currently recommended diagnostics, treatments, and vaccines for tuberculosis

The main diagnostic tests for tuberculosis are rapid molecular assays, sputum smear microscopy (developed more than 100 years ago), and culture-based methods. A few other tests using novel technologies have been approved by WHO for use in specific patient groups or settings, including lateral flow lipoarabinomannan antigen detection (for people with HIV who have very low CD4 cell counts) and microscopic observation drug susceptibility testing. The only rapid molecular test recommended by WHO that can simultaneously test for tuberculosis (with much better accuracy than smear



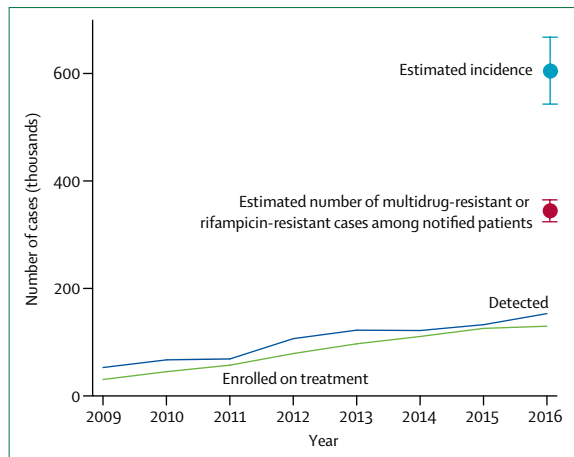
**Figure 7: Estimates of the global burden of drug-resistant tuberculosis, 2016**

(A) Absolute numbers of rifampicin-resistant incident cases for countries with at least 1000 incident cases. (B) Rifampicin-resistant new cases. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

microscopy) and drug resistance (to rifampicin) is the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). This assay was first recommended by WHO in 2010 for diagnosis of pulmonary tuberculosis in adults,<sup>28</sup> in 2013, the recommendation was widened to include children and testing for some forms of extrapulmonary tuberculosis.<sup>29</sup> Culture-based methods are the reference

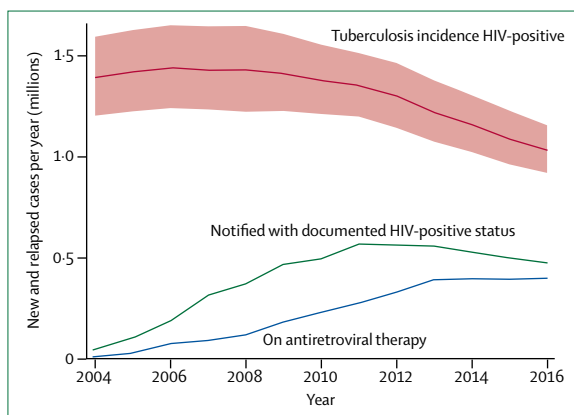
standard, but these require more sophisticated laboratory capacity and can take up to 3 months to obtain results.<sup>7</sup>

In addition to Xpert MTB/RIF, tests for drug-resistant tuberculosis recommended by WHO include rapid line probe assays that test for resistance to first-line drugs (rifampicin and isoniazid),<sup>30</sup> a rapid line probe assay that tests for resistance to second-line drugs (fluoroquinolones



**Figure 8: Global progress in detection and treatment of drug-resistant tuberculosis, 2009–16**

Notified patients comprise cases of tuberculosis that were officially reported. WHO has not published time-series of estimates for either the incidence of drug-resistant tuberculosis or numbers of drug-resistant cases among officially reported tuberculosis cases. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.



**Figure 9: Global progress in detection and treatment of HIV-associated tuberculosis, 2004–16**

Notified cases are those cases of tuberculosis that were officially reported at national level and then to WHO. The shaded area around the red line represents the uncertainty interval. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

and injectables),<sup>31</sup> and sequencing technologies. Despite advances in diagnostics, culture-based methods are still the reference standard for drug susceptibility testing.<sup>7</sup>

The recommended treatment for drug-susceptible tuberculosis is a 6 month combination regimen of four first-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide.<sup>32</sup> The Global Drug Facility supplies a complete 6 month course for about US\$40 per person. Since 2000, the treatment success rates reported to WHO show a global mean of 80–86%.<sup>7</sup> For people with HIV who are not already on antiretroviral therapy, WHO recommends initiation of antiretroviral drugs within 2–8 weeks (depending on CD4 count) of starting tuberculosis treatment.

Drug regimens to treat rifampicin-resistant and multidrug-resistant tuberculosis are longer and require more expensive and toxic second-line drugs. Before 2016, the regimens recommended by WHO typically lasted for 20 months and cost \$2000–\$5000 per person. Since 2016, a shorter (9–12 months), standardised regimen has been recommended for patients (other than pregnant women) with pulmonary tuberculosis that is rifampicin-resistant or multidrug-resistant, provided there is no resistance to second-line drugs.<sup>30,33</sup> Drug susceptibility testing is necessary to establish if these criteria are met. The shortened regimen consists of seven drugs (kanamycin, moxifloxacin, protonamide, clofazimine, pyrazinamide, plus high-dose ethambutol and high-dose isoniazid) and costs about \$1000 per person. Clinical trials show cure rates of 80% can be achieved for drug-resistant tuberculosis using this shortened regimen,<sup>34</sup> but programmatic data generally show much worse outcomes because of high rates of loss to follow-up, unevaluated treatment outcomes, and treatment failure.<sup>7</sup>

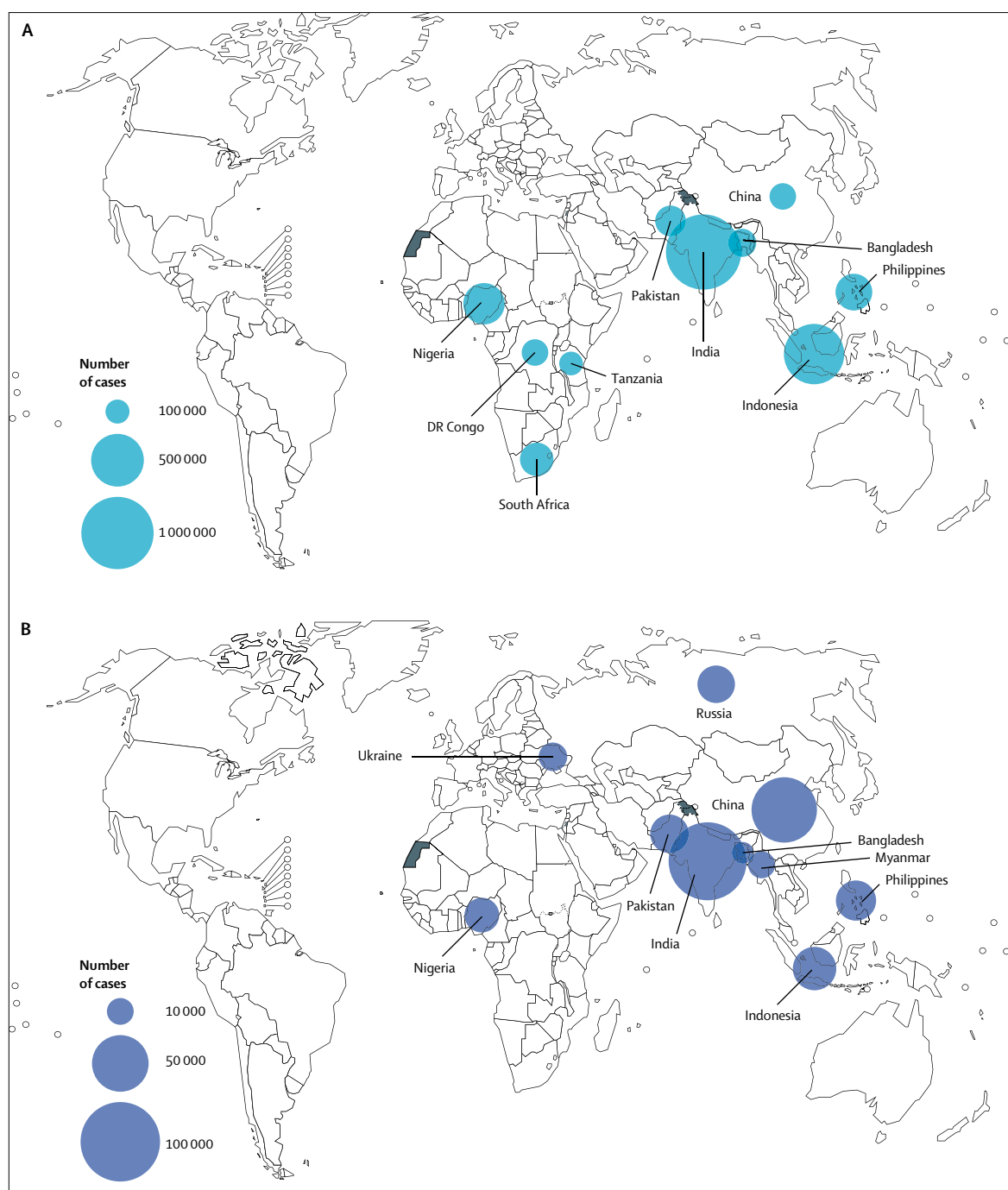
Drug regimens for treatment of latent tuberculosis infection include isoniazid once daily for 6 or 9 months, isoniazid plus rifampicin once daily for 3–4 months, rifampicin once daily for 3–4 months, and isoniazid plus rifapentine once a week for 3 months.<sup>35–37</sup> WHO guidance defines two priority risk groups in all countries: people with HIV who do not have active tuberculosis (but who are at much higher risk of developing it compared with people who are HIV-negative), and children aged under 5 years who are household contacts of people with bacteriologically-confirmed pulmonary tuberculosis.<sup>35</sup>

The BCG vaccine is the only licensed vaccine available for prevention of tuberculosis. First used in the 1920s, it is mostly effective in preventing severe forms of tuberculosis in infants and young children. Evidence for BCG protection against pulmonary tuberculosis in older children and adults is more variable, ranging from 0 to 80%.<sup>38</sup> Although the HIV status of most infants is unknown at birth, and routine BCG administration continues in many countries, BCG should not be used in children who are HIV-positive.<sup>39,40</sup>

### Progress in care and prevention service delivery Increased diagnosis, reporting, and treatment

Global progress in diagnosis and treatment of tuberculosis, drug-resistant tuberculosis, and HIV-associated tuberculosis is shown in figures 2, 8, and 9. In 2016, 6.3 million new cases of tuberculosis were reported (up from 6.1 million in 2015), equivalent to 61% of the estimated incidence of 10.4 million. Most of the global increase in tuberculosis notifications since 2013 was due to a 37% increase in reporting in India during 2013–16. In 2016, 476 774 cases of tuberculosis among people who were HIV-positive were reported, equivalent to 46% of the estimated incidence. Of these cases, 85% were on antiretroviral therapy. In 2016, 129 689 people were started on treatment for drug-resistant tuberculosis,





**Figure 10: Gaps in detection and treatment of tuberculosis and drug-resistant tuberculosis in 2016, top ten countries**

(A) Top ten countries with the largest gap between estimated tuberculosis incidence and case notifications. (B) Top ten countries with the largest gaps between estimated incidence of rifampicin-resistant tuberculosis and enrolments on treatment with second-line treatment regimens. Reproduced from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

which was only a small increase from 125 629 in 2015 and represented just 22% of the estimated incidence. The global male to female ratio for notifications of all new cases of tuberculosis (not drug-resistant cases specifically) was 1.7. As this ratio is less than that observed in national

tuberculosis prevalence surveys, it appears that notification data understate the share of the burden accounted for by men in some countries. Globally in 2016, children (aged <15 years) accounted for 6.9% of the new tuberculosis cases that were notified.

**Panel 1: Development pipeline for new tuberculosis diagnostics, as of August, 2017****Technologies in development***Molecular detection of tuberculosis and drug resistance*

- Gendrive MTB/RIF ID (Epistem, Manchester, UK)
- Xpert XDR-TB cartridge (Cepheid, Sunnyvale, CA, USA)
- TruArray MDR-TB (Akkoni Biosystems, Frederick, MD, USA)
- INFINITIMTB Assay (AutoGenomics, Carlsbad, CA, USA)
- FluoroType XDR-TB assay (Hain Lifescience, Nehren, Germany)
- MeltPro TB assay (Zeesan Biotech, Fujian, China)
- QuantuMDx (Newcastle, UK)

**On the market (evidence for use not submitted to WHO for evaluation)***Molecular detection of tuberculosis and drug resistance*

- iCubate System (iCubate, Huntsville, AL, USA)
- Genechip, TB drug resistance array (Capital Bio, Beijing, China)
- EasyNAT TB Diagnostic kit (Ustar Biotechnologies, Hangzhou, China)
- Truelab/Truenat MTB (Molbio/Bigtec Diagnostics, Alto Santacruz, Goa, India)

**Technologies endorsed by WHO***Molecular detection of tuberculosis and drug resistance*

- Xpert MTB/RIF Ultra for detection of tuberculosis and rifampicin resistance in pulmonary, extrapulmonary, and paediatric samples (Cepheid)
- Line probe assays for detection of *Mycobacterium tuberculosis*, isoniazid, and rifampicin resistance in acid-fast bacilli smear-positive sputum or *M tuberculosis* cultures (Hain Lifescience; Nipro, Osaka, Japan)
- Line probe assays for detection of resistance to fluoroquinolones and second-line injectable agents (Hain Lifescience)
- TB LAMP for detection of tuberculosis (Eiken Chemical, Tokyo, Japan)

*Non-molecular technologies*

- Alere Determine TB-LAM (Tuberculosis detection in people seriously ill with HIV) (Alere, Waltham, MA, USA)
- Interferon  $\gamma$  release assay for diagnosis of latent tuberculosis infection (Oxford Immunotec, Abingdon, UK; Qiagen, Germantown, MD, USA)

*Culture-based technologies*

- Commercial liquid culture systems and rapid speciation
- Culture-based phenotypic drug susceptibility testing using 1% critical proportion in Löwenstein-Jensen, Middlebrook 7H10/7H11, and Mycobacteria Growth Indicator Tube media

*Microscopy*

- Light and light-emitting diode microscopy (diagnosis and treatment monitoring)

**Scheduled for WHO evaluation in 2018 or 2019***Molecular detection of tuberculosis and drug resistance*

- Molecular technologies for genotypic drug resistance testing (including sequencing technologies)
- FluoroType MTBDR (Hain Lifescience)
- m2000 RealTime MTB System (Abbott, Lake Bluff, IL, USA)
- BD Max MDR-TB (Becton Dickinson, Franklin Lakes, NJ, USA)
- GeneXpert Omni (Cepheid)

*Radiology*

- Chest x-ray
- Computer-aided detection

Data taken from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

Making large inroads into the gaps between the estimated burden and the actual number of cases detected and treated requires major progress in a small subset of countries (figure 10). In 2016, 76% of the total global gap between tuberculosis incidence and reported cases was accounted for by ten countries—the top three were India (25%), Indonesia (16%), and Nigeria (8%). In the same year, ten countries accounted for 75% of the global gap between estimated incidence and enrolment in treatment for drug-resistant tuberculosis; India and China accounted for 39% of this gap. The African region accounted for most of the gaps related to detection and treatment of tuberculosis in people who were HIV-positive. Actions required to close these gaps are discussed further below.

**Treatment outcomes**

Between 2000 and 2015, 56 million people were documented as notified cases with successful treatment outcomes, with the annual number reaching 5 million in 2015. Tuberculosis treatment (combined with anti-retroviral therapy for people with HIV) is estimated to have averted 53 million deaths in 2000–16. According to the latest data reported to WHO in 2017, the treatment success rate globally was 83% for new cases registered in 2015 (78% for those co-infected with HIV) and 54% for people enrolled in treatment for drug-resistant tuberculosis (rifampicin-resistant or multidrug-resistant) in 2014 (30% for those with extensively drug-resistant tuberculosis).

**Tuberculosis prevention services**

Provision of treatment for latent tuberculosis infection has improved in recent years, especially in the two priority risk groups (ie, people who are HIV-positive without active tuberculosis, and children aged less than 5 years who are household contacts of people with bacteriologically-confirmed pulmonary tuberculosis). The number of HIV-positive people who were newly enrolled in HIV care and started on treatment for latent tuberculosis infection was almost 1 million across 60 countries in 2016, up from negligible numbers in 2006. South Africa accounted for the largest share of the total (41%) in 2016, as in previous years, followed by Mozambique, Zimbabwe, and Malawi. Data on the number of children aged under 5 years who were started on treatment for latent tuberculosis infection have only been compiled by WHO since 2016, but show an increase of 85% between 2015 and 2016 (from 87 242 to 161 740).<sup>7</sup> Despite this progress, major gaps in prevention services remain. Of the 30 countries with high tuberculosis and HIV burden, 18 did not report any provision of treatment for latent tuberculosis infection in 2016 to people who were HIV-positive and in the 12 countries that did, coverage ranged from 2·4% in Indonesia to 73% in Zimbabwe. The number of children who were treated

in 2016 represented only 13% of the 1.3 million estimated to be eligible.

BCG vaccine coverage is high in most countries with a national policy to provide it. In 2016, 154 countries reported providing BCG vaccination as a standard part of childhood immunisation programmes, of which 111 reported greater than 90% coverage.

### Progress in research and development

A comprehensive review of research on tuberculosis was recently published by WHO,<sup>41</sup> with a focus on the period since 2005. This review showed that between 2009 and 2016 a total of \$4.6 billion was invested into tuberculosis research, mostly for development of new diagnostics, drugs, and vaccines (61%). The remaining money was allocated to basic research (21%), operational research (10%), and infrastructure or unspecified projects (8%). Most funding was from a few regions, led by the USA (\$1.8 billion), followed by the European Union and UK (\$269 million each). Contributions from other countries were less than \$62 million each. The leading recipients of funding were product development partnerships, agencies, and universities in the USA; other recipients in the top 15 were the UK Medical Research Council, FIND (Geneva, Switzerland), University of Cape Town (Cape Town, South Africa), the International Union Against Tuberculosis and Lung Disease (Paris, France), and the National Institute for Research in Tuberculosis (Chennai, India). In 2015, the total investment in tuberculosis research was 0.25% of global expenditures on medical research.<sup>42</sup>

The pipelines as of August, 2017, for new diagnostics, drugs, treatment regimens, and vaccines are shown in panels 1 and 2, and table 2.<sup>43–46</sup> Overall, pipelines are progressing, but slowly. Various diagnostic technologies are in development and evaluation of GeneXpert Omni, a platform for rapid molecular testing close to the point of care, is expected in 2018. There are 17 drugs in phase 1, 2, or 3 trials, including eight new compounds (delpazolid, GSK-3036556, OPC-167832, PBTZ169, pretomanid, Q203, SQ109, and sutezolid), two drugs that have received accelerated or conditional regulatory approval based on phase 2b results (bedaquiline and delamanid), and seven repurposed drugs (clofazimine, linezolid, levofloxacin, moxifloxacin, nitazoxanide, rifampicin [high dose], and rifapentine). Various new combination regimens are in phase 2 or phase 3 trials. 12 vaccine candidates are in clinical trials, with three in phase 1 and nine in phase 2 or phase 3.

In addition to trials related to new diagnostics, drugs, and vaccines, topics being investigated in clinical trials include treatment for latent tuberculosis infection among migrants in the UK, the long-term sequelae of pulmonary tuberculosis in four African countries, use of a high protein supplement to treat wasting due to tuberculosis in Guinea-Bissau, use of biomarkers to predict treatment

#### Panel 2: Development pipeline for new tuberculosis drugs and treatment regimens, as of August, 2017

##### Phase 1

- GSK-3036656
- OPC-167832
- Q203

##### Phase 2

- Delpazolid (LCB01-0371)
- PBTZ169
- SQ109
- Sutezolid
- Levofloxacin
- Linezolid
- Nitazoxanide
- Rifampicin (high dose)
- Rifapentine
- Bedaquiline and delamanid (ACTG 5343 DELIBERATE trial)
- Bedaquiline, pretomanid, and pyrazinamide regimen
- Bedaquiline, pretomanid, moxifloxacin, and pyrazinamide regimen
- Delamanid, linezolid, levofloxacin, and pyrazinamide regimen (MDR-END trial)

##### Phase 3

- Bedaquiline
- Delamanid
- Pretomanid
- Clofazimine
- Rifampicin (high dose)
- Rifapentine
- Bedaquiline, pretomanid, linezolid, with or without moxifloxacin or clofazimine for multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis (TB PRACTECAL trial)
- Bedaquiline, pretomanid, and linezolid (NIX-TB trial)
- Bedaquiline with two optimised background regimens (oral, 9 months; with oral and injectables, 6 months; STREAM trial)
- Bedaquiline and linezolid with optimised background regimen for multidrug-resistant tuberculosis (NEX trial)
- Bedaquiline and delamanid with various existing regimens for multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis (endTB trial)
- Rifapentine and moxifloxacin for drug-susceptible tuberculosis (TB Trial Consortium Study 31/A5349)

Data taken from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

duration, specificity of screening in diagnostics in people who are HIV-positive, diagnostic accuracy of platforms for breath-based testing for tuberculosis, and the effect of enhanced glycaemic monitoring on treatment outcomes for tuberculosis patients with diabetes (table 3).

Topics covered by investment in operational research included treatment access and delivery, public and private collaboration, how to address the joint epidemics of tuberculosis and HIV, community participation, infection control, and measurement of disease burden.

Further discussion about priorities in tuberculosis research and development in the context of the SDGs and the End TB Strategy is provided elsewhere.<sup>41,47</sup>

	Viral vector	Protein or adjuvant	Mycobacterial: whole cell or extract	Mycobacterial: live
Phase 1	Ad5-Ag85A (McMaster University and CanSino); ChAdOx185A-MVA85A (ID/IM/Aerosol; University of Oxford)	..	..	MTBVAC (Biofabri, European Tuberculosis Vaccine Initiative, and University of Zaragoza)
Phase 2a	TB/FLU-04L (Research Institute for Biological Safety Problems)	H56:IC31 (Statens Serum Institut, Valneva, and Aeras); H4:IC31 (Sanofi Pasteur, Statens Serum Institut, and Aeras); ID93 + GLA-SE (Infectious Disease Research Institute, Wellcome Trust, and Aeras)	RUTI (Archivel Farma)	..
Phase 2b	..	M72/AS01E (GlaxoSmithKline and Aeras)	DAR-901 booster (Dartmouth College and Global Health Innovative Technology Fund)	VPM1002 (Statens Serum Institut, Max Planck Institute for Infection Biology, Vakzine Projekt Management, and Tuberculosis Vaccine Initiative)
Phase 3	..	..	Vaccae (Anhui Zhifei Longcom)	..

Data taken from Global Tuberculosis Report 2017,<sup>7</sup> by permission of WHO.

**Table 2: Development pipeline for new tuberculosis vaccines, as of August, 2017**

	Topic	Trial registration number
Completion and acceptability of treatment across primary care and the community for latent tuberculosis (CATAPULT)	Cluster-randomised trial investigating whether recent migrants to the UK are more likely to complete treatment for latent tuberculosis infection if they are treated in the community	NCT03069807
Prevention of tuberculosis in prisons	Double-blind randomised controlled trial to determine if isoniazid is effective in prevention of tuberculosis in a prison population	NCT03028129
Pathogenesis and risk factors of long-term sequelae of pulmonary tuberculosis (TBSEQUEL)	Multicentre observational cohort study in four African countries aiming to advance understanding of the clinical, microbiological, and host immune factors affecting long-term sequelae of pulmonary tuberculosis	NCT03251196
Treating tuberculosis wasting with a high-protein supplement (NUTRIATO)	Open-label trial to test the effect of Lacprodan whey protein concentrate on anthropometric measures, treatment outcomes, and health-related quality of life, against standard practice during antituberculosis treatment in patients with a body-mass index <20 kg/m <sup>2</sup> living in Guinea-Bissau	NCT03302949
Using biomarkers to predict tuberculosis treatment duration	Randomised non-inferiority trial to assess whether 4 months of treatment and a PET or CT scan is inferior to 6 months of treatment for people with less severe tuberculosis	NCT02821832
Alcohol drinkers' exposure to preventive therapy for tuberculosis (ADEPTT)	Open-label trial to examine the safety and tolerability of and adherence to 6 months of daily isoniazid in 300 people with tuberculosis and HIV (200 alcohol drinkers and 100 non-drinkers) in Uganda	NCT03302299

**Table 3: Ongoing operational studies**

**Panel 3: Tuberculosis SDG monitoring framework—14 indicators for which there is evidence of a direct link with tuberculosis incidence, linked to seven goals**

**SDG 3 (Ensure healthy lives and promote wellbeing)**

- Prevalence of HIV, smoking (among those aged ≥15 years), diabetes, and alcohol use disorder (four risk factors that are tuberculosis risk determinants)
- Coverage of essential health services (composite indicator, includes tuberculosis treatment as one of 16 tracer indicators), percentage of total health expenditures that are out-of-pocket, and health expenditure per capita (three indicators related to universal health coverage)

**SDGs 1, 2, 7, 8, 10, and 11**

- SDG 1 (End poverty): proportion of the population living below the international poverty line, proportion of population covered by social protection floors or systems
- SDG 2 (End hunger): prevalence of undernourishment
- SDG 7 (Affordable and clean energy): proportion of the population with primary reliance on clean fuels and technology
- SDG 8 (Sustained economic growth): gross domestic product per capita
- SDG 10 (Reduced inequalities): Gini index for income inequality
- SDG 11 (Sustainable cities and communities): proportion of the urban population living in slums, informal settlements, or inadequate housing

SDG=Sustainable Development Goal.

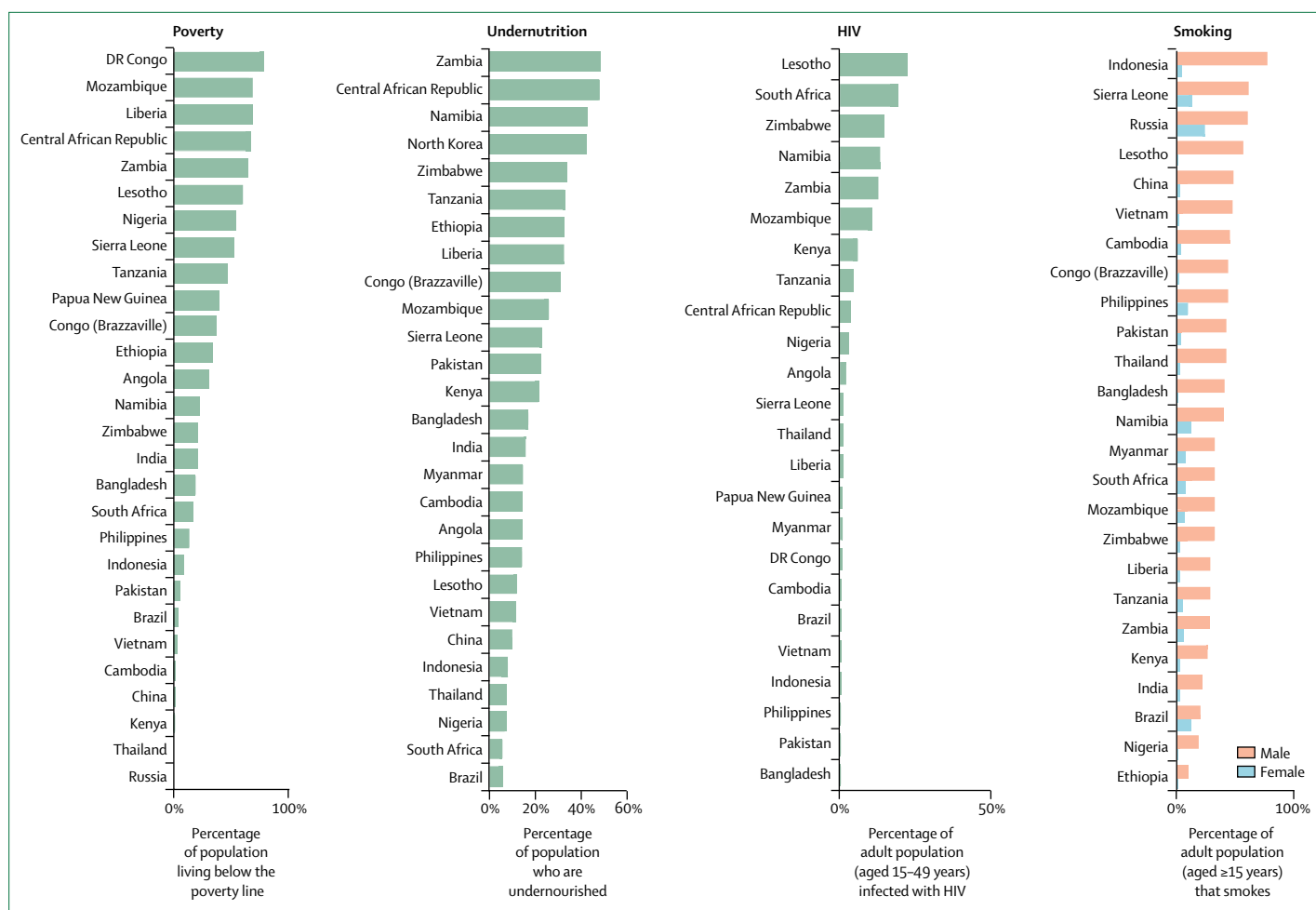
**Actions needed to accelerate progress**

**Closing coverage gaps in testing for HIV and drug susceptibility**

Insufficient coverage of testing for HIV infection and drug susceptibility in people already diagnosed with tuberculosis is part of the reason for gaps in detection and treatment of HIV-associated and drug-resistant tuberculosis (figures 8, 9). In 2016, global coverage of testing for rifampicin resistance was 33% for people with newly diagnosed tuberculosis and 60% for those previously treated (41% overall). This low coverage explains why most of the estimated 350 000 cases of drug-resistant tuberculosis among notified cases went undetected in 2016. Figures for testing and documentation of HIV status were better—57% globally and 82% in the African region, in which the burden of HIV-associated tuberculosis is highest—but were still short of what is needed.

**Closing gaps in detection and reporting of tuberculosis**

To close the remaining gaps in detection and treatment of HIV-associated and drug-resistant tuberculosis and between the estimated incidence of tuberculosis (all



**Figure 11: Status of selected Sustainable Development Goal indicators associated with tuberculosis in 30 high tuberculosis burden countries**  
Values are from databases maintained by WHO and the World Bank, for the latest available year.

forms) and reported cases (figure 2), both under-reporting and underdiagnosis of all forms of tuberculosis must be addressed.

Under-reporting could explain a large part of the gap between incidence and notification, especially in countries with large private sectors or where public hospitals are detecting large numbers of tuberculosis cases, but not reporting them (figure 10). India and Indonesia are good examples, and studies suggest that as much as half of detected cases might go unreported to national authorities in these countries.<sup>7</sup> Studies to quantify the amount of under-reporting of detected tuberculosis cases are underway in China, Indonesia, and Vietnam and are planned in Mongolia, South Africa, and a few European countries.<sup>7</sup>

Underdiagnosis is either due to failure to detect disease in people that do present for care at health facilities, or because of people with tuberculosis not seeking care, for example because of geographical or financial barriers. Data from recent national tuberculosis prevalence surveys show that many patients identified by these surveys had

previously sought care, and that there were also people who reported symptoms and had relatively advanced disease (based on chest x-ray results) who had not sought care. In Nigeria, recommendations from the national tuberculosis prevalence survey included strengthening basic diagnostic and treatment services.<sup>48</sup> National prevalence surveys are currently underway in Mozambique, Myanmar, Namibia, South Africa, Swaziland, and Vietnam.

From a global perspective, closing detection and treatment gaps in certain countries will have the biggest effect on reducing incidence and mortality from tuberculosis (figure 10). Identifying the main reasons for these gaps, and addressing them through actions included in national strategic plans (for tuberculosis specifically and the health sector as a whole), is required in these and other countries.

#### Increased and sustained financing for health service delivery

Addressing gaps in detection, reporting, and treatment requires increased and sustained financing, both for



### Search strategy and selection criteria

We extracted most of the information used in this review from the WHO Global Tuberculosis Report 2017. This report is largely based on WHO's global tuberculosis database, which is managed by the Global TB Programme and contains data from annual rounds of data collection implemented from 1995 to 2017. Around 200 countries that account for over 99% of the world's population and tuberculosis cases report data each year. Data from global databases maintained by other WHO departments, UNAIDS, and the World Bank were also used. The report's chapter on research and development was based on recent publications, particularly those by Unitaid and Treatment Action Group, and communications with staff at the Global Alliance for TB Drug Development and the secretariats of the Stop TB Partnership's working groups on diagnostics, drugs, and vaccines. The production of the Global Tuberculosis Report 2017 was led by KF. The estimates of tuberculosis disease burden published in the report were primarily produced by PG.

We used our existing knowledge of publications about tuberculosis and supplemented this with a specific search and review of the latest (published between Jan 1, 2016, and Jan 1, 2018) publications in peer-reviewed journals, conference presentations, and abstracts through PubMed, Google Scholar, Cochrane Library, Embase, and websites of tuberculosis related international organisations (WHO, Stop TB Partnership, Treatment Action Group, TB Alliance, National Institutes of Health—National Institute of Allergy and Infectious Diseases, and The European and Developing Countries Clinical Trials Partnership [EDCTP]). We used the search terms "tuberculosis" and "*Mycobacterium tuberculosis*", combined with each of the terms "review", "epidemiology", "prevalence", "diagnosis", "treatment", and "prevention". We reviewed studies cited by articles identified in this search strategy and selected those that were relevant. Some review articles are cited to provide readers with more detail and references than this paper can accommodate.

The Review was also informed by the authors' participation in the preparations for, and outcomes of, a Global Ministerial Conference on tuberculosis held in Moscow in November, 2017, and at the 2nd meeting of the WHO Global Task Force on TB Research held in Geneva in February, 2018.

tuberculosis-specific interventions and to enable progress towards universal health coverage.

Financing for tuberculosis prevention and care has been increasing for more than 10 years, mostly from domestic sources, reaching an estimated \$6.9 billion in low-income and middle-income countries in 2017.<sup>7</sup> However, this number was \$2.3 billion short of the estimated \$9.2 billion required in 2017, and was much less than the \$12 billion estimated to be required in 2020.<sup>49</sup>

WHO has monitored funding for tuberculosis since 2002 and specific studies of resource needs and potential sources of funding have also been done. These studies have consistently shown that most of the funding required for tuberculosis care and prevention could be mobilised domestically in middle-income countries (84% of global cases in 2017), whereas international donor funding of around \$2 billion per year (compared with the \$1 billion provided in 2017) is required to support low-income countries and some middle-income countries that are making the financial transition from mixed sources of funding (domestic and donor) to full domestic funding.<sup>49,50</sup> For example, in Brazil, Russia, India, China, and South Africa, 95% of funding for tuberculosis in 2017 was from domestic sources, whereas international donors accounted

for 56% of funding for tuberculosis in low-income countries. India is an example of the potential for increased domestic commitments in middle-income countries given a favourable political context.<sup>7</sup> In 2017, the Indian national government announced substantial increases in domestic funding for tuberculosis, following commitment from the Prime Minister to a strategic plan with the goal of ending the country's tuberculosis epidemic by 2025.

A much broader 2017 analysis<sup>51</sup> compared estimates of the resources required to expand health services towards universal health coverage and achieve other SDG health targets in low-income and middle-income countries, with projections of total health expenditures in the same countries. In most middle-income countries, total health expenditures projected for the period 2016–30 exceeded the funding needed, but in low-income countries they fell far short.<sup>51</sup>

Growth in total health expenditure is necessary but not sufficient to achieve universal health coverage. Financing for health care needs to be generated via pooling of contributions across the population, using mechanisms such as insurance or taxation, otherwise excessive financial burdens will be faced by those in need. Although some countries with a high burden of tuberculosis are building or expanding insurance systems that include tuberculosis in the benefit package (eg, Indonesia, Philippines, and Vietnam), in most countries there is a long way to go. Out-of-pocket expenditures on health care account for more than 30% of total health expenditures in most countries with a high burden of tuberculosis, and the first surveys of costs faced by tuberculosis patients and their households implemented since the launch of the End TB Strategy are revealing a high financial and economic burden.<sup>7</sup>

### Greater attention to underlying determinants of tuberculosis infection and disease

Reducing gaps in service delivery should substantially reduce the overall number of tuberculosis deaths, both by reducing deaths among people who develop tuberculosis and by reducing the period during which people are infectious and can transmit the disease, thereby having an effect on incidence. However, in the absence of a new vaccine or equivalent drug treatment that is effective at preventing new cases in adults, history shows that accelerating reductions in tuberculosis incidence requires addressing the broader, underlying determinants of infection and disease.

WHO has developed a tuberculosis SDG monitoring framework (panel 3) that identifies 14 indicators for which there is evidence of an association with tuberculosis incidence, linked to seven of the SDGs.<sup>52–55</sup> The latest status of a selection of these indicators for WHO's list of 30 high tuberculosis burden countries is shown in figure 11. Many countries have major challenges ahead to address determinants such as poverty, undernutrition, HIV infection, and smoking (particularly among men).

Globally, of the 10·4 million incident cases of tuberculosis in 2016, an estimated 1·9 million were attributable to undernutrition, 1·0 million to HIV infection, 0·8 million to smoking, and 0·8 million to diabetes.<sup>7</sup>

### Increased investment in research and development

Achieving the 2030 targets set in the SDGs and WHO's End TB Strategy will only be possible if the rate of reduction in tuberculosis incidence accelerates from 2025 onwards beyond anything achieved at national level in the past. A new vaccine or equivalent treatment that will substantially lower the probability of latent tuberculosis infection developing into active disease among the almost 2 billion people already infected is needed by 2025. For there to be any chance of such a breakthrough, increased investment in research and development is essential. Recent data show that just over \$0·7 billion was invested in research in 2016,<sup>56</sup> compared with an annual requirement estimated at \$2 billion per year,<sup>49</sup> which itself might be too conservative.

### Multisectoral accountability framework

Since acceleration of progress requires action across the health sector and beyond, the declaration adopted at the WHO Global Ministerial Conference held in November, 2017, calls for the development of a multisectoral accountability framework. Such a framework can be used to galvanise and sustain political commitment and activity based on a regular cycle of monitoring, review, and action, including review at the highest political levels nationally and globally (eg, as in the unified accountability framework that has been developed for women's, children's, and adolescents' health).<sup>57</sup> Development of a draft version of an accountability framework for tuberculosis is anticipated in 2018, in advance of the UN General Assembly high-level meeting on tuberculosis scheduled for September, 2018.

### Conclusion

Despite usually being curable, tuberculosis remains one of the leading causes of death, and is the infectious disease that causes the most deaths worldwide. The burden of ill-health and death due to tuberculosis has decreased in recent decades, but progress in care and prevention must substantially accelerate in the next few years if there is to be any chance of reaching the ambitious targets of the SDGs and the End TB Strategy. This acceleration will require closing detection, reporting, and treatment gaps in the context of overall progress towards universal health coverage, actions to address the broader, underlying determinants of tuberculosis infection and disease (such as poverty, undernutrition, smoking, HIV infection, and diabetes), and much larger investments in research and development.

Commitments made in the Declaration from the WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era that was held

in November, 2017, and the UN General Assembly high-level meeting on tuberculosis scheduled for September, 2018,<sup>5,58</sup> provide hope that the efforts required to put countries and the world on the path to ending the tuberculosis epidemic can be galvanised.

### Contributors

AZ and MR initiated the idea for this Review. KF developed the first draft and PG prepared the figures. All authors contributed to the submitted version of the manuscript. KF and AZ finalised the manuscript following editorial and peer review.

### Declaration of interests

KF and PG are staff of the WHO Global TB programme and MR was the Director of the Global TB Programme 2003–17. AZ has had advocacy links with the WHO Global TB Programme and has served on several of its committees and advisory groups.

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