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Drug resistant TB – latest developments in epidemiology, diagnostics and management

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ABSTRACT

Aim: The aim of this review is to inform the reader on the latest developments in epidemiology, diagnostics and management.
Epidemiology: Drug-resistant Tuberculosis (DR-TB) continues to be a current global health threat, and is defined by higher morbidity and mortality, sequelae, higher cost and complexity. The WHO classifies drug-resistant TB into 5 categories: isoniazid-resistant TB, rifampicin resistant (RR)-TB and MDR-TB, (TB resistant to isoniazid and rifampicin), pre-extensively drug-resistant TB (pre-XDR-TB) which is MDR-TB with resistance to a fluoroquinolone and finally XDR-TB that is TB resistant to rifampicin, plus any fluoroquinolone, plus at least one further priority A drug (bedaquiline or linezolid). Of 500,000 estimated new cases of RR-TB in 2020, only 157 903 cases are notified. Only about a third of cases are detected and treated annually.
Diagnostics: Recently newer rapid diagnostic methods like the GeneXpert, whole genome sequencing and Myc-TB offer solutions for rapid detection of resistance.
Treatment: The availability of new TB drugs and shorter treatment regimens have been recommended for the management of DR-TB.
Conclusion: Despite advances in diagnostics and treatments we still have to find and treat two thirds of the drug resistant cases that go undetected and therefore go untreated each year. Control of TB and elimination will only occur if cases are detected, diagnosed and treated promptly.

Introduction, Background and Epidemiology

Drug resistant tuberculosis (TB) is a major global health risk, driving the ongoing TB epidemic and increasing the morbidity and mortality of TB worldwide (WHO TB report 2021). Incomplete and insufficient treatment regimens can lead to antimicrobial resistance. Earlier detection requires access to care and rapid diagnostic tools, which may be limited in many areas. Once multidrug-resistant TB (MDR-TB) treatment is started adherence and tolerability may be a challenge. Recent evidence suggests that MDR-TB is an important contribution of Post-TB Lung Disease (PTLD), which is responsible of disability and suffering often requiring rehabilitation (Akkerman et al., 2020r; Migliori et al., 2021, Menzies et al., 2021, Allwood et al., 2020, Hsu et al., 2020; Tiberi et al., 2019, Visca et al., 2020, Visca et al., 2019, Muñoz-Torrico et al., 2020, 2016). Half of lifetime disability-adjusted life-years (DALYs) caused by incident TB is caused by PTLD (Quaife et al., 2020, Mpagama et al., 2021, Duarte et al., 2021).

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Concerns exist on the future deterioration of the MDR-TB epidemic given the important stress COVID-19 caused to TB services (McQuaid et al., 2021, Migliori et al., 2021a,b), resulting in drop of TB case notifications, increased TB deaths (Motta et al., 2020) and decline in TB incidence slowing (WHO Global tuberculosis report 2021). For this reason, the WHO is revising the targets on TB incidence and mortality (WHO Global tuberculosis report 2021).

Drug resistant TB can be classified further depending on sensitivity to antimicrobials. TB may be purely rifampicin resistant (RR-TB), MDR-TB meaning resistance to both isoniazid and rifampicin (WHO 2021). MDR-TB may develop further resistance to any fluoroquinolone, classified as pre-extensively drug-resistant TB (pre-XDR-TB) (WHO 2021). Finally, extensively drug resistant TB (XDR-TB) is the most challenging to treat and has resistant to rifampicin, plus any fluoroquinolone and one further priority A drug (bedaquiline or linezolid)[1]. These highly resistant infections are more difficult to eradicate and carry a worse outcome for those infected.

In 2020, 71% of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, an increase from 2018 and 2019 figures globally (WHO Global tuberculosis report 2021). The total number of people detected with DR-TB decreased by 22% between 2019 and 2020, with 157, 903 new cases of DR-TB detected (132,222 cases of MDR/RR-TB and 25,681 cases of pre-XDR-TB or XDR-TB). Similarly, there was a significant decline in the total number TB case notifications per year between 2019 and 2020, falling by 18% (7.1 million to 5.8 million) (WHO 2021).

The number of people worldwide reported to be enrolled onto treatment for MDR/RR-TB has declined by 15% (177,100 and 150,359 in 2019 and 2020 respectively) (WHO 2021). This reflects that roughly 2 in 3 individuals who develop MDR/RR-TB each year are not receiving appropriate treatment (WHO 2021). This may be influenced not only by antimicrobial resistance, but also availability of drugs, political unrest, and socioeconomic disadvantages in many areas. In addition, the fall in these figures reflects the huge impact of COVID-19 in terms of accessing TB services (WHO 2021). It is important to improve diagnosis and access to care in those countries most affected.

In contrast, the treatment success rate for MDR/RR-TB has been steadily improving. Globally the success rate has increased from 50% to 59% between 2012 and 2018 (the most recent data available (WHO 2021). By the end of 2020, 109 countries were using bedaquiline and 90 countries were using modified regimens to improve uptake, such as shorter courses and prolonged oral courses (WHO 2021). Rifampicin resistance (RR) testing is continuing to increase, with a rate of 93% in the WHO European Region (WHO 2021). Moreover 18 out of 30 MDR/RR-TB burden countries attained coverage of RR of at least 80% (WHO 2021). Testing for fluoroquinolone resistance remains significantly lower at around 50% worldwide (WHO 2021).

Diagnosing drug resistant Tuberculosis

M. tuberculosis is slow-growing despite advances in culture, phenotypic drug susceptibility testing takes weeks to yield a result and is not widely available for the newer drugs. Molecular testing is increasingly the method of choice for diagnosis and assessment of drug-resistant mutations for TB. Several molecular methods have been developed over the past decade. These include the Xpert® MTB/RIF, Ultra, MTB-XDR, BDMax, Line probe assay (LPA), and Loop-mediated isothermal amplification (LAMP) (Ciesielczuk et al., 2020). All of them have different advantages and disadvantages in relation to turnaround time for results, operator expertise required, cost, sensitivity dependent on sample type, and drug resistance mutations which can be detected (Kon, 2021).

While the available molecular tests can provide rapid results for some drug-resistance conferring mutations, they are unable to cover the entire genome and numerous mutations causing resistance. Importantly, in addition to the available molecular tests primarily focussing on identification of rifampicin and isoniazid resistance, there are now some tests that also determine fluoroquinolone resistance, a prerequisite for the shorter all oral regimen.

Whole genome sequencing (WGS) has so far been prohibitive in most settings due to the time, cost and expertise it requires, next generation sequencing is promising as it may offer some solutions to WGS. However, newer molecular tests have been developed to allow for a targeted amplification step, followed by next generation sequencing of the amplicons. One such assay is GenoScreen's Deeplex® Myc-TB, which provides resistance prediction to 15 anti-TB drugs, including first and second-line antibiotics, as well as the more recently introduced bedaquiline, clofazimine and linezolid, with a turnaround time of <48h. In addition, the targeted gene amplification and subsequent sequencing provide genotyping data on the strain of *M. tuberculosis* present, as well as identification of other mycobacterial species (GenosScreen Services: GenoScreen Deeplex Myc-TB 2022).

Other tests that incorporate a targeted amplification step followed by sequencing have also been described recently. Gliddon *et al.* describe targeted isothermal amplification of three regions of the *M. tuberculosis* genome, followed by nanopore sequencing, with excellent sensitivity and specificity for rifampicin and isoniazid resistance. The low cost and fast turnaround time of their workflow may be particularly relevant in resource-limited settings (Gliddon et al., 2021).

A study comparing targeted next generation sequencing directly from sputum samples with the currently used methods of drug resistance testing, including phenotypic testing, has made it a suitable alternative for a range of anti-TB drugs (Kambli 2021).

From the current developments in the diagnosis and identification of mutations of MDR-TB, it is clear that the molecular methods employed are increasingly focusing on platforms that incorporate targeted nucleic acid amplification followed by next generation sequencing. This allows for an increase in mutations which can be identified, while reducing turnaround time and cost of using sequencing to identify mutations conferring antibiotic resistance.

Management of DR-TB

The management of DR-TB has recently been revolutionised by all oral anti-TB drug regimens which are more effective, less toxic, require shorter hospital admissions (if any) and are generally better tolerated, these are likely to have improved adherence and treatment outcomes. Recent systematic reviews and meta-analyses shed further light on safety and effectiveness of new drugs (ref) (Hatami et al., 2022; Nasiri et al., 2022), on which new evidence is accumulating (Furin and Akkerman, 2020; Seung et al., 2020, Vambe et al., 2020, Lachenal et al., 2020, Ndjeka et al., 2020, Sachdeva et al., 2020, Santiago et al., 2020, Bernal O et al., 2020, Zabsonre et al., 2020, Edwards CG et al., 2020, Rutta et al., 2020, Furin et al., 2020, Padayatchi et al., 2020). Further drug resistance and intolerance to TB drugs may limit the effectiveness of drug regimens; together with prior treatment failures, addictions, alcoholism, HIV co-infection and comorbidities rendering clinical management particularly challenging. DR-TB cases require more time and resources for longer duration of treatment, monitoring and follow up, and surgery is not uncommon.

Unfortunately, resistance to bedaquiline is emerging, and is a concern given the efforts to develop and make this new drug available (Ghodousi et al., 2021; Sinha et al., 2022). A recent study in Moldova reported 15% prevalence of bedaquiline resistance in their MDR-TB cohort (Chesov et al., 2021). Emerging bedaquiline resistance is being reported in several countries raising concerns that DST and/or regimens are not sufficiently robust to avoid accrual of

Table 1
TB drug development pipeline by study phase and mechanism of action.

Phase	Drug	Class of compound	Mechanism of action
IV	delamanid	Nitroimidazole	Cell wall synthesis inhibitor, inhibits cell respiration
III	bedaquiline	Diarylquinoline	Inhibits ATP synthase and bacterial respiration
	pretonamid	Nitroimidazole	Cell wall synthesis inhibitor, inhibits cell respiration
IIb	delpazolid (LCB01-0371)	Oxazolidinone	Inhibits protein synthesis (23S ribosome)
IIb	sutezolid (PNU-100480)	Oxazolidinone	Inhibits protein synthesis (23S ribosome)
IIb	SQ109	1,2-ethylene diamine	MmpL3 inhibitor (cell wall synthesis)
IIa	pyrifazimine (TBI-166)	Riminophenazine	Inhibits ion transport and bacterial respiration
IIa	GSK3036656 (GSK-656)	Oxaborole	LeuRS inhibitor (protein synthesis)
IIa	telacebec (Q203)	Imidazopyridine	QcrB (ATP synthesis) and cell repiration inhibitor
IIa	TBA-7371	Azaindole	Inhibits cell wall synthesis (DprE1)
Ib/IIa	BTZ-043	Benzothiazinone	Inhibits cell wall synthesis (DprE1)
Ib/ IIa	macozinone (PBTZ169)	Benzothiazinone	Inhibits cell wall synthesis (DprE1)
Ib/ IIa	OPC-167832	Carbostyril	Inhibits cell wall synthesis (DprE1)
Ib	TBI-223	Oxazolidinone	Inhibits protein synthesis (23S ribosome)
Ia/Ib	TBAJ-587	Diarylquinoline	Inhibits ATP synthase
Ia/Ib	TBAJ-876	Diarylquinoline	Inhibits ATP synthase
Ia/Ib	BVL-GSK098	Amido piperidine	Ethionamide (cell wall synthesis inhibitor) booster
Ia/Ib	GSK2556286 (GSK-286)		Cholesterol catabolism inhibitor
Ia/Ib	SPR720	Benzimidazole	GyrB bacterial DNA synthesis inhibitor

	ATP synthase inhibitor
	Protein synthesis inhibitor
	Cell wall synthesis inhibitor

resistance. New drugs are in clinical development give hope, however given long development times and mechanism of action overlap means there is no certainty of success, (Table 1), therefore we should reinforce how important it is to use our antimicrobial armamentarium appropriately for benefit of future generations.

Good communication with the patient is essential: the diagnosis should be given together with all the information about the disease and what treatments are available, help with adherence and completing treatment should be offered and patient preferences should be taken into account. Contact tracing should be implemented in all TB cases but especially in DR TB cases once diagnosed. Social issues should be addressed, and patients should receive support for these. All drug resistant cases should be discussed at a local, regional or national "consilium" (e.g. the Global TB Network Consilium) Tiberi et al., 2019 and a monitoring system for the frequent and often severe adverse events should be implemented (active Tuberculosis Drug safety monitoring, aDSM) (Borisov et al., 2019).

We will outline and discuss the principles for building a DR-TB regimen based on the latest World Health Organization (WHO) recommendations (WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240007048). Table 2 shows the new WHO MDR-TB drug classification and steps for building a long MDR-TB regimen.

The treatment of DR-TB requires a drug regimen composed of a minimum of 4 drugs to improve efficacy, reduce relapse rates and prevent further development of resistance.

For MDR/RR-TB patients i) with no previous exposure to second-line TB drugs >1 month, and ii) without fluoroquinolone resistance on drug susceptibility testing (DST) and iii) who do not have extensive pulmonary TB disease (cavities) or severe extrapulmonary TB (spinal/CNS/miliary), iv) not pregnant, v) age >6 years the recommended treatment option is the *shorter, all-oral, bedaquiline-containing regimen* with a 4–6-month intensive phase of bedquiline (6 months)-levofloxacin/moxifloxacin-clofazimine-pyrazinamide-ethambutol-high dose isoniazid-ethionamide followed by a 5-month continuation phase of levofloxacin/moxifloxacin-clofazimine-pyrazinamide and ethambutol. As the efficacy, safety and tolerability of the *shorter all oral regimen* are not completely known, any further modification should be performed under strict obligatory operational research conditions.

The intensive phase may be prolonged from 4 to 6 months (pending sputum smear and culture conversion), however not for longer than 6 months. Following documented evidence of conversion, a continuation phase of a fixed duration of 5 months is recommended. All medicines in this regimen should be taken once daily, except bedaquiline which is taken every day for the first 2 weeks followed then thrice weekly for the remaining 22 weeks. Very few modifications are permitted (i.e. replacing prothionamide with ethionamide or levofloxacin with moxifloxacin). Levofloxacin is generally preferred over moxifloxacin for fewer adverse events and less QTc prolongation. As a significant number of patients will develop adverse events from their DR-TB regimen it is important that all adverse events be accurately recorded and managed by aDSM (Borisov 2019): this is especially important given the new

Table 2
New WHO MDR-TB drug classification for building a long MDR-TB regimen.

Priority Drug Groups	TB Drug	
Group A:	levofloxacin *OR*	Lfx
Include all three drugs	moxifloxacin	Mfx
	bedaquiline	Bdq
	linezolid	Lzd
Group B:	clofazimine	Cfz
Add one or both drugs	cycloserine *OR*	Cs
	terizidone	Trd
Group C:	ethambutol	E
Add to complete the regimen and when drugs from Groups A and B cannot be used either due to resistance, toxicity or tolerability.	delamanid	Dlm
	pyrazinamide	Z
	imipenem–cilastatin *OR*	Ipm–Cln
	meropenem *WITH* amoxicillin/clavulanate	Mpm
	amikacin	Am
	(*OR* streptomycin)	(S)
	ethionamide *OR*	Eto
	prothionamide	Pto
	p-aminosalicylic acid	PAS

drugs and regimens that have been repurposed or given the accelerated regulatory approvals.

DR-TB patients with extensive pulmonary disease, severe forms of extrapulmonary TB, additional resistance to fluoroquinolones or those who have been exposed to treatment with second-line medicines for more than 1 month will require an *individualised longer regimen*. The design of this regimen is aided through a prioritised grouping of drugs recommended by the WHO (see Table), using the following key principle of including at least three Group A agents (i.e. bedaquiline, levofloxacin/moxifloxacin and linezolid) and at least one Group B agent (cycloserine/terizidone and/or clofazimine). Of note the American Thoracic Society/European Respiratory Society guidelines recommend a minimum of 5 drugs, the difference with the WHO guidelines being related to the specific perspective of high income/low TB incidence countries (Migliori et al., IJTLD 2020). If through resistance or tolerability a regimen cannot be composed of group A or B drugs alone, then Group C drugs may be added to the regimen.

The duration of the *individualised longer regimen* is 18 months.

The 6-9 month long bedaquiline, pretonamid and linezolid treatment regimen (or BPaL) may be used under operational research conditions for MDR/RR-TB/pre-XDR-TB patients who have not had prior exposure to bedaquiline or linezolid (defined as <2 weeks). BPaL use requires aDSM as further evidence on efficacy and safety is required before it can be implemented more widely. The WHO has however stated that if the design of an effective regimen based on existing recommendations is not possible, then the BPaL regimen may be considered as a last resort under programmatic conditions (outside operational research), with the caveat that the patient would require higher standards of monitoring for response to treatment and adverse events, as well as existing provision of effective patient support (Migliori et al., IJTLD 2020). Clinical judgment is key taking into consideration expected efficacy, safety, patient preference, availability of DST, patient treatment history, severity and site of the disease. Again a discussion in a local, regional or national consilium is recommended (Tiberi et al., 2019).

A patient-centred approach should be provided. Patients should receive comprehensive health education, counselling and share decisions regarding their health as well as understand the importance of treatment adherence (WHO 2020, Nahid 2019). Language and cultural barriers should be addressed, provision of acceptable and convenient directly observed or video observed therapy (VOT) should also be considered. All treatment should be delivered together with patient-centred care and support, informed consent where necessary, principles of good clinical practice, active TB drug safety monitoring and management, and regular assessments for treatment effectiveness. Patients may require social and holistic provision. Treatment adherence interventions like home visits/messages/call and/or digital medication monitor, material support to patient, nutritional and/or psychological support, and drug and alcohol services may be offered to those on TB treatment.

More evidence is emerging on the frequency of PTLD problems requiring pulmonary rehabilitation (Migliori et al., IJTLD 2021, Menzies et al., 2021, Allwood et al., 2020, Tiberi et al., 2019, Visca et al., 2020, Visca et al., 2019, Muñoz-Torrico et al., 2020). Up to 50% of patients develop post TB-treatment; obstructive, restrictive or mixed-mode functional damages, with reduced effort tolerance at the 6-minute walking test and hampered quality of life (Tiberi et al., 2019, Allwood et al., 2021, Visca D, et al., 2020). The proportion is up to 90% in MDR-TB patients, due to longer treatment, which is more likely to have sub-optimal effectiveness because of the extensive drug resistant patterns often involved (Silva et al., 2022). One of the main reasons MDR TB patients have higher rate of lung damage is due to delayed diagnosis and delayed effective treatment administration.

Patients with DR-TB should ideally be treated in clinic, and admission to hospital if possible avoided (Migliori et. al.. ERJ 2019, Migliori et al., Pulmonology 2021).

Conclusion

DR-TB is a threat and an obstacle to global TB elimination efforts. It is clear that despite recent efforts we are failing to diagnose and treat 300.000 people a year with this form of TB. More attention and investment in diagnostics, pharmaceuticals and TB services are needed to ramp up detection rates and improve access to treatment and better control this pandemic. DST is essential for both shorter and longer regimens and more needs to be done to ensure that programmes have timely access to reliable DST. Drug-susceptible TB trials are investigating the options to reduce the treatment duration down to 4 months, for MDR-TB the research efforts are devoted to the possibility to reduce it to 6-9 months. New WHO recommendations are bridging the implementation gap and facilitate access to treatment with all oral, shorter, less toxic treatment regimens. MDR-TB only requires 6-9 months of treatment for the majority of cases. BPaL regimen may be used through operational research. New drug trials evaluating several combinations of drugs and regimens are underway to find the shortest, most effective and better tolerated treatments.

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Conflict of Interest

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