

Tuberculosis

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Abstract | Tuberculosis (TB) is an airborne infectious disease caused by organisms of the *Mycobacterium tuberculosis* complex. Although primarily a pulmonary pathogen, *M. tuberculosis* can cause disease in almost any part of the body. Infection with *M. tuberculosis* can evolve from containment in the host, in which the bacteria are isolated within granulomas (latent TB infection), to a contagious state, in which the patient will show symptoms that can include cough, fever, night sweats and weight loss. Only active pulmonary TB is contagious. In many low-income and middle-income countries, TB continues to be a major cause of morbidity and mortality, and drug-resistant TB is a major concern in many settings. Although several new TB diagnostics have been developed, including rapid molecular tests, there is a need for simpler point-of-care tests. Treatment usually requires a prolonged course of multiple antimicrobials, stimulating efforts to develop shorter drug regimens. Although the Bacillus Calmette–Guérin (BCG) vaccine is used worldwide, mainly to prevent life-threatening TB in infants and young children, it has been ineffective in controlling the global TB epidemic. Thus, efforts are underway to develop newer vaccines with improved efficacy. New tools as well as improved programme implementation and financing are necessary to end the global TB epidemic by 2035.

In 1882, Robert Koch discovered the causative agent of tuberculosis (TB), an airborne infectious disease caused by organisms of the *Mycobacterium tuberculosis* complex. In 2016, TB continues to be a major cause of morbidity and mortality, primarily in low-income and middle-income countries¹.

Although primarily a pulmonary pathogen, *M. tuberculosis* can cause disease throughout the body. Furthermore, TB can present as a dynamic spectrum, from asymptomatic infection to a life-threatening disease^{2,3} (FIG. 1). From a clinical and public health perspective, patients with TB are pragmatically classified as having latent TB infection (LTBI), which is an asymptomatic and non-transmissible state, or active TB disease, which is transmissible (in active pulmonary TB) and for which culture-based or molecular diagnostics can be used. Patients with active TB disease experience general symptoms, such as fever, fatigue, lack of appetite and weight loss, and those with pulmonary disease can have persistent cough and haemoptysis (coughing up blood) in advanced disease. However, some patients with active, culture-positive disease may be asymptomatic and are best described as having subclinical TB^{2,3} (FIG. 1).

Standard treatment for TB comprises four first-line antimicrobials: isoniazid, rifampicin, pyrazinamide and ethambutol. Resistance to all drugs can occur. Indeed, multidrug-resistant TB (MDR-TB) — defined

as *M. tuberculosis* resistant to at least isoniazid and rifampicin — is a well-recognized entity that has been reported in virtually all countries¹. Extensively drug-resistant TB disease, which causes even more severe disease manifestations, is not only resistant to isoniazid and rifampicin but also to any fluoroquinolone and any of the three injectable second-line aminoglycosides. Diagnostic and therapeutic options vary for LTBI and active TB disease, and for drug-sensitive and drug-resistant TB disease.

In this Primer, we discuss the epidemiology, microbiology, immunology, pathogenesis, diagnosis, treatment and prevention of *M. tuberculosis* infection and TB, including drug-resistant TB, childhood TB and HIV-associated TB. We also review the pipeline of novel diagnostics, vaccines and drugs, provide an overview of the End TB Strategy and summarize key research priorities.

Epidemiology

According to the WHO, in 2014, an estimated 9.6 million people developed active TB disease, of whom 1.5 million died¹. The burden of TB is heterogeneously distributed (FIG. 2). For example, TB incidence is >250-fold higher in South Africa (834 cases per 100,000 population per year) than in the United States (3 cases per 100,000 population per year)¹. Rates of developing

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active TB disease are very high in exposed infants, but much lower in children 2–10 years of age; risk then rises during adolescence and plateaus around 25 years of age, remaining high throughout adult life⁴. The incidence of active TB disease is approximately twofold higher in men than in women⁵, and approximately 10% of all new cases worldwide occur in children⁶.

Among major known risk factors for TB, HIV infection is the strongest⁷; 12% of all new active TB disease cases and 25% of all TB-related deaths occur in HIV-positive individuals. The majority (75%) of HIV-associated active TB disease cases and deaths occur in Africa⁸. Indeed, a systematic review showed that active TB disease was the leading cause of hospitalization among HIV-infected adults (18%) and children (10%)⁹. TB-related in-hospital mortality was 25% among adults and 30% among children with HIV infection⁹. Nevertheless, as HIV-positive individuals make up only 0.5% of the world's population, other risk factors are responsible for the remaining fraction of TB cases in the general population. For example, with all due limitations of such analyses, including the need to assume a causal relationship and lack of precision, an estimated 27% of TB cases worldwide are attributable to undernutrition and 22% to indoor air pollution¹⁰. Other risk factors for TB include type 2 diabetes mellitus¹¹, excessive alcohol use¹² (both of which roughly triple the risk of TB) and smoking (which doubles the risk)¹³. Thus, addressing these social and behavioural determinants could help to expand the current biomedical paradigm for TB control¹⁰.

The natural history of TB is defined by its airborne route of transmission and the diversity of its clinical manifestations (FIG. 1). Compared with infectious agents such as measles virus and varicella zoster virus, *M. tuberculosis* is not highly infectious (an average infectious individual might infect 3–10 people per year¹⁴, of whom only a minority will progress to active TB disease). However, among those with active TB disease, the average duration of infectiousness — as inferred from the incidence to prevalence ratio — is >1 year in many high-burden settings¹⁵. TB is also frequently fatal; in the absence of treatment, approximately 50% of individuals who develop active TB disease will succumb to it¹⁶.

Between 5% and 15% of individuals infected with *M. tuberculosis* will progress (over months to a few years) to active TB disease¹⁷, whereas the remainder retain a persistent risk of developing active TB disease

throughout their lifetime¹⁸. In many settings, up to 50% of all people with culture-positive active TB disease do not have a prolonged productive (phlegm or mucus-producing) cough, and at least 25% have no symptoms whatsoever¹⁹. Thus, the progression from LTBI to active TB disease can be clinically subtle, despite the fact that individuals with subclinical TB can transmit the organism to others²⁰.

Trends in the epidemiology of TB reveal marked disparities. From 1900 to 1980, TB-related deaths in western Europe and the United States fell by >100-fold²¹. As much of this decline occurred before the discovery of effective anti-TB drugs, it is generally thought that much of this decrease resulted from general improvements in hygiene and socioeconomic conditions. However, progress in most high-burden settings has been much slower. The current worldwide rate of decline in incidence is only about 1.5% per year¹. More-rapid progress has been seen in certain areas; for example, China halved its prevalence of active TB disease and reduced TB-related mortality by an estimated 80% over a period of 20 years (1990–2010)²². By contrast, the incidence of active TB disease increased during the same time period in Africa, primarily because of the effect of the HIV epidemic¹. Treatments for TB saved an estimated >43 million lives between 2000 and 2014; nevertheless, the WHO estimates that over one-third of all individuals who develop active TB disease are never diagnosed or notified to public health authorities, based on the difference between estimated and notified cases — these 'missing 3.6 million' constitute a major challenge in ongoing efforts to control TB¹.

The emergence of drug resistance is a major concern, and its distribution is particularly heterogeneous. Globally, the prevalence of MDR-TB is estimated at 5% (3.5% in new cases of active TB disease and 20.5% in previously treated cases), but this prevalence varies from approximately 1% in many countries in sub-Saharan Africa, western Europe and North America to >20% in areas of the former Soviet Union, such as Azerbaijan, Belarus, Kyrgyzstan and Moldova²³. Of particular concern in recent years has been the problem of drug-resistant TB in China (where one-quarter of all active TB disease cases are resistant to either isoniazid or rifampicin)²⁴ and India (which has witnessed the emergence of so-called totally drug-resistant strains)²⁵. Within individual countries, the prevalence of MDR-TB can vary by a factor of ≥ 10 (REF. 26) at the sub-district level; within cities, the per-capita incidence of MDR-TB can vary almost 100-fold²⁷ from one health centre to the next. Most cases of MDR-TB are estimated to reflect transmission rather than initial acquisition²⁸. Thus, a high priority for the response to drug-resistant TB is to identify and target 'hotspots' of MDR-TB transmission²⁹.

Mechanisms/pathophysiology

Microbiology

Ongoing transmission of *M. tuberculosis* infection³⁰ and LTBI reactivation³¹ are globally responsible for TB disease. The majority of TB cases are attributed to *M. tuberculosis* (*sensu stricto*) or the closely related organism

Mycobacterium africanum; a minority of cases are due to zoonotic members of the *M. tuberculosis* complex, such as *Mycobacterium bovis* or *Mycobacterium caprae*³². *M. tuberculosis* has no known environmental reservoir; humans are its only known reservoir³³. Thus, *M. tuberculosis* is both a pathogen and a symbiont, which has implications for our understanding of host–pathogen interactions.

Host–pathogen interactions. Genomic studies have shown substantial genetic variability among isolates from around the world (several thousand single-nucleotide polymorphisms across a genome of 4.4 million base pairs), which reflects either accumulated genetic drift associated with patterns of human migration or variable pathogenicity of different lineages³⁴. It has been proposed that hypervirulent strains exist, based on epidemiological studies. If true, genomic study of such strains could uncover lineage-specific virulence factors³⁵ that can ultimately be used to prioritize patient care and infection control decisions. Although several attributes of *M. tuberculosis*, including increased transmissibility in

humans, drug resistance and mortality in an experimental model³⁴, have been linked with specific strains, findings were inconsistent between studies, challenging their immediate translation into clinical care. Furthermore, the interactions between host and *M. tuberculosis* are complex. Thus, studying *M. tuberculosis* virulence factors in the absence of host determinants of susceptibility can obscure synergistic interactions. For instance, a specific host–pathogen interaction might explain why strains of the East-Asian lineage are highly infective and pathogenic in Asian populations³⁶ but have a normal clinical and epidemiological presentation when imported into Canada³⁷ or Switzerland³⁸. Conversely, strains that are otherwise unremarkable, according to genomic and laboratory characterization, can be associated with outbreaks given the appropriate social and epidemiological setting³⁹.

Virulence. Given that the risk of progression from LTBI to active TB disease is many orders of magnitude higher than the risk of developing disease from the live vaccine

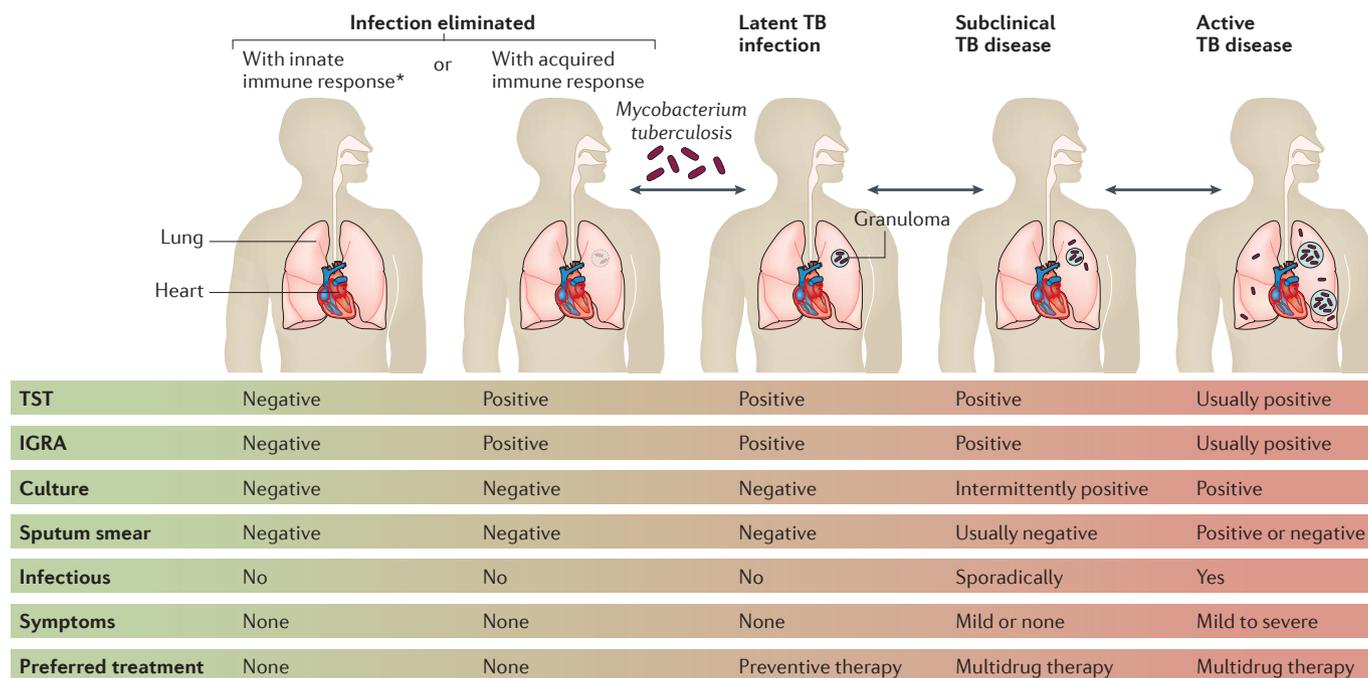


Figure 1 | The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease. Although tuberculosis (TB) disease can be viewed as a dynamic continuum from *Mycobacterium tuberculosis* infection to active infectious disease, patients are categorized as having either latent TB infection (LTBI) or active TB disease for simplicity in clinical and public health settings. Individuals can advance or reverse positions, depending on changes in host immunity and comorbidities. Exposure to *M. tuberculosis* can result in the elimination of the pathogen, either because of innate immune responses or because of acquired T cell immunity. Individuals who have eliminated the infection via innate immune responses or acquired immune response without T cell priming or memory (denoted by *) can have negative tuberculin skin test (TST) or interferon- γ release assay (IGRA) results. Some individuals will eliminate the pathogen, but retain a strong memory T cell response and will be positive on the TST or the IGRA. These individuals will not benefit from LTBI treatment. If the pathogen is not eliminated, bacteria persist in a

quiescent or latent state that can be detected as positive TST or IGRA results; these tests elicit T cell responses against *M. tuberculosis* antigens. These patients would benefit from receiving one of the recommended LTBI preventive therapy regimens (mostly 6–9 months of isoniazid). Patients with subclinical TB might not report symptoms, but will be culture-positive (but generally smear-negative because of the low bacillary load). Patients with active TB disease experience symptoms such as cough, fever and weight loss, and the diagnosis can usually be confirmed with sputum smear, culture and molecular tests. Patients with active TB disease might sometimes be negative on the TST or the IGRA because of anergy that is induced by the disease itself or immune suppression caused by comorbid conditions, such as HIV infection or malnutrition. Individuals with subclinical or active TB disease should receive one of the recommended treatment regimens for active TB disease, which consist of an intensive phase with four drugs, followed by a longer continuation phase with two drugs.

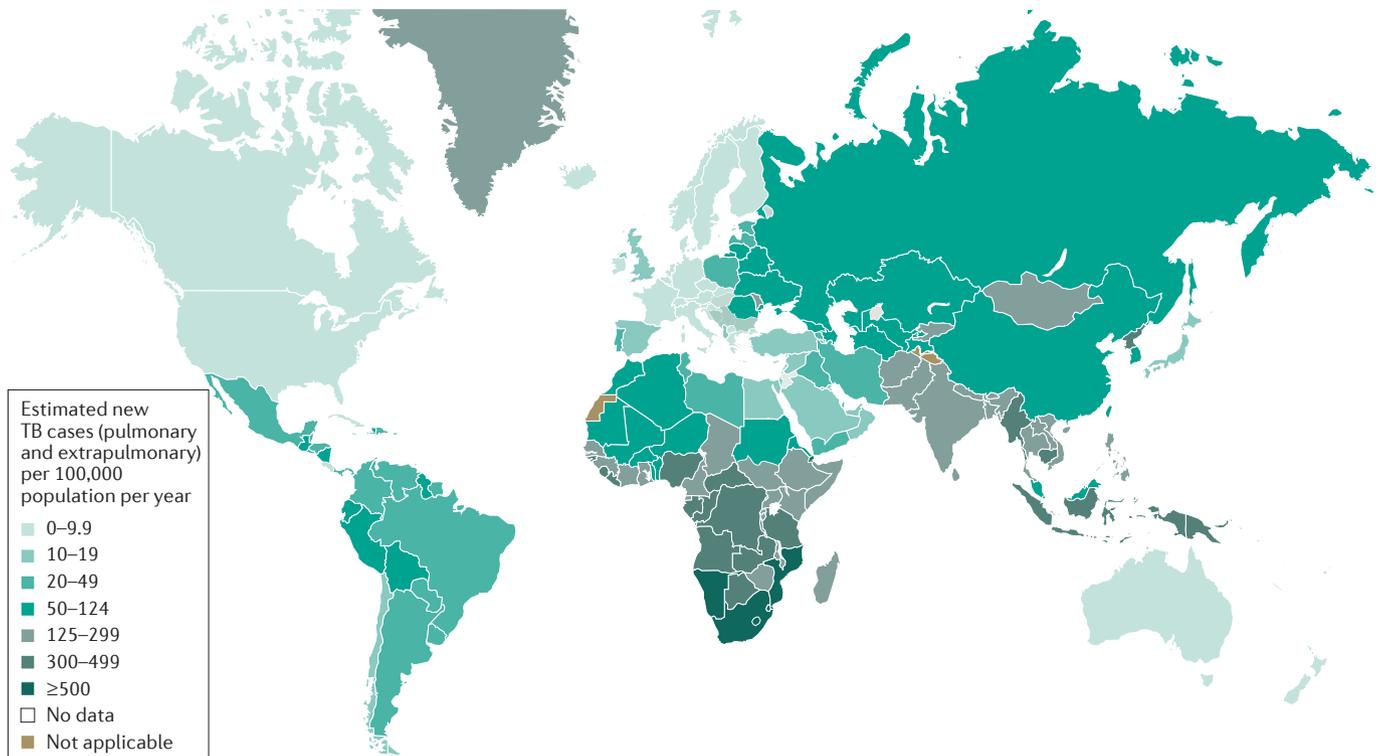


Figure 2 | **Global incidence of active TB disease (pulmonary and extrapulmonary).** High-income countries — including most countries in western Europe, Canada, the United States, Australia and New Zealand — have the lowest rates of active tuberculosis (TB) disease, typically <10 cases per 100,000 population per year. By contrast, lower-income countries have higher rates of TB. The data to base these estimates were acquired by a combination of case notifications with expert opinion, prevalence surveys, case notifications with standard adjustment and capture–recapture methodologies. Reprinted from Global Tuberculosis Report 2015, 20th edition, World Health Organization, 18, figure 2.6, Copyright (2015).

strain, *M. bovis* Bacillus Calmette–Guérin (BCG), it follows that genomic differences between *M. tuberculosis* and BCG can be used to search for the basis of attenuated virulence⁴⁰. Indeed, genomic comparisons uncovered several differences, most notably the region of difference 1 (RD1)^{40–42}, that help to explain why the vaccine can be given to millions of newborn infants each year with a low risk of progression to disease.

RD1 contains genes that encode a bacterial secretion system, known as the ESX-1 secretion system⁴³. Once the bacteria have been internalized in a phagosome by the host macrophages, the ESX-1 secretion system mediates the delivery of bacterial products into the macrophage cytoplasm (see below)⁴⁴. On a translational level, the absence of RD1 in the BCG strains enabled the development of immunological assays to distinguish the host response to *M. tuberculosis* infection from the response caused by the BCG vaccine (BCG-osis)⁴⁵. Because many non-tuberculous mycobacteria also lack RD1, these assays also help to distinguish infection with *M. tuberculosis* from infection by commonly encountered environmental mycobacteria, such as *Mycobacterium avium*⁴⁵.

Although the ESX-1 secretion system plays a major part in the pathogenesis of active TB disease, the demonstration that ESX-1 antigens are conserved in a few non-tuberculous mycobacteria⁴⁶ (for example, *Mycobacterium kansasii* and *Mycobacterium marinum*)

has prompted a reconsideration of the primacy of ESX-1 in *M. tuberculosis* virulence. That is, ESX-1 is thought to be necessary, but not solely responsible, for the full virulence of *M. tuberculosis*⁴⁷. A better understanding of what sets *M. tuberculosis* apart from other mycobacteria might provide insights into the pathogenic mechanisms of active TB disease and targets for new diagnostics and vaccines.

LTBI

Exposure to *M. tuberculosis* leads to two broad outcomes: elimination or persistence of the pathogen. In the first case, the pathogen is eliminated either because of innate immune responses (in this case, tuberculin skin tests (TSTs) or interferon- γ (IFN γ) release assays (IGRAs) might be negative) or because of adaptive immune responses (in which case, TSTs and IGRAs might be positive or negative, depending on whether memory T cell responses have been primed)^{2,3} (FIG. 1). Regardless of how the pathogen is eliminated, this individual will not benefit from LTBI therapy. It has long been recognized that, even among close household contacts of patients with TB, nearly half of exposed individuals have negative TST results⁴⁸. The finding that there is a genetic predisposition to remaining persistently TST negative despite ample exposure provides one potential explanation for why some people are naturally resistant to TB⁴⁹.

However, if *M. tuberculosis* infection is not eliminated, the pathogen can persist in a quiescent or latent state and, typically, the individual will develop positive TST and IGRA results (but no symptoms). This individual would probably benefit from LTBI therapy. Unfortunately, a positive TST or IGRA result does not automatically imply LTBI, as individuals who eliminate the infection successfully might still be TST or IGRA positive because of memory T cell responses^{2,3}. This finding partly explains the low predictive (prognostic) value of TSTs and IGRAs⁵⁰.

Immunology. Our understanding of the early phase of *M. tuberculosis* infection in humans is very limited, but experimental studies in small mammals (such as mice, guinea pigs and rabbits) and non-human primates have substantially helped to identify the importance of early events during primary infection⁵¹. The route of entry of *M. tuberculosis* is via the respiratory tract; following

inhalation, *M. tuberculosis* is translocated to the lower respiratory tract, where it encounters alveolar macrophages, which are the dominant cell type that *M. tuberculosis* infects (FIG. 3). These cells internalize the bacteria by receptor-mediated phagocytosis, with numerous different receptors contributing to this process. This process had long been studied without taking into account the microenvironment that is present in the alveolus. Surfactants, which are abundant in the fluid that lines the epithelium, might have an important role in this initial host–pathogen interaction⁵². For example, surfactant protein D can prevent *M. tuberculosis* phagocytosis by alveolar macrophages⁵³.

Once internalized, *M. tuberculosis* actively blocks phagosome fusion with the lysosome, ensuring its survival⁵⁴. Then, through the activity of the ESX-1 secretion system, *M. tuberculosis* can disrupt the phagosomal membrane, causing the release of bacterial products, including mycobacteria DNA, into the macrophage

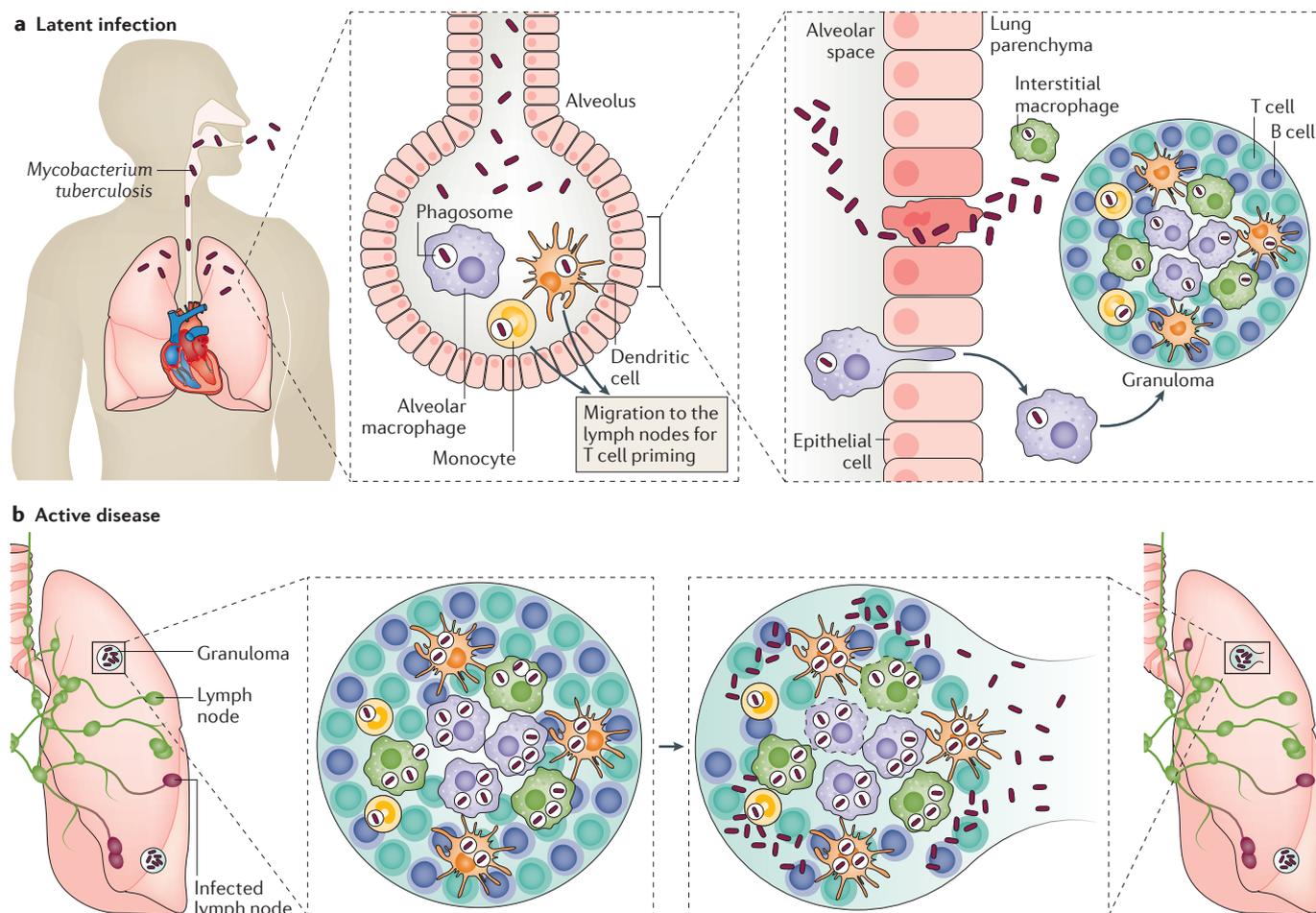


Figure 3 | *Mycobacterium tuberculosis* infection. a | Infection begins when *Mycobacterium tuberculosis* enters the lungs via inhalation, reaches the alveolar space and encounters the resident alveolar macrophages. If this first line of defence fails to eliminate the bacteria, *M. tuberculosis* invades the lung interstitial tissue, either by the bacteria directly infecting the alveolar epithelium or the infected alveolar macrophages migrating to the lung parenchyma. Subsequently, either dendritic cells or inflammatory monocytes transport *M. tuberculosis* to pulmonary lymph nodes for T cell

priming. This event leads to the recruitment of immune cells, including T cells and B cells, to the lung parenchyma to form a granuloma. **b** | The bacteria replicate within the growing granuloma. If the bacterial load becomes too great, the granuloma will fail to contain the infection⁷⁵ and bacteria will disseminate eventually to other organs, including the brain. At this phase, the bacteria can enter the bloodstream or re-enter the respiratory tract to be released — the infected host is now infectious, symptomatic and is said to have active TB disease.

cytosol; a few bacteria might also be found in the cytosol in the ensuing days^{55,56}. The advantages of delivering bacterial products into the cytosol are an active area of investigation^{57,58}; one possibility is that the activation of the cytosolic surveillance pathway, resulting in the induction of a type I IFN response, can promote the growth of intracellular bacterial pathogens, such as *M. tuberculosis*^{59–63}. Furthermore, experimental studies have shown that the type of cell death (apoptosis versus necrosis) experienced by infected macrophages is crucial, not only for the innate response to infection but also for the ensuing adaptive immune response^{64–66}. In addition, studies suggest that the ontogeny of macrophages markedly affects the function and fate of these cells^{67,68}. Further investigation is required to determine the importance of residential alveolar macrophages versus bone marrow-derived macrophages that are recruited to the lung in the outcome of *M. tuberculosis* infection.

After infecting the alveolar macrophages in the airways, *M. tuberculosis* gains access to the lung interstitium, where the process of infection evolves. However, how *M. tuberculosis* accesses the parenchyma is unknown. There are two possible mechanisms: one involving *M. tuberculosis* directly infecting epithelial cells and the second transmigration of *M. tuberculosis*-infected macrophages across the epithelium (FIG. 3). Regardless of the route, *M. tuberculosis* accesses the parenchyma, which leads to the recruitment of an increasing number of cells to the site of infection, generating a multicellular host response called a granuloma.

As the primary infection is established, either infected dendritic cells⁶⁹ or inflammatory monocytes⁷⁰ transport *M. tuberculosis* to pulmonary lymph nodes for T cell priming. *M. tuberculosis* has been shown to actively delay initial T cell priming as well as T cell trafficking into the lung^{69,71}. HIV infection substantially reduces the number of CD4⁺ T cells and is, therefore, a risk factor for progression from *M. tuberculosis* infection to active TB disease. However, some studies indicate that the risk of active TB disease is enhanced during the early stage of HIV infection — when the number of CD4⁺ T cells is normal — suggesting that other, T cell-independent immune responses are also impaired⁷². In addition, for the purposes of vaccination, it is unclear whether enhanced T cell responses provide better protection. In fact, studies in an experimental mouse model of TB have shown that increasing the total CD4⁺ T cell responses in a programmed death 1 (PD1)-dependent manner led to reduced protection and enhanced mortality^{73,74}. Thus, understanding the regulatory mechanisms involved in immunity to TB is fundamental for generating a strong host defence that hinders bacterial growth while maintaining host tolerance.

The granuloma. An important research priority is decoding the underlying mechanisms that are involved in the initiation and maintenance of the granulomas, as they are involved in both the control of the infection and, in some cases, the persistence of the pathogen⁷⁵. The granuloma illustrates the duality of *M. tuberculosis*

infection: from the host's perspective, the granuloma is a bacterial 'prison' with the potential to 'wall off' infection from the rest of the body; however, from the bacterial perspective, it is a growing collection of phagocytic cells to infect and replicate within. For instance, *M. tuberculosis* ESX-1 secretion system can initiate a type I IFN response, which has been directly linked to the recruitment to the nascent granuloma of a unique myeloid population (CD11b⁺F4/80⁺Gr1^{int}) that is highly permissive to *M. tuberculosis* infection⁷⁶. Interestingly, a study has demonstrated that immune responses are geographically segregated around the granuloma, with its centre containing pro-inflammatory components, whereas the surrounding tissue has anti-inflammatory ones⁷⁷. It has also been proposed that the granuloma might have a maximal bacterial burden (or carrying capacity), beyond which the infection will continue to progress⁷⁵. If the granuloma contains the infection without inducing substantial tissue pathology, then the person has LTBI and could be a candidate for preventive treatment (see below).

Progression to active TB disease

In most individuals with LTBI, the combination of macrophages, dendritic cells and T cells is sufficient to maintain a controlled, asymptomatic infection. However, in a subset of hosts, for reasons that are not completely clear, the infection can progress to clinical disease, in as early as weeks or as long as decades. Certain natural experiments in human immunology provide clues as to the reasons why some individuals with LTBI are unable to contain the infection and progress to active TB disease.

From a bacteriological vantage, it seems that an important contributor to the progression to disease is presenting intact antigenic proteins. Genomic studies of clinical isolates have shown that *M. tuberculosis* genes that are predicted to be involved in the production of immunodominant CD4⁺ T cell antigens do not vary across strains and lineages, suggesting the possibility that *M. tuberculosis* might benefit from antigen-specific CD4⁺ T cell activation in humans⁷⁸. This hypothesis derives further indirect support from the HIV-TB syndemic; although HIV is clearly a risk factor for progression from LTBI to active TB disease in an individual, HIV/AIDS is negatively associated with contagion⁷⁹. The importance of immunodominant antigens extends beyond understanding the pathogenesis of disease to the translational goal of defining a strategy for vaccination. Traditionally, identification of immunodominant *M. tuberculosis* antigens for generating a repertoire of *M. tuberculosis*-specific T cells was considered the foundation for T cell-mediated protective immunity and, therefore, an effective vaccine-based strategy. However, despite inducing a modest level of enhanced T cell-mediated responses, a vaccine that was generated using an immunodominant *M. tuberculosis* antigen has failed to improve protection in a human trial⁸⁰. After nearly a century of BCG vaccination, we still do not know exactly the basis for BCG protection and to what extent this protection is mediated by CD4⁺ T cells or through innate immune pathways⁸¹.

From a host vantage, three natural epidemiological experiments have informed on the risk of active TB disease, and hence on crucial pathways in controlling infection: HIV (discussed above), tumour necrosis factor (TNF) neutralizing antibodies and inborn errors in immunity. The role of TNF in containing *M. tuberculosis* infection was experimentally demonstrated in mice in the early 1990s and confirmed in observational studies that showed an increased risk of active TB disease in patients receiving anti-TNF treatments. However, further investigation has shown that TNF mechanisms are complex. Rather than TNF simply being protective, with anti-TNF therapy being a risk factor for disease, an emerging interpretation suggests that there is an ideal set point for TNF in controlling *M. tuberculosis* infection; excessive activation worsens the existing immunopathology and insufficient activation leads to lack of immune containment^{82,83}. This model is supported by the adjunctive use of anti-inflammatory agents, such as steroids, to address the inflammatory pathology of TB in confined anatomical spaces (for example, the brain)⁸⁴.

Inborn errors in immunity can shed light on the mechanisms of the immune response to TB⁸⁵. Over 100 million infants are vaccinated with BCG each year, and only a small number develop disseminated BCG disease; thus, it has been possible to map mutations in genes encoding proteins that are crucial for mycobacterial containment. Many of these proteins are involved in the IL-12–IFN γ axis. Although these defects were originally identified in patients with disease due to BCG vaccine or non-tuberculous mycobacteria, in some cases, the identified mutations have also been linked to active TB disease⁸⁵. Several other genes have been linked to experimental TB in animal models, some of which were subsequently linked to TB and/or leprosy in human genetic studies. In conclusion, a genetic susceptibility is likely to explain in part why some people with LTBI progress to active TB disease; however, unravelling the precise immunological pathways that are crucial for control of mycobacterial infection requires further investigation⁸¹.

Mechanisms of drug resistance

TB is the infectious disease in which the phenomenon of drug resistance was first described in 1948, during the very first human trial of TB therapy⁸⁶. As each new anti-TB drug has been introduced into clinical practice, widespread emergence of resistant strains has been described, usually within a decade.

M. tuberculosis develops drug resistance through genetic mutations (there are no reports of resistance developed by the acquisition of new DNA). Although there is an ever-expanding list of genes that have been linked to resistance, allelic exchange experiments have confirmed the causality between mutation and drug resistance for only a subset of mutated genes⁸⁷. In these genes, the two major mechanisms of drug resistance are target modification (for example, a mutant bacterial RNA polymerase that eludes the action of rifampicin) or a defective enzyme that converts a pro-drug into an active drug (for example, a mutant bacterial catalase that fails to activate isoniazid).

The understanding of resistance mechanisms is hampered by limitations in both the phenotypic and the genotypic drug susceptibility tests⁸⁸. The result of phenotypic tests is dichotomous (the *M. tuberculosis* strain is either susceptible or resistant to a set drug dose), and these tests are best standardized for only some drugs (for example, isoniazid, rifampicin and ethambutol). Furthermore, genotypic drug susceptibility tests could fail to identify a mutation in a phenotypically resistant isolate. Finally, finding a mutation in a phenotypically resistant isolate using gene (or genome) sequencing does not necessarily equate to finding the causal mutation of the resistance. The observed mutation could be any of these kinds of mutations: causal, stepping-stone, compensatory or companion (that is, merely a marker of the strain circulating in that particular setting). In other words, the identified mutation might not cause drug resistance on its own. Diagnostic assays designed to detect drug resistance should be based only on causal mutation. Thus, understanding the type of the identified mutation is crucial.

To this end, several groups have begun to perform whole-genome sequencing on clinical isolates, with the short-term goal of identifying novel resistance-associated mutations and the long-term goal of developing a test that could detect resistance faster than culture-based drug susceptibility tests and replace them^{89,90}. Studies show the feasibility of this approach; however, this approach suffers from imperfect sensitivity (there are still phenotypically resistant isolates in which the causal mutation cannot be identified⁹¹) and high costs, so culture-based tests remain a cornerstone of clinical care⁹².

Diagnosis, screening and prevention

Diagnosis

The choice of a diagnostic tool for TB depends on the purpose of testing (detecting LTBI, active TB disease or drug resistance).

LTBI. Two tests are available for the identification of LTBI: the TST and the IGRA. The IGRA can also distinguish between BCG-induced and *M. tuberculosis* infection-induced positive TST responses⁴⁵.

The TST, performed using the Mantoux technique, consists of an intradermal injection of 5 tuberculin units (5 TU) of purified protein derivative (PPD) S or 2 TU of PPD RT23. In a person who has cell-mediated immunity to these antigens, a delayed-type hypersensitivity reaction will occur within 48–72 hours. Interpretation of the TST takes into account the size of induration, the pre-test probability of *M. tuberculosis* infection and the risk of developing active TB disease if the person was truly infected. A simple, web-based, interactive algorithm — the Online TST/IGRA Interpreter (www.tstin3d.com) — incorporates all these parameters and also computes the risk of serious adverse events due to LTBI treatment⁹³.

Although the TST has several advantages, particularly in low-resource settings, including low reagent and equipment costs and limited skill and laboratory requirements, it has two major limitations. First, its specificity is

compromised by late (that is, post-infancy) or repeated BCG vaccination (booster vaccinations) and, to a limited extent, by exposure to non-tuberculous mycobacteria⁹⁴. Second, it has limited predictive value⁴⁵. Most individuals with positive TST results do not progress to active TB disease. Currently, efforts are underway to develop or validate new skin tests that can replace PPD with more-specific RD1 antigens⁹⁵.

In the early 2000s, IGRAs were introduced, with the hope to replace TSTs⁹⁶. IGRAs are *in vitro* blood tests of cell-mediated immune response: they measure T cell release of IFN γ following stimulation by RD1-encoded antigens (namely, the 6kDa early secretory antigenic target and culture filtrate protein 10)^{42,97}. RD1 antigens are more specific for *M. tuberculosis* than PPD antigens because they are not encoded in the genome of any BCG vaccine strains or of most species of non-tuberculous mycobacteria (exceptions are *M. marinum*, *M. kansasii*, *Mycobacterium szulgai* and *Mycobacterium flavescens*)⁹⁸. However, like TSTs, IGRAs have poor predictive value^{45,50}.

After hundreds of research studies, it is clear that both the TST and the IGRA are acceptable but imperfect tests for LTBI^{45,95}. They have reduced sensitivity in immunocompromised patients⁴⁵ and neither test is able to accurately differentiate between LTBI and active TB disease^{45,99} nor to distinguish between new infections and re-infection events, a distinction that could be relevant in settings in which individuals who had previously received preventive therapy are at risk of becoming re-infected⁴⁵. In summary, none of the currently available LTBI tests meets the need for a highly predictive test that can help to identify the individuals who are at increased risk for the development of active TB disease and would, therefore, benefit most from LTBI therapy (preventive therapy).

Notably, because all LTBI tests have low predictive value, widespread screening of low-risk populations is counterproductive. North American occupational health programmes are an example in which repeated IGRA testing in health care workers has shown high rates of test conversions and reversions, raising concerns about test reproducibility⁴⁵. Thus, LTBI screening should be performed only if it is supported by a serious intent to follow-up with therapy if the test is positive.

Active TB disease. For detection of active TB disease, four main technologies are used: imaging techniques (chest X-rays and PET-CT), microscopy (sputum smears), culture-based methods and molecular tests. Whereas imaging tests are used for screening, active TB disease requires a microbiological diagnosis. TABLE 1 provides an overview of the various diagnostic technologies that have been reviewed and endorsed by the WHO.

Chest radiography is an established triage or screening test (FIG. 4a), and the emergence of digital radiology and computer-aided diagnostic software are important recent advances¹⁰⁰. Because X-rays lack specificity, abnormal chest X-rays need to be followed up with microbiological tests. Advanced imaging modalities are

providing new insights into the diversity of lung lesions, although they are too expensive and not recommended for routine use¹⁰¹ (FIG. 4b).

Although sputum smear microscopy has many limitations, it continues to be the most widely used active TB disease test in low-income and middle-income countries¹⁰². However, the ongoing roll-out of Xpert MTB/RIF (Cepheid Inc., Sunnyvale, California, USA), a molecular assay based on the automated GeneXpert technology (Cepheid Inc.), is measurably shifting the TB diagnostics landscape, with >17 million cartridges procured via subsidized pricing programmes since its introduction in 2010 (REFS 103,104). Owing to superior accuracy than sputum smear microscopy^{105–108}, the WHO now conditionally recommends Xpert MTB/RIF as the first-line diagnostic test in all adults or children who are suspected of having active TB disease¹⁰⁹.

Furthermore, in HIV-positive individuals, sputum smear microscopy detects only 22–43% of active TB disease¹¹⁰. Thus, the WHO strongly recommends Xpert MTB/RIF as an initial diagnostic test in these patients¹⁰⁹. In addition, the detection of lipoarabinomannan (LAM) antigen in urine has emerged as a potential point-of-care test to detect HIV-associated active TB disease, with a modest reduction in mortality in a highly selected group of hospitalized HIV-positive patients¹¹¹. A LAM rapid test is now recommended by the WHO to assist and expedite the diagnosis of active TB disease in two specific populations: in HIV-positive adult in-patients with signs and symptoms of pulmonary and/or extrapulmonary TB who have a CD4⁺ T cell count of ≤ 100 cells per μl , or HIV-positive patients who are seriously ill regardless of their CD4⁺ T cell count or with an unknown CD4⁺ T cell count¹¹².

Diagnosing paediatric TB and monitoring treatment response are challenging, as collecting respiratory specimens is difficult (young children are unable to produce sputum) and the disease might be extrapulmonary¹¹³. Children with active TB disease often present with nonspecific symptoms (for example, failure to thrive), so history of contact with an adult with active TB disease should be considered. There is no adequate gold-standard test for childhood TB, and diagnosis requires an algorithm. Sputum smear microscopy is often negative because of the low number of bacilli in children with TB. Thus, the diagnostic algorithm relies on signs, symptoms, evidence of *M. tuberculosis* infection (a positive TST or IGRA), history of contact with active TB disease and the results of chest X-ray (for example, showing hilar adenopathy), liquid culture and molecular tests (Xpert MTB/RIF). If sputum can be collected (from older children and adolescents), at least two specimens must be submitted for microscopic examination, Xpert MTB/RIF testing and culture. In young children (<7–8 years of age), two to three fasting gastric aspirates can also be collected.

A meta-analysis showed that, when used to detect active TB disease in children, Xpert MTB/RIF has a sensitivity that is 36–44% higher than sputum smear microscopy¹⁰⁸. Compared with cultures of expectorated or induced sputum samples or gastric aspirate

Table 1 | Technologies reviewed by the WHO for the diagnosis of active TB disease and the detection of drug resistance

Test	Assay principle	Use	Sensitivity (%)	Specificity (%)	TAT*	Target setting [‡]	Year endorsed	Refs
Imaging techniques								
Chest X-ray	Imaging of the lungs	Active TB disease screening	87 (using TB abnormality as a threshold)	89 (using TB abnormality as a threshold)	Same day	Secondary and tertiary centres	Included in the WHO guidelines for many years	217
Microscopy								
Conventional sputum smear microscopy	Direct visualization of mycobacteria using light microscopy	Active TB disease diagnosis	32–94	50–99	Same day	Peripheral and reference laboratories	Included in the WHO guidelines for many years	218
LED fluorescence smear microscopy [§]	Direct visualization of mycobacteria using fluorescence microscopy	Active TB disease diagnosis	52–97	94–100	Same day	Peripheral and reference laboratories	2011	218
Culture-based techniques								
Liquid culture with DST	Mycobacterial culture on liquid media	<ul style="list-style-type: none"> • Active TB disease diagnosis • Drug resistance 	<ul style="list-style-type: none"> • 89 (among smear-positive and culture-positive) • 73 (among smear-negative and culture-positive) 	>99	10–21 days	Reference laboratory	2007	219
Antigen detection techniques								
LAM lateral flow assay [§]	Antigen detection	Active TB disease diagnosis in HIV-positive individuals	<ul style="list-style-type: none"> • 44 (all) • 54 (in HIV-positive individuals) 	<ul style="list-style-type: none"> • 92 (all) • 90 (in HIV-positive individuals) 	Same day	Peripheral laboratory	2015 (conditional recommendations in selected groups)	112
Molecular techniques (nucleic acid amplification tests)								
Xpert MTB/RIF ^{§,}	NAAT (qPCR)	<ul style="list-style-type: none"> • Active TB disease diagnosis • Drug resistance (rifampicin) 	<ul style="list-style-type: none"> • 98 (smear-positive and culture-positive) • 67 (smear-negative and culture-positive) • 95 (rifampicin resistance) 	<ul style="list-style-type: none"> • 99 (smear-negative and culture-negative) • 98 (rifampicin resistance) 	Same day	District or sub-district laboratory	2010	105
First-line LPA (GenoType MTBDRplus [†] and NIPRO [†])	NAAT (LPA)	<ul style="list-style-type: none"> • Active TB disease diagnosis • Drug resistance (isoniazid and rifampicin) 	<ul style="list-style-type: none"> • 98 (rifampicin resistance) • 84 (isoniazid resistance) 	<ul style="list-style-type: none"> • 99 (rifampicin resistance) • >99 (isoniazid resistance) 	1–2 days	Reference laboratory	2008	220
Second-line LPA (GenoType MTBDRsl [†])	NAAT (LPA)	Drug resistance (fluoroquinolones and second-line injectable drugs)	<ul style="list-style-type: none"> • 86 (fluoroquinolone resistance) • 87 (second-line injectable drugs) 	<ul style="list-style-type: none"> • 98 (fluoroquinolone resistance) • 99 (second-line injectable drugs) 	1–2 days	Reference laboratory	2016	121
Loopamp Mycobacterium tuberculosis complex assay ^{§,**}	NAAT (LAMP)	Active TB disease diagnosis	76–80	97–98	Same day	Peripheral laboratory	2016	120

DST, drug susceptibility testing; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; LED, light-emitting diode; LPA, line probe assay; NAAT, nucleic acid amplification test; qPCR: quantitative PCR; TAT, turnaround time; TB, tuberculosis. *May require longer TAT owing to batching of specimens. [‡]Peripheral laboratories (basic microscopy centres) are typically located at the primary-care level. District-level laboratories are the next level of referral and have better infrastructure. The tertiary hospital or reference laboratory that offers the most sophisticated infrastructure are the highest and final level of referral. [§]Amenable to rapid 'test and treat'. ^{||}Newer versions of GeneXpert (Cepheid Inc., Sunnyvale, California, USA) instrument (OMNI) and cartridge (Xpert Ultra MTB/RIF) are currently under development and yet to be reviewed by the WHO. [†]Hain Lifescience GmbH, Nehren, Germany. ^{††}NIPRO Corporation, Osaka, Japan. ^{**}Eiken Chemical, Tokyo, Japan.

samples, Xpert MTB/RIF has a sensitivity of 62–66% and a specificity of 98%¹⁰⁸. Because Xpert MTB/RIF is superior to sputum smear microscopy, the WHO has recommended it as the preferred front-line test in children (and adults) with suspected active TB disease, TB lymphadenitis and TB meningitis¹⁰⁹. In some settings, upfront testing with Xpert MTB/RIF has also helped to identify substantially larger numbers of children with MDR-TB¹¹⁴.

Drug resistance. For the detection of drug resistance, there are phenotypic, culture-based (that is, testing the ability of bacteria to grow in the presence of anti-TB drugs) and molecular-based (based on the detection of genetic mutations in *M. tuberculosis* that confer drug resistance) methods (TABLE 1). In many settings, the implementation of Xpert MTB/RIF as a diagnostic tool for active TB disease has greatly increased the upfront detection of MDR-TB^{114–116}. The Xpert MTB/RIF roll-out has paved the way for universal drug susceptibility testing and has attracted new product developers to the TB field^{104,117}. However, pragmatic trials of Xpert MTB/RIF have shown that the clinical impact of this new technology might be blunted in weak health systems, with gaps in the TB care cascade^{104,118,119}. Besides Xpert MTB/RIF, the WHO has endorsed the use of loop-mediated isothermal amplification for the diagnosis of pulmonary TB¹²⁰ and molecular line probe assays for rapid drug susceptibility testing of first-line drugs (such as isoniazid and rifampicin) as well as selected second-line drugs (such as fluoroquinolones and injectable second-line drugs)^{121,122}.

New diagnostics. Given the limitations of the available diagnostics, the development of new diagnostic tools is a priority. Several diagnostic tools are in the pipeline^{117,123}. Although the pipeline seems robust at first glance, most products are designed for laboratory settings, making use of the only proven TB biomarker: bacterial nucleic acid sequences. Such molecular tests might not meet affordability and ease-of-use requirements for integration into primary care. To meet these needs, short-term, medium-term and longer-term approaches are required.

In the short term, the goal is to expand the range of molecular technologies that could replace sputum smear microscopy¹¹⁷. The decentralized deployment of such techniques in low-income countries is challenging because of technical and infrastructure issues, as the GeneXpert technology experience shows^{124–127}. However, rugged systems such as the GeneXpert OMNI system (a portable, battery-operated platform intended for peripheral microscopy centres) might help to overcome this issue. Aligned with this device, two new diagnostic test cartridges are in development: the Xpert MTB/RIF Ultra and the Xpert XDR. The Xpert MTB/RIF Ultra cartridge is expected to have a higher sensitivity than the existing Xpert MTB/RIF assay and will soon be commercialized; its use will be reviewed by the WHO in 2017. The Xpert XDR cartridge will provide information on drug resistance for additional key drugs (isoniazid, fluoroquinolones and aminoglycosides).

Besides their diagnostic application, new molecular tools can identify drug resistance mutations and help reach the post-2015 target of a universal drug susceptibility test for all individuals with active TB disease at the

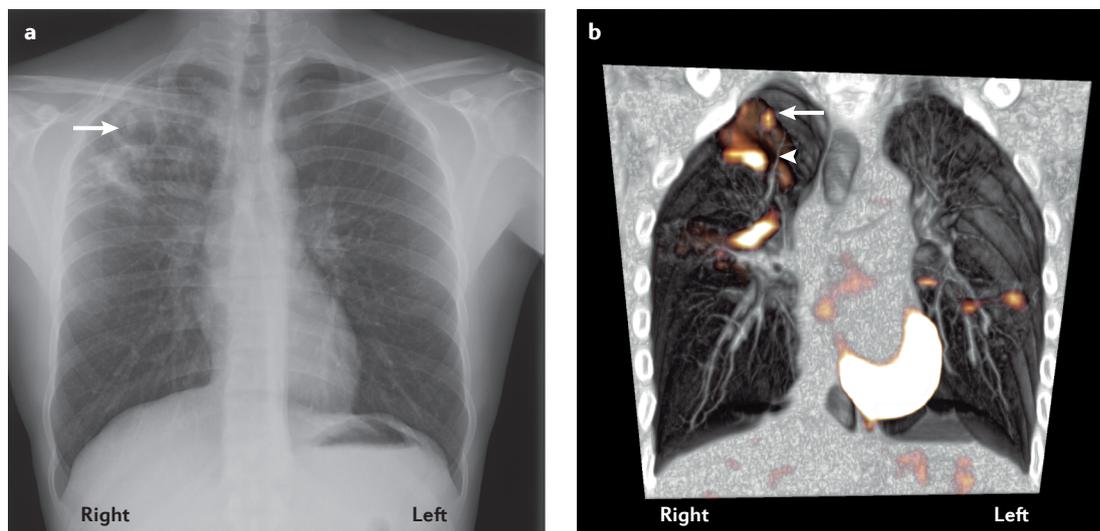


Figure 4 | Imaging tools for active TB disease. **a** | Conventional chest X-ray. The image shows typical features of active pulmonary tuberculosis (TB) disease: a large cavity in the right upper lobe of the lung (arrow) with surrounding infiltrates or consolidation (owing to inflammation and oedema). An abnormal chest X-ray is suggestive of TB, but not confirmatory. **b** | High-resolution CT scan. Three-dimensional rendering using ¹⁸F-fluorodeoxyglucose (FDG) PET-CT scan of the posterior half of the thoracic cavity of a person who was newly diagnosed with bilateral pulmonary TB. The orange colour depicts FDG uptake in regions with abnormalities with standardized uptake values ranging from 5 to 9. A 1–2 cm air-filled cavity in the right upper lobe (arrow) is embedded within an area of nodular disease with intense uptake, whereas an area of ground glass opacity located below this feature (arrowhead) shows only modest uptake of the tracer. Image in part **a** courtesy of B. Rabinovitch, Montreal Chest Institute, Montreal, Canada. Image in part **b** courtesy of C. E. Barry 3rd, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.

time of diagnosis. New forthcoming drug regimens will require adequate companion diagnostics to ensure rapid completion of the ‘test and treat’ approach¹²⁸. To this end, next-generation sequencing tools are showing great promise^{89,90}, but translational work is required to make them affordable and deployable in low-income, high-burden countries. In the medium term, the priority is to develop a rapid, low-cost, non-sputum-based test to be used at the primary-care level, where the majority of people first seek care¹¹⁷. Such a test requires the identification of a suitable biomarker signature (primarily antigens, antibodies, volatile organic compounds or enzymatic markers). Although several promising biomarkers have been identified^{129–131}, validation is ongoing and no tests are likely to be submitted for policy endorsement until 2019 (REF. 132).

In the longer term, the main goal is to identify a biomarker that can reliably predict which individuals with LTBI are at the highest risk of progressing to active TB disease, so that these individuals can receive preventive treatment and the vast LTBI ‘pool’ can be successfully reduced^{117,133}. Another goal is to develop a biomarker-based test to monitor treatment efficacy, as current molecular tests are not suitable for this purpose. The pipeline for such tests is currently weak. Increased investments are necessary to support biomarker discovery, validation and translation into clinical tools¹³³.

BCG vaccine

Globally, >90% of newborns are vaccinated annually with BCG, the only currently licensed vaccine to prevent the development of active TB disease^{134,135}. BCG policies and practices across the world are available at The BCG World Atlas (<http://www.bcgatlas.org>)¹³⁵. The BCG vaccine was first used in humans in 1921 and has been evaluated in numerous interventional trials and observational studies looking at less-common manifestations of active TB disease. In clinical trials, the efficacy of the BCG vaccine against pulmonary TB in adults has been reported to be 0–80%^{136,137}. The reasons for this observed variability in BCG vaccine efficacy are unknown. It has been noted that BCG vaccine efficacy varies with distance from the equator¹³⁶, but it is unclear whether greater efficacy at greater latitude depends on the force of exposure to selected non-tuberculous mycobacteria, to all non-tuberculous mycobacteria, to *M. tuberculosis* itself or on other, still undefined causative factors. Case–control studies in infants and children <5 years of age have found the efficacy of the BCG vaccine in protecting from severe, extrapulmonary forms of active TB disease to be between 50% and 80%¹³⁸. In children, the BCG vaccine has also been associated with protection from *M. tuberculosis* infection¹³⁷.

TB morbidity and mortality can be high in children <5 years of age, so the BCG vaccine is invaluable in preventing active TB disease in this age group. However, most cases of transmissible, pulmonary active TB disease occur in adolescents and adults, in whom the efficacy of the BCG vaccine is uncertain^{139,140}. Moreover, a meta-analysis of paediatric BCG vaccine efficacy has indicated that the duration of protection is generally up to 10 years, with vaccine efficacy waning over

time¹⁴¹. Thus, it is unlikely that the current BCG regimens substantially contribute to the control of the global TB epidemic, as in most countries, the BCG vaccine is administered once, at birth, and its protection is unlikely to extend consistently into adolescence¹³⁵.

New vaccines

Despite the variability in its efficacy, the BCG vaccine has proven that protective immunity against TB can be induced by a vaccine, even though the protective mechanism is not well elucidated. Indeed, the main goal of current vaccination research is to help prevent active TB disease from developing in the 10% of infected individuals who cannot contain the infection on their own as LTBI. Ideally, a vaccine also might prevent the establishment of *M. tuberculosis* infection entirely (for example, as measured by prevention of conversion of an IGRA). Novel trial designs can be used to assess the ability of a vaccine to achieve these goals¹⁴². To maximize the efficacy of vaccination on morbidity and mortality, transmissible active TB disease must be prevented in the populations most at risk. Because *M. tuberculosis* infection is mostly spread by adolescents and adults with active pulmonary TB disease, much of the new vaccine development focuses on vaccines that are designed for these age groups. However, as the BCG vaccine is only partially effective even in infants and not recommended for HIV-exposed infants, an improved vaccine for newborns is also desirable.

Modelling has shown that a vaccine with 60% efficacy delivered to 20% of adolescents and adults could avert 30 million cases of active TB disease in the first 20 years (a total of 35 million cases could be averted if also administered to 90% of newborns)¹⁴³. Another modelling study also concluded that vaccines targeted at adolescents and adults could have a much greater effect on the global TB burden over the 2024–2050 time horizon than vaccines targeted at infants, and that such vaccines could be relatively cost-effective¹⁴⁴.

The development of TB vaccines faces numerous challenges (BOX 1). Despite these limitations, at least 13 vaccine candidates are currently being tested clinically (TABLE 2), which are classified into three platform types: whole-cell or lysates of mycobacteria, viral vector vaccines and adjuvanted recombinant protein vaccines. The *M. tuberculosis*-specific antigenic make-up ranges from several thousand antigens in mycobacterial vaccines to four or fewer in the viral vector and recombinant protein vaccines.

Management

The WHO has estimated that 80% of all patients diagnosed with active TB disease each year are infected with *M. tuberculosis* strains that are fully susceptible to all available antibiotics and the remaining 20% with drug-resistant strains (13.3% isoniazid mono-resistant and 5.3% MDR)^{1,23}. Extrapolating from these estimates, approximately 1.9 million people developed active drug-resistant TB disease in 2014 — a major burden. Drug resistance requires longer and more-toxic treatment regimens for patients.

Box 1 | Hurdles for TB vaccine development

Many countries with a high tuberculosis (TB) burden are also confronted with the emergence and spread of drug-resistant TB. An efficacious vaccine should work equally well against drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis*, as vaccine targets are likely to be completely independent of drug targets. Thus, a new TB vaccine could help to preserve the therapeutic efficacy of TB antibiotics and overcome the crucial drug-resistance challenge. However, the development of TB vaccines has only limited support from private sector biopharmaceutical companies because of scientific and economic barriers.

Key scientific challenges include the lack of a validated, predictive animal model or correlate of protection. As a result, vaccine efficacy trials, which are costly, time-consuming and can only be carried out relatively late in development, have been the first opportunity to understand the promise of a vaccine candidate. Thus, TB vaccine development has been highly inefficient without an easy way to triage candidates early in development. Current approaches to improve efficiency focus on implementing novel pre-proof-of-concept trials that look for a meaningful biological effect, including 'prevention of (established) infection' and 'prevention of recurrence' in high-risk populations, and on optimizing and validating a non-human primate or another animal model as a safe, predictive model of the human disease^{142,215}. All designs of vaccine efficacy trials should also include sample collection, to support discovery and validation of correlates of protection²¹⁶.

Another challenge is that assessment of any candidate vaccine for infants must be compared against the licensed vaccine (Bacillus Calmette–Guérin (BCG)), which not only protects (at least partially) against TB in infants but also protects against leprosy. This increases the number of requirements for any vaccine that attempts to replace the BCG vaccine in infants.

Despite TB globally being the leading cause of death due to a single pathogen, the market is limited for TB vaccines¹⁴³. Most cases of active TB disease, even in high-income countries, occur among the poor who have limited ability to pay. This reality affects the market forecast for a new vaccine and, therefore, limits investment in TB vaccine research and development by the for-profit sector.

LTBI

In 2014, the WHO published its first comprehensive guideline on LTBI management¹⁴⁵, recommending that only selected risk groups should undergo LTBI screening¹⁴⁵: HIV-positive individuals; adults and children who had contact with patients with active pulmonary TB disease; and patients initiating anti-TNF treatment, on dialysis with end-stage renal disease, preparing for organ or haematological transplantation or with silicosis. The rationale for giving these subgroups priority is that they are at very high risk of progressing from LTBI to active TB disease, and receiving LTBI treatment could prevent it. Treatment of LTBI in individuals who have had contact with patients with active MDR-TB disease is controversial. The WHO recommends close monitoring of these individuals, preferably for at least 2 years. Clinicians could consider individually tailored treatment regimens (based on the drug susceptibility profile of the patient with active MDR-TB disease that the individual had been exposed to) when benefits would outweigh harms, particularly for children <5 years of age¹⁴⁵.

LTBI treatment regimens recommended by the WHO include 6–9 months of isoniazid, 3 months of rifapentine plus isoniazid, 3–4 months of isoniazid plus rifampicin or 3–4 months of rifampicin alone¹⁴⁵. All regimens are known to be efficacious^{8,145}, but patient compliance can be poor with the longer regimens¹⁴⁶. Rifampicin-containing regimens are shorter and might be more suitable in populations with a high prevalence

of isoniazid mono-resistant strains. Regardless of the regimen, it is important to ensure adherence and provide patients with adequate counselling.

Active drug-sensitive TB disease

The current preferred regimen (TABLE 3) for active drug-sensitive TB disease is a minimum of 6 months of therapy with rifampicin, isoniazid, pyrazinamide and ethambutol during the first 2 months (the intensive phase of treatment), followed by isoniazid and rifampicin for 4 months (the continuation phase)^{147,148}. Treatment efficacy and progress are usually monitored with repeat sputum smears, cultures and chest X-rays.

Although the standard 6-month regimen has a high success rate (approximately 86% under routine, programmatic field conditions¹; the regimen itself has higher efficacy), it also has several limitations. In part because of the long duration of the treatment, a certain proportion of patients will develop toxicity¹⁴⁹. The common adverse events are mild increases in the level of liver enzymes, skin rash, gastrointestinal intolerance, neuropathy and arthralgia and can be managed symptomatically without discontinuation of the offending drugs. Serious adverse events are severe hepatitis, immune thrombocytopenia, agranulocytosis, haemolysis, renal failure, optic neuritis and ototoxicity. Furthermore, prolonged therapy undermines patient compliance. As a result, supportive measures are necessary to ensure optimal adherence, as lack of treatment completion contributes to treatment failure, relapse and the emergence of drug resistance.

The most common adherence monitoring approach is directly observed therapy (DOT), in which every dose of treatment is directly supervised by a health professional, although the effectiveness of this measure is controversial¹⁵⁰. Although DOT continues to be valuable in many settings, various alternative methods are now being tried out to improve adherence, including mobile phone reminders, smart pill boxes, video DOT and the use of call centres to follow-up with patients. Regardless of the method, it is crucial to use a team-based, patient-centric approach that incorporates education, counselling and patient empowerment¹⁵¹.

Active drug-resistant TB disease

Early and rapid diagnosis and timely initiation of an effective regimen against active drug-resistant TB disease is essential for optimizing treatment outcomes, minimizing disease transmission and reducing further drug resistance^{152,153}. Designing an appropriate regimen is a complex task as it depends on the characteristics of the patient and the specific drug susceptibility profile of the organism^{152–154} (BOX 2).

Currently, therapies for active drug-resistant TB disease have a poor evidence base, are lengthy, use drugs of uncertain efficacy and are characterized by high toxicity (TABLE 4). Indeed, adherence rates are poor in TB endemic countries and so are the outcomes (approximately 50% treatment success for active MDR-TB disease in most TB endemic countries)¹. Furthermore, several toxicity-related parameters require close monitoring during therapy¹⁵⁵, in addition to regular medical examinations,

placing an extra burden on health care systems. On the basis of promising results of a seven-drug regimen that is being used in numerous countries, the WHO updated its treatment guidelines for active drug-resistant TB disease in May 2016. The recommendation calls for using this shorter regimen under specific conditions¹⁵⁶. Although expected to benefit the majority of patients with active MDR-TB disease, worsening resistance is possible if the regimen is used inappropriately or without appropriate drug sensitivity testing.

In an increasing number of patients, appropriate effective regimens cannot be devised or fail. Such cases of extensively drug-resistant TB (BOX 3) have been reported in several countries, including India, China, South Africa, Russia and other countries in eastern Europe¹⁵³. New agents such as bedaquiline or delamanid might be beneficial for these patients, even though an

effective regimen could still be challenging to construct. However, lack of or limited access to these drugs or the absence of available drugs to be used in conjunction with either bedaquiline or delamanid means that such patients might remain therapeutically destitute. Thus, there is a pool of essentially incurable patients with active drug-resistant TB disease. This phenomenon is well documented in many countries, including India and countries in eastern Europe and sub-Saharan Africa, where community-based transmission of untreatable strains has been demonstrated¹⁵⁷. This finding has raised numerous legal, ethical and logistical dilemmas about long-term accommodation, access to palliative care and individual rights to unrestricted work and travel for these patients¹⁵³. Transmission of such untreatable extensively drug-resistant strains poses a major challenge for global TB control.

Table 2 | Global pipeline of TB vaccine candidates listed by indication

Vaccine candidate	Development partners	Description	Current phase
Prevention of active TB disease in infants (BCG replacement)			
VPM 1002*	Serum Institute of India (India), Max Planck Institute (Germany), Vakzine Projekt Management GmbH (Germany) and TuBerculosis Vaccine Initiative (The Netherlands)	Recombinant BCG	Phase IIb
MTBVAC†	Biofabri (Spain), TuBerculosis Vaccine Initiative and University of Zaragoza (Spain)	Live attenuated <i>Mycobacterium tuberculosis</i>	Phase I
Prevention of active TB disease in individuals with LTBI			
Vaccae	Anhui Zhifei Longcom (China)	Heat-inactivated, whole-cell <i>Mycobacterium vaccae</i>	Phase III
Adjunctive immunotherapy in individuals with LTBI			
RUTI	Archivel Farma (Spain)	Detoxified, fragmented <i>M. tuberculosis</i>	Phase II
Prevention of active TB disease recurrence in recently cured patients			
ID93+GLA-SE	Infectious Disease Research Institute (United States) and the Wellcome Trust (United Kingdom)	Adjuvanted recombinant protein expressing <i>M. tuberculosis</i> antigens Rv3619, Rv3620, Rv1813 and Rv2608	Phase IIb
Prevention of active TB disease in uninfected individuals and in those with LTBI			
H1or H56:IC31	Statens Serum Institut (Denmark), Valneva (France) and Aeras (United States)	Adjuvanted recombinant protein expressing <i>M. tuberculosis</i> antigens Ag85B, ESAT-6 [H1]; or Ag85B, ESAT-6, Rv2660c [H56]	Phase II
M72/ASO1E	GlaxoSmithKline (GSK) Vaccines (United Kingdom) and Aeras	Adjuvanted recombinant protein expressing <i>M. tuberculosis</i> antigens 32A and 39A	Phase IIb
DAR-901	Dartmouth College (United States)	Whole-cell, inactivated non-tuberculous mycobacterium	Phase II
H4:IC31	Sanofi Pasteur (France), Statens Serum Institut and Aeras	Adjuvanted recombinant protein expressing <i>M. tuberculosis</i> antigens Ag85B and TB10.4	Phase II
Ad5 Ag85A	McMaster University (Canada) and CanSino (China)	Viral vector (human adenovirus 5) expressing <i>M. tuberculosis</i> antigen Ag85A	Phase II
ChAdOx1-85A/MVA85A	University of Oxford (United Kingdom)	Viral vectors (Chimp adenovirus/modified Vaccinia Virus Ankara) heterologous prime–boost expressing <i>M. tuberculosis</i> antigen Ag85A	Phase I
MVA85A/MVA85A	University of Oxford	Viral vector (modified Vaccinia Virus Ankara) intradermal followed by aerosol; prime–boost vaccine	Phase I
TB/FLU-04L	Research Institute for Biological Safety Problems (Republic of Kazakhstan)	Viral vector (influenza A virus)	Phase I

Information as reported by the vaccine sponsors to Aeras. To date, tuberculosis (TB) vaccine candidates have been designed predominantly to stimulate a T helper 1-type CD4⁺ T cell response. The viral vector candidates alone or in combination typically also stimulate a CD8⁺ T cell response. The whole-cell and lysate mycobacteria-based candidates have the greatest potential to stimulate other aspects of the host innate and adaptive immune system, including, for example, donor unrestricted T cells (such as $\gamma\delta$ -cells, mucosal-associated invariant T cells, CD1-restricted T cells and natural killer T cells), as they present the broadest array of antigens. All candidates tested stimulate antigen-specific antibody responses. The contribution of these various responses to protection is not yet clear. BCG, Bacillus Calmette–Guérin; ESAT-6, 6 kDa early secretory antigenic target; LTBI, latent TB infection. *Also for the prevention of active TB disease recurrence in recently cured patients. †Also for the prevention of active TB disease in adolescents and adults.

Table 3 | Drug regimens for drug-sensitive pulmonary TB

Intensive phase		Continuation phase			
Drugs*	Interval and dose†	Drugs	Interval and dose‡,§	Total doses	Important practice points ^{¶,}
• Isoniazid • Rifampicin • Pyrazinamide • Ethambutol	Daily for 8 weeks or 5 days per week for 8 weeks	• Isoniazid • Rifampicin	Daily for 18 weeks or 5 days per week for 18 weeks	182 or 130	Preferred regimen for patients with newly diagnosed pulmonary TB
• Isoniazid • Rifampicin • Pyrazinamide • Ethambutol	Daily for 8 weeks or 5 days per week for 8 weeks	• Isoniazid • Rifampicin	3 days per week for 18 weeks	110 or 94	Preferred alternative regimen when more-frequent DOT during the continuation phase is difficult to achieve
• Isoniazid • Rifampicin • Pyrazinamide • Ethambutol	3 days per week for 8 weeks	• Isoniazid • Rifampicin	3 days per week for 18 weeks	78	Use with caution in HIV-positive patients and/or cavitory disease; missed doses can lead to treatment failure, relapse and acquired drug resistance
• Isoniazid • Rifampicin • Pyrazinamide • Ethambutol	Daily for 2 weeks, then 2 days per week for 6 weeks [¶]	• Isoniazid • Rifampicin	2 days per week for 18 weeks	62	Do not use 2 days per week regimens in HIV-positive patients and/or patients with cavitory disease or who are smear-positive; missed doses lead to inferior efficacy of the therapy

DOT, directly observed therapy; TB, tuberculosis. *Other combinations might be appropriate in certain circumstances.

†Minimum duration; when DOT is used, drugs might be given 5 days per week and the necessary number of doses adjusted accordingly. DOT should be used when drugs are administered <7 days per week. §Based on expert opinion, patients with cavitation on initial chest X-ray and with a positive culture test result at completion of 8 weeks of therapy should receive a 31-week continuation phase. ¶Vitamin B6 is given with isoniazid to individuals who are at risk of neuropathy (for example, pregnant women; breastfeeding infants; HIV-positive individuals; or patients with diabetes, alcoholism, malnutrition, chronic renal failure or advanced age). For patients with peripheral neuropathy, experts recommend an increased vitamin B6 dose. ¶Alternatively, some US TB control programmes consist of intensive-phase regimens of 5 days per week for 3 weeks, then 2 days per week for 6 weeks. Adapted from REF. 148.

Reports of possible totally drug-resistant strains highlight two key issues^{153,158}. First, the development and introduction of new drugs have not kept pace with the emergence of drug-resistant strains. This failure reflects a lack of public and private investments since the 1970s, when TB incidence fell in most high-income countries and the need for new drugs was perceived as less pressing. Second, by introducing new drugs in settings with a high prevalence of drug-resistant strains without correcting one of the fundamental causes of the emergence of such strains (such as weak health care systems with poor management of patients with TB), the risk of amplifying anti-TB drug resistance is considerable.

Beyond drug therapy, there is a role for surgery in the management of drug-resistant TB. In patients with unilateral disease (or apical bilateral disease in selected cases) with adequate lung function in whom medical treatment has failed, surgical treatment to remove the entire affected area of the lung can be effective. However, in patients with rifampicin-resistant TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) is associated with improved treatment success¹⁵⁴.

Solutions for MDR-TB and shorter regimens

Optimizing existing drugs. Because the need for new regimens is urgent and new drug development is long, expensive and with uncertain results, attempted interim solutions include using highly intermittent regimens, existing anti-TB drugs that were never widely prescribed,

higher doses of currently used anti-TB drugs^{159,160} and 're-purposed' drugs (drugs that were originally designed for other diseases that could prove effective against drug-resistant TB). For example, rifapentine has similar *in vitro* anti-mycobacterial activity as rifampicin but with a fivefold longer half-life. When substituting for rifampicin, it has been shown to be effective when given once or twice a week¹⁶⁰.

Furthermore, fluoroquinolones are a class of antibiotics that are widely used for the treatment of infections of the lower respiratory tract. They have excellent *in vitro* activity against *M. tuberculosis*, are as effective as isoniazid in the initial phase of treatment of drug-sensitive TB¹⁶¹ and are essential drugs in drug-resistant TB treatment¹⁶². However, three large trials have demonstrated that short (4 months) fluoroquinolone-based regimens could not achieve similar cure rates as the standard 6-month regimen for drug-sensitive TB^{160,163,164}.

Another possible re-purposed drug is linezolid, which has been used most successfully in patients with strains that are resistant to isoniazid, rifampicin or fluoroquinolones¹⁶⁵. However, experience with linezolid is limited because of its high cost and toxicity. Similarly, carbapenems have been beneficial in patients with highly resistant strains¹⁶⁶, but are expensive and, with some exceptions (such as faropenem), they need parenteral administration. To improve the treatment of TB (all types), the most promising approaches remain the discovery of novel compounds and the development of new regimens.

Newly approved drugs and the current pipeline. At the end of 2012, the US FDA approved bedaquiline (a diarylquinoline), the first truly new anti-TB drug in approximately 40 years¹⁶⁷. In 2014, the European Commission authorized bedaquiline and another new compound, delamanid (a nitroimidazo-oxazole derivative), for the treatment of adults with pulmonary MDR-TB¹⁶⁸. Bedaquiline has now been approved in many other countries. Both bedaquiline and delamanid work through novel mechanisms, bedaquiline through inhibition of ATP synthase and delamanid through inhibition of mycolic acid synthesis, and there is no known cross-resistance with other approved anti-TB drugs. In addition, in preclinical models, both drugs seem to have very good 'sterilizing' properties, which measure their ability to kill tuberculous organisms when there are very few left in the body or when they are growing or reproducing very slowly; this ability might translate into a shorter duration of TB therapy^{169,170}.

However, these new drugs were approved based on very limited evidence. Hence, well-designed and well-executed randomized trials will be needed to determine whether these two drugs can be administered together, the optimal treatment duration, their actual ability to contribute to treatment shortening and the optimal companion drugs. The ultimate goals are shortening and simplifying TB therapy while also increasing the cure rates and developing regimens that cause fewer adverse effects, especially in treating drug-resistant TB¹⁷¹.

In terms of drug development, the TB drug pipeline is now the largest it has ever been¹⁷² (FIG. 5), with multiple early TB drug discovery projects, the majority of which are incorporated into the TB Drug Accelerator, a programme sponsored by the Bill & Melinda Gates Foundation for collaborative TB drug discovery¹⁷³.

HIV-associated TB

HIV poses a challenge for global TB control¹⁷⁴. Worldwide in 2014, 12% of all new cases of active TB disease occurred in HIV-positive individuals (1.2 million people)¹. Although there is geographical variation, it is estimated that HIV-positive individuals are 26-fold more likely to develop active TB disease than HIV-negative individuals¹. This increased risk is observable as early as HIV seroconversion and further exacerbates as CD4⁺ T cell counts decrease⁷. Thus, HIV-positive individuals have a very high risk of progressing to active TB disease, although they are not necessarily more-infectious to others.

Antiretroviral therapy (ART) has been demonstrated to reduce active TB disease incidence by providing immune reconstitution; the lower the CD4⁺ T cell count, the higher the ART-associated protection¹⁷⁵. The combined use of ART and isoniazid preventive treatment has also been shown to reduce active TB disease incidence and severe illnesses among HIV-positive individuals^{176,177}. Nevertheless, the risk of developing active TB disease remains twofold higher in HIV-positive individuals even if their CD4⁺ T cell count is within normal range¹⁷⁸ and they can still develop active TB disease even if they are receiving ART¹⁷⁹. The proportion of patients diagnosed with TB at the start of ART in sub-Saharan Africa ranges between 5% and 40%¹⁸⁰.

HIV changes the presentation of active TB disease: it generally reduces pulmonary cavity formation and sputum bacillary load and frequently involves the lower lobes¹¹⁰. All HIV-positive individuals should be regularly screened for active TB disease, particularly if they experience the following symptoms: cough, fever, weight loss and night sweats^{110,181,182}. Individuals who report any one of these symptoms might have active TB disease and require immediate evaluation and treatment. Individuals who report no symptoms should be provided with preventive LTBI treatment, after ruling out active TB disease, depending on TB epidemiology and burden in the area^{8,145,183}.

In settings where diagnostic tools might not be available, TB treatment should then be empirically provided to HIV-positive individuals with suspected active TB disease who are seriously ill and in life-threatening conditions. In these settings, the WHO algorithms recommend starting treatment for suspected active TB disease in HIV-positive patients who are in serious respiratory distress based only on the clinician's judgement¹⁸⁴.

HIV-positive individuals, particularly if they have low CD4⁺ T cell counts, have a higher risk of extrapulmonary TB, which could result in rapid clinical deterioration and death. The most common forms of extrapulmonary TB include lymph node, pleural and disseminated TB. Pericardial and meningeal TB are less frequent but deadlier. Diagnosing extrapulmonary TB is difficult; the WHO recommends Xpert MTB/RIF to detect TB lymphadenitis and TB meningitis^{109,185}. Patients diagnosed with active TB disease who are HIV-positive or live in an HIV-prevalent setting should receive daily isoniazid and rifampicin for 6 months and also pyrazinamide and ethambutol for the first 2 months¹⁴⁷. Treatment for TB meningitis should last 9–12 months given the serious

Box 2 | Principles of managing MDR-TB

- A 9–12-month regimen (conditional WHO recommendation with very-low-quality evidence) might be used in selected patients, in appropriate settings, taking into account previous treatment and local resistance profiles
- If patients are not eligible for the shorter regimen, a longer treatment regimen is used. The composition of the regimen includes pyrazinamide in addition to at least four second-line drugs to which the organism is likely or proven to be susceptible for a duration of ≥20 months
- The second-line drugs should include a later-generation fluoroquinolone (such as moxifloxacin, levofloxacin or gatifloxacin), an injectable agent (such as amikacin, kanamycin or capreomycin*) and two or more core second-line agents (such as ethionamide, prothionamide, cycloserine, terizidone, clofazimine or linezolid)
- First-line drugs (such as isoniazid or ethambutol) could be added to strengthen the regimen
- When toxicity or resistance occurs, additional agents can be added, including bedaquiline and delamanid, such that four drugs that are likely to be effective are being used
- A single new drug should not be added to a failing regimen
- Adherence and psychosocial support measures and, if necessary, counselling against substance abuse are essential
- Patients should be monitored for adverse drug reactions, which occur commonly

MDR-TB, multidrug-resistant tuberculosis. *Capreomycin cross-resistance with aminoglycosides is not complete and it might be a therapeutic option in specific and appropriate contexts, and in light of aminoglycoside resistance if no safe or effective alternatives are available.

Table 4 | First-line and second-line drugs used for the treatment of drug-resistant TB (WHO classification)

Class	Mechanism of action	Drugs	Key adverse events	Important practice points
Group A: fluoroquinolones				
Fluoroquinolones	Inhibition of DNA gyrase	<ul style="list-style-type: none"> Levofloxacin Moxifloxacin Gatifloxacin* 	QTc prolongation (levofloxacin less so than moxifloxacin)	<ul style="list-style-type: none"> Monitor QTc when fluoroquinolones are combined with other QTc-prolonging agents, for example, bedaquiline or clofazimine Levofloxacin is the fluoroquinolone of choice in bedaquiline-containing regimens
Group B: second-line injectable anti-TB drugs				
Aminoglycosides	Inhibition of protein synthesis	<ul style="list-style-type: none"> Kanamycin Amikacin Capreomycin (Streptomycin)[‡] 	<ul style="list-style-type: none"> Nephrotoxicity (all) Ototoxicity (all) Electrolyte derangement (all) 	<ul style="list-style-type: none"> Avoid combination of aminoglycosides with other potentially nephrotoxic agents, for example, tenofovir or amphotericin B Use with caution in patients with diabetes mellitus or renal disease
Group C: core second-line agents				
Thioamides	Inhibition of cell wall synthesis	<ul style="list-style-type: none"> Ethionamide Prothionamide 	<ul style="list-style-type: none"> Nausea and vomiting (all) Hypothyroidism (all) 	<ul style="list-style-type: none"> If nausea and vomiting persist, consider drug-induced hepatitis or pancreatitis Monitor thyroid-stimulating hormone levels in patients receiving ethionamide
Oxazolidinones	Inhibition of protein synthesis	<ul style="list-style-type: none"> Cycloserine Terizidone Linezolid Clofazimine 	<ul style="list-style-type: none"> CNS effects, including psychosis, confusion and depression (terizidone and cycloserine) Peripheral neuropathy (linezolid) Myelosuppression (linezolid) Ocular toxicity (linezolid) QTc prolongation (clofazimine) Skin and conjunctival pigmentation (clofazimine) 	<ul style="list-style-type: none"> Avoid concomitant use of linezolid with zidovudine, stavudine or didanosine; if myelosuppression occurs, stop linezolid use and transfuse as appropriate Monitor QTc when using clofazimine, especially when combined with QTc-prolonging agents
Group D: add-on agents				
D1, various classes: isonicotinic acid hydrazide (high-dose isoniazid); nicotinamide analogue (pyrazinamide); aminoalcohols (ethambutol)	Inhibition of mycolic acid synthesis	High-dose isoniazid	<ul style="list-style-type: none"> Hepatotoxicity Peripheral neuropathy CNS toxicity 	Use with pyridoxine to prevent peripheral neuropathy
	Disruption of plasma membranes	Pyrazinamide	<ul style="list-style-type: none"> Hepatotoxicity Gout 	–
	Inhibition of cell wall synthesis	Ethambutol	Ocular toxicity	–
D2, various classes: diarylquinoline (bedaquiline); nitro-dihydroimidazooxazole (delamanid)	Inhibition of mitochondrial ATP synthase	Bedaquiline	<ul style="list-style-type: none"> QTc prolongation Arthralgia Hepatitis Headache 	<ul style="list-style-type: none"> Close monitoring of QTc is recommended Efavirenz should be changed to nevirapine or a protease inhibitor because of reduced bedaquiline exposure. Alternatively, an integrase inhibitor can be used
	Inhibition of mycolic acid synthesis	Delamanid	<ul style="list-style-type: none"> Nausea Vomiting Dizziness QTc prolongation 	<ul style="list-style-type: none"> Close monitoring of QTc is recommended No significant anticipated drug–drug interactions with antiretroviral drugs
D3, various classes: amino-phenol (para-aminosalicylic acid); carbapenems; thiosemicarbazone (thiocetazone)	Inhibition of DNA precursor synthesis	Para-aminosalicylic acid	Gastrointestinal toxicity	Monitor thyroid-stimulating hormone levels in patients receiving para-aminosalicylic acid
	Inhibition of peptidoglycan synthesis	Imipenem plus cilastatin or meropenem plus clavulanate (available orally with amoxicillin)	Seizures	Monitor for CNS adverse events
	Inhibition of mycolic acid synthesis	Thiocetazone [§]	Severe skin reactions (for example, Stevens–Johnson syndrome and toxic epidermal necrolysis), especially in patients with HIV infection	Close monitoring for severe skin reactions; avoid use if the patient is HIV-positive

CNS, central nervous system; QTc, corrected QT interval; TB, tuberculosis. *This drug is being assessed for inclusion in the 2017 Essential Medicines List.

[‡]Streptomycin can be used when the isolate is susceptible and none of the other injectable drugs are available. [§]Only use in HIV-negative individuals.

Box 3 | Principles of managing extensively drug-resistant TB

- Regimens should be constructed using similar principles as outlined for multidrug-resistant tuberculosis (MDR-TB) (BOX 2)
- Drugs such as linezolid, bedaquiline and delamanid (if available) often need to be used, such that at least four drugs that are likely to be effective are used concurrently
- Lack of access to newer and repurposed drugs means that, in reality, patients often only receive one or two effective drugs, resulting in poor treatment outcomes
- Additional drugs, including meropenem and clavulanate, are used, but their role and effectiveness are unclear
- As cross-resistance across different fluoroquinolones is not complete, moxifloxacin can still be used in the presence of fluoroquinolone (for example, ofloxacin) resistance

risk of disability and mortality, and treatment for TB of the bones or joints should last 9 months because of the difficulties of assessing treatment response.

The WHO recommends that all HIV-positive individuals with drug-sensitive or drug-resistant active TB disease should also begin ART within the first 2 months of TB treatment, regardless of their CD4⁺ T cell count. Randomized controlled trials^{186–190}, systematic reviews and meta-analyses^{191,192} have confirmed the benefit of combined TB and HIV treatment in reducing mortality rates. Preferred ART regimens are described in the 2016 WHO guidelines¹⁸⁴; in adults, first-line treatment consists of a combination of two nucleoside reverse-transcriptase inhibitors and a non-nucleoside reverse-transcriptase inhibitor or an integrase inhibitor.

TB is the leading cause of death among people with HIV infection, accounting for one in five HIV-related deaths¹. The management of HIV-TB is complicated by several factors. First, drug–drug interactions between antitubercular and antiretroviral agents make it difficult to design an effective and safe treatment regimen and can cause severe adverse effects, such as hepatotoxicity and neurotoxicity. Second, by restoring the immune system, ART can trigger immune reconstitution inflammatory syndrome (IRIS), a condition in which the host's inflammatory response to an infection (in this case, *M. tuberculosis* infection) is disproportionate and worsens the patient's status. Whereas the incidence of severe (grade 3 or grade 4) non-IRIS adverse events was similar whether the patients had started ART early or late during TB treatment, significantly higher rates of IRIS-related adverse effects occurred in the early ART group. Similarly, a small but significant increased risk of IRIS-related mortality has been reported^{186,189,190}. Patients with HIV infection with drug-sensitive or drug-resistant active TB disease and profound immunosuppression (CD4⁺ T cell counts of <50 cells per µl) should receive ART within the first 2 weeks of initiating TB treatment¹⁸⁴, unless the patients are diagnosed with TB meningitis. In these patients, ART should be delayed to 2 months after the start of TB treatment to reduce the risk of severe adverse effects¹⁹³.

Childhood TB

Models suggest that childhood active TB disease is more frequent than official reports indicate, and cases of MDR-TB are far more numerous than prior estimates^{194,195}. Active TB disease typically causes pulmonary

disease in adults, but the spectrum of disease is different in children, ranging from paucibacillary lymphadenitis to severe disseminated (miliary) disease^{6,113,196}.

Children who have had contact with adult patients with active TB disease are at high risk of *M. tuberculosis* infection and developing active TB disease, so they are prioritized for LTBI testing and treatment¹⁴⁵. The principles of LTBI treatment in adults also apply to children. In general, children tolerate anti-TB drugs well with low risk of toxicity. However, developmental differences in pharmacokinetics and pharmacodynamics require that drug dosages in children be adjusted for body weight and age. History of drug resistance among adult patients with active TB disease with whom children have had contact might be helpful in regimen selection.

The basic principles and recommended standard regimens for the treatment of active TB disease in children are similar to those applied to adults¹⁹⁷. Treatment should be given daily at least in the intensive phase, and might be extended up to 9–12 months in severe forms of active disease¹⁹⁷. Management of HIV infection in children with active TB disease is described in the WHO guidelines^{184,197}. Treatment of MDR-TB in HIV-positive children follows the same principles as treatment of HIV-negative children.

Quality of life

Several studies have documented lower self-reported health-related quality of life among patients with active TB disease¹⁹⁸ than healthy individuals or those with LTBI. Impairment of lung function with chronic pulmonary disability, bronchiectasis, aspergillomas and chronic pulmonary aspergillosis are known complications and are more frequent in patients with drug-resistant TB than in patients with drug-sensitive TB¹⁹⁹. Patients with impaired lung function might require long-term pulmonary rehabilitation and chest physiotherapy.

If patients are untreated, the prognosis for individuals affected by drug-resistant TB is similar to the prognosis for individuals with drug-sensitive TB (10-year case fatality rates of approximately 70%)¹⁶. The current WHO-recommended MDR-TB regimen has an approximate 50% cure rate, whereas the cure rate in endemic settings of extensively drug-resistant TB in the absence of drugs such as bedaquiline, delamanid and linezolid is approximately 20%^{157,200}. Thus, TB (and drug-resistant TB in particular) poses a grave threat to human health and quality of life. High-quality patient care, consistent with the International Standards for TB Care²⁰¹, is crucial to ensure good outcomes and preserve quality of life. Unfortunately, international standards are often not met in many low-income, high-burden countries, particularly in the private health sector, which is a major provider of health care in many countries with a high TB prevalence^{202–206}. Poor quality of care is, therefore, a key driver of TB mortality in high-burden countries, and might explain the persistently high TB incidence in some settings. Whereas national programmes are accountable to national and international authorities regarding their implementation of proper standards of care, one of the greatest

challenges in TB control is still engaging and regulating the private sector²⁰⁶. Innovative public–private mix approaches are required to overcome this challenge, including social franchising, insurance-based initiatives, intermediary agencies and provider consolidation, with a heavy emphasis on the use of information and communication technologies²⁰⁶.

Outlook

The global TB epidemic is not a homogeneous entity that is characterized by a gradual decline in incidence, but rather a heterogeneous collection of local micro-epidemics, in which transmission in each setting is driven by different catalysts: from HIV-induced immune defects to inadequate diagnosis and treatment²⁰⁷. In regions where increased attention and resources have been devoted to fighting TB (for example, New York City²⁰⁸, Peru²⁰⁹, Alaska²¹⁰ and China²²), remarkable success has been achieved. By contrast, in regions where catalysts of transmission have been left unaddressed (for example, economic collapse and incarceration in some eastern European countries and HIV in countries in sub-Saharan Africa before the widespread availability of ART), TB has resurged. As the goal of the global response to TB transitions from controlling to ending the epidemic, increased awareness of the heterogeneities in

transmission dynamics and catalysts of local epidemics will be essential to success.

In May 2014, the World Health Assembly approved a new strategy for the modern era to reach the ambitious target of ending the global TB epidemic by 2035 (REFS 211,212): the End TB Strategy. The goal will be met when TB-related deaths and active TB disease incidence are reduced by 95% and 90%, respectively, compared with the 2015 values, which would mean that global active TB disease incidence is lower than 10 per 100,000 population.

The End TB Strategy builds on four principles: stewardship and accountability of governments; engagement of civil society; respect of human rights, ethics and equity; and adaptation to local conditions. These principles are structured in three pillars. The first pillar (‘integrated, patient-centred care and prevention’) considers interventions for diagnosis, treatment, management and prevention, promoting all available technological advances. The second pillar (‘bold policies and supportive systems’) focuses on broad health systems and policies, including universal health coverage, social and financial protection, and the engagement of all health care providers. The third pillar (‘intensified research and innovation’) is devoted to research and development of new tools.

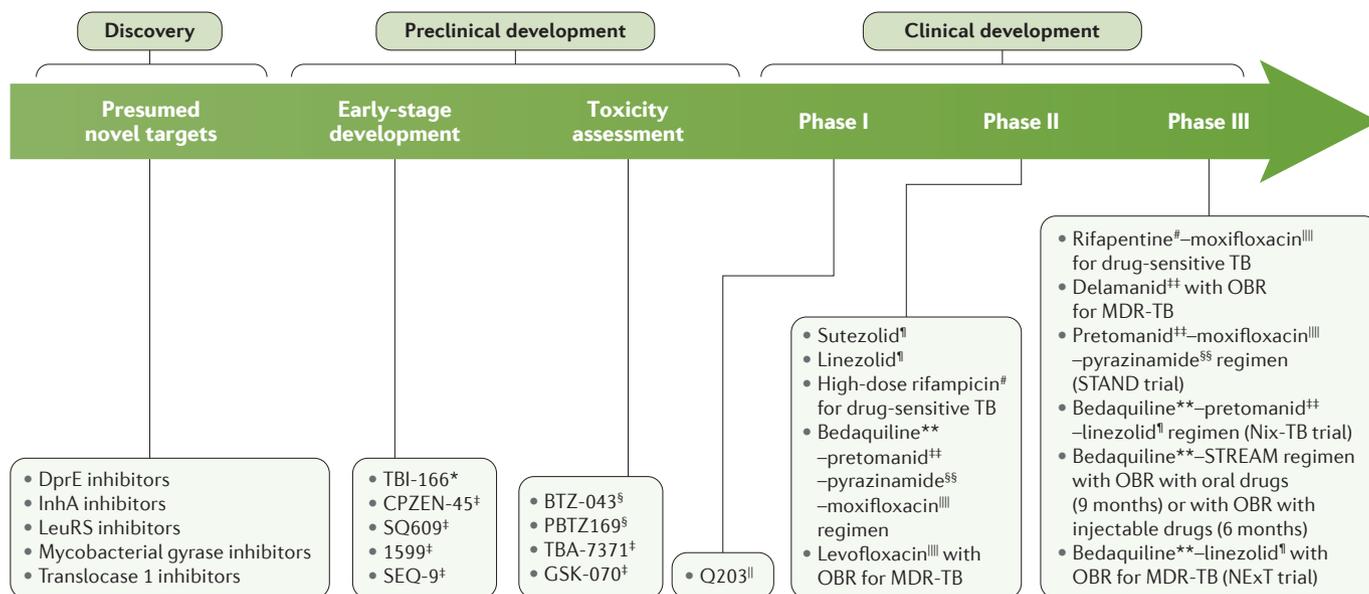


Figure 5 | The global TB drug pipeline. The pipeline is based on data compiled by the New Drugs Working Group of the Stop TB Partnership¹⁷² and based on voluntary reporting by drug developers. As a result, the compounds and regimens listed, especially under ‘Discovery’ and ‘Preclinical development’, are likely to be under-reported. Most compounds listed in ‘Discovery’ are derived from whole-cell screening, and true target identification and validation is still ongoing. Among products under clinical development, ten compounds (either new or repurposed) are currently being evaluated either in phase I trials or as part of anti-tuberculosis (TB) drug regimens. Most of these compounds belong to three chemical classes — oxazolidinones (denoted as [¶]), nitroimidazoles (denoted as ^{††}) or fluoroquinolones (denoted as ^{|||}). The main goal of many phase II and phase III trials is to combine new or repurposed compounds in treatment regimens that would be drastically shorter and simplified, have increased or similar

efficacy to the present standard of care and decreased or similar associated toxicity. Most TB treatment-shortening trials are targeted at individuals with TB that is resistant to standard first-line therapy, and some trials have the goal of discovering universal regimens that are equally effective against drug-sensitive and drug-resistant TB, which would eliminate the need for drug sensitivity testing. *Rimnophenazine. [†]New chemical class. [§]Benzothiazinone. ^{||}Imidazopyridine amide. [#]Rifampicin. ^{**}Diarylquinoline. ^{§§}Pyrazine (pyrazinoic acid amide). DprE, decaprenylphosphoryl- β -D-ribose 2'-epimerase; InhA, enoyl acyl carrier protein reductase; LeuRS, leucyl-tRNA synthetase; MDR, multidrug resistant; Nix-TB, New Investigational Drugs for Extensively Drug-Resistant TB; OBR, optimized background regimen; STAND, Shortening Treatment by Advancing Novel Drugs; STREAM, Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB.

Reaching the targets set for 2035 will not be possible unless a substantial decrease in TB incidence occurs. Currently, TB incidence declines by 1.5% annually, but the gains in reducing TB incidence could still be lost if the rising threat of MDR-TB is not adequately tackled²¹². The model projecting a further reduction in TB incidence is built on two basic assumptions. First, that implementation of current (or soon-to-be available) interventions and tools are optimized, enabling a 10% annual reduction by 2025 (the highest ever reached at national scale). Achieving this result will require effective rapid molecular diagnostics, universal drug susceptibility testing and systematic screening of high-risk populations (which also implies providing curative or preventive treatment to individuals who test positive), as well as bolder policies on universal coverage and social protection, which would alleviate the socioeconomic causes of disease. The second assumption is that research efforts deliver new revolutionizing transformational tools and interventions.

Research needs and priorities

Effective TB research must span from basic to translational and clinical²¹³. The pathogenesis and immunology of *M. tuberculosis* infection and active TB disease remain only partly understood. For instance, the ontogeny of macrophages markedly affects their function and fate^{67,68}, but current primary cell line models are not derived from the alveolar tissue. The dynamics that regulate progression from exposure to *M. tuberculosis* to LTBI and from LTBI to active TB disease need to be clarified to develop new rapid, simple diagnostic tools, which need to be available at the point of care. To develop tests with reliable predictive value, it is crucial to identify biomarkers or bio-signatures that can resolve the LTBI spectrum², so that individuals who are at highest risk of progressing from LTBI to active TB disease can be recognized and treated¹³³. Preliminary research has shown promising results for a blood RNA signature²¹⁴. High-resolution lung imaging might also be able to separate phenotypes on the TB spectrum¹⁰¹.

A complete understanding of how *M. tuberculosis* develops resistance has the potential to revolutionize TB care, so efforts to catalogue resistance-associated

mutations are ongoing, using epidemiologically representative strain collections coupled with patient outcome data⁸⁸. Genome sequencing and molecular platforms that detect mutations that confer drug resistance also need to be developed to support the introduction of new drug regimens for active TB disease¹²⁸. Current regimens are long, cumbersome and toxic. New medicines and universal regimens (that can be used in both drug-sensitive TB and MDR-TB) are being studied to shorten duration, facilitate administration and enable safe use in people with comorbidities. However, the development pipeline remains very limited. Regimens that simplify and shorten LTBI treatment are also a priority, as any attempt to eradicate TB needs to address the huge pool of individuals with LTBI.

The current vaccine development pipeline includes 13 different candidates aiming at preventing both the establishment of LTBI and the progression from LTBI to active disease, but they represent limited diversity in the immune responses they induce. Increasing the understanding of the protective human immune response, identifying animal models that predict vaccine efficacy in humans, discovering a correlate of protection and developing a controlled human infection model would each, if successful, represent a game-changer in accelerating vaccine development.

Finally, it is important to optimize delivery of existing or new tools and rapid transfer of innovations to high-burden settings through well-planned implementation research projects, taking into account that these tools might have to be adapted to different conditions. This strategy will require, in turn, socio-anthropological, epidemiological, health system and policy research. It is also clear that strengthening of health systems is crucial for successful introduction of new technologies. Ultimately, global targets will be reached only when governments and their partners decide to invest intensively in both research and implementation efforts. In this context, lack of adequate financing of national TB programmes is a major challenge in many low-income countries. Thus, high-income countries must continue investing in TB control and research and, via multi-lateral or bi-lateral financial mechanisms, support the efforts of low-income settings.

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Author contributions

Introduction (M.P.); Epidemiology (D.D.); Mechanisms/pathophysiology (M.A.B. and M.D.); Diagnosis, screening and prevention (M.P., C.C.B., M.A.B. and A.G.); Management (D.M., M.S., K.D., H.G. and S.S.); Quality of life (M.P., K.D. and M.R.); Outlook (M.R.); Overview of Primer (M.P.). M.P. and M.A.B. contributed equally to this work.

Competing interests

M.P. declares no financial conflicts. He serves as a consultant for the Bill & Melinda Gates Foundation, and on advisory

committees of Foundation for Innovative New Diagnostics (FIND) and TB Alliance. M.A.B. receives royalties for an antigen used in one of the IGRA tests (QuantIFERON) but did not contribute to this section of the document. He serves on the Vaccine Advisory Committee for Aeras. K.D. has obtained speaker fees at industry-sponsored symposia and grants from FIND, eNose Company, Statens Serum Institut and bioMeriux, and grants and personal fees from ALERE, Oxford Immunotec, Cellectis (now Qiagen), Cepheid, Antrum Biotech and Hain Lifescience. In addition, K.D. has a patent "Characterisation of novel tuberculosis specific urinary biomarkers" pending, a patent "A smart mask for monitoring cough-related infectious diseases" pending and a patent "Device for diagnosing EPTB" issued. C.C.B. is employed by FIND, a not-for-profit organization driving the development and delivery of new diagnostics for tuberculosis (TB). FIND has contractual relationships with > 20 *in vitro* diagnostic companies, several of which are mentioned in the article. M.R. declares no financial conflicts. He serves as observer on the Board of Directors of the TB Alliance and as External Clinical Research Expert for the US National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS Clinical Trials Network Strategic Working Group, NIH. All other authors declare no competing interests.