Tuberculosis 2019 1

Management of drug-resistant tuberculosis

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Drug-resistant tuberculosis is a major public health concern in many countries. Over the past decade, the number of patients infected with *Mycobacterium tuberculosis* resistant to the most effective drugs against tuberculosis (ie, rifampicin and isoniazid), which is called multidrug-resistant tuberculosis, has continued to increase. Globally, 4·6% of patients with tuberculosis have multidrug-resistant tuberculosis, but in some areas, like Kazakhstan, Kyrgyzstan, Moldova, and Ukraine, this proportion exceeds 25%. Treatment for patients with multidrug-resistant tuberculosis is prolonged (ie, 9–24 months) and patients with multidrug-resistant tuberculosis have less favourable outcomes than those treated for drug-susceptible tuberculosis. Individualised multidrug-resistant tuberculosis treatment with novel (eg, bedaquiline) and repurposed (eg, linezolid, clofazimine, or meropenem) drugs and guided by genotypic and phenotypic drug susceptibility testing can improve treatment outcomes. Some clinical trials are evaluating 6-month regimens to simplify management and improve outcomes of patients with multidrug-resistant tuberculosis. Here we review optimal diagnostic and treatment strategies for patients with drug-resistant tuberculosis and their contacts.

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Introduction

Drug-resistant tuberculosis is a major public health concern in many countries (figure 1). Global surveillance for tuberculosis drug resistance was initiated in 1995 and surveillance data on drug-resistant tuberculosis are available for 37 of the 40 countries with the highest burden.[1] These reports focus on patients with tuberculosis due to *Mycobacterium tuberculosis* resistant to the two most effective drugs against tuberculosis (ie, rifampicin and isoniazid). *M tuberculosis* resistant to isoniazid but not rifampicin is called isoniazid-monoresistant, whereas *M tuberculosis* resistant to both rifampicin and isoniazid is called multidrug-resistant. *M tuberculosis* resistant to rifampicin but susceptible to isoniazid, or with unknown susceptibility to isoniazid, is called rifampicin-monoresistant. However, because most rifampicin-monoresistant tuberculosis with unknown susceptibility to isoniazid is resistant to that drug, rifampicin-monoresistant tuberculosis is routinely treated as multidrug-resistant tuberculosis. In this Series paper, we will use the term multidrug-resistant tuberculosis to refer both to disease with organisms that are resistant to isoniazid and rifampicin and those that are resistant to rifampicin with unknown susceptibility to isoniazid, but not to disease

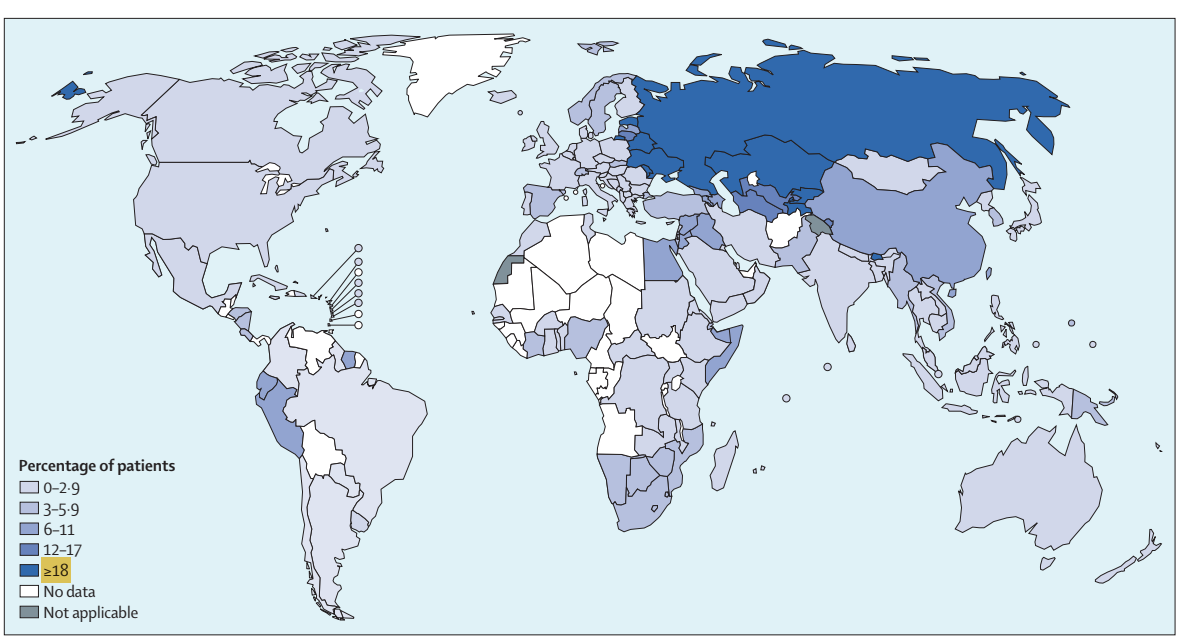

Figure 1: **Percentages of patients with multidrug-resistant tuberculosis globally**
Figures are based on the most recent year for which data have been reported to WHO, which varies among countries. Data cover the period from 2002–18. The number of multidrug-resistant tuberculosis cases detected globally per year has tripled from about 50 000 cases in 2009 to over 150 000 cases in 2017. Reproduced from reference 1, by permission of WHO.

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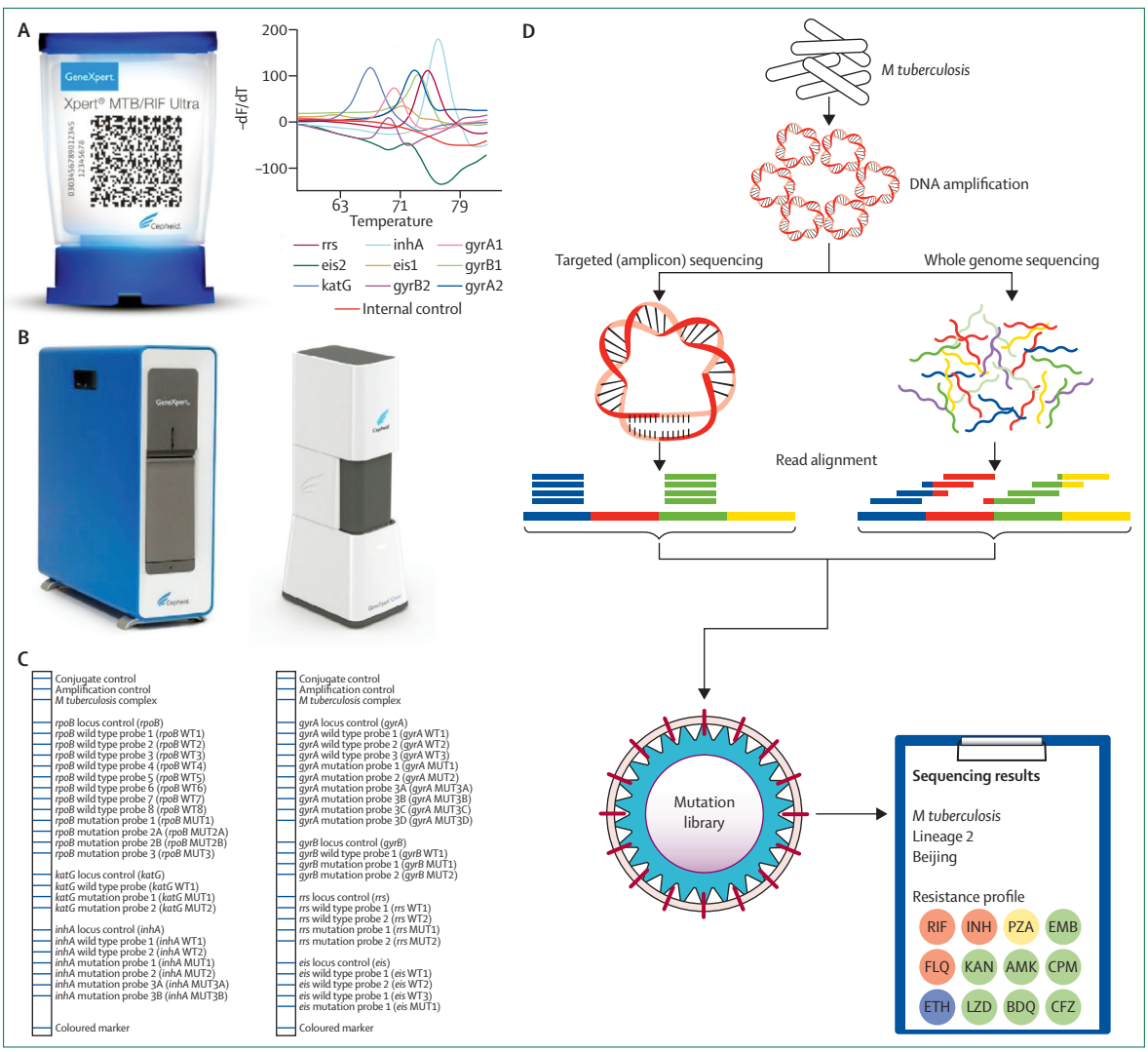

Figure 2: **Molecular drug resistance detection methods for *Mycobacterium tuberculosis***
(A) GeneXpert MTB/RIF Ultra cartridge for the detection of *M tuberculosis* and RIF resistance-conferring mutations, and melt curve of GeneXpert MTB/XDR assay capable of detecting *M tuberculosis* and resistance-conferring mutations for INH, the FLQs, and second-line injectables. (B) Portable single module GeneXpert devices Edge (left) and Omni (right), which are battery-operated and will allow for point-of-care diagnosis, thus facilitating community-based active case finding (Omni in development and not currently available for in vitro diagnostic use). (C) Hain line probe assays GenoType MTBDR*plus* version 2.0 (left), used to detect resistance-conferring mutations for RIF and INH, and GenoType MTBDRsl version 2.0 (right) used to detect resistance-conferring mutations for the FLQs and second-line injectables. (D) Next-generation sequencing-based methods. *M tuberculosis* is either amplified with primers targeting drug resistance conferring genes and lineage-specific targets or randomly fragmented. The library is then sequenced. The resulting sequences are aligned to a reference genome and known resistance-conferring and lineage mutations identified; automated pipelines can provide advice about a suggested bespoke regimen. In addition to the technologies outlined here other molecular platforms including those with standardised targeted sequencing or with multiplexed bench top molecular devices are currently in development. RIF=rifampicin. INH=isoniazid. PZA=pyrazinamide. EMB=ethambutal. FLQ=fluoroquinolone. KAN=kanamycin. AMK=amikacin. CPM=capreomycin. ETH=ethionamide. LZD=linezolid. BDQ=bedaquiline. CFZ=clofazimine.

with organisms that are resistant to rifampicin but susceptible to isoniazid.

As surveillance is incomplete, the burden of multidrug-resistant tuberculosis must be estimated. In 2017, an estimated 558 000 (range 483 000–639 000) individuals with newly developed multidrug-resistant tuberculosis—460 000 (82%) had multidrug-resistant tuberculosis and 98 000 (18%) had monoresistant tuberculosis, mostly with unknown susceptibility to isoniazid but probably a few with susceptibility to isoniazid—and 230 000 deaths (range 140 000–310 000) occurred globally; 3·6% of all new patients with tuberculosis and 17% of previously treated patients had multidrug-resistant tuberculosis.[1] In some countries, like Kazakhstan, Kyrgyzstan, Moldova, and Ukraine, over 25% of all new patients with tuberculosis have multidrug-resistant tuberculosis and the population incidence rates per year are high in countries such as Myanmar, Nigeria, and South Africa.[1]

6·7% of patients with multidrug-resistant tuberculosis are estimated to have tuberculosis that is also resistant to fluoroquinolones and second-line injectable drugs (ie, amikacin, capreomycin, and kanamycin), and is defined as extensively drug-resistant tuberculosis;[1] a revision of this definition has been proposed on the basis of an updated drug classification and treatment approach.[2]

As only 22 of the 40 highest burden countries have done more than a single drug resistance survey, our ability to assess trends over time is poor.[1] However, among countries with data from three or more surveys, the proportion of multidrug-resistant tuberculosis among all patients with tuberculosis has shown an upward trend as the burden of multidrug-resistant tuberculosis is either increasing faster or decreasing more slowly than the overall burden of tuberculosis.[1]

A substantial gap exists between the performance of recommended treatment regimens for multidrug-resistant tuberculosis in clinical trials, in which 78–80% of patients achieve a successful treatment outcome,[3,4] and programmatic results, in which only 55 (55%) of 100 patients achieve a successful treatment.[1] Although these results can partly be explained by clinical trial selection bias and the level of patient support provided to trial participants, the long duration (ie, 9–24 months) of recommended treatment regimens for multidrug-resistant tuberculosis and the widespread use of standardised regimens on the basis of incomplete drug-resistance profiling also contribute to these poor treatment outcomes.

The advent of new drug classes against tuberculosis and increased availability of rapid drug susceptibility testing (DST) provide hope for substantial improvement in the proportion of patients with multidrug-resistant tuberculosis who can achieve successful outcomes.[5] Additionally, an increasing awareness exists that multidrug-resistant tuberculosis could be averted via tuberculosis preventive therapy (TPT) delivered within the context of household contact tracing. This Series paper assesses evidence-based strategies to optimise multidrug-resistant tuberculosis treatment and summarises progress towards shortening the duration of treatment of multidrug-resistant tuberculosis.

Diagnosis of drug-resistant tuberculosis

Global access to DST is poor, with only about 30% of notified patients having isolates tested for rifampicin resistance.[1] Several diagnostic options exist, with distinct advantages and disadvantages (appendix pp 3–4). The method used will depend on several factors including the burden of disease and local access to resources; these factors have been discussed in detail elsewhere.[6] The pros and cons of traditional culture-based methods (eg, with agar plates or Mycobacteria Growth Indicator Tube 960) are outlined in the appendix pp 3–4.[6] Discrepancies between genotypic and phenotypic testing might occur for several reasons, including heteroresistance, level of resistance, and unknown or atypical mutations. Critical concentration cut points are determined taking into account minimal inhibitory concentration distributions, pharmacokinetic and pharmacodynamic considerations, and outcome data; these cut points were updated in 2018.[7]

Automated cartridge-based molecular testing with the GeneXpert platform (Cepheid, Sunnyvale CA, USA) has revolutionised the diagnosis of multidrug-resistant tuberculosis in endemic countries.[8,9] The GeneXpert Ultra cartridge adopted in 2018 is about 5% more sensitive than the previous G4 cartridge for the diagnosis of tuberculosis but both the specificity and positive predictive value are lower (figure 2).[10] Previous tuberculosis, including rifampicin-monoresistant tuberculosis, might produce a false positive result because of residual DNA at the site of disease.[11] The manufacturer plans to introduce a cartridge for drug-resistant tuberculosis (figure 2) by the end of 2019 with relatively high sensitivity for isoniazid (83%), fluoroquinolones (88%), and second-line injectable drugs (71%).[12] See Online for appendix

	Drug resistance predicted by*	Mutations associated with high-confidence drug resistance	Mutations associated with low-level drug resistance†
First-line drugs			
Rifampicin			
rpoB	Xpert, LPA, and WGS	Most commonly S531L but >20 other mutations described	D516Y, H526L‡, L533P, L511P, H526N, and I572F
Isoniazid			
inhA	LPA and WGS	c-15t with I194T and c-15t with S49A	c-15t
katG	LPA and WGS	S315I, S315N, and S315T	..
Group A drugs			
Bedaquiline			
Rv0678	WGS	Q22L, T33A, S63R, I67fs, R72W, R135G, and L136P	185ins_cag‡
atpE	WGS	A83G, A83T, G167C, and G187C	..
pepQ	WGS	Insufficient data	..
Levofloxacin and moxifloxacin			
gyrA	LPA and WGS	G88C, D94G, D94H, D94N, and D94Y	D89N, A90V, S91P, and D94A
gyrB	LPA and WGS	..	D461H†, D461N‡, D499D†, and A504V‡
Linezolid			
rplC	WGS	T460C	..
rrl	WGS	g2299t, g2814t	..
Group B drugs			
Clofazimine			
Rv0678	WGS	>30 mutations described (eg, Q22L, T33A, S63R, I67fs, R72W, G74A, T131C, R135G, 136P, C204A, and T407C)	..
Rv1979c	WGS	Insufficient data	..
pepQ	WGS	Insufficient data	..
Cycloserine			
alr	WGS	t-8c, M319T, Y364D, Y364C, R373L, and R373G	..

(Table 1 continues on next page)

	Drug resistance predicted by*	Mutations associated with high-confidence drug resistance	Mutations associated with low-level drug resistance†
(Continued from previous page)			
Group C drugs			
Amikacin			
rrs	LPA and WGS	a1401g and a1484t	Eis c-14t and rrs c1402t
Streptomycin			
rpsL	WGS	K43R, K43T, K88Q, and K88R	..
rrs	WGS	a514c, a514t, c462t, c513t, and c517t	..
Delamanid			
fbiA	WGS	D49Y and L250Stop	..
ddn	WGS	W88Stop	..
Ethambutol			
EmbB	WGS	M306I, M306V, D354A, G406D, G406C, G406S, and Q497R	..
embC-embA	WGS	c-8t, c-12t, and c-16t (often in linkage with *embB* mutations)	..
Ethionamide and prothionamide			
inhA	LPA and WGS	c-15t	..
ethA	WGS	Pooled frameshifts and premature stop codons	..
Imipenem and meropenem			
..	WGS	Insufficient data	..
Para-aminosalicylic acid			
folC	WGS	E153A, E153G, S150G, F152S, I43T, I43A, and E40G	..
ribD	WGS	g-12a	..
Pyrazinamide			
pncA	WGS	>300 mutations described	V180I‡, A170V‡, D110G‡, S65A‡, and E37V‡

LPA=line-probe assays. WGS=whole genome sequencing. *Xpert identifies mutations in an 81 base pair section of the *rpoB* gene where most mutations occur that result in rifampicin resistance, but cannot distinguish between mutations leading to high-level or low-level drug resistance. †In the absence of mutations causing high-confidence drug resistance, the presence of these mutations might suggest a dose increase to overcome resistance at standard dosing. In this case, the agents should not be counted among the active drugs in the regimen if included (at least four active drugs are recommended in combination therapy). ‡Additional data needed.

Table 1: **Genomic mutations of *Mycobacterium tuberculosis* associated with phenotypic drug resistance[16-18]**

Alternative semi-automated genotypic methods include the first-line and second-line line-probe assays (MTBDR*plus* and MTBDR*sl*, Hain Lifescience, Nehren, Germany) that enable relatively rapid diagnosis (ie, 1–5 days) of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis.[13,14] Although line-probe assays provide readouts for rifampicin, isoniazid, fluoroquinolones, and second-line injectable drugs (eg, the GeneXpert drug-resistant tuberculosis cartridge), the number of drug readouts are low and fluoroquinolone sensitivity is about 80% in smear negative samples.[15] In some cases, specific mutations on line-probe assays might indicate that high dose fluoroquinolone treatment could still be feasible (table 1).

In contrast to GeneXpert and line-probe assays, next-generation whole genome sequencing has several advantages (see appendix pp 3–4, table 1, and figure 2 for resistance-encoding mutations).[16,19] Although genomic readouts have generally been thought to be rule-in tests (ie, high positive predictive value but sub-optimal sensitivity), data from 2019 suggest that whole genome sequencing can also reliably confirm susceptibility, at least for first-line drugs.[19] Targeted sequencing platforms attempt to circumvent the drawback of poor sensitivity from clinical samples by enabling readouts directly from sputum through targeted amplification of resistance and coding genes[20] (eg, Deeplex Myc-TB assay, Genoscreen, Lille, France). A combination of phenotypic and genotypic approaches is required for optimal diagnosis of tuberculosis drug resistance.

Design of treatment regimens for drug-resistant tuberculosis

Monoresistance to isoniazid is the most common form of tuberculosis drug resistance. In 2017, the average global prevalence of isoniazid resistance (without concurrent rifampicin resistance) was 7·1% (95% CI, 6·2–8·0).[1] Detection of isoniazid-monoresistant tuberculosis is crucial because treatment of patients with isoniazid-monoresistant tuberculosis with a standard first-line treatment results in treatment failure, relapse, and acquired multidrug-resistant tuberculosis.[21] For the treatment of isoniazid-monoresistant tuberculosis, substitution of isoniazid by a later generation fluoroquinolone (levofloxacin or moxifloxacin) as part of a standard treatment regimen together with rifampicin, pyrazinamide, and ethambutol is recommended.[22,23] In contrast to the standard treatment regimen for drug-susceptible tuberculosis, all four drugs are administered daily for a duration of at least 6 months (appendix p 5).

The optimal treatment for patients with rifampicin-monoresistant, isoniazid-susceptible tuberculosis is not known. In the absence of better evidence WHO suggests that patients with rifampicin-monoresistant tuberculosis with proven isoniazid susceptibility should be treated like patients with multidrug-resistant tuberculosis but with the addition of isoniazid.[22] We suggest that treatment with so-called group A agents plus isoniazid should be sufficient (appendix p 5). In a study from 1977, treatment over 9 months with isoniazid, streptomycin, and pyrazinamide resulted in high cure rates[24] but long-term treatment with streptomycin is no longer recommended. However, these results suggest that 9 months of treatment might be sufficient.

Clinical trial data confirming the contribution of individual drugs to favourable outcome in multidrug-resistant tuberculosis are scarce. However, evidence from an individual patient data meta-analysis (including >12 000 patients from 25 countries) showed that improved treatment outcomes were associated with inclusion of each of the following in a multidrug-resistant tuberculosis treatment regimen: later generation fluoro-quinolones, bedaquiline, linezolid, clofazimine, and carbapenems.[25] Pyrazinamide was only associated with improved outcomes when the isolate was tested susceptible by DST. Amikacin and streptomycin had

	Route	Adult daily dosing	Dosage for children (<15 years)	Dosage for renal insufficiency	Dosage for hepatic impairment	Adverse events	Median risk of serious adverse event (95% credible interval)*[22]	Comments
Group A drugs								
Bedaquiline	Orally	400 mg once daily for 2 weeks followed by 200 mg three times per week (with food)	200 mg once daily for 2 weeks, then 100 mg once daily on Mondays, Wednesdays, and Fridays (bodyweight of 16–30 kg); 400 mg once daily for 2 weeks, then 200 mg once daily on Mondays, Wednesdays, and Fridays (bodyweight >30 kg)	No change needed	No adjustment in mild to moderate hepatic impairment	QT prolongation, nausea and vomiting, and arthralgia and myalgia	2·5% (0·7–7·6)	Close ECG monitoring recommended when used with other drugs that prolong the QTc interval
Levofloxacin	Orally and intra-venous	750–1000 mg once daily	15–20 mg/kg once daily	750–1000 mg three times weekly	Rarely associated with hepatotoxicity	Flatulence, abdominal distension, diarrhoea, arthralgia and myalgia, tendonitis, risk of tendon rupture, QT prolongation, depression, psychosis, suicidal ideation, seizures, peripheral neuropathy, phototoxicity, ototoxicity, and metallic taste	4·1% (1·9–8·8)	Permanent side-effects involving muscles, tendons or joints, and the nervous system warrant close monitoring
Moxifloxacin	Orally and intra-venous	400–800 mg once daily	10–15 mg/kg once daily	No change needed	No adjustment in mild to moderate hepatic impairment	Flatulence, abdominal distension, diarrhoea, arthralgia and myalgia, tendonitis, risk of tendon rupture, QT prolongation, depression, psychosis, suicidal ideation, seizures, peripheral neuropathy, phototoxicity, ototoxicity, and metallic taste	2·9% (1·4–5·6)	Permanent side-effects involving muscles, tendons or joints, and the nervous system warrant close monitoring; close ECG monitoring recommended when using moxifloxacin with other drugs that prolong the QTc interval
Linezolid	Orally and intra-venous	300–600 mg once daily	15 mg/kg once daily (bodyweight <15 kg); 10–12 mg/kg once daily (bodyweight ≥15 kg)	No change needed	Rarely associated with elevated transaminases	Myelosuppression, leukopenia, thrombocytopenia, anaemia, lactic acidosis peripheral neuropathy, optic neuritis, ototoxicity, and alopecia	17·2% (10·1–27·0)	Close monitoring of blood count and awareness of peripheral neuropathy is mandatory; severe adverse events are frequent in long-term therapy; consider adding pyridoxine
Group B drugs								
Clofazimine	Orally	100 mg once daily	2–5 mg/kg once daily	No change needed	Use with caution, 100 mg once daily or less in severe liver diseases	Skin discoloration, phototoxicity, nausea and vomiting, and hepatitis QT prolongation	3·6% (1·3–8·6)	Monitor QTc interval; in case of severe skin discoloration dose reduction to five times a week or discontinuation
Cycloserine and terizidone†	Orally	Usually 750 mg once daily	15–20 mg/kg once daily	750 mg three times weekly	No adjustment	Depression, psychosis, suicidal ideation, seizures, peripheral neuropathy, and ototoxicity	7·8% (5·8–10·9)	Monitor mental status
Group C drugs								
Ethambutol	Orally and intra-venous	15–25 mg/kg once daily	15–25 mg/kg once daily	15–25 mg/kg three times weekly	No adjustment	Optic neuritis, peripheral neuropathy, nausea and vomiting, and arthralgia and myalgia	4·0% (2·4–6·8)	Monitor visual acuity; visual disturbance is often rapid in onset and might begin with loss of red–green discrimination
Delamanid	Orally	100 mg twice daily	50 mg twice daily (bodyweight of 20–34 kg); 100 mg twice daily (bodyweight ≥34 kg)	Not recommended (insufficient safety data)	Not recommended for patients with moderate or severe hepatic impairment	QT prolongation and nausea and vomiting	Insufficient data	Close ECG monitoring recommended when used with other drugs that prolong the QTc interval

(Table 2 continues on next page)

Substance	Route	Adult daily dosing	Dosage for children (<15 years)	Dosage for renal insufficiency	Dosage for hepatic impairment	Adverse events	Median risk of serious adverse event (95% credible interval)*[22]	Comments
(Continued from previous page)								
Pyrazinamide	Orally	1500–2000 mg once daily	30–40 mg/kg once daily	1500–2000 mg once daily, three times weekly	Use with caution	Phototoxicity, hepatitis, and arthralgia and myalgia	8·8% (5·6–13·2)	Monitor for hepatotoxicity; in drug-induced hepatotoxicity re-exposure is not suggested
Imipenem and cilastatin	Intra-venous	Imipenem: 1000 mg twice or three times daily; cilastatin: fixed dose combination	Imipenem should not be used in patients under 15 years	500 mg twice daily	Rarely associated with elevated transaminases, probably safe	Rash, nausea and vomiting, and seizures	Insufficient data	Should be administered together with Clavulanic acid available as as fixed dose combination with cilastin; long-term intravenous access recommended
Meropenem	Intra-venous	1000–2000 mg twice or three times daily	20–40 mg/kg per dose three times daily	Dose after dialysis for haemodialysis	No adjustment	Rash, nausea and vomiting, and seizures	Insufficient data	Should be administered together with clavulanic acid available as fixed dose combination of amoxicillin 750 mg and clavulanic acid 125 mg twice daily or three times daily, long-term intravenous access recommended
Amikacin	Intra-muscular and intra-venous	15 mg/kg once daily 5–7 days per week; 15 mg/kg once daily three times per week can be used after culture conversion (maximum daily dose is 1 g)	15 mg/kg once daily 5–7 days per week 15 mg/kg once daily 3 times per week can be used after culture conversion (maximum daily dose is 1 g)	Not recommended in severe renal impairment; 15 mg/kg per dose after dialysis two to three times weekly for haemodialysis	No adjustment	Peripheral neuropathy, ototoxicity, and nephrotoxicity	10·3% (6·6–17·0)	Close monitoring of audiology, renal function and electrolytes mandatory; duration of therapy in multidrug-resistant tuberculosis is 7–8 months; patients should have a vena cava superior catheter with subcutaneous reservoir implanted for daily intravenous therapy
Streptomycin	Intra-muscular and intra-venous	15 mg/kg once daily 5–7 days per week; 15 mg/kg once daily three times per week can be used after culture conversion (maximum daily dose is 1 g)	5 mg/kg once daily 5–7 days per week 15 mg/kg once daily 3 times per week can be used after culture conversion (maximum daily dose is 1 g)	Not recommended in severe renal impairment; 15 mg/kg per dose after dialysis two to three times weekly for haemodialysis	No adjustment	Peripheral neuropathy, ototoxicity, and nephrotoxicity	4·5% (2·3–8·8)	Most multidrug-resistant strains of *Mycobacterium tuberculosis* are also resistant to streptomycin
Ethionamide and prothionamide	Orally	750 mg once daily	10–15 mg/kg once daily	No change needed	Use with caution	Depression, suicidal ideation, peripheral neuropathy, nausea and vomiting, flatulence, abdominal distension, diarrhoea, hepatitis, arthralgia and myalgia, optic neuritis, ototoxicity, hypothyroidism, alopecia, metallic taste, and gynecomastia	9·5% (6·5–14·5)	Monitor liver and thyroid function; prothionamide or ethionamide are often not tolerated in combination with para-aminosalicylic acid
Para-aminosalicylic acid	Orally and intra-venous	4 g orally three times per day or 12 g intravenous once daily	100–150 mg/kg per dose twice daily	No change needed	Use with caution	Nausea and vomiting, flatulence, abdominal distension, diarrhoea, hepatitis, hypothyroidism	14·3% (10·1–20·7)	Para-aminosalicylic acid is often not tolerated in combination with protionamide or ethionamide; intravenous application (available in Europe) by central venous line only

ECG=electrocardiogram. *Adverse events resulting in permanent discontinuation of the indicated tuberculosis medicine (or classified as Grade 3–5). †Terizidone is the fusion product of two molecules of cycloserine and one molecule of terephtalaldehyde.

Table 2: **Dosages and adverse events of drugs in WHO groups A–C recommended for the treatment of multidrug-resistant tuberculosis**

modest benefits on treatment outcomes, and kanamycin and capreomycin were associated with worse outcomes.[25] Despite limitations of these data, WHO revised their recommendations for treatment of patients with drug-resistant tuberculosis in 2018–19 predominantly on the basis of this evidence and now classifies medications for treatment of multidrug-resistant tuberculosis into three groups[22] (appendix pp 6–7): group A agents, which are considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated; group B agents, which are conditionally recommended as agents of second choice; and group C agents, which can be used when a regimen cannot be composed with group A or B agents.

The starting treatment regimen should consist of at least four drugs that are likely to be active. In clinical practice this treatment regimen means that all patients with rifampicin-monoresistant tuberculosis detected by GeneXpert MTB/RIF, and possibly confirmed by a line-probe assay, should receive all group A and at least one group B drug, unless these drugs are unavailable, not tolerated (table 2), or not indicated on the basis of DST.

Detection of rifampicin resistance alone does not provide sufficient information for the optimal design of a multidrug-resistant tuberculosis treatment regimen. Among the group A and B agents included in the starting regimen, rapid molecular tests for the prediction of drug resistance are available only for fluoroquinolones. Drug resistance to fluoroquinolones has been observed in up to 33% of patients with multidrug-resistant tuberculosis.[26] When fluoroquinolone resistance is detected, meropenem and amoxicillin-clavulanate is an evidence-based choice when intravenous access can be provided, and a subcutaneous central venous catheter for access (eg, port-a-cath) is preferred; otherwise, delamanid or second-line injectable drugs might be useful alternatives. However, use of second-line injectable drugs requires careful monitoring for ototoxicity, which can be difficult to assure in settings with few resources. Pyrazinamide and ethambutol can be used, but only when susceptibility has been shown. Para-aminosalicylic acid and ethionamide or prothionamide are associated with substantial toxicity and should not be used except as a last resort.

The treatment regimen should be modified if results from phenotypic DST become available documenting resistance, or intolerable adverse events develop to any of the drugs in the regimen. On the basis of the revised WHO classification of medications for multidrug-resistant tuberculosis treatment we suggest a stepwise approach for the design of a treatment regimen guided by phenotypic DST (table 3). Unfortunately, this approach is restricted by general scarcity of availability and access to phenotypic or molecular susceptibility testing for bedaquiline, linezolid, clofazimine cycloserine or terizidone, and delamanid. At this time, susceptibility to these agents is probable. Their widespread use will lead to emerging resistance against these agents. Universal and comprehensive availability of DST is urgently needed to detect drug resistance against all drugs recommended for the treatment of multidrug-resistant tuberculosis.

Duration and management of multidrug-resistant tuberculosis treatment

Two types of standardised multidrug-resistant tuberculosis treatment regimens (ie, a long and a short treatment regimen) are recommended by WHO.[22] They differ by drug combinations and treatment duration. For the long regimen, 18–20 months of treatment are suggested (at least 15 months after culture conversion), whereas the short regimen is given for 9–11 months. However, the applicability of the fixed short regimen is reduced in regions with high rates of drug resistance to fluoroquinolones or other second-line agents that are part of this regimen.[26]

Culture conversion status at month 6 of treatment is the single proven marker associated with end of treatment outcomes.[27,28] Several biomarkers are under investigation to predict treatment duration including transcriptomic approaches.[29] Current WHO guidance defines cure as three or more consecutive negative cultures completed at least 30 days apart after the intensive phase of treatment (a cut off 8 months after the start of treatment is suggested by WHO). However, this definition has several shortcomings, including underestimation of cure secondary to the inability of many patients to produce sputum after several months of effective treatment and improper assessment of the failure rate by not taking into account relapse after treatment that is not recognised because of loss to follow-up.[30] A more accurate set of outcome definitions have been proposed that consider the 6-month culture status and include 1 year of follow-up after treatment.[27,30] As extended follow-up after treatment is challenging in many settings, tuberculosis programme engagement is imperative.

Because of the large pill burden and frequent drug toxicities (especially with antiretroviral therapy co-administration), supervised therapy is desirable. When available, therapeutic drug monitoring should be considered, especially if malabsorption is suspected. Socioeconomic, nutritional, and psychosocial support is crucial to optimise a successful outcome. All patients need to be treated with compassion and dignity. The goal is a complete, patient-centred solution that is respectful of and responsive to individual patient preferences, needs, and values. Delivering integrated patient-centred care can produce substantial benefit to patients with tuberculosis globally (figure 3).[33]

multidrug-resistant tuberculosis

Among patients living with

d, with the regimen refined once DST is available.[34] therapy should be as as the is and ideally . of baseline

	Drugs	Comments
Step	Bedaquiline	Given for the first 6 months of treatment; some experts recommend using the drug for 9 months or longer
Step two	Levofloxacin or moxifloxacin	No preference for either although has prolonging potential than moxifloxacin, discontinuation of bedaquiline in a fluoroquinolone-containing regimen because of QTc prolongation is uncommon
Step		Linezolid is frequently associated with adverse drug events and requires very close monitoring in long-term treatment
Step four	Clofazimine and cycloserine or terizidone	These drugs are probably more potent than step five drugs and at least one of them should generally be part of the regimen unless contraindicated
Step five	Pyrazinamide* and prothionamide or ethionamide†	Add if steps one to four do not lead to four or more active drugs; use pyrazinamide before prothionamide or ethionamide if pyrazinamide susceptibiity is assured; prothionamide and ethionamide probably not as potent as step four drugs; drug resistance against pyrazinamide* or prothionamide or ethionamide must be ruled out
Step	and and	Add if steps one to five do not lead to four or more active drugs and for better tolerability; administration via a subcutaneous er is desirable for injectable agents like or amikacin; ; amikacin administered for the first 6–8 months of treatment only; capreomycin and kanamycin should be avoided
Step seven	Delamanid, para-aminosalicylic acid, and ethambutol*	Add one or more if steps one to six do not lead to four or more active drugs

The choice of drugs should be guided by drug susceptibility testing. Drugs should be added step by step until the regimen consists of at least four effective (or probably effective) and tolerated drugs. In the absence of a biomarker to guide physicians for an individual duration of therapy, the treatment regimen should be administered for 18–20 months. However, the optimal duration of therapy is not only dependant on the level of drug resistance and choice of the treatment regimen, but also on the extent of the disease, the immune status of the host, and the kinetic of the treatment response. Close monitoring of adverse events is mandatory for second-line antituberculosis drugs. *Depending on the geographical setting most multidrug-resistant tuberculosis strains might be resistant to pyrazinamide and ethambutol. Do not include pyrazinamide or ethambutol in the regimen unless proven by drug susceptibility testing. However, drug susceptibility testing is often unavailable or inaccessible and thus resistance to pyrazinamide must be assumed. †Do not include prothionamide or ethionamide in the initial regimen if molecular drug susceptibility testing shows a mutation in the promotor of the *inhA* gene (mostly positions 8 or 15).

Table 3: S

as mortality is in the of therapy.[35] However, patients with HIV-associated multidrug-resistant tuberculosis often have advanced tuberculosis disease and increased risk of immune reconstitution inflammatory syndrome, drug interactions, and toxicities if antiretroviral therapy is initiated.[36] The management of drug toxicities is particularly challenging.[34]

New and repurposed drugs promise to improve outcomes of patients with HIV-associated multidrug-resistant tuberculosis.[37] is well tolerated, safe, and efficacious in patients living with [38,39] However, patients must be monitored for QT prolongation. Moreover, bedaquiline should not be used with efavirenz,[40] and use with lopinavir-ritonavir requires careful monitoring.[41] Dolutegravir, endorsed by WHO in July, 2019, as part of a first-line antiretroviral therapy regimen, has no known interactions with bedaqualine and might be better tolerated.[42] Delamanid has no known interactions with antiretroviral therapy.[43] Updated information on drug–drug interactions between antiretroviral and antituberculosis medicines is now available.[44,45]

Treatment of infants, children, and in pregnancy

Of 25 000–32 000 children with multidrug-resistant tuberculosis annually, only 3–4% receive multidrug-resistant tuberculosis treatment, resulting in a 21% case fatality rate.[46] Bacteriological confirmation of tuberculosis, which is generally necessary to initiate treatment for multidrug-resistant tuberculosis in adults, is important to pursue but very challenging in children. Most paediatric tuberculosis is diagnosed clinically in the absence of bacteriological confirmation. To consider the DST of the presumptive index patient to guide the choice of treatment is important because 75–88% of child contacts have the same *M tuberculosis* strain as their close contact with multidrug-resistant tuberculosis;[47] usually a parent or other family member. Treatment response is generally monitored clinically.

Evidence amassed before 2014 showed that 119 (14%) of 842 children treated for multidrug-resistant tuberculosis received injectable-sparing regimens, which resulted in successful outcomes for 41 (72%) of 57 children with confirmed multidrug-resistant tuberculosis and 58 (94%) of 62 children with probable multidrug-resistant tuberculosis.[48] Emerging evidence regarding new (ie, bedaquiline and delamanid) and repurposed (ie, linezolid and clofazimine) medications support the use of injectable-free regimens in all children,[49] as outlined in the 2018–19 WHO guidelines.[22] Treatment with second-line injectable drugs is traumatic and requires audiological monitoring because hearing loss occurs in about 25% of children.[50] In most settings and clinical scenarios, risk benefit analysis favours a multidrug-resistant tuberculosis regimen with delamanid, para-aminosalicylic acid, or ethambutol, or all three drugs (step seven in table 3), as opposed to injectable agents (step six in table 3). Irrespective of treatment duration, individualised DST-guided treatment is preferred in children. Of note, this approach is harder to achieve in children because their DST results are infrequently available.

To keep children with their parent or caregiver during treatment of multidrug-resistant tuberculosis and minimise hospitalisation is imperative. Although many children with multidrug-resistant tuberculosis receive crushed adult tablets, access of children to dispersible

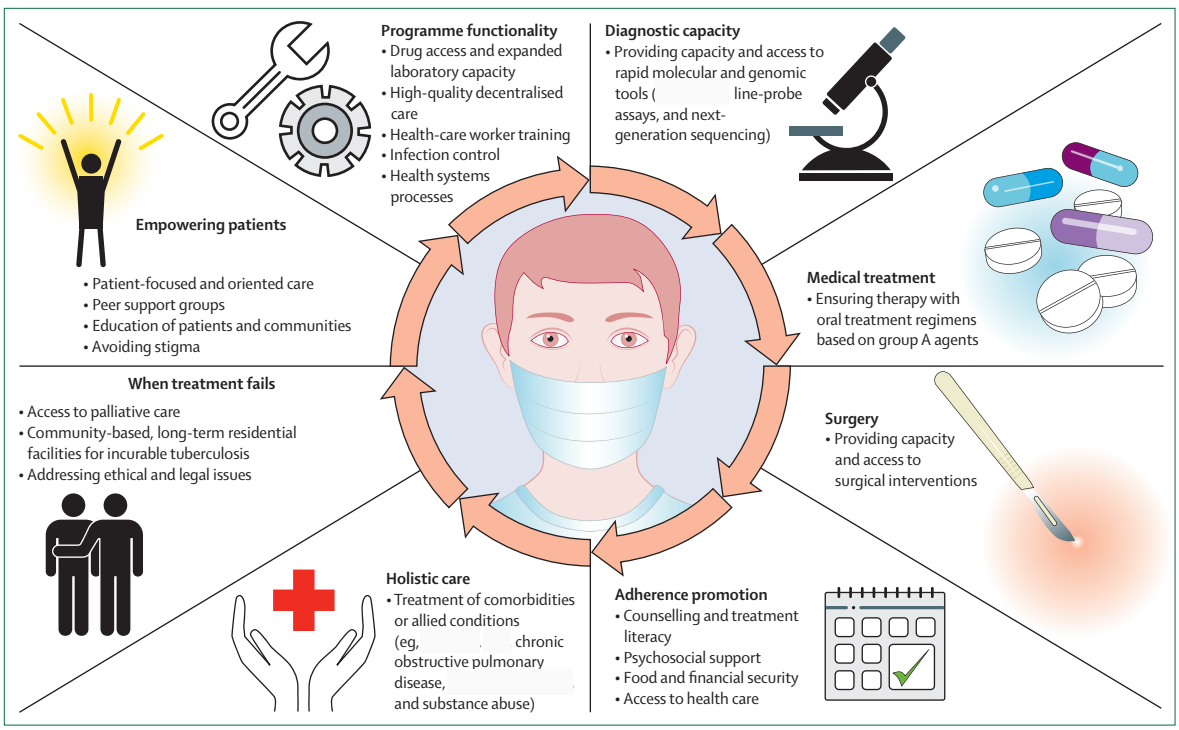

Figure 3:
The modern multidisciplinary care of multidrug-resistant tuberculosis should encompass early diagnosis with expanded access to rapid molecular tools and optimal treatment with oral regimens based on group A. Programmes should provide decentralised, well resourced, high-quality care with access to comprehensive testing and evaluation, new drugs, and expanded laboratory capacity with systems that enable treatment and quality of care monitoring (often the cascade of care is suboptimal and with substantial gaps[21]). Adherence promotion with counselling, psychosocial support, food, and financial security (patient-level costs are often too high), and access to health care is crucial. Patients should receive holistic care with treatment of comorbidities. Care should be patient focused and oriented (the first pillar of WHO's EndTB strategy to end tuberculosis[32]), encompassing patient choice, and be empowering, dignified, and respectful.[6] Patients who cannot be treated successfully with medical treatment alone, or who terminate medical treatment, should have access to surgical intervention and palliative care if appropriate. Multidisciplinary, long-term, community-based residential facilities should be available to cater for patients who cannot be cured and who cannot be managed at home.[6]

formulations of drugs to treat children with multidrug-resistant tuberculosis is increasing, thus simplifying treatment.[51] Expected data on efficacy, safety, and pharmacokinetics of new drugs in children promise less toxic, more tolerable, and increasingly efficacious future treatment.[52]

Pregnancy is not a contraindication to treatment of multidrug-resistant tuberculosis but poses potential risks to the mother and fetus.[53,54] As pregnant women are usually excluded from drug trials information of the safety of novel drugs for the mother and fetus is very sparse.[55] As teratogenic risk is greatest in the first trimester, treatment might be delayed until the second trimester for mild disease and with informed consent. Despite a scarcity of data, fluoroquinolones and bedaquiline are considered the drugs of choice whereas numerous drugs should be avoided including aminoglycosides (fetal ototoxicity), ethionamide (maternal nausea and vomiting and fetal teratogenicity), and linezolid (haematological toxicity and peripheral neuropathy). Immediately after childbirth, maternal treatment should be reinforced with injectable agents if needed, and infants should receive the BCG vaccine. The mother and infant should generally not be separated. Sputum smear positive mothers should wear a surgical mask in a well ventilated area in the presence of the infant and family members. Minimal con-centrations of tuberculosis medications are found in breast milk and no evidence exists regarding ill effects of this exposure.

Pulmonary rehabilitation, smoking cessation, and surgery

Patients successfully cured of multidrug-resistant tuberculosis can be left with profound disability and poor quality of life as a result of airway obstruction, fibrosis, and bronchiectasis, after tuberculosis.[56,57] An American Thoracic Society and European Respiratory Society statement stressed that survivors of tuberculosis could benefit from pulmonary rehabilitation but the supporting evidence is scant.[58] A comprehensive 3-week pulmonary rehabilitation programme in patients with sequelae after tuberculosis was associated with improvement in physical performance and lung function tests.[59]

Tobacco smoking is an independent risk factor for multidrug-resistant tuberculosis (odds ratio [OR] 1·57, 95% CI 1·33–1·86).[60] Most South African patients with multidrug-resistant tuberculosis expressed an interest in nicotine replacement therapies and other aids to quit smoking, and nicotine replacement therapies are

associated with higher quit rates in patients with tuberculosis than smokers generally.[61,62] Measures aimed at reducing tobacco use and smoking cessation interventions should be incorporated as an integral component of drug-resistant tuberculosis management. Although ongoing cigarette smoking delays sputum culture conversion,[63] no prospective studies looking at the effect of smoking cessation on multidrug-resistant tuberculosis outcomes exist.

WHO guidelines recommend surgery as a useful adjunct when the multidrug-resistant tuberculosis disease is limited and skilled thoracic surgeons and good postoperative care are available.[22] The timing of surgery is clinically determined. Indeed, operative intervention when *M tuberculosis* cultures become negative is ideal, but growing recognition exists that waiting too long for surgical intervention is counterproductive. Localised disease, reasonable pulmonary reserve, and a patient who is not too malnourished are all prerequisites for a successful outcome. A systematic review[64] from 2016 showed that surgery was associated with a successful outcome in 371 (81·9%) of 453 patients (OR 2·62, 95% CI 1·94–3·54) and another meta-analysis[65] found that partial lung resection was associated with improved treatment success (adjusted OR 3·0, 95% CI 1·5–5·9) but pneumonectomy was not.

Management of multidrug-resistant tuberculosis contacts

Multidrug-resistant tuberculosis could be averted via TPT delivered within the context of household contact tracing as endorsed by WHO.[66–68] Before TPT initiation, tuberculosis must be excluded in contacts. As evidence shows a high degree of concordance,[69] the drug-resistance pattern of a known index patient might guide delivery of TPT in household contacts. Although *M tuberculosis* infection can be confirmed via testing,[70] proof of infection is not required to initiate TPT in contacts living with HIV or those older than 5 years.

Evidence from 2017 suggests that TPT reduces multidrug-resistant tuberculosis risk by up to 90% (95% CI 9–99).[71] Cost-effectiveness analysis further supports the use of fluoroquinolone-based TPT, with or without an additional drug; a regimen based on a combined fluoroquinolone and ethambutol treatment was most cost-effective followed by fluoroquinolone alone.[71] However, the optimal regimen for multidrug-resistant TPT is unknown, and that the value of standard preventive therapy regimens (eg, isoniazid, rifampicin, and isoniazid and rifapentine) in contacts of individuals with multidrug-resistant tuberculosis is likely to be low is evident. Observational evidence suggests that fluoroquinolones can be successfully used when the index patient's isolate is susceptible to fluoroquinolones,[71] and two clinical trials (TB-CHAMP, ISRCTN92634082; V-QUIN, ACTRN12616000215426) are underway to establish the efficacy of such treatment; a third clinical trial to determine the use of delamanid for treatment of household contacts of patients with multidrug-resistant tuberculosis is also recruiting participants (PHOENIx multidrug-resistant tuberculosis, NCT03568383). As long-term paediatric exposure to levofloxacin is safe,[72] children should also receive fluoroquinolone-based TPT (ie, levofloxacin or moxifloxacin) in settings in which fluoroquinolone efficacy is probable. Dispersible paediatric fluoroquinolone formulations have been developed, but data from 2019 suggest that the recommended dosing might be sub-optimal.[73] Large-scale implementation of TPT in high-burden settings is challenged by weak health systems resulting in poor adherence and supply chain interruption.

Ongoing clinical trials and future perspectives

The STREAM trial[3] published in 2019 has reset the standard for multidrug-resistant tuberculosis trials. This trial,[3] which is the first multidrug-resistant tuberculosis non-inferiority trial, established the efficacy of the standard 20–24-month regimen. This regimen had been recommended since 1993[74] but had never been carefully evaluated. This trial[3] established a success rate of 79% for the standard regimen, and showed that the so-called modified Bangladesh 9–11-month regimen was non-inferior, with a success rate of 78%. The trial[3] was done in four countries and included over 30% HIV-co-infected participants, so the results are broadly generalisable. However, even before publication, a movement away from use of injectable agents existed, which are part of both the standard and the modified Bangladesh regimen, because of frequent severe hearing loss with use of these agents.[22] The introduction of bedaquiline, pretomanid (a novel nitroimidazooxazine drug candidate that has been recommended for approval by the Advisory Committee to the US Food and Drug Administration), and delamanid, along with the recognition that clofazimine and linezolid have substantial antimycobacterial activity, has led to a number of trials of all oral regimens for multidrug-resistant tuberculosis.

These clinical trials are currently evaluating 15 treatment regimens, with a variety of drug combinations (appendix p 8). Most of the trials have a comparator group of either the standard 20–24-month or the 9–11-month regimen. The multiplicity of combinations that are being studied not only increases the chance for success, but will probably yield several shortened oral regimens for multidrug-resistant tuberculosis treatment, an outcome that will aid greatly in managing patients with allergy or intolerance to one of the agents. The success of the Nix-TB trial,[75] a 6-month extensively drug-resistant tuberculosis treatment regimen including bedaquiline, pretomanid, and linezolid, suggests that a shortened treatment duration is a realistic goal, although the Nix regimen is probably too toxic for general treatment of multidrug-resistant tuberculosis.

That new diagnostic approaches, including next-generation sequencing approaches (whole genome sequencing or targeted sequencing), will facilitate precision medicine and individualised multidrug-resistant tuberculosis treatment regimens in the future is probable. Sequencing of *M tuberculosis* genomes directly from uncultured sputa has been possible in some cases already and could, if this sequencing became generally available, decrease the time from diagnosis to adequate treatment substantially.[76] New portable battery-operated tools such as GeneXpert Edge and Omni (figure 2) will enable community-based case finding, and with the advent of MinION (Nanopore Technologies, Oxford, UK), a pocket-sized portable sequencing technology, comprehensive automated point-of-care diagnosis of drug-resistant tuberculosis is conceivable. The robust pipeline of new chemical entities with antituberculosis activity holds promise for new, effective, and better-tolerated antituberculosis agents.[77] A study from 2018 highlighting drug gradients within tuberculosis lesions and across the walls of tuberculosis cavities associated with resistance amplification[78] suggests that new approaches to drug delivery, including nanoparticles and adjunct inhaled antibiotics, warrant further investigation. New therapies are likely to be developed that exploit the molecular mechanisms underpinning resistance development, including early up-regulation of efflux pumps, and accelerated generation of resistant mutants through, for example, bacterial stress responses and error-prone DNA repair.[79,80] Novel approaches including the use of efflux pump inhibitors and host-directed therapies are also being investigated to optimise the treatment of drug-resistant tuberculosis.[6,81] Biomarkers, including prognostic quantitative readouts, are required to guide the optimal treatment duration and number of drugs that should be used within a regimen. The clinical effect of using drug-specific therapeutic drug monitoring requires clarification. Fundamental issues such as how to optimally improve treatment adherence are neglected and are crucial to address if resistance amplification is to be prevented. Digital adherence technologies such as smartphone-based technologies and digital pillboxes might facilitate individualised approaches for monitoring adherence.[82]

In addition to targeting the bacterium, attempts to augment the host response are being explored. A wide range of host-directed therapies are being studied (appendix p 9).[83,84] Most are in early trial stage for drug-susceptible tuberculosis but trials in multidrug-resistant tuberculosis with azithromycin, etoricoxib, and recombinant human interleukin-2 are underway.[85] A meta-analysis[86] of adjunctive vitamin D in 1850 participants in eight observational studies showed a dramatic acceleration of sputum culture conversion (adjusted hazard ratio 13·44, 95% CI 2·96–60·90), including in the small subgroup with 37 participants with multidrug-resistant tuberculosis. This effect was not seen in drug-susceptible tuberculosis. An observational study[87] from Belarus administered autologous mesenchymal stromal cell infusion to 36 patients with multidrug-resistant tuberculosis receiving chemotherapy, with 29 (81%) of 36 recipients having successful outcomes versus 15 (42%) of 36 surveillance controls receiving individualised chemotherapy alone.

Conclusions

The burden of multidrug-resistant tuberculosis is predicted to rise in high-burden countries during the forthcoming decades.[88] Therefore, reaching the goal of WHO's EndTB strategy of a 90% decrease of the 2015 tuberculosis incidence by 2035[35] will require aggressive new strategies and increased investments, and commitments to prevent, diagnose, and treat multidrug-resistant tuberculosis.[89,90] Highly effective tailor-made regimens based on comprehensive DST are already available at specialised academic centres for tuberculosis care, mostly based in the developed world. Individual drug dosing guided by therapeutic drug monitoring, personalised host-directed therapies, and biomarker-guided individualisation of multidrug-resistant tuberculosis durations of therapy might soon become available for patients treated at such centres.[81] Under optimised circumstances, outcomes for treatment of multidrug-resistant tuberculosis are comparable with those of patients with drug-susceptible tuberculosis.[91] However, individualised management is out of reach for the great majority of patients with multidrug-resistant tuberculosis. The global health community needs to redouble its efforts to strengthen health systems in resource-poor areas so that optimal prevention, diagnosis, and treatment of multidrug-resistant tuberculosis are available to all patients with multidrug-resistant tuberculosis infection and disease.

Moreover, increased vigilance to prevent further emergence of drug resistance will be needed. Licensed in 2014, bedaquiline and delamanid were the first tuberculosis drugs to be developed in over four decades. Less than 2 years was needed for the first clinical isolate of *M tuberculosis* resistant against both of these novel agents to be reported.[92] Further, bedaquiline resistance and failure are already commonly seen in routine clinical practice.[93] If global leaders are serious about antibiotic stewardship, substantial investments must be made to not only increase diagnostic capacity for drug resistance testing but also universal access to novel diagnostic methods, treatment regimens (including the rapid and affordable roll-out of novel effective drugs like bedaquiline), and training (figure 3) to improve the abysmal cascade of care for multidrug-resistant tuberculosis (appendix p 2).[94] Standardised therapies that facilitate resistance amplification must be replaced by individual treatment regimens. If treatment can be understood also as prevention, a chance might exist to turn the tide.

Contributors
All authors participated in the design of the review, literature search, writing, and reviewing of all chapters and agreed to submit the manuscript.

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