Tuberculosis

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Tuberculosis remains the leading cause of death from an infectious disease among adults worldwide, with more than 10 million people becoming newly sick from tuberculosis each year. Advances in diagnosis, including the use of rapid molecular testing and whole-genome sequencing in both sputum and non-sputum samples, could change this situation. Although little has changed in the treatment of drug-susceptible tuberculosis, data on increased efficacy with new and repurposed drugs have led WHO to recommend all-oral therapy for drug-resistant tuberculosis for the first time ever in 2018. Studies have shown that shorter latent tuberculosis prevention regimens containing rifampicin or rifapentine are as effective as longer, isoniazid-based regimens, and there is a promising vaccine candidate to prevent the progression of infection to the disease. But new tools alone are not sufficient. Advances must be made in providing high-quality, people-centred care for tuberculosis. Renewed political will, coupled with improved access to quality care, could relegate the morbidity, mortality, and stigma long associated with tuberculosis, to the past.

Introduction

Tuberculosis—the leading cause of death worldwide from an infectious disease among adults—has been considered a global public health emergency for the past 25 years.[1] Although public health approaches to tuberculosis have saved tens of millions of lives, modest progress has been made to control (let alone to end) tuberculosis. Drug-resistant forms of tuberculosis are currently on course to be the world's deadliest pathogens, responsible for a quarter of deaths due to antimicrobial resistance.[2] Great ambition and radical action are needed to tackle this completely curable pathogen, which remains one of the greatest health problems in the world.

The global tuberculosis situation is dire, but now is also a time of great promise and discovery for the disease. Numerous advances have been made in our understanding of the epidemiology, risk factors, and pathophysiology of tuberculosis, and new diagnostics and treatment for all forms of tuberculosis infection and disease are appearing on the horizon. Access to these innovations remains a substantial challenge for the majority of people living with the disease, but if the political will that seems to be building in the tuberculosis community and beyond[3] is put into action, with a focus on the rights of people affected by the disease, the next decade might finally see the devastation caused by this age-old disease start to abate.

Search strategy and selection criteria

We searched the Cochrane library, PubMed, and Ovid for items published between Jan 1, 1946, and Nov 21, 2018. We used the search terms "tuberculosis" in combination with "epidemiology", "pathophysiology", "risks", "diagnosis", "test", "treatment", "prevention", "vaccine", "infection", "quality", "political will", "patient-centered", "person-centered", "drug-resistant", "drugs", "access", and "prognosis". We prioritised research published since 2014, but we also included other papers of substantial clinical impact.

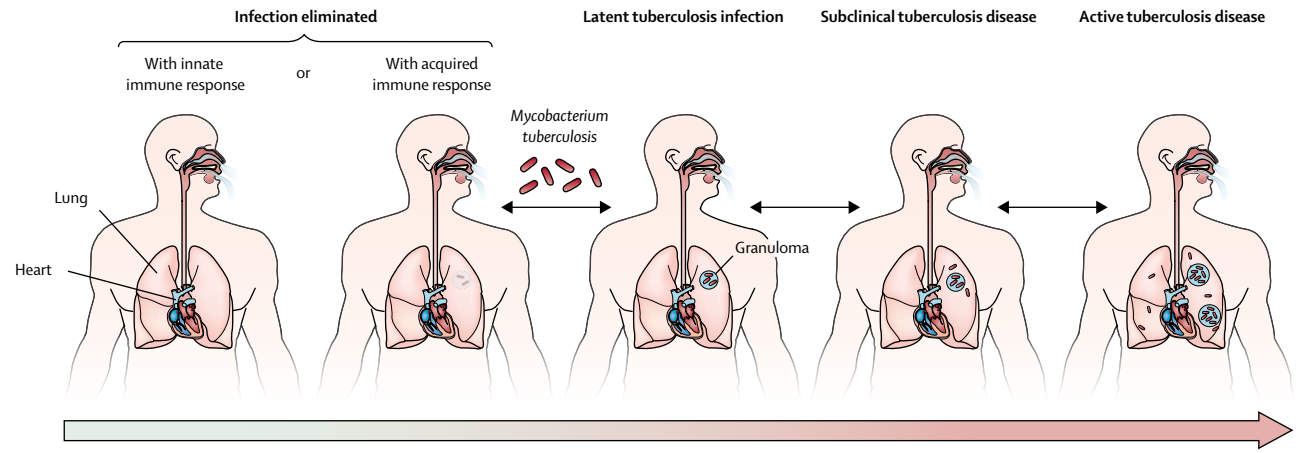
Epidemiology, pathogenesis, and risk factors

Tuberculosis continues to cause considerable morbidity and mortality globally. According to WHO,[4] an estimated 10 million people became newly sick with tuberculosis in 2017; 8·7 million (87%) of these individuals reside in 30 high-burden countries. Among these 10 million individuals, only 6·4 million were diagnosed and officially notified. 1·3 million people are estimated to die from tuberculosis each year.[4]

Tuberculosis is a disease of poverty. Although most high-income countries have estimated tuberculosis incidences of less than ten per 100 000 population per year, the 30 high tuberculosis burden countries (which are predominantly low-income and middle-income countries) have an estimated collective tuberculosis incidence of 183 per 100 000 population per year, with the incidence being above 400 per 100 000 population per year in eight countries.[4] Within countries, the tuberculosis burden is also primarily borne by the poorest people.[5]

Global tuberculosis incidence is estimated to be slowly declining by 1·6% per year, far from the 4–5% estimated to be required to reach WHO's End TB Strategy targets[6] By contrast, mortality is declining more rapidly at 4·1% per year. Global Burden of Diseases, Injuries, and Risk Factors[7] data for tuberculosis (1990–2016) show that if current trends in incidence continue, few countries are likely to meet the UN Sustainable Development Goals' target to end the epidemic by 2030.

In many settings, drug-resistant tuberculosis is also a major threat to tuberculosis control efforts. Each year, more than half a million people become sick with rifampicin-resistant forms of tuberculosis, but in 2017, only 160 684 people were diagnosed or notified, and only 139 114 were started on treatment.[4] Modelling suggests that, in the absence of rapid diagnosis and specific treatment for rifampicin-resistant tuberculosis, tuberculosis incidence will continue to increase.[8–10] Currently, prevalence of rifampicin-resistant tuberculosis is increasing in several key countries including Russia, Myanmar, China, and South Africa.[11]



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Figure 1: **Spectrum of tuberculosis infection and disease**
Reproduced from Pai et al,[14] by permission of Springer Nature. IGRA=interferon-γ release assay. TST=tuberculin skin test.

Mycobacterium tuberculosis and humans have coexisted for thousands of years.[12] Although 1·7 billion people globally are estimated to be infected with *M tuberculosis*, only some of these people will go on to develop active tuberculosis.[13] Our understanding of the pathophysiology of tuberculosis continues to evolve, and there is growing acceptance that, beyond the classical model of distinct latent and active forms of tuberculosis disease, the complex bacterial and host dynamics result in the pathology of tuberculosis disease falling on a spectrum (figure 1).[15]

On an individual basis, immunity to tuberculosis also appears to fluctuate over time, even within a single human host.[16] In a recent study, immune responses found within individual granulomas suggest that local immune responses at the site of infection are as important in controlling tuberculosis infection as systemic immunity.[17] Data also show that some individuals exposed to tuberculosis do not become infected, whereas others rapidly succumb to infection and disease even, with minimal exposure.[18]

In terms of tuberculosis drug resistance, data suggest that many people who present with drug-resistant tuberculosis are infected with drug-resistant strains.[19] Other data show that non-adherence to the prescribed antibiotic drug regimen might have a lesser role in the development of drug resistance than other causes of acquired drug resistance, including inefficient serum drug concentrations, drug gradients in pulmonary tissue, and the presence of drug efflux pumps at the surface of bacteria.[20] Additionally, new analyses of older data also show the time course of progression from infection to disease. Although there has long been a shared belief within the scientific community that people newly infected with *M tuberculosis* have the highest risk of progression to disease within the first several years after infection, analysis of historical data has confirmed that the incubation of *M tuberculosis* is probably shorter than previously thought: around 24 months.[21] This finding suggests that identifying recently exposed individuals (eg, close contacts) at high risk of progression, and offering them preventive therapy, might be an effective strategy to prevent progression to disease. Some biomarkers show promise for identifying individuals at highest risk of progression.[22]

A substantial amount of work has looked at how pathogen and host factors, including local immune responses and disease tolerance, can explain the pathogenesis and risk factors for developing tuberculosis disease, but important work has also been done on socioeconomic risk factors that might be just as predictive of who becomes infected with, and sick from, tuberculosis. People from low socioeconomic-status populations are known to be at high risk of becoming sick from tuberculosis,[23] and in low-burden tuberculosis countries, substantial declines in tuberculosis morbidity

and mortality have occurred as a result of improvement in overall living conditions.[24] A seminal study done in Peruvian shanty towns found that some modifiable socioeconomic risk factors, including indoor air pollution, living in a house with a low number of windows per room, and socioeconomic position of the household, can be powerful predictors of tuberculosis infection and disease.[25] Furthermore, people who have had one episode of tuberculosis are at increased risk of developing tuberculosis again, further exacerbating the vicious cycle of poverty and tuberculosis.[26] Addressing socioeconomic factors, including smoking and indoor air pollution, could be just as important as addressing host and pathogen factors in easing the global burden of tuberculosis. A controlled human infection model to improve the understanding tuberculosis infection is an unmet need in the field.

Diagnosis

Although multiple advances have been made in the diagnosis of tuberculosis, no reliable, simple, point-of-care test exists to definitively diagnose the disease. Clinicians often seek bacteriological diagnosis, but this evidence is also supplemented by clinical findings, radiological evidence, and tests for bacterial products that indicate the presence of *M tuberculosis*. WHO currently endorses a range of diagnostic and drug susceptibility tests (appendix).

See Online for appendix

New developments exist for the use of radiological screening for and diagnosis of tuberculosis, and interest in this area is increasing. Digital chest x-rays with computer-aided detection of tuberculosis have been increasingly used in various settings, including prisons, among household contacts, and for people who have worked in the mining sector.[27] Although research is required to refine the use of computer-aided detection, chest x-ray appears to be making a comeback as a triage test, and this assessment method is now recommended by WHO for screening and diagnosis of tuberculosis in some populations.[28]

Tuberculosis bacteria shed multiple proteins and byproducts when they replicate in the human host, and one of these substances, lipoarabinomannan (LAM), forms the basis of the urinary LAM test, the use of which has been associated with a mortality reduction for tuberculosis.[29] The test has the advantages of being administered at the point of care and making use of an easily obtained specimen type (urine). Although initial evidence for the clinical utility of urinary LAM testing was disappointing (showing a low degree of sensitivity),[30] a clear mortality benefit is shown when used in hospitalised people with HIV and a CD4 count of less than 200 cells per µL.[31] In 2018, a study found the test not only to be associated with a higher rate of case detection and a lower rate of mortality, but also to be cost-effective.[32] The existing urinary LAM test is currently recommended for all patients who have HIV and a CD4 count of less than 100 cells per µL, are seriously ill, and are hospitalised.[33] Higher sensitivity LAM assays have been developed and show great promise for rapid tuberculosis diagnosis, even among people without HIV, including children and those in the outpatient setting.[34,35]

Developments continue in the field of tuberculosis biomarkers, with multiple promising candidates identified for risk of infection, risk of disease, likelihood of cure, and disease protection.[36] Most of these biomarkers are associated with host immunity and include proteins, metabolites, cell markers, and signals of transcription.[37] Although numerous reports of correlation with different phases of tuberculosis have been reported, most notably in children,[38] to date, no predictive biomarker signatures are close to commercialisation and no clinically useful biomarker tests are available on the market.

In terms of bacteriological testing, our understanding of the bacterium itself also needs to be improved, including understanding factors that affect its growth and virulence.[39] Most advances have been in the area of molecular testing both for the presence of *M tuberculosis* and for drug resistance. The Xpert MTB/RIF test (Cepheid, CA, USA), which can detect genetic material from *M tuberculosis* along with mutations that cause resistance to rifampicin, remains the genotypic diagnostic test of choice. Although access to this form of testing remains restricted, time-trend analyses show increasing market penetration in many high-burden countries.[40,41] A more sensitive version of the assay, called Xpert MTB/RIF Ultra, has been developed. The new test, which has a sensitivity for *M tuberculosis* detection similar to culture assays (which are known to be highly sensitive), but the advantages of requiring fewer resources and yielding faster results, has been endorsed by WHO and is being used in South Africa; however, this test does have a lower specificity for detection of *M tuberculosis*, and so interpretation of so-called trace-positive results remains a challenge. An expanded version of the Xpert cartridge, called Xpert XDR, which allows for detection of resistance to isoniazid, injectable agents, and fluoroquinolones was also shown to be effective in a large validation study,[42] and is expected to become commercially available in 2019. There have been some breakthroughs in sample collection and processing to allow for broader use of these Xpert MTB/RIF tests in paediatric populations, including the use of stool samples.[43] In terms of hardware used for these tests, in 2015, Cepheid had announced a novel, portable, battery-operated, point-of-care version of their GeneXpert system. However, the release of this technology, called GeneXpert Omni, has been repeatedly pushed back because of technical challenges. Meanwhile, in July, 2018, Cepheid announced the launch of the GeneXpert Edge, a portable, single-module, near-patient technology that can be used in decentralised settings. Cartridges available for use on the Edge include Xpert MTB/RIF, Xpert MTB/RIF Ultra, and Xpert HIV-1 Qual assays.

Other genotypic tests based on nucleic acid amplification are being developed, and some are commercially available for centralised laboratories, including RealTime MTB (Abbott, IL, USA), FluoroType MTBDR (Hain Lifescience, Nehren, Germany), and BD MAX MDR-TB (Beckton, Dickinson and Company, NJ, USA), whereas the chip-based Truenat MTB (Molbio Diagnostics, Goa, India) is designed for microscopy centres.[44] Line probe assays, which can detect drug resistance to isoniazid, rifampicin, injectable agents, and fluoroquinolones, are also available and WHO-endorsed, but require additional laboratory capacity.[45]

Whole-genome sequencing is becoming an increasingly appealing option for detection of drug resistance in *M tuberculosis* and can also be used to improve the understanding of tuberculosis transmission.[46] This technology relies on identifying mutations in the *M tuberculosis* genome that are associated with phenotypic drug resistance, and data show a correlation between the genetic mutations and culture-based drug susceptibility results, at least for the four first-line drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide).[47] As technology enables sequencing directly from specimens and more genotypic or phenotypic correlations are confirmed, whole-genome sequencing is likely to become the preferred method for tuberculosis drug-resistance testing in the next decade,[48] especially given its potential use in outbreak investigations.[49]

For the diagnosis of latent tuberculosis infection, two main immune-based approaches are currently used and included in WHO guidelines:[50] the tuberculin skin test (TST) and the interferon-γ release assay (IGRA). Although the IGRA has higher specificity than the TST, neither test can accurately differentiate between latent tuberculosis infection and active tuberculosis. Both tests have low sensitivity in a variety of immunocompromised populations. Cohort studies have shown that both TST and IGRA tests have low predictive value for progression from infection to active tuberculosis.[51] Therefore, testing only people at risk of progression and use of all clinical data, in addition to test results, is important. User-friendly calculators, such as the Online TST/IGRA Interpreter, are available to assist with evaluation of results. C-Tb (Statens Serum Institut, Copenhagen, Denmark), a skin test that is based on the more *M tuberculosis*-specific ESAT-6 and CFP10 antigens, has a similar safety profile to the TST, and accuracy similar to IGRAs in phase 3 clinical trials in adults and children.[52,53]

Whatever sampling and testing techniques are used, a more active approach to finding people with tuberculosis is essential. Active case finding (as opposed to waiting for people to present to the health system with signs and symptoms of tuberculosis) involves systematic efforts to seek out people who might have the disease.[54] Although a detailed review of active case finding is beyond the scope of this Seminar, multiple strategies are involved, usually focused on high-risk groups, such as household contacts, people living with HIV, and people living in congregate settings. Strategies include systematic screening, community-based activities, and deployment of novel screening and diagnostic technologies.[55] A 2017 randomised controlled trial of different tuberculosis diagnostic tools used during intensified case finding, for example, found that when coupled with active mobile van screening services, the Xpert MTB/RIF resulted in an increased proportion of people being started on treatment for tuberculosis.[56]

Treatment

The treatment landscape for tuberculosis has changed dramatically over the past 5 years, with the introduction of two new drugs, bedaquiline and delamanid, and multiple clinical trials whose results are being used to radically alter the care of people with all forms of tuberculosis.[57] More tuberculosis treatment studies are happening than ever before in the history of the disease, and not only will these studies help improve the care of people living with tuberculosis, but they should also help show aspects of tuberculosis pathophysiology that can be used to develop better, targeted therapies for people with tuberculosis.

To date, no major changes in treatment of drug-susceptible tuberculosis have been made. For pan-susceptible tuberculosis, treatment still consists of four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) given for a total of 2 months followed by two drugs (isoniazid and rifampicin) given for an additional 4 months. Data from a 2014 study show that a so-called hard-to-treat phenotype, defined by high smear grades and cavitation, can require durations of more than 6 months to achieve cure.[58] Studies have shown that daily administration of therapy results in improved treatment outcomes compared with thrice-weekly treatment, and WHO recommends all people diagnosed with tuberculosis be offered daily treatment with fixed-dose combinations.[59] Of note, studies show that some combination tablets can result in subtherapeutic concentrations of certain key drugs (especially rifampicin)[60] but the clinical implications of this occurrence are not entirely clear.

For more on the **Online TST/IGRA Interpreter** see http://www.tstin3d.com

Therapeutic advances in the treatment of drug-susceptible tuberculosis have focused on two areas: high-dose rifampicin and the addition or substitution of fluoroquinolones in the regimen. Although high-dose rifampicin shows early promise for treatment-shortening,[61–65] randomised controlled trials with the fluoroquinolones did not show a treatment-shortening benefit.[66–69] Multiple studies to assess shorter tuberculosis treatment regimens are ongoing, including regimens containing rifapentine, clofazimine, and the novel drugs bedaquiline and PA-824, also known as pretomanid (an experimental nitroimidazole agent for drug-resistant tuberculosis).[70]

Isoniazid-resistant forms of tuberculosis are the most common forms of drug-resistant tuberculosis in the

	Class and mechanism of action	Phase completed and regulatory approval	Summary of findings	Adverse events	Drug–drug interactions and overlapping toxicities	Access and pricing[75]	Ongoing trials[76]
Bedaquiline[77-79]	Diarylquinoline; inhibits mycobacterial ATP synthase	Phase 2b US FDA, EMA, SAHPRA, multiple other countries	Significantly faster time to culture conversion; significantly higher culture conversion; significantly improved treatment outcomes when compared with placebo	QTc prolongation (moderate), hepatitis	Cannot use with efavirenz; use with protease inhibitors results in increased bedaquiline concentration but clinical significance not clear; cannot use with rifampicin; caution when used with other QTc prolonging agents	Available to <20% of individuals that need it; US$400 for a 6-month course via GDF	endTB (NCT02754765), TB PRACETCAL (NCT02589782), NiX-TB (NCT02333799), STREAM 2 (NCT02409290), NeXT (NCT02454205), ZeNix (NCT03086486), Janssen C211 (NCT02354014), ACTG 5343 (NCT02583048), Janssen Japan Trial (NCT02365623), SimpliciTB (NCT03338621), P11018 (NCT02906007)
Delamanid[80-85]	Nitroimidazole; inhibits mycolic acid synthesis	Phase 3 EMA, Japanese Regulatory Authority	Faster time to culture conversion compared with placebo; no differences in final outcomes but study did not have statistical power for detection	QTc prolongation (mild), generally well tolerated	No clinically significant drug–drug interactions	Available to <5% of individuals that need it; $1700 for a 6-month course from GDF	endTB, MDR-END (NCT02619994), ACTG 5453, Otsuka 213 (NCT01424670), Otsuka 233 (NCT01859923), Otsuka 232 (NCT01856634), IMPAACT 2005 (NCT03141060)
Pretomanid[86-88]	Nitroimidazole; inhibits mycolic acid synthesis, generates mycobacterial nitrogen oxide	Phase 2b; currently undergoing regulatory review	Has only been tested in combination regimens and not as a single agent	Hepatitis, animal studies show ocular and reproductive toxic events	No clinically significant drug–drug interactions	Not available	SimpliciTB, NiX-TB, TB PRACTECAL, ZeNix
Linezolid[89-111]	Oxazolidinone; inhibits mycobacterial protein synthesis	Phase 2b, phase 3 (non-placebo controlled); no registered indication for tuberculosis	Improved outcomes (in delayed-start trial and non-placebo controlled trials), significantly higher rates of culture conversion, and faster times to culture conversion in people who received linezolid at the start of treatment compared with those who had a delayed start	Toxic effects on bone marrow, peripheral neuritis, optic neuritis	Caution when used in patients on zidovudine due to overlapping toxic effects on bone marrow; caution when given with other drugs that are associated with peripheral neuropathy (eg, isoniazid); use with caution when given with other drugs associated with optic neuritis or neuropathy (eg, ethambutol)	$1·30 per tablet from GDF	endTB, NiX-TB, TB PRACTECAL, ZeNix, NeXT, MDR-END, MDR-PK2 (NCT02619994)
Sutezolid[93,94]	Oxazolidinone; inhibits mycobacterial protein synthesis	Phase 2a	Significant 14-day early bactericidal activity	No severe adverse events reported in 14-day early bactericidal activity trial	Not available	Not available	Obtained by the Medicines Patent Pool for further testing
Clofazimine[95,96]	Inhibits mycobacterial DNA synthesis, increases activity of mycobacterial phospholipase A2	Phase 3 (non-placebo controlled)	Improved treatment outcomes, significantly faster time to culture conversion, and higher rates of culture conversion compared with people that did not receive clofazimine	Skin discoloration, QTc prolongation	Caution when used with other QTc prolonging agents	$1·00 per tablet from GDF	endTB, STREAM 2, TB PRACTECAL
Carbapenems (imipenem-cilastatin, meropenem)[97]	β-lactams; inhibit mycobacterial cell wall synthesis	Phase 2a	Significant 14-day early bactericidal activity	Seizures, rash, hepatitis	Cannot use with penicillin allergy; must be given with clavulanic acid to be effective in tuberculosis; must be given intravenously	$3·10 for one 500 mg vial of imipenem; $0·14 for one 125 mg tablet of clavulanic acid (only available in combination with 875 mg amoxicillin)	None known

FDA=Food and Drug Administration. EMA=European Medicines Agency. SAHPRA=South African Health Products Regulatory Authority. GDF=Global Drug Facility.

Table 1: **Summary of new and repurposed drugs for treating rifampicin-resistant tuberculosis**

world,[71] although no data-driven guidelines exist on when to systematically test people for isoniazid-resistant tuberculosis. With the roll-out of molecular tests, isoniazid-resistant tuberculosis is likely to be more commonly diagnosed in the coming years. No formal trials have been done to guide therapy, but a 2017 meta-analysis found that although there was great heterogeneity in treatment practice, with more than 55 regimens used, regimens containing fluoroquinolones resulted in improved outcomes.[72] WHO has recommended that fluoroquinolones be given to people with isoniazid-resistant tuberculosis, but also note the need for formal clinical studies to assess the optimal therapy for this form of tuberculosis.[73] Rifampicin monoresistant tuberculosis (with retained susceptibility to isoniazid) is increasingly documented, and this strain might constitute an important population of patients with monoresistant tuberculosis in the future.[74] Since treatment recommendations are the same as for those with multidrug-resistant tuberculosis (although this situation could change in the future), the treatment of these two entities will be considered together in this Seminar.

The treatment of rifampicin-resistant tuberculosis has substantially changed with the introduction of bedaquiline and delamanid, and with increasing use of repurposed agents such as linezolid and clofazimine. For the first time, WHO has recommended all-oral therapy for a majority of people with rifampicin-resistant tuberculosis, and regimens of 9–12 months' duration (compared with the standard 18–24 months of therapy) are also being rolled out for the treatment of rifampicin-resistant tuberculosis. These therapeutic advances have already been shown to greatly improve the treatment of rifampicin-resistant tuberculosis. Ongoing trials aim to assess new and repurposed drugs for the treatment of rifampicin-resistant tuberculosis (table 1).

Bedaquiline was first recommended by WHO in 2013,[98] and was recommended again in 2017.[99] While phase 3 studies of bedaquiline are pending, widespread experience with the drug has accumulated via compassionate use and observational cohort studies.[101–103] A majority of these have shown treatment success exceeding 75%, notable since most people who received bedaquiline early in the course of its use were patients with highly resistant tuberculosis and few therapeutic treatment options.[104] The largest cohorts of patients to receive bedaquiline are from South Africa, where high treatment success and reduced mortality have been reported among people receiving the drug.[105] Although QTc prolongation was seen in patients receiving bedaquiline, few patients required discontinuation of the medication.[106] These results led the South African Government to commit to providing bedaquiline for all people with rifampicin-resistant tuberculosis in the country.[107] A 2018 case-control study done in South Africa compared the treatment outcomes of people who received bedaquiline instead of injectable agents and found that the patients who received bedaquiline had higher treatment success compared with those who received injectable agents, and a delay in bedaquiline initiation was significantly associated with mortality.[108] Use of bedaquiline was also found to be cost-effective when compared with injectable drug-based therapy.[109]

Although bedaquiline was only administered for 24 weeks in these clinical trials (in part to reach trial endpoints more quickly), many patients on bedaquiline will have few therapeutic options and will require bedaquiline for longer periods.[110] A study done in France found that people who received bedaquiline for prolonged periods had no additional safety problems.[111]

Bedaquiline is now recommended by WHO as a core drug in the treatment of rifampicin-resistant tuberculosis and it is part of the newly recommended all-oral regimens.[112] Bedaquiline is also a component of most regimens being tested in rifampicin-resistant tuberculosis clinical trials and is likely to remain part of the rifampicin-resistant tuberculosis treatment option for some time. The drug is also being tested in drug-susceptible tuberculosis as part of the SimpliciTB trial (NCT03338621) being run by Tuberculosis Alliance (known as TB Alliance).

Access to bedaquiline has remained a major global problem with fewer than 20% of those in need of the drug being able to access it.[113] A joint donation programme funded by Janssen Pharmaceutica (Beerse, Beligium) and the US Agency for International Development has allowed for 60 000 courses of bedaquiline to be provided free of charge, but current pricing of bedaquiline (US$400 for a 6-month course of treatment) means it will be unobtainable by most people and programmes.[114] Global advocates are calling for a price no higher than $1 per day for bedaquiline treatment, given that most of the drug's development was through tax-payer funded studies.[115] Given the prominent role of bedaquiline in the treatment of rifampicin-resistant tuberculosis access, ensuring access through affordability will be an important step in fighting this strain.[116]

The second novel drug to be both conditionally approved by stringent regulatory authorities and recommended by WHO in 2014 for the treatment of tuberculosis is delamanid.[117] A phase 3 trial done with delamanid when the drug was added to a multidrug backbone regimen for 24 weeks compared with the addition of placebo found that the reduction in median time to sputum culture conversion over 6 months was not significant in the primary analysis (although significance was achieved when alternative methods for handling missing cultures were used).[118] Delamanid has been shown to be safe and effective in short-term pharmacokinetic studies in children aged 2 years and older,[119,120] and the treatment is recommended by WHO as the drug of choice for treating children younger than 6 years with rifampicin-resistant tuberculosis.[121] Thus, few observational cohort studies exist that include people who have been treated with delamanid. Those studies that have been done support the

efficacy and safety of delamanid,[122,123] and data increasingly show that delamanid can be safely given in combination with bedaquiline. This combination had been discouraged in the early days of delamanid's approval, given a potential concern about additive or synergistic QTc prolongation if the two drugs were combined. In a cohort study of individuals requiring both bedaquiline and delamanid for the treatment of highly resistant forms of rifampicin-resistant tuberculosis, no individuals had an absolute QTc interval (corrected by use of the Fridericia formula) greater than 500 msec.[124]

Another medication in the nitroimidazole class that has been developed further in the past 5 years is pretomanid.[125] This chemical entity has been in development for more than a decade and has been advanced as a component of treatment regimens in several clinical trials.[86] Concerns were raised about the safety of pretomanid after a study using the medication in combination with moxifloxacin and pyrazinamide resulted in fulminant hepatitis in a series of participants with pan-susceptible disease.[87] The drug continues to be assessed in trials in both drug-susceptible and drug-resistant tuberculosis; these include the SimpliciTB trial and, perhaps the most promising, the NiX-TB trial (NCT02333799),[88] which is sponsored by TB Alliance. In this single arm study, people with extensively drug-resistant tuberculosis were given a 6-month to 9-month regimen of high-dose linezolid (1200 mg daily), bedaquiline, and pretomanid. Of the 75 participants with results, 89% achieved cure and have been followed for at least 12 months for relapse.[69] High rates of linezolid toxicity have been reported with this regimen, and ongoing studies (eg, clinical trial NCT03086486) are assessing dose optimisation of this drug. If confirmed, the results of this trial could substantially transform the treatment of rifampicin-resistant tuberculosis. Pretomanid has not been used outside of clinical trials and TB Alliance has submitted a new drug application to the US Food and Drug Administration for regulatory approval. No head-to-head comparisons between delamanid and pretomanid have been made.

Various other novel chemical entities are in development for tuberculosis,[126] including benzothiazone agents, decaprenylphosphoryl-beta-D-ribose oxidase (also known as DprE1) inhibitors and mycobacterial respiratory chain inhibitors such as telacebec (previously Q203; Qurient, Seongnam, South Korea), and imidazopyridines.[127] Although in the early stages of development, these drugs could offer additional treatment options in a field where few therapeutics exist. The process for drug development in tuberculosis, however, is anaemic and hampered by a dearth of funding, a long trialling process, regulatory delays, and a seeming difficulty for countries to roll out new drugs even when their efficacies have been established.[128]

In addition to new medications for the treatment of tuberculosis, interest in repurposed drugs is increasing. Chief among these drugs is linezolid, an oxazolidinone antibiotic that has been shown to be effective in two randomised trials among people with tuberculosis,[89,90] and which is a regimen component of multiple ongoing and planned clinical trials.[91] The safety of linezolid is a concern as the drug has been associated with bone marrow suppression, optic neuritis, and peripheral neuropathy;[92] however, studies are ongoing to find strategies to reduce these toxic effects, including alternate-day dosing and discontinuation of the medication after 2–3 months of therapy. Other oxazolidinones have been tested for use in tuberculosis treatment with sutezolid (Sequella; Rockville, MD, USA) showing some promise in an early study.[93] Testing of this drug has been delayed but it has now been acquired by the Medicines Patent Pool and might proceed into phase 2b trials.[94]

Another repurposed agent, clofazimine, has been shown to be effective against rifampicin-resistant tuberculosis in a randomised, non-placebo controlled trial done in China.[95] The study suggested that the drug might be especially effective against mycobacteria that are not actively replicating. Clofazimine is currently being studied in clinical trials for both treatment of rifampicin-resistant tuberculosis and for shortening of treatment for drug-susceptible tuberculosis, however QTc prolongation and skin pigmentation are primary safety concerns.[96]

In 2018, a large meta-analysis, which included patient data from more than 12 500 individuals, was done to assess the role of individual drugs in the treatment of rifampicin-resistant tuberculosis.[129] Although the limitations of meta-analyses (eg, population heterogeneity, absence of formal control groups, and incomplete data sets) should be kept in mind when interpreting their findings, this study had multiple unexpected outcomes. Commonly used agents, such as kanamycin, capreomycin, pyrazinamide, ethionamide, and para-aminosalicylic acid, were found to be associated with worse treatment outcomes, even when used in people with susceptibility to these medications, suggesting that the toxicity of these agents might be worse than previously thought. Capreomycin was associated with higher mortality. Regimens containing bedaquiline, linezolid, or the third generation fluoroquinolones were associated with improved treatment outcomes and lower mortality than regimens that did not contain one or more of these medications. In addition, the drugs clofazimine and cycloserine were found to be associated with improved treatment outcomes. The data also showed no benefit to administering drugs to which the individual had documented resistance and thus called into question the common practice of treating rifampicin-resistant tuberculosis with multiple agents without a strong evidence-base.

This individual patient data meta-analysis formed the basis of evidence that was used by WHO in July, 2018, to issue new treatment recommendations for rifampicin-resistant tuberculosis.[130] WHO recommends that the majority of individuals are treated with all oral regimens

that include the drugs bedaquiline, linezolid, a third generation fluoroquinolone, clofazimine, and cycloserine (table 2).[130] In essence, these recommendations challenged the therapeutic hierarchy at the time, and called for the up-front use of medications such as bedaquiline, linezolid, and clofazimine (which had previously been relegated for use only in salvage situations) and called for the commonly used agents (such as the injectables, ethionamide, and pyrazinamide) to be used only in cases when other therapeutic options were not available. For the first time ever, all-oral regimens are now recommended for the majority of people living with rifampicin-resistant tuberculosis. Even the definitions that were previously used to define the highly resistant forms of tuberculosis, known as extensively drug-resistant and pre-extensively drug-resistant, are irrelevant given that the injectable drugs are no longer core agents in the treatment of drug-resistant tuberculosis.[131]

In addition to regimens including more effective drugs, a substantial amount of clinical research has found that shorter regimens can be used for the treatment of rifampicin-resistant tuberculosis. A 9–12 month regimen, often known as the Bangladesh regimen (since its effectiveness was first shown in the country)[132] has been shown to be effective among carefully selected patients in numerous observational cohort studies.[133,134] A phase 3 trial (STREAM 1; ISRCTN78372190) of the Bangladesh regimen, which contains kanamycin, isoniazid (high dose), pyrazinamide, ethambutol, moxifloxacin (high dose), clofazimine, and ethionamide, found that overall outcomes were non-inferior to a longer 18–24 month regimen.[135,136] However, although the shorter treatment course had lower loss to follow-up, this regimen also had a higher prevalence of failed treatment, relapse, and death. WHO recommended this regimen in 2016,[137] and has maintained the recommendation in their 2018 guidance, although the organisation now notes that the shorter regimen should not be given to people with resistance to any drug in the regimen (except isoniazid) and that outcomes might be worse than with administration of bedaquiline, linezolid, or both. The continued use of the injectable agents in the shorter regimen is problematic given the high amounts of hearing loss reported with this class of drugs.[138] An ongoing trial called STREAM 2 (NCT02409290) is assessing a regimen with bedaquiline replacing the injectable agents, and results are expected in 2022.

Multiple ongoing trials exist that look at shorter, all oral regimens for the treatment of rifampicin-resistant tuberculosis (appendix). Given the long time period it takes to recruit, enrol, treat, and follow-up people in this type of trial, it could be years before these results are available.[139]

Although treatment for tuberculosis is currently selected on the basis of drug susceptibility alone, growing evidence suggests that disease severity should be more broadly considered in therapeutic determinations. This situation is already the standard in the management of paediatric rifampicin-resistant tuberculosis, where children with non-severe disease are treated for 9–12 months,[140] and forms drug-susceptible extrapulmonary tuberculosis (including meningitis and osteoarticular disease), which are treated for prolonged 12-month durations. Multiple components of tuberculosis treatment regimens that are considered fixed, including the number of drugs used and the duration of therapy, could possibly be altered on the basis of the extent of disease. Data show that cavitary disease and smear-positivity at 2 months predict relapse,[141] and similar results have been found in people with drug-resistant tuberculosis.[142] Patients with these indicators will probably require longer treatment than those without such clinical features. Treatment choice should take into account considerations for special populations (including children, adolescents, and people living with HIV, diabetes, or other comorbidities), the use of adjunctive therapies, and long-term effects (appendix).

	Drugs	Comments
Group A	Levofloxacin or moxifloxacin; bedaquiline; linezolid	Include all three medicines (unless they cannot be used)
Group B	Clofazimine; cycloserine or terizidone	Add both medicines (unless they cannot be used)
Group C	Ethambutol; delamanid; pyrazinamde; imipenem-cilastatin or meropenem (both must be given with clavulanic acid); amikacin or streptomycin; ethionamide or prothionamide; para-aminosalicylic acid	Add to complete a four-drug to five-drug regimen and when medicines from groups A and B cannot be used

Table 2: **2018 WHO grouping of medications for second-line drug-resistant tuberculosis[130]**

Support for successful outcomes

Adherence support aimed at ensuring successful tuberculosis treatment has historically relied on the use of directly observed therapy (DOT). The use of DOT has shown mixed results in multiple studies and meta-analyses, largely because the term appears to be a catch-all phrase for radically different treatment support approaches. When coupled with emotional support, nutritional supplementation, and other types of enablers, DOT can be a way to ensure daily contact with vulnerable individuals and close monitoring for the development of adverse events.[143] At the other end of the spectrum, DOT can add a substantial burden to the lives of people living with tuberculosis (eg, patients are required to collect their treatment from a facility each day),[144,145] which could increase the loss to follow-up. Data show that self-administered treatment, even among people with rifampicin-resistant tuberculosis results in similar outcomes.[146] Nowadays self-administered treatment can be enhanced by digital tools that could improve adherence (eg, phone-based and smartphone-based technologies or digital pillboxes). Although published data are scarce, several studies are ongoing.[147]

The first pillar of WHO's End TB Strategy is patient-centred care;[148] however, although the term is often used,

	Description	Examples
Holistic care	Care that sees the patient as a whole and addresses multiple individual needs	Effective and integrated care of comorbidities such as diabetes, HIV, and harmful substance use[152]
Individualised care	Care that reflects each patient's needs, preferences, and concerns	The provision of individualised treatment for rifampicin-resistant tuberculosis based on detailed drug susceptibility testing[153]
Empowering care	Care that recognises patients as active consumers	Mechanisms for supporting self-administration of treatment[154]
Respectful care	Care that encourages informed decision making and self-determination	Patient choice in regimen composition is based on understanding of efficacy and adverse events[155]

Table 3: **Key attributes of patient-centred care for tuberculosis**[156]

little information is available to define what this means and advise how to deliver it. Ideally, this term should mean that services and support for individuals affected by tuberculosis should be focused on them and their needs as opposed to the needs of the health system.[149] Such care would include socioeconomic support, and new data now show that conditional cash transfer programmes (where people are given a monthly spend during their threatment) for people with tuberculosis are associated with a decreased risk of mortality.[150] This finding is not surprising given that people living with tuberculosis often face catastrophic costs, and providing tuberculosis services as part of universal health coverage is likely to be the best way to decrease the cost and impact of this disease on people's lives.[151] To truly provide patient-centred care (table 3), or what some advocates refer to as person-centred care, the tuberculosis community needs to embrace a human rights framework in the treatment of tuberculosis.[157] Patient-centred care should also focus on mental health care, pain relief, and the principles of palliative care for tuberculosis (appendix).

All services provided to people with tuberculosis, from the time of presentation with initial symptoms to the time of discharge with non-relapsing cure, must be of the highest quality possible. Unfortunately, much work is to be done in terms of quality of care. Studies from India and South Africa published in the past 2 years show large gaps in the cascade of care for tuberculosis and multidrug-resistant tuberculosis.[158,159] Simulated patient studies among tuberculosis care providers in India, Kenya, China, and South Africa show that a wide spectrum exists in the quality of services offered to people with tuberculosis, with many receiving suboptimal services.[160–162] Thus, improving quality of tuberculosis care must be a key consideration for achieving better outcomes and will require system-wide action to develop high-quality health systems.[163]

Prevention

Prevention efforts have focused on tuberculosis vaccination and the treatment of latent tuberculosis or tuberculosis infection. Immunisation with the BCG vaccine is known to protect children from severe and disseminated forms of disease, decrease infection by 30%, and potentially offer some protection to adult populations.[164] In general, the vaccine is not thought to be immunogenic enough to induce long-term immunity, although some studies show that intrapulmonary administration might be more immunogenic and development of an inhaled BCG vaccine could be an important strategy to pursue.[165] A 2018 phase 2b study of a novel vaccine candidate known as M72/AS01$_E$ (GlaxoSmithKline, London, UK) was found to provide more than 50% protection from progression to active tuberculosis among adults with tuberculosis infection and could be a candidate to advance into larger studies.[166]

In the past few years, major advances in the treatment of tuberculosis infection have occurred. Substantially shorter tuberculosis prevention regimens have been developed, and have been shown to be effective in both adults and children, including those living with HIV. Such regimens, including a 4-month regimen of rifampicin was tested in both adults and children and found to be as effective as 9 months of daily isoniazid.[167] This regimen has the added benefit of using a drug with well established dosing and safety data available from populations of all ages,[168] and which can be used with almost all forms of antiretroviral therapy within known dose-adjustment parameters. However, concerns about the development of drug resistance when using a single drug in patients with undiagnosed active tuberculosis disease remain.

Other shorter regimens for the treatment of tuberculosis infection have focused on the use of rifapentine. The 12-week regimen of high-dose isoniazid given with high-dose rifapentine once a week has now been shown to be safe, and dosing has been established in children as young as 2 years.[169] Preliminary data suggest that a 1-month regimen of daily isoniazid and rifapentine might be as effective as 9 months of daily isoniazid in the treatment of tuberculosis infection among adults living with HIV.[170] Both of these regimens include the drug rifapentine, and although there were initial concerns about using this drug with the antiretorviral agent dolutegravir,[171] data presented on the combination of dolutegravir and rifapentine co-administration in people living with HIV (NCT03435146)[172] found no grade 3–4 events, suggesting that the combination is safe in people with HIV. Additionally, there is concern that these shorter, rifapentine-based regimens might not confer sufficient protection among people with HIV living in high-tuberculosis settings, and studies on annual cycled courses are now underway.[173] Both of these rifapentine-based regimens could substantially shorten treatment for people who have been infected with tuberculosis. WHO recommends that one of four regimens be used for the treatment of tuberculosis infection: daily isoniazid for 6 to 9 months, daily rifampicin for 4 months, daily isoniazid and rifampicin for 3 months, or weekly isoniazid and rifapentine for 12 weeks (appendix).

People who have been exposed to rifampicin-resistant tuberculosis previously had few options to treat

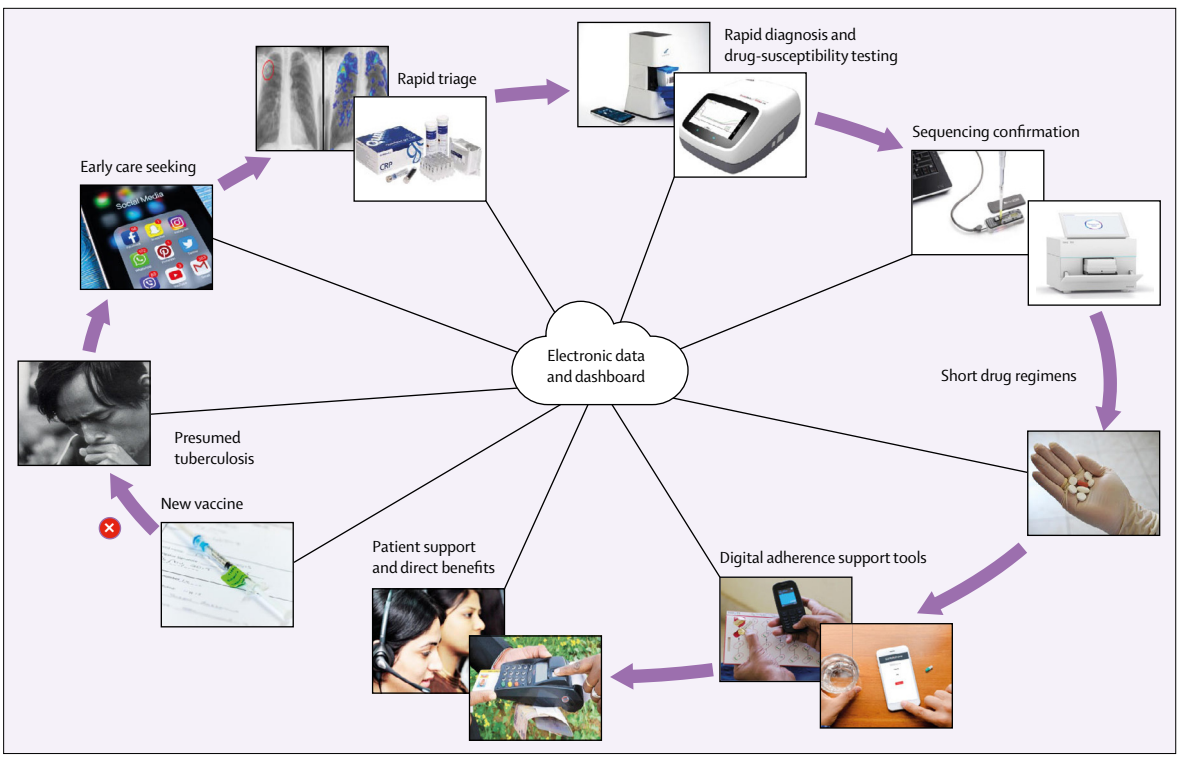


Figure 2: **Schematic for a modern tuberculosis care delivery system**
Reproduced from Pai.[176]

their infection. Individualised regimens with multiple drugs based largely on fluoroquinolone were only available in selected settings. However, a meta-analysis of such preventive therapy found a 90% reduction in the risk of development of tuberculosis among contacts that were provided with such treatment. Furthermore, use of fluoroquinolone-based preventive therapy was also found to be cost-effective.[50] These findings led to WHO recommending the treatment of drug-resistant forms of tuberculosis infection with regimens selected on the basis of the drug-susceptibility pattern of the known contact.[174] Three studies (V-QUIN [ACTRN12616000215426], TB CHAMP [NCT02365623], and PHOENIx [NCT03568383]) are either ongoing or planned to formally assess treatment of drug-resistant tuberculosis infection with treatment regimens including either levofloxacin or delamanid. The results of these studies are expected in 3–5 years. In the meantime, however, given the poor outcomes of people who become sick with drug-resistant forms of tuberculosis, the benefit of such treatment is likely to outweigh the risks in most situations.

How to modernise tuberculosis care

For too long, tuberculosis care has relied on antiquated tools that are no longer fit for purpose. This can and must change.[175] As described in this Seminar, many new tools and solutions already exist in some form (figure 2); however, these developments have not come together to serve those who need them the most. For some improvements to be made, such as the development of a better vaccine or a shorter drug therapy, new investments are urgently needed. High-quality systems for data management need to be established and maintained for national and international monitoring, resource allocation, and accurate problem solving.[177]

Political will to end tuberculosis

On Sept 26, 2018, a UN meeting focused on tuberculosis was held in New York, NY, USA.[178] The pledges made by multiple, high-level delegations, including heads of state from high burden tuberculosis countries, such as South Africa, could herald a new level of political commitment in the fight against tuberculosis. Although similar meetings held to discuss HIV and Ebola led to substantial increases in funding for research and treatment, the effects of the UN tuberculosis meeting are not yet apparent. New global accountability systems are badly needed to ensure that "ending tuberculosis" does not become yet another slogan tied to limited action of little benefit for those most affected by tuberculosis.[178]

Conclusions

Although tuberculosis continues to be one of the most important public health problems of the 21st century, clinical and scientific advances exist that stand to

revolutionise the diagnosis, treatment, and prevention of all forms of this disease. Access to these diagnostic and therapeutic advances must be guaranteed for all as part of a human rights-based approach to tuberculosis. The political will to eliminate tuberculosis is stronger than ever; this intention must be matched with unparalleled implementation efforts to spare millions of men, women, and children from the unnecessary burden of this disease.

Contributors

JF led the conception of this Seminar. All authors contributed to literature review and writing.

Declaration of interests

HC reports grants from the Wellcome Trust, the National Research Foundation, and the UK Medical Research Council, outside of the submitted work. MP serves on the Access Advisory Committee of TB Alliance, New York, NY, USA, and on the Scientific Advisory Committee of the Foundation for Innovative New Diagnostics, Geneva, Switzerland; these non-profit agencies were not involved in the preparation of this manuscript. JF declares no competing interests.

References

1 Nathavitharana RR, Fiedland J. A tale of two global emergencies: tuberculosis control efforts can learn from the Ebola outbreak. *Eur Respir J* 2015; **46:** 293–36.

2 Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf (accessed Nov 9, 2018).

3 President of the UN General Assembly. Scope, modalities, format and organization on the high-level meeting on the fight against tuberculosis. https://undocs.org/en/A/72/L.40 (accessed Nov 22, 2018).

4 WHO. Global tuberculosis report 2018. Sept 18, 2018. https://www.who.int/tb/publications/global_report/en/ (accessed March 11, 2019).

5 Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009; **68:** 2240–46.

6 GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2018; **18:** 261–84.

7 GBD Tuberculosis Collaborators. Global, regional, and national burden of tuberculosis, 1990–2016: results from the Global Burden of Diseases, Injuries, and Risk Factors 2016 Study. *Lancet Infect Dis* 2018; **18:** 1329–49.

8 Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. *Lancet Public Health* 2017; **2:** e47–55.

9 Trauer JM, Denholm JT, McBryde ES. Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-Pacific. *J Theor Biol* 2014; **358:** 74–84.

10 Mehra M, Cossrow N, Kambili C, Underwood R, Makkar R, Potluri R. Assessment of tuberculosis burden in China using a dynamic disease simulation model. *Int J Tuberc Lung Dis* 2013; **17:** 1186–94.

11 Ismail NA, Mvusi L, Nanoo A, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. *Lancet Infect Dis* 2018; **18:** 779–87.

12 Comas I, Coscolla M, Luo T, et al. Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nature Genet* 2013; **45:** 1176–82.

13 Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; **13:** e1002152.

14 Pai M, Behr M, Dowdy D, et al. Tuberculosis. *Nat Rev Dis Primers* 2016; **2:** 16076.

15 Drain P, Bajema K, Dowdy D, et al. Incipient and sub-clinical tuberculosis: a clinical review of early stages and progression of infection. *Clinical Microbiol Rev* 2018; **31:** e00021–18.

16 Michelsen SW, Soborg B, Diaz LJ, et al. The dynamics of immune responses to Mycobacterium tuberculosis during different stages of natural infection: a longitudinal study among Greenlanders. *PLoS One* 2017; **12:** e0177906.

17 Torrelles J, Schlesinger L. Integrating lung physiology, immunology and tuberculosis. *Trends Microbiol* 2017; **25:** 688–97.

18 Seshadri C, Sedaghat N, Campo M, et al. Transcriptional networks are associated with resistance to *Mycobacterium tuberculosis* infection. *PLoS One* 2017; **12:** e0175844.

19 Shah NS, Auld S, Brust J, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. *N Engl J Med* 2017; **376:** 243–53.

20 Dheda K, Lenders L, Magombedze G, et al. Drug penetration gradients associated with acquired drug resistance in patients with tuberculosis. *Am J Respir Crit Care Med* 2018; **198:** 1208–19.

21 Behr M, Edelstein P, Ramakrishnan L. Revisiting the time table of tuberculosis. *BMJ* 2018; **362:** K2736.

22 Zak DE, Penn-Nicholson A, Scriba TJ, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet* 2016; **387:** 2312–22.

23 Oxlade O, Murray M. Tuberculosis and poverty: why are the poor at greater risk in India? *PLoS One* 2012; **7:** e47533.

24 Ortblad K, Salomon J, Barnighause T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; **386:** 2354–62.

25 Saunders MJ, Wingfield T, Tovar MA, et al. A score to predict and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: a prospective derivation and external validation cohort study. *Lancet Infect Dis* 2017; **17:** 1190–99.

26 Batista JdL, de Albuquerque Mde F, Maruza M, et al. Incidence and risk factors for tuberculosis in people living with HIV: cohort from HIV referral health centers in Recife, Brazil. *PLoS One*; **8:** e63916.

27 Pande T, Cohen C, Pai M, Khan A. Computer-aided detection of pulmonary tuberculosis on digital chest radiographs: a systematic review. *Int J Tuberc Ling Dis* 2016; **20:** 1226–30.

28 WHO. Chest radiography in tuberculosis detection: summary of current WHO recommendations and guidance on programmatic approaches. 2016. http://apps.who.int/iris/bitstream/handle/10665/252424/9789241511506-eng.pdf?sequence=1 (accessed Nov 10, 2018).

29 Lawn S, Gupta-Wright A. Detection of lipoarabanomanna (LAM) in urine is indicative of disseminated tuberculosis with renal involvement in patients living with HIV and advanced immunodeficiency. *Trans R Soc Trop Med Hyg* 2016; **110:** 180–85.

30 Lawn SD. Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. *BMC Infect Dis* 2012; **12:** 103.

31 Peter JG, Zijenah LS, Chanda D, et al. Effect on mortality of point-of-care, urine-based lipoarabanomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel group, multi-country, open-label, randomised, controlled trial. *Lancet* 2016; **387:** 1187–97.

32 Gupta-Wright A, Corbett EL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial. *Lancet* 2018, **392:** 292–301.

33 WHO. The use of the lateral flow urine lipoarabanomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. 2015. http://apps.who.int/iris/bitstream/handle/10665/193633/9789241509633_eng.pdf?sequence=1 (accessed Nov 9, 2018).

34 Sigal G, Pinter A, Lowary T, et al. A novel, sensitive immunoassay targeting the MTB-lipoarabanaomannan epitope meets the WHO's performance target for tuberculosis diagnosis. *J Clin Microbiol* 2018; **56:** e01338–18.

35 Paris L, Magni R, Zaidi F, et al. Urine lipoarabinomannan glycan in HIV-negative patients with pulmonary tuberculosis correlates with disease severity. *Sci Transl Med* 2017; **9:** eaal2807.

36 Goletti D, Lee M, Wang J, et al. Update on tuberculosis biomarkers: from correlates of risk to correlates of active disease and of cure from disease. *Respirology* 2018; **23:** 455–66.

37 La Manna MP, Orlando V, Li Donni P, et al. Identification of plasma biomarkers for discrimination between tuberculosis infection/disease and pulmonary non tuberculosis disease. *PLoS One* 2018; **13:** e0192664.

38 Togun TO, MacLean E, Kampmann B, Pai M. Biomarkers for diagnosis of childhood tuberculosis: a systematic review. *PLoS One* 2018; **13:** e0204029.

39 Kana BD, Gordhan BG, Downing KJ, et al. The resuscitation-promoting factors of *Mycobacterium tuberculosis* are required for virulence and resuscitation from dormancy but are collectively dispensable for growth in vitro. *Mol Microbiol* 2007; **67:** 672–84.

40 Cazabon D, Pande T, Kik S, et al. Market penetration of Xpert MTB/RIF in high tuberculosis burden countries: a trend analysis from 2014–2016. Gates Open Research. 2018. https://gatesopenresearch.org/articles/2-35/v1 (accessed Nov 23, 2018).

41 Albert H, Nathavitharana R, Isaacs C, et al. Development, roll out, and impact of Xpert MTB/RIF for tuberculosis: what lessons have we learnt and how can we do better? *Eur Respir J* 2016; **48:** 516–25.

42 Xie Y, Chakrovarty D, Armstrong S, et al. Evaluation of a rapid molecular drug-susceptibility test for tuberculosis. *N Engl J Med* 2017; **377:** 1043–54.

43 Walters E, van der Zalm M, Palmer M, et al. Xpert MTB/RIF on stool is useful for the rapid diagnosis of tuberculosis in young children with severe pulmonary disease. *Pediatr Infect Dis J* 2017; **36:** 837–43.

44 Seki M, Kim C, Hayakawa S, Mitarai S. Recent advances in tuberculosis diagnostics in resource poor settings. *Eur J Clin Microbiol Infect Dis* 2018; **37:** 1405–10.

45 Singh BK, Sharma SK, Sharma R, et al. Diagnostic utility of a line probe assay for multidrug resistant-TB in smear-negative pulmonary tuberculosis. *PLoS One* 2017; **12:** e0182988.

46 Satta G, Lipman M, Smith G, et al. *Mycobacterium tuberculosis* and whole-genome sequencing: how close are we to unleashing its full potential? *Clin Microbiol Infect* 2018; **24:** 604–49.

47 The CRyPTIC Consortium and the 100 000 Genomes Project, Allix-Béguec C, Arandjelovic I. Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing. *N Engl J Med* 2018; **379:** 1403–15.

48 Cox H, Mizrahi V. The coming of age of drug-susceptibility testing for tuberculosis. *N Engl J Med* 2018; **379:** 1474–75.

49 Walker TM, Ip CLC, Harrell RH, et al. Whole-genome sequencing to delineate *Mycobacterium tuberculosis* outbreaks: a retrospective observational study. *Lancet Infect Dis* 2013; **13:** 137–46.

50 WHO. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. 2018. https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ (accessed March 11, 2019).

51 Pai M, Denkinger C, Kik S, et al. Gamma interferon release assays for detection of *M tuberculosis* infection. *Clinical Microbiol Rev* 2014; **27:** 3–20.

52 Aggerbeck H, Ruhwald M, Hoff ST. et al. C-Tb skin test to diagnose *Mycobacterium tuberculosis* infection in children and HIV-infected adults: a phase 3 trial. *PLoS One* 2018; **13:** e0204554.

53 Ruhwald M, Aggerbeck H, Vázquez Gallardo R, et al. Safety and efficacy of the C-TB skin test to diagnose *Mycobacterium tuberculosis* infection, compared with interferon γ release assay and the tuberculin skin test: a phase 3, randomised, double-blind controlled trial. *Lancet* 2017; **5:** 259–68.

54 Getahun H, Raviglione M. Active case finding for TB in the community: time to act. *Lancet* 2010; **376:** 1205–06.

55 Morishita F, Garfin AMCG, Lew W, et al. Bringing state-of-the-art diagnostics to vulnerable populations: the use of a mobile screening unit in active case finding for tuberculosis in Palawan, the Philippines. *PLoS One* 2017; **12:** e0171310.

56 Calligaro GL, Zijenah LS, Peter JG, et al. Effect of new tuberculosis diagnostic technologies on community-based intensified case finding: a multicenter, randomised controlled trial. *Lancet* 2017; **17:** 441–50.

57 Zumla AI, Gillespie SH, Hoelscher M, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect Dis* 2014; **14:** 327–40.

58 Jo KW, Yoo JW, Hong Y, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. *Respir Medi* 2014; **108:** 654–59.

59 Gopalan N, Santhanakrishnan K, Palaniappan N, et al. Daily vs intermittent tuberculosis therapy for persons with HIV: a randomized clinical trial. *JAMA Intern Med* 2018; **178:** 485–93.

60 Hao L, Guo S, Liu C, et al. Comparative bioavailability of rifampicin and isoniazid in fixed-dose combinations and single-drug formulations. *Int J Tuberc Lung Dis* 2014; **18:** 1505–12.

61 Milstein M, Lecca L, Peloquin C, et al. Evaluation of high-dose rifampicin in patients with new, smear-positive tuberculosis (HIRIF): study protocol for a randomized controlled trial. *BMC Infect Dis* 2016; **16:** 453.

62 Boeree MJ, Diacon AH, Dawson R, et al. PanACEA Consortium: a dose-ranging trial to optimize the dose of rifampicin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015; **191:** 65.

63 Boeree MJ, Heinrich N, Aarnouste R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017; **17:** 39–49.

64 Velasquez G, Brooks M, Coit J, et al. Efficacy and safety of high-dose rifampicin in pulmonary tuberculosis: a randomised, controlled trial. *Am J Respir Crit Care Med* 2018; **198:** 657–66.

65 Beyrer C, Shisana O, Baral S, et al. The science of Durban, AIDS 2016. *J Int AIDS Soc* 2017; **20:** 21781.

66 Gillespie S, Crook A, McHugh T, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014; **371:** 1577–87.

67 Merle C, Fielding K, Sow O, et al. A four-month gatifloxacin-containing regimen for tuberculosis. *N Eng J Med* 2014; **371:** 1588–98.

68 Jindani A, Harrison T, Nunn A, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med* 2014; **371:** 1599–608.

69 Imperial M, Nahid P, Phillips P, et al. A patient-level pooled analysis of treatment shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018; **24:** 1708–15.

70 Low M. The tuberculosis treatment pipeline: a breakthrough year for the treatment of XDR-TB. July 2017. http://www.pipelinereport.org/2017/tbtx (accessed Jan 14, 2019).

71 Chien JY, Chen YT, Wu SG, Lee JJ, Wang JY, Yu CJ. Treatment outcome of patients with isoniazid mono-resistant tuberculosis. *Clin Microbiol Infect* 2015; **21:** 59–68.

72 Chien J-Y, Wang J-Y. Isoniazid-resistant tuberculosis treatment with first-line drugs. *Lancet Infect Dis* 2017; **17:** 259–60.

73 WHO. Guidelines on the treatment of isoniazid-resistant tuberculosis. 2017. https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-izoniazid-resistant-tb/en/ (accessed Nov 9, 2018).

74 Coovadia YM, Mahomed S, Pillay M, et al. Rifampicin mono–resistance in mycobacterium tuberculosis in KwaZulu–Natal, South Africa: a significant phenomenon in a high prevalence TB–HIV region. *PLoS One* 2013; **8:** e77712.

75 Stop TB Partnership. GDF products list. http://www.stoptb.org/gdf/drugsupply/drugs_available.asp (accessed Nov 22, 2018).

76 RESIST-TB. Clinical trials progress report. June 6, 2018. http://www.resisttb.org/?page_id=1602 (accessed Nov 22, 2018).

77 Ismail N, Omar S, Joseph L, et al. Defining bedaquiline susceptibility, resistance, cross resistance, and associated genetic determinants: a retrospective cohort study. *EBioMedicine* 2018; **28:** 136–42.

78 Kunkel A, Furin J, Cohen T. Population implications of the use of bedaquiline in people with extensively drug-resistant tuberculosis: are fears of resistance justified. *Lancet Infect Dis* 2017; **17:** e429–33.

79 Belard S, Heuvelings CC, Janssen S, Grobusch MP. Bedaquiline for the treatment of drug-resistant tuberculosis. *Expert Rev Anti Infect Ther* 2015; **13:** 535–53.

80 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug resistant pulmonary tuberculosis. *New Engl J Med* 2012; **366:** 2151–60.

81 Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013; **41:** 1393–400.

82 Lewis J, Sloan D. The role of delamanid in the treatment of drug-resistant tuberculosis. *Ther Clin Risk Manag* 2015; **11:** 779–91.

83 Gupta R, Geiter LJ, Hafkin J, Wells CD. Delamanid and QT prolongation in the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2015; **19:** 1261–62.

84 Hewison C, Ferlazzo G, Avaliani Z, et al. Six month response to delamanid treatment in MDR-TB Patients. *Emerg Infect Dis* 2017; **23:** 10.

85 Drug-Resistant Tuberculosis Scale-Up Treatment Action Team. Global report August, 2018. http://drtb-stat.org/wp-content/uploads/2019/01/DR-TB-STAT-August-2018-Global-Summary.docx.pdf (accessed Nov 9, 2018).

86 Li S, Tanseen R, Tyagi S, et al. Bactericidal and sterilizing activity of a novel regimen with bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. *Antimicrob Agents Chemother* 2017; **61:** 28630203.

87 TB Alliance. Clinical trial of BPaMZ will replace phase 3 STAND trial. Dec 21, 2016. https://www.tballiance.org/news/clinical-trial-bpamz-regimen-will-replace-phase-3-stand-trial (accessed Nov 9, 2018).

88 Conradie F, Diacon A, Everitt D, et al. The NIX-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; Feb 13–16, 2017. 80LB.

89 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.

90 Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-tuberculosis: a study in China. *Eur Respir J* 2015; **45:** 161–70.

91 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.

92 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012; **16:** 447–54.

93 Wallis RS, Dawson R, Friedrich SO, et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. *PLoS One* 2014; **9:** e94462.

94 Andrews J. To be or not to be exclusive: the sutezolid story. *Lancet Glob Health* 2016, **4:** e89–90.

95 Tang S, Yao L, Hao X, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. *Clin Infect Dis* 2015; **60:** 1361–67.

96 Dalcolmo M, Guyoso R, Sotgiu G, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. *Eur Respir J* 2017; **49:** 1602445.

97 Jaganath D, Lamichhane G, Shah M. Carbapenems against *Mycobacterium tuberculosis*: a review of the evidence. *Int J Tuberc Lung Dis* 2016, **20:** 1436–47.

98 WHO. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. 2013. https://apps.who.int/iris/bitstream/handle/10665/84879/9789241505482_eng.pdf?sequence=1 (accessed Nov 23, 2018).

99 Mbuagbaw L. WHO. 2017. A review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: data analysis report. http://www.who.int/tuberculosis/publications/2017/Appendix_GDGReport_Bedaquiline.pdf (accessed July 7, 2017).

100 Ndjeka N, Conradie F, Schnippel K. et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *Int J Tuberc Lung Dis* 2015; **19:** 979–85.

101 Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017; **49:** 1700387.

102 Guglielmetti L, Hewison C, Avaliani Z, et al. Examples of bedaquiline introduction for the management of multidrug-resistant tuberculosis in five countries. *Int J Tuberc Lung Dis* 2017; **21:** 167–74

103 Vambe D, Dlamini T, Furin J, et al. Operational aspects of bedaquiline implementation in Swaziland: report from the field. *Public Health Action* 2017; **7:** 240–42.

104 Guglielmetti L, Le Dû D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; **60:** 188–94.

105 Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018; **6:** 669–706.

106 Reuter A, Furin J. Bedaquiline use in South Africa reveals a lifesaving policy in action. *Lancet Respir Med* 2018; **6:** 653–55.

107 Republic of South Africa. Department of Health. Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children. 2018. http://www.tbonline.info/media/uploads/documents/dr_tb_clinical_guidelines_for_rsa_september_2018.pdf (accessed Jan 14, 2019).

108 Zhao Y, Fox T, Manning K, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug resistant tuberculosis: a retrospective cohort study. *Clin Infect Dis* 2018; published online Aug 24. DOI:10.1093/cid/ciy727.

109 Schnippel K, Firnhaber C, Conradie F, et al. Incremental cost-effectiveness of bedaquiline for the treatment of rifampicin-resistant tuberculosis in South Africa: model-based analysis. *Appl Health Econ Health Policy* 2018; **16:** 43–54.

110 Furin J, Lessem E, Cox V. Recommending prolonged bedaquiline use for the treatment of highly resistant strains of tuberculosis. *Eur Respir J* 2017; **11:** 50.

111 Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J* 2016; **49:** 1601799.

112 WHO. Rapid Communication: key changes to the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). August, 2018. http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf (accessed Nov 9, 2018).

113 Cox V, Brigden G, Crespo RH, et al. Global programmatic use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2018; **22:** 407–12.

114 Furin J, Brigden G, Lessem E, et al. Global progress and challenges in the implementation of new medications for the treatment of multidrug-resistant tuberculosis. *Emerg Infect Dis* 2016; **22:** e1–7.

115 Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-tuberculosis cohort study. *Int J Tuberc Lung Dis* 2016; **20:** 177–86.

116 Lessem E, Cox H, Daniels C, et al. Access to new medications for the treatment of drug-resistant tuberculosis: patient, provider and community perspectives. *Int J Infect Dis* 2014; **32:** 56–60.

117 WHO. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. 2014. https://www.who.int/tb/publications/Delamanid_interim_policy/en/ (accessed Nov 28, 2018).

118 von Groot-Bidilingmeier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for the treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019; published online Jan 7. http://dx.doi.org/10.1016/S2213-2600(18)30426-0.

119 Hafkin J, Frias M, Hesseling A, et al. Pharmacokinetics and safety of delamanid in pediatric MDR-tuberculosis patients, ages 6–17 years. International Conference on Antimicrobial Agents and Chemotherapy; San Diego, CA, USA; Sept 18–21, 2015. A-960.

120 Hafkin J, Frias M, De Leon A, et al. Long-term safety, tolerability, and pharmacokinetics of delamanid in pediatric MDR-TB patients ages 12–17 years. 46th Union World Conference on Lung Health; Cape Town, South Africa; Dec 2–6, 2015. EP-115–04.

121 WHO. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. 2016. http://apps.who.int/iris/bitstream/handle/10665/250614/9789241549899-eng.pdf?sequence=1 (accessed Nov 9, 2018).

122 Mohr E, Hughes J, Reuter A, et al. Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa. *Eur Respir J* 2018; **51:** 1800017.

123 Mok J, Kang H, Hwang S, et al. Interim outcomes of delamanid for the treatment of MDR-TB and XDR-TB in South Korea. *Clin Infect Dis* 2018; **73:** 503–08.

124 Ferlazzo G, Mohr E, Laxmeshwar C, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. *Lancet Infect Dis* 2018; **18:** 536–44.

125 Barthod L, Lopez J-G, Curti C, et al. News on therapeutic management of MDR-tuberculosis: a literature review. *J Chemother* 2018; **30:** 1–15.

126 Stop TB Partnership Working Group on New Drugs. Clinical pipeline. https://www.newtbdrugs.org/pipeline/clinical (accessed Jan 14, 2019).

127 Hoagland D, Liu J, Lee RB, Lee RE. New agents for the treatment of drug-resistant *Mycobacterium tuberculosis*. *Adv Drug Deliv Rev* 2016; **102:** 55–72.

128 Horsburgh CR, Rusen ID, Mitnick CD. Optimizing MDR-TB clinical trials: insights from the first global MDR-TB Clinical Trials Landscape Meeting. *Int J Tuberc Lung Dis* 2016; **20:** 1–3.

129 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR- tuberculosis Treatment–2017. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; **392:** 821–34.

130 WHO. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis: 2018 Update. Pre-final text. 2018. https://www.who.int/tuberculosis/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf (accessed Jan 14, 2019).

131 Lange C, Chesov D, Furin J, Udwadia Z, Dheda K. Revising the definition of extensively drug-resistant tuberculosis. *Lancet Respir Med* 2018; **6:** 893–95.

132 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.

133 Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis* 2015; **19:** 517–24.

134 Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014; **18:** 1188–94.

135 WHO. Position statement on the continued use of the shorter MDR-TB treatment regimen following an expedited review of the STREAM Stage 1 preliminary results. 2018. http://www.who.int/tb/publications/2018/Position_statement_shorter_MDR_TB_regimen/en/ (accessed Nov 9, 2018).

136 Nunn AJ, Philipps P, Meredith S, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; published online March 13. DOI:10.1056/NEJMoa1811867.

137 WHO. WHO treatment guidelines for drug resistant tuberculosis: 2016 update. 2016. https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/ (accessed Nov 23, 2018).

138 Reuter A, Tisile P, von Delft D, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? *Int J Tuberc Lung Dis* 2017; **21:** 1114–26.

139 Mitnick CD, Rusen I, Bain LJ, Horsburgh CR. Issues in design and interpretation of MDR-TB clinical trials: report of the first Global MDR-TB Clinical Trials Landscape Meeting. *BMC Proc* 2015; **9** (suppl 8)**:** S1.

140 Harausz EP, Garcia-Prats AJ, Seddon JA, et al. New and repurposed drugs for pediatric multidrug-resistant tuberculosis. Practice-based recommendations. *Am J Respir Crit Care Med* 2017; **195:** 1300–10.

141 Romanowski K, Balshaw R, Benneditti A, et al. Predicting tuberculosis relapse in patients treated with the standard 6-month regimen: an individual patient data meta-analysis. *Thorax* 2018; published online Nov 12. DOI:10.1136/thoraxjnl-2017-211120.

142 Te Riele J, Buser V, Calligaro G, et al. Relationship between chest radiographic characteristics, sputum bacterial load, and treatment outcomes in persons with extensively drug-resistant tuberculosis. *Int J Infect Dis* 2018; **3:** 65–71.

143 Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K. 'I cry every day': experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. *Trop Med Int Health* 2013; **18:** 1128–33.

144 Benbaba S, Isaakidis P, Das M, Jadhav S, Reid T, Furin J. Direct observation (DO) for drug-resistant tuberculosis: do we really DO? *PLoS One* 2015; **10:** e0144936.

145 Daftary A, Padayatchi N, O'Donnell M. Preferential adherence to antiretroviral therapy over tuberculosis treatment: a qualitative study of drug-resistant TB/HIV co-infected patients in South Africa. *Glob Public Health* 2014; **9:** 1107–16.

146 Mohr E, Daniels J, Beko B, et al. DOT or SAT for rifampicin-resistant tuberculosis? A non-randomied comparison in a high HIV-prevalence setting. *PLoS One* 2017; **12:** e0178054.

147 Subbaraman R, de Mondesert L, Musiimenta A, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *BMJ Glob Health* 2018; **3:** e001018.

148 WHO. The End TB Strategy. 2015. https://www.who.int/tb/strategy/end-tb/en/ (accessed Nov 23, 2018).

149 O'Donnell MR, Daftary A, Frick M, et al. Re-inventing adherence: toward a patient-centered model of care for drug-resistant tuberculosis and HIV. *Int J Tuberc Lung Dis* 2016; **20:** 430–34.

150 De Souza R, Nery J, Rasella D, et al. Family health and conditional cash transfer in Brazil and its effect on tuberculosis mortality. *Int J Tuberc Lung Dis* 2018; **22:** 1300–06.

151 Fuady A, Houweling T, Mansyur M, Richadus J. Catastrophic total costs in tuberculosis affected households and their determinants since Indonesia's implementation of universal health coverage. *Infect Dis Poverty* 2018; **7:** 3.

152 Hermans SM, Castelnuovo B, Katabira C, et al. Integration of HIV and tuberculosis services results in improved tuberculosis treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda. *J Acquir Immune Defic Syndr* 2012; **60:** e29–35.

153 Cox H, Hughes J, Black J, Nicol MP. Precision medicine for drug-resistant tuberculosis in high-burden countries: is individualised treatment desirable and feasible? *Lancet Infect Dis* 2018; **18:** e282–87.

154 Holzman SB, Zenilman A, Shah M. Advancing patient-centered care in tuberculosis management: a mixed-methods appraisal of video directly observed therapy. *Open Forum Infect Dis* 2018; **5:** ofy046.

155 Rennie TW, Bothamley GH, Engova D, Bates IP. Patient choice promotes adherence in preventive treatment for latent tuberculosis. *Eur Respir J* 2007; **30:** 728–35.

156 Odone A, Roberts B, Dara M, et al. People- and patient-centered care for tuberculosis: models of care for tuberculosis. *Int J Tuberc Lung Dis* 2018; **22:** 133–38.

157 Citro B, Lyon E, Mankand M, et al. Developing a human rights-based approach to tuberculosis. *Health Hum Rights* 2016; **18:** 1–8.

158 Subbaraman R, Nathavitharana RR, Satyanarayana S, et al. The tuberculosis cascade of care in India's public sector: a systematic review and meta-analysis. *PLoS Med* 2016; **13:** e1002149.

159 Naidoo P, Theron G, Rangaka M, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. *J Infect Dis* 2017; **216:** S702–13.

160 Kwan A, Daniels B, Saria V, et al. Variations in the quality of tuberculosis care in urban India: a cross-sectional, standardized patient study in two cities. *PLoS Med* 2018; **15:** e1002653.

161 Daniels B, Dollinger A, Bedoya G, et al. Use of standardized patients to assess quality of health care in Nairobi, Kenya: a pilot, cross-section study with international comparisons. *BMJ Glob Health* 2017; **2:** e000333.

162 Sylvia S, Xue H, Zhou C, et al. Tuberculosis detection and the challenges of integrated care in rural China: a cross-sectional standardized patient study. *PLoS Med* 2017; **14:** e1002405.

163 Kruk ME, Gage AD, Arsenault C, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. *Lancet Glob Health* 2018; **6:** e1196–252.

164 Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014; **58:** 470–80.

165 Thomas Z, McShane H. Aerosol immunization for tuberculosis: matching route of vaccination to route of infection. *Trans R Soc Trop Med Hyg* 2015; **109:** 175–81.

166 Van Der Meeren O, Hatherhill M, Nduba V, et al. Phase IIB controlled trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2018; **379:** 1621–34.

167 Menzies D, Adjobimay M, Ruslami R, et al. Four months of rifampicin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med* 2018; **379:** 440–53.

168 Diallo T, Abdjominey M, Ruslami R, et al. Safety and side effects of rifampicin versus isoniazid in children. *N Engl J Med* 2018; **379:** 454–63.

169 Borisov A, Bahmra-Morris S, Njie G, et al. Update of recommendations for use of once weekly isonizid and rifapentine regimen to treat latent tuberculosis infection. *MMWR Morb Mortal Wkly Rep* 2018, **67:** 723–26.

170 Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. *N Engl J Med* 2019; **380:** 1001–11.

171 Brooks K, George J, Pau A, et al. Cytokinemediated, systemic adverse drug reactions in a drug-drug interaction study of dolutegravir with once weekly isoniazid and rifapentine. *Clin Infect Dis* 2018; **67:** 193–201.

172 Dooley K, Churchyard G, Savic R, et al. Safety and PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; March 6, 2019. 80LB.

173 Marks S, Mase S, Morris S. Systematic review, meta-analysis, and cost-effectiveness of treatment of latent tuberculosis infection to reduce progression to multidrug-resistant tuberculosis. *Clin Infect Dis* 2017; **64:** 1670–77.

174 Granich R. Is the global tuberculosis control strategy too big to fail? *Lancet* 2018; **392:** 2165.

175 Melese M, Habte D, Girma B, et al. Use of indicators of standards of care to improve tuberculosis program management in Ethiopia. *J Clin Tuberc Other Mycobact Dis* 2018; **10:** 17–23.

176 Pai M. TB care reimagined. 2018. https://naturemicrobiologycommunity.nature.com/channels/301-gallery/posts/40073-my-dream-tb-clinic (accessed Nov 21, 2018).

177 Zumla A, Petersen E. The historic and unprecedented United Nations General Assembly high-level meeting on tuberculosis—'Unite to End TB': an urgent global response to a global epidemic. *Int J Infect Dis* 2018; **75:** 118–20.

178 The Lancet. Tuberculosis at the United Nations: a missed chance. *Lancet Infect Dis* 2018; **18:** 1161.