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**Title:**

# The Global Tuberculosis Epidemic - Progress in Patient Care, Prevention and Control Efforts in Year Three of the 'End TB Era'

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## SEARCH STRATEGY AND SELECTION CRITERIA

We extracted information for this review from the World Health Organization (WHO) *Global Tuberculosis Report 2017*. This report is based on annual rounds of data collection from all countries that have been implemented by WHO's Global TB Programme since 1995 and analysis of data from databases maintained by other WHO departments, UNAIDS and the World Bank. In WHO's 2017 round of data collection for tuberculosis, 201 countries and territories that account for over 99% of the world's population and tuberculosis cases reported data.

Information on developments on new interventions (diagnostics, drugs, vaccines, and projected costs) were also summarized in WHO's *Global Tuberculosis Report 2017*, based on recent publications as well as direct communications with staff at the Global Alliance for TB Drug Development (TB Alliance), Unitaid, and Treatment Action Group (TAG), and the secretariats of the Working Groups of the Stop TB Partnership on diagnostics, drugs and vaccines. Recent publications on tuberculosis as well as conference presentations and abstracts were also reviewed.

**ABSTRACT**

Tuberculosis is now the top cause of death from an infectious disease globally. On the occasion of World Tuberculosis Day March 24th 2018, we provide an up-to-date review of the status of the epidemic, currently 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 is done in the context of the United Nations' (UN) Sustainable Development Goals and WHO's End TB Strategy, which share the aim of ending the global tuberculosis epidemic.

Globally in 2016, an estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 64% were in seven countries: India, Indonesia, China, the Philippines, Pakistan, South Africa and Nigeria. There were 1.7 million deaths from tuberculosis, including 0.4 million deaths among people co-infected with HIV (officially classified as deaths due to HIV/AIDS). Drug-resistant tuberculosis remains a major risk to global health security, with 600 000 new cases with resistance to rifampicin (the most powerful first-line drug) in 2016, of which 82% of had multidrug-resistant tuberculosis.

Progress in care and prevention means that the global mortality rate (per 100 000 population) is falling at 3.4% per year and incidence is falling at 1.9% per year. Since 2000, the annual number of tuberculosis deaths has fallen by 24% and the mortality rate by 37%, and an estimated 53 million deaths have been averted through successful treatment. Nonetheless, there are still large and persistent gaps in prevention, diagnosis and treatment. For example, in 2016 the 6.3 million new cases reported was 61% of the estimated incidence, only one in five of the estimated cases of drug-resistant tuberculosis was enrolled in treatment, and overall 16% of people with tuberculosis died from the disease.

Actions needed to accelerate progress towards global milestones and targets set for 2020, 2025, 2030 and 2035 include closing coverage gaps in testing, reporting and access to health care, increased and sustained financing for service delivery and research and development, and addressing the broader social and economic determinants of infection and disease.

## INTRODUCTION

Each year, World Tuberculosis Day marks the announcement by Dr Robert Koch on 24 March 1882 that he had discovered *Mycobacterium tuberculosis* as the cause of the diseease.[1] At that time, cause of death data from national vital registration systems in European countries and Japan show tuberculosis mortality rates of over 100 per 100 000 population. 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 cases overall.[2] Studies of human skeletons show that tuberculosis has affected humans for thousands of years.[3]

Starting from the 1940s, the combination of social and economic development and the discovery, development and use of effective drug treatments resulted in rapid declines in case and mortality rates in western Europe, North America and some other parts of the world,[4,5] to the extent that tuberculosis is often regarded as a disease of the past. However, for many countries this has remained a distant reality. Tuberculosis was declared a global health emergency by the World Health Organization (WHO) in 1993[6] and despite major progress in subsequent years, in the second decade of the 21st century it remains one of the world's top causes of death and ill-health.[7]

On the occasion of World Tuberculosis Day March 24th 2018, this article provides an up-to-date review of global strategy and targets for tuberculosis, the status of the epidemic, currently 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 tuberculosis. It comes almost exactly halfway between two unprecedented events to bring tuberculosis to the high political level: the first global ministerial conference on tuberculosis, hosted by WHO and the Russian Federation in November 2017; and the first session for heads of state to discuss tuberculosis at the United Nations (UN) general assembly in September 2018.[8] It follows previous reviews published by the Lancet in 2010 and 2012.[9,10]

## GLOBAL END TB STRATEGY AND SDG TARGETS

From 2000 to 2015, global and national efforts to reduce the burden of tuberculosis disease 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).[11] The Stop TB Partnership, established in 2001, adopted this target and set two additional targets, which were to halve tuberculosis prevalence and mortality rates by 2015 compared with their levels in 1990. The global tuberculosis strategy developed by WHO for the decade 2006–2015, the Stop TB Strategy, had the overall goal of reaching all three targets.[12] In October 2015, WHO published its assessment of whether the 2015 tuberculosis targets were achieved at global, regional and country levels.[13]

In 2016, the MDGs were succeeded by the Sustainable Development Goals (SDGs), which were adopted by the UN in September 2015.[14] The SDG framework of goals, targets and indicators is for the period 2016–2030. WHO initiated work on a new global tuberculosis strategy in 2012, which was completed in 2014. The End TB Strategy was unanimously endorsed by all WHO Member States at the 2014 World Health Assembly and is for the period 2016–2035.[15,16]

The SDGs and End TB Strategy share the common aim of ending the global tuberculosis epidemic. This is expressed as the goal of the End TB Strategy, and in the SDGs it is part of Target 3.3, which also includes ending the epidemics of HIV, malaria and neglected tropical diseases.[17] The language of "ending epidemics" is much more ambitious than the MDG language of "halting and reversing" epidemics (or "stopping" them, as in the Stop TB Strategy). The tuberculosis indicator for SDG Target 3.3 is incidence per 100 000 population per year.

SDG 3 also includes a target (Target 3.8) related to universal health coverage in which tuberculosis is explicitly mentioned. The WHO/World Bank definition of universal health coverage 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.[18] Target 3.8 includes a composite indicator based on 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: tuberculosis incidence, the number of tuberculosis deaths, and the percentage of tuberculosis patients and their households that face catastrophic costs as a result of the disease (**Table 1**). The 2030 targets are a 90% reduction in the number of tuberculosis deaths and an 80% reduction in tuberculosis incidence compared with 2015. For the third indicator, a milestone of zero is set for 2020, to be sustained thereafter. The trajectories required to achieve the milestones and targets for reductions in tuberculosis incidence and the number of tuberculosis deaths are shown in **Figure 1**.

To achieve the 2020 and 2025 milestones, the global rate of decline in tuberculosis incidence must accelerate to 4–5% per year by 2020 (similar to what is currently being achieved in some high tuberculosis burden countries)[7] and to 10% per year by 2025 (emulating the fastest national declines of the past).[4,5] The proportion of people with tuberculosis who die from the disease must fall to 10% by 2020 and to 6.5% by 2025 (comparable to current levels in high-income countries).[7] Such reductions require provision of diagnostic and treatment services within the broader context of universal health coverage, so that all those in need can access care; and multisectoral action to address the social and economic determinants of tuberculosis infection and progression to disease. Achieving the targets set for 2030 and 2035 depends on technological breakthroughs from the

research and development pipelines by 2025, so that incidence can fall at much faster rates (on average, 17% per year) in the period 2025–2035. 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.[16]

## CURRENT STATUS OF THE TUBERCULOSIS EPIDEMIC

This section summarizes the main findings published in WHO's latest global tuberculosis report.[7]

### *Tuberculosis incidence and deaths*

Global estimates of tuberculosis incidence and the number of tuberculosis deaths in the period 2000–2016 are shown in **Figure 2**. In 2016, there were an estimated 10.4 million (95% uncertainty interval, 8.8–12.2 million) incident cases, a number that has been relatively stable since 2000. Of these, 1.0 million (10%) were among people living with HIV. The number of incident cases per 100 000 population has been falling slowly, at an average rate of 1.4% per year 2000−2016 and 1.9% between 2015 and 2016. The number of tuberculosis deaths has been falling, from a best estimate of 1.7 million in 2000 to 1.3 million in 2016 among HIV-negative people (a reduction of 24%) and from 0.5 million to 0.4 million among HIV-positive people (these deaths are officially classified as caused by HIV/AIDS).[19] The tuberculosis mortality rate (deaths per 100 000 population per year) among HIV-negative people is falling at 3.4% per year (4% when deaths among HIV-positive people are included), and decreased by 37% between 2000 and 2016.

Regionally, the tuberculosis incidence rate is falling fastest in the WHO European Region (4.6% from 2015 to 2016). The decline since 2010 has exceeded 4% per year in several countries with a high burden of tuberculosis, including Ethiopia, Kenya, Lesotho, Namibia, the Russian Federation, Tanzania, Zambia and Zimbabwe. The fastest declines in mortality are in the European and Western Pacific regions (6.0% and 4.6% per year respectively since 2010).

Tuberculosis affects all countries in the world (**Figure 3a**), but 18 had more than 100 000 new cases in 2016 (**Figure 3b**). Of these, seven accounted for 64% of the global total: India (27%), Indonesia (10%), China (9%), the Philippines (5%), Pakistan (5%), South Africa (4%) and Nigeria (4%). Three WHO regions accounted for 87% of cases: South-East Asia (45%), Africa (25%) and the Western Pacific (17%). The European Region (3%) and the Americas each accounted for 3% of the total, with the remainder (7%) in the Eastern Mediterranean Region. Africa accounted for 74% of the estimated 1.0 million new cases among people living with HIV. The number of incident cases relative to population size varied from under 10 per 100 000 population in most high-income countries to above 500 in a few countries including the Democratic People's Republic of Korea, Lesotho, Mozambique, the Philippines and South Africa (**Figure 3a**). Tuberculosis affects men,

women and children in all age groups (**Figure 4**), but most cases are in adults (90%) and males (65%).

Although the number of deaths is falling globally (**Figure 2**), tuberculosis remains one of the leading causes of death worldwide (**Figure 5a**). In 2015, the latest year for which WHO has published estimates for all causes of deaths, it ranked as the ninth top cause of death worldwide. Since 2012, it has also been the leading cause from a single infectious agent, ranking above HIV/AIDS (**Figure 5b**). In 2016, about 82% of tuberculosis deaths among HIV-negative people occurred in the WHO regions of Africa and South-East Asia; these regions also accounted for 85% of the combined total of tuberculosis deaths in HIV-negative and HIV-positive people. India accounted for 33% of global tuberculosis deaths among HIV-negative people, and for 26% of the combined total of tuberculosis deaths in HIV-negative and HIV-positive people.

When estimates of numbers of deaths are divided by the estimated number of incident cases to approximate the proportion of people with tuberculosis who die from the disease, the global estimate for 2016 was 16%. However, the number varies widely among countries (**Figure 6**), from under 5% in some countries to above 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 where it has been measured (**Figure 7a**). Globally, an estimated 4.1% (95% confidence interval [CI]: 2.8–5.3%) of new cases and 19% (95% CI: 9.8–27%) of previously treated cases had rifampicin-resistant tuberculosis in 2016 and thus required treatment with second-line drugs (see also next section). The estimated number of incident cases worldwide in 2016 was 600 000, of which 490 000 (82%) had multidrug-resistant tuberculosis (defined as resistance to both rifampicin and isoniazid). There were 45 countries with at least 1000 incident cases in 2016 (**Figure 7b**), and three countries accounted for almost half the global total: India (25%), China (12%) and the Russian Federation (10%).

***Improvements to data available to track the epidemic***

Tracking the tuberculosis epidemic in terms of cases and deaths is best done using data from national notification and vital registration systems that meet quality and coverage standards,[20] while periodic surveys 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 to countries since 2006, with strategic areas of work focused on strengthening of routine surveillance and periodic surveys, as well as regular review of the methods used to translate available data into estimates of disease burden.[7,21] Although there is still some way to go before all countries have robust surveillance systems or repeat survey data, there has been considerable

progress in recent years.[7,22] In 2016, WHO estimates of tuberculosis incidence were based on direct measurements from recent national surveys of the prevalence of tuberculosis disease for 24 countries that accounted for 68% of the global burden of cases, and on a standard adjustment (to account for under-reporting and under-diagnosis) to routine notification data for 134 countries with 15% of the global burden. In the period 2007–2016, 25 national prevalence surveys (13 in Asia, 12 in Africa) were completed using methods recommended in the 2010 edition of a WHO handbook,[23] 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 (this included use of estimates published by the Institute of Health Metrics and Evaluation for 18 countries). Data on drug resistance were available for 160 countries (continuous surveillance for 90, and national survey data for 60) that accounted for >99% of the world's tuberculosis cases. Case notification data are reported to WHO by over 200 countries every year, with close to 100% of global notifications disaggregated by age and sex since 2013 (up from under 50% in 2005).

### *Latent tuberculosis infection*

Estimates of the burden of latent tuberculosis infection were recently updated.[24] Globally, 23% (uncertainty interval, 20–26) of the world's population were estimated to be infected with *Mycobacterium tuberculosis* in 2014, equivalent to 1.7 billion people. The lifetime risk of developing disease if infected is 5–15%.[25] In some low-burden countries, reactivation (as opposed to recent transmission) accounts for about 80% of new cases of disease.[26]

## CURRENTLY RECOMMENDED DIAGNOSTICS, TREATMENT AND VACCINES FOR TUBERCULOSIS

### *Diagnostic tests*

Diagnostic tests for tuberculosis disease include rapid molecular assays, sputum smear microscopy (developed more than 100 years ago) and culture-based methods. The only rapid molecular test currently recommended by WHO is the Xpert® MTB/RIF assay (Cepheid, USA), which can provide results (including for rifampicin resistance) within 2 hours. It was initially recommended (in 2010) for diagnosis of pulmonary tuberculosis in adults;[27] since 2013, it has also been recommended for use in children and to diagnose specific forms of extrapulmonary tuberculosis.[28] The test has much better accuracy than sputum smear microscopy. Culture-based methods remain the current reference standard, but require more developed laboratory capacity and take up to 12 weeks to provide results.[7]

Besides Xpert MTB/RIF, tests for drug-resistant tuberculosis include 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-tuberculosis drugs (referred to as a

second-line LPA); and sequencing technologies. First-line LPAs were first recommended by WHO in 2008;[29] the second-line LPA was first recommended in 2016.[30] Culture-based methods remain the reference standard for drug susceptibility testing.[7]

***Treatment regimens***

The currently recommended treatment for drug-susceptible tuberculosis is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide.[31] The Global TB Drug Facility supplies a complete 6-month course for about US$ 40 per person. Treatment success rates of at least 85% nationally are regularly reported to WHO.[7] WHO recommends antiretroviral therapy for all tuberculosis patients co-infected with HIV.

Treatment for rifampicin-resistant and multidrug-resistant tuberculosis is longer, and requires more expensive and more toxic second-line drugs. Until early 2016, the treatment regimens recommended by WHO typically lasted for 20 months, and cost US$ 2000–5000 per person. As a result of new evidence from several countries, WHO issued updated guidance in 2016.[29] Shortened regimens of 9–12 months are now recommended for patients (other than pregnant women) with pulmonary rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis, provided there is no resistance to second-line drugs. The cost of a shortened drug regimen is about US$ 1000 per person. The latest clinical trial data show that cure rates of 80% can be achieved,[32] but programmatic data generally show much worse outcomes due to high rates of loss to follow-up, unevaluated treatment outcomes and treatment failure.

Preventive treatment regimens for latent tuberculosis infection include isoniazid daily for 6 or 9 months, isoniazid plus rifampicin daily for 3–4 months, rifampicin daily for 3–4 months and isoniazid plus rifapentine once a week for 3 months.[33-35] WHO guidance defines two priority risk groups in all countries: people living with HIV and children under 5.

***BCG Vaccination***

The bacilli-Calmette-Guérin (BCG) vaccine, first used in the 1920s, remains the only licensed vaccine for the prevention of tuberculosis. 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%.[36] 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 HIV-infected children.[37,38]

## PROGRESS IN CARE AND PREVENTION SERVICE DELIVERY

This section summarizes the main findings from WHO's latest global tuberculosis report.[7]

***Increased numbers being diagnosed, reported and treated***

Global progress in diagnosis and treatment of tuberculosis, drug-resistant tuberculosis and HIV-associated tuberculosis is shown in **Figure 2** (left panel), **Figure 8** and **Figure 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 notifications since 2013 is explained by a 37% increase in India 2013–2016. In 2016, there were 476 774 reported cases of tuberculosis among people living with HIV, equivalent to 46% of the estimated incidence. Of these, 85% were on antiretroviral therapy. A total of 129 689 people were started on treatment for drug-resistant TB, a small increase from 125 629 in 2015 but only 22% of the estimated incidence. The global male:female (M:F) ratio for notifications was 1.7, which is less than ratios observed in national tuberculosis prevalence surveys, indicating that notification data understate the share of the burden accounted for by men in some countries. Globally, children (aged <15 years) accounted for 6.9% of the new tuberculosis cases that were notified in 2016.

Making large inroads into the gaps between the estimated burden and numbers detected and treated requires progress in a particular subset of countries (**Figure 10**). In 2016, ten countries accounted for 76% of the total gap between tuberculosis incidence and reported cases; the top three were India (25%), Indonesia (16%) and Nigeria (8%). Ten countries accounted for 75% of the incidence-treatment enrolment gap for drug-resistant TB; India and China accounted for 39% of the global gap. Most of the gaps related to HIV-associated tuberculosis were in the WHO African Region, which has 74% of the estimated incidence of tuberculosis in people living with HIV. 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 a successful treatment outcome, with the number reaching 6 million in 2015. Tuberculosis treatment (combined with antiretroviral therapy for those living with HIV) is estimated to have averted 53 million deaths 2000–2016. The latest treatment outcome data reported to WHO show treatment success rates of 83% for tuberculosis (2015 cohort), 78% for HIV-associated tuberculosis (2015 cohort), 54% for drug-resistant tuberculosis (rifampicin or multidrug-resistant tuberculosis) (2014 cohort) and 30% for extensively drug-resistant tuberculosis (2014 cohort).

***Tuberculosis prevention***

Preventive treatment for tuberculosis is expanding, especially in the two priority risk groups of people living with HIV and children under 5. However, most people eligible for treatment are not accessing it. The number of people living with HIV who were newly enrolled in HIV care and started on preventive treatment was almost 1 million across 60 countries in 2016, similar to the level of 2015. As in previous years, South Africa accounted for the largest share of the total (41%), followed by Mozambique, Zimbabwe and Malawi. However, of the 30 high TB/HIV burden countries, 18 did not report any provision of preventive treatment in 2016. In the 12 high TB/HIV burden countries that did report data, coverage ranged from 2.4% in Indonesia to 73% in Zimbabwe. Kenya reported that 390 298 people living with HIV were started on preventive treatment in 2016, but did not distinguish between those newly enrolled in HIV care from those enrolled in previous

years.The number of children aged under 5 years who were reported to have been started on preventive treatment increased by 85% between 2015 and 2016 (from 87 242 to 161 740), but was still 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 vaccination as a standard part of childhood immunization programmes, of which 111 reported coverage above 90%.

## PROGRESS IN RESEARCH AND DEVELOPMENT

The pipelines for new diagnostics, drugs, treatment regimens and vaccines are progressing slowly.[39-42] Figure 11 shows the current pipelines as of October, 2017. Various diagnostic technologies are in development and evaluation of GeneXpert Omni®, a close-to-care platform for rapid molecular testing, is expected in 2018. There are 17 drugs in Phase I, II or III trials, including eight new compounds, two drugs that have received accelerated or conditional regulatory approval based on Phase IIb results (bedaquiline and delamanid), and seven repurposed drugs. Various new combination regimens are in Phase II or Phase III trials. There are 12 vaccine candidates in clinical trials: three in Phase I, and nine in Phase II or Phase III.

## ACTIONS NEEDED TO ACCELERATE PROGRESS

Reaching the milestones and targets set in the SDGs and End TB Strategy requires faster progress in care, prevention and research. This section discusses key actions needed to accelerate progress.

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

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

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

To close the remaining part of the gap in detection and treatment of HIV-associated and drug-resistant tuberculosis and close the gap between the estimated incidence of tuberculosis (all forms) and reported cases (**Figure 2**, **left panel**), both underreporting and under-diagnosis of all forms of

tuberculosis must be addressed. In countries with large private sectors and public health services (especially hospitals) that are detecting large numbers of tuberculosis cases, underreporting may explain a large part of the incidence-notification gaps illustrated in **Figure 10a**, including India and Indonesia.[7] Under-diagnosis is due to either failure to detect cases that do present for care at health facilities, or that people with tuberculosis do not seek care – for example due to geographic or financial barriers. Data from recent national tuberculosis prevalence surveys show that many of the cases detected in 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. A good example of the latter is Nigeria, where recommendations from the survey included strengthening basic diagnostic and treatment services.[43]

From a global perspective, closing gaps in detection and treatment in the countries shown in **Figure 10** will have the biggest impact. 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 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 US$ 6.9 billion in low and middle-income countries in 2017.[7] However, this still fell US$ 2.3 billion short of the estimated US$ 9.2 billion required in 2017 and was much less than the US$ 12 billion estimated to be required in 2020.[44]

WHO has monitored funding for tuberculosis since 2002 and specific studies of resource needs and potential sources of funding have also been undertaken. These have consistently shown that most of the funding required for tuberculosis care and prevention could be mobilized from domestic sources in middle-income countries (84% of global cases in 2017), while about US$ 2 billion per year is needed form international donors (compared with the US$ 1 billion provided in 2017) to support low-income countries as well as some middle-income countries that are making the financial transition from mixed sources of funding (domestic and donor) to full domestic funding.[44,45] In the BRICS (Brazil, Russian Federation, India, China and South Africa) in 2017, for example, 95% of funding for tuberculosis was from domestic sources while in low-income countries 56% of available funding was from international donors. An recent example of the potential for increased domestic commitments in middle-income countries given a favourable political context is India.[7] In 2017, the national government announced substantial increases in domestic funding for tuberculosis, following commitment from the Prime Minister to a strategic plan that has the goal of ending the country's tuberculosis epidemic by 2025.

A much broader analysis published in 2017 provides the same message.[46] This compared estimates of the resources required to expand health services towards universal health coverage and achieve other SDG health targets with projections of total health expenditures in low and middle-income countries. In most middle-income countries, total health expenditures projected for the period 2016–2030 exceeded the funding needed, while in low-income countries they fell far short.

Growth in total health expenditures 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 (for example, Indonesia, Philippines and Viet Nam), in most there is a long way to go. Out-of-pocket expenditures on health care account for a high proportion (>30%) of total health expenditures in most countries with a high burden of tuberculosis,[47] 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.[7]

***Broader determinants of tuberculosis infection and disease***

Reducing gaps in service delivery should substantially reduce the number of tuberculosis deaths, by reducing the proportion of people with tuberculosis who die from the disease and having some impact on incidence (by cutting the period during which people are infectious and can transmit the disease). In the absence of a new vaccine or equivalent drug treatment that is effective at preventing cases in adults, however, history shows that accelerating declines in tuberculosis incidence requires addressing the broader determinants of infection and disease.

In 2017, WHO developed a TB-SDG monitoring framework (Box 1) that includes 14 indicators under 7 SDGs for which there is evidence of an association with tuberculosis incidence.[48-50] The latest status of a selection of these indicators for WHO's list of 30 high tuberculosis burden countries is shown in Figure 12. It is evident that many countries have major challenges ahead to address determinants such as poverty, undernutrition, HIV infection and (among men) smoking. Globally, of the 10.4 million incident cases of tuberculosis in 2016, an estimated 1.9 million were attributable to undernourishment, 1.0 million to HIV infection, 0.8 million to smoking and 0.8 million to diabetes.

***Increased investment in research and development***

Achieving the 2030 targets set in the SDGs and End TB Strategy will only be possible if the rate of decline in tuberculosis incidence accelerates, from 2025 onwards, beyond anything achieved at national level in the past. In particular, a new vaccine or equivalent treatment that will substantially lower the probability a 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 about US$ 0.7 billion was invested in 2016,[51] compared with an annual requirement estimated at US$ 2 billion per year,[45] which itself may be too conservative.

***Multisectoral accountability framework***

The actions needed to accelerate progress require action across the health sector and beyond. For this reason, 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 galvanize and sustain political commitment and action based on a regular cycle of monitoring, review and action, including review at the highest political levels nationally and globally (as for example in the "unified accountability framework" that has been developed for women's, children's and adolescents' health).[52] It is anticipated that a draft version of an accountability framework will be discussed at the UN high-level meeting on tuberculosis scheduled for September 2017.

## CONCLUSIONS

Despite progress in care and prevention, tuberculosis remains one of the world's leading causes of ill-health and death and the current pace of progress is not fast enough to reach targets set in the SDGs and End TB Strategy. Commitments made in the Declaration from the WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era that was held in November 2017 and the upcoming UN General Assembly High-Level Meeting on TB in September 2018[8,53] provide hope that the multisectoral efforts required to put countries and the world on the path to ending the tuberculosis epidemic can be galvanized.

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## CONFLICTS OF INTEREST

KF, PG, MR are staff of the WHO Global TB programme. AZ has had advocacy links with the WHO Global TB Department and has served on several of its committees.

## AUTHOR CONTRIBUTIONS

Alimuddin Zumla and Mario Raviglione initiated the idea. Katherine Floyd developed the first draft and Philippe Glaziou prepared the figures. All authors contributed to subsequent drafts and finalization of the manuscript.

## LEGENDS TO BOX, TABLE AND FIGURES

### LEGEND TO BOX

**Box 1: TB-SDG monitoring framework: 14 indicators for which there is evidence of a direct link with TB incidence, under 7 goals**

### LEGEND TO TABLE

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

### LEGENDS TO FIGURES

**Figure 1**: Projected incidence and mortality curves required to reach End TB targets and milestones, 2015-2035

**Figure 2**: Global trends in the estimated number of incident cases and number of tuberculosis deaths (in millions) 2000-2016

**Figure 3**: Estimated tuberculosis incidence by country in 2016
Figure 3a: Rates by 100,000 population per year
Figure 3b: Absolute numbers, for countries with at least 100,000 incident cases

**Figure 4**: Global distribution of incident cases by age and sex, 2016

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Figure 11b: Drugs and treatment regimens
Figure 11c: Vaccines

**Figure 12**: Status of selected SDG indicators associated with tuberculosis in 30 high tuberculosis burden countries

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

| Indicators | Milestones | | Targets | |
|---|---|---|---|---|
| | **2020** | **2025** | **2030** | **2035** |
| Percentage reduction in the absolute number of TB deaths *(compared with 2015 baseline)* | 35 | 75 | 90 | 95 |
| Percentage reduction in the TB incidence rate *(compared with 2015 baseline)* | 20 | 50 | 80 | 90 |
| Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown) | 0 | 0 | 0 | 0 |

**Box 1: TB-SDG monitoring framework: 14 indicators for which there is evidence of a direct link with TB incidence, under 7 goals**

**SDG 3 (Ensure health lives and promote well-being)**

- Prevalence of HIV, smoking (among those aged ≥15 years), diabetes and alcohol use disorder (four risk factors that are TB 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; 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/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 (GDP) 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

**Figure 1. Projected incidence and mortality curves that are required to reach End TB Strategy targets and milestones, 2015-2035.**

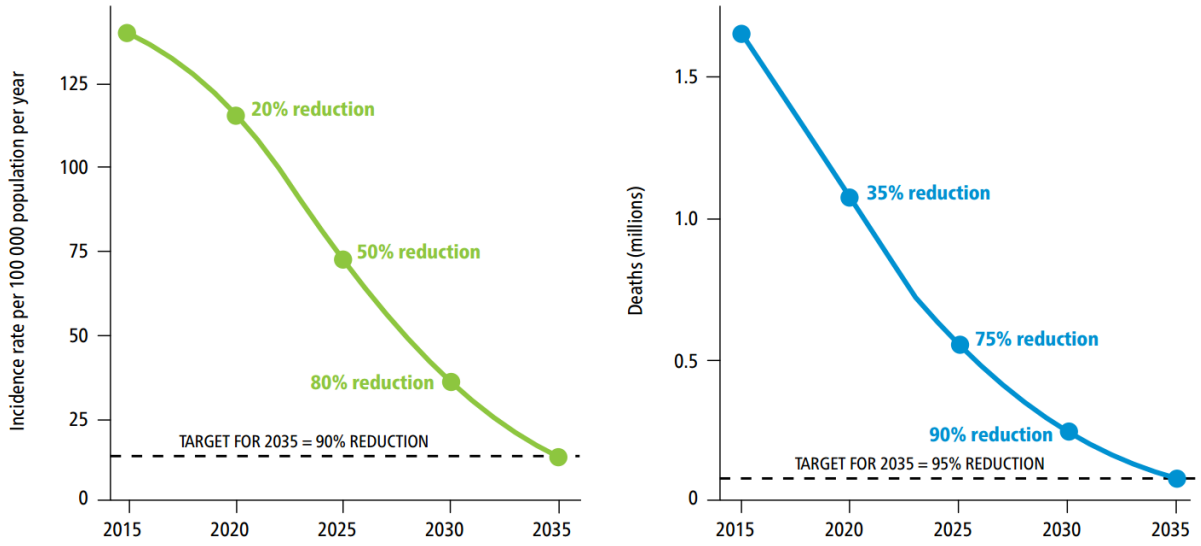



**Figure 2. Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000-2016. Shaded areas represent uncertainty intervals.**

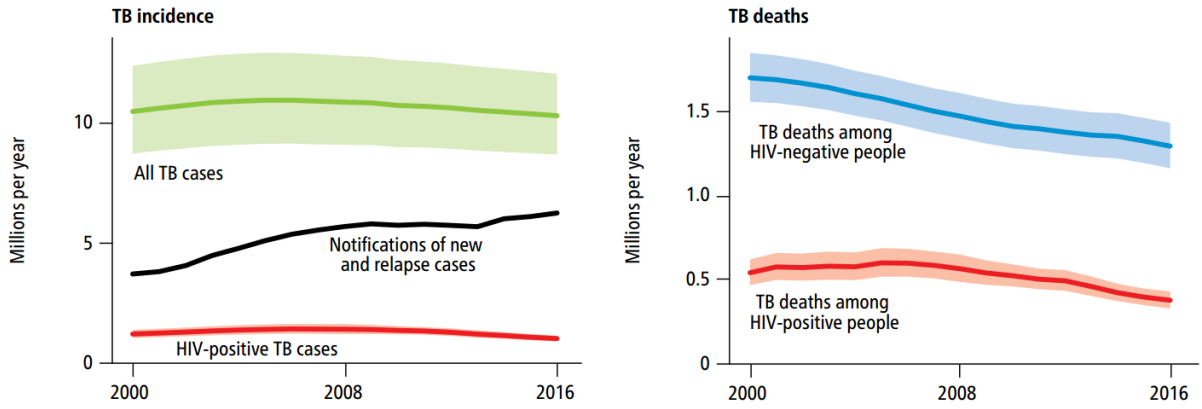
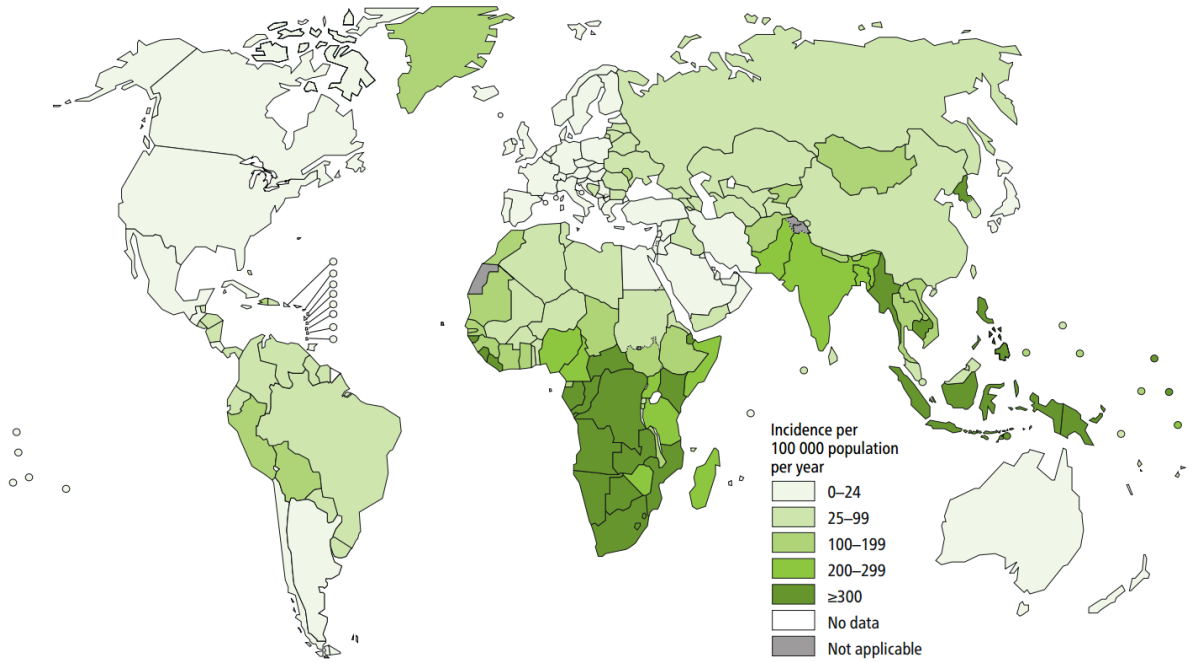


**Figure 3. Estimated tuberculosis incidence by country in 2016**

**a) rates per 100 000 population per year**




**b) absolute numbers, for countries with at least 100 000 incident cases**

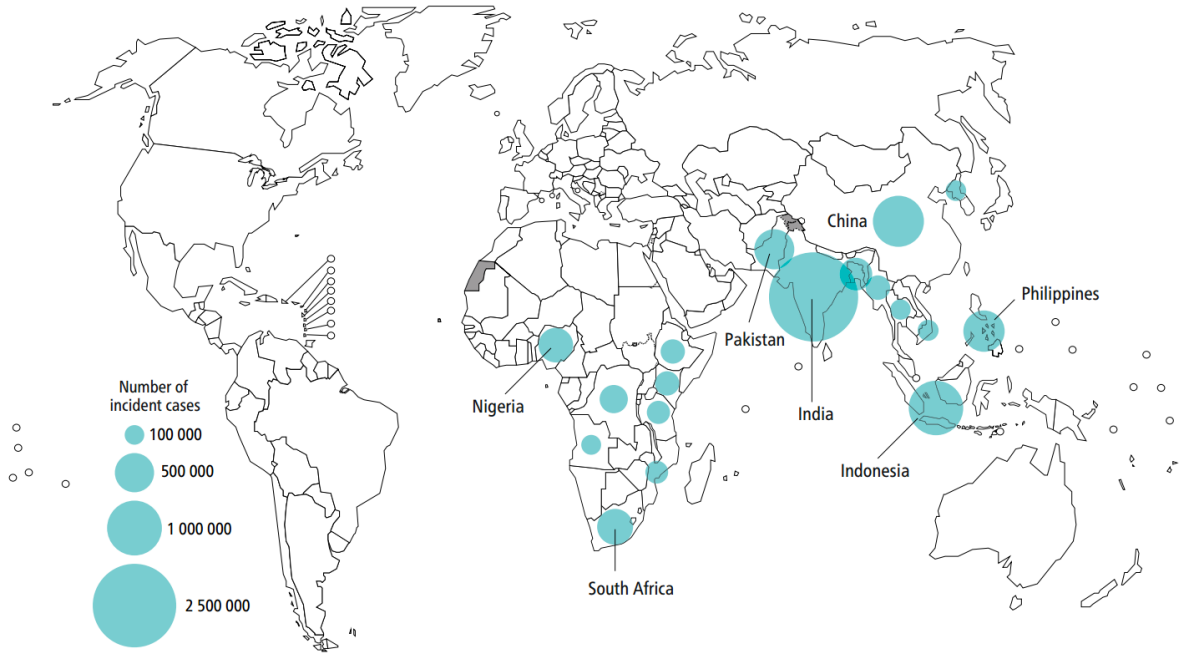


**Figure 4. Global distribution of incident cases by age and sex (female in red, male in green), notified cases are represented with dashed lines, 2016**

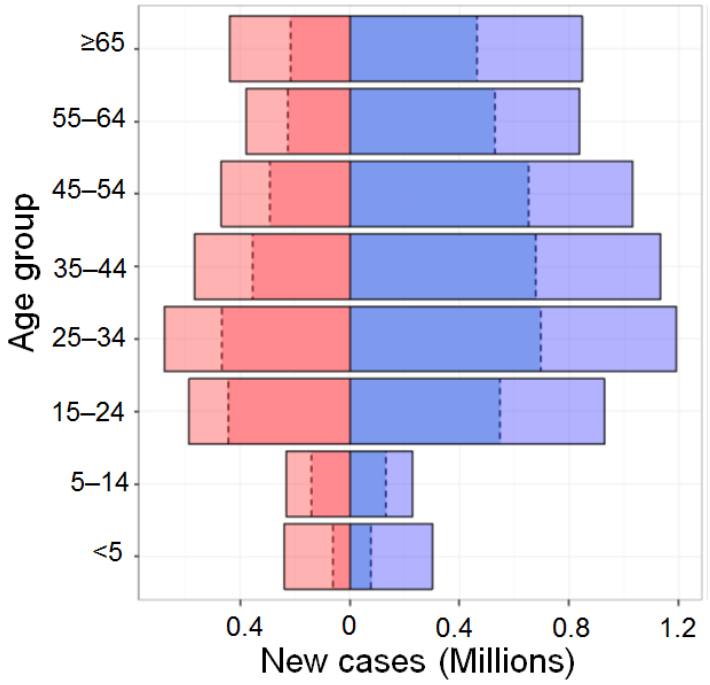
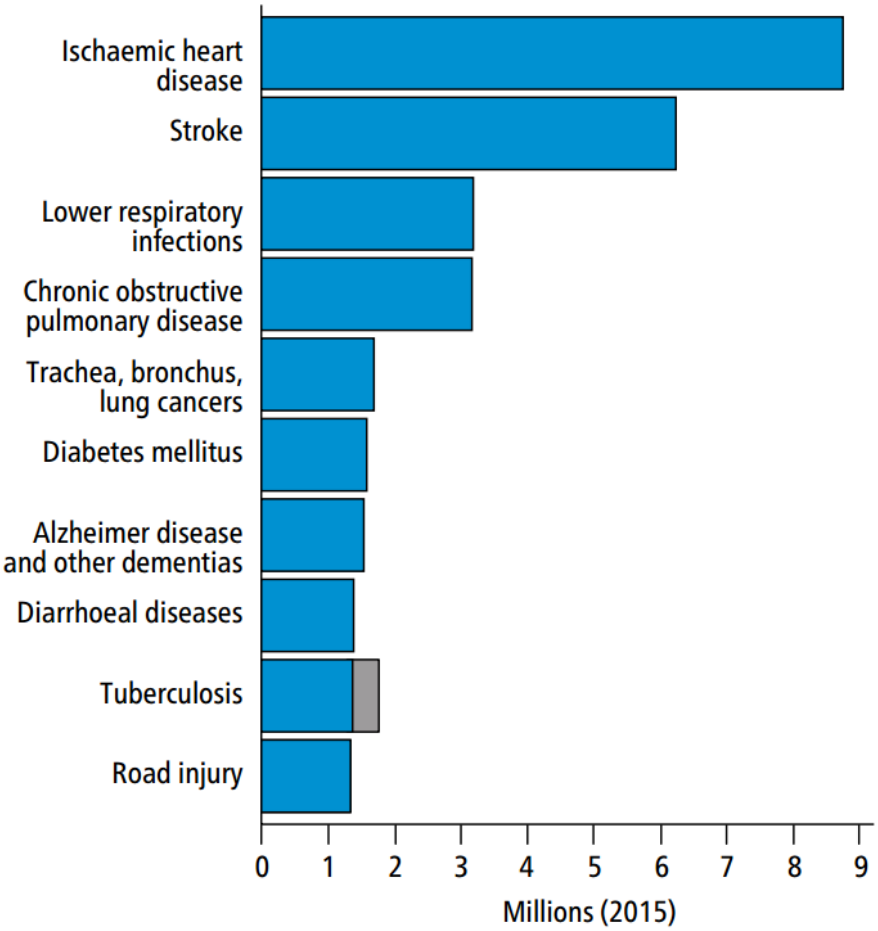


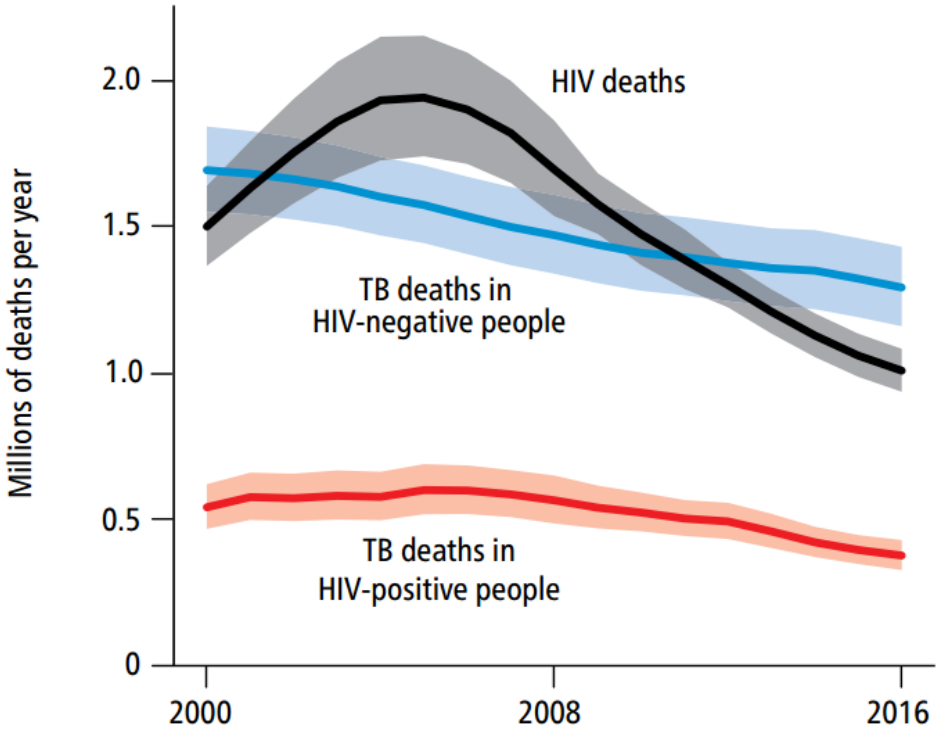
**Figure 5. Tuberculosis deaths in context**

**a) top ten causes of death in 2015 (deaths in people with HIV shown in grey).***




* This is the latest year for which estimates for all causes are currently available. See WHO Global Health Observatory data repository, available at http://apps.who.int/gho/data/node.main.GHECOD (accessed 28 August 2017).
For HIV/AIDS, the latest estimates of the number of deaths in 2016 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2017/HIV_estimates_with_uncertainty_bounds_1990-2016. For TB, the estimates for 2016 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.

**b) Trends in deaths caused by tuberculosis and HIV/AIDS, 2000–2016.*** Shaded areas represent uncertainty intervals.




* For HIV/AIDS, the latest estimates of the number of deaths in 2016 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2017/HIV_estimates_with_uncertainty_bounds_1990-2016. For TB, the estimates for 2016 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. Deaths from TB among HIV-positive people accounted for 37% of deaths classified as caused by HIV/AIDS in 2016.

**Figure 6. Estimates of the case fatality ratio, including HIV-negative and HIV-positive people, 2016**

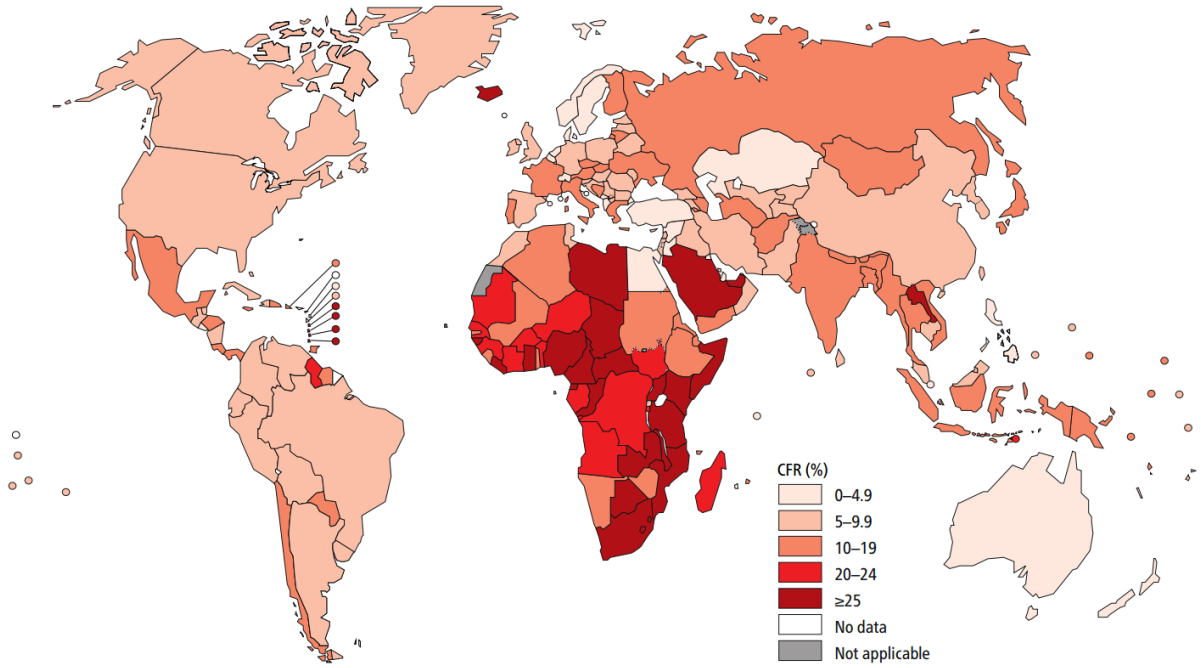
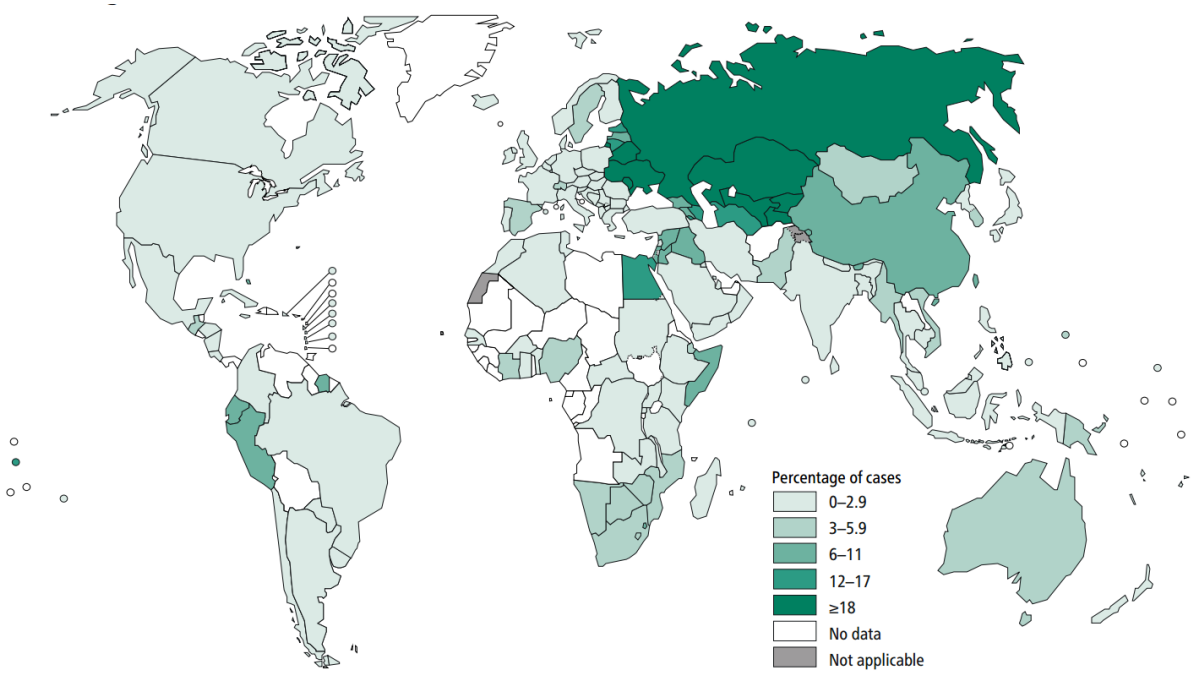


**Figure 7. The burden of drug-resistant tuberculosis in 2016**

**a) estimated percentage of new cases with rifampicin-resistant tuberculosis**




**b) Absolute numbers of incident cases, for countries with at least 1000 incident cases**

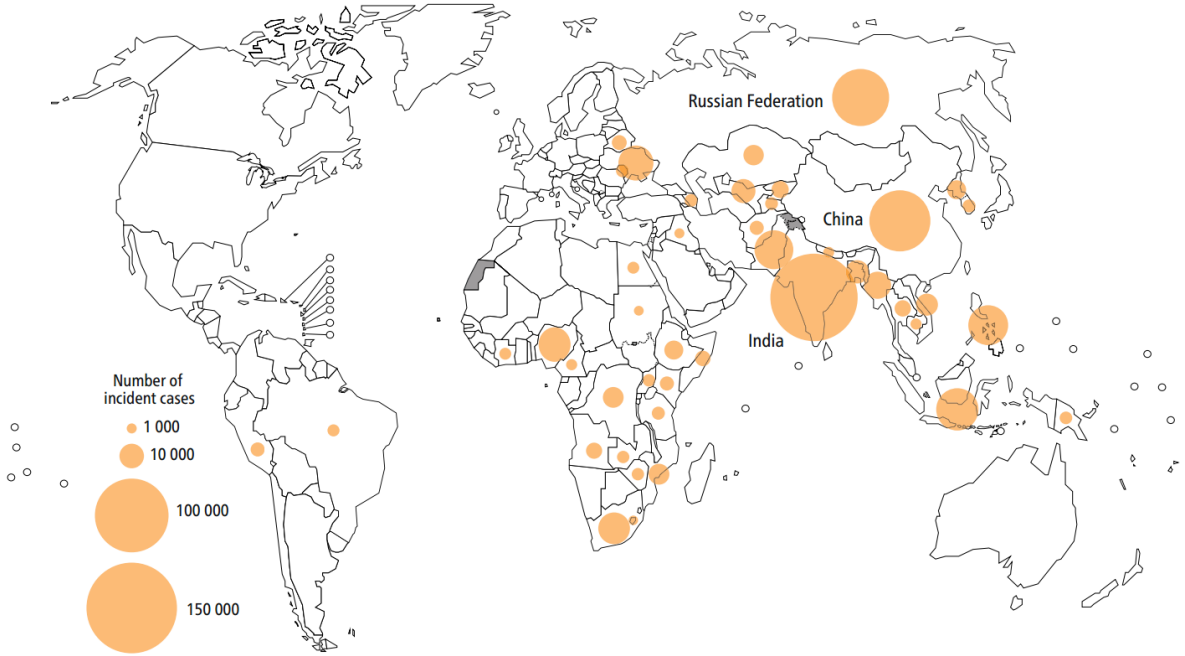


**Figure 8. Global progress in detection and treatment of drug-resistant tuberculosis, 2009–2016**

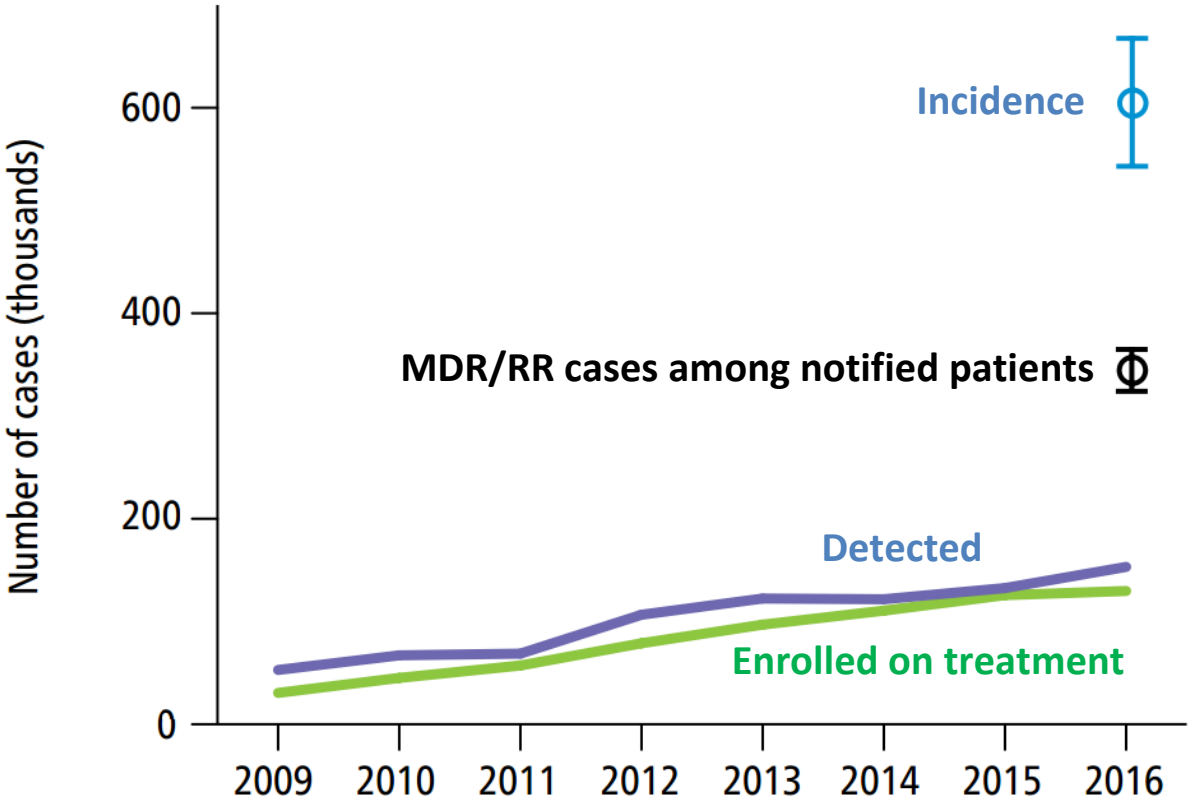



**Figure 9. Global progress in detection and treatment of HIV-associated tuberculosis, 2004–2016**

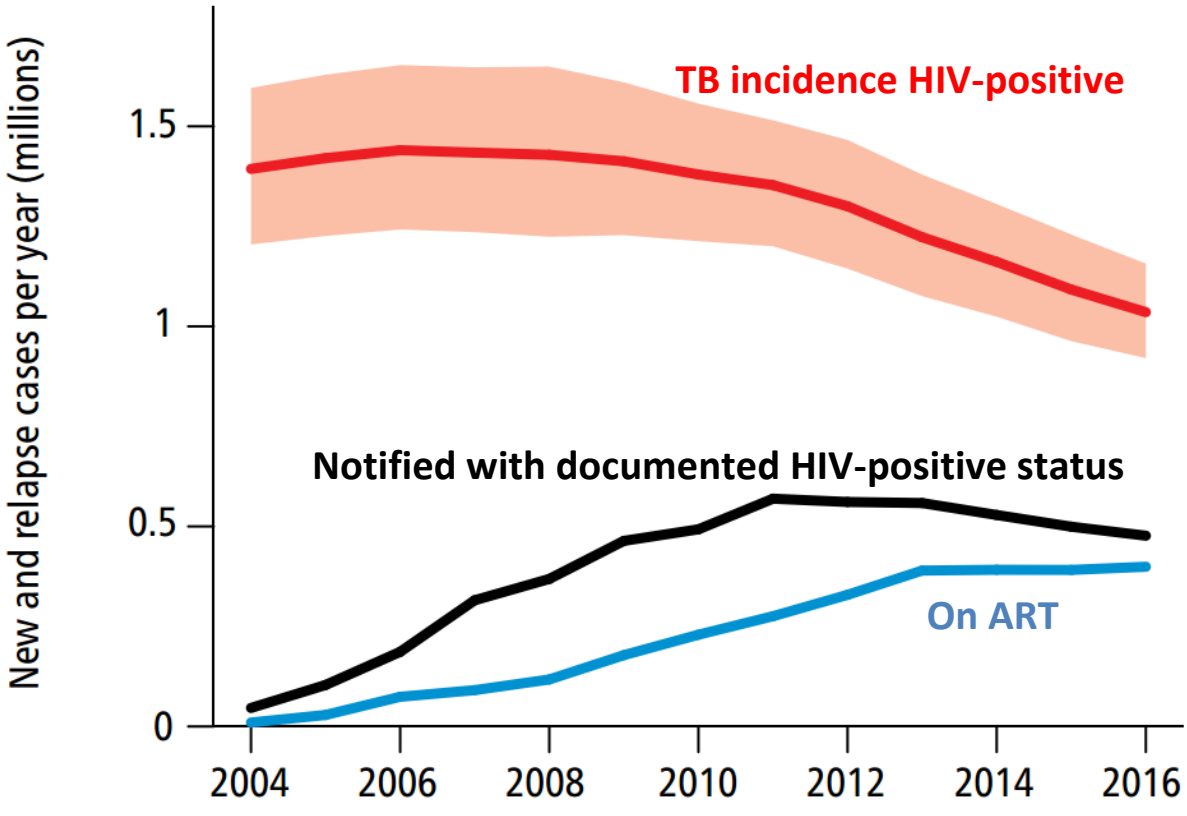
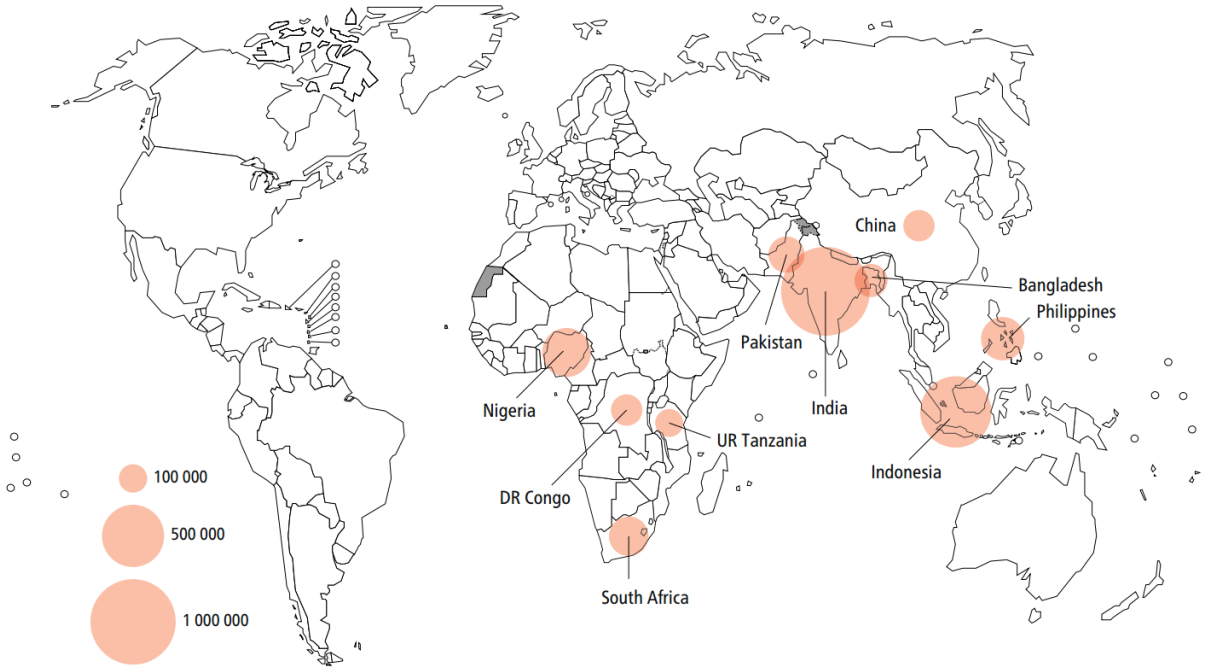


**Figure 10. Gaps in detection and treatment of tuberculosis and drug-resistant tuberculosis by country in 2016**

**a) top ten countries with the largest gap between estimated tuberculosis incidence and case notifications**




**b) top ten countries with the largest gaps between the estimated incidence of rifampicin-resistant tuberculosis and enrolments on treatment with second-line treatment regimens**

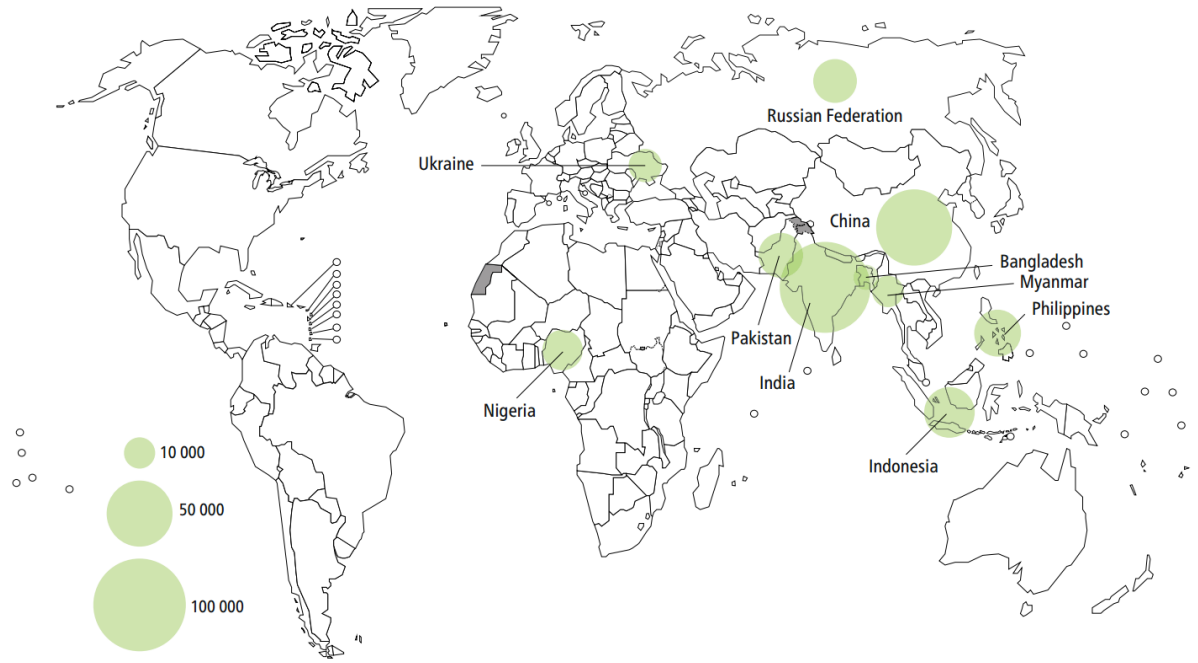
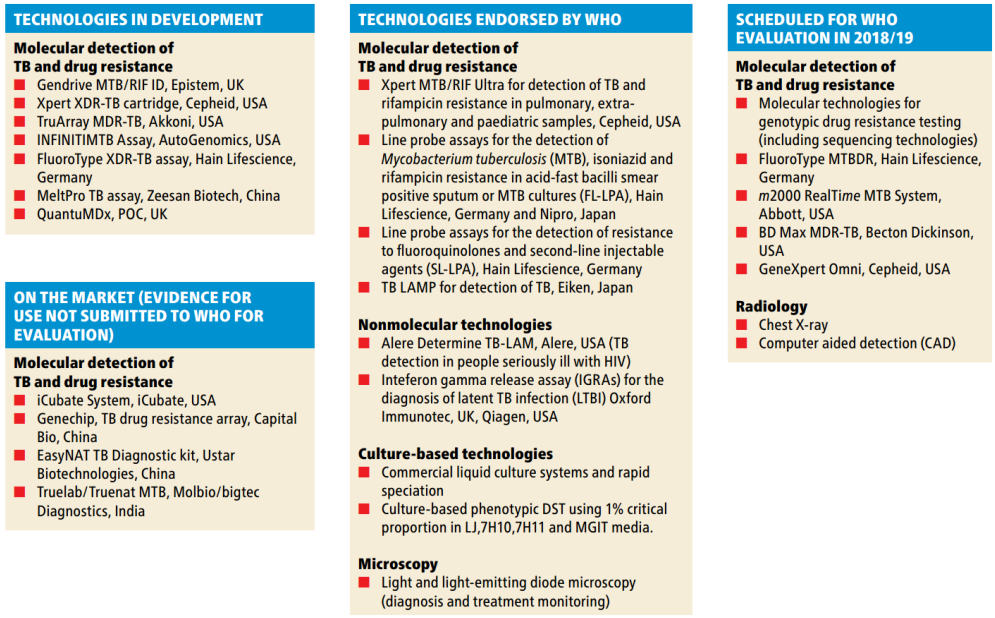


**Figure 11. Status of development of new tuberculosis diagnostics, drugs, treatment regimens and vaccines in August 2017***

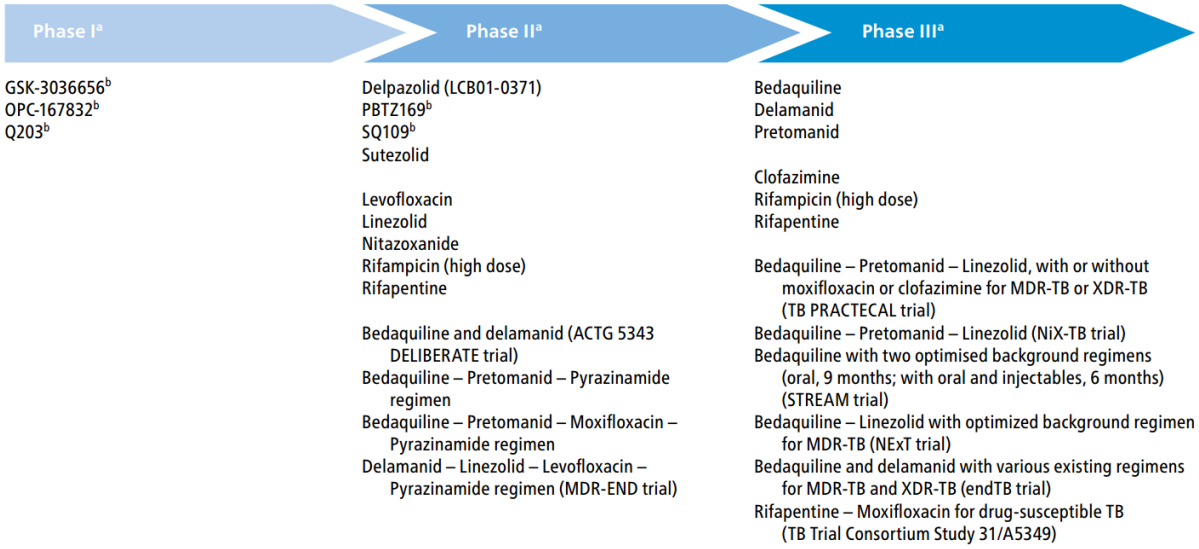
**a) Diagnostics**




* This is not an exhaustive list of technologies in development but includes all those described in the TAG Tuberculosis Diagnostics Pipeline Report 2017.

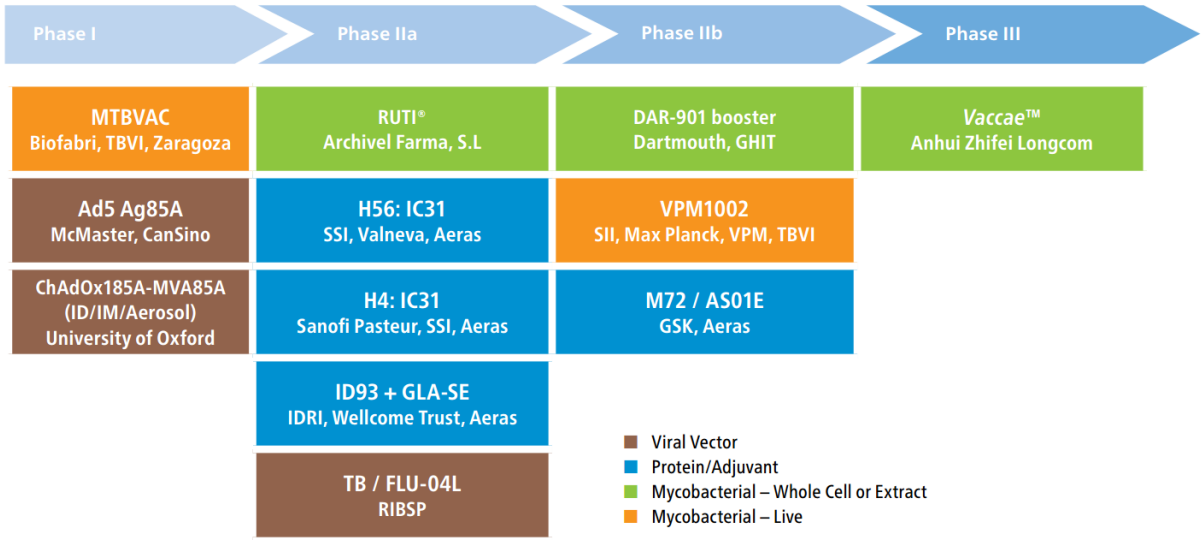
Lessem E. The Tuberculosis Diagnostic Pipeline. New York. Treatment Action Group 2016 (http://www.pipelinereport.org/sites/default/fles/2017-Pipeline-Report-TB-Diagnostics.pdf ).

**b) Drugs and treatment regimens**




[a] New drug compounds are listed first, followed by repurposed drugs and then by regimens.
[b] New chemical class.
Source: Adapted from the Stop TB Partnership Working Group on New TB Drugs pipeline. More information on these products and other ongoing projects can be found at http://newtbdrugs.org

**c) Vaccines***




* Information was self-reported by vaccine sponsors to WHO; the Stop TB Partnership Working Group on New TB Vaccines helped to coordinate their feedback.

**Figure 12: Status of selected SDG indicators associated with tuberculosis incidence in 30 high tuberculosis burden countries.** The bars show the population prevalence for each indicator (expressed as the percentage of the national population), for the latest year for which data are available. The data for smoking apply to those aged 15 and above.