

Tuberculosis

Keertan Dheda, Clifton E Barry 3rd, Gary Maartens



Although the worldwide incidence of tuberculosis has been slowly decreasing, the global disease burden remains substantial (~9 million cases and ~1·5 million deaths in 2013), and tuberculosis incidence and drug resistance are rising in some parts of the world such as Africa. The modest gains achieved thus far are threatened by high prevalence of HIV, persisting global poverty, and emergence of highly drug-resistant forms of tuberculosis. Tuberculosis is also a major problem in health-care workers in both low-burden and high-burden settings. Although the ideal preventive agent, an effective vaccine, is still some time away, several new diagnostic technologies have emerged, and two new tuberculosis drugs have been licensed after almost 50 years of no tuberculosis drugs being registered. Efforts towards an effective vaccine have been thwarted by poor understanding of what constitutes protective immunity. Although new interventions and investment in control programmes will enable control, eradication will only be possible through substantial reductions in poverty and overcrowding, political will and stability, and containing co-drivers of tuberculosis, such as HIV, smoking, and diabetes.

Introduction

Tuberculosis is a communicable infectious disease, transmitted almost exclusively by cough aerosol, caused by the *Mycobacterium tuberculosis* complex, and characterised pathologically by necrotising granulomatous inflammation usually in the lung (~85% of cases), although almost any extrapulmonary site can be involved. Tuberculosis probably emerged about 70 000 years ago, accompanied by migration of modern human beings out of Africa;¹ it remains a global plague, and untreated, has a mortality of ~70% in smear-positive people.² Tuberculosis has killed roughly 1 billion people in the past two centuries,³ still ranks amongst the top ten causes of death worldwide, results in substantial chronic lung disability, and reduces gross domestic product (GDP) substantially in endemic countries. Audio and video links in the [appendix](#) provide insight into living conditions and challenges facing patients with tuberculosis in an endemic country.

Epidemiology of tuberculosis

The precipitous decline in burden of tuberculosis in the UK occurred before interventions such as tuberculosis chemotherapy became available, highlighting the importance of socioeconomic factors (overcrowding, poor nutrition, etc) in the genesis of tuberculosis ([appendix](#)).⁴

Although global tuberculosis incidence has slowly declined during the past 13 years (rate of ~1·5% per year),⁵ disease burden remains remarkably substantial. In 2013, an estimated 9 million incident cases of tuberculosis (equivalent to 126 cases per 100 000 population) were reported,⁵ with more than 60% of the burden concentrated in the 22 high-burden countries (map of global epidemiology shown in the [appendix](#)). However, the case detection rate was only around 64%, and worryingly, around 3·3 million people with tuberculosis were missed (undiagnosed or not reported). By contrast, tuberculosis mortality has declined substantially in the past 20 years from almost 30 per 100 000 to around 16 per 100 000 people in 2013.⁵

In 2013, 1·1 million people were estimated to have tuberculosis–HIV co-infection (13% of the global incident caseload). About 80% of these cases occurred in the Africa (map of global disease burden shown in the [appendix](#)), and HIV-associated tuberculosis deaths accounted for about 25% of the total number of tuberculosis-related deaths.⁵ In 2013, 480 000 new cases of multidrug-resistant (MDR) tuberculosis were estimated to have occurred worldwide, resulting in about 210 000 deaths. MDR tuberculosis was reported in about 3·5% of new cases and 20·5% of retreated cases ([appendix](#)).⁵ Several worrying trends exist with drug-resistant tuberculosis ([appendix](#)), including widespread emergence of extensively drug resistant (XDR) tuberculosis⁶ and resistance beyond XDR tuberculosis.⁷ In 2013, 550 000 incident cases of tuberculosis in children and 80 000 deaths in children with HIV were reported.⁵ Children are a vulnerable and often neglected subgroup; further aspects of management of tuberculosis in children are reviewed elsewhere.^{8,9}

Key risk factors associated with tuberculosis (and the magnitude of risk; [table 1](#))^{10,11} include poverty and overcrowding, undernutrition, alcohol misuse, HIV, silicosis, chronic renal failure needing dialysis, fibro-apical

Published Online
September 14, 2015
[http://dx.doi.org/10.1016/S0140-6736\(15\)61211-9](http://dx.doi.org/10.1016/S0140-6736(15)61211-9)
Lung Infection and Immunity Unit, Division of Pulmonology and UCT Lung Institute (Prof K Dheda PhD), and Division of Clinical Pharmacology (Prof G Maartens MMed), Department of Medicine, and Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences (C E Barry 3rd), University of Cape Town, Cape Town, South Africa; and Tuberculosis Research Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, USA (K Dheda, C E Barry 3rd, G Maartens)

Correspondence to:
Prof Keertan Dheda, Lung Infection and Immunity Unit, Division of Pulmonology and UCT Lung Institute, Department of Medicine, University of Cape Town, South Africa
keertan.dheda@uct.ac.za

See [Online](#) for [appendix](#)

Search strategy and selection criteria

We searched the Cochrane Library, PubMed, MEDLINE, and Embase up to and including May 31, 2015. We used the search terms “tuberculosis” or “TB” in combination with the terms “epidemiology”, or “pathogenesis”, or “diagnosis”, or “treatment”, or “drugs”, or “vaccines”, or “prognosis”, or “prevention”. We mostly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

	Fold risk of developing active tuberculosis	Risk of progression to active tuberculosis in those with presumed latent tuberculosis
HIV*	20–40	50–110
Silicosis	3–4	30
CRF needing dialysis	7–50	10–25
TNF α inhibitors	1.5	1.7–9.0
Treatment with glucocorticoids	2	4.9
Diabetes	3	2.0–3.6
Undernourished or underweight	12	2–3
Smoking	2	2–3
Biomass fuel exposure	2	Insufficient data
Alcohol use	3	1.5
Male sex (after adolescence)	2	Scarce and discordant data
Age	High incidence <4 years and >20 years	2.2–5.0 (young age when infected—ie, ≤ 4 years)
Malignancy	4–5	16 (carcinoma of head and neck)
Genetic polymorphisms	Many genes associated with increased risk†	Genes might be associated with risk of infection but not of disease†
Transplantation-related immunosuppression	15–20	20–74
COPD	2 (in those using inhaled corticosteroids)	Insufficient data
Overcrowding and poverty	Increased risk	Increased risk
Recent tuberculosis infection (≤ 2 years)	NA	15.0
Apical fibronodular changes on chest radiograph	NA	6–19

CRF=chronic renal failure. COPD=chronic obstructive pulmonary disease. The comprehensively referenced table is available in the appendix. *Tuberculosis incidence five-fold higher even in HIV co-infected people on antiretroviral therapy.¹⁰ †Specific genes outlined in the referenced reviews in the appendix. Adapted from Lawn and colleagues,¹¹ by permission of Lippincott Williams & Wilkins.

Table 1: Risk factors associated with tuberculosis

radiographic changes, diabetes, tobacco smoking, and immune-suppressive therapy. However, attributable risk, which varies according to global burden of the associated risk factor, has been estimated as follows: HIV (11%), smoking (15.8%), diabetes (7.5%), alcohol abuse (9.8%), undernutrition (26.9%), and indoor air pollution (22.2%).¹² These data have obvious implications for public health interventions and highlight the need for integration of health services for communicable and non-communicable diseases. Modelling studies, notwithstanding their limitations, suggest that tuberculosis elimination is probably only achievable by 2050 if therapeutic and diagnostic interventions (early case detection and high cure rates) are combined with preventive strategies (vaccines and treatment of the latent tuberculosis reservoir in 2 billion people in high-burden and low-burden settings).¹³ The WHO-endorsed End TB Strategy outlines global strategy and targets for tuberculosis prevention, care, and control after 2015 (appendix).

Pathogenesis of tuberculosis

Transmission

Tuberculosis transmission occurs when the organism is

aerosolised by the cough of an infected patient and inhaled into the alveoli of a new host. In some cases, transmission is highest within family units, but outbreaks in almost any setting are common, from schools to factories to public transportation. Two studies^{14,15} in low-incidence settings used molecular methods involving repetitive genetic elements to show that a large fraction of cases, even in low-incidence settings, were the result of recent transmission rather than reactivation of latent disease. Such techniques have shaped how we think about tuberculosis transmission,¹⁶ but are now giving way to whole genome sequencing (WGS), which provides a higher degree of confidence in strain identities compared with conventional methods.¹⁷ WGS has reopened the question of reactivation versus recent transmission in low-incidence settings and has been used to establish that *M tuberculosis* clades are geographically restricted and coevolved with modern human beings.¹ This geographical restriction of clades seems to be breaking down with the widespread emergence of clades that evolved in Asia (now often referred to as the Beijing lineage).

Large gaps exist in our knowledge about how best to reduce transmission, apart from the obvious need to improve case finding, since many cases of tuberculosis are undiagnosed. Work using carbon dioxide concentrations in air as a proxy for rebreathing have suggested one practical method to measure transmission risk in different settings,¹⁸ and re-emphasised the crucial role of ventilation in reducing risk. Epidemiological data suggest that some strains might transmit more easily than others, but the molecular mechanisms underpinning these observations are unclear. Host factors might have a role in transmission, but patients with HIV do not seem to be either more or less capable of transmitting tuberculosis.¹⁹

Outcomes after infection

Exposure to *M tuberculosis* infrequently leads to symptomatic disease. Thus, although the statistic that one-third of the world's population is infected with *M tuberculosis* sounds alarming, only about 12% of these immune-sensitised individuals actually develop disease.²⁰ Disease development is a function of the host's immunocompetence; individuals with HIV, for example, are at increased risk of progression to active disease. However, disease development is also a reflection of the evolutionary strategy of *M tuberculosis* as a pathogen, which during human existence has needed to ensure transmission to the next host. *M tuberculosis* has to undertake a delicate balancing act: cause enough disease to ensure transmission but not so much that patients rapidly die, taking the pathogen's progeny with them. The solution to this equation in modern, mostly urban high-density human populations might be very different than in historic low-density hunter-gatherer human populations, which might be reflected in newly emerging strain clades.²¹ Because of

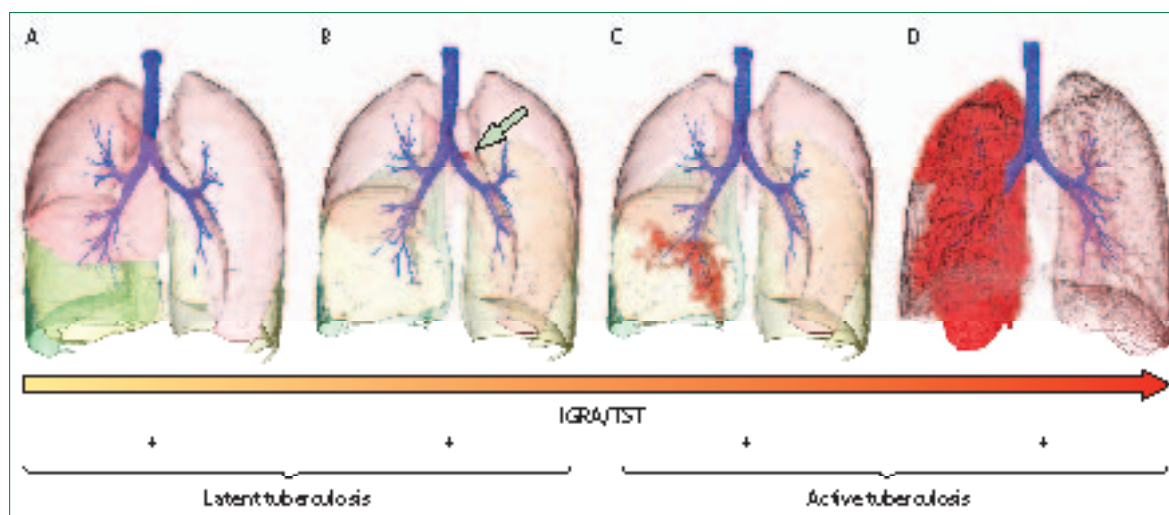


Figure 1: Outcomes of infection with *Mycobacterium tuberculosis*

M tuberculosis infection has variable outcomes in different hosts. The individual (A) has been exposed but, through innate or adaptive immune function, has cleared the invading bacilli completely. Immunodiagnostic tests might be positive or negative in such people. This individual was interferon gamma release assay (IGRA) positive but is at no risk of relapse disease, and this outcome occurs in about 90% of infected individuals. We speculate that such individuals have sterilising immunity with no viable organisms in their tissues. Infected cells containing live *M tuberculosis* bacteria can also migrate to the draining lymph nodes (B; marked with an arrow); in non-human primates²³ and human beings,²⁶ this might often be accompanied by very small parenchymal lesions or infiltrates that are not visible by chest radiograph but might be visible on chest CT. The infection has progressed (C), but disease is fairly minimal, restricted to the right-lower lobe. Individuals with minor disease can report with variable symptoms or be asymptomatic and this state has been referred to as subclinical disease; non-human primates can similarly show acid-fast bacilli in gastric aspirates but seem clinically healthy, and are referred to as percolators. An individual has extensive consolidative disease throughout the right posterior and apical segments and lower lobe (D). Some individuals have recurrent active tuberculosis, but mechanisms underlying this susceptibility are unclear. Immunodiagnostic tests at any stage of disease might be negative because both tuberculin skin test (TST) and IGRA have suboptimum sensitivity for diagnosis of latent and active tuberculosis. Even for active tuberculosis, TST and IGRA sensitivity is around 80%.

this evolving situation, historic dogmas about the life cycle of *M tuberculosis* are constantly being revised and revisited.

Results of studies in non-human primates, which are natural hosts of *M tuberculosis*, have shown several key features of what we would have previously referred to as latent tuberculosis infection.²² As in human beings, infection of cynomolgus macaques only occasionally proceeds directly to symptomatic infection in a fraction of animals; the remainder control the infection to a variable extent.²³ The infected, asymptomatic animals seem to be clinically identical to human beings with latent tuberculosis, including showing a strong propensity for disease reactivation when treated with anti-TNF.²⁴ Necropsy of non-human primates with latent tuberculosis shows a striking range of disease, ranging from subclinical infection that features active lesions with bacterial replication, to sterile granulomas or infected lymph nodes in individual animals.²⁵ The variability of the extent of disease in these animals caused a substantial rethinking of what might constitute latent tuberculosis infection in human beings and led to the concept that latent infection might actually be a range of subclinical forms of the disease (figure 1).^{26,27} To identify the subset of patients with latent tuberculosis infection who are at high risk for progression and target prophylactic treatment to this small group of patients might ultimately be possible.²⁸

Immunopathogenesis

After inhalation, bacteria are taken up by resident macrophages. After a series of complex interactions with the host, including a delay in onset of adaptive immunity, more macrophages are recruited to the site, specific T cells begin to accumulate, and a granuloma is formed (appendix). Although granulomas are typically thought to be protective, studies in infected zebrafish have highlighted the dynamic nature of these cellular granulomatous lesions and suggest that the granuloma additionally functions as a protective niche that enables bacterial replication.²⁹ The fate of individual granulomas, even in one person, seems to depend on local factors. If too much local inflammation occurs, the granuloma begins to form a centralised area of necrosis that can ultimately liquefy, providing a rich source of infectious organisms for transmission. The local and dynamic nature of the outcome of infection in individual granulomas has been shown by serial PET-CT scanning in patients with active tuberculosis who were not responding to therapy.³⁰ The cellular immunology of the host response to tuberculosis infection has been reviewed extensively.³¹ However, poor understanding of the nature of protective immunity to tuberculosis was highlighted by the failure of a large phase 3 vaccine trial.³² Understanding is needed of why most individuals never develop disease. Interest has been renewed in study of the 10–20% of individuals who are highly exposed but

who never develop immune sensitisation.³³ Finally, human challenge studies with Bacille-Calmette-Guérin (BCG) might provide additional insight into these questions.³⁴ Key aspects about the pathogenesis of drug-resistant tuberculosis are outlined in the appendix.

Diagnosis

Diagnosis of latent tuberculosis

Commercially available tests used to diagnose latent tuberculosis, and relevant readouts, are outlined in the appendix. In low burden settings, guidelines have little agreement about which immunodiagnostic tests to use in close contacts of index cases, in immune-compromised people, and in some recent immigrants to low-incidence settings.³⁵ Generally, in low-incidence settings, guidelines advocate exclusion of active tuberculosis and then recommend chemoprophylaxis on the basis of results of immunodiagnostic tests (either tuberculin skin test [TST] or interferon gamma release assay [IGRA], as advocated in the WHO guideline, or TST followed by IGRA) in tandem with risk stratification (eg, infectiousness of the index case, or age of the contact).^{36–38} Immune-compromising conditions, including HIV co-infection, reduces the sensitivity of TST and IGRA³⁹ and lowers the cutoff for a positive TST (5 mm rather than 10 mm induration). Replacement of TST by IGRA is not recommended in middle-to-high incidence settings.³⁸

Diagnosis of active tuberculosis

Global diagnostic capacity is low, and the case detection rate is suboptimum (64% in 2013).⁵ Expansion of active, rather than passive, case finding is needed to close the detection gap. Diagnosis of latent tuberculosis, optimum passive case finding approaches, groups to be targeted for active case finding, and effect on mortality and disease burden are outlined in panel 1.^{39–53} A community-based, low-cost, sensitive, user-friendly, high-throughput, and same-day point-of-care screening (triaging) test for tuberculosis is clearly needed.⁴⁰ Such tests should have high sensitivity and negative predictive values, and should be rule-out tests. By contrast, more specific rule-in tests, which include detection of drug resistance (figure 2), could be done at centralised health-care centres (eg, microscopy centres and district hospitals). Notably, around 15% of the burden of tuberculosis is due to extrapulmonary tuberculosis (40–50% in the context of HIV co-infection), and a non-sputum-orientated diagnostic strategy is also needed (panel 1). Thus, ideally a non-sputum-based point-of-care test that can be used to diagnose all forms of tuberculosis is needed.

Despite suboptimum sensitivity (~50%; limit of detection of ~10⁴ organisms per mL), smear microscopy is the standard of care in most high-burden settings. To minimise patient dropout, at the cost of a negligible decrease in diagnostic yield, same-day microscopy (two samples collected at the same visit) is recommended.⁵⁴ Sample centrifugation and fluorescence microscopy

improves sensitivity by around 10%.⁵⁵ Light-emitting-diode (LED) microscopy (appendix), endorsed and recommended by WHO, has several cost and operational advantages.⁵⁶ Automated high-throughput smear microscopy is under investigation.

Automated liquid culture (limit of detection of ~10 organisms per mL)⁵⁷ is widely regarded as the gold standard confirmatory test for diagnosis and is more sensitive and rapid, but more costly and prone to contamination, than solid media.⁵⁸ The traditional gold standard for phenotypic drug susceptibility testing, the proportion method with solid agar (1% threshold), is being superseded by standardised methods such as MGIT 960 (BD). In-house methods include microscopic observation of drug susceptibility, nitrate reductase assay (NRA), and colorimetric redox indicator assays (CRI).⁵⁹ Choice of optimum method is dependent on context and resources.

Commercially available confirmatory tests include various nucleic acid amplification tests (NAATs), some of which include testing for drug resistance (appendix). Sputum samples can be directly assessed with the WHO-endorsed Gene Xpert MTB/RIF⁶⁰ and Hain MTBDRplus assays.^{61,62} The Xpert assay works well for patients with suspected pulmonary tuberculosis and for specific forms of extrapulmonary tuberculosis (meningitis in people with HIV⁶³ and lymphadenitis, but not pleural, pericardial, or abdominal tuberculosis).^{60,64} Sensitivity of Xpert was around 89% in smear-positive and around 67% in smear-negative pulmonary tuberculosis,⁶⁵ with high specificity, and the level of detection in sputum is around 150 organisms per mL.⁶⁶ The Xpert assay could feasibly be done by minimally trained health-care workers in peripheral facilities.⁶⁷ Xpert is cost-effective in endemic settings⁶⁸ and enables rapid diagnosis of rifampicin-resistant tuberculosis (thus potentially affecting transmission). However, Xpert is unable to detect isoniazid-mono-resistant tuberculosis, might give a positive result after completion of treatment,⁶⁹ and cannot be used for treatment monitoring. Controlled trials have failed to show reductions in morbidity,⁷⁰ mortality,^{70,71} or tuberculosis burden.^{67,70,71} In populations with an MDR tuberculosis prevalence of less than 10%, the positive predictive value for rifampicin resistance is likely to be less than 85%, and confirmatory testing with an alternative method is advisable.⁷² The decision of whether to continue MDR tuberculosis treatment when drug susceptibility results are discordant is challenging because of hetero-resistance (the presence, within a larger population of fully susceptible mycobacteria, sub-populations with lesser susceptibility) and might be guided by *rpoB* gene sequencing and clinical features (eg, presence of risk factors for MDR tuberculosis).

Several next-generation NAAT technologies are in advanced stages of development (appendix), including Xpert cartridges with alternative technology able to detect second-line drug resistance. Genotypic drug-resistance tests, including to second-line drugs, might be undertaken

Panel 1: Diagnosis of latent and active tuberculosis

Diagnosis of latent tuberculosis

- Diagnosis of latent tuberculosis cannot be made with certainty, and mycobacterial load in people with presumed latent tuberculosis is not measurable
- The likelihood of latent tuberculosis is inferred indirectly through quantifying the effector memory T-cell response in the skin (tuberculin skin test [TST] and RD-1-specific skin tests, such as C-TB)^{39,40} or the blood (interferon gamma release assays [IGRAs], Quantiferon Gold In-Tube and Plus, and TSPOT-TB; appendix)
- Detectable memory T cells might signify active tuberculosis, previous tuberculosis, recent or remote exposure, latent tuberculosis, or exposure to specific environmental mycobacteria;⁴¹ therefore, neither IGRAs nor TST can distinguish latent from active tuberculosis
- Results of randomised controlled trials suggest that treatment of TST-positive people reduces the short-term risk of tuberculosis development by about 70%⁴²
- Surrogate performance measures suggest that IGRA sensitivity in active tuberculosis is around 80%,⁴³ specificity is better than in TST (especially when Bacille-Calmette-Guérin is administered after birth),⁴⁴ IGRA reversion occurs spontaneously in a substantial number of cases,^{45,46} and short-term positive predictive value for active tuberculosis is poor (~1–2%) for IGRA and TST^{47,48}
- A research priority is to identify which patients with latent tuberculosis are at high risk of progression to active tuberculosis

Diagnosis of active tuberculosis

Passive case finding strategy

- Passive case finding (symptom-triggered testing in people presenting at health-care facilities) fails to detect 40–50% of the total burden⁴⁹
- Optimum testing algorithms are context-specific (dependent on tuberculosis prevalence, HIV and multidrug-resistant tuberculosis prevalence, affordability, cost-effectiveness thresholds, and access to diagnostic methods and capacity)^{49,50}

Active case finding strategy

- Targeted screening of high-risk groups is recommended (close contacts, people with HIV, prisoners, miners [especially silica-exposed miners], people with untreated fibrotic chest radiograph lesions, people in high prevalence settings [>1% prevalence of tuberculosis], people passively seeking health care, and people in shelters, slums, and shanty towns, where several risk factors predominate)⁴⁹
- The predictive value of different screening algorithms is outlined in detail by WHO⁴⁹
- Results of modelling studies suggest that improved point-of-care diagnostics could have transformative effects only if used in the context of targeting screening and active case finding⁵¹
- On the basis of three systematic reviews, only limited or poor quality evidence suggests that smear-microscopy-based active case finding detects earlier and less severe disease, and affects disease burden or outcomes⁴⁹
- Improved methods and approaches for active case finding are urgently needed to minimise transmission and increase detection

Limitations of sample collection

- A strategy relying on spontaneously expectorated sputum is inadequate in about one-third of tuberculosis cases (more inadequate in children and HIV co-infection) because of several factors (eg, extrapulmonary tuberculosis cases [~15%], poor quality sputum samples, suboptimum sputum volumes, bacillary concentrations below the test detection threshold, or inability to obtain sputum [~10% of cases])
- Alternative sampling techniques might be needed (eg, sputum induction, bronchoscopy, gastric aspiration, and organ-specific aspiration or biopsy)
- Motivation and instruction for health-care workers about how to obtain an adequate sputum sample is crucial,⁵² and is the preferred first step in people with sputum-scarce or smear-negative tuberculosis⁵³

with the Hain MTBDRsl assay (with isolates or smear-positive sputum),⁷³ array-based methods, or targeted or next-generation whole-genome sequencing. The feasibility⁴⁵ and effect of rapid detection of drug resistance using with genome sequencing⁷⁴ needs prospective validation.

The Determine urine lipoarabinomannan (LAM) point-of-care lateral flow assay (appendix) is a low-cost useful rule-in test in people with HIV with a CD4 cell count of less than 200 cells/ μ L, especially in those who are sputum scarce or smear negative.^{75,76} Sensitivity increases with decreasing CD4 cell count.⁷⁷ Whether the urine LAM assay can affect mortality in HIV-endemic settings is unclear. Several other protein and nucleic acid candidate⁵⁵ antigenic targets have been identified in urine.⁷⁸

Alternative novel approaches to diagnosis (figure 2)

that need validation include detection of volatile organic compounds in breath and sweat,⁷⁹ targeted fluorescent-labelled tuberculosis-specific enzyme-based probes,⁴⁰ blood-based host transcriptomic signatures,^{80,81} and computer-assisted chest radiograph diagnosis.⁴⁰ Remarkably, immunodiagnostic tests with serum-based antibody and antigen detection are still used in endemic countries despite their proven poor accuracy and WHO's recommendations against their use.^{82,83}

Clinical presentation of tuberculosis

The clinical presentation of tuberculosis has been reviewed in detail elsewhere. The clinical manifestations of tuberculosis are protean because any organ might be involved. The classic symptoms of fever, drenching night

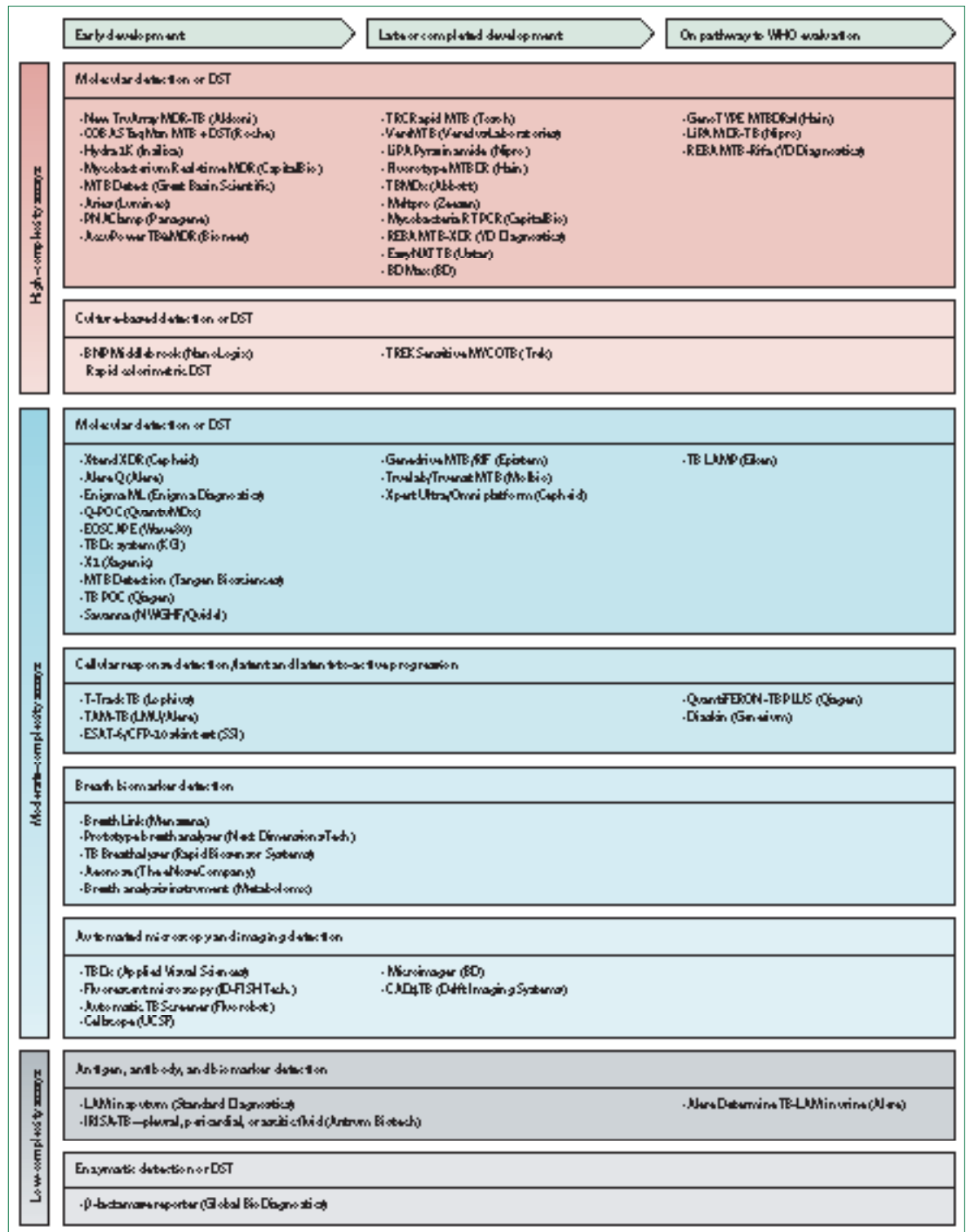


Figure 2: Summary of diagnostic tests in various phases of development

Phases of development include early prototype stage, locked in design phase, commercially available, and on the pathway to WHO evaluation. Drugs are classified according to assay complexity. DST=drug susceptibility testing. MDR=multidrug-resistant. TB=tuberculosis. MTB=Mycobacterium tuberculosis. XDR=extensively drug-resistant. Coproduced with the Foundation for Innovative New Diagnostics.

sweats, and weight loss, accompanied by symptoms from the involved organs, are important clues to the presence of tuberculosis. Several clinical presentations of tuberculosis are outlined in the appendix.

Treatment of tuberculosis

Drug-sensitive tuberculosis

The evidence base for the recommended regimen for drug-sensitive tuberculosis (isoniazid and rifampicin for 6 months, together with pyrazinamide and ethambutol for the first 2 months) was established four decades ago, but the regimen is highly effective. Although called short course, the regimen's main drawback is the duration of therapy. The proportion of patients defaulting therapy increased linearly after 4 weeks and varied between 7% and 53·6% in a systematic review.⁸⁴

Directly observed therapy (DOT) was widely implemented by tuberculosis control programmes as a strategy to improve adherence and reduce default without good evidence that it was effective. Clinic-based DOT, which is widely practiced, substantially increases costs to both providers and patients,⁸⁵ and is a paternalistic method of adherence support. Proponents of DOT argue that it is “the only current documented means” to ensure cure and limit emergence of drug resistance.⁸⁶ However, a meta-analysis comparing outcomes of DOT with self-administered therapy reported no difference in cure, relapse, or acquired drug resistance, but DOT decreased the proportion of patients defaulting therapy.⁸⁷ WHO no longer recommends universal DOT and encourages a flexible approach to supervision of treatment in health-care facilities, the workplace, or the community, with the exception of selected populations (eg, injection drug users or prisoners) for whom DOT is still recommended.⁸⁸

In resource-limited settings, therapy is monitored in patients with sputum smear-positive pulmonary tuberculosis by repetition of the sputum smear at 2 months and 5 months. Treatment success is defined by completion of therapy with negative follow-up sputum smears. The median time to sputum culture conversion in sputum-smear-positive pulmonary tuberculosis is 4–6 weeks, but is longer in African patients after adjustment for confounders.⁸⁹ The observed lower rifampicin concentrations in African patients,⁹⁰ which has been linked to the high allele frequency of a polymorphism the *SLCO1B1* gene,⁹¹ could explain slower culture conversion times.

Short course therapy is generally well tolerated. The most serious adverse drug reaction is drug-induced liver injury, which can be caused by rifampicin, isoniazid, or pyrazinamide. The reported incidence of drug-induced liver injury varies from 5% to 33%,⁹² but most studies include a large proportion of patients with asymptomatic elevation of transaminases. Transient elevation of transaminases occurs commonly in the first few weeks of therapy, a phenomenon termed hepatic adaptation. Inexperienced clinicians might inappropriately interrupt or

change therapy in patients with hepatic adaptation. Routine monitoring of liver function tests is not recommended, even in high-income countries,⁹² unless the patient is at high risk of hepatotoxicity (eg, alcohol misuse, chronic viral hepatitis, or pregnancy). Potentially hepatotoxic drugs should be withdrawn if clinical hepatitis occurs, and two second-line drugs added to ethambutol. When hepatitis is settling, re-challenge with rifampicin and isoniazid, and possibly also with pyrazinamide, should be considered. Outcomes of three re-challenge regimens did not differ significantly, and the regimens were successful in about 90% of participants in a randomised controlled trial.⁹³ Our preference is to use the American Thoracic Society's re-challenge regimen⁹² because it is fairly simple.

Adjunctive corticosteroids

Adjunctive corticosteroids reduce inflammation and improve outcomes in some forms of tuberculosis. Corticosteroids reduce death and residual neurological deficit in tuberculous meningitis.⁹⁴ A meta-analysis⁹⁵ of trials in the rifampicin era in all forms of tuberculosis reported a mortality benefit for corticosteroids in patients with tuberculous meningitis and pericarditis, but not in those with pulmonary tuberculosis. However, no mortality benefit was reported for corticosteroids in patients with tuberculous pericarditis in the large IMPI trial,⁹⁶ which was published after the meta-analysis. Participants randomised to corticosteroids in the IMPI trial had a three-fold increased risk of developing cancers, which were mostly HIV associated—an important reminder of the dangers of corticosteroids in patients who are already immune suppressed. At present, evidence is insufficient to support use of adjunctive corticosteroids in any form of tuberculosis in patients with HIV.

HIV co-infection

Patients with HIV-associated tuberculosis have an increased recurrence rate, which results from re-infection rather than relapse.⁹⁷ Whether short course therapy for tuberculosis is more toxic in patients with HIV than in those without HIV is unknown.⁹⁸ Assigning causality of adverse events to individual drugs is difficult in patients with HIV because they often have comorbidities and take many concomitant medications.

Rifampicin strongly induces many drug-metabolising enzymes and transporters. Concentrations of many antiretroviral drugs are reduced by coadministered rifampicin, necessitating increased antiretroviral doses or switching from rifampicin to rifabutin,⁹⁹ which is a weak inducer.

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response to subclinical or treated tuberculosis, typically presenting about 2 weeks after starting antiretroviral therapy (ART), with fever accompanied by new, recurrent, or worsening lymph node enlargement, pulmonary infiltrates, or serositis (appendix). Incidence of IRIS increases exponentially

Panel 2: Medical and surgical management of drug-specific resistance profiles**Isoniazid mono-resistant tuberculosis**

- Treat for 6 months with rifampicin, pyrazinamide, and ethambutol,^{107–109} or for 9 months with rifampicin and rifampicin in the 2 month intensive phase and rifampicin and ethambutol in the continuation phase³⁶

Multidrug-resistant (MDR) tuberculosis

- Ideally use at least four drugs to which the strain has proven or likely susceptibility (drugs previously taken for 3 months or longer are generally avoided; excludes pyrazinamide and ethambutol)¹¹⁰
- Use a backbone of a later-generation fluoroquinolone (eg, moxifloxacin or levofloxacin), plus an injectable drug (amikacin, kanamycin, or capreomycin)¹¹⁰
- Add any first-line drug and additional group four drugs (eg, cycloserine, terizidone, ethionamide, or prothionamide) to which the isolate is susceptible
- Injectable drugs are generally used for 6–8 months, and 21–24 months of treatment is recommended¹¹⁰
- Oxazolidinones (linezolid) can be used for an effective regimen in fluoroquinolone-resistant MDR (and extensively drug-resistant [XDR]) tuberculosis, but monitoring for toxicity (neuropathy and bone marrow depression) is needed^{111–113}
- Bedaquiline or delamanid can be added to the regimen if toxicity or high-grade resistance precludes a regimen containing four or more drugs likely to be effective (both drugs prolong QT interval, thus needing monitoring)^{114,115}
- Psychosocial and financial support are crucial to maintain adherence
- Patients should be monitored for adverse drug reactions,

which are common¹¹⁶

- A single drug should not be added to a failing regimen

XDR tuberculosis and resistance beyond XDR tuberculosis

- Regimens should be based on prevailing patterns of drug resistance and on similar principles to those outlined for MDR tuberculosis (use of four or more drugs is likely to be effective)
- Adverse events such renal failure, hypokalaemia, hypomagnesaemia, and hearing loss are associated with capreomycin¹¹⁶
- Differential susceptibility to fluoroquinolones can occur;¹¹⁷ clofazamine, linezolid, and high-dose isoniazid (guided by genotypic testing) might be useful to optimise the regimen¹¹⁸
- Other group four (oral bacteriostatic second-line drugs) and five drugs (drugs with unclear efficacy or role in treatment of drug-resistant tuberculosis)⁶ are often used, but their effectiveness is uncertain

Surgical management of MDR and XDR tuberculosis

- Candidates for surgery include patients with unilateral disease (or apical bilateral disease in selected cases) with adequate lung function who have not responded to medical treatment¹¹⁹
- Surgical intervention might be appropriate in patients at high risk of relapse or treatment failure despite response to therapy (eg, XDR tuberculosis or resistance beyond XDR tuberculosis)¹¹⁹
- Facilities for surgical lung resection are restricted and often inaccessible
- PET-CT might be useful to clarify the presence of contralateral disease and might have prognostic use, but its role in this context needs validation (PET-CT images are shown in the appendix)^{120,121}

with decreasing CD4 cell counts.¹⁰⁰ Deferring ART initiation to 8 weeks rather than 2 weeks after starting therapy for tuberculosis reduces risk of IRIS, but increases risk of death in patients with CD4 cell counts of less than 50 cells/ μ L.¹⁰¹ Tuberculosis–IRIS has a low mortality,¹⁰⁰ except for cases with neurological involvement.¹⁰² Tuberculosis–IRIS is characterised by increased concentrations of proinflammatory and anti-inflammatory cytokines,¹⁰³ and of proinflammatory markers of innate and myeloid cell activation.¹⁰⁴ Data from studies in mice of IRIS due to mycobacterial infections suggest that increased responsiveness of infected macrophages to signalling from rapid restoration of mycobacterial antigen-specific CD4 T lymphocytes underlies the observed immunopathology.¹⁰⁵ Prednisone reduced duration of hospital admissions and the need for therapeutic procedures in a placebo-controlled trial¹⁰⁶ of participants with tuberculosis–IRIS.

Treatment of drug-resistant tuberculosis and emergence of incurable strains

Principles of treatment for MDR and XDR tuberculosis

are outlined in **panel 2**.^{107–121} The recommended MDR tuberculosis regimen is toxic, poorly tolerated (appendix), prolonged (up to 24 months), and not based on data from controlled trials. Treatment success rates in many countries are only around 50%.⁶ The load of MDR tuberculosis in endemic countries has necessitated treatment decentralisation to peripheral clinics, in which outcomes are equivalent or better.¹²² Emergence of incurable tuberculosis (XDR tuberculosis failures and resistance beyond XDR-tuberculosis), totally drug-resistant (TDR) tuberculosis, can result in community-based transmission of untreatable strains,⁷ and has raised legal, ethical, and logistical dilemmas about placement of patients and their rights to unrestricted travel and work.¹²³

New antituberculosis drugs and regimens

After decades of stagnation, a range of new antituberculosis drugs (appendix) are in clinical development (**table 2**), two of which, bedaquiline and delamanid, have been registered for use in drug-resistant tuberculosis, whereas others such as SQ109 have shown limited efficacy in early studies.¹²⁴

	Phase completed	Mechanism of action	Approval	Mechanism of resistance	Common adverse events or cautions	Drug interactions with rifampicin and antiretrovirals*	Ongoing or planned trials†
Bedaquiline/TMC 207 (class: diarylquinoline)	2b	Inhibition of <i>Mycobacterium tuberculosis</i> ATP synthase	USA (FDA); European Union (EMA); Russian Federation (Pharmstandard); South Korea (MFDS); South Africa (MCC)	AtpE gene mutation (encodes subunit c of ATP synthase) Mutations in Rv067 coding for repressors of <i>M tuberculosis</i> efflux pump‡	Increased rates of unexplained deaths (11.4 vs 2.5% in the control group) Prolonged QTc Caution in patients with liver dysfunction	Rifampicin reduces steady-state bedaquiline by 79% Efavirenz reduces steady-state bedaquiline by 52% Lopinavir-ritonavir increases steady-state bedaquiline by 288% No clinically significant interaction with nevirapine	STREAM 2, NIX-TB, PRACTECAL, END-TB, NEX-T RCT, A5343
PA-824/pretomanid (class: nitroimidazole)	2b	Inhibition of mycolic acid biosynthesis and generation of mycobactericidal nitrogen oxide derivatives (dormant <i>M tuberculosis</i>)	None	Mutations in fbiA, fbiB, fbiC lead to impaired coenzyme F420 synthesis Mutation in Rv3547 coding for deazaflavin-dependent nitroreductase (inhibit activation of pro-drug)	Caution in patients with renal dysfunction gastrointestinal tract toxicity	Rifampicin reduces PA-824 by 66% Efavirenz reduces PA-824 35% No significant interaction with lopinavir-ritonavir	STAND-TB (NC-006), NIX-TB, PRACTECAL, NC005, APT
Delamanid/OPC 67683 (class: nitroimidazole)	2b	Inhibits mycolic acid biosynthesis	European Union (EMA)	Mutation in mycobacterial Rv3547 prevents activation of delamanid	Prolonged QTc Potential CNS toxicity when used with isoniazid or fluoroquinolones	Rifampicin reduces delamanid concentrations by 45% No significant interaction with efavirenz and lopinavir-ritonavir	A5343, END-TB, Phase 3 delamanid trial (in progress), C213 (planned)
SQ-109 (class diamines)	2a	Inhibits mycobacterial cell wall synthesis specifically targeting transmembrane transporter encoded by <i>mmpL3</i> gene	None	Mutation in the <i>mmpL3</i> gene could potentially confer resistance	Gastrointestinal tract toxicity	No clinical data available for interactions	PanACEA; ongoing phase 3 study in Russian patients with MDR tuberculosis
Sutezolid/PNU-100480; AZD5847 (class: oxazolidinones)	2a	Inhibits protein synthesis	None	Lower MIC for <i>M tuberculosis</i> than linezolid	Peripheral neuropathy Transaminitis	No clinical data available for interactions	Planning in progress

FDA=Food and Drug Administration. EMA=European Medicines Agency. MCC=Medicines Control Council. MDR=multidrug-resistant. MFDS=Ministry of Food and Drug Safety. MIC=minimal inhibitory concentration. *A reduction in the concentrations of the parent drug due to a co-administered inducing drug might be compensated for by an increase in concentrations of the active metabolite. Unless otherwise stated, the % changes are in area under curve. †Current or planned drug-resistant tuberculosis trials ([updated list](#)). Phase 1 early bactericidal activity studies using AZD5847 (ClinicalTrials.gov, number NCT01516203), and meropenem and faropenem (an orally available carbapenem; ClinicalTrials.gov, number NCT02349841) have been completed, but data were unavailable at the time of writing. ‡This mechanism also confers resistance to clofazimine. The comprehensively referenced table with additional details about phase 2 studies is available in the appendix. Recently published phase 3 fluoroquinolone-related trials are described in the text. Outcomes of published studies of high-dose rifamycins including rifapentine are described in the text, although others are ongoing or not yet published. The STAND study will assess a 4-month regimen for drug-sensitive tuberculosis. Additionally, ACTG 5312 is assessing the efficacy of high-dose isoniazid. Recent phase 2 and 3 study findings of novel and repurposed agents have been reviewed elsewhere.

Table 2: New or repurposed drugs against active tuberculosis in phase 2 and 3 clinical trials

Several antimicrobial drugs developed for other infectious diseases have useful activity against *M tuberculosis*. These so-called repurposed drugs are the later-generation fluoroquinolones, moxifloxacin, levofloxacin, and gatifloxacin; the oxazolidinone, linezolid; and the anti-leprosy drug, clofazimine.

Mouse models are important in preclinical development of new drugs and regimens. Although mouse models of tuberculosis do not closely resemble human disease, they are often used to assess duration of therapy. Clinical development of new drugs and regimens is undertaken in patients with pulmonary tuberculosis by assessing their effect on sputum bacillary concentrations for 7–14 days in early bactericidal activity studies, or by assessing sputum culture conversion rates for 8 weeks. Although both approaches have limitations, they are valuable tools to identify optimum doses of individual drugs and to select drug combinations.

Shorter regimens for drug-sensitive tuberculosis

One or more drugs used in short course regimens—rifampicin and pyrazinamide—will be used in novel regimens to shorten duration of treatment. Results of early bactericidal activity studies show that increased doses of rifampicin or rifapentine increase the rate of decline in quantitative sputum cultures.^{125–127} The concentrations of rifampicin and pyrazinamide were key determinants of sterilising activity for 8 weeks in a study of patients with pulmonary tuberculosis,¹²⁸ suggesting that increased doses of pyrazinamide and rifampicin should be used in future studies of treatment-shortening regimens. Increased exposures to rifapentine, a long-acting rifamycin, are likewise associated with sputum culture conversion within 8 weeks.¹²⁷ Several novel regimens with fluoroquinolones, bedaquiline, or pretomanid, or a combination, have shown potential to shorten treatment duration in phase 2 clinical trials.^{129,130}

For the updated list of current or planned drug-resistant tuberculosis trials see http://www.resisttb.org/?page_id=1602

Three randomised controlled trials^{131–133} of 4-month regimens shown in mice to need shorter duration of therapy with the fluoroquinolones gatifloxacin or moxifloxacin (together with rifampicin, pyrazinamide, and isoniazid, or ethambutol) all showed higher relapse rates than standard short course therapy. Sputum culture conversion was faster in the moxifloxacin groups than in the standard therapy group in the REMoxTB trial,¹³³ as was the case in the 8 week studies,¹³⁴ which prompted treatment shortening trials. However, the larger sample size in the REMoxTB trial enabled increased precision to detect the magnitude of difference in sputum culture conversion and suggested that treatment shortening by about a month might be possible with moxifloxacin-based regimens.¹³³ Phase 3 treatment-shortening trials will be done with 5-month regimens, and the search for more potent regimens continues.

New drugs and regimens for drug-resistant tuberculosis

New drugs and regimens are urgently needed for MDR and XDR tuberculosis. High-dose isoniazid resulted in faster sputum culture conversion in a small randomised controlled trial,¹³⁵ but caused a ten-fold increased risk of peripheral neuropathy and is likely to only benefit patients with low-level isoniazid resistance. A 9-month regimen including clofazimine and high-dose isoniazid resulted in high cure rates in a non-randomised cohort study¹³⁶—results of a randomised controlled trial comparing this regimen to the standard 21–24-month regimen are awaited. Bedaquiline,¹³⁷ delamanid,¹³⁸ and linezolid¹³⁹ have all shown improved sputum culture conversion rates when added to optimised background therapy in patients with drug-resistant pulmonary tuberculosis. Clarification of the optimum combination of drugs and duration of therapy for MDR tuberculosis needs further studies (table 2), but less toxic, shorter, and more effective regimens are likely to be developed in the near future.

Prognosis and post-tuberculous lung disease

The 10-year case fatality rates are 70% for untreated smear-positive tuberculosis and 20% for smear-negative tuberculosis.² The corresponding case fatality rates for people with HIV are 83% for smear-positive patients and 74% for smear-negative patients.² Increasing age, more extensive disease, and HIV co-infection are associated with increased mortality. Mortality with treatment is around 2·5% for people without HIV and around 14% in people with HIV.^{140,141}

Pulmonary tuberculosis can cause substantial chronic morbidity owing to residual post-tuberculous bronchiectasis, chronic obstructive pulmonary disease (COPD), aspergillomas, and lung destruction (appendix).¹⁴² These disorders cause substantial and progressive lung disability, culminating in respiratory failure or massive haemoptysis. Aspergillomas occur in residual cavities (examples from explanted lungs shown in the appendix)

and might cause massive haemoptysis needing surgery or bronchial artery embolisation (the optimum management strategy is unclear), or chronic invasive aspergillosis.¹⁴³ Case series have reported encouraging results with voriconazole in patients with aspergillomas who refuse, or are unfit for, surgery,¹⁴⁴ but controlled data are needed. In developing countries, tuberculosis is an important cause of COPD, mainly owing to small airways disease and gas trapping rather than emphysema.¹⁴⁵ The natural history of post-tuberculous COPD and responses to conventional COPD treatment are unclear. Patients with progressive post-tuberculous bronchiectasis are often managed erroneously with repeated courses of empiric treatment for tuberculosis. The pathogenesis of dysfunctional extracellular matrix deposition and clearance mechanisms, lung cavitation,¹⁴⁶ and lung remodelling due to tuberculosis are incompletely understood.¹⁴³ Immunotherapeutic approaches to minimisation or prevention of cavitation and fibrosis, both of which might result in post-tuberculous lung disease, need further study.

Prevention of tuberculosis

Preventive therapy

Preventive therapy for people at high risk of tuberculosis is an important component of the strategies to eliminate tuberculosis outlined by WHO in their post-2015 strategy.¹⁴⁷ In high-burden countries, preventive therapy is usually limited to people with HIV and children aged less than 5 years with household contacts. In low-burden countries, immigrants from high-burden countries and all close contacts with latent tuberculosis are targeted for preventive therapy. The most widely used regimen for preventive therapy in people with and without HIV is isoniazid for 6–12 months, with generally increased efficacy with longer duration.¹⁴⁸

The efficacy of preventive therapy in HIV-infected adults is determined by their TST status.¹⁴⁹ Decreasing CD4 lymphocyte counts in patients with untreated HIV infection are associated with increased risk of false-negative TSTs¹⁵⁰ and tuberculosis.¹⁵¹ The fact that TST positivity is associated with benefit from preventive therapy is difficult to explain because the test's ability to diagnose latent tuberculosis infection is poorest in people at highest risk of tuberculosis. In people with HIV infection, some extent of cellular immunity to tuberculosis, for which a positive TST is a proxy, seems to be needed for preventive therapy to be effective. Unfortunately, the duration of benefit after isoniazid preventive therapy is short.¹⁵² WHO recommends isoniazid for 36 months for people with positive or unknown TST status,¹⁵³ after the results of the BOTUSA study,¹⁵⁴ which showed that 36 months of isoniazid was substantially more effective for prevention of tuberculosis than 6 months in participants with positive TST status. It is important to rule out active tuberculosis before initiation of preventive therapy in HIV-infected people to limit selection of drug resistance. Absence of the classic

Panel 3: Prevention of tuberculosis—contact tracing, infection control, and vaccines

Close contacts

- Identification and early treatment of contacts with active tuberculosis should reduce morbidity and risk of transmission, but is poorly implemented in most high-burden countries
- WHO recommends investigation of close contacts for active tuberculosis or latent infection when the index case has any one of the following characteristics: pulmonary tuberculosis with positive sputum smears, multidrug-resistant tuberculosis, a child aged less than 5 years, or HIV co-infection
- Prevalence of active tuberculosis is 3.1% in low-to-middle-income countries and 1.4% in high-income countries, and prevalence of latent tuberculosis in contacts was 51.5% in low-to-middle-income countries and 28.1% in high-income countries; household contact tracing would reduce tuberculosis incidence by an estimated 2% per year if cases of active tuberculosis were identified and treated

Infection control

- Very limited evidence exists for efficacy of the various interventions recommended for personal and environmental protection
- Patients with suspected pulmonary tuberculosis should be nursed in negative-pressure isolation rooms with at least 12 air changes per hour, which is not feasible in high-burden countries
- WHO recommends natural ventilation in resource-limited settings; opening windows provides natural ventilation that exceeds 12 air changes per hour, and wind-driven roof turbines achieve a high number of air changes per hour and are not easily blocked by staff or patients
- Personal protection with properly fitted face masks that have the capacity to filter droplet nuclei should be used by health-care staff exposed to patients with suspected pulmonary tuberculosis
- Surgical face masks, which are much cheaper than N95 masks, reduce infectiousness when worn by patients with multidrug-resistant tuberculosis

Vaccines

- Bacille-Calmette-Guérin (BCG) is effective at preventing severe childhood forms of tuberculosis but, for several reasons, protection wanes by adolescence
- At present, 15 vaccine candidates are in clinical trials (appendix)
- These vaccines are either designed to replace BCG (pre-exposure vaccine), be given in infancy or adolescence to augment BCG-mediated protection (prime-boost strategy), or to shorten or potentiate treatment (therapeutic vaccine)
- Categories of vaccines include live attenuated *Mycobacterium tuberculosis*, re-engineered BCG, mycobacterial whole cells or extract, adjuvant-complexed single or fusion tuberculosis-specific proteins, and mycobacterial proteins expressed through a viral vector or plasmid DNA
- Vaccine candidates have been selected on the basis of protection in animals (mycobacterial stasis in mice, guinea pigs, and non-human primates) and their ability to induce T-helper-1-based CD4 T-cell immune responses in human beings; this approach is being questioned because MVA85A induced a very strong CD4 T-helper 1 response in early studies but failed to provide protection in the phase 2b clinical trial
- Vaccine development is hindered by several challenges, including scarcity of correlates of protective immunity, poor correlation of efficacy between animals and human beings, and restricted funding and capacity for clinical trials
- Several alternative approaches and vaccine concepts are being investigated, including alternative clinical trial and challenge models (including human), interrogation of infectious dose, use of non-protein antigens, and identification of alternative components of the immune system that might be relevant to host immunity (eg, innate and regulatory components, and revisiting the role of antibodies in protection)

The comprehensively referenced panel is available in the appendix.

tuberculosis symptoms of fever, night sweats, and weight loss to exclude active tuberculosis perform less well in people on ART.¹⁵⁵ Isoniazid preventive therapy reduces the risk of tuberculosis in people receiving ART, but, unlike in trials in the pre-ART era, the benefit was seen irrespective of TST status.¹⁵⁶

Interest in the use of rifamycin-based regimens for preventive therapy is increasing. 3-month regimens of rifampicin or rifapentine plus isoniazid are generally well tolerated, and are as effective as 6–12 months of isoniazid in people with or without HIV.¹⁴⁸ Results from a mathematical model suggest that rifamycin-based regimens might cure latent tuberculosis in people with HIV, whereas isoniazid monotherapy does not.¹⁵²

Contact tracing and infection control

Limitation of transmission of airborne pathogens such as *M tuberculosis* in health-care facilities is challenging. Rapid diagnosis and prompt initiation of effective therapy are the foundations of tuberculosis infection control. When close contacts should be traced, the potential gains, key points for contact tracing, and evidence for efficacy of infection control interventions are outlined in [panel 3](#).

Vaccines and research priorities

An effective tuberculosis vaccine is needed for eradication of tuberculosis. Even a vaccine of limited efficacy (~60%) delivered to just 20% of the population could save millions

of lives.¹⁵⁷ The effectiveness of existing vaccines, the planned assessment pipeline, new approaches, and other key aspects of tuberculosis vaccines are outlined in panel 3 and the appendix.

Research priorities in tuberculosis, the importance of operational and patient-centred research, and the importance of a health systems approach have been reviewed in detail elsewhere.^{158,159} Key research priorities in terms of pathogenesis and transmission, diagnosis, drugs and treatment, vaccines, operational, economic and public health research, and cross-cutting themes are outlined in the appendix.

Conclusion

Incidence of tuberculosis is decreasing much more slowly than expected and it remains a global scourge. Encouragingly, after several decades of inertia, advances have been made in the form of several new diagnostics and drugs. However, these advances alone will not achieve the ambitious target set out in the End TB Strategy (appendix). A widely available low-cost screening test is urgently needed to improve detection rates, and an efficient new vaccine and more effective preventive therapy are needed to eradicate tuberculosis. However, these developments need an improved understanding of tuberculosis pathogenesis. In tandem, public health efforts are needed to reduce the major drivers of tuberculosis, including smoking, diabetes, biomass fuel exposure, and HIV co-infection. Finally, political stability and alleviation of poverty and overcrowding worldwide will be essential for eradication of tuberculosis.

Contributors

KD, CEB, and GM contributed equally to the preparation of this Seminar.

Declaration of interests

KD reports grants from Foundation of Innovative New Diagnostics (FIND), eNose Company, Statens Serum Institut, and bioMeriux, and grants and personal fees from ALERE, Oxford Immunotec, Cellestis (now Qiagen), Cepheid, Antrum Biotec, and Hain Lifescience. Additionally, KD 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. CEB reports grants from Cepheid, Hain Life science, YD Dagnostics, and FIND. GM served on the data safety and monitoring board for Janssen for the TMC207 C208 and C207 phase 2 trials in patients with multidrug-resistant MDR tuberculosis, 2007–2012.

Acknowledgments

We acknowledge Helen Wainwright, Graeme Meintjes, Qonita Said-Hartley, Sulaiman Moosa, and Gregory Calligaro for the radiographic and tissue section images in the appendix, and Grant Theron, Aliasgar Esmail, and Laurene Viljoen for assistance with specific inserts and manuscript processing.

References

- Comas I, Coscolla M, Luo T, et al. Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nat Genet* 2013; **45**: 1176–82.
- Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011; **6**: e17601.
- Ryan F. The Forgotten Plague: how the battle against tuberculosis was won—and lost. Boston, MA: Back Bay Books, 1994.
- Cohen T, Dye C. Epidemiology. In: Davies PDO, Gordon SB, Davies G, eds. Clinical tuberculosis. 5th edn. Florida, USA: CRC Press, 2014: 19–36.
- Global tuberculosis Report WHO. Geneva, Switzerland: World Health Organization, 2014.
- Dheda K, Gumbo T, Gandhi NR, et al. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. *Lancet Respir Med* 2014; **2**: 321–38.
- Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet* 2014; **383**: 1230–39.
- Berti E, Galli L, Venturini E, de Martini M, Chiappini E. Tuberculosis in childhood: a systematic review of national and international guidelines. *BMC Infect Dis* 2014; **14** (suppl 1): S3.
- Perez-Velez CM, Marais BJ. tuberculosis in children. *N Engl J Med* 2012; **367**: 348–61.
- Pai M, Menzies D. Interferon-gamma release assays for diagnosis of latent tuberculosis infection. In: Von Reyn FC, Baron E, eds. In UpToDate: Wolters Kluwer Health, 2014: 1–16.
- Lawn SD, Badri M, Wood R. tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS* 2005; **19**: 2109–16.
- Lönnroth K, Castro KG, Chakaya JM, et al. tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet* 2010; **375**: 1814–29.
- Dye C, Glaziou P, Floyd K, Ravigione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; **34**: 271–86.
- Alland D, Kalkut GE, Moss AR, et al. Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and conventional epidemiologic methods. *New Engl J Med* 1994; **330**: 1710–16.
- Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. *New Engl J Med* 1994; **330**: 1703–09.
- Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? *Clin Microbiol Infect* 2013; **19**: 889–901.
- Gardy JL, Johnston JC, Ho Sui SJ, et al. Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *N Engl J Med* 2011; **364**: 730–39.
- Wood R, Morrow C, Ginsberg S, et al. Quantification of shared air: a social and environmental determinant of airborne disease transmission. *PLoS One* 2014; **9**: e106622.
- Cruciani M, Malena M, Bosco O, Gatti G, Serpelloni G. The impact of human immunodeficiency virus type 1 on infectiousness of tuberculosis: a meta-analysis. *Clin Infect Dis* 2001; **33**: 1922–30.
- Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997; **119**: 183–201.
- Portevin D, Gagneux S, Comas I, Young D. Human macrophage responses to clinical isolates from the *Mycobacterium tuberculosis* complex discriminate between ancient and modern lineages. *PLoS Pathog* 2011; **7**: e1001307.
- Robertson BD, Altmann D, Barry C, et al. Detection and treatment of subclinical tuberculosis. *tuberculosis (Edinb)* 2012; **92**: 447–52.
- Capuano SV 3rd, Croix DA, Pawar S, et al. Experimental *Mycobacterium tuberculosis* infection of cynomolgus macaques closely resembles the various manifestations of human *M. tuberculosis* infection. *Infect Immun* 2003; **71**: 5831–44.
- Lin PL, Myers A, Smith L, et al. Tumor necrosis factor neutralization results in disseminated disease in acute and latent *Mycobacterium tuberculosis* infection with normal granuloma structure in a cynomolgus macaque model. *Arthritis Rheum* 2010; **62**: 340–50.
- Lin PL, Ford CB, Coleman MT, et al. Sterilization of granulomas is common in active and latent tuberculosis despite within-host variability in bacterial killing. *Nat Med* 2014; **20**: 75–79.
- Ghesani N, Patrawalla A, Lardizabal A, Salgame P, Fennelly KP. Increased cellular activity in thoracic lymph nodes in early human latent tuberculosis infection. *Am J Respir Crit Care Med* 2014; **189**: 748–50.

- 27 Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol* 2009; 7: 845–55.
- 28 Esmail H, Barry CE 3rd, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. *Philos Trans R Soc Lond B Biol Sci* 2014; 369: 20130437.
- 29 Ramakrishnan L. Revisiting the role of the granuloma in tuberculosis. *Nat Rev Immunol* 2012; 12: 352–66.
- 30 Coleman MT, Chen RY, Lee M, et al. PET/CT imaging reveals a therapeutic response to oxazolidinones in macaques and humans with tuberculosis. *Sci Transl Med* 2014; 6: 265ra167.
- 31 Orme IM, Robinson RT, Cooper AM. The balance between protective and pathogenic immune responses in the TB-infected lung. *Nat Immunol* 2015; 16: 57–63.
- 32 Dorhoi A, Kaufmann SH. Perspectives on host adaptation in response to *Mycobacterium tuberculosis*: modulation of inflammation. *Semin Immunol* 2014; 26: 533–42.
- 33 Cobat A, Gallant CJ, Simkin L, et al. Two loci control tuberculin skin test reactivity in an area hyperendemic for tuberculosis. *J Exp Med* 2009; 206: 2583–91.
- 34 Matsumiya M, Satti I, Chomka A, et al. Gene expression and cytokine profile correlate with mycobacterial growth in a human BCG challenge model. *J Infect Dis* 2015; 211: 1499–509.
- 35 Denkiner CM, Dheda K, Pai M. Guidelines on interferon- γ release assays for tuberculosis infection: concordance, discordance or confusion? *Clin Microbiol Infect* 2011; 17: 806–14.
- 36 NICE. tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: National Institute for Health and Care Excellence, 2011.
- 37 Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection. *MMWR* 2010; 59: 1–25.
- 38 WHO. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization, 2015.
- 39 Pai M, Denkiner CM, Kik SV, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. *Clin Microbiol Rev* 2014; 27: 3–20.
- 40 Dheda K, Ruhwald M, Theron G, Peter J, Yam WC. Point-of-care diagnosis of tuberculosis: past, present and future. *Respirology* 2013; 18: 217–32.
- 41 Dheda K, van Zyl Smit R, Badri M, Pai M. T-cell interferon-gamma release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings. *Curr Opin Pulm Med* 2009; 15: 188–200.
- 42 Ferebee SH, Mount FW. tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. *Am Rev Respir Dis* 1962; 85: 490–510.
- 43 Sester M, Sotgiu G, Lange C, et al. Interferon- γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2011; 37: 100–11.
- 44 Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? *Int J Tuberc Lung Dis* 2006; 10: 1192–204.
- 45 Dorman SE, Belknap R, Graviss EA, et al, and the tuberculosis Epidemiologic Studies Consortium. Interferon- γ release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med* 2014; 189: 77–87.
- 46 Adams S, Ehrlich R, Baatjies R, et al. Incidence of occupational latent tuberculosis infection in South African healthcare workers. *Eur Respir J* 2015; 45: 1364–73.
- 47 Diel R, Lodenkemper R, Nienhaus A. Predictive value of interferon- γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. *Chest* 2012; 142: 63–75.
- 48 Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon- γ release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; 12: 45–55.
- 49 WHO. Systematic screening for active tuberculosis: Principles and recommendations. Geneva: World Health Organization, 2013.
- 50 WHO. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization, 2011.
- 51 Sun AY, Pai M, Salje H, Satyanarayana S, Deo S, Dowdy DW. Modeling the impact of alternative strategies for rapid molecular diagnosis of tuberculosis in Southeast Asia. *Am J Epidemiol* 2013; 178: 1740–49.
- 52 Khan MS, Dar O, Sismanidis C, Shah K, Godfrey-Faussett P. Improvement of tuberculosis case detection and reduction of discrepancies between men and women by simple sputum-submission instructions: a pragmatic randomised controlled trial. *Lancet* 2007; 369: 1955–60.
- 53 Peter JG, Theron G, Pooran A, Thomas J, Pascoe M, Dheda K. Comparison of two methods for acquisition of sputum samples for diagnosis of suspected tuberculosis in smear-negative or sputum-scarce people: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 471–78.
- 54 WHO. Same-day diagnosis of tuberculosis by microscopy. Geneva: World Health Organization, 2011.
- 55 Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006; 6: 570–81.
- 56 Whitelaw A, Peter J, Sohn H, et al. Comparative cost and performance of light-emitting diode microscopy in HIV-tuberculosis-co-infected patients. *Eur Respir J* 2011; 38: 1393–97.
- 57 van Zyl-Smit RN, Binder A, Meldau R, et al. Comparison of quantitative techniques including Xpert MTB/RIF to evaluate mycobacterial burden. *PLoS One* 2011; 6: e28815.
- 58 Cruciani M, Scarparo C, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. *J Clin Microbiol* 2004; 42: 2321–25.
- 59 WHO. Noncommercial culture and drug-susceptibility testing methods for screening patients at risk for multidrug-resistant tuberculosis. Geneva: World Health Organization, 2011.
- 60 WHO. Xpert MTB/RIF implementation manual. Geneva: World Health Organization, 2014.
- 61 WHO. The use of molecular line probe assay for the detection of resistance to second-line anti-tuberculosis drugs. Geneva: World Health Organization, 2013.
- 62 Barnard M, Gey van Pittius NC, van Helden PD, Bosman M, Coetzee G, Warren RM. The diagnostic performance of the GenoType MTBDRplus version 2 line probe assay is equivalent to that of the Xpert MTB/RIF assay. *J Clin Microbiol* 2012; 50: 3712–16.
- 63 Patel VB, Theron G, Lenders L, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculosis meningitis in a high burden setting: a prospective study. *PLoS Med* 2013; 10: e1001536.
- 64 Pandie S, Peter JG, Kerbelker ZS, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous pericarditis compared to adenosine deaminase and unstimulated interferon- γ in a high burden setting: a prospective study. *BMC Med* 2014; 12: 101.
- 65 Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev* 2014; 1: CD009593.
- 66 Theron G, Peter J, van Zyl-Smit R, et al. Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in a high HIV prevalence setting. *Am J Respir Crit Care Med* 2011; 184: 132–40.
- 67 Theron G, Zijenah L, Chanda D, et al, and the TB-NEAT team. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet* 2014; 383: 424–35.
- 68 Langley I, Lin HH, Egwaga S, et al. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. *Lancet Glob Health* 2014; 2: e581–91.
- 69 Friedrich SO, Rachow A, Saathoff E, et al, and the Pan African Consortium for the Evaluation of Anti-tuberculosis Antibiotics (PanACEA). Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment. *Lancet Respir Med* 2013; 1: 462–70.
- 70 Cox HS, Mbhele S, Mohess N, et al. Impact of Xpert MTB/RIF for TB diagnosis in a primary care clinic with high TB and HIV prevalence in South Africa: a pragmatic randomised trial. *PLoS Med* 2014; 11: e1001760.

- 71 Churchyard GJ, Stevens WS, Mametja LD, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health* 2015; 3: e450–57.
- 72 WHO. Rapid Implementation of the Xpert MTB/RIF diagnostic test: Technical and operational 'How-to' Practical considerations. Geneva: World Health Organization, 2011.
- 73 Theron G, Peter J, Richardson M, et al. The diagnostic accuracy of the GenoType®MTBDRsl assay for the detection of resistance to second-line anti-tuberculosis drugs. *Cochrane Database Syst Rev* 2014; 10: CD010705.
- 74 Köser CU, Bryant JM, Becq J, et al. Whole-genome sequencing for rapid susceptibility testing of *M. tuberculosis*. *N Engl J Med* 2013; 369: 290–92.
- 75 Peter JG, Theron G, van Zyl-Smit R, et al. Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. *Eur Respir J* 2012; 40: 1211–20.
- 76 Lawn SD, Dheda K, Kerkhoff AD, et al. Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. *BMC Infect Dis* 2013; 13: 407.
- 77 Minion J, Leung E, Talbot E, Dheda K, Pai M, Menzies D. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. *Eur Respir J* 2011; 38: 1398–405.
- 78 Young BL, Mlamla Z, Gqamana PP, et al. The identification of tuberculosis biomarkers in human urine samples. *Eur Respir J* 2014; 43: 1719–29.
- 79 Chambers ST, Scott-Thomas A, Epton M. Developments in novel breath tests for bacterial and fungal pulmonary infection. *Curr Opin Pulm Med* 2012; 18: 228–32.
- 80 Anderson ST, Kaforou M, Brent AJ, et al, and the ILULU Consortium, and the KIDS TB Study Group. Diagnosis of childhood tuberculosis and host RNA expression in Africa. *N Engl J Med* 2014; 370: 1712–23.
- 81 Berry MP, Graham CM, McNab FW, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* 2010; 466: 973–77.
- 82 Steingart KR, Flores LL, Dendukuri N, et al. Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: an updated systematic review and meta-analysis. *PLoS Med* 2011; 8: e1001062.
- 83 Flores LL, Steingart KR, Dendukuri N, et al. Systematic review and meta-analysis of antigen detection tests for the diagnosis of tuberculosis. *Clin Vaccine Immunol* 2011; 18: 1616–27.
- 84 Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. *Trop Med Int Health* 2008; 13: 703–12.
- 85 Steffen R, Menzies D, Oxlade O, et al. Patients' costs and cost-effectiveness of tuberculosis treatment in DOTS and non-DOTS facilities in Rio de Janeiro, Brazil. *PLoS One* 2010; 5: e14014.
- 86 Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tuberculosis: the importance of direct observation. *Bull World Health Organ* 2007; 85: 407–09.
- 87 Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. *Clin Infect Dis* 2013; 57: 21–31.
- 88 WHO. THE STOP TB STRATEGY, Building on and enhancing DOTS to meet the TB-related Millennium Development Goals. Geneva: World Health Organization, 2006. http://whqlibdoc.who.int/hq/2006/WHO_HTM_STB_2006.368_eng.pdf?ua=1 (accessed July 1, 2015).
- 89 Mac Kenzie WR, Heilig CM, Bozeman L, et al. Geographic differences in time to culture conversion in liquid media: tuberculosis Trials Consortium study 28. Culture conversion is delayed in Africa. *PLoS One* 2011; 6: e18358.
- 90 Weiner M, Peloquin C, Burman W, et al. Effects of tuberculosis, race, and human gene SLCO1B1 polymorphisms on rifampin concentrations. *Antimicrob Agents Chemother* 2010; 54: 4192–200.
- 91 Chigutsa E, Visser ME, Swart EC, et al. The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: dosing implications. *Antimicrob Agents Chemother* 2011; 55: 4122–27.
- 92 Saukkonen JJ, Cohn DL, Jasmer RM, et al, and the ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; 174: 935–52.
- 93 Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. *Clin Infect Dis* 2010; 50: 833–39.
- 94 Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008; 1: CD002244.
- 95 Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; 13: 223–37.
- 96 Mayosi BM, Ntsekhe M, Bosch J, et al, and the IMPI Trial Investigators. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. *N Engl J Med* 2014; 371: 1121–30.
- 97 Crampin AC, Mwaungulu JN, Mwaungulu FD, et al. Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in Malawi. *AIDS* 2010; 24: 417–26.
- 98 McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis* 2007; 196 (suppl 1): S63–75.
- 99 CDC. tuberculosis National Center for HIV/AIDS VH, STD, and TB Prevention, Division of tuberculosis Elimination, Managing Drug Interactions in the Treatment of HIV-Related tuberculosis National, 2013. http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf (accessed July 1, 2015).
- 100 Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, and the IeDEA Southern and Central Africa. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; 10: 251–61.
- 101 Uthman OA, Okwundu C, Gbenga K, et al. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis. *Ann Intern Med* 2015; 163: 32–39.
- 102 Yuzbasiyan-Gurkan V, Johnson V, Brewer GJ. Diagnosis and characterization of presymptomatic patients with Wilson's disease and the use of molecular genetics to aid in the diagnosis. *J Lab Clin Med* 1991; 118: 458–65.
- 103 Tadokera R, Meintjes G, Skolimowska KH, et al. Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome. *Eur Respir J* 2011; 37: 1248–59.
- 104 Andrade BB, Singh A, Narendran G, et al. Mycobacterial antigen driven activation of CD14++CD16- monocytes is a predictor of tuberculosis-associated immune reconstitution inflammatory syndrome. *PLoS Pathog* 2014; 10: e1004433.
- 105 Barber DL, Andrade BB, Sereti I, Sher A. Immune reconstitution inflammatory syndrome: the trouble with immunity when you had none. *Nat Rev Microbiol* 2012; 10: 150–56.
- 106 Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010; 24: 2381–90.
- 107 American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. Atlanta: US Department of Health and Human Services, 2003.
- 108 Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; 133: 423–30.
- 109 Hong Kong Chest Service/British Medical Research Council. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1987; 136: 1339–42.
- 110 WHO. WHO updated references on management of drug-resistant tuberculosis: guidelines for the programmatic management of drug-resistant tuberculosis—2011 update. Geneva: World Health Organization, 2011.
- 111 Lange C, Abubakar I, Alffenaar JW, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in

- Europe: a TBNET consensus statement. Lausanne: ERS Publications, 2014.
- 112 Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; **40**: 1430–42.
 - 113 Chang KC, Yew WW, Tam CM, Leung CC. WHO group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis. *Antimicrob Agents Chemother* 2013; **57**: 4097–104.
 - 114 WHO. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization, 2013.
 - 115 WHO. The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim policy guidance. Geneva: World Health Organization, 2014.
 - 116 Müller B, Borrell S, Rose G, Gagneux S. The heterogeneous evolution of multidrug-resistant *Mycobacterium tuberculosis*. *Trends Genet* 2013; **29**: 160–69.
 - 117 Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2010; **51**: 6–14.
 - 118 Muller B, Streicher EM, Hoek KG, et al. inhA promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? *Int J Tuberc Lung Dis* 2011; **15**: 344–51.
 - 119 WHO. The role of surgery in the treatment of pulmonary TB and multidrug- and extensively drug-resistant TB. Regional Office for Europe, Copenhagen: World Health Organization, 2014.
 - 120 Chen RY, Dodd LE, Lee M, et al. PET/CT imaging correlates with treatment outcome in patients with multidrug-resistant tuberculosis. *Sci Transl Med* 2014; **6**: 265ra166.
 - 121 Vorster M, Sathekge MM, Bomanji J. Advances in imaging of tuberculosis: the role of ¹⁸F-FDG PET and PET/CT. *Curr Opin Pulm Med* 2014; **20**: 287–93.
 - 122 Loveday M, Wallengren K, Brust J, et al. Community-based care vs. centralised hospitalisation for MDR-TB patients, KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis* 2015; **19**: 163–71.
 - 123 Dheda K, Migliori GB. The global rise of extensively drug-resistant tuberculosis: is the time to bring back sanatoria now overdue? *Lancet* 2012; **379**: 773–75.
 - 124 Heinrich N, Dawson R, du Bois J, et al, and the Pan African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA), and the Pan African Consortium for the Evaluation of Antituberculosis Antibiotics PanACEA. Early phase evaluation of SQ109 alone and in combination with rifampicin in pulmonary TB patients. *J Antimicrob Chemother* 2015; **70**: 1558–66.
 - 125 Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrob Agents Chemother* 2007; **51**: 2994–96.
 - 126 Boeree MJ, Diacon AH, Dawson R, et al, and the PanACEA Consortium. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015; **191**: 1058–65.
 - 127 Dorman SE, Savic RM, Goldberg S, et al, and the tuberculosis Trials Consortium. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial. *Am J Respir Crit Care Med* 2015; **191**: 333–43.
 - 128 Chigutsa E, Pasipanodya JG, Visser ME, et al. Impact of nonlinear interactions of pharmacokinetics and MICs on sputum bacillary kill rates as a marker of sterilizing effect in tuberculosis. *Antimicrob Agents Chemother* 2015; **59**: 38–45.
 - 129 Dawson R, Diacon AH, Everitt D, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet* 2015; **385**: 1738–47.
 - 130 Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. *Am J Respir Crit Care Med* 2015; **191**: 943–53.
 - 131 Jindani A, Harrison TS, Nunn AJ, et al, and the RIFAQUIN Trial Team. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med* 2014; **371**: 1599–608.
 - 132 Merle CS, Fielding K, Sow OB, et al, and the OFLOTUB/Gatifloxacin for tuberculosis Project. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014; **371**: 1588–98.
 - 133 Gillespie SH, Crook AM, McHugh TD, et al, and the REMoxTB Consortium. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014; **371**: 1577–87.
 - 134 Rustomjee R, Lienhardt C, Kanyok T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2008; **12**: 128–38.
 - 135 Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2008; **12**: 139–45.
 - 136 Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010; **182**: 684–92.
 - 137 Diacon AH, Pym A, Grobusch MP, et al, and the TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371**: 723–32.
 - 138 Gler MT, Skripconka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; **366**: 2151–60.
 - 139 Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; **367**: 1508–18.
 - 140 Field N, Lim MS, Murray J, Dowdeswell RJ, Glynn JR, Sonnenberg P. Timing, rates, and causes of death in a large South African tuberculosis programme. *BMC Infect Dis* 2014; **14**: 3858.
 - 141 Odone A, Amadasi S, White RG, Cohen T, Grant AD, Houben RM. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e112017.
 - 142 Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GA. Lung remodeling in pulmonary tuberculosis. *J Infect Dis* 2005; **192**: 1201–09.
 - 143 Moodley L, Pillay J, Dheda K. Aspergilloma and the surgeon. *J Thorac Dis* 2014; **6**: 202–09.
 - 144 Cucchetto G, Cazzadori A, Conti M, Cascio GL, Braggio P, Concia E. Treatment of chronic pulmonary aspergillosis with voriconazole: review of a case series. *Infection* 2015; **43**: 277–86.
 - 145 Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration* 2013; **86**: 76–85.
 - 146 Ong CW, Elkington PT, Friedland JS. tuberculosis, pulmonary cavitation, and matrix metalloproteinases. *Am J Respir Crit Care Med* 2014; **190**: 9–18.
 - 147 WHO. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization, 2013. http://apps.who.int/gb/ebwha/pdf_files/EB134/B134_12-en.pdf (accessed July 1, 2015).
 - 148 Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. *Ann Intern Med* 2014; **161**: 419–28.
 - 149 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010; **1**: CD000171.
 - 150 Kerkhoff AD, Gupta A, Samandari T, Lawn SD. The proportions of people living with HIV in low and middle-income countries who test tuberculin skin test positive using either a 5 mm or a 10 mm cut-off: a systematic review. *BMC Infect Dis* 2013; **13**: 307.
 - 151 Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr* 2000; **23**: 75–80.
 - 152 Houben RM, Sumner T, Grant AD, White RG. Ability of preventive therapy to cure latent *Mycobacterium tuberculosis* infection in HIV-infected individuals in high-burden settings. *Proc Natl Acad Sci USA* 2014; **111**: 5325–30.
 - 153 WHO. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with hiv in resource-constrained settings. Geneva: World Health Organization, 2011.

- http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf?ua=1 (accessed July 1, 2015). 1
- 154 Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377**: 1588–98.
- 155 Rangaka MX, Wilkinson RJ, Glynn JR, et al. Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic. *Clin Infect Dis* 2012; **55**: 1698–706. 5
- 156 Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; **384**: 682–90.
- 157 Evans TG, Brennan MJ, Barker L, Thole J. Preventive vaccines for tuberculosis. *Vaccine* 2013; **31** (suppl 2): B223–26. 10
- 158 WHO. An international roadmap for tuberculosis research. Geneva: World Health Organization, 2011.
- 159 Dheda K, Zumla A, Onyebujoh P. Research priorities in tuberculosis. In: A treatise of tuberculosis. In: Zumla A, Schaaf S, eds. London: Elsevier, 2008. 15

20

25

30

35

40

45

50

55

1

Tuberculosis and its epidemiology

- Tuberculosis is a communicable infectious disease caused by the *Mycobacterium tuberculosis* complex, and characterised pathologically by necrotising granulomatous inflammation usually involving the lungs, although almost any extra pulmonary site can be involved.
- Tuberculosis constitutes a disease spectrum but two major sub-types predominate (latent and active).
- Although global incidence of tuberculosis has been slowly decreasing, incidence is increasing in some parts of the world, such as Africa; the global burden of the disease is substantial (almost 9 million new cases and ~1·5 million deaths in 2013).

Presentation and diagnosis

- Presenting symptoms of tuberculosis include persistent fever, weight loss, drenching night sweats, persistent cough (often with sputum production), and sometimes haemoptysis. The classic radiological presentation includes unilateral upper zone infiltrates, often with cavitation; however, atypical presentation is common, especially in immunosuppressed individuals. Extrapulmonary tuberculosis includes tuberculosis lymphadenitis, pleural tuberculosis, pericardial tuberculosis, abdominal tuberculosis, and tuberculosis-meningitis, although almost any organ can be involved.
- Diagnosis of tuberculosis is often delayed because case finding is passive, and is challenging because biological sampling might be non-representative and traditional diagnostic tools have suboptimum accuracy. Smear microscopy only detects around 50% of cases, and culturing the organism takes around 4–6 weeks.
- Alternative commercially available approaches to diagnosis include nucleic acid amplification tests (NAATs). NAAT variants include line probe assays—eg, the HAIN MTBDRplus, and the GeneXpert MTB/RIF assay—although several technologies are likely to soon emerge.
- NAATs are fairly expensive, miss roughly one-third of smear-negative cases, perform poorly in some forms of extrapulmonary tuberculosis, and are not ideal point-of-care tests.
- The Determine lipoarabinomannan (LAM) lateral flow assay detects LAM antigen in urine, but is useful only in a highly selected population (HIV-infected people with CD4<200 cells/mL).
- Drug susceptibility testing (DST) is traditionally done by culturing the organism in selective media (phenotypic DST), although NAATs are used for rapid genotypic DST. Rapid genotypic DSTs (eg, Gene Xpert and Hain MTBDRplus) have high rule-in value for multidrug-resistant (MDR) tuberculosis with clinical specimens and isolates, but false-positive results might be problematic in settings with low prevalence of MDR tuberculosis.

20

Treatment and prevention

30

- Uncomplicated drug-sensitive tuberculosis is treated with a four-drug regimen, often given as fixed-dose combination tablets for a total duration of 6 months. Adverse events needing a change in dose or frequency occur uncommonly and include hepatitis, skin reactions, nausea, and vomiting.
- Several situations need a change in either the selection of drugs, dosage, or duration of therapy, including pre-existing liver disease, renal dysfunction, pregnancy, treatment in the intensive care unit, and with involvement of organs such as the brain and bone.
- Tuberculosis treatment in HIV-infected individuals is complicated by drug–drug interactions (antiretroviral therapy [ART] and tuberculosis treatment), pill burden, overlapping toxicity, immune reconstitution inflammatory syndrome, and optimally timing ART relative to tuberculosis treatment depending on CD4 cell count.
- Adherence-enabling mechanisms including counselling, psychosocial support, economic and financial support, help with caregiving, and meeting transport needs are a crucial part of management, but are often neglected.
- MDR tuberculosis is usually treated with at least four drugs to which the organism is susceptible. Treatment duration is 21–24 months and consists of an intensive phase (usually 6–8 months) with an injectable agent. However, the standardised WHO regimen has a poor evidence base, inconveniently long duration, and substantial toxicity, and treatment is accompanied by painful injections for 6–8 months.
- Several newer tuberculosis drugs such as bedaquiline and delamanid might enable shortening and improvement in efficacy and tolerability of the current MDR regimen, and these drugs have been conditionally registered in several countries, ahead of published phase 3 trial data, for the first time after almost 50 years of no drugs for tuberculosis being registered. Studies are ongoing and planned to address their optimal use in the context of drug-resistant and drug-sensitive tuberculosis.
- Strategies to prevent tuberculosis include: addressing socioeconomic drivers (poverty, overcrowding, and political instability); reducing susceptibility through controlling and averting HIV co-infection, diabetes, smoking and nutritional deficiency; minimising transmission through active case finding; rapid diagnosis and treatment initiation; and treatment of latent tuberculosis.
- Traditional methods for diagnosis of latent tuberculosis, such as the tuberculin skin test (TST) are being superseded in some parts of the world by interferon gamma release assays (IGRA). However, both tests have poor agreement, suboptimum sensitivity, poor specificity in some contexts, and poor positive predictive value (PPV) for those with latent tuberculosis most likely to develop active tuberculosis in the short term (PPV ~2%). Latent tuberculosis is treated with single or combination drugs for several months, and treatment is necessary if tuberculosis is to be eradicated, especially in low burden countries.