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Primer

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Multidrug-resistant tuberculosis

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Abstract

Tuberculosis (TB) remains the foremost cause of death by an infectious disease globally. Multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB; resistance to rifampicin and isoniazid, or rifampicin alone) is a burgeoning public health challenge in several parts of the world, and especially Eastern Europe, Russia, Asia and sub-Saharan Africa. Pre-extensively drug-resistant TB (pre-XDR-TB) refers to MDR/RR-TB that is also resistant to a fluoroquinolone, and extensively drug-resistant TB (XDR-TB) isolates are additionally resistant to other key drugs such as bedaquiline and/or linezolid. Collectively, these subgroups are referred to as drug-resistant TB (DR-TB). All forms of DR-TB can be as transmissible as rifampicin-susceptible TB; however, it is more difficult to diagnose, is associated with higher mortality and morbidity, and higher rates of post-TB lung damage. The various forms of DR-TB often consume >50% of national TB budgets despite comprising <5–10% of the total TB case-load. The past decade has seen a dramatic change in the DR-TB treatment landscape with the introduction of new diagnostics and therapeutic agents. However, there is limited guidance on understanding and managing various aspects of this complex entity, including the pathogenesis, transmission, diagnosis, management and prevention of MDR-TB and XDR-TB, especially at the primary care physician level.

Sections

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Introduction

Globally, tuberculosis (TB) has once again become the leading cause of death by an infectious disease[1]. In 2022, TB was the largest drug-resistant airborne epidemic and more than 1 billion people have succumbed to the disease over the past two centuries[2,3]. Effective drugs against the TB-causing bacterium, *Mycobacterium tuberculosis*, were first developed in the 1940s. Drug-susceptible TB (DS-TB) can be cured with a 6-month regimen that consists of four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE), although there are regimens as short as 4 months[4]. However, over time, resistance to these first-line drugs, the main ones being rifampicin and isoniazid, has developed (see Mechanisms section below).

Box 1

Drug-resistant forms of TB

Isoniazid-monoresistant tuberculosis (TB)[a]
Isoniazid resistance detected
Rifampicin resistance not detected

Rifampicin-resistant tuberculosis (RR-TB)[a]
Rifampicin resistance detected
Isoniazid resistance not detected

Multidrug-resistant tuberculosis (MDR-TB)[b]
Rifampicin and isoniazid resistance detected[c]
Resistance to a fluoroquinolone not detected

Pre-extensively drug-resistant tuberculosis (pre-XDR-TB)
Rifampicin and isoniazid resistance detected[c]
Fluoroquinolone resistance detected
Bedaquiline and linezolid resistance not detected

Extensively drug-resistant tuberculosis (XDR-TB)
Rifampicin and isoniazid resistance detected[c]
Fluoroquinolone resistance detected
Group A drug (bedaquiline and/or linezolid) resistance detected (in addition to the above)

Drug-resistant tuberculosis (DR-TB)[d]
Collective term for all the above resistance profiles

See refs. 4,6,219,226. [a]Tests for susceptibility to the first-line drugs ethambutol and pyrazinamide are not routinely undertaken because they are technically difficult. If tested for, the presence of susceptibility does not change the above-mentioned definitions or efficacy of available regimens. [b]As drug susceptibility testing often has high specificity and suboptimal sensitivity, failure to detect drug resistance does not imply that the isolate is susceptible (for example, ~10% of the pre-XDR-TB and 10% of isoniazid-resistant TB may still be susceptible to isoniazid and fluoroquinolones, respectively). [c]For the purpose of patient-level clinical management, WHO MDR-, pre-XDR- and XDR-TB definitions do not require demonstration of isoniazid resistance. Thus, only rifampicin and group A drug-resistance readouts are required to define MDR-, pre-XDR- and XDR-TB; the demonstration of isoniazid resistance is not required. [d]Rifampicin-resistant TB is also a collective term used for all of the above drug resistance profiles, except isoniazid monoresistant TB.

Multidrug-resistant tuberculosis (MDR-TB) refers to TB that has resistance to both rifampicin and isoniazid, whereas rifampicin-resistant tuberculosis (RR-TB) refers to rifampicin resistance only (pyrazinamide and ethambutol resistance are not considered) (Box 1). Because both RR-TB and MDR-TB have a similar prognosis and management strategy, they are collectively referred to as MDR/RR-TB[5].

In 2019, based on the impact of specific drugs, the WHO released a revised classification of second-line drugs used to treat MDR/RR-TB[6]. Group A drugs (levofloxacin or moxifloxacin, bedaquiline and linezolid), improved mortality and outcomes; group B drugs (clofazimine and cycloserine or terizidone) improved treatment-related outcomes, and group C drugs were useful treatment adjuncts (ethambutol, delamanid, pyrazinamide, imipenem-cilastin or meropenem (with clavulanic acid), amikacin or streptomycin, ethionamide or prothionamide, and *p*-aminosalicylic acid).

Pre-extensively drug-resistant TB (pre-XDR-TB) refers to MDR/RR-TB that is also resistant to a fluoroquinolone (levofloxacin or moxifloxacin)[5] and extensively drug-resistant TB (XDR-TB) is additionally resistant to the other group A drugs, that is, bedaquiline and/or linezolid[5]. Collectively, these groups are referred to as drug-resistant TB (DR-TB). In this Primer, we discuss all forms of DR-TB. However, there are instances in which the data available distinguish between the different forms of DR-TB; therefore, we refer to these when appropriate.

In 2020, the COVID-19 pandemic destabilized TB control and, in 2022, it was estimated that ~10.6 million people became newly ill with TB and ~410,000 of these were patients with MDR/RR-TB[1]. Drug resistance remains a major problem in several parts of the world, especially in Eastern Europe, Russia, Asia and sub-Saharan Africa. Although only ~5% of the total burden of TB strains are rifampicin resistant, mortality is substantially higher — contributing ~15–20% to global TB mortality[7]. Remarkably, only one in three patients with MDR/RR-TB is ever detected[1], and late diagnosis means that morbidity is higher (more substantial post-TB lung disease and chronic pulmonary disability; Supplementary Box 1 for first-hand patient journeys). MDR/RR-TB is also very costly to manage with substantial negative economic consequences for both patients and countries.

It is estimated that DR-TB will cost the global economy about US$16.7 trillion between 2015 and 2050 (ref. 2), and ~20–25% of the total global estimated cost of antimicrobial resistance by the year 2050 will be due to DR-TB[8]. In countries that include India, Russia, China and South Africa, 2017 gross domestic product losses due to absence from work or early mortality varied from approximately $1 billion to $8 billion excluding catastrophic costs on affected households[8]. The 2017 cost to Europe alone was approximately US$5 billion. According to national surveys between 2016 and 2022, 82% of patients with DR-TB and their households faced catastrophic costs related to the illness, compared with 47% of those with drug-susceptible disease[7]. Similar to South Africa (where DR-TB was <5% of total TB burden), almost all the countries in the WHO Europe Region spent more money for medicines to treat DR-TB than they spent for DS-TB[9]. The costs for the medicines alone of one treatment course for XDR-TB can exceed €300,000 in Western Europe[10].

Indeed, of the top 50 interventions for antimicrobial resistance (a global priority almost on the same footing as global warming[11]), published by the WHO in 2023, approximately ten of the priority areas are dedicated to DR-TB[12]. Of note, data from 2018 have shed more light on the pathogenesis of DR-TB, including variable drug penetration into TB lesions (for example, cavities)[13], demonstrating that resistance amplification is caused by more than patient non-adherence.

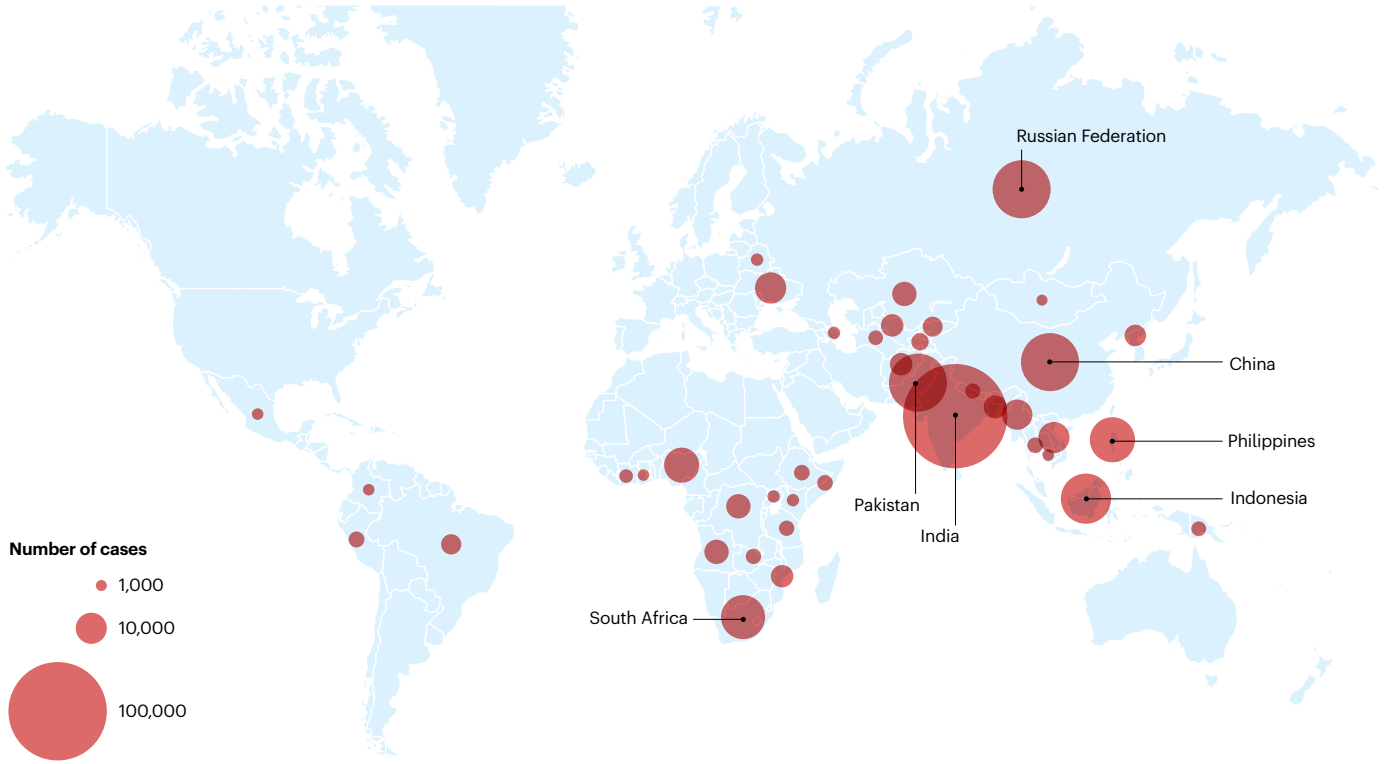


Fig. 1 | Estimated incidence of MDR/RR-TB in 2022 by the WHO for countries with at least 1,000 incident cases. Global map displaying a range of estimated incidence of cases of multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). The seven countries with the highest burden in terms of numbers of MDR/RR-TB cases, which accounted for two-thirds of global MDR/RR-TB cases in 2022, are labelled. Reprinted with permission from ref. 1, WHO.

Although it is gratifying that five new or repurposed TB drugs have revolutionized the treatment of DR-TB after a gap of almost 50 years, there are several remaining controversies around the composition and length of treatment regimens, and management in specific contexts. Drug resistance in TB is a highly complex topic and there is limited up-to-date direction and guidance on managing and understanding the many facets of this disease.

In this Primer, we address current gaps in the understanding of DR-TB by summarizing its epidemiology, pathogenesis, diagnosis, management and prevention, including important updates from the WHO. We also discuss other aspects, including transmission, socio-ethical dilemmas and palliative care, as well as approaches to antibiotic stewardship and public health case-finding strategies.

Epidemiology

Clinical epidemiology

The WHO estimates that ~10.6 million people fell ill with TB in 2022; of these, 3.3% were newly diagnosed with MDR-TB and 17% had been previously treated for TB and were diagnosed with MDR-TB[7], amounting to an estimated total of ~410,000 new cases of MDR-TB[1] (Fig. 1). Although these numbers are slightly lower than those estimated in 2015, the proportion of all DR-TB cases that are also XDR seems to be rising and is currently estimated at ~18%[1].

Geographical variation. Global figures mask marked geographical heterogeneity. The proportion of TB that is found to be drug resistant among new and previously treated patients is ~45% in Turkmenistan compared with 1% in Bangladesh[7]; notably all countries in which >20% of new TB diagnoses are drug resistant are in Central Asia and Eastern Europe[7,14]. Despite the small decline in the proportion of cases that are drug resistant[7], the number of people diagnosed with DR-TB increased by 6.4% in 2021 (ref. 7) – consistent with the estimated rise in all TB that has been attributed to COVID-19-related disruptions in TB case detection and treatment[15]. Although multiple studies have identified locally specific risk factors for DR-TB in comparison with DS-TB (incarceration in the Russian Federation[16], immigrant status in Europe[17], South Korea[18] and China[19]), previous TB treatment is the only host-specific determinant of DR-TB that has been consistently identified across these different locales. Notably, the WHO estimates that only one in three patients with MDR/RR-TB is detected and treated[1].

Social determinants. DR-TB remains a disease associated with poverty[20], and ecological analyses show that country-specific gross domestic product is strongly correlated with TB incidence[21]. In the early 1900s, before the development of anti-TB therapy, TB incidence and mortality in the industrialized world declined rapidly[22], likely because of improvements in living conditions and nutrition. This highlights the importance of an intersectoral approach to TB in which determinants of health must be addressed in conjunction with strategies aimed at TB control and treatment.

On an individual level, multiple factors associated with TB risk including undernutrition, overcrowding and smoking are also more prevalent in indigent populations[23]. One study estimated that 24% of TB in the 30 high-burden countries is due to undernutrition[24].

Comorbidities. In addition to social determinants, comorbidities have a major role in susceptibility to TB infection, with HIV, diabetes mellitus, malignancies and silicosis all being strong risk factors for TB progression and severity. The WHO estimates that, annually, 0.86 million new TB cases are associated with HIV globally, with many originating from southern Africa[7]. It has been observed that among people living with HIV, the risk of MDR/RR-TB and the risk of primary multidrug resistance (multidrug resistance associated with transmission) was 1.42-fold and 2.7-fold higher than for those not living with HIV, respectively[25]. People living with HIV and MDR/RR-TB also experience higher case fatality rates with one study from seven countries reporting a 19.0% case fatality rate compared with 9.4% for patients with MDR/RR-TB not living with HIV[26]. Diabetes mellitus is also a potent risk factor for TB progression, and as the burden of diabetes mellitus has grown globally over the past three decades, now reaching a global prevalence of 6.1%[27], the co-occurrence of TB and diabetes mellitus is increasingly common. The WHO estimates that 0.37 million cases of incident TB were associated with diabetes mellitus[7]. Diabetes mellitus also increases the risk of MDR/RR-TB by approximately twofold[28] and is associated with an increased risk of poor treatment outcomes[7,29] (Supplementary Table 1). With global diabetes mellitus prevalence projected to reach 10% in 2050 (ref. 27), diabetes mellitus is expected to have an increasingly important role in the epidemiology of TB in the coming decades.

Molecular epidemiology

Tools that enable the molecular characterization of *M. tuberculosis* strains have had an increasingly important role in the study of drug resistance in TB[7]. Over the past three decades, molecular tools have been used to differentiate lineages and study their phenotypic consequences[30] (for example, the presence of cavitary lesions, site of TB infection, mutation rate) as well as to track the evolution of drug resistance in individuals and populations over time and resolve long-standing debates about drug resistance in TB. For example, genomic epidemiological studies (matching the genomic fingerprints/barcodes of two strains) show that many patients with DR-TB with previously treated TB have been re-infected with a new drug-resistant strain, suggesting that some cases of purported relapse are due to a new transmission event, likely owing to community-based transmission and sometimes owing to nosocomial spread of DR-TB in the setting of hospitalization for TB treatment[31]. Molecular tools have also been used to assess the relative fitness of drug-resistant *M. tuberculosis* strains, both in longitudinal studies of TB contacts and in studies that have inferred the population structure of *M. tuberculosis* strains from phylogenetic reconstructions of transmission chains. One study from Peru matched genotypes between index patients with TB and their household contacts and observed that drug-resistant *M. tuberculosis* strains can be equally likely as drug-susceptible strains to be transmitted and cause disease[32]; a finding that was confirmed in a cough aerosol sampling study[33]. Similarly, a case-only study in South Africa reported that 212 of 386 patients with XDR-TB diagnosed over 3 years in KwaZulu Natal were part of a single genomically defined transmission cluster, suggesting that this specific XDR *M. tuberculosis* strain was highly transmissible[34].

Whole-genome sequencing has also been used to show that the fitness of drug-resistant *M. tuberculosis* strains is heterogeneous, dependent not only on the specific mutation that confers resistance, but also on the presence of compensatory mutations that may offset the metabolic consequences of drug-resistance mutations as well as on the specific lineage of the drug-resistant *M. tuberculosis* strain. One study from Georgia found that drug-resistant *M. tuberculosis* strains from lineage 4 were less fit than their drug-susceptible counterparts but those from lineage 2 were more fit and that this advantage arose from epistatic interactions between the specific drug resistance and compensatory mutations as well as other pre-existing genetic features specific to the circulating lineage 2 clade[35]. Notably, other studies have shown that some lineages harbour mutations that confer resistance to bedaquiline, delamanid and pretomanid; phylogenetic reconstructions indicate that some of these variants pre-existed the roll-out of these drugs[36,37]. These findings emphasize the need for ongoing real-time molecular surveillance to promptly identify transmissible drug-resistant *M. tuberculosis* strains and implement control measures to interrupt their circulation. Moreover, a phylogenomic approach to reconstruct the acquisition of drug-resistance mutations in a highly prevalent MDR/RR-TB strain from Moldova suggested a temporal association between national TB policies, including the hospitalization of patients with DR-TB, and the evolution of drug-resistant *M. tuberculosis* in Moldova[38].

Transmission and the spectrum of TB infection

The earlier phase of the DR-TB epidemic in the early 1990s was characterized mainly by acquired resistance but by the end of the decade, most newly ill people with DR-TB were infected by already resistant strains (primary resistance)[39]. This is hypothesized to repeat itself for new and repurposed drugs such as bedaquiline and linezolid. Evidence suggests that individuals with DR-TB are as infectious as those with DS-TB, and transmissions occur to a similar extent[32]. It is also clear that there is considerable heterogeneity in infectiousness of individuals with DR-TB and the determinants of this are poorly understood but may include lineage and strain type[37] and epigenetic factors (as one large study could not identify genomically encoded markers associated with highly infectious strains)[35]. Thus, a small proportion of individuals are likely to transmit most of the disease (the superspreader phenomenon), which is also observed with other respiratory infections such as measles and COVID-19 (ref. 40). There have been numerous instances of DR-TB outbreaks globally[41–45], highlighting the need for prompt diagnosis and transmission-interrupting action.

It is known that certain factors increase the likelihood of infectiousness, such as a high concentration of mycobacteria in sputum, cavitary disease, the presence of cough, advanced HIV co-infection and younger fitter patients who are highly mobile and with significant cough strength[33]; however, there is no consensus on how to define infectiousness, and the optimum way to measure infectiousness is controversial. A model in guinea pigs has yielded very useful data about transmission but is not practical for routine use[46], whereas a cough aerosol sampling system has been validated against human end points, such as tuberculin skin test (TST) conversion (which is a proxy of transmission and latent TB infection)[32,47]. By contrast, transmission can be measured by TST or interferon-γ release assay (IGRA) conversion in the newly infected host[48], prospective follow-up of such individuals and near-identical DNA fingerprinting readouts (whole-genome sequencing analysis). However, these methods all have their drawbacks; for example, IGRA has poor predictive value for TB infection (and progression to active TB disease)[49], and other biomarkers (for example, TST or IGRA conversion) are prone to long latency periods before active TB disease emerges. A public health strategy oriented to community-based active case finding (ACF, active searching for cases) facilitates rapid and early diagnosis, thus minimizing transmission within the community and amplification of the epidemic[50].

Although individuals exposed to drug-resistant strains of *M. tuberculosis* may eliminate the infection, with only a small number

progressing over the short term (<2 years) to active disease (Fig. 2), infected persons can develop incipient TB (an asymptomatic form of TB disease) and subclinical TB (asymptomatic but with microbiological evidence of TB present), which represents at least 50–60% of the total DR-TB burden in any community[51]. The precise definition of subclinical TB is contentious (and symptoms may be absent, ascribed to another condition, for example, smoker's cough, or under-reported owing to disease stigmatization and other factors)[52]. Incipient TB is likely amenable to TB preventive treatment. These different categories of TB (drug resistant or susceptible) merge into one another and may progress or revert between stages, making up the spectrum of TB infection (Table 1). This is an additional reason why a community-based ACF strategy should be adopted to facilitate early diagnosis and treatment of DR-TB.

Mechanisms/pathophysiology

Mechanisms of drug resistance

The mechanisms of drug resistance in TB are complex (Fig. 3). *M. tuberculosis* is transmitted via the airborne route to the host, which results in lung granuloma (an aggregation of macrophages) formation, a progressive localized pneumonitis and consequent cavity formation, with resultant re-aerosolization of the organism perpetuating onward

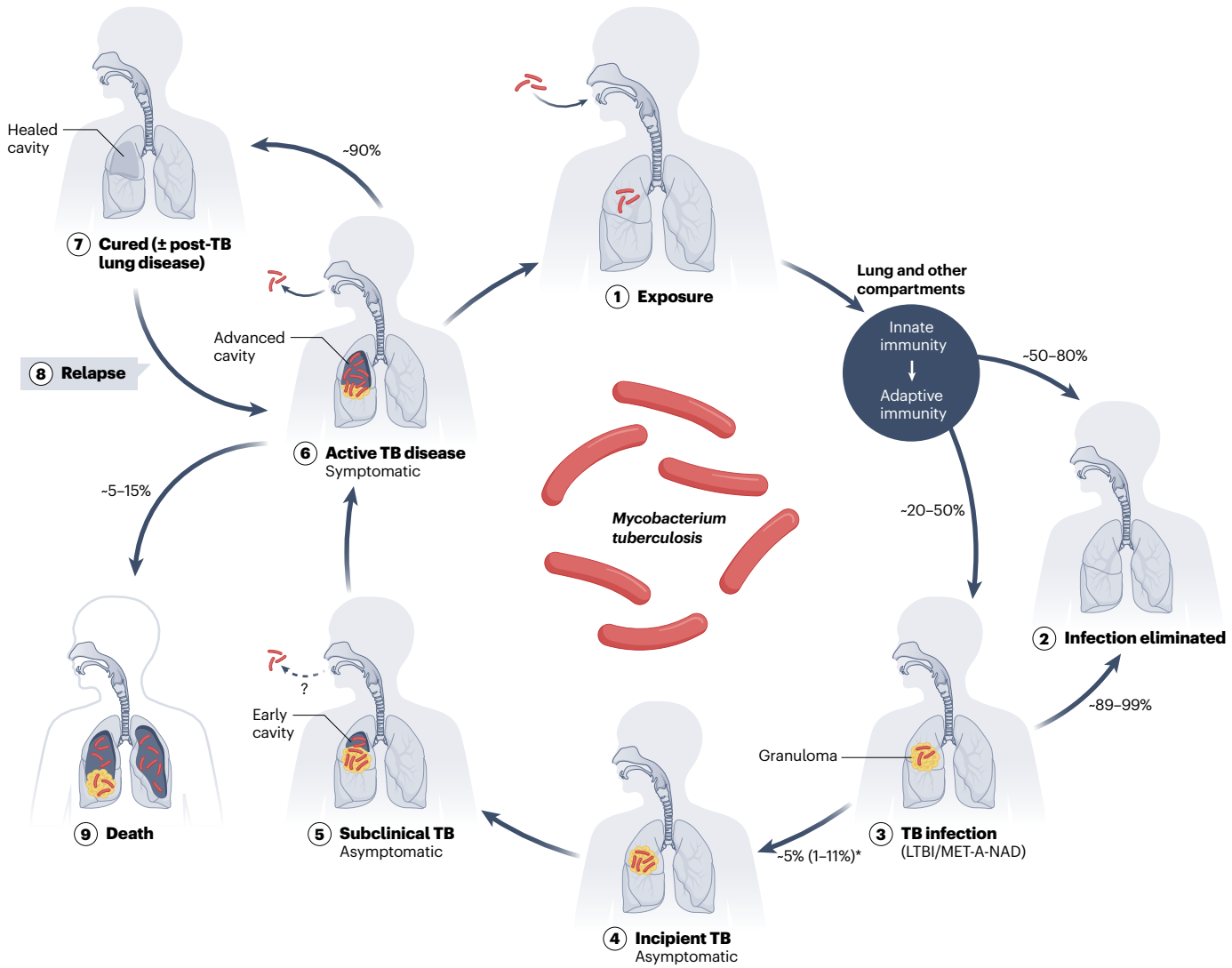


Fig. 2 | The life cycle of *Mycobacterium tuberculosis* (whether drug susceptible or drug resistant). Individuals exposed to *Mycobacterium tuberculosis* aerosol (step 1) may eliminate the infection (step 2) at the site of disease or in the lung or other compartments through innate or adaptive immune mechanisms. 'Lung and other compartments' includes the alveolar space, lung interstitium, airways, mediastinal lymph nodes, whole blood and other specific organ systems where *M. tuberculosis* has seeded. Alternatively, individuals (approximately two-thirds) may rapidly progress from *M. tuberculosis* infection (step 3) to active disease (step 6) within a few months (~2 to ~18 months), or after many years through intervening asymptomatic disease stages of incipient tuberculosis (TB) (step 4) or subclinical TB (step 5)[211]. Those with active disease may succumb over several months or years (step 9) or be cured in most cases (step 7). However, such patients are at higher risk of relapse (step 8), leading to further transmission and exposure (step 1). Note that there is no consensus on the term latent TB infection (LTBI); the WHO guidance recommends using the term TB infection, which we have adopted here[225], along with an alternative, MET-A-NAD (memory T cell immune response, asymptomatic, no active disease). *2–5% may rapidly progress from infection to active disease (~2 to ~18 months).

Table 1 | The immunodiagnostic, clinical and radiological features of the spectrum of TB infection

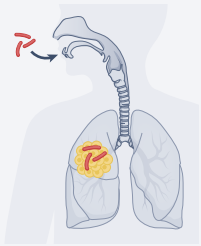
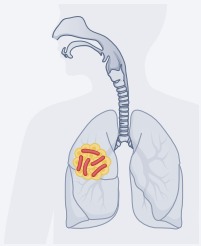
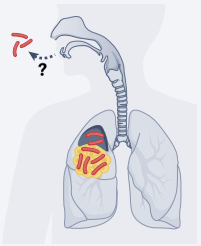
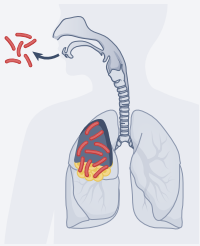
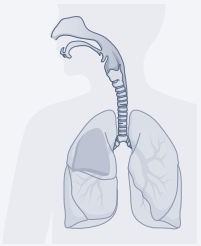
Bio-phenotype	Non-TB[a]	TB infection (MET-A-NAD)[b]	Asymptomatic TB (incipient)	Asymptomatic TB (subclinical)	Symptomatic TB (active TB disease)		Post-TB lung disease
Image	–						
Description of biotype	Unexposed or infection eliminated by innate or adaptive immunity, or cured	Probability of TB infection may be ascertained through several determinants (such as exposure history, smear positivity of transmitting patient, comorbidities in the host)	Incipient TB (microbiologically negative using conventional sampling[c])	Subclinical TB (microbiologically positive using conventional sampling[c])	Minimal disease extent	Moderate to extensive disease extent	Lung damage (obstructive airways disease, bronchiectasis, fibrocavitary disease)
Exposure and risk score[d]	Low to variable	Low to variable	Moderate to high	Moderate to high	Moderate to high	Moderate to high	Not applicable
Symptoms	Absent	Absent	Absent	Absent	Present	Present	Absent or present
Signs	Absent	Absent	Absent	Possibly present (e.g. lung crackles)	Present	Present	Absent or present
Microbial burden[e]	None	+	++	+++	++++	+++++	Absent/++
Imaging — chest radiograph	Normal	Normal	Usually normal	Often abnormal (may be normal)	Abnormal	Abnormal	Abnormal
Imaging — CT or PET–CT	Normal	Normal	May be abnormal	Abnormal	Abnormal	Abnormal	Abnormal
TB DNA in sputum or saliva[f]	Negative	Negative	Likely negative	Positive	Positive[f]	Positive[f]	May be positive
TB culture	Negative	Negative	Likely negative	Positive	Positive[c]	Positive[c]	Negative
TB antigen (urine)	Negative	Negative	Negative	Likely negative	Likely negative	Positive	May be positive
IGRA/TST[g]	Likely negative but may be positive	Likely positive but may be negative	Likely positive but may be negative	Likely positive but may be negative	Likely positive but may be negative	Likely positive but may be negative	Likely positive but may be negative
Endotype (biomarker)[f,h]	No reliable biomarker	Experimental[f,h]	Yes (transcriptomic signature)	Yes (transcriptomic signature)	Yes (transcriptomic signature)	Yes (transcriptomic signature)	Unclarified
Histopathology[i]	Normal	May develop granulomas[i]	May develop granulomas[i]	Granulomas and necrosis	Granulomas and necrosis	Granulomas and necrosis	Fibrosis, cavitation, airway damage, etc.

Table 1 (continued) | The immunodiagnostic, clinical and radiological features of the spectrum of TB infection

Bio-phenotype	Non-TB[a]	TB infection (MET-A-NAD)[b]	Asymptomatic TB (incipient)	Asymptomatic TB (subclinical)	Symptomatic TB (active TB disease)		Post-TB lung disease
Infectiousness	No	No	Possible (but unknown)	Probable (but unknown)	Lower risk (but may be infectious)	Higher risk (but may be non-infectious)	No
Risk of progression	None	~1–11% to active disease and 89–99% revert/clear infection[211]	10% with active TB on CXR progress to symptomatic TB (1% if inactive TB on CXR); 12% of subclinical TB may revert annually[172]		Not applicable	Not applicable	Higher risk of re-infection than in individuals without previous TB

CXR, chest X-ray; IGRA, interferon-γ release assay; TB, tuberculosis; TST, tuberculin skin test. [a]The different entities within the spectrum are dynamic and may progress or regress with time, e.g. subclinical TB may progress to symptomatic active TB or regress to other asymptomatic forms of TB infection. Yellow circles represent intrapulmonary granulomas; dark grey areas represent cavity formation (also sometimes seen in subclinical TB); light grey areas represent healed fibrocavitary disease. Further details about the spectrum of disease can be seen in Fig. 2. [b]There is no consensus on the appropriate term for this entity. The WHO guidance uses the term TB infection, which we have adopted here; although others still use the term 'latent TB infection' (LTBI). We propose the functional term, MET-A-NAD (memory T cell immune response, asymptomatic, no active disease), which more specifically describes the immunodiagnostic and clinical findings. [c]Expectorated sputum, induced sputum using hypertonic saline, sample obtained using bronchoscopy (bronchial washings, alveolar lavage, transbronchial biopsy or tissue sampling, and/ or needle aspiration of mediastinal lymph nodes). [d]Exposure risk scores may take into account exposure time, burden, infectiousness of the index case. [e]Microbial burden in LTBI and incipient TB cannot be detected or quantified with conventional microbiological techniques. Additionally, the lung microbiome may differ in the various categories; whether it impacts disease, or whether it is cause or effect remain unclear. [f]TB DNA may include DNA in biological samples such as sputum or tissue, cell-free DNA and DNA in T cells or lymph nodes. [g]These immunodiagnostic tests can only infer the presence of possible or probable LTBI as it cannot be microbiologically proved. Even in persons not exposed to *Mycobacterium tuberculosis*, some environmental mycobacteria produce RD-1 antigens and may lead to false positive results, and in those with active TB a false negative rate of 10–20% may occur. Thus, LTBI is an immunopathological concept whose presence is inferred by imperfect and indirect tests. The pathological precise nature of LTBI in the human host remains unclarified[212]. [h]In addition to antigen-specific cytokine responses (for example, IFNγ and TNF), T cell activation markers such as HLA-DR may be more specific for recent infection. [i]Although granulomas have been demonstrated in *M. tuberculosis*-exposed macaques who do not have features of active TB, the long-term stability of these lesions and whether they represent LTBI or a form of asymptomatic TB is unclear. It has been suggested that lesions may be immunologically silent and that cell-free forms of *M. tuberculosis* may exist.

transmission (Fig. 2). The immunopathogenesis of human pulmonary TB is incompletely understood, there are no well-established correlates of protection (biomarkers associated with protection against infection). Furthermore, there is little understanding as to why some people (in the absence of obvious risk factors such as HIV or diabetes) get TB and others do not[53].

Acquired drug resistance can be established through genomic mutations or epigenetic alterations (Fig. 3b,c,d). In the patient, spontaneous random mutants of *M. tuberculosis* can be selectively amplified owing to variability in drug pharmacokinetics or drug mismatch (between the desired and the actual concentration of a drug at the disease site), which can be facilitated by factors such as reduced drug exposure that often do not relate to patient non-adherence (Fig. 3d,e). In addition, there is widespread transmission of the resistant *M. tuberculosis* organisms at population level (primary resistance; Fig. 3f).

Mutational frequency and generation of variants. Spontaneous and random chance mutation is the main source of acquisition of genomic resistance to known antimycobacterial drugs (plasmid transfer does not occur in *M. tuberculosis*)[39,54,55]. Thus, there are spontaneously occurring drug-specific mutants, even to drugs not yet used in regimens[56,57]. Fluctuation assays, which are used to detect induction of mutations in the presence of a specific drug, have shown differences in the rate (per bacterium per generation) of spontaneously occurring in vitro mutants: 2.25×10^{-10} for rifampicin (R), 2.56×10^{-8} for isoniazid, 2×10^{-12} for rifampicin + isoniazid together, 2.56×10^{-7} for ethambutol, 1×10^{-25} for a three-drug first-line regimen, 5×10^{-5} for delamanid and 1×10^{-8} for bedaquiline[58–62]. Thus, a TB cavity (an excavated lesion in the lung) that contains ~10^8 organisms can contain two or three isoniazid-resistant organisms. Monotherapy will thus eradicate susceptible organisms but not resistant ones, which will multiply, leading to sequential acquisition of resistance (Fig. 3a). The frequency of mutant generation is a function of the bacillary load of replicating bacteria and exposure to suboptimal concentration of a drug (that is, below the concentration expected to produce a therapeutic effect)[63–65], which may also be mediated by differential penetration of the drugs into TB lesions[13,66,67] (Fig. 3d). Exposure to a low dose of drug favours mutant selection and resistance amplification[60]. Of note, a mutation encoding drug resistance may be associated with a bacterial fitness cost (discussed below). Prodrugs (such as isoniazid, pyrazinamide, ethionamide, delamanid and pretomanid) require activation inside the cells; if the prodrug-activating enzymes are not essential for mycobacterial growth and survival, spontaneously generated mutants can subvert the mechanism (causing drug resistance) at no cost to the mycobacterial cell.

Genomic mechanisms of resistance. Most of the known drug-resistance mechanisms are linked to mutations in genes known to be involved in drug resistance[68], which includes genes encoding transcriptional regulators[69]. The type of mutation and its position can strongly influence minimal inhibitory concentration (MIC). Thus, MIC values may be useful to guide addition of higher doses of drugs such as fluoroquinolones and isoniazid. *M. tuberculosis* strain and lineage can also modulate the likelihood of resistance[36]. Low-level resistance can be overcome by increasing dosage of the drug[70] (for example, moxifloxacin, isoniazid) but may be underestimated by phenotypic drug susceptibility testing (pDST) performed at the critical concentration[71,72]. The WHO catalogue versions 1 and 2 (refs. 73,74) provides a list of mutations based on the confidence of their association with the drug-resistance phenotype[71,72].

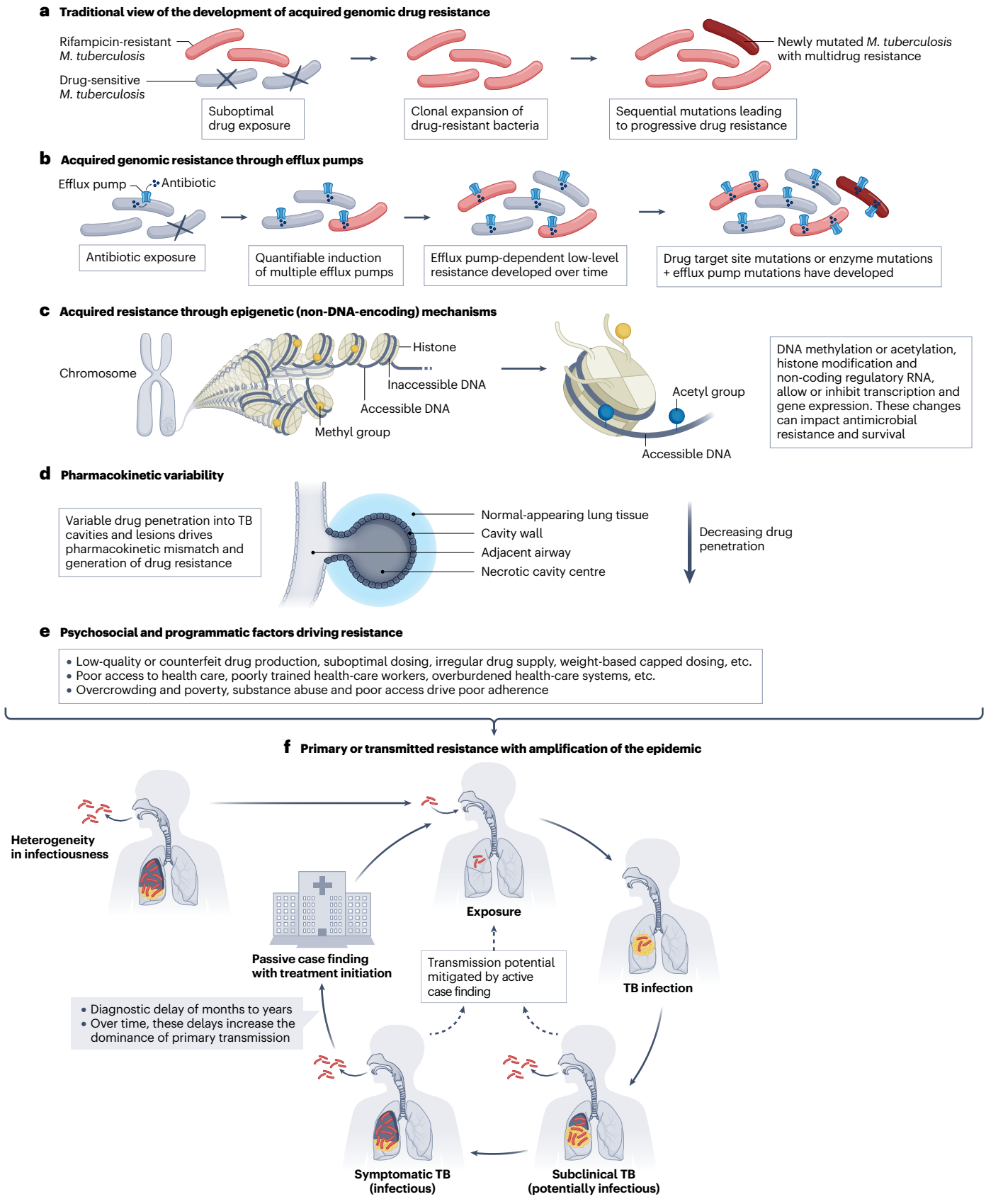

a Traditional view of the development of acquired genomic drug resistance
Rifampicin-resistant M. tuberculosis
Drug-sensitive M. tuberculosis
Suboptimal drug exposure
Clonal expansion of drug-resistant bacteria
Sequential mutations leading to progressive drug resistance
Newly mutated M. tuberculosis with multidrug resistance
b Acquired genomic resistance through efflux pumps
Efflux pump
Antibiotic
Antibiotic exposure
Quantifiable induction of multiple efflux pumps
Efflux pump-dependent low-level resistance developed over time
Drug target site mutations or enzyme mutations + efflux pump mutations have developed
c Acquired resistance through epigenetic (non-DNA-encoding) mechanisms
Chromosome
Histone
Inaccessible DNA
Accessible DNA
Methyl group
Acetyl group
Accessible DNA
DNA methylation or acetylation, histone modification and non-coding regulatory RNA, allow or inhibit transcription and gene expression. These changes can impact antimicrobial resistance and survival
d Pharmacokinetic variability
Variable drug penetration into TB cavities and lesions drives pharmacokinetic mismatch and generation of drug resistance
Normal-appearing lung tissue
Cavity wall
Adjacent airway
Necrotic cavity centre
Decreasing drug penetration
e Psychosocial and programmatic factors driving resistance
• Low-quality or counterfeit drug production, suboptimal dosing, irregular drug supply, weight-based capped dosing, etc.
• Poor access to health care, poorly trained health-care workers, overburdened health-care systems, etc.
• Overcrowding and poverty, substance abuse and poor access drive poor adherence
f Primary or transmitted resistance with amplification of the epidemic
Heterogeneity in infectiousness
Exposure
TB infection
Passive case finding with treatment initiation
Transmission potential mitigated by active case finding
• Diagnostic delay of months to years
• Over time, these delays increase the dominance of primary transmission
Symptomatic TB (infectious)
Subclinical TB (potentially infectious)

Fig. 3 | Pathogenesis of drug resistance and amplification of the drug-resistant TB epidemic. a, Spontaneously occurring drug-resistant *Mycobacterium tuberculosis* organisms proliferate with inappropriate drug exposure or interruption of therapy. **b**, Direct extrusion of individual or multiple drugs by efflux pumps contribute to the development of high-level resistance. Efflux pump efficiency may be increased by mutations over time. **c**, Acquired resistance may also occur through non-DNA-encoding mechanisms (epigenetic mechanisms). **d**, Selective interruption of drug therapy or suboptimal or no effective drug at the site of disease may occur owing to pharmacokinetic variability. This may be due to variability in metabolism, absorption and/or elimination of drugs, but may also be due to heterogeneity in drug penetration of tuberculosis (TB) lesions and cavities, resulting in pharmacokinetic mismatch (inappropriate concentration of drug relative to minimum inhibitory concentration). **e**, Psychosocial and programmatic factors may impact drug delivery, adherence, monitoring and detection of low-level resistance, contributing to high-level acquired resistance. **f**, With time, there is an increasing level of transmission of drug-resistant strains, which results in amplification of the epidemic (primary or transmitted resistance) and this becomes the dominant mechanism of resistance acquisition. There is considerable heterogeneity in the infectiousness of individuals with TB disease, and most transmission occurs within the community (such as households, transport networks, schools and workplaces). A passive case-finding public health strategy means that diagnosis occurs late with most transmission having already occurred. Thus, targeted active case finding strategies will mitigate transmission through earlier diagnosis and reduce further amplification of the epidemic. Other offsets of earlier diagnosis may include reduced lung damage and ameliorated chronic pulmonary disability (post-TB lung disease).

Sometimes, mutations, instead of impacting the function of an enzyme or key protein, can upregulate efflux pumps that excrete the drug from the cytoplasm (Fig. 3b). For example, resistance to bedaquiline and clofazimine is linked to the activation of the pump encoded by the *mmpS5–mmpL5* operon owing to mutations in the transcriptional repressor encoded by *Rv0678* (refs. 75–77).

In addition to genetic mutations, resistance may also be mediated by changes in cellular processes that do not involve alterations in the DNA sequence (Fig. 3c). Examples of these epigenetic mechanisms include DNA methylation or acetylation, histone protein modification and various RNA-based mechanisms (short and long non-coding RNA and RNA methylation, which produce different forms of the protein)[60]. These mechanisms may also mediate post-translational modification of proteins (and thus are also not mediated by sequence-encoded changes). Although epigenetic changes have been best studied for their effects on immune modulation, there is accumulating evidence that they have an important role in mediating drug resistance[78–80]. Epigenetic mechanisms have been found to mediate or facilitate resistance to several drugs including isoniazid[81,82], *p*-aminosalicylic acid[83], ethambutol[84] and streptomycin[78–80,85].

Pharmacokinetics. Drug disposition (comprising absorption, distribution, metabolism and excretion) of second-line drugs may be influenced by host factors (age, sex, genetics, comorbidities) or by drug interactions with companion drugs (for example, antiretrovirals for treatment of HIV)[86]. Fortunately, for most second-line drugs, dosing is flat (instead of in milligrams per kilogram), and standard dosing produces target-range concentrations in most patients (unlike isoniazid and rifampicin for DS-TB). Bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) is now a recommended standard-of-care regimen for those with MDR/RR-TB who are not pregnant and are older than 14 years[4]. Bedaquiline is a cytochrome P450 (CYP) isoenzyme 3A (CYP3A; a liver enzyme) substrate, and its concentrations are thus affected by CYP3A inducers and inhibitors (for example, efavirenz and boosted protease inhibitors, respectively)[87,88]. It has a long terminal half-life, and higher clearance (and lower exposures) of bedaquiline has been associated with Black race, perhaps explained by population differences in *CYP3A5*3* SNP frequencies[89]. For bedaquiline, there is a strong exposure–response relationship[90,91], so high adherence to maintain constant therapeutic exposures is crucial to successful use of this drug.

Delamanid is extensively protein bound (99.5%) and metabolized by albumin[92]. It is neither a substrate, an inhibitor or an inducer of CYP enzymes, so drug interaction liability for this drug is low. Its maximum concentration is at 4 h post-dose, and it has a long terminal half-life of 30–38 h. Its main metabolite, DM-6705, has a half-life of 121–425 h, and it is responsible for the modest effect of the drug on the QT interval (time from the beginning of the QRS complex to the end of the T wave; see Table 2)[93]. The drug is largely excreted in the faeces. Absorption is enhanced by food (and even more with a high-fat meal)[92,94,95].

Pretomanid, by contrast, has multiple metabolic pathways, with CYP3A being responsible for ~20% of its metabolism. Its concentrations are also reduced by CYP3A inducers, such as efavirenz[96]. Toxicities (hepatotoxicity specifically) seem to be driven by co-administration with pyrazinamide instead of by high pretomanid exposure[97].

Among the drugs in the BPaLM regimen, linezolid has the narrowest therapeutic margin, and doses needed for efficacy typically cause toxicity in a subset of patients[98]. Toxicity is driven by cumulative exposure, mostly occurring after longer than 8 weeks of treatment[99], with trough concentration being the pharmacokinetic (PK) parameter most highly associated with its well-described mitochondrial toxicities. Older age, low weight and renal dysfunction are associated with higher concentrations of linezolid[100].

Moxifloxacin, given at a fixed daily dose, is conjugated in the liver and does not have meaningful drug interactions with HIV drugs. Although its pharmacokinetic–pharmacodynamic (PK–PD) relationships are not well-characterized for TB, some evidence suggests that doses greater than the standard dose do not improve outcomes but do produce more musculoskeletal adverse effects[72]. Important PK characteristics of other second-line anti-TB drugs are described in Table 3 (refs. 72,101). In summary, PK determinants and related factors may result in suboptimal drug concentrations at the site of disease thus driving resistance amplification (Fig. 3).

Heterogeneity in the drug penetration of lesions. Biopsy samples and explanted lungs from individuals failing DR-TB treatment have established that there is considerable heterogeneity in the penetration of drugs into TB lesions[13]. With specific regard to TB cavities, it has been demonstrated that relative to the blood compartment and the outer wall of the TB cavity, concentrations of moxifloxacin and other drugs were substantially lower in the centre of the cavity and within the liquified caseum (necrotic material) where there were high concentrations of mycobacteria[13]. This differential drug penetration has been associated with the acquisition of drug-specific resistance[13], and the mutational analysis of the sputum sample reflected only part of the resistance profile noted within the TB cavity (likely because only some mutants were expectorated or grown from sputum). These phenomena may in part explain why, despite perfect adherence, ~10–15% of

Table 2 | Adverse effects and possible association with medicines used for the treatment of MDR/RR-TB

System involved	Adverse event	Medicine possibly causing the adverse event
Cardiac	QT prolongation	**Bdq, FQ, Cfz, Dlm**
Dermatological	Rash and pruritus	Any drug
	Hypersensitivity	Dlm, HdH, injectables (Am, Sm), Lzd, Mpm–Clv
	Drug reaction with eosinophilia and systemic symptoms	E, HdH
	Stevens–Johnson syndrome	Cs, E, FQ, HdH, Lzd, Sm
	Photosensitivity	Cfz, FQ, Z
	Lichenoid eruptions	Cs, E, HdH, Sm
	Drug-induced lupus	HdH
	Xerosis, ichthyosis	Cfz
	Pink or red discoloration of skin	**Cfz**
	Superficial fungal infection	FQ, Lzd
	Acneiform lesions	Cfz, Eto/Pto, HdH
	Hair loss	Eto/Pto, HdH, Lzd
Endocrine	Hypothyroidism (reversible)	**Eto/Pto**, PAS
	Gynaecomastia	Eto/Pto
	Dysglycaemia	FQ, Lzd
	Impotence	Eto/Pto
	Menstrual irregularity	Eto/Pto
Gastrointestinal	Hepatotoxicity	Bdq, Cfz, **Eto/Pto, HdH**, Mfx, PAS, **Z**
	Deranged liver function	Mpm–Clv,
	Nausea, vomiting, loss of appetite	Bdq, Cfz, Cpm–Clv, Dlm, **Eto/Pto**, HdH, FQ, Lzd, **PAS**, Z
	Metallic taste/change of taste	Eto/Pto, FQ
	Flatulence, diarrhoea	Cpm–Clv, Eto/Pto, FQ, HdH, Lzd, PAS
	Cramping with liquid product	HdH
	Enteropathy with bleeding	Cfz
	Pancreatitis	Lzd
	Elevated amylase	Bdq
Haematological	Myelosuppression/ pancytopenia	HdH, Ipm, **Lzd**, Sm
	Red cell aplasia	HdH, Lzd
	Leukopenia	Cfz, E, Eto/Pto, FQ, HdH, injectables (Sm), Ipm, **Lzd**
	Thrombocytopenia	E, Eto/Pto, FQ, HdH, injectables (Sm), Ipm, **Lzd**, PAS, Z
	Haemolytic anaemia	FQ, HdH, Ipm, Sm
	Aplastic anaemia	HdH, Lfx
	Eosinophilia	Cfz, E, FQ, injectables (Am, Sm), Ipm, HdH
	Coagulopathy	Cfz, HdH, Ipm, Mfx, PAS, Sm
Metabolic disorder	Lactic acidosis	Lzd
Musculoskeletal	Joint pain	Bdq, E, Eto/Pto, FQ, HdH, **Z**
	Hyperuricaemia/gouty arthritis	Z
	Tendonitis and tendon rupture	**FQ**
Nephrotoxicity	Renal toxicity	**Injectables (Am, Sm)**
	Electrolyte loss (hypokalaemia, hypocalcaemia, hypomagnesaemia)	**Injectables (Am, Sm)**
Neurotoxicity	Peripheral neuropathy	Cs, E, Eto/Pto, FQ, HdH, injectables (Am, Sm), **Lzd**
	Headache	Bdq, Cs, FQ, HdH
	Dizziness	Cs, Dlm, Eto/Pto, FQ, HdH, injectables (Am, Sm), Lzd
	Insomnia	Dlm, FQ
	Tremulousness	FQ
	Lethargy, inability to concentrate	Cs, Lzd
	Seizure	Cpm–Clv, Cs, FQ, HdH (overdose), Lzd (part of serotonin syndrome)
	Serotonin syndrome	Lzd (under the influence of TCA or SSRI or tyramine-rich diet)
	Depression, personality changes, suicidal ideation	Cfz**, Cs**, Eto/ Pto, FQ, HdH, Dlm
	Psychosis	Cs, FQ, HdH
Ocular toxicity	Optic neuritis	**E**, Eto/Pto, HdH, **Lzd**
	Pigmentary corneal deposits	Cfz
	Bull's eye pigmentary maculopathy, retinopathy	Cfz
Ototoxicity	Hearing loss	**Injectables (Am, Sm)**
	Vestibular disturbance	Cs, Eto/Pto, FQ, HdH, **injectables (Am, Sm)**, Lzd

See refs. 213–217. Drugs causing commonly seen and/or important adverse events are shown in bold. Am, amikacin; Bdq, bedaquiline; Cfz, clofazimine; Clv, clavulanate; Cpm, carbapenems; Cs, cycloserine (also called terizidone when it exists as a double molecule); Dlm, delamanid; E, ethambutol; Eto, ethionamide; FQ, fluoroquinolones; HdH, high-dose isoniazid; Ipm, imipenem; Lfx, levofloxacin; Lzd, linezolid; MDR/RR-TB, multidrug-resistant or rifampicin-resistant tuberculosis; Mfx, moxifloxacin; Mpm, meropenem; PAS, *p*-aminosalicylic acid; Pto, prothionamide; Sm, streptomycin; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; Z, pyrazinamide.

persons taking MDR/RR-TB therapy develop resistance to second-line drugs such as fluoroquinolone[102]. These findings not only have implications for selection of drugs in regimens (choosing agents based on drug penetration rather than mycobactericidal activity), drug dosing and delivery methods (adjunct inhaled antibiotics) but are also a stark reminder that resistance amplification is often not the fault of the patient when acquired drug resistance occurs.

Heteroresistance and fitness cost. Heteroresistance, defined as the co-existence of susceptible and resistant strains in the same clinical samples, has been linked to either co-infection with genetically different strains (on the same occasion or on different occasions) or co-existence of subclones of the parent wild-type strain with different susceptibility profiles[103]. The frequency varies between 5% and 10% and is drug dependent (~5% for isoniazid, ~7% for rifampicin and ~10% for fluoroquinolones)[104], and detection in terms of sensitivity varies depending on the type of test used (highest with pDST, excellent with the line probe assays, modest with nested assays and targeted sequencing assays, which detect ~50% of heteroresistance)[105]. However, the mechanisms leading to heteroresistance are still poorly understood.

Bacterial fitness is defined as the capacity of bacteria to survive and grow in a hostile environment[60,106]. Mutations associated with drug resistance may influence bacterial fitness, and this may be mitigated by compensatory mutations. The fitness cost can be lineage related; the same mutation can impact the bacterial fitness cost differently in strains with different genetic backgrounds[106]. For example, in the lineage 2, but not the lineage 4 strain, resistance to rifampicin was mitigated by compensatory mutations, confirming the positive effect of the epistatic interaction between the compensatory and resistance-related mutations[35].

Initially, and based on laboratory studies[106], the concept of fitness cost was assumed to be associated with lower transmissibility of drug-resistant strains. However, molecular epidemiological studies have disproved this hypothesis, demonstrating efficient transmission of drug-resistant strains in various regions worldwide[107–109], and individuals with DR-TB were shown to be as infectious as those with DS-TB. Realistically, sequence variations may give rise to a range of fitness impact (less fit, unaffected or more fit) depending on whether vital functions, such as replication or protein synthesis, are affected and the nature of compensatory mutations[110].

Diagnosis, screening and prevention

Signs and symptoms

Classic symptoms of both DS-TB and DR-TB include fever, loss of weight and appetite, night sweats, cough (sometimes with blood) and chest pain. It is now well recognized that symptoms, although generally chronic, can be of less than 2 weeks duration and can present as an acute lower respiratory tract infection[111]. TB can be associated with trivial symptoms or may be asymptomatic (subclinical TB). Signs are commensurate with the organ involved and in the case of the lung may include crackles, bronchial breathing over cavities (amphoric breathing) and sometimes wheezing (owing to endobronchial and small airway involvement). The differential diagnosis at clinical presentation for pulmonary TB may include community-acquired pneumonia due to bacterial or viral infections, non-tuberculous mycobacterial disease, *Pneumocystis* pneumonia (especially in the presence of hypoxia and in immunocompromised persons), malignancy and pulmonary vascular pathologies.

Screening and diagnosis

The current global public health strategy, except for screening high-risk groups such as close contacts and people living with HIV, is predominantly one of passive case finding (the patient self-reports with symptoms to a health-care facility). However, by that time there has been uninterrupted transmission and infection of many persons in the community. As ~50% of the total TB case-load within a community is relatively asymptomatic (subclinical TB)[112], two of every five patients with TB remain undetected by community surveys globally (and up to one out of three with MDR-TB)[1]. Current diagnostic methods are suboptimal, and as a consequence of the slow global

Table 3 | Important pharmacokinetic characteristics of second-line anti-tuberculosis drugs

Drug	ADME considerations	DDI with ARVs	PK notes
Bedaquiline	CYP3A4/5 substrate Long terminal half-life	EFV reduces Bdq concentrations (avoid) Bdq exposure increased by boosted PI (use with caution)	Strong PK–PD correlation Black race has been associated with 50% decrease in Bdq exposure; however, same dosing is recommended Daily dosing regimens are being explored in trial settings QT prolongation is driven by M2 metabolite of Bdq
Pretomanid	CYP3A substrate	EFV reduces pretomanid concentrations (avoid)	PK studies in children not yet completed
Linezolid	No P450 metabolism Some cases of renal clearance	No clinically significant DDI with ARVs	Use with caution in renal dysfunction, advanced age Very narrow therapeutic margin Inhibitor of MAO A and B
Moxifloxacin	Glucuronide and sulfate conjugation in the liver	No significant DDI with ARVs	Do not co-administer with iron, magnesium or calcium, as these bind to the drug and lower absorption
Delamanid	Low drug interaction liability Low solubility when given with other drugs	No significant DDI with ARVs	Higher once-daily dosing is sometimes used after the first 8 weeks
High-dose isoniazid	NAT2 acetylator genotype affects PK[a]	Isoniazid may increase EFV concentrations by inhibiting CYP2A6	Works against *inhA*- but not *katG*-mutated strains

ADME, absorption, distribution, metabolism and excretion; ARV, antiretroviral; Bdq, bedaquiline; CYP, cytochrome P450; DDI, drug–drug interaction; EFV, efavirenz; MAO, monoamine oxidase; PD, pharmacodynamic; PI, protease inhibitor; PK, pharmacokinetic. [a]*N*-acetyltransferase 2 (NAT2) is a metabolizing enzyme. Individuals with slow NAT2 acetylator status have isoniazid concentrations that are about threefold higher than those with fast NAT2 genotype.

Table 4 | Diagnostics approaches for DR-TB

Location/placement of assay and methodology	Drugs	Advantages	Limitations
Phenotypic			
Centralized assay[a]: culture of isolate in solid or liquid culture and broth microdilution (Fig. 4)	Drugs for which the WHO-recommended critical concentration is available: rifampicin, isoniazid, pyrazinamide, levofloxacin, moxifloxacin, bedaquiline[b], linezolid, clofazimine, delamanid[b], amikacin, streptomycin	Established reference standard for DST	High complexity
		Level or threshold of resistance (minimum inhibitory concentration) well delineated	Expensive total cost especially when added up for each drug
			Long turnaround time, 2–8 weeks
	Drugs not recommended by WHO for pDST or critical concentration unavailable: ethambutol, D-cycloserine, ethionamide, prothionamide, *p*-aminosalicylic acid, carbapenems		Automated platforms have high infrastructural requirements
			Need for biosafety level 2+
			Limited access to soluble powders for newer drugs
	WHO recommendation pending: pretomanid CC, broth microdilution commercial plates		Not available for all drugs
Genotypic			
Near-patient technology[c]: automated or semi-automated NAATs (cartridge-based)	Rifampicin (RRDR only; a hot spot on the *rpoB* gene that encodes rifampicin resistance)	Rapid, <2 h	Costs
		Low complexity	Rifampicin resistance readout only
		Decentralized placement possible	Misses mutations outside the RRDR (defines ~5% of resistance)
		Different sample types may be analysed (e.g. urine, stool, tongue swabs)	Requires a sputum sample in the case of pulmonary TB
			Limited sensitivity using a sputum sample (detection range ~40–70% of smear-negative disease; as low as ~30–50 organisms/ml and may miss 50% of low-burden disease in the community)[114]
			Does not perform well using certain paucibacillary sample types (e.g. TB meningitis, pleural TB, pericardial TB)
Near-patient technology: automated or semi-automated NAATs	Isoniazid (*katG*, *inhA* promoter, *fabG1*, *oxyR–ahp* intergenic region), levofloxacin/moxifloxacin (*gyrA*, *gyrB*), ethionamide (*inhA* promoter) and aminoglycosides (amikacin, streptomycin) (*rrs*, *eis* promoter)	Rapid, <2 h	Costs
		Low complexity	Additional machinery is required for its comprehensive resistance testing (i.e. cartridge not interchangeable with the other automated NAAT systems)
		Decentralized placement possible	Limited sensitivity for ethionamide as the assay uses a shared genetic marker with isoniazid (*inhA* promoter)
Centralized assay: fully automated end-to-end NAATs	Rifampicin (RRDR only) and isoniazid (*katG* and *inhA* promoter only)	Rapid, 3–7 h	Costs
		Mid–high throughput	Moderate complexity
			Not able to decentralize
			Endorsement based on moderate evidence
			Limited sensitivity when using a sputum sample
Centralized assay: line probe assay	Rifampicin (RRDR only), isoniazid (*katG* and *inhA* promoter), levofloxacin/moxifloxacin (*gyrA*, *gyrB*), aminoglycosides (*rrs*/*eis* promoter) and pyrazinamide (*pncA*)	Rapid, 3–5 h	High complexity
			Dedicated rooms for DNA extraction, PCR preparation and amplification/ post-amplification (as cross-contamination can occur)
			Subjective interpretation
			Poorer performance on smear-negative samples

Table 4 (continued) | Diagnostics approaches for DR-TB

Location/placement of assay and methodology	Drugs	Advantages	Limitations
Genotypic (continued)			
Centralized assay: NGS, tNGS, WGS	Tier 1 and tier 2 genomic regions[d] (ref. 73)	Rapid (i.e. ~1–3 days) for tNGS only (WGS requires 5 days after the isolate is cultured, i.e. 12–40 days)	High complexity
	High-confidence[e] resistance predictors (% sens/spec/PPV): rifampicin (*rpoB*) (93.8/98.2/95.4), isoniazid (*fabG1*, *ahpC*, *inhA*, *katG*, *mshA*[b], *ndh*[b]) (91.2/98.4/96.9), ethionamide (*fabG1*, *ethA*, *inhA*) (75.7/91.4/89.9), pyrazinamide (*pncA*, *panD*[b]) (72.3/98.8/91.1), levofloxacin (*gyrA*[f], *gyrB*) (84.4/98.3/91.1), moxifloxacin (*gyrA*[f], *gyrB*) (87.7/91.6/62.9), linezolid (*rplC*, *rrl*) (38.2/99.8/73.4), amikacin (*rrs*, *eis*) (76.4/99.1/87.4), streptomycin (*gid*, *rpsL*, *rrs*) (82.4/95.4/89.9), ethambutol (*embA*, *embB*, *embC*, *embR*[b]) (86.7/93.3/71.2)	Comprehensive resistance profiling when genetic markers conferring resistance are known (WGS can detect all drug resistance-associated targets but tNGS only those included in the assay, e.g. delamanid and Pa are not included in tNGS assays at the time of writing)	Mutation catalogue limited for new and repurposed drugs owing to scant evidence and association of genetic marker with resistance
			Costs
		Bypass need for pDST methods	tNGS can be used on a sputum sample but poorer performance using smear-negative samples
	Limited high-confidence resistance predictors: clofazimine (*Rv0678*, *mmpL5*) (not available), bedaquiline (*Rvo678*, *mmpL5*, *atpE*) (not available), delamanid (*ddn*, *fbiA*, *fbiB*, *fbiC*, *fgd1*, *fgd2*) (6.1/100/83.3) and pretomanid (*ddn*) (not available)	Additional genomic data can be used for surveillance	Limited to referral and reference laboratory
			WGS requires biosafety level 3
		Newly WHO-recommended technique[218]	WGS pragmatically limited to cultured clinical isolate

High-confidence mutations encoding the specific drug are also outlined. DST, drug susceptibility testing; NAAT, nucleic acid amplification test; NGS, next-generation sequencing; Pa, pretomanid; pDST, phenotypic drug susceptibility testing; PPV, positive predictive value; RRDR, rifampicin resistance determining region; sens, sensitivity; spec, specificity; TB, tuberculosis; tNGS, targeted next-generation sequencing; WGS, whole-genome sequencing. [a]These tests are instrument based, require specialized laboratory infrastructure and specialized technical skills. [b]Interim critical concentration (CC) recommendation (CC refers to the minimum concentration of an antimicrobial agent required to inhibit the growth of a specific microorganism). [c]These tests can be instrument based, preferably battery operated, therefore not requiring any special infrastructure as well, and they can be placed in health clinics without labs. Health-care workers with basic technical skills (basic pipetting) not requiring precision can perform these tests. [d]Tier 1 comprised gene sequences considered most probably to contain resistance mutations and tier 2 are genes with a reasonable pre-test probability of containing resistance. [e]Confidence-graded mutations as predictors of phenotypic drug susceptibility as per WHO catalogue of mutations. [f]Mutations in *gyrA* are associated with varying levels of resistance to fluoroquinolones — mutations associated with low-level resistance can guide management with high-dose treatment.

decline in TB incidence, there is a crucial need for increased prioritization of community-based ACF[113]. However, there is debate about the optimal strategy (indiscriminate door-to-door versus targeted screening in the community, or variations of these), the diagnostic tools to be used for ACF (such as X-ray screening, which may used in computer-assisted detection (CAD), sputum-based molecular testing, smear microscopy) and how this should be used in practice (for example, molecular testing alone or using a biomarker (for example, X-ray) to guide molecular testing). Unfortunately, there is no available effective TB screening test and CAD often fails to meet target product profile thresholds especially in those with previous TB, the elderly and people living with HIV[112]. Strategies for future ACF include the use of a mini-mobile clinic approach that incorporates a low-cost vehicle, point-of-care battery-operated molecular testing and linkage to care[114]. Multicentric randomized controlled trials are ongoing to address some of the knowledge gaps around ACF (for example, NCT04303104 and NCT05220163)[115,116].

Diagnostic testing

Whether by passive or active case finding, the diagnosis of DR-TB involves several steps and challenges, including first obtaining a representative biological sample (patients may be sputum scarce or have extrapulmonary TB), followed by diagnosis of *M. tuberculosis* infection using existing diagnostic tools (sensitivity is often suboptimal, and research has shown that molecular tests miss up to half the community-based TB case-load compared with culture)[114]. Diagnosis remains particularly challenging in children and people living with HIV.

Drug susceptibility testing. The WHO recommends (step 3, benchmark 9) that all patients with bacteriologically confirmed TB undergo universal drug susceptibility testing (DST) to determine whether their TB is resistant to commonly used anti-TB drugs[50]. Testing for isoniazid and fluoroquinolone resistance, in addition to rifampicin, is increasingly important, especially in settings where the prevalence of resistance to these drugs is >5%[50]. Ideally, testing should also be performed at lower prevalence[50] or when there are other features that increase the risk of drug resistance (known contact with DR-TB, poor response to conventional treatment, history of previous TB or exposure to specific drugs and poor adherence, including factors that drive poor adherence)[60].

Traditional and sensitive diagnostic methods of pDST use cultured isolates subjected to bacterial growth in the presence of antibiotics[117], which is the current reference method for most drugs. However, drawbacks include lengthy time to result, highly complex and labour-intensive process[117] and the requirement for specialized infrastructure, which limits its accessibility and impact (Table 4 and Fig. 4). pDST is available using both solid and liquid medium but critical concentrations are interim or not yet established for all new DR-TB drugs[118].

Over the past decade, several advances have been made to improve the detection of drug resistance by understanding the molecular mechanism associated with drug resistance at a genomic level[54]. This has resulted in development of rapid molecular diagnostic assays for genotypic DST. Rapid molecular tests have been recommended[119] as an option for smear replacement technology for the primary diagnosis of pulmonary TB in presumptive patients (including children), and

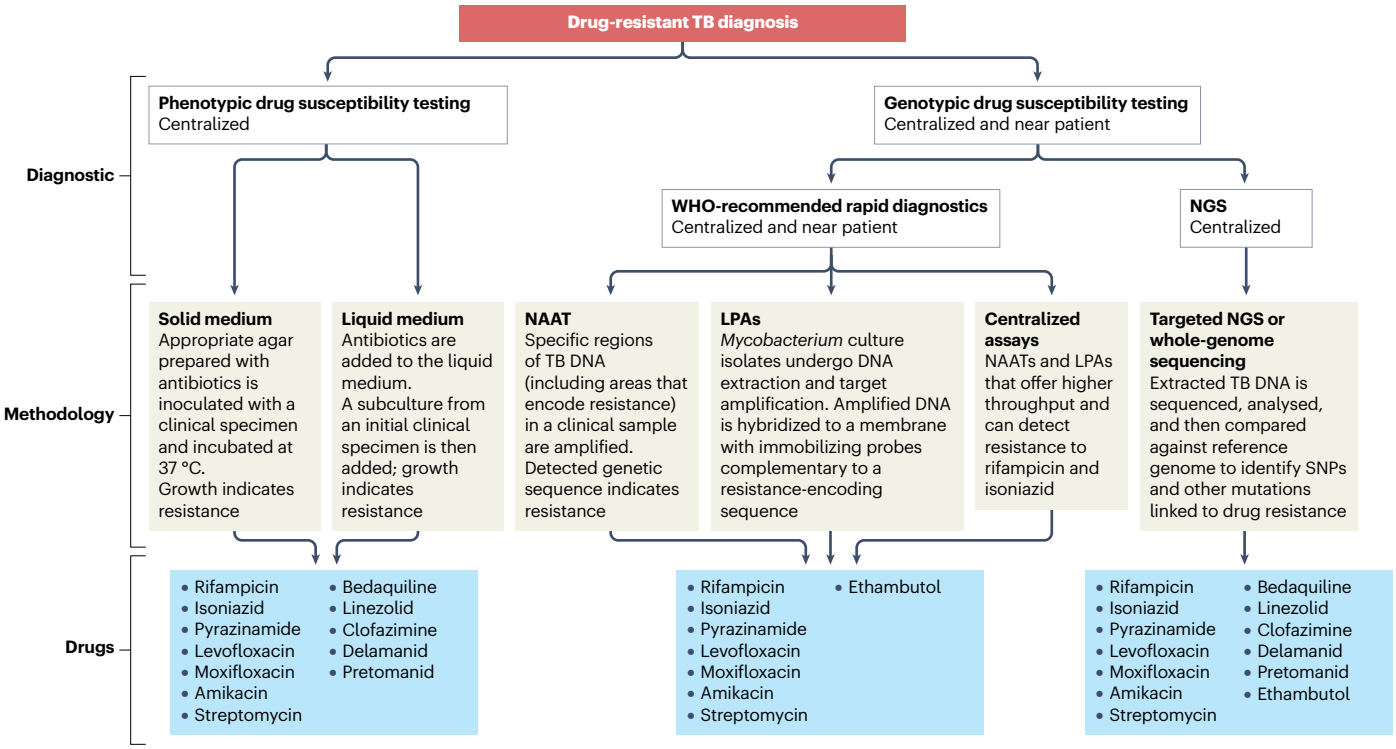


Fig. 4 | Established and potential future approaches for the diagnosis of drug-resistant tuberculosis. Outlined are the types of methodology used for specific drugs to determine susceptibility and the location (centralized or near patient) of each technology. LPA, line probe assay; NAAT, nucleic acid amplification test; NGS, next-generation sequencing; TB, tuberculosis.

they can simultaneously detect rifampicin resistance through detection of specific genetic markers that confirm *M. tuberculosis* species (for example, *IS6110* insertion) and rifampicin resistance (rifampicin resistance determining region (RRDR) *rpoB* 1–4). Using proper infection control measures, rapid molecular tests can be deployed as a near-patient technology in clinics[120] or at point of care in the community setting[114]. However, these assays are limited to the selected drugs detected by the assay and their sensitivity is restricted to the genetic markers they probe. The WHO has endorsed several platforms[5] that provide DST readouts of first-line drugs (rifampicin + isoniazid), and those that detect resistance to fluoroquinolones and second-line injectables (although the latter are no longer recommended in DR-TB regimens). Phenotypic and genotypic test discordance may also occur owing to technical factors, misclassification bias, heteroresistance, and depending on the clinical context, such discordance is often treated as MDR/RR-TB when the discordance is rifampicin specific[39,60]. A similar consideration would apply to discordant isoniazid resistance readouts.

Addressing the diagnostic gap has been facilitated by the development of methods using next-generation DNA sequencing[121] that have leveraged the WHO-endorsed catalogue of mutations[122]. These methods have been successfully evaluated for drug-resistance detection: from a sputum sample using the targeted approach (targeted next-generation sequencing; tNGS)[123–125] or from clinical isolates using the whole-genome sequencing approach[126,127]. The sensitivity of these methods is heavily dependent on the amount of DNA available in a sputum sample (≥95% of sputum DNA is non-TB in origin and thus there is a limited amount of mycobacterial DNA). Research is ongoing to develop strategies to improve concentration or amplification of bacterial genomes directly from a sputum sample. tNGS is rapid and holds the most promise as a tool to provide comprehensive information about resistance for many drugs simultaneously; however, it is highly complex to perform, dependent on skilled personnel, has complex infrastructural requirements and high costs, which are currently prohibitive for wide-scale application. Table 4 outlines the high-confidence genetic markers that confer resistance to anti-TB drugs and the limitations of each sequencing method.

One of the key issues faced by TB programmes is the misalignment of diagnostic tools with the introduction of new or repurposed drugs; to date, WHO-approved or commercial assays for genomic DST are not available for new and repurposed drugs such as pretomanid, delamanid, linezolid and bedaquiline. Furthermore, the genetic basis of resistance to such drugs may not have been fully understood before drug introduction, therefore impeding the development of rapid molecular methods. Newer molecular methods may provide a mutation-based prediction of resistance (ideally within days) with relatively high levels of accuracy when high-confidence gene targets are identified[54,128].

Prevention

Prevention of DR-TB disease, in addition to addressing social determinants of health and infection control aspects, can be accomplished by four major strategies: first, by preventing the emergence of isoniazid resistance; second, by preventing acquisition of rifampicin resistance in persons with isoniazid-resistant TB; third, by prompt identification and

treatment of persons with DR-TB, so that transmission of drug-resistant *M. tuberculosis* is minimized; and fourth, by preventing progression from infection (Fig. 3) to disease among persons infected with drug-resistant strains of *M. tuberculosis* but without disease.

Preventing the emergence of isoniazid monoresistance. Both clinical and molecular evidence supports the conclusion that the first step in the development of MDR-TB is acquisition of isoniazid resistance[129,130]. Several factors can contribute to the emergence of isoniazid resistance among persons being treated for DS-TB, including failure to adhere to the regimen, rapid isoniazid acetylation, which is known to reduce drug concentration within the patient, and failure of adequate drug penetration to areas of extensive disease[131–133]. Neither assessment of isoniazid acetylator status nor monitoring of isoniazid concentrations is routinely performed, with the result that emergence of drug resistance to isoniazid is observed in ~1% of persons being treated for DS-TB[134,135].

Preventing acquisition of rifampicin resistance. Emergence of rifampicin resistance during treatment of persons with isoniazid resistance can occur if isoniazid resistance has not been recognized, which results in treatment with an inadequate regimen, or owing to various factors that may cause PK mismatch[136]. Unfortunately, although molecular tests for isoniazid resistance are available, they are not widely used, so inadequate treatment of isoniazid-resistant TB occurs far too often. In addition, persons with HIV infection, especially those treated with intermittent regimens, can develop rifamycin resistance without isoniazid resistance; for this population intermittent regimens are to be avoided under any circumstances.

Prompt identification and treatment of persons with MDR-TB. Although acquired resistance was previously the major route by which MDR/RR-TB is contracted, in the past decade primary resistance has become predominant[137]. MDR/RR strains of *M. tuberculosis* are effectively transmitted to contacts, and failure to promptly diagnose persons with MDR/RR-TB and start them on effective treatment regimens has led to substantial community transmission. Until all persons with TB are promptly diagnosed and assessed for rifampicin resistance, MDR strains of *M. tuberculosis* will continue to spread in the community; interrupting such transmission will require ACF and broad availability of genotypic resistance testing. The WHO now recommends a 6-month course of daily levofloxacin be considered as preventive therapy for persons of all ages in contact with MDR/RR-TB[138].

Preventing progression from infection to disease among persons infected with drug-resistant strains of *M. tuberculosis*. For persons infected with isoniazid-monoresistant organisms, rifamycin-based regimens are available for treatment to prevent progression to disease[139]. For a person infected with MDR/RR strains of *M. tuberculosis* that are fluoroquinolone susceptible, 6 months of fluoroquinolone preventive therapy is effective and recommended[140,141]. A trial of delamanid for TB infection has also been initiated, but results will not be available for some time[142]. A phase II study of a promising TB vaccine, M72/AS01E, suggested that it could prevent progression from infection to disease[143], which would be especially useful for treatment of persons infected with MDR-TB.

Preventing emergence of resistance to other antimycobacterial agents used for the treatment of MDR/RR-TB. It will be essential to prevent the emergence of resistance to the agents currently effective in treatment of MDR/RR-TB, especially fluoroquinolones, bedaquiline, linezolid and pretomanid or delamanid. This will require availability and implementation of rapid diagnostic tests for these agents, so that patients do not receive regimens that are inadequate to prevent emergence of such additional resistance. Unfortunately, tests are scarce and not widely implemented[144].

Management

Treatment regimens for drug-susceptible TB

The standard treatment regimen for adults with pulmonary TB caused by organisms not known or suspected to be drug resistant involves a 2-month intensive phase using HRZE, followed by a 4-month continuation phase with rifampicin and isoniazid[4,145,146]. In 2021, a 4-month regimen containing rifapentine, moxifloxacin, isoniazid and pyrazinamide was found to be non-inferior to the standard 6-month regimen in terms of efficacy and safety[147], resulting in WHO endorsement of this regimen as an alternative treatment option for nonpregnant patients aged ≥12 years with drug-susceptible pulmonary TB[148]. In children under 16 years of age with paucibacillary non-severe DS-TB, a 4-month treatment regimen with rifampicin, isoniazid, pyrazinamide, with or without ethambutol was non-inferior to 6 months of standard treatment[149] and was conditionally endorsed by the WHO in 2022.

Treatment regimens for resistant forms of TB

Treatment regimen for isoniazid-monoresistant TB. Isoniazid resistance compromises the effectiveness of treatment with the standard HRZE regimen. WHO recommends treatment of rifampicin-susceptible, isoniazid-resistant TB with a combination of rifampicin, ethambutol, pyrazinamide and levofloxacin over a duration of 6 months, although the recommendation is conditional with evidence of low certainty[136,150] (Table 5).

Treatment regimens for MDR/RR-TB. Until 2016, the recommended duration of treatment for MDR/RR-TB was at least 18 months with a combination of at least four active drugs, often containing an injectable[6,151]. Treatment success with this regimen did not exceed 60% globally[7] and was associated with a high rate of adverse drug effects[152] and high costs[10]. The landscape has rapidly changed since then, first with the introduction of the 9- to 12-month 'Bangladesh' regimen, which includes an injectable[153] and subsequently with all-oral regimens of 6–9 months' duration[154–158].

In 2020, the results of the NiX-TB trial became available. NiX-TB is an open-label, single-group phase III study that examined the safety and efficacy of an all-oral three-drug regimen containing bedaquiline, pretomanid and linezolid (also known as BPaL) administered over 6 months in patients with treatment-intolerant or non-responsive MDR-TB or XDR-TB (as per the pre-2021 definition, that is, resistance to rifampicin (with or without resistance to isoniazid) plus resistance to a fluoroquinolone and a second-line injectable drug)[155]. With this regimen, 90% (95% CI 83–95%) of patients achieved a favourable outcome, albeit, with a high frequency of adverse effects attributed to the daily high-dose of linezolid (81% of patients developed peripheral neuropathy and 48% developed anaemia and/or thrombocytopenia).

Lower daily doses of linezolid were evaluated in ZeNiX-TB and TB-PRACTECAL studies[154,158]. The TB-PRACTECAL trial[158] evaluated the efficacy and safety of three 24-week BPaL-based treatment regimens with linezolid (BPaL, BPaLC (with clofazimine), BPaLM (with moxifloxacin)), in comparison with standard-of-care treatment. Only BPaLM was selected in stage 2 and at the end of 72 weeks post-treatment initiation,

Table 5 | Options and factors to be considered for selection of treatment regimens for patients with different forms of DR-TB[4,219]

Regimen[a]	H resistant, rifampicin susceptible	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB[219]	XDR-TB[219]	Extensive pulmonary TB[b]	Extrapulmonary TB	Age ≤14 years
6-month Rifampicin, levofloxacin, pyrazinamide, ethambutol	Yes	No	No	No	Yes — prolongation could be considered on an individual basis taking into account mycobacterial factors, host factors, programme-related factors and other factors	Yes — consider consultation with specialists	Yes
6-month BPaLM/BPaL (bedaquiline once daily for 2 weeks followed by three times a week, pretomanid daily and linezolid daily for 18 weeks, then lower dose daily for 8 weeks, with or without moxifloxacin)	No	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes — except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral 4- to 6-month initial phase of bedaquiline (at least 6 months), levofloxacin or moxifloxacin, ethionamide or prothionamide, ethambutol, high-dose isoniazid, pyrazinamide and clofazimine, then 5-month continuation phase of levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide Linezolid (2 months) may be substituted for ethionamide or prothionamide Bedaquiline could be extended to 9 months particularly if the initial phase is extended from 4 to 6 months	No	Yes	No	No	Yes[c]	Yes — except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month[4]	No	No	Yes[d]	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse effects						
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness						
	Patient or family preference						
	Access to and cost of regimen component drugs						

BPaL, bedaquiline, pretomanid and linezolid; BPaLM, bedaquiline, pretomanid, linezolid and moxifloxacin; CNS, central nervous system; DR-TB, drug-resistant tuberculosis; MDR/RR-TB, multidrug-resistant or rifampicin-resistant tuberculosis; pre-XDR-TB, pre-extensively drug-resistant tuberculosis; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis. [a]For drug dosing, please refer to the Annex of the 2022 update of the WHO operational handbook on tuberculosis. Module 4 treatment — drug-resistant tuberculosis (DR-TB) treatment[148]. [b]Extensive pulmonary TB is the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest X-ray. [c]With extension of initial or total treatment duration by 2 months. [d]When 6-month BPaL could not be used.

89% of the patients in the BPaLM arm experienced treatment success, compared with 52% of patients in the standard-of-care arm. Thus, BPaLM was both non-inferior and superior to the standard-of-care treatment. Furthermore, more severe adverse effects occurred more often in the standard-of-care arm than in the BPaLM arm (59% compared with 19%). Moreover, BPaLM (with a lower dose of linezolid than in NiX-TB) was much better tolerated than BPaL in the NiX-TB study[159].

Based on the results of these two trials and data provided by the Department of Health of the Government of South Africa, the WHO updated the guidelines on DR-TB in 2022, recommending the BPaLM regimen as the preferred regimen for patients with MDR/RR-TB when fluoroquinolone susceptibility is presumed or documented[4] (Table 5) and BPaL alone for patients with additional fluoroquinolone resistance (pre-XDR-TB). For patients who are not eligible for the shorter BPaLM regimens (Table 5; for example, unavailability of pretomanid or TB with other specific characteristics) but have isolates susceptible to fluoroquinolones, an all-oral regimen of 9–11 months is recommended. Thus, injectables (for example, amikacin) should no longer be used to treat MDR/RR-TB but they may still be considered in rescue regimens for XDR-TB, or resistance beyond XDR-TB, in which there are no other treatment options. The management of DR-TB in children is addressed in Box 2. Although those under 14 years of age are not eligible for pretomanid-based regimens, it is recommended they receive the short 9-month all-oral regimen containing new drugs. It is important to note that the cost of implementing BPaLM and BPaL regimens (excluding patient-incurred costs) is potentially 40–90% lower than current regimens, despite containing two innovative new drugs (bedaquiline and pretomanid)[160].

Box 2

Key considerations for management of DR-TB in children

- Children (particularly those under 5 years of age and adolescents) should be prioritized for family-friendly multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) preventive, diagnostic and treatment services as they are at particular risk of developing severe forms of MDR/RR-TB.
- Most children with MDR/RR-TB should be managed as outpatients at a health facility close to their home, while remaining in the care of their parents. Hospital-based care should be reserved for medical indications (for example, acutely ill children such as those requiring oxygen supplementation) or dire social circumstances (for example, absence of a caregiver)[227].
- Age-appropriate counselling and differentiated adherence support should accompany treatment of infection or disease; peer support may be particularly important in the adolescent group.
- Minimization of pill burden is particularly important and child-friendly formulations should be accessed (linezolid, bedaquiline, delamanid and levofloxacin are available in paediatric formulations)[228].
- Although the safety of pretomanid has not been established in children under 15 years of age, the drugs bedaquiline[229], delamanid[230] and linezolid are all recommended for children of any age[231]. Use of second-line injectables (for example, amikacin) should be avoided in children owing to the high risk of toxicity (including ototoxicity).
- Children generally have TB disease with a low bacillary burden (that is, paucibacillary) and trial experience from drug-susceptible tuberculosis (DS-TB) demonstrates that children can be safely managed with shorter regimens than adults[149]. Based on programmatic data and experience from trials such as BEAT-TB, it is now recommended that most forms of RR-TB in children can be managed with all-oral 6- to 9-month regimens (with more complicated forms such as bone and brain TB requiring longer duration)[231–234].
- MDR/RR-TB regimens for children and adolescents follow the same principles of treatment as for adults. Regimens can be individually constructed following WHO recommendations. At least four drugs to which the bacillus is thought to be susceptible should be included, and category A drugs (linezolid, bedaquiline and levofloxacin) should be prioritized. For fluoroquinolone-susceptible drug-resistant tuberculosis (DR-TB), the endTB regimens could potentially be used after WHO endorsement in children and adolescents (9 months of pyrazinamide combined with either bedaquiline–linezolid–moxifloxacin (endTB1) or bedaquiline–linezolid–clofazimine–levofloxacin (endTB2) or bedaquiline–delamanid–linezolid–levofloxacin (endTB3))[235].
- Drugs are given on the basis of body weight. Children tend to experience fewer adverse effects than adults. Linezolid has a high rate of adverse effects, and thus should be used with close monitoring. Owing to the challenges of monitoring for peripheral neuropathy and optic neuritis in young children some experts recommend using shorter durations of linezolid in younger children (for example, 2 months)[233,234].
- For non-expectorating children — follow-up and treatment response are mostly assessed clinically.
- Children have a right to benefit from scientific progress and should be included in newer trials; unfortunately, only those older than 14 years have been included in the recent PRACTECAL (NCT02589782), Nix-TB (NCT02333799 trials) and endTB (NCT02754765) trials[159,236,237].

Treatment regimen for rifampicin monoresistance. The presence of rifampicin resistance renders first-line regimens less effective. The WHO recommendations for the treatment of MDR-TB also apply to RR-TB, as the prognosis for both entities is similar[148] (Table 5). If rifampicin monoresistance is confirmed, isoniazid may be included in the regimen, although data to guide the optimal choice of companion medicines and the duration of therapy are lacking, and sensitivity for the detection of isoniazid resistance by genotypic methods is not perfect (thus ~10% of isoniazid resistance may remain undetected)[148]. Approximately 1 in 20 patients with isoniazid resistance will be missed[238]. In the presence of possible rifampicin monoresistance, isoniazid susceptibility should be ensured by phenotypic testing.

Emerging bedaquiline resistance. The availability of bedaquiline has dramatically improved the management of patients affected by DR-TB. However, there are concerns of emerging bedaquiline resistance resulting in ineffective short-course regimens for patients affected by DR-TB. New diarylquinolines may have the potential to overcome low-level bedaquiline resistance[239–241] based on mutations in the *rv0678* gene[242]. Bedaquiline-sparing regimens of 9 months' duration have led to treatment success in 75–86% of patients in randomized controlled clinical trials[235,243].

Treatment regimens for XDR-TB. In the absence of sufficient data to support safety and efficacy of the BPaLM regimen for patients with XDR-TB, and based on the basis of results of an individual patient data meta-analysis[238], the WHO has suggested that patients with XDR-TB[219], or those with MDR/RR-TB treatment failure, should receive an individualized 18-month (or longer) treatment regimen that is constructed on the basis of the drug-resistance profile, the patient's medical history (this should specifically include knowledge of drugs and/or regimens that failed the patient previously, as such drugs are unlikely to be effective) and the WHO hierarchical grouping of second-line agents[4]. Patients receiving the 18-month regimen may include those with poor prognostic factors, resistance to a single group A drug such as linezolid or bedaquiline (or pretomanid), complicated extrapulmonary TB (for example, TB meningitis) or a poor clinical response (Table 5).

Treatment duration. In individual cases, when using the shorter regimens, clinicians may extend treatment beyond the recommended duration, especially when there is poor treatment response or in the setting of a poorer prognosis (such as late

(continued from previous page)
culture conversion, smear-positive disease, previous dug exposure, immunosuppressive conditions, low BMI, extensive disease, substance abuse or programme-related factors); however, this practice is not evidence based, its use is individualized and context dependent, and its effectiveness remains unclear. Encouragingly, there are several ongoing phase II and III trials (WHO Research Tracker[244]), and some have reported interim results (endTB[236]) or the final outcomes have been published (STREAM stage 2 (ref. 245) and Beat-TB[246]). Results from the endTB trial reported that 90% of patients who received 9 months of therapy with bedaquiline, clofazimine, levofloxacin, linezolid and pyrazinamide achieved a successful treatment outcome, substantially more than in the control group treated with a standard MDR-TB regimen for 18–24 months[235]. These emerging data will inform future WHO guidance. Indeed, data will emerge from several new research consortia and public–private partnerships (UNITE4TB[247], SMART4TB[248] and PAN-TB[249]) that have raised close to US$600 million in investments for TB treatment-related research.

Adverse effects

It is important to promptly address adverse effects of treatment and provide effective patient support to optimize treatment adherence and effectiveness. Adverse effects undermine treatment adherence and can result in treatment interruption, life-threatening complications and death[161] (Supplementary Box 1). The use of multiple drugs in the TB regimen and their possible additive contribution to adverse effects (in addition to the use of concomitant antiretroviral therapy) makes it challenging to identify causality. Table 2 shows major treatment-related adverse effects and possible drug causes. Close observation and experience are required to promptly detect an adverse event and manage drug intolerance.

Management of treatment of DR-TB in special patient populations

The treatment of patients affected by DR-TB is complicated by the management of comorbidities, such as HIV co-infection, diabetes mellitus, liver disease, renal failure, undernutrition, and in special situations such as pregnancy and breastfeeding[161]. Comorbidities are best addressed by early detection and timely management, including of adverse effects, dosage adjustments and recognition of drug–drug interactions and malabsorption (Table 6). Special situations often require additional counselling or mobilization of social resources to enhance treatment adherence. Pregnant or breastfeeding women should have access to all-oral, shorter regimens that do not contain pretomanid, as safety data are limited[4].

Role of therapeutic drug monitoring

There is overwhelming evidence that MDR-TB is augmented by way of isoniazid resistance (mediated specifically by the *katG* mutation), which preceded subsequent resistance to rifampicin across lineage and geographical regions[129]. As PK variability (with some patients naturally having too-low drug concentrations)[162] is thought to be a major contributor to the risk of acquired drug resistance (and/or poor treatment response), therapeutic drug monitoring (TDM; measuring drug levels within patient blood) is commonly practised, where available[39,60]. The goal is to ensure that patients have drug exposures in the target range, typically defined by population averages (given that concentrations that prevent clinical resistance have not been convincingly established)[163]. Whether or not TDM improves treatment outcomes and reduces risk of resistance is unclear, even if the rationale for using it is well founded[164]. However, given the high PK variability in rifampicin and the fact that exposures produced by currently recommended doses are on the steep part of the dose–response curve[165], ensuring adequate drug concentrations, either by TDM or higher dosing overall, represents an important component of DR-TB prevention strategies[164]. Few data currently exist to support TDM for drugs used to treat MDR/RR-TB. However, given the crucial role that bedaquiline has in curing patients with MDR/RR-TB (coupled with the rising threat of bedaquiline resistance) and the narrow therapeutic margin of linezolid[166,167], a case can be made for developing TDM strategies for these drugs, recognizing that barriers to access would need to be overcome for TDM to have a population-level effect on treatment efficacy and/or emergence of resistance. Measuring linezolid before dose and 2 h after dose will capture minimum concentration (C_{min}, relevant for toxicity) and maximum concentration (C_{max}, relevant for efficacy)[168]. To our knowledge, there is not a TDM sampling strategy for bedaquiline. Use of dried blood spots (DBSs) can reduce practical challenges of TDM in that DBS samples typically do not require a cold chain and can be shipped to a pharmacology lab for testing via standard post. DBSs have been developed for linezolid but are not, to our knowledge, in clinical use. No DBS exists for bedaquiline[169].

Personalized medicine versus the pan-TB approach

With new, highly effective and well-tolerated compounds from new drug classes becoming available, there is potential for drugs to be combined in one treatment regimen irrespective of the patient's *M. tuberculosis* drug-resistance profile[136]. Such a 'pan-TB' regimen could potentially turn back the clock, creating a situation like the 1960s when the four drugs of the standard anti-TB regimen were highly effective. The advantages of such a regimen, without the need for DST, may include reduction in the complexity of management, rapid reduction in mortality and curtailment of transmission on a wide scale. However, the major problem in implementation would be monitoring of emerging drug resistance, which will occur following the natural laws of evolution[70,103]. Indeed, even with good adherence, ~10–15% of isolates developed resistance to fluoroquinolones[102], which is now widespread[70,103]. A similar situation may also occur with the roll-out of the BPaLM regimen in the absence of sufficient DST capacities in most affected countries[170]. Thus, any potential advantages would be neutralized within a decade or two and replaced by transmission of highly resistant strains.

An alternative, with several advantages[171,172], is to design accurate treatment regimens based on pathogen-specific genotypic data and the likelihood of adverse effects, including patient preferences[128], thus implementing a personalized medicine and patient-centred approach. Although much more difficult to implement in low-resource settings, the advantages would include preservation of a meagre pipeline of new drugs, thus prolonging the utility of existing regimens, minimizing the development of resistance, ongoing promotion of new drug and

Table 6 | Management of DR-TB in the presence of comorbidity or in special situations[213,220–224]

Patient subgroups	Background	Management advice
People living with HIV	HIV increases the risk of progressing from TB infection to TB disease and accelerates the progression of TB disease	Screen all patients with TB disease for HIV
		Work closely with the HIV care provider
	TB increases HIV replication (hence a vicious cycle)	Initiate ART as soon as TB treatment is well tolerated, ideally within 2 weeks when CD4 is <50, and within 2–8 weeks when CD4 is >50 (except in TB meningitis when ART must be deferred for 4–6 weeks if CD4 is <50)
	People living with HIV with low CD4 count are more likely to have atypical TB presentation, including sputum smear-negative pulmonary TB, atypical chest radiographic findings (normal appearance, absence of cavitation, opacities predominantly in mid and lower zones) or extrapulmonary TB	Note also DDI between TB drugs and drugs used for other opportunistic infections. Refer to DDI checkers such as Medscape Drug Interaction Checker.
	TB treatment may be complicated by IRIS, especially when ART is initiated within the first 2 weeks of TB treatment in those with advanced HIV infection	Beware of shared toxicity between TB drugs and ART. For example, tenofovir may be associated with renal impairment and electrolyte abnormalities, protease inhibitors with hepatotoxicity and QT prolongation, dolutegravir with headache, nausea and diarrhoea, and lamivudine with lactic acidosis
		Avoid predictable treatment adverse effects and detect them early for timely management
	Intermittent use of rifampicin increases the risk of acquiring rifampicin monoresistance	Beware of IRIS, which should be differentiated from HIV progression, DR-TB progression, other opportunistic infections and drug reactions
		Beware of malabsorption
	DDIs between rifamycin and some ART regimens increase the risk of ineffective treatment or treatment-related complications, thereby increasing the risk of acquiring drug resistance	Therapeutic drug monitoring may be considered in cases of malabsorption and/or DDI
		Optimize nutritional status
	Treatment adherence may be reduced by pill burden or adverse effects from multiple medications (TB drugs, ART, other antimicrobials for opportunistic infection), comorbidities and psychosocial problems (including substance abuse and related mental health disorders)	Address psychosocial problems
		Consider supervised administration of drugs
DM	DM increases the risk of progressing from TB infection to TB disease	Screen all patients with TB for DM
	DM is associated with poorer treatment outcomes and an increased risk of adverse effects	Always estimate creatinine clearance and adjust dosing when drugs predominantly cleared by the kidney are used
	TB treatment is made more difficult by underlying neuropathy, renal impairment and reduced gastric motility	Monitor for treatment adverse effects
		If available, therapeutic drug monitoring may be considered in difficult cases
Liver disease	Second-line TB drugs that may cause hepatotoxicity include high-dose isoniazid, pyrazinamide, ethionamide/prothionamide, PAS, bedaquiline (uncommon), moxifloxacin (uncommon) and carbapenems (uncommon)	In the case of end-stage liver disease, consider use of levofloxacin and linezolid, with addition of bedaquiline or ethambutol if appropriate, after carefully balancing benefits and risks
	Second-line TB drugs that are rarely hepatotoxic include levofloxacin, linezolid, clofazimine, cycloserine, ethambutol, injectables (aminoglycosides). However, clofazimine is partially metabolized by the liver	In the case of fluoroquinolone resistance, use bedaquiline, pretomanid and linezolid, and closely monitor liver biochemistry
Renal failure	End-stage renal disease increases the risk of progressing from TB infection to TB disease	To estimate creatinine clearance using the Cockcroft–Gault equation, and dosing, it may be ideal to use the actual body weight for underweight patients, the ideal body weight for normal-weight patients and the modified ideal body weight for patients with overweight or obesity
	Data regarding clearance of TB drugs are not well documented for creatinine clearance 30–50 ml/min and those undergoing peritoneal dialysis. When a drug is predominantly eliminated by the kidney, it is generally recommended to reduce the dosing frequency to three times per week for those with creatinine clearance <30 ml/min and to five times per week for those with creatinine clearance 30–50 ml/min	Dosing adjustment in the presence of renal insufficiency is recommended for the following second-line TB drugs: levofloxacin, cycloserine, ethambutol, pyrazinamide and injectables (aminoglycosides)
	The general strategy for adjusting dosing of TB drugs that are predominantly cleared by the kidney is to reduce dosing frequency rather than the dose	In the case of ESRF, it may be practical and safe to give TB drugs immediately after haemodialysis
		If available, therapeutic drug monitoring may be considered in difficult cases

Table 6 (continued) | Management of DR-TB in the presence of comorbidity or in special situations[213,220–224]

Patient subgroups	Background	Management advice
Pregnancy	For pregnant patients with DR-TB, rapid initiation of TB treatment with either the most effective shorter all-oral regimen or a longer regimen constructed using the standard WHO-recommended approach is recommended because benefits generally outweigh risks for both the pregnant patient and the neonate	Advise patients to avoid pregnancy during TB treatment
	The safety of many second-line drugs (except for pretomanid) in pregnancy has been substantiated by emerging data from cohort studies. Safety has been reported in small cohorts for bedaquiline, moxifloxacin/levofloxacin, linezolid, clofazimine, cycloserine, delamanid and carbapenems with clavulanic acid. Management should be guided by drug susceptibility testing, with counselling of the patient about benefits and risks before using TB drugs with potential harms	Group A and B drugs can and should be used (with prior counselling and with monitoring for treatment adverse effects). Pyrazinamide should be used if it is likely active according to drug susceptibility testing and without other contraindications
	Known or potential teratogens should be avoided whenever possible. Aminoglycosides are associated with ototoxicity and nephrotoxicity to both patient and fetus; thus, contraindicated. Ethionamide/prothionamide is associated with neural tube defects. PAS can aggravate pregnancy-related gastrointestinal symptoms and can be associated with hypothyroidism. Pretomanid has not been studied in pregnancy and is associated with testicular toxicity in mice. These drugs should be used only when treatment options are limited and benefits outweigh risks	Although not yet approved by the WHO, an all-oral 6-month regimen comprising bedaquiline, delamanid, linezolid and either levofloxacin or clofazimine may be considered for pregnant patients with DR-TB, as the regimen has been shown to be non-inferior to the standard-of-care treatment. The same applies to the 9-month endTB regimen (published in abstract form at the time of writing)
	DR-TB treatment of pregnant patients should also include nutritional supplementation and measures to avoid TB treatment interruptions during labour and delivery	
Breastfeeding	Based on what is known about breast milk and most TB drugs, there is generally no absolute contraindication to breastfeeding during DR-TB treatment	Counsel the patient or the family about use of essential TB drugs. Although breast milk is likely best for neonates in most settings, the parent's preferences should always be respected. Whether breastfeeding or infant formula feeding is chosen, the patient with DR-TB should be supported to complete TB treatment
	Except for bedaquiline, ethionamide/prothionamide and pretomanid, most TB drugs are present in the breast milk at low levels that are insufficient to treat or prevent TB, and likely do not exceed the recommended doses in infants, for example, delamanid. Bedaquiline is present at very high concentrations in breast milk that are theoretically therapeutic. Ethionamide or prothionamide and pretomanid in breastfeeding have not been studied	If bedaquiline is used during breastfeeding, monitor for QT prolongation and hepatotoxicity in the breastfed child
	Avoid use of pretomanid owing to its association with reproductive toxicity in animals	Among mothers receiving high-dose isoniazid, cycloserine and ethionamide/prothionamide, pyridoxine supplementation should be given to both the mother and the breastfed infant
		If ethionamide/prothionamide or PAS is used, monitor for hypothyroidism and hepatotoxicity
Critically ill patients	Factors such as starvation, sepsis, reduced mesenteric flow, delayed gastric emptying and feed intolerance can all aggravate intestinal absorption of oral medications	Use parenteral preparations whenever possible
		Linezolid, fluoroquinolones and aminoglycosides are all available as intravenous preparations
		Oral preparations may be resumed when the patient improves and gut absorption is assured
		Continuous nasogastric feeding may be associated with suboptimal absorption
		Intravenous steroids may have an add-on role in miliary or disseminated TB, TB with CNS or pericardial involvement and adrenal insufficiency
Indigent patients	Impoverished patients are often malnourished. Attention to their nutritional status is conducive to effective treatment. Low BMI at treatment initiation of rifampicin-resistant TB increases the risk of unfavourable treatment outcomes and death, with adjusted odds ratios (95% confidence interval) of 1.7 (1.4–1.9) and 3.1 (2.4–3.9), respectively	To facilitate adherence and avoid catastrophic costs, whenever necessary, consider home visits, close monitoring and incentives in terms of nutritional support and travelling expenses for clinic visits

ART, antiretroviral therapy; CNS, central nervous system; DDI, drug–drug interaction; DM, diabetes mellitus; DR-TB, drug-resistant TB (includes multidrug-resistant/rifampicin-resistant tuberculosis); ESRF, end-stage renal failure; IRIS, immune reconstitution inflammatory syndrome; PAS, *p*-aminosalicylic acid; TB, tuberculosis.

diagnostic development, and prevention of the emergence of highly resistant strains. The personalized approach could also impact treatment in other ways such as improving outcomes. Biomarkers based on host RNA signatures are being developed to guide individualization of the duration of anti-TB treatments[173] and human gene-expression profiles are being explored to provide endotype-specific host-directed therapies[174]. However, until newer and improved diagnostics are more widely implemented core regimens with limited flexibility seem to be more applicable in TB-endemic countries.

Treatment outcomes and surgical aspects

Following an expert consultation meeting the WHO revised the treatment outcome definitions for all forms of TB in 2021 (refs. 5,175). These revised definitions aim for programmatic use and rely on the assignment of an outcome at the end of the treatment course. They acknowledge that more prolonged follow-up (because of lengthy regimens) is challenging given the limited capacity of the health-care systems in countries where TB is endemic. The new definitions add the new component of 'sustained treatment success', which is suggested for use under operational research only[9,176]. The new definitions also recognize that discontinuation of a single key group A drug may have a more profound impact on outcomes than two or more alternative drugs (the requirement for discontinuation of two drugs for treatment failure is no longer specified in the WHO definition). The definition of failure and the embedded definition of bacteriological response remain central to the outcome definitions to account for the changing potency and mycobactericidal activity of the drug combinations used in individual regimens. Culture negativity at the 6-month time-point and beyond has been shown to be a good marker to indicate relapse-free cure in low- and high-burden settings of TB[9,177–179]. Future treatment outcome definitions could be guided by results of long-term post-treatment follow-up to find markers that best indicate relapse-free cure[180,181]. Such an approach will likely provide a useful perspective that can be considered in future outcome definitions.

The inherent nature of medical treatment failure (severe illness; limited longevity) and considerable selection bias (limited disease and the need to be fit for surgery), means that data from controlled clinical trials evaluating the impact of surgical interventions are still unavailable. However, in selected circumstances, results from an individual patient data meta-analysis suggest that partial lung resection, but not pneumonectomy, is associated with improved treatment success, although this result may have been due to selection bias inherent in the studies performed[182]. Data suggest that PET–CT activity and positivity in the contralateral lung (the lung or part of it not planned to be resected) is poorly predictive of surgical outcomes, and that a suitable group A-based rescue regimen is just as important for success as the surgical resection itself[183].

Person-centred care

The WHO declared TB a public health emergency in 1993; directly observed therapy short course (DOTS) was promoted as the predominant approach to combat it[39,60]. Although widely implemented, DOTS was limited in its success[22]. Criticism of DOTS included its potential ability to undermine the dignity of individuals, contribution to the catastrophic costs incurred by poor individuals who may be required to forgo employment and shoulder travel expenses to attend daily therapy and lack of impact on reduction of the development of drug resistance[132]. DOTS has since been surpassed by the more collaborative endTB goals and an increasing recognition of the need for a person-centred public health approach in which the communities and persons affected by TB are active participants. Much of this has been successfully modelled by the global HIV response.

In addition to the biomedical strategies outlined thus far, DS-TB and DR-TB programmes should address the psychosocial factors that underpin transmission and disease and work to remove health system barriers to care (Supplementary Box 1). This requires decentralized and family-friendly TB services, which provide necessary adherence such as food support, transport vouchers and access to income replacement[184]. Care for comorbidities (including HIV, diabetes, mental health and substance use disorders) should be integrated into TB services. Treatment literacy, age-appropriate counselling and differentiated adherence support should be offered (examples include video-observed therapy, peer support models and adolescent-specific adherence support; much space remains for innovation in this field).

Palliative care

Interventions to improve treatment outcomes in patients thought to be affected by 'incurable' TB include implementations of personalized medicine; however, despite the application of innovative methods some patients affected by DR-TB may remain incurable. Palliative care aims to improve the life of patients facing terminal illness, through the prevention and relief of suffering[185–187]. Access to palliative care is a human right, and TB programmes have an ethical obligation to provide it, including for persons with incurable forms of DR-TB[185]. In these cases, in addition to extensive counselling and support for individuals and their loved ones, care providers and patients should seek collaborative solutions that aim to uphold the patient's right to self-determination and access to socially inclusive palliative care, while also preventing disease transmission to others (including health-care workers and children).

Quality of life

International efforts have been made to define minimum standards of care for the DS-TB and DR-TB care cascade[175,188,189]. However, the gap between theory and reality remains vast[190,191].

In addition to increased DR-TB services coverage, quality of care must considered[190]. Improving DR-TB services starts with inviting the individuals and communities for whom these services are being provided, together with the health workers at grassroots level, as key partners in design, improvement, innovation and implementation of DR-TB care[190,192,193]. This includes providing feedback on existing DR-TB services, identifying quality care gaps and impactful improvement projects, and actively participating in the implementation of DR-TB tools and services[190]. Helpful examples of how this has been done successfully are available in the HIV domain[194]. Without this participation, evidence-based interventions in DR-TB care are unlikely to have the desired effect[195]. Similarly, top-down imposed quality improvement projects — often with targets and incentives set by external funders — rarely translate into sustainable change[196]. Sustainable improvement in quality of DR-TB services requires that all levels of health services work together — with strong national tuberculosis programme leadership — and a focus on overall health system strengthening[190]. DR-TB care should be decentralized with facility level ownership and accountability of quality of services[190].

Post-TB lung disease

Unfortunately, TB is a disease in which symptoms and complications such as pulmonary disability may continue after microbiological cure[197].

Various structural forms of lung disease may persist after TB treatment and these may include obstructive airways disease (TB is amongst the most common causes of chronic obstructive pulmonary disease in many TB-endemic countries[197]), bronchiectasis and fibrocavitary disease[198]. A combination of these entities can occur in the same individual and often there is severe fibrocavitary destructive disease. Residual disability after successful treatment of TB is common; in one meta-analysis, almost 60% of patients after treatment had abnormal spirometry, ~25% had an Medical Research Council (MRC) dyspnoea score of 3–5 (effort tolerance was restricted to only 100 m or less), and lung cancer was four times more common in patients after TB treatment[198]. However, there are hardly any data about the frequency of post-TB lung disease specifically in patients with DR-TB. Limited data indicate that post-DR-TB treatment obstructive disease together with poor physical health scores are common[199], and in two small studies (each with fewer than 50 participants with MDR/RR-TB), almost all had pulmonary function test abnormalities after treatment, and lung damage was extensive[200]. In an analysis of more than 14,000 persons, lung function impairment in those with MDR/RR-TB was worse than in those with DS-TB, and impairment was severe in 10–15% of survivors[201]. This may be related to later diagnosis and treatment initiation in patients with DR-TB compared with DS-TB[202]. Remarkably, there are no reliable data about the natural history of post-DR-TB lung disease, the incidence of secondary respiratory infections (viral, bacterial or mycobacterial), and nothing is known about the effectiveness of interventions to ameliorate the severity of the disability or symptoms.

Socio-ethical dilemmas

The treatment journey may be particularly challenging for individuals who are also facing poverty, mental illness or a substance use disorder, which are often associated with poorer TB treatment outcomes and can result in additional stigma and discrimination (including by health staff)[203,204]. The interwoven complexities of TB, mental health, social determinants of health and rigid health services are complex[205] and can result in socio-ethical dilemmas in which the tension between the individual's right to autonomy and the public's right to a safe environment must be carefully navigated[206]. One example of this is when a person with TB repeatedly struggles to take their treatment or does not wish to receive treatment yet continues to travel and work to provide for their family. Another socio-ethical dilemma may present itself when managing patients who are functionally incurable (therapeutically destitute); often caused by *M. tuberculosis* strains with resistance to all or almost all existing anti-TB agents. A suboptimal treatment regimen may improve the individual's clinical condition, but at the risk of increasing resistance in the TB strain, resulting in a greater public health threat by a TB 'superbug'[206].

The WHO released a guide that outlines ethical principles to be used in facing these dilemmas[185]. In all these scenarios the individual and family affected must be approached without judgement, and with compassion and kindness[185]. Human dignity and individual rights (carefully balanced against the rights of the public) remain paramount. It is important to acknowledge that most socio-ethical dilemmas have been born as the result of system failures; solutions can often be found when health services are willing to be flexible and partner with the individual and their community to find creative solutions. Adherence may be achieved when treatment is provided in a person-centred way, there is aggressive management of adverse effects and comorbid conditions (including mental Illness or substance use disorder) and with adequate patient support (including counselling, treatment enablers and family engagement).

Outlook

Ending DS-TB and DR-TB is not just a public health problem, but a development challenge and opportunity. One of the targets of the Sustainable Development Goals (SDGs)[207] for the period 2015–2030 is to end the global TB epidemic. In line with this target, the WHO end TB strategy[208], approved by the World Health Assembly in 2014, calls for a 90% reduction in TB deaths and an 80% decrease in TB incidence by 2030. The resolution calls on governments to adapt and implement the strategy with high-level commitment and financing.

One of the three pillars of the end TB strategy is intensified research and innovation. The key components of this pillar of the strategy are discovery, development and rapid uptake of new tools, interventions and strategies; and research to optimize implementation, and impact and promote innovation.

The development of policies to tackle the problem of DR-TB is challenged by lack of high-quality evidence. To stimulate and guide additional research and innovation in areas with insufficient evidence, the WHO regularly convenes several guideline development groups to develop new policies and also to identify the research gaps that hinder the development of policies (TB Knowledge Sharing Platform). The research gaps that are particularly evident are those around the care and management of DR-TB. Another neglected aspect in general, and highly relevant to DR-TB, is screening for TB and community-based ACF of TB given the realization that 36.1–79.7% (median 50.4%) of the TB and DR-TB burden is subclinical[51]. Supplementary Table 2 provides a high-level summary of the research goals and activities to fill the knowledge gaps with anticipated deliverables that relate to the management of DR-TB in several research areas.

Although MDR/RR-TB forms only ~5% of the global TB burden (~410,000 newly ill patients per year)[1], more than 20% of *M. tuberculosis* isolates are now resistant to at least one major first-line or second-line TB drug[39]. Besides the considerable morbidity and mortality associated with DR-TB, including to health-care workers, drug resistance remains a major threat to TB control in many countries because of the extremely high costs associated with the management of the condition, often eclipsing the cost of managing DS-TB. It is estimated that DR-TB will contribute to ~30% of the total costs to the global economy due to antimicrobial resistance by 2050 (ref. 8).

Encouragingly, new automated point-of-care diagnostic technologies and targeted genomic sequencing approaches hold promise to optimize diagnosis and facilitate a personalized medicine approach to DR-TB; thus helping to minimize resistance amplification. There needs to be a paradigm shift in global health strategy with a much bigger focus on community-based ACF, thus circumventing transmission and preventing amplification of the epidemic. To aid this, newer tools and biomarkers are urgently required to identify the most infectious patients so that they may be targeted for transmission-interrupting interventions and early treatment initiation. Shorter all-oral regimens using newer drugs have been developed[4]; however, antibiotic stewardship measures (rational use of antibiotics to prevent resistance) will have to be implemented to protect these new drugs. Thus, development of rapid DST tools for newer drugs remains a major priority. Nevertheless, despite these advances, resistance to the newer drugs has rapidly emerged, leading to substantial numbers of therapeutically destitute patients in TB-endemic countries[209]. This raises major socio-ethical dilemmas, and more thought should be given towards creation of palliative care facilities and long-term community-based facilities where such patients can live a meaningful existence[210]. The goals and priorities outlined in Supplementary Table 2 should occur in tandem

with improved global investment in TB, strengthening of health-care systems, change in global economic policies to reduce poverty and overcrowding, and a strong change in political will, to control TB, both globally and in TB-endemic countries.

The COVID-19 pandemic illustrated what could be done within a short period of time to create new diagnostics, drugs and vaccines[15]. The challenges with DR-TB are complex, and a reinvigorated global approach is required to tackle this scourge of DR-TB, as it is far from eradicated[210].

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