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Updated considerations in the diagnosis and management of tuberculosis infection and disease: integrating the latest evidence-based strategies

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Abstract

Introduction: Tuberculosis (TB) is a leading infectious cause of global morbidity and mortality, affecting nearly a quarter of the human population and accounting for over 10 million deaths each year. Over the past several decades, TB incidence and mortality have gradually declined, but 2021 marked a threatening reversal of this trend highlighting the importance of accurate diagnosis and effective treatment of all forms of TB.

Areas Covered: This review summarizes advances in TB diagnostics, addresses the treatment of people with TB infection and TB disease including recent evidence for treatment regimens for drug-susceptible and drug-resistant TB, and draws attention to special considerations in children and during pregnancy.

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Declaration of interest

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Expert Opinion: Improvements in diagnosis and management of TB have expanded the available options for TB control. Molecular testing has enhanced the detection of TB disease, but better diagnostics are still needed, particularly for certain populations such as children. Novel treatment regimens have shortened treatment and improved outcomes for people with TB. However, important questions remain regarding the optimal management of TB. Work must continue to ensure the potential of the latest developments is realized for all people affected by TB.

Keywords

Tuberculosis; diagnostics; TB preventive therapy; multi-drug resistant TB

1. Introduction

The bacterial etiology of tuberculosis (TB) consists of organisms in the *Mycobacterium tuberculosis* complex. These bacteria are transmitted from person-to-person via the airborne route. People with TB disease of the respiratory system expel airborne droplet nuclei (1–5 micron in size) containing these bacteria when they cough, sneeze, sing, or talk. When a susceptible person inhales air containing these droplet nuclei, infection may result. Transmission is likely to occur in poorly ventilated environments and following several hours or days of exposure. The clinical spectrum of TB ranges from asymptomatic infection to severe, life-threatening disseminated disease [1]. In 2014, Houben et al. estimated that approximately 1.7 billion people, or 23% of the global population, harbor latent TB infection (TBI) [2]. Most recently, the World Health Organization (WHO) reported that 10.6 million people (134/100,000 population) had TB disease in 2021. This represented an increase of 4.5% from 10.1 million in 2020, reflecting a reversal following several years of slow decline in global TB incidence. Fifteen percent of incident TB cases occurred in children < 15 years of age, and it is estimated that over 200,000 pregnant women have TB annually [3]. In addition, WHO reported a global estimate of 450,000 incident cases of rifampicin- or multi-drug resistant (RR/MDR) TB in 2021, reflecting an increase of 3.1% from 437,000 in 2020; up to 25,000 of these cases are estimated to occur among children [4]. During 2021, an estimated 1.6 million people died of TB; this included 187,000 among people living with HIV (PLWH). Over 90% of pediatric TB deaths occurred among children who did not receive treatment, highlighting TB diagnostic challenges in this vulnerable population [5]. The year 2021 marked the first estimated global increase in TB mortality in decades; higher TB burden mortality has been associated with disruptions in health care services linked to the COVID-19 pandemic [6].

This report will focus on advances in diagnostic modalities, the treatment of people with TBI and TB disease, and draw attention to special considerations in children and during pregnancy.

Modern day treatment of TB with antimicrobial agents dates to 1943, when Albert Schatz, Elizabeth Bugie, and Selman Waxman reported the isolation of streptomycin from *Streptomyces griseus* [7]. This agent was found to have broad spectrum activity against Gram-positive and Gram-negative bacteria, and later observed to inhibit growth

of *Mycobacterium tuberculosis (Mtb)*. By 1945 the benefit of streptomycin against TB was established in clinical trials and soon combined with para-amino salicylic acid (PAS), also discovered in 1945. With the introduction of isoniazid (INH) in 1952, clinical trials for people with TB included the treatment regimen consisting of INH, SM, and PAS. The U.S. Public Health Service (USPHS) and British Medical Research Council (BMRC) launched a series of randomized controlled clinical trials over the next three decades which incorporated newer anti-TB agents, such as ethambutol (EMB), pyrazinamide (PZA), and rifampicin (RIF) to establish the safety and efficacy of modern-day recommended six-month regimens consisting of INH, PZA, RIF, and EMB for people with drug-susceptible TB disease [8]. Another lesson gained from these various trials was the crucial role for drug combinations with activity against TB to attain cure and prevent the selection of drug-resistant strains of *Mtb*. In more recent years, the introduction and demonstrated effectiveness of other repurposed and new drugs with anti-TB activity – such as rifapentine, linezolid, fluoroquinolones, clofazimine, bedaquiline, delamanid, and pretomanid have demonstrated the safety and efficacy of new combination regimens for the treatment of people with drug-susceptible and drug-resistant forms of TB [9]. The following sections will elaborate on the latest developments and extant recommendations for the optimal treatment of people with TB.

2. Diagnosis of tuberculosis

Despite recent advancements in the diagnosis of TB disease, there remain many diagnostic challenges as highlighted by the 2022 WHO Global TB Report [6]. Alarmingly, there is a wide gap of >4 million persons between the number of people estimated to have TB and those newly diagnosed with disease. Additionally, only 63% of diagnosed cases worldwide were confirmed bacteriologically; there has been limited worldwide roll-out of rapid molecular diagnostic tests, and only an estimated 1 in 3 people with MDR TB were diagnosed [6]. The large diagnostic gap has been exacerbated by the COVID-19 pandemic and furthermore stresses the need for improved strategies and technologies to enhance TB diagnosis. A fully comprehensive review of TB diagnosis including the discussion of implementation and scale up of TB infection and disease testing, strategies for enhancing active case finding approaches, and use of cell free DNA or serum antibodies for TB detection are beyond the scope of this review. We focus our discussion on newly developed, implemented, or in progress advances in TB diagnostic technologies with most of the emphasis on detection of people with TB disease and the current status of detecting people with TBI.

2.1. Tuberculosis infection (TBI)

A key pillar in the strategy to end TB is scaling up TB preventive therapy (TPT) among the large global reservoir of persons with TB infection to prevent later development of active TB. While substantial progress has been made providing TPT among persons living with HIV, treatment of TB infection remains limited in other high-risk groups and only 12.5 million of a targeted 30 million persons with TB infection were treated during 2018–2021 [6]. While TPT administration is multifaceted, a key component is the accurate diagnosis of TB infection.

The most widely used test for diagnosing TBI remains the tuberculin skin test (TST) which was developed over 100 years ago [10]. To overcome the limitations of using purified protein derivative (PPD), which contains a heterogenous mixture of mycobacterial antigens, blood-based interferon-gamma release assays (IGRAs) using more specific *Mtb* antigens, ESAT-6 and CFP-10, were developed and are now recommended for use in all settings [11]. However, the use of IGRAs may be limited due to the requirement for laboratory equipment and reagents, trained laboratory staff, and higher cost than TST. Additionally, the most commonly utilized IGRAs, including the QFT-Gold In-Tube and T-SPOT.TB assays as well as the TST, have a low positive predictive value for progression to active TB (around 3–4%) [12,13]. Higher cutoff levels have potential to improve the predictive value of IGRAs, as demonstrated by a study of infants with IFN-γ > 4.0 IU/mL (PPV 16%) [14]. Overall lower sensitivity of IGRAs in young children, pregnant women and immunocompromised individuals highlights the need for more robust tests in these populations [15–18]. Current efforts to enhance TB infection testing are centered on enhancing IGRAs or skin-based testing as described below.

A recent landscape analysis identified 15 *in vitro* tests in development or already commercialized for detecting TB infection, with 13 being whole-blood IGRAs and 14 using ESAT-6 and CFP-10 with or without additional antigens [19]. Most of these assays rely on similar principles to the approved QuantiFERON-TB Gold Plus (QFT-Plus; QIAGEN, Venlo, The Netherlands) assay in which the amount of IFN-γ is measured after whole blood stimulation with TB antigens, with enhancements made to automate or simplify the test read-out process including one assay that employs a lateral flow immunoassay (LFA) method. While such tests would be welcomed, they still rely on measuring a host response and are anticipated to provide minimal advantages over existing IGRAs.

A novel approach being used by one manufacturer (R-Biopharma, Pfungstadt, Germany) is the development of enzyme-linked immunosorbent assay (ELISA) and LFA-based tests to measure IFN-γ induced protein 10 (IP-10) secretion after blood stimulation with CFP-10 and ESAT-6 (12). Expression of IP-10 has been reported to be much higher than IFN-γ and hence it may have increased analytic accuracy for TB infection (13). Another innovative approach is demonstrated by the GBTsol Latent TB test kit (Glory Biotechnologies Corp., Republic of Korea) which identifies TB infection by directly measuring antigen specific T-cells through capture of major histocompatibility complex (MHC)-peptide complexes within one hour of blood collection (14). While these novel approaches offer promise, no performance data have been released to date.

In their 2022 guidance on tests for TB infection, WHO approved three additional TSTs including the Cy-TB (Serum Institute of India), Diaskintest (Generium, Russian Federation), and the C-TST (Anhui Zhifei Longcom, China) tests for use; all of which utilize ESAT6-CFP10 antigens and employ the Mantoux method for placing and reading. These skin tests offer the theoretical advantage of being more specific than PPD-based skin testing and available results to date for the Diaskintest and Cy-TB tests show they are safe and have similar efficacy to IGRA testing [20–22]. They still require reading after 48–72 hours and no data are yet available on their ability to predict progression to active TB.

While enhancement in existing IGRA and TST based testing methods are a valuable development and offer operational advantages, there is an urgent need to develop tests that can better predict TB and those that can employ direct molecular detection of *Mtb*. Building on promising results demonstrating that a host transcriptomic signature can reliably predict risk of active tuberculosis, the CORTIS trial used a reduced 11 gene transcriptomic signature (RISK11) to guide TPT administration [23,24]. While those with a RISK11 signature were more likely to have prevalent TB or incident TB within 3 months, TPT did not reduce risk of TB disease [24]. Regarding *Mtb* molecular testing, a recent study found that *Mtb* DNA can be detected in blood harvested stem cells expressing the CD34 surface marker and furthermore that the prevalence of *Mtb* DNA detected decreased after isoniazid-based therapy [25]. Another study detected cell-free Mtb DNA in blood of adults and children with TB with high sensitivity >85% [26]. These innovative studies open new areas of investigation for TB infection diagnostics and treatment and provide hope that soon we will have methods to better predict progression to TB disease, which is needed to scale up TPT to persons who need treatment the most. Recent comprehensive reviews of TB infection testing including a framework for evaluation have been published [19,27,28].

2.2. Tuberculosis disease

While most cases of TB disease globally are still detected using smear microscopy and/or mycobacterial culture which are fraught with numerous limitations, the explosion of molecular technologies and increased activity in test development provides promise for enhancing rapid case detection and hope to eliminate diagnosis as being the weakest link in the TB cascade of care. We utilize the WHO guidance on target product profiles for diagnostics and the recent TB Treatment Action Group pipeline report to frame our discussion below [29,30].

2.2.1. Point of care (POC) tests for TB screening and triage—There is a critical need to develop better screening tests beyond symptom assessment for community TB screening, including the detection of subclinical TB disease to determine who needs further testing and to help prevent transmission. We highlight new radiology-based tools supported in the WHO 2021 guidance on TB screening and additional innovative approaches in the development phase.

In 2021, WHO endorsed use of computer-aided diagnosis (CAD) software for automated reading of digital chest radiographs for screening and triage of pulmonary TB for persons ≥ 15 years of age [31]. Since this endorsement, multiple commercial CAD programs have become available, and the use of such artificial intelligence (AI) technology offers the potential advantages of increased consistency and accuracy of reads including in settings without trained radiologists. One large study in primary health clinics in South Africa found that CAD use with digital x-ray followed by molecular testing and culture demonstrated a similar yield of active TB diagnosis screening but with a much lower number needed to test (NNT) versus symptom screening (9.7 vs. 17.8 NNT respectively) [32]. A recent meta-analysis of three CAD programs among self-referred persons found a similar overall sensitivity for detecting active TB (~90%) with performance each program varying by HIV and sputum smear microscopy status [33]. The development of ultraportable x-rays

will facilitate the implementation of CAD digital x-ray use for TB screening and triage but available data to date highlights that CAD performance is variable and CAD scoring thresholds may need to be calibrated to specific settings. Also, available data in children are insufficient to recommend its use in this population.

The potential role of AI for TB diagnosis may extend beyond x-ray to powering cough-based apps and digital stethoscopes to identify cough patterns and vibroacoustic biosignatures, respectively, that can help identify persons needing further TB testing [34]. Preliminary data from cough-based apps have found a sensitivity of > 90% for active TB and furthermore such a tool would offer home-based screening via a mobile phone [30].

Another exciting development is the use of host immune response signatures as a triage test for TB. The Cepheid Xpert MTB Host Response (HR) was developed to generate a "TB Score" based on mRNA expression of 3 host genes using fingerpick blood samples. In the first clinical study conducted it was able to discriminate between pulmonary TB and other respiratory diseases with high accuracy (AUC of 0.94) and at a sensitivity of 90%; it had a specificity of 86% in TB detection. Results were not affected by HIV status and/or geographical location [35]. This test and other similar tests measuring the host immune response to TB including the RISK6 gene signature test (QuantuMDx) and the TAM-TB assay (Beckman Coulter) offer great potential as a non-sputum triage test with promise in hard-to-diagnose populations including children, persons living with HIV (PLWH), and extra pulmonary TB (EPT) [30,36].

2.2.2. Point of care sputum tests to replace smear microscopy—The development of rapid molecular testing for *Mtb* has been a landmark achievement in TB diagnostics and has provided accurate test replacements for insensitive sputum smear microscopy testing. However, challenges remain to optimize impact of rapid molecular testing, including limited implementation and scale-up and need for regional laboratory infrastructure [6].

The WHO endorsement of the Xpert MTB/RIF Assay (Cepheid) in 2010 changed the face of TB diagnostics and initiated an era of diagnostic development. The high performance of the Xpert MTB/RIF test including a pooled sensitivity of 85% for MTB and 96% for rifampicin resistance with ≥ 98% specificity among adults offered an accurate and much needed replacement for smear microscopy. While Xpert sensitivity is lower among children who have paucibacillary disease (pooled sensitivity for sputum 65%), use of multiple samples and combined testing of alternate sample types (gastric aspirates, nasopharyngeal aspirates, urine and/or stool) can enhance sensitivity [37,38]. The next generation version, the Xpert Ultra, which was recommended for use in 2017, increased sensitivity of *Mtb* detection to 88% in adults (73% in children) with a slightly lower specificity (96% in adults, 97% in children), thought to be due detection of non-viable bacteria [38,39]. The Xpert Ultra test also has higher sensitivity in detecting TB meningitis, lymphadenitis, and pleural effusion versus smear microscopy [40]. Testing stool with the Xpert Ultra has also been found to have improved sensitivity compared to the standard Xpert for diagnosing pulmonary TB in children [41]. Limitations of the Xpert test are that it is run on the GeneXpert platform which requires a computer, continuous power supply, annual maintenance, and relatively

high cost. Additionally, it only tests for rifampicin resistance and, while it has been shown to result in a faster time to TB treatment, its impact on clinical outcomes is unclear [42]. An Xpert TB prototype cartridge has been developed and found to have moderate sensitivity for the detection of isoniazid, fluoroquinolones, and injectable agents used in the treatment of drug-resistant TB [43]; however, with recent global emphasis on using fully oral (enteral) regimens for MDR TB, the role of testing for resistance against injectable agents and their potential impact will likely be limited. To increase access of the Xpert system to peripheral care centers, the GeneXpert Omni platform was developed as a battery-powered unit that can be used for POC testing and is expected to be released soon [44].

Line probe assays (LPA) including the Genotype MTBDR*plus* (Haine Lifesciences-Bruker) have been endorsed for over a decade and offer an accurate method to detect *Mtb* and drug resistance to isoniazid and rifampicin. Importantly, use of the LPA has been shown to increase time to optimal treatment regimen initiation and decrease time to sputum culture conversion among persons with MDR TB [45]. Later generation Genotype assays were developed to enhance sensitivity and the MTBDR*sl* detects resistance to fluoroquinolones and injectable agents.

More affordable devices meant to be used in peripheral health care settings have also been endorsed by WHO, including the Loopamp MTBC assay and Truenat assays. Loop-mediated isothermal amplification (LAMP) uses an isothermal PCR amplification technique that requires minimal laboratory equipment and while endorsed as replacement to smear microscopy since 2016, has been underutilized to date. The Truenat assays including Truenat MTB Plus and Truenat MTB-RIF Dx (Molbio Diagnostics) run on the Truelab platform which uses a chip-based, micro real time PCR technique that can provide results in one hour [46]. Initial results are comparable to the Xpert Ultra and the WHO has a conditional recommendation to use Truenat as an initial test for *Mtb* and rifampicin resistance detection.

Beyond the above-mentioned endorsed tests, there are many more nucleic acid amplification (NAAT) tests in development including both 1) high throughput devices meant for centralized labs and 2) point of care NAATs meant for field, remote, and/or low resource settings [44]. A wide array of available molecular-based TB tests will help ensure we have the right diagnostic tools for all settings. Further needs include moving away from a one-disease based diagnostic approach to combining detection of multiple infectious diseases into one multiplex assay and to conduct rigorous studies on the implementation and clinical impact of molecular TB diagnostics.

2.2.3. Point of care non-sputum tests for diagnosis of TB disease—Given the challenges with obtaining sputum samples in many patients and to help in diagnosing EPTB, a non-sputum-based test has been a long sought-after goal in TB diagnostics. Advances in urine lipoarabinomannan (LAM) detection, oral sample testing and aerosolized breath samples are exciting innovations described below.

Urine LAM: The Determine TB Lam test (Abbot) which detects *Mtb* LAM in the urine is the first and only test approved by WHO for the diagnosis of TB disease. While implementation has been associated with decreased mortality among immunosuppressed

PLWH, the test has low sensitivity and is not approved for use in persons without HIV. To enhance LAM detection in the urine, Fujifilm developed the SILVAMP TB Lam, which uses silver particles to bind LAM and amplify detection still using an LFA platform [47]. A diagnostic accuracy meta-analysis found that the SILVAMP had >2 times the sensitivity to detect TB among PLWH in both inpatient and outpatient settings [48]. An additional study showed promise in detecting TB among persons without HIV [49]. While initial results are encouraging, there are limited data on persons not infected with HIV, technical challenges to implementing the SILVAMP-TB as a POC test, and recent results demonstrating variability in test performance by test lot. To further enhance urine LAM testing, multiple companies are working on "next generation" versions incorporating new methods such as urine concentration and for signal amplification [30]. This will potentially enable the use of urine-based LAM testing to be useful for all TB suspects including HIV negative persons and those with EPTB.

Oral samples: The use of tongue swab and saliva samples offer a much easier to obtain sample possibly even for home self-collection for the diagnosis of pulmonary TB. After validating and optimizing a tongue swab sample collection protocol, Andama and colleagues evaluated the performance of Xpert Ultra testing on two combined tongue samples among 183 adult TB suspects. Compared to Xpert Ultra testing on sputum, they found a sensitivity of 78% and when compared to a microbiological reference standard, a sensitivity of 72% while retaining a specificity of 100% [50]. A recent study using Xpert Ultra testing on a single saliva sample among confirmed TB patients found a high sensitivity of 90% with a lower sensitivity among PLWH (71%) [51]. Both studies found a semiquantitative Xpert Ultra grade lower in tongue and saliva samples than sputum samples. Further work to optimize oral sample testing will help define the role of such testing which may include a benefit to being used in combination with other tests such as urine LAM [52].

Breath Testing: The most well-developed breath-based testing methods utilize molecular testing of face mask obtained samples. An early study demonstrated the proof of principle that Mtb could be detected from mask sampling and this same group conducted a comprehensive study among patients with known TB and persons with presumed TB [53,54]. In the latter study, a face mask containing gelatin membrane sampling matrix was worn for eight 1-hour intervals over a 24-hour period. After sampling, masks were dissolved in solution until DNA extraction and then PCR testing were performed. Among known TB patients most face mask samples were positive (86%) while among 8 patients diagnosed with TB prospectively, 6 were identified exclusively with face mask sampling [54]. These promising data indicate that face mask sampling may be a useful non-sputum sample and a valuable approach to detect subclinical disease and during mass testing. Additional studies using the detection of volatile organic compounds via an electronic nose or other device offer potentially promising alternative methods to use breath-based testing for TB detection [55].

2.3. Rapid drug-susceptibility testing to be used at/near point of care

As described above, the implementation of rapid molecular testing platforms have revolutionized TB diagnosis and rapid detection of drug resistance to INH, RIF and

fluoroquinolones but a major limitation is the rapid detection of resistance to additional key drugs used to treat drug-resistant disease, including bedaquiline, delamanid and pretomanid, and linezolid [56]. Recent advancements in genomic sequencing have moved next generation sequencing closer to the patient, including 1) an enhanced understanding of genetic mutations associated with phenotypic resistance and 2) the development of rapid, efficient high throughput sequencing platforms.

Performing whole genome sequencing on a collection of > 10,000 geographically diverse *Mtb* isolates, the CRyPTIC consortium found that genotypic mutations correctly predicted resistance to RIF (97%), INH (98%), EMB (95%), and PZA (91%) in most cases [57]. Further work by the CRyPTIC consortium has validated microtiter plates for phenotypic susceptibility testing including for bedaquiline and delamanid, and subsequently through a genome-wide association study of their *Mtb* collection identified resistance mutations associated with 13 anti-tuberculosis drugs including bedaquiline, linezolid, and delamanid [58,59]. In conjunction, WHO developed a TB sequencing database in 2019 called ReSeqTB to curate, standardize, and unify phenotypic and genotypic *Mtb* database resulting in a recent and first release of a catalogue of *Mtb* mutations and their association with drug resistance [60,61]. This critical work has laid the foundation for the development of targeted next-generation sequencing (tNGS) testing for *Mtb*.

The tNGS method offers an attractive approach to move forward with sequencing based *Mtb* diagnostics which can be performed directly on clinical samples and offer a more feasible option than WGS for comprehensive, fast, affordable, and informative testing of sputum samples [62]. In tNGS, specific areas of the *Mtb* genome are targeted to identify genetic mutations known to be associated with drug resistance. Results are expected within 1–2 days of sample collection, thus providing key data to rapidly inform optimal regimen design and potentially improve clinical outcomes. Currently, only the Deeplex Myc-TB tNGS assay is commercially available and WHO is expected to review data in 2023. Further data are expected soon from the UNITAID and FIND supported Seq & Treat project which is evaluating tNGS platforms in the form of end-to-end solutions from sample prep and processing to bioinformatics and data reporting. A major limitation to most tNGS approaches is that due to technical and equipment requirements they will be placed in central labs. The Oxford MinION nanopore sequencer is one portable device that offers promise to bring tNGS closer to patients [63].

2.4. Summary of diagnostics for TB

The above advances in approved and in-pipeline diagnostic test platforms for TB will greatly improve the toolkit for diagnosing active TB disease including the rapid detection of drug resistance. Further understanding of *Mtb* biology and pathogenesis and implementation science approaches to optimize roll out and impact of new testing methods will be required to continue to move the pendulum forward in TB diagnostics.

3. Treatment of drug-susceptible TB

3.1. Treatment regimens for drug-susceptible TB

For people with drug-susceptible TB (DS TB), standard treatment has long been a 6-month regimen consisting of INH, RIF, PZA, and EMB. This regimen (abbreviated 2HRZE/4HR) is administered as 2 months of all four drugs in an intensive phase, followed by 4 months of INH and RIF in a continuation phase (Table 1) [64]. As noted above, the evidence for this regimen is primarily drawn from several randomized clinical trials conducted by the BMRC and USPHS. A key component of successful treatment of people with DS TB has included ensuring adherence to treatment throughout the full course of therapy. Past studies by BMRC showed that the use of directly observed therapy (DOT) enabled outpatient care with excellent treatment outcomes. For several years, guidelines from WHO and CDC/ATS/IDSA recommended the use of DOT as standard of care for people with TB [65,66]. The use of DOT relied on trained nurses or ancillary health personnel, including trained community health workers or family members, to observe the ingestion of prescribed anti-TB drugs throughout the course of therapy.

In more recent years, international consensus has moved away from strict reliance on DOT in favor of patient-centered support and adherence promotion measures that rely on the use of incentives and enablers, video DOT, medication monitoring devices, and education about the importance of adhering to prescribed treatment [67]. These latter approaches were more widely adopted during COVID-19 associated physical distancing and lockdown mitigation measures [68].

Anti-TB drugs are recommended to be given daily and in fixed-dose combination (FDC) tablets when possible. Notably, systematic reviews have not found a difference in clinical outcomes with FDC dosing compared to separate formulations and the pharmacokinetics of FDCs require further research [69]. Better understanding the pharmacokinetics of these drugs remain important in the context of assuring adequate dosing, particularly that of rifampicin given its propensity for common drug-drug interactions and important sterilizing activity.

While the standard 6-month 2HRZE/4HR regimen is safe and globally has been consistently associated with approximately 85% successful outcomes, the relatively long duration of therapy has made shorter regimens for DS TB the subject of investigation for decades. Previous trials of several shorter regimens including fluoroquinolones did not demonstrate non-inferiority compared to the standard regimen [70–72]. However, a recent randomized controlled open-label trial (TB Trials Consortium Study 31/A5349) found a 4-month regimen including moxifloxacin and rifapentine (8 weeks of daily INH, rifapentine, moxifloxacin, and PZA followed by 9 weeks of daily INH, rifapentine, and moxifloxacin, abbreviated 2HPMZ/2HPM) non-inferior to 2HRZE/4HR with a primary endpoint of TB-free survival at 12 months [73]. The non-inferiority margin was 6.6%, and this trial included children 12 years of age and older and PLWH with CD4 count > 100 cells/mm^3. Of note, this regimen is not recommended for people with extrapulmonary tuberculosis, history of QT prolongation, concurrent use of QT-prolonging drugs or other medications with known drug-drug interactions [74]. In contrast, a regimen only substituting rifapentine for

rifampicin did not demonstrate non-inferiority to 2HRZE/4HR. Results are pending from a trial of another strategy for shortening treatment duration to 4 months by increasing the rifampicin dose (RIFASHORT, NCT02581527). The TRUNCATE-TB trial evaluated novel treatment strategies compared to standard therapy for DS TB. Participants randomized to the "TRUNCATE Strategy" received novel 5-drug regimens for 8–12 weeks and were carefully monitored for TB relapse. If relapse occurred, participants were started on standard therapy. By design, most trial participants were not at high risk for TB relapse. This strategy with a regimen of bedaquiline, linezolid, INH, PZA, and EMB was non-inferior to standard of care for the primary outcome of death, ongoing treatment, or active disease at 96 weeks. At week 96, the mean TB treatment duration in the standard of care arm was 180 days compared to 84 days in the bedaquiline-linezolid arm. Only 2 (1%) of participants had acquired bedaquiline resistance [75].

Among children with non-severe TB, WHO and CDC recently endorsed a 4-month treatment-shortening regimen informed by results of the SHINE trial [76,77]. The SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children) was a non-inferiority, randomized controlled trial comparing a 4-month regimen (2 months HRZ+/−E followed by 2 months HR) with the standard 6-month regimen among children aged 16 and below. Enrolled participants had symptomatic TB that was "non-severe", defined as smear-negative peripheral lymph node TB, intrathoracic lymph node TB without airway obstruction, uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs without a miliary pattern. Sixteen (2.8%) versus 18 (3.1%) children reached the primary efficacy outcome (treatment failure) in the 16- versus 24-week arms respectively and there were no appreciable differences in adverse events by arm. Of note, children and adolescents with significant co-morbidities including HIV or severe acute malnutrition were not eligible for treatment shortening. The need to assess TB severity using chest radiography may limit implementation in resource-limited settings where access to chest radiographs and trained pediatric radiologists for interpretation may be compromised [76].

Overall, shorter regimens and treatment strategies for both adults and children have potential barriers to implementation, including the cost of new drugs relative to standard drugs, increased pill burden, the need for drug susceptibility testing for new or repurposed drugs, and lack of data in extrapulmonary TB or among PLWH with CD4 count < 100 cells/mm^3. Risk-based treatment strategies such as those developed in TRUNCATE-TB will require new resources and mindset for TB programs where a "one size fits all" approach with standard therapy has been the norm [78]. However, they hold great promise for improving treatment for people with DS-TB.

3.2. Special situations in DS TB

While TB can affect many body sites, most forms of extrapulmonary DS TB are treated with the standard 6-month regimen, though some groups recommend longer duration for osteoarticular TB [64]. Another notable exception is TB of the central nervous system (CNS), which usually requires 9–12 months of therapy, with the inclusion of adjunctive corticosteroids for tuberculous meningitis (TBM) [79]. TBM is the most lethal form of TB

disease, particularly among PLWH who experience mortality of approximately 40% [80]. TBM is difficult to treat in part due to inadequate or unknown drug delivery to the CNS. For drug-susceptible TBM, standard first-line drugs are recommended, though open questions include whether these drugs achieve adequate CNS concentrations or if increased dosing or additional agents may improve outcomes [81]. Higher doses of rifampicin for children (30 mg/kg) in the TBM-KIDS trial was associated with improved neurocognitive outcomes [82]. Shorter duration of therapy for TBM in children is being explored in the SURE trial (Short Intensive Treatment for Children with TB Meningitis), which will evaluate 6 vs 12-month treatment outcomes using daily high dose rifampicin, isoniazid, pyrazinamide and levofloxacin (ISRCTN40829906). Fluoroquinolones or other drugs are added as part of an intensified regimen in adult TBM studies, with promising outcomes to date and evidence of high concentrations in cerebrospinal fluid [83]. Additional investigation is needed regarding appropriate dosing and duration of corticosteroids for TBM. It is critical to note that for PWLH, while the standard recommendation is for early antiretroviral therapy (ART) initiation within 2 weeks of initiating TB treatment, this is associated with adverse events in HIV-TBM. If there is clinical concern for TBM, delay of ART initiation by several weeks may be considered depending on the feasibility of close monitoring for adverse events. There are important drug-drug interactions between ART and DS TB therapy, particularly the rifamycins, that impact ART selection, timing, and dosing but are beyond the scope of this review [84,85].

3.3. TB infection

TB preventive therapy to prevent development of active TB disease has relied on INH monotherapy for 6 to 9 months (6H or 9H) [86]. These regimens are limited by the long duration of therapy, hepatotoxicity, and poor birth outcomes when used in pregnancy [87,88]. Several short course regimens are now available, supported by evidence for their efficacy, safety, and improved completion rates compared to 6H/9H. INH and RIF daily for 3 months (3HR) has efficacy similar to 6H according to a network meta-analysis [89]. RIF monotherapy daily for 4 months (4R) was found to be non-inferior to 9H in an open label trial [90]. A weekly regimen of INH and rifapentine administered as twelve doses over three months (3HP) resulted in similar success and higher completion rate compared to INH monotherapy in several clinical trials including both adults and children [91–93]. While definitive safety data for 3HP use in pregnancy are lacking, a PK study did not find evidence to support the need for dose adjustments in pregnancy and no adverse events were noted [94]. One trial evaluated a regimen of INH and rifapentine given daily under direct observation for 1 month (1HP) in PLWH with noninferiority shown for safety and efficacy [95]. This regimen has a conditional recommendation from WHO as an alternative regimen for TBI, and upcoming trials will evaluate 1HP in children (IMPAACT 2024) and pregnant people (NCT05122026) [96,97]. Individual regimen selection depends on drug-drug interactions including ART for PLWH, drug availability or cost (particularly for rifapentine), comorbid conditions, and baseline risk for toxicity.

3.4 Summary of treatment of DS TB

Recent trials have provided evidence supporting shorter regimens for DS TB treatment (4 months and possibly shorter) and TB preventive therapy (3–4 months). While these options

have great potential to improve DS TB treatment, additional development and evaluation of these regimens is needed to move them closer to all people with DS TB. Operational clinical studies must assess the long-term efficacy of this shortened regimen in people with extensive (e.g., bilateral cavitary lung disease) pulmonary TB as well as in other people with DS-TB who remain culture positive at the end of the first two months of treatment. Future approaches to the optimal use of shortened regimens for people with DS TB may require an improved understanding of individual drug pharmacokinetics, immune response, and bacterial burden. Knowledge of these variables could serve to inform a more personalized approach to drug dosing and duration of effective therapeutic regimens.

4. Treatment of Drug-resistant TB

4.1. Newer drugs for drug-resistant TB:

Only 1 in 3 of the 450,000 people diagnosed annually with RR/MDR TB were started on appropriate treatment regimens, despite remarkable recent advances in DR TB therapy. Over the last decade, the newer TB drugs bedaquiline, delamanid, and pretomanid and repurposed drugs linezolid, clofazimine, and fluoroquinolones have revolutionized the treatment of people with drug-resistant TB. These newer agents advanced TB therapeutic options from “better deaf than dead” injectable-based regimens with a high pill burden to 3–4 drug 6-month all-oral regimens (see Table 2 for a brief history of WHO-endorsed RR/MDR TB regimens).

Bedaquiline is a mycobacterial ATP synthase inhibitor and was approved by the U.S. Food and Drug Administration (FDA) in 2012 – the first new antituberculosis drug to be approved in 40 years [98]. Bedaquiline has modest and delayed bactericidal activity but is a potent sterilizing agent [99,100]. Bactericidal activity is the ability to decrease the quantity of viable bacilli and sterilizing activity is the ability to kill dormant bacilli, responsible for TB relapse. In a landmark phase 2b trial, patients with smear-positive MDR TB were randomized to an optimized background regimen with and without bedaquiline over 24 weeks [101]. Bedaquiline significantly reduced time to culture conversion and increased culture conversion rates, paving the way for a new era in RR/MDR treatment.

Delamanid and pretomanid are nitroimidazoles (the same drug class as metronidazole) that are the latest new antituberculosis drugs approved (2014 and 2019, respectively) [102]. They inhibit mycolic acid synthesis and are mycobacterial respiratory poisons acting against dormant organisms. Both drugs have relatively modest bactericidal activity but their activity against dormant organisms lead to potent sterilizing activity [99,103–105]. In a phase 2 trial, patients with MDR TB were randomized to an optimized background regimen with and without delamanid over 8 weeks [106]. Delamanid significantly increased culture conversion rates and trial participants were offered the option to enter an open-label study and receive delamanid for an additional total 24 weeks in addition to an optimized background regimen [107]. Participants who received ≥ 24 weeks of delamanid had a higher rate of favorable outcomes compared to those who received ≤ 8 weeks of delamanid (74.5% *vs* 55%, respectively). Pretomanid was developed under the Critical Pathway to TB Drug Regimens, where a novel drug is tested early on as part of a multidrug regimens and efficacy clinical trials evaluate the novel multidrug regimen instead of the novel drug alone (in this case

bedaquiline, pretomanid, and linezolid (BPaL) as described in the regimens section below) [108]. To our knowledge, head-to-head delamanid and pretomanid comparisons are lacking [102]. From a programmatic standpoint, pretomanid offers the advantage of once daily dosing compared to delamanid twice daily dosing.

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis and was approved by FDA in 2000 for Gram-positive bacterial infections [109]. Linezolid has modest bactericidal and sterilizing activity but has been part of most recently tested RR/MDR TB regimens with high cure rates [110]. In a landmark trial published in 2012, people with pulmonary XDR TB and no response to available antimycobacterial agents in the past 6 months were randomized to linezolid 600 mg daily immediately or 2 months post-randomization without changes in the background regimen [111]. Four-month sputum culture conversion rates were significantly higher in the group that started linezolid earlier (79% *vs* 35%) and most patients (87%) achieved sputum culture conversion six months after starting linezolid.

Clofazimine is a riminophenazine dye that was first described in 1957; however, its antimycobacterial mechanism of action remains unclear [112,113]. Clofazimine has very little bactericidal activity [114] but has sterilizing activity, particularly when co-administered with other sterilizing drugs [115]. Clofazimine concentrates in macrophages and appears to retain activity against “persisters”, *Mtb* populations that become antibiotic non-susceptible during treatment in the absence of resistance-associated mutations [116]. Early clofazimine trials for TB were disappointing in comparison to isoniazid and streptomycin, and thus clofazimine was mostly discarded as a TB drug [113]. Clofazimine was revived as a promising anti-TB agent following the 2010 report on the “Bangladesh regimen” [117]. In this observational study enrolling people with MDR TB, clofazimine was part of a 9-month regimen that led to an 87.9% cure rate, which was much shorter than contemporary WHO-approved regimens and revolutionary at the time.

The quinolone drug class was first introduced in the 1960’s with nalidixic acid, an agent with spectrum limited to gram negative bacteria mainly used to treat urinary tract infections [118]. Quinolones are bactericidal agents that block bacterial DNA replication by targeting bacterial gyrase and topoisomerase IV enzymes [119]. The fluoroquinolones gatifloxacin, moxifloxacin, and high-dose levofloxacin (1 gm) have higher *Mtb* bactericidal activity comparable to isoniazid (the most bactericidal first-line drug) [120–122]. Moxifloxacin and high-dose levofloxacin (1 gm) have sterilizing activity, although moxifloxacin likely has superior sterilizing activity compared to levofloxacin (data on gatifloxacin sterilizing activity are lacking) [123–125]. There are differences between quinolones in their anti-mycobacterial activity [126,127]. Moxifloxacin and levofloxacin are currently recommended while ciprofloxacin and ofloxacin are not recommended for TB therapy (of note gatifloxacin is no longer available due to concerns for dysglycemia). Observational studies published in 2000–2001 [128,129] suggested quinolones increased MDR TB cure rates and gatifloxacin was part of the 9-month “Bangladesh regimen” described above [117].

The introduction of these novel drugs led to a re-evaluation of drugs used for MDR-TB. In the absence of high-quality clinical trial data comparing all possible regimens, an individual

patient data meta-analysis investigated the associations between individual drugs and number of drugs with pulmonary MDR TB outcomes [130]. The dataset contained outcomes for > 12,000 people from 25 countries treated for pulmonary MDR TB between 2009 and 2016 and the finding led to the reclassification of MDR-TB drugs and redefinition of XDR-TB (Tables 3, 4) [130–132]. Based on these data, bedaquiline, linezolid, moxifloxacin, and levofloxacin were classified as group A drugs, and clofazimine and cycloserine (or terizidone) were classified as group B drugs (see Table 4 for group C drugs). Additionally, pre-XDR TB is now defined as resistance to rifampin, isoniazid, and fluoroquinolones and XDR TB is now defined as pre-XDR plus resistance to bedaquiline and/or linezolid (Table 3).

4.2. Data supporting current pulmonary MDR-TB regimens and selected recent clinical trials

The 2022 WHO Drug-Resistant TB guidelines recommend three regimens for people with pulmonary MDR TB (Table 1) [133]. These regimens include (1) an 18–20-month regimen based on data from the above-mentioned individual patient data meta-analysis [130], (2) 9–12-month all-oral bedaquiline-containing regimen largely based on the South African National Tuberculosis Programme experience, and (3) 6-month all-oral 3–4-drug BPaL (bedaquiline, pretomanid, and linezolid) with and without moxifloxacin based on the Nix [134], Ze-Nix [135], and PRACTECAL [136] clinical trials. Here, we will present data from selected pulmonary MDR-TB clinical trials. Of note, between-trial comparisons are challenging because outcome definitions were not uniform.

The 18–20-month regimen (known as “longer regimen”) should include at least 4 drugs, preferably all three group A drug and one group B drug (Table 4). In case of suspected resistance or intolerance to > 1 Group A drug, Groups B and C drugs are added to build a regimen with at least 4 active drugs. Treatment should be continued for 15–17 months after sputum culture conversion and injectables should be given for 6–7 months if injectables are used. The number of drugs and duration is also based on the individual patient data meta-analysis [130]. Of note, the 2019 ATS/CDC/ERS/IDSA Drug-Resistant TB guidelines [131] recommend building a regimen with at least 5 active drugs. This difference is in part because the individual patient data metanalysis dataset used for the WHO guidelines contained more persons who received bedaquiline and other effective drugs. Although this regimen is supported by robust observational data, there are no clinical trials comparing this to other MDR TB treatment regimens.

The Van Deun et al 2010 publication of an observational study conducted in Bangladesh was an important step towards shortening treatment for people with pulmonary MDR TB [117]. In this study, six regimens were tested sequentially and a regimen of gatifloxacin, ethambutol, pyrazinamide, and clofazimine for 5 months supplemented by kanamycin, high-dose isoniazid, and prothionamide for ≥ 4 months (continued if no culture conversion by month 4) had the highest successful outcome rate (87.9%). The first ever phase 3 randomized controlled trial for multidrug resistant TB (STREAM 1) found that a modified version of the Bangladesh regimen (substituting high dose moxifloxacin for gatifloxacin) was non-inferior to the 20-month WHO standard of care regimen (Table 5) [137]. Although

treatment adherence rate was higher in the shorter regimen arm, there were high rates of adverse effects in both trial arms (Table 6).

Following the introduction of bedaquiline, two clinical trials (STREAM 2 [138] and NExT [139]) compared bedaquiline-based to injectable-based treatment regimens. Both trials included persons with RR/MDR TB without resistance to fluoroquinolones or injectable drugs and no prior bedaquiline exposure. STREAM 2 compared a 9-month bedaquiline-based all-oral regimen and a 6-month bedaquiline-based regimen that included kanamycin for the first two months to the modified Bangladesh regimen tested in STREAM 1 [137,138]. Both experimental regimens included levofloxacin and clofazimine, and neither included linezolid. Both experimental regimens met non-inferiority study criteria and were found to be superior to the control regimen. The NExT trial compared injectable-based treatment regimens recommended by WHO to a 6-month all-oral bedaquiline-based regimen that included the levofloxacin and linezolid but did not include clofazimine [139]. This clinical trial was stopped early once bedaquiline became standard of care in South Africa -- where the trial was being conducted. The successful outcome rate for the all-oral regimen was two-fold higher than the injectable-based control regimen (51.0% vs 22.7%, respectively). Taken together, STREAM 2 and NExT demonstrate that all-oral bedaquiline-based regimens are superior to contemporary injectable-based regimens for persons with pulmonary MDR TB without fluroquinolone resistance or prior bedaquiline exposure. Of note, kanamycin is the most used injectable anti-TB agent globally (ahead of capreomycin, amikacin, and streptomycin [140]) and was used in STREAM 1 and 2 and NExT. Interestingly, amikacin and streptomycin have been associated with better treatment outcomes (higher rates of cure and lower mortality) compared to kanamycin and capreomycin, as suggested by the individual patient data meta-analysis.

The WHO-recommended 9-month all-oral treatment regimen (Table 1) is largely based on South African programmatic data where this regimen was rolled out [133]. These data suggest the 9-month regimen has similar outcomes compared to longer oral regimens containing at least bedaquiline and linezolid and that 2 months of linezolid dosed at 600 mg daily has similar outcomes compared to 6 months of ethionamide. People with fluoroquinolone-resistant TB, ≥1 month of exposure to second line drugs, extensive pulmonary TB, severe forms of extrapulmonary TB (e.g., osteomyelitis), or genotypic evidence of *inhA* and *katG* mutations were not eligible for these regimens in South Africa and therefore there is paucity of data to support usage of these regimens in these other clinical scenarios.

STREAM-2 and NExT showed that 6–9-month all-oral 5-drug regimens were effective for pulmonary MDR TB, but Nix-TB [134], Ze-Nix [135], and TB-PRACTECAL [136] advanced the field a step further by showing that a 6-month all-oral drug regimen consisting of 3–4 drugs were also effective for the treatment of people with pulmonary MDR-TB. These three trials investigated regimens containing bedaquiline, pretomanid, and linezolid ("BPaL") with different linezolid doses [135] and with and without a 4th drug (moxifloxacin or clofazimine) [136]. Nix-TB was a single arm trial (i.e., no comparator regimen) of 6 months of BPaL with linezolid dosed at 1200 mg daily. The results were encouraging with a 6-month and 2-year post-treatment favorable outcomes rates of 90% and 88%, respectively.

However, linezolid-associated side effects were very common and 66% of participants required a linezolid interruption. Ze-Nix was a follow-up randomized controlled trial that tested 6 months of BPaL with 4 linezolid doses: 1200 mg daily for 26 weeks or 9 weeks and 600 mg daily for 26 weeks of 9 weeks. Of note, Ze-Nix bedaquiline dose differs from the approved dose and the dose used in the other trials described in this section (Table 5). All Ze-Nix trial regimens were associated with high favorable treatment outcome rates and rates of linezolid-associated side effects and drug interruptions were directly related to linezolid dose and duration of use. The authors concluded “the risk-benefit ratio” favored the linezolid 600 mg dose for 6 months.

TB-PRACTECAL was a 2-stage trial [136]. In stage 1, the primary outcome was 2-month culture conversion comparing BPaL, BPaL with clofazimine, and BPaL with moxifloxacin. Linezolid was dosed at 600 mg daily for the first 16 weeks and 300 mg daily for the last 8 weeks in all regimens. The 2-month culture conversion rates for BPaL, BPaL with clofazimine, and BPaL with moxifloxacin among 60 participants in each arm were 46%, 67%, and 77%, respectively. Of note, the 2-month culture conversion rate among Nix-TB and Ze-Nix participants was ≥ 70% (defined as two negative cultures ≥7 days apart in Nix/Ze-Nix and ≥14 days apart in PRACTECAL). Based on superior 2-month culture conversion rates, TB-PRACTECAL stage 2 compared BPaL with moxifloxacin to contemporary WHO-recommended standard of care regimens (control). The trial was stopped early for benefit and the published results are restricted to participants who completed 72 weeks of follow-up. BPaL with moxifloxacin had significantly better outcomes compared to the control regimen (89% vs 52%, respectively) meeting study criteria for non-inferiority and superiority. Although the plan was to stop recruiting study participants for investigational regimens not selected for stage 2, participants receiving BPaL alone or with clofazimine were also recruited for stage 2 and both regimens had a higher rate of positive treatment outcomes compared to the control regimen. Based on Nix, Ze-Nix, and TB-PRACTECAL, the WHO 2022 MDR-TB guidelines recommend BPaL with linezolid dosed at 600 mg daily for the duration of therapy with or without moxifloxacin. Aside from omitting moxifloxacin when resistance is present, there are no published data on clinical factors (e.g., presence or absence of cavities) to inform risk benefit decisions of adding moxifloxacin to BPaL.

There is growing interest in bedaquiline and linezolid-containing regimens that use delamanid instead of pretomanid. The BEAT-India [141] and BEAT-South Africa clinical trials aim to fill this knowledge gap. BEAT-India is a single arm study that enrolled people with MDR and additional fluoroquinolone or second-line injectable resistance to receive bedaquiline, delamanid, linezolid (600 mg daily), and clofazimine for 6 months. The results are in line with outcomes reported in Nix, Ze-Nix, and PRACTECAL: end-of-treatment and 6-month post-treatment favorable outcome rates were 91% and 86%, respectively. PLWH were excluded from BEAT-India, a key difference between BEAT-India and the other trials described here. BEAT-South Africa [142] is an open label non-inferiority trial that compared a 9-month all-oral 7-drug regimen that contained bedaquiline but not delamanid or pretomanid (the contemporary South African MDR TB treatment standard) to a 6-month all-oral 5-drug regimen containing bedaquiline, delamanid, linezolid, clofazimine, and levofloxacin (preliminary results reported at the World Conference on Lung Health,

2022). This trial has at least two interesting features. First, children aged 6-year-old and above and persons who were pregnant or breastfeeding were eligible for inclusion. Second, the regimens were adjusted based on fluoroquinolone line-probe assay results. In the investigational arm, clofazimine was stopped if the assay indicated fluoroquinolone susceptibility, levofloxacin was stopped if the assay indicated fluoroquinolone resistance, and levofloxacin and clofazimine were continued when the assay was indeterminate. In an interim analysis of approximately 200 participants, the investigational regimen had a 52-week successful outcome rate of 86% and was non-inferior to the control regimen (the complete trial sample size is 400 participants with outcomes measured at 72 weeks). Altogether, the BEAT trials suggest that bedaquiline, delamanid, and linezolid combined with ≥ 1 drug have similar outcomes compared to BPaL with or without moxifloxacin. Currently, there are no head-to-head comparisons between these regimens or data to guide selection of one regimen over the other.

While most of the above noted RR/MDR TB treatment trials excluded children, the principles of shorter all-oral regimens can be applied to children and adolescents with RR/MDR TB, who historically have had better treatment outcomes compared to adults. WHO recommends a 6–9 month bedaquiline-containing all-oral treatment regimen of 4–5 effective drugs for non-severe pediatric RR/MDR TB, 9–12 months for severe pediatric RR/MDR TB, and >12 months for children with disseminated TB, TBM, osteoarticular TB, or resistance to 2 or more Group A drugs [77]. An open-label pediatric Phase 2 study of 24 weeks of bedaquiline added to an anti-MDR TB background regimen (NCT02354014) demonstrated palatability of the dispersible 20 mg tablet and similar safety and PK profiles compared to adults among children aged 5 to 18 years [143]. Children had high culture-conversion rates after 4 months of treatment in the initial trial (>75%) as well as in a subsequent observational study of adolescents aged 11–17 years with drug-resistant TB (100%) [144]. The most common adverse events were leukopenia (3/10 [30%]), QTcF interval prolongation, anemia and peripheral neuropathy (each occurring 1/10 [10%]); no serious adverse events were reported in this case series [144]. The DRAMATIC Trial (NCT03828201) will evaluate a 5-drug regimen of bedaquiline, delamanid, levofloxacin, clofazimine, and linezolid in children with RR/MDR TB, randomizing groups by duration of treatment between 4 to 10 months. Earlier inclusion of children in clinical trials and availability of pediatric-friendly formulations (dispersible tablets or liquid suspension for children under 5 years) are of utmost importance as future RR/MDR drugs are developed. The WHO operational handbook contains detailed dosing recommendations for second-line drugs in children [77].

There is an urgent need for additional data to inform treatment of RR/MDR TB during pregnancy. Though evidence is limited, the BEAT-South Africa trial (which included seven pregnant people) and other observational treatment studies of second-line agents have found overall good outcomes for pregnant people with RR/MDR TB and their infants [145]. Notable exceptions to the general safety of second-line agents in pregnancy include amikacin, associated with maternal hearing loss and fetal nephrotoxicity, and ethionamide, associated with fetal neural tube defects. These medications should only be used if alternate options are not available. Clinicians may consider enhanced monitoring of QTc for pregnant persons taking bedaquiline, fluoroquinolones, clofazimine, and delamanid, in particular

when there is a history of cardiac arrythmias. Periodic monitoring of thyroid-stimulating hormone (TSH) can be considered for pregnant persons treated with ethionamide or para-aminosalicylic acid (PAS). Infants born to mothers taking bedaquiline while breastfeeding should be monitored for potential toxicity (QTcF prologation and/or hepatotoxicity) given the potential for high levels of bedaquiline in breast milk [146].

Overall, there is very strong evidence that several all-oral 6–9-month regimens can achieve high cure rates for adults with MDR and pre-XDR pulmonary TB, provided they receive high quality care and have support to finish therapy. However, children, pregnant or breastfeeding persons, and people with severe forms of extra-pulmonary TB were generally excluded from clinical trials and there is less evidence to guide therapy in these scenarios. It is predictable that resistance to bedaquiline, linezolid, nitroimidazoles, and other novel drugs will emerge under selective pressure [147], and we will likely continue to need novel drugs and regimens until TB is eliminated.

4.3 Selected safety considerations of newer drugs

It is challenging to compare drug-related adverse event rates and severity between the above-described clinical trials given non-uniform definitions. Nonetheless, adverse effects are clearly common among participants with trial-defined serious adverse effects rates generally around 20% in investigational regimen arms (Table 6). Comparatively, < 10% participants in the 4-month fluoroquinolone-based trials (Study 31/ACTG5349 [73], OFLOTUB [72], RIFAQUIN [71], and REMoxTB [70]) had trial-defined serious adverse events. Here, we will review the following MDR TB treatment-related adverse effects of special interest: QT prolongation, linezolid-related neuropathy and myelosuppression, and pretomanid testicular toxicity concerns. We recommend the UCSF Curry Drug-Resistant Tuberculosis Survival Guide for a comprehensive review of drug-related adverse events and their management, which is beyond the scope of this review [148].

Several drugs used for MDR TB can cause QT prolongation (bedaquiline, delamanid, clofazimine, and fluoroquinolones) and thus possibly increase the risk of aberrant and potentially fatal ventricular tachycardias, such as *torsades de pointes* [149]. Combining multiple QT-prolonging agents may have an additive effect and providers should be aware drugs with long half-lives (bedaquiline, delamanid, clofazimine) QT effects may persist weeks after their discontinuation, in contrast to drugs with short half-lives such as currently available fluoroquinolones [150,151]. Combining multiple QT-prolonging agents may have an additive effect and providers should be aware drugs with long half-lives (bedaquiline, delamanid, clofazimine) QT effects may persist weeks after their discontinuation, in contrast to drugs with short half-lives such as currently available fluoroquinolones [150,151]. There is interindividual variability in the magnitude of drug induced QTc effects related to non-modifiable (e.g., gender, structural heart disease) and modifiable (e.g., electrolyte disturbances) factors [149,152]. Cardiotoxicity has been at the forefront of MDR TB drug safety concerns at least since bedaquiline's phase 2b study, where there was a significantly higher number of deaths in the bedaquiline group (13%) compared to the control group (2%), despite increase in culture conversion rates among bedaquiline recipients [101]. Clinically significant QT prolongation was uncommon in the clinical trials reviewed

here. However, these trials had QT-related exclusion criteria. A systematic review and meta-analysis on combined bedaquiline delamanid use included 13 studies with > 1000 persons [153]. Most studies were observational, and thus had less stringent inclusion criteria compared to clinical trials. The pooled QTc prolongation rate was 7.8% (95%CI 4.1–11.6%) and only 0.8% of participants had a cardiac event. A prospective multi-country observational study (endTB) included people with MDR TB who were administered bedaquiline and/or delamanid (n=2296) [154]. Most participants (95.7%) took ≥ 1 additional QT-prolonging drug (fluoroquinolone and/or clofazimine) and only 2.7% developed a QTc ≥ 500 msec. Of note, in keeping with TB demographics, most participants in these studies were young (e.g., endTB median age 36 years-old). Altogether, the evidence suggests that several MDR TB drugs QT-prolonging effect, clinically significant events are likely uncommon. However, more data are needed to determine when (which patients and drugs) and how (frequency and duration) QT should be monitored in programmatic settings.

Linezolid peripheral neuropathy, optic neuritis, and myelosuppression are secondary to its mitochondrial toxicity that is dose and duration dependent [135,155,156]. Linezolid-associated peripheral neuropathy is more common than anemia, thrombocytopenia, and optic neuritis which occurred in 77%, 37%, 6%, <2% of Nix-TB participants (linezolid dose 1200 mg daily), respectively [134,156]. The median time between starting linezolid in Nix-TB and developing neurologic or hematologic events was 14 weeks and 8 weeks, respectively and these adverse events were not corelated [136,156]. In a contemporary adult MDR TB cohort, peripheral neuropathy is the most common side effect, and it occurred in 26.4% of endTB participants. In endTB, linezolid was started at 600 mg daily and 27.8% of linezolid recipients had neurotoxicity or myelosuppression [154]. Importantly, although neurological side effects generally improve with linezolid discontinuation or dose reduction, improvement can be slow and incomplete [156]. Dosing strategies are important to mitigate toxicity. Based on Ze-Nix, it appears linezolid 600 mg daily offers the best risk-benefit balance for adults with RR/MDR TB [134]. There is interest in individualizing linezolid doses by measuring blood levels, as early evidence suggested linezolid trough levels > 2 μg/dL correlate with toxicity [155]. Albeit promising, trough predictive value, probability of attaining therapeutic levels with linezolid doses < 600 mg, and feasibility of therapeutic drug monitoring is under investigation [156–158]. Studies to inform optimal dosing among children are also needed; a PK study in children evaluating 10 mg/kg/dose once daily for age > 10 years and 10 mg/kg/dose twice daily for age <10 years (maximum 600 mg per day) found high rates of adverse events (~60%) and higher drug exposure in children compared to adults taking 600 mg once daily [159]. Utilizing PK modeling, this study recommended lower once-daily dosing for children that has been incorporated into WHO guidance for pediatric weight-band dosing [77]. Anemia was the most common adverse event described in children (10/17, 59% overall; 5/10, 50% with grade 3 or 4), and linezolid should be avoided among children with a baseline hemoglobin < 8 g/dL. Some experts advise limiting linezolid duration to 8 weeks among children with non-severe RR/MDR TB to avoid long-term toxicities.

Pretomanid pre-clinical models were concerning for decreased fertility, testicular atrophy, and lower sperm counts among male rodents – a nitroimidazole class effect [160]. This is has led to caution regarding pretomanid use for young males, who are commonly affected

by TB. A recent study found no difference in sex hormones between males in TB treatment trials exposed and not exposed to pretomanid [160]. A survey found that 12% of male trial participants fathered children after pretomanid exposure. PaSEM is an ongoing phase 2 trial evaluating sperm counts before, during, and after pretomanid exposure [161]. Altogether, current evidence suggests pretomanid has no clinically-significant testicular toxicity in humans. WHO guidelines do not recommend BPaL regimens to children < 15 (irrespective of gender) due to lack of pretomanid safety and pharmacokinetic data in this population. There is no current evidence on the use of pretomanid during pregnancy.

4.4. TB infection among persons exposed to MDR TB

There are no published randomized controlled trials for TBI among persons exposed to MDR TB. Currently, there are at least three ongoing randomized controlled trials for TBI among MDR TB contacts. TB-CHAMP [162] and VQUIN [163] are comparing 6 months of levofloxacin to placebo and PHOENix MDR-TB [164] is comparing 6 months of delamanid (dosed once daily) to 6 months of isoniazid. [163] are comparing 6 months of levofloxacin to placebo and PHOENix MDR-TB [164] is comparing 6 months of delamanid (dosed once daily) to 6 months of isoniazid. In the absence of clinical trials, current TBI treatment recommendations for this population are based on observational studies [165]. A systematic review and meta-analysis that included studies published up to 2014 found six observational studies that reported the rates of TB disease among 316 persons treated and not treated for TBI and were exposed to MDR TB. Regimens were varied and generally consisted of two drugs, mostly a fluoroquinolone with pyrazinamide. TBI treatment was associated with a 90% reduction in MDR TB incidence but given the small sample size the 95% confidence intervals were very wide (9%−99%). Additionally, 51% of persons who received pyrazinamide-containing regimens discontinued treatment for adverse effects, a higher rate compared to other regimens. Based on this evidence, the 2018 WHO TBI guidelines recommend individualized decision-making regarding treatment or not treatment and regimens for persons with TBI who were exposed to MDR TB in addition to “strict clinical observation and close monitoring for the development of active TB”. Conversely, the 2019 ATS/CDC/IDSA/ETS guidelines recommend 6–12 months of fluoroquinolone with or without a second drug, based on the source case drug susceptibility test results [131]. Pyrazinamide should be avoided as the second drug due to the large number of discontinuations.

4.5. Isoniazid mono-resistant tuberculosis

Isoniazid mono-resistant TB is generally defined as resistance to isoniazid with susceptibility to the first-line drugs rifampicin, pyrazinamide, and ethambutol [131]. The global prevalence of isoniazid-resistant TB is approximately 10% and is higher among previously treated, compared to newly diagnosed, persons [166,167]. A systematic review and meta-analysis found that isoniazid mono-resistant TB treatment with first-line 4-drug therapy was associated with high pooled rates of failure (11%), relapse (10%), and acquired multidrug resistant TB (8%) [166]. These rates were much lower for drug-susceptible TB treated with first-line 4-drug therapy, with pooled failure, relapse, and acquired multidrug resistant TB rates of 1%, 5%, and 0.3%, respectively. Current WHO and ATS/CDC/IDSA/ERS guidelines recommend 6 months of rifampicin, ethambutol, pyrazinamide, and a

fluoroquinolone for pulmonary isoniazid mono-resistant TB [131]. This guidance is based on an individual patient data meta-analysis of 3293 persons with pulmonary isoniazid mono-resistant TB treated with rifampicin, ethambutol, pyrazinamide with and without a fluoroquinolone drug or isoniazid [167]. The key findings were that outcomes were similar between persons treated for 6 or more than 6 months of daily rifampicin, ethambutol, and pyrazinamide (irrespective of isoniazid use). Addition of a fluoroquinolone to a 6-month regimen of daily rifampicin, ethambutol, and pyrazinamide was significantly associated with positive outcomes (aOR 2.8) compared to not adding a fluoroquinolone. Lastly, 117 of 118 persons who were treated with 6 months of daily rifampicin, ethambutol, a fluoroquinolone, and shorter pyrazinamide (1–3 months) course had successful outcomes. Based on this evidence, the ATS/CDC/IDSA/ERS guidelines (but not the WHO guidelines) allow for a 2-month pyrazinamide course along with daily rifampicin, ethambutol, and fluoroquinolone for six months. Our practice is to treat TBI among TB contacts to isoniazid mono-resistant cases with four months of daily rifampicin.

Five important topics in drug-resistant TB are beyond the scope of this review. First, surgical resection of the infected lung is recommended in selected cases [131]. Second, HIV co-infection is common among people living with MDR TB and anti-retroviral therapy is key to improving outcomes in this population [168] and clinicians must be aware of drug-drug interactions between antiretrovirals and anti-mycobacterial agents. Third, rifampicin-resistant isoniazid-susceptible TB is increasingly recognized but there are limited data to guide optimal treatment [169]. This is generally treated as MDR TB, potentially exposing patients to unnecessary longer or/and more toxic regimens. Fourth, the management of people with *rpoB* mutations (the gene that determines rifampicin resistance) who test rifampicin-susceptible on current phenotypic tests (referred to as discordant or disputed mutations) is unclear [170,171]. It is generally treated as MDR TB, potentially exposing patients to unnecessary longer or/and more toxic regimens. Lastly, the cost-effectiveness of shorter bedaquiline-based regimens is under investigation [172–174] and a target of advocacy efforts [175].

4.6. Summary of treatment of DR TB

The treatment of DR TB has been transformed with the development of shorter all-oral regimens, as short as 6–9 months in some situations, with improved outcomes and reduced toxicity compared to previous regimens. Further operational research will further inform and support the optimal use of these new and repurposed drugs. Just as for DS TB, additional understanding of individual drug pharmacokinetics, immune response, bacterial burden, and role of host-directed therapies will serve to inform a more personalized approach to the treatment of people with DR TB.

5. Conclusions:

TB remains a significant global health problem causing illness, disability, and death. In this context, the diagnosis and management of people with all forms of TB are crucial elements of a comprehensive package of prevention and care aimed at eliminating global TB. As reviewed here, diagnostics for TB infection and TB disease have improved but are

still inadequate, particularly in key vulnerable populations such as children, people with immunocompromised status, and other co-morbid conditions. Novel therapeutic regimens for both TB infection and TB disease have finally shortened the duration of therapy and increased the proportion of successful outcomes for people treated for TB. This is particularly notable in the treatment of drug-resistant TB with the implementation of new and repurposed anti-TB drugs. Despite this remarkable progress, substantial work remains to ensure appropriate diagnosis and effective treatment can be consistently implemented for TB prevention and control in all countries of the world.

6. Expert Opinion

Tuberculosis is an ancient human disease, and despite over a century of diagnostic, preventive, and therapeutic options for management, it remains a leading cause of global mortality. Recent data reveal an alarming reversal in the previous slow decline in TB incidence, highlighting the inadequate progress in TB prevention and control and emphasizing the need for improved diagnostics and treatment to achieve stated WHO goals to end TB [176]. The advances discussed in this review have great potential to impact the TB epidemic. Improvements on existing tools are needed, but new approaches such as diagnostic tests based on non-sputum samples or host response are more likely to transform the approach to identifying people with TB so that they can be provided optimal treatment regimens.

After decades of reliance on a standard regimen for all people with DS TB and suboptimal outcomes for people treated for DR TB, recent clinical trials have finally demonstrated the feasibility of new and shorter treatment regimens for improved outcomes with lower likelihood of toxicity. Novel anti-TB regimens are important steps forward, but certain barriers will need to be addressed, including the cost of new drugs relative to standard regimens, global access to new drugs, the need for drug susceptibility testing, and lack of data in certain subsets of TB disease or patient populations. Continued investments in research to study new regimens are needed, including appropriate dosing to minimize the risk of adverse effects, the utility of therapeutic drug monitoring for improved adherence, their use in children, pregnancy, and PLWH, and management when resistance develops. The potential of a risk-stratified approach to treatment also warrants further evaluation. As with any advance in clinical or public health, the key to realizing the promised benefits lies in implementation and reaching people affected by disease. Global TB management and care has the advantage of an existing infrastructure (i.e., National TB Programs) to deliver and coordinate care but has been limited by inadequate funding. Along with increased political will and funding, research into the management of TB must advance to reverse current trends and improve care for all people with TB.

The future of research into TB management remains broad. In addition to the needs addressed above, directions include advancement of existing tools and the development of novel ones. Drug formulations such as long-acting injectable medications may improve tolerability or adherence for TB treatment [177]. Continued evolution in the understanding of the complex host-pathogen interaction in TB infection will support the development of host-directed therapy that may improve treatment outcomes and provide targets to address

the burden of complications due to TB, such as post-TB lung disease [178]. In addition to the need for vaccines to prevent acquisition of TB infection, therapeutic vaccines or anti-TB monoclonal antibodies offer the potential of adjunctive measures to improve the immune response in the management of TB [179]. The pace of discovery in the field of TB has accelerated such that several years from now, there will likely be new diagnostic options, additional novel treatment regimens, and complementary strategies to address TB infection. While not reviewed here, the identification and deployment of safe and effective vaccines to prevent disease progression in people with TBI will also revolutionize the global response. These discoveries and their implementation into practice must continue until there is an end to the TB epidemic.

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Article highlights

- There has been an alarming recent increase in TB incidence and mortality, emphasizing the need for accurate diagnosis and effective treatment
- Diagnosis of TB infection still relies on tuberculin skin testing or interferon-gamma release assays. Rapid molecular tests have enhanced diagnosis of TB disease but are not available in many settings. New and improved diagnostics are needed to address global TB burden.
- For drug-susceptible TB, shorter regimens for TB preventive therapy (3–4 months) and TB treatment (4 months and potentially shorter) are now available.
- Drug-resistant TB can also be treated with shorter all-oral regimens, in some patients as short as 6–9 months.
- Continued research is needed to evaluate new regimens, determine appropriate dosing, and inform management in certain clinical scenarios and important populations such as children, those who are pregnant, and people living with HIV.

Table 1:

Current WHO guidelines for treatment of people with pulmonary tuberculosis

2022 Guidelines	Regimen (Leading numbers indicate the duration of treatment in months)	Comments
Drug-susceptible TB		
• Adults • Children and adolescents who do not meet criteria for non-severe TB	2HRZE/4HR	Strong recommendation
• People ≥12 years old	2HPMZ/2HPM	Conditional recommendation
• Children age 3 months to 16 years • Non-severe TB	2HRZ(E)/2HR	Ethambutol in first 2 months in settings with high prevalence of HIV or isoniazid resistance
Drug-resistant TB		
• RR/MDR • ≥15 years old • ≤1 month exposure to Bdq, Pa, Lzd[A] • Not pregnant or breastfeeding	6BdqPaLzd$_{600}$Mxf (Also known as BPaLM)	Can be used without moxifloxacin in case of fluoroquinolone resistance
• RR/MDR and no FQ-R • ≤1 month to Bdq, Fq, Eto, Lzd, Cfz • No extensive TB[B]	Adults: 4–6 Bdq[6]-Lfx[Mfx]-Eto-Emb-Pza-$_{hd}$Inh-Cfz / 5 Lfx[Mfx]-Cfz-Pza-Emb[C]	Can substitute 6 months of Eto for 2 months of Lzd$_{600}$ Use Lzd regimen for women who are pregnant or breastfeeding
	Children[D]: 4–6 Bdq[6]-Lfx-Cfz-Pza-Emb-$_{hd}$Inh-Eto / 5 Lfx-Cfz-Pza-Emb	If smear or culture positive at 4 months, extend initial phase until conversion
• Not eligible for above regimens	Adults: Individualized regimens based on WHO grouping (treatment duration 18–20 months)	Start treatment with at least 4 drugs[E]
	Children: Individualized regimens based on FQ and other resistance	Add a 5th drug in severe disease

Abbreviations: MDR, multidrug resistant; RR, rifampicin resistant; FQ-R, fluoroquinolone resistance; WHO, World Health Organization

Drug abbreviations: Bdq, bedaquiline, Clf, clofazimine, Dlm, delaminid; E or Emb, ethambutol; Eto, ethionamide; H, isoniazid; $_{hd}$Inh; high-dose isoniazid; Lzd, linezolid; Lfx, levofloxacin; Mxf, moxifloxacin; P, rifapentine; Pa, pretomanid; Pza or Z, pyrazinamide; R, rifampicin.

Numbers in front of drug regimens indicate the duration of treatment in months. Example: 6BqdPaLzd$_{600}$Mxf indicates six months of bedaquiline, pretomanid, linezolid (600 mg daily), and moxifloxacin. High-dose isoniazid is described as $_{hd}$Inh.

A. Regimen can be used if exposure to these drugs ≥1 month and resistance is ruled out

B. Bilateral cavities or extensive parenchymal damage

C. Extend Lfx[Mfx]-Eto-E-Z-Hh-Cfz to 6 months if smear-positive at the end of 4 months (total duration 12 months)

D. See WHO Operational Handbook, Module 5, 2022 for age and weight-based pediatric dosing recommendations

E. 2019 ATS/CDC/ERS/IDSA guidelines recommend starting with at least 5 drugs

Table 2:

History of previous WHO guidelines for treatment of adults with multidrug resistant pulmonary tuberculosis

Year and eligibility (if applicable)	Regimen(Leading numbers indicate the duration of treatment in months)	Comments
2022 (first time a 6–9-month all-oral regimen is recommended)		
• Depending on exposure and resistance to certain drugs	• 6BdqPaLzd$_{600}$Mxf (BPaLM) • 4–6 Bdq[6]-Lfx[Mfx]-Eto-Emb-Pza-$_{hd}$Inh-Cfz / 5 Lfx[Mfx]-Cfz-Pza-Emb • Individualized regimens based on WHO grouping (18–20 months)	See Table 1 for details
2019 (first time an all-oral regimen is recommended)		
• MDR/RR and no FQ-R • Not pregnant • ≤1 month exposure to second-line drugs[A]	4–6 Kan-Mfx-Eto-Emb-Pza-$_{hd}$Inh-Cfz / 5 Mfx-Cfz-Pza-Emb[B]	
• Not eligible for above regimens	Individualized regimens based on WHO grouping (treatment duration 18–20 months)	Start treatment with at least 4 drugs.
2016 (first guideline that includes novel drugs Bdq and Dlm)		
• No prior second line drug treatment and fluoroquinolone and second line injectable resistance excluded or unlikely • Not pregnant	4–6 Kan-Gfx [Mfx]-Pto-Cfz-$_{hd}$Inh- Pza-Emb / 5 Gfx [Mfx]-Pto-Cfz	
• Not eligible for regimen above	Individualized regimens based on WHO grouping (treatment duration 18–20 months)	Start treatment with at least 5 drugs (4 core second line drug and pyrazinamide).
2011 (first guideline based on an individual patient data meta-analysis)		
	Number of drugs and duration as in 2006 guidelines. Emphasize using pyrazinamide. Increasing the number of drugs for extensive disease no longer recommended.	≥6 months of injectables for all patients if injectables are likely to be effective
2008		
	Number of drugs and duration as in 2006 guidelines. Drug grouping changed and ciprofloxacin no longer recommended (Table 4).	≥6 months of injectables for all patients if injectables are likely to be effective
2006		
	18–24 months of at least 4 drugs that are likely effective based on WHO grouping (Table 4) Consider >4 drugs if extensive disease present	≥6 months of injectables for all patients if injectables are likely to be effective
1996–2000		
	1 Individualized treatment regimen of 4–5 drugs based on remaining effective anti-TB drugs or previously not used first- and second-line drugs (excluding those with cross-resistance to failed/previously used drugs) **2** Standardized treatment regimen, WHO Category II or national program standard[C]	Guidelines for the Establishment of DOTS-Plus Pilot Projects released in 2000.

Abbreviations: MDR, multidrug resistant; RR, rifampicin resistant; FQ-R, fluoroquinolone resistance; WHO, World Health Organization

Drug abbreviations: Bdq, bedaquiline, Dlm, delaminid; Emb, ethambutol; Eto, ethionamide; $_{hd}$Inh; high-dose isoniazid; Lfx, levofloxacin; Kan, kanamycin; Pza, pyrazinamide; Pto, prothionamide.

Numbers in front of drug regimens indicate the duration of treatment in months.

A. Regimen can be used if exposure to these drugs ≥1 month and resistance is ruled out

B. Extend Lfx[Mfx]-Eto-E-Z-Hh-Cfz to 6 months if smear-positive at the end of 4 months (total duration 12 months)

C. WHO category II regimen: 8 months of isoniazid, rifampicin and ethambutol supplemented by streptomycin for the initial 2 months, and pyrazinamide for the initial 3 months (2SHRZE/1HRZE/5HRE)

Table 3.

WHO 2021 and 2006 definitions of drug resistant TB

Year	MDR	MDR/RR	Pre-XDR	XDR
2021	Rifampicin **and** isoniazid resistance	Either MDR or rifampicin resistance	MDR and additional resistance to any fluoroquinolone drugs	Pre-XDR and additional resistance to any fluoroquinolone and ≥1 anti-TB drug in Group A (e.g., bedaquiline or linezolid)
2006	Rifampicin **and** isoniazid resistance	Either MDR or rifampicin resistance	MDR and additional resistance to fluoroquinolone or second-line injectable anti-TB drugs	MDR and additional resistance to fluoroquinolone **and** second-line injectable anti-TB drugs

Second-line injectable drugs: amikacin, kanamycin, capreomycin

Group A fluoroquinolones: moxifloxacin and levofloxacin

RR: resistance to rifampicin detected using genotypic or phenotypic methods with or without detection to other first-line anti-TB drugs

Abbreviations: TB, tuberculosis; WHO, World Health Organization; RR, rifampicin resistant; MDR, multidrug resistant; XDR, extensively drug resistant

Table 4.

WHO grouping of anti-tuberculosis drugs used for longer duration of treatment of people with multidrug resistant TB, by adjusted death and treatment success Odds Ratios

Drug	Group	Adjusted death OR (95%CI)	Adjusted treatment success OR (95%CI)
Bedaquiline	A	0.4 (0.3 to 0.5)	2.0 (1.4 to 2.9)
Moxifloxacin	A	0.5 (0.4 to 0.6)	3.8 (2.8 to 5.2)
Levofloxacin	A	0.6 (0.5 to 0.7)	4.2 (3.3 to 5.4)
Linezolid	A	0.3 (0.2 to 0.3)	3.4 (2.6 to 4.5)
Clofazimine	B	0.8 (0.6 to 1.0)	1.5 (1.1 to 2.1)
Cycloserine (or terizidone)	B	0.6 (0.5 to 0.6)	1.5 (1.4 to 1.7)
Ethambutol	C	1.0 (0.9 to 1.2)	0.9 (0.7 to 1.1)
Pyrazinamide	C	0.7 (0.6 to 0.8)	0.7 (0.5 to 0.9)
Imipenem or meropenem with clavulanic acid	C	1.0 (0.5 to 1.7)	4.0 (1.7 to 9.1)
Amikacin	C	1.0 (0.8 to 1.2)	2.0 (1.5 to 2.6)
Streptomycin	C	0.8 (0.6 to 1.1)	1.5 (1.1 to 2.1)
Ethionamide (or prothionamide)	C	0.9 (0.8 to 1.0)	0.8 (0.7 to 0.9)
p-aminosalicylic acid	C	1.2 (1.1 to 1.4)	0.8 (0.7 to 1.0)
Delaminid	C	Insufficient data	Insufficient data
Kanamycin	NR	1.1 (0.9 to 1.2)	0.5 (0.4 to 0.6)
Capreomycin	NR	1.4 (1.1 to 1.7)	0.8 (0.6 to 1.1)
Amoxicillin-clavulanate	NR	1.6 (1.2 to 2.0)	0.6 (0.5 to 0.8)
Azithromycin/clarithromycin	NR	1.7 (1.3 to 2.1	0.6 (0.5 to 0.8)

Footnote: adapted from references [129, 130]. Treatment success was defined as cure or treatment completion. Insufficient data to calculate delamanid adjusted OR with TB outcomes in the 2018 individual patient data meta-analysis. Pretomanid not used in the studies included in the 2018 individual patient data meta-analysis.

Abbreviations: WHO, World Health Organization; CI=confidence interval; OR, odds ratio; NR, not recommended (these drugs were deemed ineffective for MDR TB treatment)

Table 5.

Completed key clinical trials of people with pulmonary multi-drug resistant tuberculosis, by regimens and treatment outcomes

Treatment Regimen (sample size[A])	Successful outcome	Deaths[B]	Failure and/or relapse[C]	Comments
STREAM 1 (Open label non-inferiority RCT; NCT02409290) • Outcome definition: Culture-negative at week 132 post-randomization with no preceding positive culture unfavorable outcome (e.g., death) • Key exclusion criteria: Fluoroquinolone and/or SLI resistance				
20-month 2011 WHO-recommended regimen (n=124)	79.8%	8.5%	5.6%	100% adherence rate was 43%
9_{hd}MxfClfEmbPza[4Kan$_{hd}$InhPto] (n=245)	78.8%	6.4%	10.6%	100% adherence rate was 75%
STREAM 2 (Open label non-inferiority RCT; NCT02409290) • Outcome definition: Culture-negative at week 76 post-randomization with no preceding positive culture or unfavorable outcome (e.g., death) • Key exclusion criteria: Fluoroquinolone and/or SLI resistance; prior bedaquiline exposure				
9_{hd}MxfClfEmbPza[4Kan$_{hd}$InhPto] (n=187)	71%	2%	10.6%	Control regimen
9BdqLfxClfEmbPza[4$_{HD}$InhPto] (n=196)	83%	3%	4.0%	Non-inferior and superior to control regimen
6BdqLfxClfEmbPza[2Kan$_{HD}$Inh] (n=134)	91%	1%	2.4%	Non-inferior and superior to control regimen
NExT (Open label RCT; NCT02454205) • Outcome definition: Completed treatment or cured at month 24 post-randomization. Drug substitution considered an unfavorable outcome. • Key exclusion criteria: Fluoroquinolone and/or SLI resistance; prior bedaquiline exposure				
18–20-month 2016 or 9–12-month 2019 injectable-based anti-TB drugs in WHO recommended regimens (n=44)	22.7%	9%	13.6%	Toxicity-related drug change rate 65.9% (83.8% were kanamycin discontinuations for bedaquiline)
6BdqLzd$_{600}$LfxPza($_{hd}$Inh or Eto or Trd) (n=49)	51.0%	8.2%	8.1%	Toxicity-related drug change rate 34.7% (64.7% were linezolid discontinuations)
Nix TB (Open label single arm trial; NCT02333799) • Outcome definition: Treatment failure or relapse 6 months post-treatment completion. • Key exclusion criteria: CD4 <50 cells/mm^3				
6BdqPaLzd$_{1200}$ (n=109)	90%	6%	1.8%	88% had favorable outcomes 2 years post treatment completion. Only 2 participants had treatment extended to 9 months. 66% participants had a linezolid interruption.
Ze-Nix (Partially blinded RCT; NCT03086486) • Outcome definition: Treatment failure or relapse 6 months post-treatment completion. • Key exclusion criteria: CD4 <100 cells/mm^3 Exposure to any trial drugs or delaminid ≥2 weeks prior to enrollment				

Treatment Regimen (sample size[A])	Successful outcome	Deaths[B]	Failure and/or relapse[C]	Comments
6BdqPaLzd$_{1200}$ (n=45)	93%	None	4.4%	Linezolid dose modification rate 51%
6BdqPa4Lzd$_{1200}$ (n=46)	89%	2%	4.3%	Linezolid dose modification rate 30%
6BdqPaLza$_{600}$ (n=45)	91%	None	4.4%	Linezolid dose modification rate 13%
6BdqPa4Lzd$_{600}$ (n=45)	84%	None	4.4%	Linezolid dose modification rate 13%
TB PRACTECAL (2-stage open label non-inferiority RCT, NCT02589782) • Outcome definitions: – Stage 1: 2-month culture conversion – Stage 2: Free of treatment failure, death, treatment discontinuation, recurrence, or loss to follow-up 72 weeks post-randomization • Key exclusion criteria: Exposure to bedaquiline, linezolid, or pretomanid for ≥4 weeks prior to enrollment				
9–20-month WHO-recommended regimens (n=66)	52%	3%	None	143 participants recruited
6BdqPaLzd$_{600–300}$Mxf (n=62)	89%	None	None	151 participants recruited Non-inferior and superior to control regimen
6BdqPaLzd$_{600–300}$Clf (n=64)	81%	2%	4%	126 participants recruited
6BdqPaLzd$_{600–300}$ (n=60)	77%	None	5%	122 participants recruited
BEAT India (Open label single arm trial; CTRI/2019/01/017310) • Outcome definition: Two consecutive cultures ≥4 weeks apart and clinical-radiological improvement and end of therapy (24 weeks) • Key exclusion criteria: Exposure to bedaquiline or linezolid for ≥2 weeks prior to enrollment; people living with HIV excluded.				
6BdqDlmLzd$_{600}$Clf (n=153)	91%	2.6%	1.9%	6-month post-treatment outcome rates: favorable (86%), death (3.2%), and failure/recurrence (3.9%)
BEAT South Africa (Interim analysis) (Open label non-inferiority RCT; NCT04062201) • Outcome definition: Completed or cure at 52 weeks post-randomization (interim analysis outcome) • Key exclusion criteria: Exposure to second-line drug for 1 to 6 months prior to enrollment				
9Bdq$_{hd}$InhEmbPzaClfLvx2Lzd (n=98)	86%	3.3%	9%	Interim analysis. The trial enrolled 400 participants.
6BdqDlmLzd$_{600}$ (Clf and/or Lvx) (n=101)	87%	3.7%	8%	Non-inferior to control regimen

Abbreviations: WHO, World Health Organization; hd high-dose; SLI, second-line injectable

Drug abbreviations: Bdq, bedaquiline, Clf, clofazimine, Dlm, delamanid; Emb, ethambutol; Eto, ethionamide; Inh; isoniazid; Lzd, linezolid; Lfx, levofloxacin; Mxf, moxifloxacin; Kan, kanamycin; Pa, pretomanid; Pza, pyrazinamide; Pto, prothionamide; Trd, terizidone. hd used to note when higher than usual dose used. Linezolid dose is of special interest and thus it is noted in subscript (e.g.; Lzd$_{600}$ means linezolid 600 mg daily).

The numbers indicate the drug duration in months. Example: 6BqdPaLzd$_{600}$Mxf means six months of bedaquiline, pretomanid, linezolid (600 mg daily), and moxifloxacin.

A. Number of participants included in the modified intention-to-treat

B. Death rates generally use the number of participants included in the safety analyses as the denominator

C. Failure and/or relapse rates with the number of participants included in the modified intention-to-treat as the denominator

Table 6.

Percent of adults experiencing severe adverse events in selected clinical trials, by treatment regimen, for pulmonary multi-drug resistant tuberculosis

Treatment Regimen	SAE	QTc prolongation	Peripheral neuropathy	Myelo-suppression	Other
STREAM 1 (NCT02409290)					
20-month 2011 WHO-recommended regimen	34%	6.4%	NR	NR	Hypokalemia 7.1%
9_{hd}MxfClfEmbPza[4Kan$_{hd}$InhPto]	32%	11.0%	NR	NR	Hypokalemia 1.1%
STREAM 2					
9_{hd}MxfClfEmbPza[4Kan$_{hd}$InhPto]	17%	6%	1	NR	Hearing loss: 9%
9BdqLfxClfEmbPza[4$_{HD}$InhPto]	18%	7%	Zero	NR	Hearing loss: 3%
6BdqLfxClfEmbPza[2Kan$_{HD}$Inh]	19%	3%	Zero	NR	Hearing loss: 4%
NExT (NCT02454205)					
18–20-month 2016 or 9–12-month 2018 injectable-based anti-TB drugs in WHO-recommended regimens	20%	2%	13.6%	2.3% (anemia)	Hearing loss by audiometry: 43%
6BdqLzd$_{600}$LfxPza($_{hd}$Inh or Eto or Trd)	25%	None	24.5%	20.4% (anemia)	Hearing loss by audiometry: 2%
Nix-TB (NCT02333799)					
6BdqPaLzd$_{1200}$	17%	No participant had a QTc≥480 ms	81% n=2 with optic neuritis, resolved with stopping Lzd	48%	Neuropathy resolved in 74% and improved in 15% of cases 2 years after treatment completion[A]
Ze-Nix (NCT03086486)					
6BdqPaLzd$_{1200}$	7%	None	38%[C] n=4 had optic neuritis	22%	
6BdqPa4Lzd$_{1200}$	9%	QTc prolongation >60 ms from baseline: 4% QTc > 500 ms: 2%	24% No cases of optic neuritis	15%	
6BdqPaLza$_{600}$	2%	None	24% No cases of optic neuritis	2%	
6BdqPa4Lzd$_{600}$	7%	QTc prolongation >60 ms from baseline: 2% QTc > 500 ms: 2%	13% No cases of optic neuritis	7%	
TB PRACTECAL (NCT02589782)					
9–20-month WHO standard of care	59%	14%	19%	8% (anemia)	Liver injury: 11%
6BdqPaLzd$_{600–300}$Mxf	19%	1%	9%	3% (anemia)	Liver injury: 4%
6BdqPaLzd$_{600–300}$Clf	32%	4%	8%	None (anemia)	Liver injury: 3%
6BdqPaLzd$_{600–300}$	22%	None	13%	None (anemia)	Liver injury: 3%
BEAT India (CTRI/2019/01/017310)					
6BdqDlmLzd$_{600}$Clf	16.9%	None had QTc > 500 ms	45% (reversed in 75% of cases)[D]	50.9% (anemia)	Hyperpigmentation or acne: 63.3% (faded in 84%)

Treatment Regimen	SAE	QTc prolongation	Peripheral neuropathy	Myelo-suppression	Other
BEAT South Africa (interim analysis NCT04062201)					
$9Bdq_{hd}$InhEmbPzaClfLfx2Lzd	16.9%	1.1%	2.6% (optic neuritis 0.5%)	9.9% (anemia)	
$6BdqDlmLzd_{600}$ (Clf and/or Lfx)	17.3%	1.6%	1.6% (optic neuritis 0.5%)	7.7% (anemia)	

Abbreviations: WHO, World Health Organization; SAE, serious adverse events; $_{hd}$ high-dose; NR, not reported

Drug abbreviations: Bdq, bedaquiline, Clf, clofazimine, Dlm, delaminid; Emb, ethambutol;Eto, ethionamide; Inh; isoniazid; Lzd, linezolid; Lvx, levofloxacin; Mxf, moxifloxacin; Kan, kanamycin; Pa, pretomanid; Pza, pyrazinamide; Pto, prothionamide; Trd, terizidone. $_{hd}$ used to note when higher than usual dose used. Linezolid dose is of special interest and thus it is noted in subscript (e.g., Lzd_{600} means linezolid 600 mg daily).

The numbers indicate the drug treatment duration in months. Example: $6BqdPaLzd_{600}$Mxf means six months of bedaquiline, pretomanid, linezolid (600 mg daily), and moxifloxacin.

A. Adverse events definitions not uniform across trials

B. 2-year outcomes reported at the 2021 Conference on Retroviruses and Opportunistic Infections

C. Higher rates of peripheral neuropathy among South African participants compared to Georgian, Moldovan, and Russian participants across all Ze-Nix trial arms

D. Linezolid reduced to 300 mg in 29% of participants