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Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment

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ABSTRACT

The emergence of antimicrobial resistance against *Mycobacterium tuberculosis*, the leading cause of mortality due to a single microbial pathogen worldwide, represents a growing threat to public health and economic growth. The global burden of multidrug-resistant tuberculosis (MDR-TB) has recently increased by an annual rate of more than 20%. According to the World Health Organization approximately only half of all patients treated for MDR-TB achieved a successful outcome. For many years, patients with drug-resistant tuberculosis (TB) have received standardized treatment regimens, thereby accelerating the development of MDR-TB through drug-specific resistance amplification. Comprehensive drug susceptibility testing (phenotypic and/or genotypic) is necessary to inform physicians about the best drugs to treat individual patients with tailor-made treatment regimens. Phenotypic drug resistance can now often, but with variable sensitivity, be predicted by molecular drug susceptibility testing based on whole genome sequencing, which in the future could become an affordable method for the guidance of treatment decisions, especially in high-burden/resource-limited settings. More recently, MDR-TB treatment outcomes have dramatically improved with the use of bedaquiline-based regimens. Ongoing clinical trials with novel and repurposed drugs will potentially further improve cure-rates, and may substantially decrease the duration of MDR-TB treatment necessary to achieve relapse-free cure.

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Key words: antimicrobial drug resistance, bedaquiline, multidrug-resistant tuberculosis, whole genome sequencing, extensively drug-resistant tuberculosis.

Abbreviations: DOT, directly observed therapy; DST, drug susceptibility testing; FQ, Fluoroquinolones; H, Isoniazid; MDR-TB, multidrug-resistant tuberculosis; MIC, minimal inhibitory concentration; R, Rifampicin; RCT, randomized controlled trial; RR-TB, rifampicin-resistant TB; SLID, second-line injectables; TB, tuberculosis; TBNET, Tuberculosis Network European Trialsgroup; TDM, therapeutic drug monitoring; WGS, whole genome sequencing; WHO, World Health Organization; XDR-TB, extensively drug-resistant TB.

INTRODUCTION

Tuberculosis (TB) is the leading cause of death attributed to a single microorganism worldwide. Without combatting antimicrobial resistance in *Mycobacterium tuberculosis*, the causative microorganism of this disease, achieving the goals of the End TB strategy of the World Health Organization (WHO) will not be possible.[1] The leaders of the G20 nations have recently highlighted that antimicrobial resistance represents a growing threat to public health and economic growth worldwide and that fostering research and development against TB, among other pathogens and diseases, should be an international priority.[2]

Between 2009 and 2016, numbers of patients identified with multidrug-resistant TB (MDR-TB), defined by resistance of *M. tuberculosis* against at least rifampicin and isoniazid, increased annually by over 20%[3,4] (Fig. 1). Estimated numbers of MDR-TB increased in the same period from 250 000 to 490 000, partly also due to improvements in rapid diagnostics and molecular or phenotypic drug susceptibility testing (DST). In 2016, 8014 patients in 72 countries were identified with extensively drug-resistant TB (XDR-TB),[3] defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable agent (amikacin,

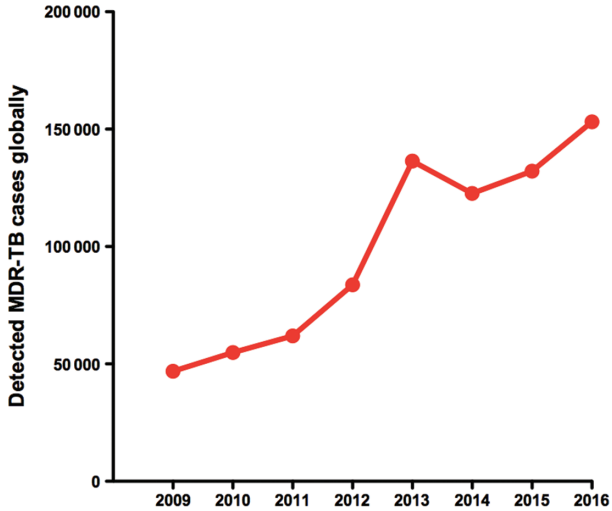

Figure 1 Number of patients identified with multidrug-resistant tuberculosis (MDR-TB) between 2009 and 2016 according to World Health Organization (WHO) global reports.

capreomycin or kanamycin). Actual numbers of patients with XDR-TB are likely much higher. Mathematical modelling predicts an increase in MDR-TB among incident TB cases and XDR-TB among incident MDR-TB patients in high-burden countries in the forthcoming decades.[5] More than 50% of recurrent TB in Europe were MDR-TB or XDR-TB.

Only 54% of patients with MDR-TB and 30% of patients with XDR-TB completed treatment successfully according to the latest WHO report[3]; probably fewer were actually cured based on WHO definitions. Death rates from MDR-TB and XDR-TB are 16% and 28%, respectively, but the real rates are likely twice these estimates if one takes into account mortality in those lost to follow-up. Some patients with M/XDR-TB treatment failure may survive for many months and pose an ongoing threat of transmission of drug-resistant *M. tuberculosis*.[6]

Despite these grim figures, dramatic improvements in the treatment outcomes have been reported for M/XDR-TB, where resources for novel diagnostics and medicines are available to individualize treatment regimens.[7,8] Here, we outline an evidence-based discussion of several key aspects of drug-resistant TB, and offer an overview of novel diagnostics and treatment strategies that offer a promising hope that M/XDR-TB is curable.

THE GLOBAL BURDEN OF MDR-TB

Annually, the WHO estimates that of the approximately 600 000 newly emerging MDR-TB or rifampicin-resistant TB (RR-TB) cases, only one fourth are detected and notified.[3] Assessments relying on the disease prevalence suggest a 16% and 80% higher frequency among estimated and notified MDR-TB patients.[9] Between 2015 and 2016, the number of reported MDR/RR-TB increased by more than 30% in 9 of the 30 high MDR-TB burden countries.[3]

The geographical distribution of MDR-TB is highly variable, consisting of several hot spots in low- and middle-income countries, from Eastern Europe to Asia. In 2016, the largest number of MDR/RR-TB was reported from the European Region (49 442), followed by South East Asia (46 269).[3] In the Western Pacific region, 21 252 cases of MDR/RR-TB were notified. The highest relative burden for a single country is reported from Belarus, where 38% of new cases and 72% of retreatment cases are estimated to have MDR/RR-TB[3] (Fig. 2). Currently, not more than one third of bacteriologically confirmed TB cases are evaluated with DST for first-line drugs and only 36% of MDR-TB patients benefit from DST for second-line drugs.[3] Similarly, not more than 20% of MDR-TB cases have access to MDR-TB treatment.[9,10] In a world challenged by unprecedented travel and migration, it is likely that the global MDR-TB map will undergo significant changes, leaving no country unaffected.

KEY CONTROL CONSIDERATIONS

Epidemiological and social perspectives

Selection pressure from inappropriate clinical use of TB drugs accounts for initial emergence of drug resistance.[11] However, more recent molecular epidemiological data suggest that ongoing transmission of MDR- and XDR-strains is the dominant mode of spread in many endemic countries.[12,13] As clinical diseases only represent a small fraction of total infections, endogenous reactivation from the much larger latent pool of infection will continue to generate more drug-resistant infectious sources in next few decades.[14]

The TB epidemic in recent human history occurred in close temporal association with rapid industrialization, urbanization, poverty, poor nutrition and poor living condition.[15] These social determinants are associated with multiple downstream risk factors, affecting not only TB risk, but also access and adherence to appropriate treatment, often leading to programmatic failure that breeds drug resistance.[16] While interventions on many of these upstream social determinants require strong government commitments, international collaboration and sustainable economic development, they, together with collaboration among programmes on TB, HIV, smoking and diabetes mellitus, are expected to work equally for drug-susceptible and drug-resistant TB.[3,16]

Programmatic perspective

With the currently available tools, case finding followed by effective chemotherapy remains the primary strategy for controlling TB.[17] Early modelling exercises by Karel Styblo suggested a need for achieving 70% case detection and 85% treatment success to reduce TB burden progressively.[17] Endogenous reactivation of remote infection may further retard the decline.[18] To ensure programme sustainability, emergence of drug resistance must not be allowed to outpace new drug development.

Recent in vitro hollow fibre experiments failed to demonstrate progressive acquisition of resistance by irregular drug exposure to a combination regimen.[19] However, such experiments did not incorporate the

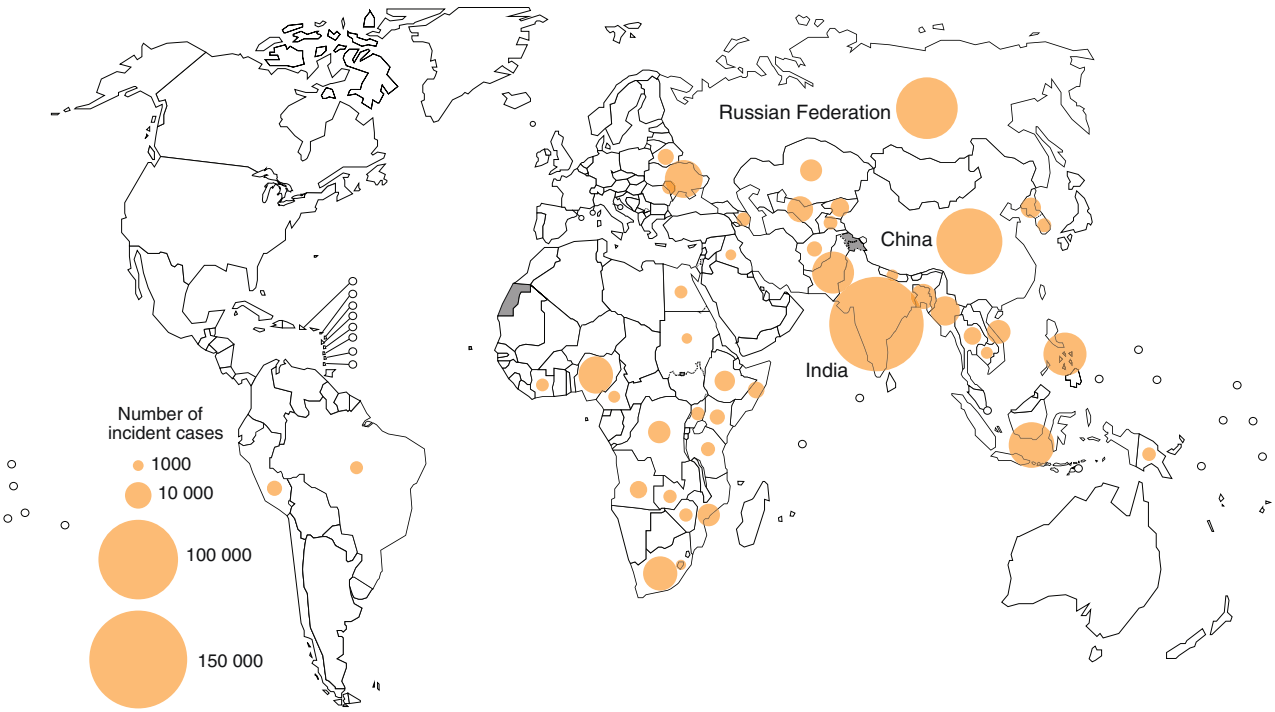

Figure 2 Estimated incidence of multidrug-resistant tuberculosis (MDR-TB)/rifampicin-resistant TB (RR-TB) for countries with at least 1000 incident cases. Areas that are not applicable are in grey. (Reproduced from World Health Organization,[3] with permission.)

intrinsic pharmacokinetic variabilities[20] and bacillary heterogeneity within complex lesions of the human host,[13] which could add to or magnify the effects of treatment non-adherence. Clinically, emergence of drug resistance has been well associated with intermittent treatment in HIV-infected patients.[21] Non-adherence necessarily reduces effective treatment duration, and insufficient duration of treatment has consistently been associated with poorer outcome.[22] Drug-resistant rates are also consistently higher in previously treated cases, especially among treatment failures.[3]

Randomized controlled trials (RCT) did not demonstrate superiority of directly observed therapy (DOT) over self-administered therapy (SAT).[23] However, none of them were able to reproduce, in their DOT arms, the high treatment completion rates in the Medical Research Council (MRC) trials[22] or successful field programmes.[3] Unlike physical interventions, the success of behavioural interventions is often highly dependent on the overall psychosocial environment. Simple allocation to DOT does not necessarily reproduce all the necessary elements for securing patient adherence, and such intrinsic study limitation cannot be adequately addressed by meta-analysis.

Public health perspective

Administrative control at source remains the most cost-effective way of controlling the spread of an airborne infection like TB in health care settings.[24] In the early guinea pig studies,[25] the transmission risk decreased rapidly after initiation of effective treatment. As the standard short course regimen is unlikely to be adequate in controlling the infectivity of M/XDR-TB, rapid detection of drug resistance is crucial to control their transmission. Similarly, suitable segregation of TB patients with different drug-resistant profiles is advisable to avoid superinfection by more drug-resistant strains. Engineering measures may be limited by building design and cost-effectiveness.[24] Ventilation acts by diluting the air and may not remove airborne droplets quickly from a continuously emitting source. Surgical face masks on patients with M/XDR-TB significantly reduces transmission,[26] but personal protective devices such as N95 face masks are not suitable for use by exposed persons round the clock.[24] Community-based care reduces nosocomial risk by avoiding aggregation of infectious sources and their mixing with vulnerable contacts.[18]

IMPROVING DIAGNOSIS

In recent years, programmatic implementation of molecular tests worldwide has dramatically reduced the time to TB diagnosis.[27–30] These tests can be applied to various biological samples (sputum, cerebrospinal fluid, pleural fluid, urine, blood, stool).[28,31] Nucleic acid amplification tests (NAATs) also enable the prediction of resistance to important first- and second-line drugs on the basis of resistance-conferring mutations.[32] However, most commercially available tests are restricted to few drug targets only, but remain suboptimal when comprehensive individualized treatment regimens need to be composed (Table 1).[45]

Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) has been endorsed by the WHO in high-incidence countries.[46] Recently, a new version of the test, Xpert

MTB/RIF Ultra, has been introduced to the market.[33] The Xpert MTB/RIF Ultra has higher sensitivity than Xpert MTB/RIF in patients with paucibacillary disease and in patients with HIV, though at the expense of a decrease in specificity.[47] In a preliminary study using cerebrospinal fluid samples, Xpert MTB/RIF Ultra appeared to be more sensitive in those with suspected TB meningitis.[48] However, focusing on rpoB mutations alone as a surrogate for rifampin resistance may lead to erroneous use of empiric regimens.[49] The initial choice of regimens may be substantially improved by a novel assay (not yet marketed) that includes resistance-conferring target sequences allowing prediction of additional resistance to isoniazid, fluoroquinolones and the second-line injectables (SLID).[50]

The line-probe assays identify patients with active TB and resistance-conferring mutations for rifampin, isoniazid, SLID and fluoroquinolones with modest to high accuracy (e.g. Hain Lifescience, Nehren, Germany; AID Diagnostika, Straßberg, Germany).[36] Not being fully automated, they are still dependent on laboratory expertise. By contrast, the Fluorotype MTB (Hain Lifescience, Nehren, Germany) may improve molecular drug-resistance prediction.[51] The learning software is able to recognize known and unknown mutations, which can later be annotated to drug resistance or susceptibility.

However, the best coverage for molecular DST is given by sequencing of the entire mycobacterial genome (whole genome sequencing, WGS).[43] This method reports all potential resistance-conferring mutations. WGS needs relatively large amounts of enriched mycobacterial DNA, which implies early positive culture materials, to sequence. Although direct sequencing from fresh clinical samples is possible in smear-positive cases using special enrichment procedures, it is still several years away from clinical implementation.[52–54] If this issue can be overcome, information obtained from WGS with computational sequence analysis, which may be uploaded to large databases, is probably the future of molecular drug-resistance prediction.[55,56] However, all mutations potentially coding for drug resistance have to be characterized by in-depth phenotypic minimal inhibitory concentration analysis.[57] More recently, 'deep sequencing' has offered the potential to detect microheteroresistance undetectable by conventional culture techniques, though the clinical significance of this observation remains unclear.[58]

SHORTER MDR-TB REGIMEN

In 2016, the WHO published new treatment guidelines for drug-resistant TB and reclassified the drugs recommended to treat MDR/RR-TB into groups from A to D (A = fluoroquinolones; B = second-line injectable drugs; C = other core second-line agents; D_{1-3} = add-on agents).[59] The previous 2011 guidelines conditionally recommended an intensive phase of 8 months for most MDR-TB patients and total treatment duration of 20 months in patients who had not been previously treated.[60] In 2010, Van Deun *et al*. reported an overall success rate of 87.9% in the treatment of a cohort of 206 MDR-TB patients who had never received second-line drugs in Bangladesh, using a standardized regimen of 9–12 months at a fraction of the cost of traditional regimens (only € 225/course).[61] This regimen was subsequently tested in 507 adult MDR-TB patients in 9 African countries with similar, promising outcomes.[62] This led, in May 2016, to the WHO's conditional recommendation of this shorter regimen of 9–12 months for patients with pulmonary MDR-TB under programmatic conditions.[63] The regimen, which has since been used in 23 countries with notable success, consists of 4–6 months of a later generation fluoroquinolone, kanamycin, prothionamide, high-dose isoniazid, clofazimine, pyrazinamide and ethambutol, followed by 5 months of the fluoroquinolone, clofazimine, pyrazinamide and ethambutol alone. In the interim analysis of Stage 1 of the Stream Trial involving 424 patients from 7 cities in Vietnam, Mongolia, South Africa and Ethiopia, 78. 1% achieved favourable outcome for the shorter MDR-TB regimen as compared to 80. 6% for the traditional 24-month regimen.[64] Although these numbers appear similar, non-inferiority of the shorter regimen has yet to be demonstrated. Final results will be available in April 2018. Because of limited global capacity for DST, WHO does not require DST for second-line drugs to be performed prior to starting this shorter regimen. Instead it allows the use of treatment history and local surveillance data to guide eligibility for this regimen. Unfortunately, in countries where second-line drugs have freely been used outside programmatic conditions, and those with high rates of more extensive patterns of drug resistance, this regimen would not be expected to work and indeed cannot be recommended. The available data shows that no more than 4% to 50% of patients in some MDR-TB hotspots like Eastern Europe, South East Asia, Pakistan and Brazil are likely to be eligible for this regimen (Table 2).[65–70]

NOVEL TREATMENT REGIMENS

Bedaquiline- or delamanid-based regimens

The results of two early bactericidal activity (EBA) studies provided evidence that the newly developed antituberculosis compounds bedaquiline[71] and delamanid[72] have antimycobacterial activity in humans. Subsequently, the results of a phase 2(b) clinical trial with optimized backbone MDR-TB regimens and either bedaquiline or placebo documented significantly higher relapse-free cure rates in the bedaquiline arm (58% vs 32% in the placebo arm).[73] Using tailor-made regimens based on comprehensive DST, patients who received bedaquiline-based treatment regimens experienced sputum culture conversion by 6 months of therapy in 96% (25 patients)[74] and 100% (20 patients)[75] of cases. Results from a retrospective multicentre cohort analysis documented sputum culture conversion at the end of therapy in 91.8% of 428 MDR-TB patients treated with bedaquiline-based regimens.[76] Preliminary results of a large phase 3 study comparing optimized backbone regimens with delamanid or placebo presented at the Conference of the International Union against Tuberculosis and Lung Diseases in Guadalajara,

Table 1 Novel diagnostic tools for the detection of *Mycobacterium tuberculosis* drug resistance

Function	Sputum test	Strengths	Limitations	References
Molecular drug susceptibility testing	GeneXpert/Ultra	Highly sensitive, quick, automated, indicates rifampicin resistance	May give rise to false positives, costly, requires electricity. May miss rifampicin resistance if mutation outside the target area	33,34
	BD ProbeTec ET DTB	Rapid turn-around time, cost effective, high sensitivity and specificity	Low sensitivity if extrapulmonary samples are smear negative	35
	Roche COBAS TaqMan MTB	Real-time PCR-based test. High sensitivity and specificity. Better specificity than Amplicor MTB PCR test	Less yield and more complicated than GeneXpert	35
	Hain GenotypeMTBDRplus (sl)	Rapid turn-around time, detects XDR-TB	Technically more demanding, not approved for smear negative and extra pulmonary samples	36
	Abbott RealTime MTB INH/RIF	The strengths of this system are the high sensitivity with paucibacillary specimens, its ability to detect isoniazid and rifampicin resistance	Not WHO approved, not available for field use	37
	Hain Fluorotype	Rapid detection of MDR-TB, semi-automated directly from samples. Can process up to 96 samples at a time	Needs trained personnel	38
	AID TB resistance LPA	High sensitivity in picking up isoniazid, rifampicin, fluoroquinolone and second-line injectable drug resistance compared to culture	Needs trained personnel, lower sensitivity for ethambutol	39
	InnoLiPA LPA	Used to detect MTB and rifampicin resistance, rapid turn-around time, semi-automated	Only used for bacteria grown on media. Does not detect isoniazid resistance. May miss rifampicin resistance if mutation outside the target area. Requires trained personnel	40
	Pyrosequencing	Detects specific mutations, can show whether a mutation is silent or clinically meaningful	Technically demanding, not easily available	41,42
	Whole genome sequencing	Will provide known and unknown mechanisms of resistance to all drugs	Highly specialized, few centres capable of doing it	43,44

MDR-TB, multidrug-resistant tuberculosis; MTB, Mycobacterium tuberculosis; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis.

Mexico, in October 2017 were inconclusive as they showed high cure rates between 76% and 78% in both arms of the study.

Repurposed drugs

Adding linezolid to a background regimen resulted in culture conversion at 4 months among 15 (79%) of 19 XDR-TB patients who failed previous treatment.[77] In another RCT, adding linezolid to a 2-year individualized regimen led to earlier culture conversion and increased the treatment success rate from 34.4 to 69.7%.[78] A meta-analysis of predominantly observational studies suggested that linezolid significantly increased the probability of favourable outcome by 55%.[79] Adverse effects, especially peripheral neuropathy, were very common with prolonged use of linezolid even at a daily dosage of 600 mg[77,78], often requiring treatment interruption or dose/frequency reduction[62,75,80]. Acquired linezolid resistance has been reported, particularly with

a daily linezolid dose of 300 mg.[77] Mitochondrial toxicity risk was found to increase with linezolid trough concentrations,[81] suggesting the possibility of better tolerance for intermittent dosing.[80]

Meta-analyses of observational studies failed to show consistent contribution of clofazimine in the treatment of M/XDR-TB.[79,82] However, confounding by indication could not be excluded as clofazimine was often used in situations with fewer alternative options. In the only available RCT, adding clofazimine led to earlier culture conversion and cavity closure in MDR-TB, and increased the treatment success rate from 53.8 to 73.6%.[83] Amoxicillin/clavulanate has not been shown to be effective against M/XDR-TB in observational studies[70,73], while preliminary data suggest a potential role of the carbapenem/clavulanate combinations.[84]

New drug combinations, ongoing trials

Encouragingly, a number of clinical trials have been initiated to address questions about the optimal regimen and duration of treatment, and minimum thresholds of drugs needed for effective treatment of MDR- and XDR-TB. These trials, including their clinical end points, and current status are outlined in Table 3.

The NExT study, STREAM II, endTB and TB-PRACTECAL, among others, will address the optimal regimen and treatment duration for MDR-TB. These studies are complementary because they all address different combinations and permutations of drugs and treatment duration. For example, the 6-month STREAM II regimen uses an injectable, whilst the 6-month NExT study is an injection-free regimen also incorporating linezolid; TB-PRACTECAL will evaluate combinations of pretomanid, while endTB will evaluate 6-month bedaquiline-based regimens with or without delamanid. In tandem, data is accumulating from observational studies and clinical experience on the ground. For example, in South Africa, bedaquiline is already extensively being used to treat MDR-TB with poor prognostic features or where an appropriate regiment cannot be constructed because of toxicity or adverse events (most commonly hearing loss due to kanamycin). The improved treatment-related outcomes among survivors in the phase 2(b) study[73] and in observational studies[67,77], the poor outcomes associated with the currently used toxic and prolonged MDR-TB regimens, raises the ethical question whether we should wait for the results of these clinical trials, or whether bedaquiline should not be rolled out for all patients with MDR-TB? The equipoise surrounding this issue, including potential mortality associated with bedaquiline and concerns about amplification of resistance, has been discussed in detail recently.[87]

The optimal regimen and duration of treatment for XDR-TB remains unclear. The national TB programme

Table 2 Applicability of the shorter course WHO recommended MDR-TB regimen (by geographic region)

Countries	Source	No. of patients (year of study)	Previously treated (%)	Resistance pattern in community drug	Percentage eligible	Reference
European region: Austria, France, Germany, Portugal, 16 countries (TBNET)	National registries, reference hospitals, TBNET	1140 of which 612 had full DST (2010–2016)	N/A	E (60%) Z (67%) FQ (37%) SLID (33%) Pto/Eto (64%)	7.8	Lange *et al.*[65]
Eastern European region: Latvia, Lithuania, Estonia, Bucharest	TB-PAN-NET project	737 (2007–2009)	54%	E (64%) Z (58%)	4.2	Balabanova *et al.*[66]
EU/EEA (26 countries)	TESSy	7550 (2010–2014)	55%	E (65) FQ (26) SLID (31)	11	Van der Werf *et al.*[67]
Brazil	Brazilian National register	3251 (2000–2010); 3156 (2011–2015)	N/A	E (33%) Z (50%) FQ (30%) E (28%) Z (46%) FQ (34%)	50–55	Dalcolmo *et al.*,[68]
Pakistan	Two centres, Peshawar, Punjab	832 (2012–2016) culture confirmed MDR-TB	41%	FQ (48%)	49	Javaid *et al.*,[69]
Singapore, Indonesia and other South East Asia countries	National TB registry	267 (2002–2016)	25%	E (43%) Z (44%) At least one drug (71%)	30	Chee *et al.*,[70]

DST, drug susceptibility testing; E, Ethambutol; EU/EEA, European Union/European Economic Area; FQ, Fluoroquinolones; MDR-TB, multidrug-resistant tuberculosis; SLID, second-line injectables; TB, tuberculosis; TBNET, Tuberculosis Network European Trialsgroup; WHO, World Health Organization; Z, Pyrazinamide.

in South Africa currently treats XDR-TB using a backbone of bedaquiline, linezolid and clofazimine. Short-term outcomes are substantially better compared to outcomes using regimens without bedaquiline.[88] The NIX study is evaluating a combination of bedaquiline, pretomanid and linezolid in patients with newly diagnosed XDR-TB or those who have failed treatment. Preliminary results are very encouraging (high conversion rates despite high rates of linezolid toxicity) though long-term and more definitive data are awaited.[85] However, disappointingly, these results are tempered by the recently released results of the delamanid phase 3 study.[86] Compared to a conventional background regimen, delamanid, when given for 6 months, did not improve 24-month treatment outcomes in patients with MDR-TB, when compared to the optimized backbone regimen (81.4 vs 81.2%). These results will need to be taken into account when planning future studies using nitroimidazoles.

It is important to remember that whilst newer and repurposed drugs will reduce the frequency of treatment failure in patients with XDR-TB, they will not eliminate it. Indeed, bedaquiline-based regimens had a 24-month favourable outcome rate of only 62% in XDR-TB[89], and our data demonstrate that unfavourable outcome rates at 24 months in those with XDR-TB were 32% (Dheda K, submitted for publication). Two learning points emerge. The first is that programmatically incurable TB is an entity that will continue to pose a management dilemma in high-burden countries, and we have now entered an era where the erection of suitable community-based long stay and palliative care facilities is imperative.[18] Second, it highlights the important need for ongoing antibiotic stewardship and strengthening of NTP's to preserve the recently introduced newer and repurposed drugs. In the meanwhile clinicians in South Africa, and elsewhere, continue to grapple with the challenge of what salvage regimen to use in XDR-TB patients who have failed bedaquiline-based regimens.

Finally, the idea of a pan TB regimen has been mooted. It has been suggested that this will likely comprise three drugs (e.g. bedaquiline, pretomanid and sutezolid) that will be used to treat all patients with TB with no pre-requisite for DST. The proposed advantages would include a reduction in mortality, transmission and disease burden. However, whether these aims can be realized remain unclear, and major concerns would include cost, lack of antibiotic stewardship, and concern about the rapid amplification of drug resistance rendering these newer agents useless over time. Clinical trials informing this issue are eagerly awaited.

REDEFINING TREATMENT OUTCOMES

The definitions for treatment outcomes from MDR-TB proposed by the WHO are limited for the application in clinical practice, since 'cure' requires that the treatment is completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase of treatment[90] (Table 4). Often the required number of sputum specimens are not available to evaluate patients for 'cure' according to this definition since many patients are unable to provide sputum specimen in the continuation phase of treatment or sputa are not collected. The WHO abstains from reporting cure rates for MDR-TB due to the lack of available data. WHO treatment outcome data report the category 'treatment success', which is the sum of those who get cured and those who complete the treatment in the absence of failure (Table 4). 'Treatment success' data are relying on data of those who have completed the treatment, not on those who are cured.

In a recent prospective observational cohort study at 23 different sites in 16 European countries, assessment of WHO-defined 'cure' was only possible for 13% of the patients in countries with a low incidence of TB (notification rate <20 per 100 000 population), 58% of the patients in countries with an intermediate incidence (notification rate of 20 to 100 per 100 000 population), and 52% of the patients in countries with a high incidence (notification rate >100 per 100 000 population), owing to a lack of sputum cultures obtained after the intensive treatment phase.[92] Fifty-seven percent of patients with 'treatment failure' were not identified by the WHO definition because they did not change two drugs in the treatment regimen despite fulfilling criteria of failure.[92] Recently, simplified treatment outcome definitions for MDR-TB have been proposed[92,93] (Table 4) that are based on the culture status at the sixth month[94] and include an observation period of 1 year after the end of therapy to define relapse-free cure (while WHO outcomes are censored on the last day of treatment). Applying these definitions to patients with M/XDR-TB leads to more accurate and plausible results[92,95] with relapse-free cure rates in M/XDR-TB that are indistinguishable from those in non-M/XDR-TB under optimal management conditions.[96]

INDIVIDUALIZED THERAPY VERSUS STANDARDIZED TREATMENT REGIMEN FOR M/XDR-TB

Standardized therapy regimens have the potential to lead to high cure rates in patients with M/XDR-TB.[61] However, strains found in M/XDR-TB patients especially from Europe show high rates of resistance to second-line drugs.[97,98] Standardized regimens such as the shorter regimen endorsed by the WHO are most likely not suitable for this setting and the implementation to such a population might lead to an increase of MDR-TB.[65,99] The proportion of favourable treatment outcomes was higher in patients undergoing individualized drug therapy when compared to standardized therapies in a large meta-analysis.[119] However, the concept of individualized therapy for M/XDR-TB patients is still not fully exhausted (Table 5).[100–102]

Molecular methods for early detection of drug resistance are available in most parts of the world.[46] Still, the link between potential resistance-conferring mutations and the corresponding minimal inhibitory concentration (MIC) is essential to fully rely on molecular tests in clinical routine.[103] In the future, individualized

Table 3 Currently registered phase 2 and 3 clinical trials for MDR-TB

Trial name	New or repurposed drug in regimen	Official trial title	Description	Status/comments	Phase	Trial registry identifier (link)
Otsuka 233	Delamanid	Phase 2, open-label, multiple-dose trial to assess the safety, tolerability, pharmacokinetics, and efficacy of delamanid in paediatric MDR-TB, HIV patients on therapy with an optimized background regimen of anti-TB drugs over a 6-month treatment period	Safety, efficacy and pharmacokinetic study of delamanid in paediatric patients with MDR-TB	Enrolment completed for cohorts age 6+ years; enrolment open for cohort age <6 years	Phase 2	NCT01859923
Janssen C211	Bedaquiline	A phase 2, open-label, multicentre, single-arm study to evaluate the pharmacokinetics, safety, tolerability and anti-mycobacterial activity of TMC207 in combination with a BR of MDR-TB medications for the treatment of children and adolescents 0 months to <18 years of age who have confirmed or probable pulmonary MDR-TB	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of bedaquiline in combination with MDR-TB therapy for HIV uninfected children and adolescents	Currently enrolling participants; follow-up ongoing	Phase 2	NCT02354014
NC-005	Pretomanid Bedaquiline	A phase 2 open-label partially randomized trial to evaluate the efficacy, safety and tolerability of combinations of bedaquiline, moxifloxacin, PA-824 and pyrazinamide during 8 weeks of treatment in adult subjects with newly diagnosed DS-TB or MDR-TB, smear-positive pulmonary TB	Study of combinations of bedaquiline, moxifloxacin, PA-824 and pyrazinamide for 8 weeks for DS-TB and MDR-TB patients, with one arm for MDR-TB patients adding moxifloxacin to bedaquiline, PA-824 and pyrazinamide	Fully enrolled and manuscript in preparation. Preliminary results suggest BPaMZ is more efficacious then BPaZ > PaMZ > HREZ. BPaMZ may have treatment shortening potential	Phase 2	NCT02193776
ACTG 5343	Bedaquiline Delamanid	A trial of the safety, tolerability and pharmacokinetics of bedaquiline and delamanid and in combination, among participants taking multidrug treatment for DR-TB	Study of drug–drug interactions and combined QT effects of bedaquiline and delamanid	Currently enrolling participants	Phase 2	NCT02583048
ACTG 5312	High-dose isoniazid	The early bactericidal activity of high-dose or standard-dose isoniazid among adult	Safety and efficacy study of different doses and generic variants of isoniazid-resistant TB	Currently enrolling participants in South Africa	Phase 2	NCT01936831

Table 3 Continued

Trial name	New or repurposed drug in regimen	Official trial title	Description	Status/comments	Phase	Trial registry identifier (link)
		participants with isoniazid-resistant or DS-TB				
Opti-Q	Levofloxacin	Prospective, randomized, blinded phase 2 pharmacokinetic/pharmacodynamic study of the efficacy and tolerability of levofloxacin in combination with optimized background regimen for the treatment of MDR-TB	Efficacy and safety study of increased doses of levofloxacin in combination with optimized background therapy	Study completed. Publication of results awaited	Phase 2	NCT01918397
MDR-END	Delamanid	Treatment shortening of MDR-TB using existing and new drugs	Comparing efficacy of a treatment regimen including delamanid, linezolid, levofloxacin and pyrazinamide for 9–12 months, with a control arm of the standard treatment regimen including injectables for 20–24 months for the treatment of FQ sensitive MDR-TB	Currently enrolling participants in Korea	Phase 2	NCT02619994
Janssen Japan trial	Bedaquiline	An open-label study to explore the safety, efficacy and pharmacokinetics of TMC207 in Japanese patients with pulmonary MDR-TB	This is an open-label, single-arm, multicentre trial to explore safety, efficacy and PK of TMC207 in Japanese participants with pulmonary MDR-TB	Currently enrolling participants in Japan	Phase 2	NCT02365623
TB-PRACTECAL	Bedaquiline Pretomanid	Pragmatic clinical trial for a more effective concise and less toxic MDR-TB treatment regimen(s)	Multicentre, open-label, multi-arm, randomized, controlled, phase 2 and 3 trials; evaluating shortened treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed anti-TB drugs for the treatment of confirmed pulmonary MDR-TB	Currently enrolling patients	Phase 2–3	NCT02589782
STREAM stage 1[†]	Bangladesh regimen	The evaluation of a standardized treatment regimen of anti-TB drugs for patients with MDR-TB: a multicentre international parallel group randomized controlled trial	Comparison of standard WHO MDR-TB regimen with 9–12 month modified Bangladesh regimen	Primary endpoint recently reported (non-inferiority of the shorter regimen was not demonstrated, i.e. shorter regimen was not as effective as the conventional arm)	Phase 3	ISRCTN78372190

Table 3 Continued

Trial name	New or repurposed drug in regimen	Official trial title	Description	Status/comments	Phase	Trial registry identifier (link)
Otsuka 213*	Delamanid	A phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of delamanid administered orally as 200 mg total daily dose for 6 months in patients with pulmonary sputum culture-positive, MDR-TB	Safety and efficacy study of delamanid or placebo for 6 months in combination with optimized background therapy for 18–24 months	Study completed. Results of preliminary analysis recently reported. Dlm had a trend towards more rapid culture conversion. However, the 24-month favourable outcomes rate was similar in the delamanid versus control arm (81.4 vs 81.2%)	Phase 3	NCT01424670
STREAM stage 2	Bedaquiline	STREAM: The evaluation of a standard treatment regimen of anti-TB drugs for patients with MDR-TB	Comparison of a 6- (containing an injectable) and 9-month (all oral) bedaquiline-containing regimen against the WHO and Bangladesh regimen	Currently enrolling participants	Phase 3	NCT02409290
NExT	Bedaquiline	Evaluating a new treatment regimen for patients with MDR-TB—a prospective open-label randomized controlled trial	Open-label RCT of a 6-month injection-free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high-dose isoniazid and pyrazinamide	Currently enrolling participants in South Africa	Phase 3	NCT02454205, PACTR201409000848428
NiX-TB	Bedaquiline Pretomanid	A phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in subjects with pulmonary TB with either XDR-TB or treatment intolerant/non-responsive MDR-TB	Bedaquiline, PA-824 and linezolid in patients with XDR-TB and MDR-TB for 6 months with an option of 9 months	Currently enrolling participants in South Africa. Preliminary interim analysis showed good culture conversion rates but significant linezolid-associated toxicity	Phase 3	NCT02333799
ZeNiX	Bedaquiline Pretomanid Linezolid	A phase 3, partially blinded, randomized trial assessing safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary TB, XDR-TB, pre-XDR-TB or non-responsive/intolerant MDR-TB	Bedaquiline, PA-824 and linezolid (at a dose of 1200 mg or 600 mg daily for 9 or 24 weeks) in patients with XDR-TB, pre-XDR and treatment intolerant or non-responsive MDR-TB for a treatment duration of 6 months	Has recently started enrolling patients	Phase 3	NCT03086486
STAND	Pretomanid	A phase 3 open-label partially randomized trial to evaluate the efficacy, safety and tolerability	Efficacy, safety and tolerability of a combination of moxifloxacin, PA-824 and pyrazinamide	Recruitment has been suspended in favour of developing NC-005-specific regimens	Phase 3	NCT02342886

Table 3 Continued

Trial name	New or repurposed drug in regimen	Official trial title	Description	Status/comments	Phase	Trial registry identifier (link)
		of the combination of moxifloxacin plus PA-824 plus pyrazinamide after 4 and 6 months of treatment in adult subjects with smear-positive pulmonary DS-TB and after 6 months of treatment in adult subjects with smear-positive pulmonary MDR-TB	treatments after 6 months of treatment in subjects with MDR-TB compared to a combination of moxifloxacin, PA-824 and pyrazinamide treatments in DS-TB subjects; there will be a comparator arm for MDR-TB			
China PZA trial	N/A	Optimization of MDR-TB treatment regimen based on the molecular drug susceptibility results of pyrazinamide	Efficacy study of introducing molecular testing of pyrazinamide susceptibility in optimizing the MDR-TB treatment regimen	Recruitment complete	Phase 3	NCT02120638
endTB	Bedaquiline Delamanid	Evaluating newly approved drugs for multidrug-resistant TB: A clinical trial	Phase 3, randomized, controlled, open-label, non-inferiority, multicountry trial evaluating the efficacy and safety of new combination regimens for MDR-TB treatment	Currently enrolling participants	Phase 3	NCT02754765
FS-1 trial	FS-1	Randomized, placebo-controlled study of safety and therapeutic efficacy of the drug FS-1 in the oral dosage form in drug-resistant pulmonary TB	Safety and efficacy of FS-1 in oral dosage form in drug-resistant pulmonary TB	Currently enrolling participants in Kazakhstan and Kyrgyzstan	Phase 3	NCT02607449
ACTG 5356	Delaminid	A phase 2a, prospective, randomized, multicentre trial to evaluate the safety, tolerability and initial efficacy of LZD dosing strategies combined with Delamanid and optimized background therapy (OBT) for the treatment of MDR-TB	Safety and efficacy of linezolid and delamanid added to OBT in MDR-TB	In the planning phase	Phase 2	N/A

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[†]The recently released NiX study interim results,[85] and the delamanid and STREAM 1 WHO shorter course regimen phase 3 results are summarized.[86]

BR, background regimen; DS-TB, drug susceptible tuberculosis; FQ, Fluoroquinolones; LZD, linezolid; MDR-TB, multidrug-resistant tuberculosis; OBT, optimized background therapy; PK, pharmakokinetic; QT, interval between the Q and the T in a curve on an Electrocardiogram; TB, tuberculosis; WHO, World Health Organization.

Table 4 MDR-TB treatment outcome definitions according to WHO 2014[91] and TBNET 2016 (simplified definitions)[92]

	WHO definitions	Simplified definitions (TBNET)
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase	A negative culture status 6 months after treatment initiation, no positive culture thereafter, and no relapses within 1 year after treatment completion
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase	Not defined
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • lack of conversion by the end of the intensive phase, or • bacteriological reversion in the continuation phase after conversion to negative, or • evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or • ADR	A positive culture status 6 months after treatment initiation or thereafter or a relapse within 1 year after treatment completion
Died	A patient who dies for any reason during the course of treatment	Death during observation
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more	Loss to follow-up was defined as non-receipt of care 6 months after treatment initiation
Not evaluated/undeclared	A patient for whom no treatment outcome is assigned. (This includes cases 'transferred out' to another treatment unit and whose treatment outcome is unknown)	An undeclared outcome was defined as an outcome that was not assessed. • owing to transferral out of the cohort • no culture status at 6 months while the patient was receiving care • no post-treatment assessment
Treatment success	The sum of cured and treatment completed	

ADR, adverse drug reaction; MDR-TB, multidrug-resistant tuberculosis; TBNET, Tuberculosis Network European Trialsgroup; WHO, World Health Organization.

dosing on the basis of the strain's MIC may be conducted to improve the drugs' bactericidal activity.[104] Therapeutic drug monitoring (TDM) can help to avoid adverse events due to toxicity from drug overdose.[105] This may be realistic since TDM has become available in specialized centres for certain drugs and may be even accessible to peripheral centres by sample collection methods such as dried blood spots.[106]

Treatment duration for patients with M/XDR-TB is not clearly defined by randomized controlled studies and the individual need for therapy differs significantly.[107] Here, the patient's immune constitution, co-infections (i.e. HIV), the extent of disease, and the pathogen's resistance status greatly influence bacteriological clearance.[102] Biomarkers that define the optimal duration of drug therapy would be of great interest to increase the number of cured patients. As examples for potential candidates, different approaches including transcriptomics and cytokine analyses have revealed markers that correlate with treatment response and predict cure at very early time points during therapy.[108–110] Genetic markers for drug toxicity, such as certain n-acetyltransferase 2 (NAT2) polymorphisms causing higher susceptibility for isoniazid induced liver toxicity, may also be identified for second-line antituberculosis drugs (e.g. linezolid) by larger-scale genetic analysis.[111] Positron emission tomography–computed tomography (PET-CT) scans can help to identify patients at risk for relapse although the interpretation of metabolically active infiltrations is still difficult.[112]

Table 5 Current standard versus future individualized management of M/XDR-TB

Current standard	Future individualized management	Gaps
Molecular testing of rifampicin drug-resistance testing by XpertMTB/RIF and/or line-probe assays (test for R, H, FQs and SLID)	WGS of the *Mycobacterium tuberculosis* genome identifying drug-resistance-conferring mutations. Initiation of M/XDR-TB therapy on the basis of comprehensive molecular drug-resistance analysis	Establishment of large databases and software to report WGS results including algorithms for drug regimens
Culture-based drug susceptibility testing results reported as 'resistant' vs 'susceptible' (weight-based drug dosing only)	Quantitative *M. tuberculosis* drug susceptibility testing (MICs) for individual drugs	Routine implementation of MIC testing (e.g. MGIT 960/EpiCenter TB eXiST, TREK plates)
	TDM combining the information from MIC testing and serum drug level measurements	Standardized procedures for drug level measurements. Software calculating drug level targets on the basis of MIC/pharmacokinetics
Twenty months for all or shorter course regimen for subset of patients	Biomarker guided individualized therapy duration	Identification and clinical implementation of biomarkers
Clinical identification of AE at the time point of onset	Identifying patients at risk for AE by identifying susceptibility genes/ polymorphisms; quantification of drug–drug interactions	Identifying susceptibility genes for individual drugs, improving software to identify drug–drug interactions of anti-TB drugs
Host-directed therapy not currently an adjunct treatment	Host-directed interventions on the basis of immune-phenotyping by identifying individual needs	Deeper knowledge of host–pathogen interaction
Treatment managed by National TB Programmes	Multidisciplinary team for individual care	Treatment in centres providing specialists for all involved fields

Data taken from Olareu ID *et al.*,[100] with permission. AE, adverse event; FQ, Fluoroquinolones; H, Isoniazid; MIC, minimal inhibitory concentration; R, Rifampicin; SLID, second-line injectables; TDM, therapeutic drug monitoring; WGS, whole genome sequencing; XDR-TB, extensively drug-resistant tuberculosis.

Although the level of evidence was reported as being low, certain patients with localized infiltrations may benefit from surgical interventions after culture conversion.[113,114] Carefully selected patients may also improve their immune system's capability to control the bacteria by host-directed therapeutic interventions.[115] As an example for a host-aimed intervention, vitamin D supplementation has not led to significant improvement of treatment outcomes except for certain subgroups of patients with specific genetic polymorphisms.[116]

PROGRAM GAPS AND RESEARCH NEEDS

Mechanisms that lead to drug resistance in *M. tuberculosis* are the same as for other microorganisms, and follow the principles of evolution that is genetic variation (which always occurs) and selection of strains based on exposure-specific determinants. Indeed, the application of standardized treatment regimens for many years to populations of mycobacteria with variable degrees of antibiotic resistance has led to the selection of drug-resistant mutants. Consequently, and despite the availability of newer drugs, we are once again, after six decades, in an era with constant threat from programmatically incurable TB.[117]

Encouragingly, we are also within a new era of comprehensive, automated and affordable DST by WGS, which will likely have substantial impact on the management of patients with MDR-TB. Tailor-made treatment regimens based on genotypic DST will minimize resistance amplification and likely lead to better treatment outcomes. While this is currently still out of reach for the majority of patients, it is very likely that the technologies will soon become available for the countries that are most affected by the global burden of MDR-TB. Bespoke management packages comprising individualized treatment regimens, individualized dosage of anti-TB drugs, and individualized biomarker-guided duration of therapy will likely optimize treatment responses, and adherence, whilst minimizing adverse events.[119] Alternative approaches and interventions including different routes of drug administration, TDM, use of efflux inhibitors, and more sensitive diagnostics to detect microheteroresistance will also prevent resistance amplification.[18] Novel and alternative repurposed drugs will also become available providing hope for cure from drug-resistant TB for those who have been labelled as untreatable, and will help to optimize therapy of MDR-TB for many affected patients.

Recently, dramatic improvements in treatment outcomes for patients with M/XDR-TB have been reported, especially in treatment regimens based on bedaquiline.[74–76] Under optimal conditions where

patient counselling, psychosocial support, and comprehensive diagnostics and drugs are available, relapse-free cure from MDR-TB may not differ from patients with pan drug-susceptible TB.[96] New drugs need to be used wisely and not as part of standardized treatment regimens otherwise this 'honeymoon phase' will be short-lived because of resistance amplification. Following the licensing of bedaquiline and delamanid, it took less than 2 years for emergence of strains resistant to both bedaqualine and delamanid, which were sequentially administered as part of suboptimal regimens.[118] In routine clinical practice, surgical lung resection may remain the only option for patients who have failed treatment with both bedaquiline- and delamanid-based regimens.

With the emergence of new drugs and novel diagnostic methods, including active case finding strategies, we have an opportunity to reduce the global burden of MDR-TB substantially. By practicing good antibiotic stewardship, including personalizing the treatment of patients with MDR-TB, we will leverage this window of opportunity to the fullest.

Disclosure statements

Dr. Lange reports personal fees from Chiesi, Gilead, Abbvie, MSD, Becton Dickinson, Janssen, Lucane, Novartis and Thermofisher, outside the submitted work. Dr. Chesov reports personal fees from Lucane Pharma, outside the submitted work. Dr. Heyckendorf reports personal fees from Hain, Chiesi, Janssen, Lucane and Gilead, outside the submitted work.

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