· Review ·

Therapeutic developments for multidrug-resistant tuberculosis

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Abstract

Tuberculosis (TB) remains the leading infectious disease globally, with 1.25 million deaths and 10.8 million new cases in 2023, including 400,000 rifampin-resistant/multidrug-resistant TB (RR/MDR-TB) cases. RR/MDR-TB accounts for 15–20% of TB-related deaths and poses significant economic and treatment challenges due to low cure rates (68%) and high costs. The heterogeneity of *Mycobacterium tuberculosis* infections complicates therapy, requiring prolonged regimens and multidrug combinations. Advances in treatment include repurposed antibiotics (e.g., linezolid), re-engineered oxazolidinones (e.g., sutezolid), and improved bedaquiline analogues addressing resistance and toxicity. Future strategies emphasize shorter, accessible regimens, reliable drug susceptibility testing (DST), and effective management of treatment failures. Targeted next-generation sequencing (tNGS) has improved resistance detection but remains limited for some second-line drugs. Phenotypic DST is still indispensable. Clinicians must address emerging drug resistance and develop salvage regimens while reducing disease transmission through public health measures. These approaches are critical to improving RR/MDR-TB outcomes globally.

Keywords: Tuberculosis, drug resistance, bedaquiline, drug susceptibility testing, next-generation sequencing

Tuberculosis (TB) remains the leading cause of death linked to an infectious disease worldwide, with approximately 1.25 million deaths in 2023. In addition, there were 10,800,000 new cases diagnosed and 400,000 of these were rifampin-resistant/multidrug-resistant TB (RR/MDR-TB) cases. However, the cure rate for RR/MDR-TB is only approximately 68% [1].

Although RR/MDR-TB accounts for approximately 5% of the total number of TB cases, mortality is substantially higher, with RR/MDR-TB cases accounting for 15%–20% of TB deaths globally. RR/MDR-TB is also very costly to manage, with substantial negative economic consequences for both patients and countries. According to national surveys conducted between 2016 and 2022, 82% of patients and households with drug-resistant TB faced catastrophic costs related to the illness, compared with 47% of those with drug-susceptible disease [2].

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Bacteriological background of MDR-TB treatment

MDR and extensively drug-resistant (XDR) TB cases are associated with different treatment options, duration, tolerability, and cure rates. Why is such an intensive treatment required to cure TB while other pulmonary infections are successfully treated with a single antibiotic for 1–2 weeks? Despite being associated with a single causative agent, *Mycobacterium tuberculosis* (Mtb), the disease is increasingly recognized as a heterogeneous infection sometimes referred to as "polymicrobial". Bacterial subpopulations consist of replicating, dormant (slow-growing or non-growing) and reactivated bacteria, which are present both extracellularly and within various immune cells.

The pathological hallmarks of pulmonary TB are immune cell aggregates called granulomas, which follow different progression trajectories and are collectively called lung lesions [3]. As they expand, damaging inflammatory processes can lead to several events: necrosis from the granuloma center outwards and fusion of the necrotic granuloma with the airways, bronchogenic spread of necrotic material containing high bacterial burden, tissue destruction and formation of open cavities or lesions filled with necrotic debris. A spectrum of lesion types can be found within a single host, creating microniches and various environmental conditions to which the infectious agent must adapt to survive, and which in turn results in differential susceptibility to chemotherapy and immune control [4-5]. To cure such a heterogeneous disease, current treatment for drug-susceptible TB requires four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) taken daily for 2 months during the intensive phase, followed by a continuation phase during which rifampicin and isoniazid are taken daily for 4 months.

The microbiological activity of drugs should be accorded greater importance when a regimen for drug-resistant TB is composed (Table 1). The activity of anti-TB drugs differs: some have relatively high bactericidal activity, while others show greater sterilizing activity, but very few drugs show both [5]. Moreover, most second-line drugs are less effective than first-line drugs.

Some of the bacteria may be located in lesions that antibiotics can reach via the vascular system, whereas others may be sequestered in niches that are poorly accessible to drugs and crucial immune factors, particu-

Table 1. The bactericidal and sterilizing activity of anti-tuberculosis drugs.

Group	Drug	Bactericidal Sterilizing activity	Sterilizing activity
Group A	Bedaquiline	high	high
	Fluoquinolone	high	high
	linezolid	high	low
Group B	Cycloserine	moderate	low?
	Clofazimine	low	high
	Amikacin	high	low
	Delamanid	high	high ?
	Imipenem-cilastin	high	low ?
Group C	Meropenem		
	Prothionamide	moderated/high	low
	P-aminosalicylic acid	low	low
	Pyrazinamid	low	high
	Ethambutol	low	low

larly the necrotic core of lesions and cavities [4]. The relative proportions of infected cells can change in response to host immune responses and antibiotic therapy. Consequently, the range of phenotypic antibiotic susceptibility in a patient can be extreme. In addition, antibiotic-induced drug tolerance can form a relapsing reservoir of bacteria. These factors collectively cause issues with poor drug access and drug action, which is the signature of TB disease and one major reason for the protracted and poorly effective treatment.

New drug development pipelines

New drug development strategies rely on "old" but clinically validated targets as well as novel mechanisms of action. This combination mitigates attrition of de novo drug discovery and optimizes chances of success.

Repurposing approved antibiotics

Moxifloxacin, a fourth-generation fluoroquinolone, is one of the pillars of MDR-TB treatment. It is included in many treatment-shortening MDR-TB clinical trials. Although less frequently used, levofloxacin plays a similar role in MDR-TB therapy. Linezolid, the first oxazolidinone antibacterial agent, is part of a new 6-month, three-drug regimen recommended by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) for the treatment of MDR- and XDR-TB [6].

Re-engineering antibiotic classes

Following the success of linezolid treatment in patients with XDR-TB who do not respond to chemotherapies, and the recent approval of a 6-month course of bedaquiline–pretomanid–linezolid for MDR-TB, re-engineered oxazolidinones with improved tolerability profiles have gained traction. Their increased tolerability is associated with increased potency, decreased mitochondrial protein synthesis inhibition or both (Table 2) [5].

Three members of the class (TBI-223, delpazolid and sutezolid) have emerged among numerous oxazolidinone optimization programs in recent years and are in clinical development for TB. TBI-223 shows attractive attributes compared with linezolid, including reduced mitochondrial protein synthesis inhibition and reduced bone marrow progenitor cell toxicity both in vitro and in animal models. Sutezolid has two favorable properties: reduced mitochondrial protein synthesis inhibition and an abundant active metabolite that complements the activity of the parent compound against intracellular and extracellular bacteria [5].

Bedaquiline has been an exemplary drug against MDR- and XDR-TB but has two important liabilities. First, its extreme hydrophobic and cationic amphiphile properties lead to extensive tissue distribution, phospholipidosis and long terminal half-life. Lingering concentrations have been measured in plasma and at the site of disease for several months after the end of therapy, conditions that favor the development of resistance. Second, bedaquiline inhibits the cardiac potassium human ether-a-go-go (hERG) channel, resulting in QTc interval prolongation in humans. The second-generation analogues TBAJ-587 and TBAJ-876 are less hydrophobic, 5- to 10-fold more potent and do not inhibit hERG at the highest concentration tested. Likewise, WX-081 (sudapyridine) does not inhibit hERG or cause QT prolongation in vivo and delivers efficacy comparable with that of bedaquiline in mice. These three agents are rapidly progressing through clinical development and collectively address the major liabilities of bedaquiline [5].

Identifying novel chemical scaffolds and their targets

Candidates that target cell wall biosynthesis pathways are strongly represented in the anti-TB drug development pipeline. Interestingly, whole Mtb cell screens have revealed two highly promiscuous cell wall drug targets: mycobacterial membrane protein large 3 (MmpL3), which is involved in export of the mycolic acid component trehalose monomycolate, and the decaprenyl-phosphoribose epimerase DprE1, which is required for arabinogalactan synthesis. Three DprE1 inhibitors belonging to three different chemical scaffolds are in clinical development for TB: OPC-167832 (quabodepistat), TBA-7371 and BTZ-043 (Table 2). There is only one MmpL3 inhibitor in clinical development, SQ109, but numerous chemically diverse series are in various stages of lead optimization and preclinical development.

Development of RR/MDR-TB regimen

Instead of regimens involving injectable agents, the WHO recommends short-course (9 or 6 months), all-oral regimens for the treatment of RR/MDR-TB. For patients who are not eligible participants for short-course treatment, a long-course regimen lasting at least 18 months is recommended [6].

6-month all-oral regimen

Following on from the Nix-TB and ZeNix-TB trials, investigators conducted an open-label, phase 2–3, multicenter, randomized, controlled, non-inferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of RR/MDR-TB [7-9]. Participants were aged 15 years or older and had RR pulmonary TB. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) were compared with 9- to 20-month standard-care regimens. The primary outcome was an unfavorable status at 72 weeks after randomization. In the modified intention-to-treat analysis, 11% of patients in the BPaLM group and 48% of those in the standard-care group had a primary-outcome event (risk difference, −37%; 96.6% confidence interval [CI], −53 to −22). In the per-protocol analysis, 4% of patients in the BPaLM group and 12% of those in the standard-care group had a primary-outcome event (risk difference, −9%; 96.6% CI, −22 to 4). In the as-treated population, the incidence of ≥grade 3 or serious adverse events was lower in the BPaLM group than in the standard-care group (19% vs 59%, respectively) [9].

Authors concluded that in patients with RR pulmonary TB, a 24-week, all-oral regimen was noninferior to the accepted standard-care treatment, and presented a better safety profile. Based on this trial, the WHO suggested the use of a 6-month treatment regimen comprising BPaLM, rather than the 9- or 18-month regimens, in patients with RR/MDR-TB (conditional recommendation, with very low certainty of evidence) [6]. This recommendation applies to patients who have pulmonary or extrapulmonary TB [except TB involving the central nervous system, osteoarticular TB and disseminated (miliary) TB]; are aged 14 years or older; have no known allergy to any of the BPaLM component drugs; have no evidence of resistance to bedaquiline, linezolid, delamanid or pretomanid, and have not been previously exposed to any of the component drugs for ≥4 weeks (if exposed to the component drugs for ≥4 weeks, the patient may receive BPaLM if resistance has been definitively ruled out); are living with or without human immunodeficiency virus (HIV); do not have XDR-TB according to the 2021 WHO definitions; are not pregnant or breastfeeding and are willing to use effective contraception, in the case of premenopausal women.

Table 2. New anti-tuberculosis drugs in development.

Candidate	Mechanism	Trial design	Sponsor	Study identifier
TBI-2233		Phase I (SAD and MAD) to evaluate safety, tolerability and PK in healthy subjects	TB Alliance	NCT03758612, NCT04865536
Sutezolid	targeting the ribosome	Phase IIb to identify the optimal dose in combination with bedaquiline delamanid and moxifloxacin for 3 months	Michael Hölscher, University of Munich	NCT03959566
Delpazolid		Phase IIb dose finding to evaluate exposure-response relationship in combination with bedaquiline, delamanid and moxifloxacin for 4 months	LegoChem Biosciences	NCT04550832
Sanfetrinem cilexetil	targeting the peptidoglycan biosynthesis	Phase IIa dose finding to evaluate the EBA, safety and tolerability, including in combination with rifampicin and/or amoxicillin-clavulanate	TASK Applied Science	NCT05388448
TBI-166 (pyrifazimine)	inhibitor of redox cycling yielding toxic reactive oxygen species	Phase IIa to evaluate EBA, safety and tolerability	Beijing Chest Hospital	NCT04670120
TBAJ-587		Phase I (SAD and MAD) to evaluate safety,tolerability and PK in healthy adults	TB Alliance	NCT04890535
TBAJ-876	targeting the ATP synthase	Phase I (SAD and MAD) to evaluate safety,tolerability and PK in healthy adults	TB Alliance	NCT04493671
WX-081 (sudapyridine)		Phase IIa to evaluate EBA, safety and tolerability in patients with drug-susceptible and drug-resistant TB	Shanghai Jiatan Pharmatech Co.Ltd	NCT04608955
OPC-167832 (quabodepistat)		Phase IIb/c dose finding to evaluate safety and efficacy in combination with delamanid and bedaquiline for 4 months in patients with drug-susceptible disease	Otsuka Pharmaceutical	NCT05221502
TBA-7371	Inhibit DprE1(arabinogalactan biosynthesis)	Phase IIa to evaluate safety, EBA and PK in adults with rifampicin-sensitive TB	Bill & Melinda Gates Medical Research	NCT04176250
BTZ-043		Phase Ib/IIa to evaluate safety, tolerability, PK, drug-drug interaction and EBA in patients with drug-susceptible TB	Michael Hölscher (University of Munic)	NCT04044001
GSK3036656	targeting leucyl-tRNA synthetase	Phase lla dose escalation to evaluate EBA, safety and tolerability in subjects with rifampicin-susceptible TB	GlaxoSmithKline	NCT03557281
SQ109	MmpL3 (mycolic acid biosynthesis) and proton motive force	Phase llb to assess efficacy, safety and tolerability in combination with a standard regimen for MADR-TB treatment	Sequella,Inc.	NA
Q203 (telacebec)	cytochrome bcc complex (respiratory chain)	Phase lla dose ranging to evaluate EBA, safety,tolerability and PK in patients with drug-susceptible TB	QQurient Co	NNCT03563599
BVL-GSK098 (alpibectir)	promotes intrabacterial conversion of ethionamide prodrug	Phase lla to evaluate EBA, safety and tolerability of ethionamide alone and in combination with BVL-GSK098 in patients with drug-susceptible TB	TASK Applied Science	NCT05473195
GSK2556286	adenylyl cyclase (cholesterol catabolism)	Phase I (SAD and MAD) to evaluate safety, tolerability, PK and food effect in healthy adults	GlaxoSmithKline	NCT04472897
GSK839	tryptophan synthetase TrpAB	Preclinical	GlaxoSmithKline	NA
DDD02049209	lysyl-tRNA synthetase	Preclinical	University of Dundee	NA
MBX-4888A (spectinamide 1810)	semi-synthetic spectinamycin analogue targeting the ribosome	Preclinical	Microbiotix,Richard Lee	NA

Abbreviations: SAD, single-ascending dose; MAD, multiple ascending dose.

Pretomanid is unavailable in some countries, which has hampered the use of 6-month regimens recommended in these countries. The BEAT-TB regimen in which delamanid is given in combination with bedaquiline, linezolid and clofazimine shows a 91% treatment success rate and offers a fluoroquinolone-free regimen for individuals unable to receive this category of medication because of resistance or intolerance [10]. The endTB clinical trial is a phase 3, multi-site, randomized, controlled trial testing multiple 6- to 9-month regimens for RR-TB with various combinations of bedaquiline, delamanid, levofloxacin, linezolid and/or clofazimine (Table 3) [11].

9-month all-oral regimen

Results from the STREAM stage 2 trial were published

Table 3. Clinical trials of drug regimens for rifampicin-resistant (RR)/multidrug-resistant (MDR)-tuberculosis (TB).

Indication	Duration (months)	Trial acronym or sponsor	Agents	Primary end point	Study identifier
DS-and MDR-TB	4 (DS)6(MDR)	SimpliciTB (phase IIc)	BPaMZ	Time to culture conversion over 8 weeks, rate of relapse 12 and 24 months after end of therapy with BPaMZ compared with HRZE; outcome: BPaMZ achieves treatment shortening, but side effects precluded completion in-10% of patients	NCT03338621
MDR-TB	6	Opti-Q or TBTC study 32 (phase II)	Levofloxacin,OBR	Dose-finding study to evaluate efficacy,PK and tolerability of increasing levofloxacin doses in combination with OBR in patients with MDR-TB	NCT01918397
MDR-TB	9	endTB(phase III)	5 study arms comprising 4 or 5 of the following agents: bedaquiline,delamanid, clofazimine,linezolid, moxifloxacin or levofloxacin, pyrazinamide	Randomized,controlled,non-inferiority open-label clinical trial evaluating efficacy and safety of five 9-month treatment regimens containing recently approved drugs for MDR-TB compared with current standard of care for MDR-TB	NCT02754765
XDR-TB	6-9	endTB-Q (phase III)	BeDeCLi	Randomized, controlled, non-inferiority open-label trial evaluating efficacy of BeDeCLi for 6 or 10 months according to disease phenotype,compared with WHO-recommended treatment	NCT03896685
MDR-and XDR-TB	6-9	BEAT-TB (phase III)	Bedaquiline,delamanid, clofazimine,linezolid, levofloxacin for MDR-TB; bedaquiline,delamanid, clofazimine,linezolid for XDR-TB	Design and outcome measures similar to end TB-Q with secondary end points as PK-PD models of drug and metabolite exposure versus efficacy and toxicity	NCT04062201
DS-TB,RR/ MDR-TB	2-4	DBOS PBOS (phase IIb/c)	Bedaquiline, OPC-167832, sutezolid,pretomanid, delamanid	Phase IIb/c, multi-arm,2-stage, duration randomized trial of efficacy and safety for 2-4 months with bedaquiline, OPC-167832 and sutezolid, plus either pretomanid or delamanid	NCT05971602

Abbreviations: RR, rifampicin-resistant; MDR, multidrug-resistant ;TB, tuberculosis; DS, drug susceptibility.

in 2022. This trial involved participants aged ≥15 years with RR-TB without fluoroquinolone or aminoglycoside resistance [12]. All participants (n = 588) were randomly assigned to the 2011 WHO regimen, a 9-month control regimen, a 9-month oral regimen with bedaquiline or a 6-month regimen with bedaquiline and 8 weeks of a second-line injectable. The primary outcome was favorable status at 76 weeks. Of the 517 participants in the modified intention-to-treat population, 133/187 (71%) in the control regimen group and 162/196 (83%) in the oral regimen group had a favorable outcome, a difference of 11.0% (95% CI 2.9–19.0), adjusted for HIV status and randomization protocol (P<0.0001 for non-inferiority). At 76 weeks, 108/222 (53%) participants in the control regimen group and 106/211 (50%) in the oral regimen group had experienced an adverse event of grade 3 or 4. In addition, five (2%) participants on the control regimen and seven (3%) on the oral regimen had died. Hearing loss (Brock grade 3 or 4) was more frequent in participants on the control regimen than in those on the oral regimen (18 [9%] vs four [2%], p=0.0015). Authors concluded that the 9-month oral regimen containing bedaquiline had superior efficacy when compared with the 9-month injectable-containing regimen, and was associated with fewer cases of hearing loss [12].

Based on this trial, the WHO recommended the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with RR/MDR-TB and in whom resistance to fluoroquinolones has been excluded [6]. The 9-month all-oral regimen comprises bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear-positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).

The 9-month all-oral regimen may be offered to patients with RR/MDR-TB without resistance to fluoroquinolones. In addition, extensive pulmonary TB and severe extrapulmonary TB should be ruled out. Extensive pulmonary TB disease refers to the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged <15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. Severe extrapulmonary TB refers to the presence of miliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged <15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe [6].

Only some patients with MDR-TB are eligible for the 9-month all-oral regimen, including those with no documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen); with no exposure to previous treatment with bedaquiline, fluoroquinolones, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen) for >1 month (if prior drug exposure duration is >1 month, patients may still receive this regimen if resistance to the specific medicine with such exposure has been ruled out); with no extensive or severe TB disease and no severe extrapulmonary TB; living with or without HIV; who are pregnant or breastfeeding (these patients may be considered eligible for the linezolid-containing 9-month regimen, but they should not receive the 9-month regimen containing ethionamide); and children and adults without bacteriological confirmation of TB or resistance patterns but who require RR/MDR-TB treatment based on

clinical signs and symptoms of TB (including radiological findings) and history of contact with someone with confirmed RR/MDR-TB (these patients may be eligible for this regimen based on the drug resistance profile of the isolate obtained from the most likely index case) [6].

Long-course regimens

A longer regimen (18–20 months) is expected to be used in the following situations: severe extrapulmonary TB; additional resistance to key medicines in the BPaLM or BPaL regimens (without moxifloxacin) or the 9-month all-oral regimen; lack of response to shorter treatment regimens; drug intolerance to the component medicines of the BPaLM/BPaL regimens or the 9-month all-oral regimen; pregnant and lactating women who would not benefit from the 9-month all-oral regimen owing to certain clinical conditions; and children aged <14 years who cannot be treated with BPaLM/BpaL or the 9-month regimen [6].

Long-course regimens can be personalized based on a hierarchical categorization of second-line medications according to their efficacy and safety. Group A drugs are associated with improved treatment outcomes and decreased mortality, group B drugs with improved outcomes but a less clear impact on mortality, and group C drugs with varying outcomes [13]. Treatment is personalized to design regimens based on pathogen-specific genotypic data and the likelihood of adverse effects, including patient preferences, thus implementing a personalized medicine and patient-centered approach.

For patients with RR/MDR-TB, all three group A agents and at least one group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two group A agents are used, both group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, group C agents are added to complete it. If bedaquiline is unavailable, more than one group C drug should be included in the regimen.

The future of RR/MDR-TB treatment

Compared with treatment of community-acquired pneumonia, current RR/MDR-TB treatment is far more satisfactory because of its limited cure rates and long duration. In addition, there is lack of effective way to approach treatment failure cases due to more new drugs keeping in pipeline. A better strategy to solve the problem of drug-resistant TB should include the following:

A shorter course of regimen with greater accessibility

Although the WHO recommends the BPaLM regimen to treat RR/MDR-TB, pretomanid is unavailable in some countries. Recently, BEAT-TB, which includes bedaquiline, delamanid, linezolid and clofazimine, was recommended by the WHO to treat MDR-TB and pre-XDR-TB. Although all four drugs are available in many countries, this new treatment regimen is required for ≥6 months. A shorter treatment regimen remains to be investigated. Clinicians should also be aware of emerging drug resistance, which will occur following the natural laws of evolution. Even with good treatment adherence, 10%-15% of MDR-TB isolates developed resistance to fluoroquinolones [14].

More reliable drug susceptibility testing

Drug susceptibility testing (DST) is indispensable for MDR-TB treatment, but the reliability and reproducibility of DST for some anti-TB drugs is limited. DST for fluoroquinolones is strongly encouraged in people

with RR/MDR-TB, as results of these tests should guide the decision on whether moxifloxacin can be retained or should be dropped from the BPaLM regimen. However, the sensitivity of genotypic DST for fluoroquinolones is approximately 87% [15], which means one sixth of fluoroquinolone resistance cases will be missed by genotypic DST. It is worth noting that genotypic DST is the gold standard for DST for some drugs. For example, sequencing of the RNA polymerase β subunit (rpoB) gene and the pyrazinamidase/nicotinamidase (pncA) gene is the reference method for DST of rifampin and pyrazinamide, respectively [16,17]. Based on this, the WHO recommends expanding the availability of genotypic DST. However, reliable commercial genomic DST is only available for some drugs, including isoniazid, rifampin and fluoroquinolones. Most second-line anti-TB drugs lack reliable genomic DST as "hot spot" for resistance to these drugs is to be investigated.

In 2024, the WHO recommended the use of targeted next-generation sequencing (tNGS) to diagnose drug-resistant TB [18]. tNGS tests can interrogate entire genes to identify specific mutations associated with resistance and may provide improved accuracy compared with other WHO-recommended rapid diagnostic tests [18]. In addition, new tNGS tests can detect resistance to new and repurposed drugs not currently included in any other molecular assays. tNGS tests are defined as tests that use massively parallel sequencing to detect resistance to TB drugs, starting from a processed clinical sample and ending with an end-user report that relates detected Mtb mutations to the presence (or absence) of drug resistance, based on the interpretation of a standard catalog of mutations. First-in-class products include Deeplex® Myc-TB (GenoScreen) for rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, bedaquiline, linezolid, clofazimine, amikacin and streptomycin [18].

However, some second-line drugs, including delamanid, P-aminosalicylic acid, pretomanid and imipinem-cilastatin/meropenem, lack reliable genotypic DST. In addition, the sensitivity of genotypic DST for some second-line drugs, including bedaquiline, linezolid and clofazimine, is limited. Therefore, phenotypic DST remains indispensable for the diagnosis and treatment of MDR-TB. Phenotypic DST tests are important for almost all anti-TB drugs, except P-aminosalicylic acid and imipinem-cilastatin/meropenem, for which phenotypic DST is both unreproducible and unreliable.

Effective management of patients with treatment failure

Every new anti-infectious drug leads to new drug-resistant bacteria. It is not surprising that new regimens will be associated with new resistance. New drug-resistant Mtb have already emerged since the introduction of bedaquiline, pretomanid and delamanid. Clinicians should develop strategies for new regimen treatment failures, including identifying salvage regimens to treat these patients. In the case of new regimen failures, there are limited effective drug options available for patients. In addition to considering DST results, clinicians should choose drugs that patients have never used before (most of these drugs will belong to group B and C). For patients with localized lesions, a multi-disciplinary team should determine the possibility of operating. It is also important to decrease disease transmission. More serious drug-resistant bacteria cause a greater public health threat. Even with effective treatment strategies, patients will remain infectious for long periods of time and should be taught healthy practices to reduce disease transmission. Public health systems should pay attention to this problem.

Outlook

In the 1950s, a regimen containing isoniazid, strep-

tomycin and P-aminosalicylic acid lasting 18 months was recommended to treat drug-susceptible TB. It has taken 20 years from 1950s to 1970s to shorten the duration of drug-susceptible TB treatment from 18 to 6 months, with the inclusion of sterilizing drugs such as rifampin and pyrazinamide in the chemotherapy regimen. New treatment regimens have allowed TB prevalence and incidence rates to decrease. However, TB has re-emerged as a serious public health threat with the spread of drug resistance since the 1990s. In the past decades, great progress has been made for the treatment of drug-resistant TB with the development of new regimens and new drugs. However, compared with other infectious diseases such as community-acquired pneumonia, the treatment of drug-resistant TB remains protracted and cure rates are far from satisfactory. More progress is urgently required in the field of TB to face the threat of a drug-resistant TB pandemic.

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Author Contributions

Hongfei Duan wrote the manuscript.

Conflicts of Interests

The author declares no conflict of interest.

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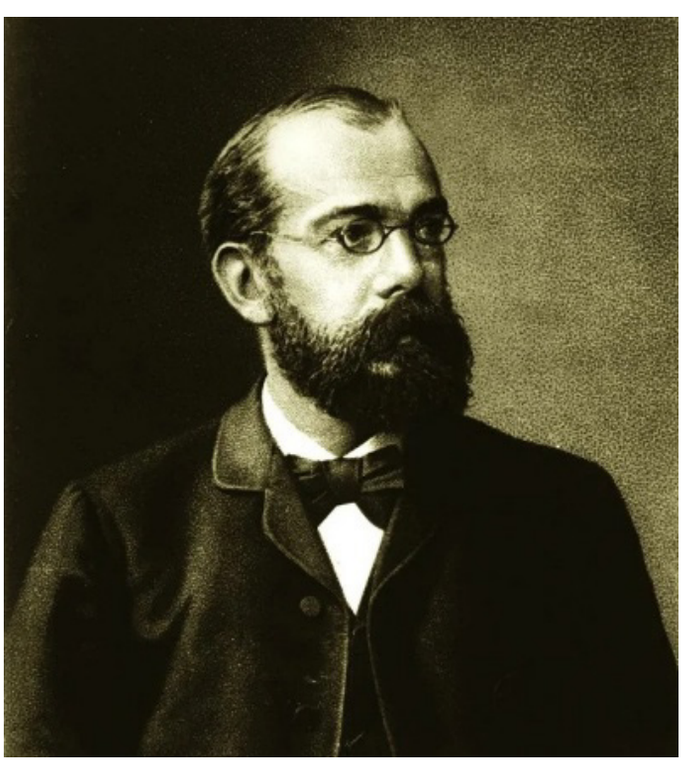

Dr. Robert Koch (1843-1910). Born in Germany. In 1866, he graduated from University of Göttingen and obtained a Ph.D degree in Medicine. He was the first one, proving that a specific microorganism was the causative pathogen of a specific disease and that a specific bacterium caused a specific disease. In 1890, he discovered tuberculin. In 1905, Koch was awarded the Nobel Prize in Physiology and Medicine for his achievement in infectious diseases.