Tuberculosis

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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.

Lancet 2016; 387: 1211–26

Published Online
September 14, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00151-8

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This online publication has been corrected. The corrected version first appeared at thelancet.com on October 5, 2015

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See Online for appendix

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 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 re-treated cases (appendix).[5] Several worrying trends exist with drug-resistant tuberculosis (appendix), including widespread emergence of extensively drug-resistant (XDR) tuberculosis[6] 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 radiographic changes, diabetes, tobacco smoking, and

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
TNFα 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

The comprehensively referenced table is available in the appendix. CRF=chronic renal failure. COPD=chronic obstructive pulmonary disease. *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**

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 co-evolved 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

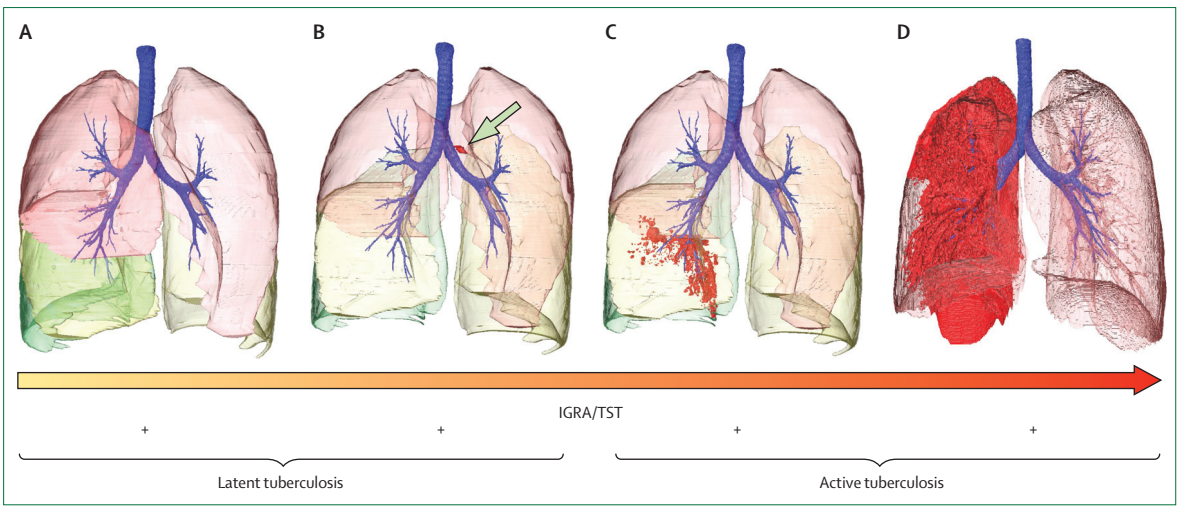

Figure 1: **Outcomes of infection with *Mycobacterium tuberculosis***
M tuberculosis infection has variable outcomes in different hosts. The individual (A) has been exposed but, through innate or adaptive immune function, has cleared the invading bacilli completely. Immunodiagnostic tests might be positive 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 primates[23] 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%.

reflected in newly emerging strain clades.[21] Because of this evolving situation, historic dogmas about the lifecycle 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 IGRA[39] 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 ~10^4 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/RIF[60] 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 HIV[63] 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 settings[68] 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,[67] 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

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 burden[49]
- 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 shantytowns, where several risk factors predominate)[49]
- The predictive value of different screening algorithms is outlined in detail by WHO[49]
- 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 finding[51]
- 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 outcomes[49]
- 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 tuberculosis[53]

be undertaken with the Hain MTBDR*sl* assay (with isolates or smear-positive sputum),[73] array-based methods, or targeted or next-generation whole-genome sequencing. The feasibility and effect of rapid detection of drug resistance with genome sequencing[74] 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 per µL, 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 candidate 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

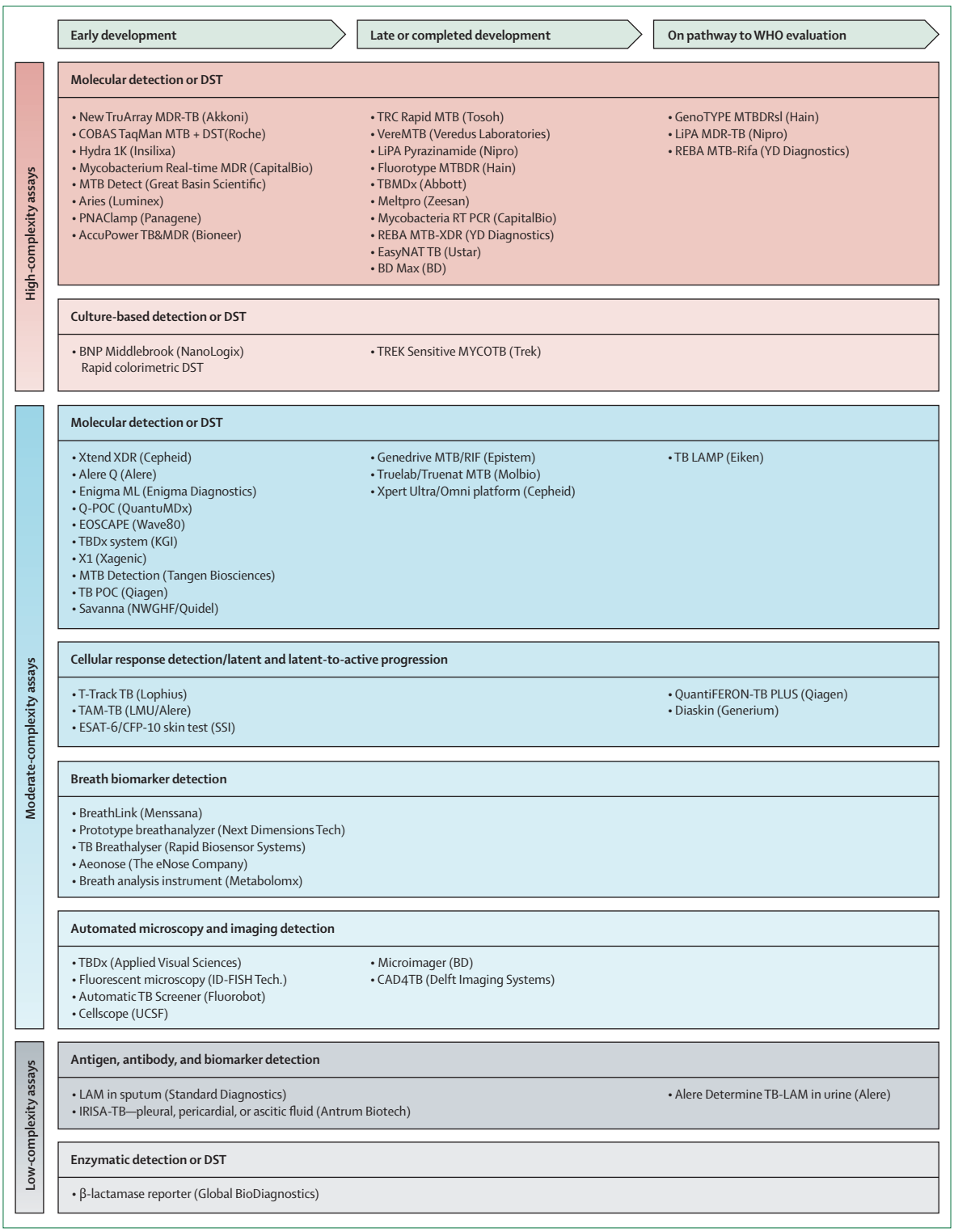

Figure 2: **Summary of diagnostic tests in various phases of development**
Phases of development include early prototype stage, locked in design phase, commercially available, and on the pathway to WHO evaluation. Drugs are classified according to assay complexity. DST=drug susceptibility testing. MDR=multidrug-resistant. TB=tuberculosis. MTB=*Mycobacterium tuberculosis*. XDR=extensively drug-resistant. Coproduced with the Foundation for Innovative New Diagnostics (FIND).

involved. The classic symptoms of fever, drenching night 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 practised, 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 regimen[92] 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-analysis[95] 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

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, ethambutol, and pyrazinamide in the 2 month intensive phase and rifampicin and ethambutol in the continuation phase[36]

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 4 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 recommended[110]
- 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]
- Bedaqualine or delaminid 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 common[116]
- 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 capreomycin[116]
- Differential susceptibility to fluoroquinolones can occur;[117] clofazamine, linezolid, and high-dose isoniazid (guided by genotypic testing) might be useful to optimise the regimen[118]
- Other group 4 (oral bacteriostatic second-line drugs) and group 5 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 treatment[119]
- 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]

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 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 per μL.[101] Tuberculosis–IRIS has a low mortality,[100] except for cases with neurological involvement.[102] Tuberculosis–IRIS is characterised by increased concentrations of pro-inflammatory and anti-inflammatory cytokines,[103] and of pro-inflammatory 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 trial[106] 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

	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 *Mycobacterium tuberculosis* 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 *M tuberculosis* 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, NExT RCT, A5343
PA-824/pretomanid (class: nitroimidazole)	2b	Inhibition of mycolic acid biosynthesis and generation of mycobactericidal nitrogen oxide derivatives (dormant *M tuberculosis*)	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 delaminid	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 *mmpL3* gene	None	Mutation in the *mmpL3* 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 *M tuberculosis* than linezolid	Peripheral neuropathy Transaminitis	No clinical data available for interactions	Planning in progress

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. 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 coadministered 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.

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

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] 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.

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

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]

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 study[136]—results of a randomised controlled trial comparing this regimen to the standard 21–24-month regimen are awaited. Bedaquiline,[137] delamanid,[138] and linezolid[139] 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 TSTs[150] 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

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, guineapigs, 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.

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 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 Daignostics, 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, 2007–12.

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.

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