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Perspective

Intricacies of Global Tuberculosis Management—EndTB-2035 on the Fence?

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Abstract: Tuberculosis (TB) is a leading cause of death from a single infectious agent in humans. The morbidity and mortality due to TB are further worsened by co-existing health conditions and the emergence of drug-resistant (DR-TB) cases. The WHO has declared TB as a global emergency and endorsed global efforts to improve diagnosis, and treatment while reducing the catastrophic cost in an EndTB strategy in 2013, with a vision to create a TB-free world. In the past decade, molecular diagnostic tools, such as nucleic acid amplification technologies (NAATs), have replaced the conventional smear microscopy of TB, thus offering better bacteriological confirmation and case detection along with drug resistance in pulmonary and extrapulmonary samples. Follow-on testing using a more advanced targeted next-generation sequencing (tNGS) system has improved the diagnosis of cases resistant to first- and second-line anti-TB drugs, including newer ones. TB treatment has been improved with the introduction of newer drugs including an all-oral regimen for DR-TB, thereby improving patient compliance. Improved TB prevention is achieved through the broadening of BCG vaccination as well as preventive therapy for asymptomatic, latent TB (LTBI) cases, which, otherwise, can reactivate to symptomatic disease. However, the recent goal of the WHO's EndTB-2035 strategy has been met with significant challenges in the areas of implementing improved diagnosis and treatment modalities in resource-limited TB endemic countries. The complexity of global TB management is confounded by malnutrition, comorbidities with other infectious and non-infectious diseases, and the socio-economic landscape of vulnerable populations. Political commitment to universal health coverage (UHC), including service coverage and reduction in catastrophic cost, are some of the essential components that need to be addressed to achieve the EndTB strategy. In this perspective, we have highlighted the intricacies of global TB management and summarized some of the key challenges that may keep the WHO's EndTB-2035 strategy on the fence.

Keywords: tuberculosis; drug resistance; molecular diagnosis; oral regimen; vaccines; preventive therapy

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1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), remains a significant public health problem globally, necessitating early and efficient diagnosis, including drug resistance profiling. In addition to clinical examination and radiological findings, microbiological methods including smear microscopy, culture, and molecular tests are used in TB diagnosis. While smear microscopy is rapid and inexpensive, culture is slow yet offers drug resistance profiling, highlighting the need for more rapid and efficient molecular

testing combined with drug resistance profiling. Current molecular testing modalities range from decentralized point-of-care (POC) tests to more centralized laboratory-based testing [1,2]. POC tests typically include low-complexity nucleic acid amplification technologies (NAATs), while centralized testing includes moderate-complexity NAATs and next-generation sequencing (NGS) consisting of the whole genome (WGS) or targeted next-generation sequencing (tNGS) [3,4]. In the past decade, three new drugs were approved by the WHO for use in TB treatment, and the definitions of drug resistance have also been revised over the years. TB treatment using all-oral regimens for any form of drug resistance with shortened duration offers promise to improve patient compliance [5,6]. BCG is the only vaccine approved by the WHO to prevent TB, with good coverage in childhood vaccination programs across different countries. Latent TB infection (LTBI) is identified and tested using approved kits in risk groups, and several effective options for TB preventive therapy are available [7,8]. In 2015, the WHO released the EndTB strategy with milestones for reducing TB incidence, deaths, and catastrophic costs by 2035, with UN sustainable development goals set for 2030 [9]. This perspective highlights the changing landscape of TB diagnosis, treatment, prevention, and global status on achieving the milestones to EndTB-2035 (Table 1). To address the gaps in achieving the EndTB-2035 goals, policies on universal health coverage (UHC) and annual funding for TB prevention, diagnosis, and treatment are targeted.

Table 1. Changing landscape in TB diagnosis, treatment, and prevention from 2020 to 2024 *.

Category		Year 2020	Year 2024
		Pre-COVID-19	**Post-COVID-19**
Burden	Incidence	10 million (56% men, 32% women, and 12% children)	10.8 million (55% men, 33% women, and 12% children)
	Mortality	1.2 million deaths	1.25 million deaths
Diagnosis	Diagnostic tests	Upfront molecular testing using low-complexity NAATs, LAMP, and Urine-LAM Follow-on molecular testing for first and second-line drug resistance	Follow-on testing includes rapid molecular testing by tNGS for all anti-TB drugs
	Bacteriological confirmation and rifampicin testing	57% of diagnosed people were bacteriologically confirmed using molecular tests, with 61% tested for rifampicin resistance	62% of diagnosed people were bacteriologically confirmed using molecular tests, with 79% tested for rifampicin resistance
	RR/MDR-TB cases	0.21 million	0.16 million, with an additional 28,982 cases of XDR-TB
Treatment	Regimen for RR/MDR-TB	Shorter oral and longer oral BDQ-containing regimen for RR/MDR-TB patients BPaL regimen in operational research mode	Shorter oral, longer oral and BPaLM regimen for RR/MDR-TB patients BPaL regimen for pre-XDR or XDR-TB patients
	RR/MDR-TB treatment enrolment	0.18 million	0.18 million
	Treatment success rate for RR/MDR-TB	57%	68%

Table 1. *Cont.*

Category		Year 2020	Year 2024
		Pre-COVID-19	**Post-COVID-19**
Prevention	Treatment options for LTBI	6H, 4R, and 3HR	6H, 4R, and 3HR, with the addition of 3HP and 1HP
	Number of potential LTBI cases offered TPT	4.1 million	4.7 million
	BCG vaccination coverage	89%	87%

* Data derived from the WHO Global TB report [10,11]. Absolute numbers for different categories are given wherever available. Abbreviations: TB—Tuberculosis; NAAT—Nucleic acid amplification technology; LAMP—Loop-mediated isothermal amplification; LAM—Lipo arabino mannan; RR/MDR—Rifampicinresistant/multi-drug-resistant; pre-XDR—Pre-extensively drug-resistant tuberculosis; XDR—Extensively drug-resistant tuberculosis; BDQ—Bedaquiline; B—Bedaquiline, Pa—Pretomanid; L—Linezolid; M—Moxifloxacin; H—Isoniazid; R—Rifampicin; P—Rifapentine; TPT—TB preventive therapy; BCG—Bacillus Calmette-Guerin.

2. Technical Challenges in TB Testing

2.1. Improvement in Bacteriological Confirmation and Rifampicin Status with Upfront Molecular Testing

The WHO endorsed the use of rapid molecular tests as an initial diagnostic test for TB as early as 2019 to strengthen the TB laboratory to achieve the EndTB strategy. In 2019, the guideline development group of the WHO made key recommendations to the use of Xpert MTB/RIF, Xpert MTB/RIF Ultra, and Truenat MTB and MTB plus as the initial diagnostic test for use in pulmonary TB along with rifampicin (RIF) testing across all ages. With Truenat MTB and MTB plus, Truenat Dx RIF was performed as reflex testing when Mtb was detected in the sample. While Xpert MTB/RIF was recommended as an initial diagnostic test and RIF testing for pulmonary TB in adults and children, its sensitivity was suboptimal among smear-negative and PL-HIV, which was overcome by Xpert MTB/RIF Ultra [3,4,12]. Among children, Xpert MTB/RIF and Xpert MTB/RIF Ultra were recommended for pulmonary TB detection in sputum, stool, gastric lavage, and nasopharyngeal samples, with its RIF testing in sputum and nasopharyngeal samples with higher confidence. Sputum production or induction in children is challenging, and hence the use of alternative samples for pulmonary TB offers a better diagnosis [3,4]. The diagnosis of extrapulmonary samples is very challenging as obtaining quality samples from different sites could be invasive and tough besides its paucibacillary status [13]. Among the extrapulmonary samples, Xpert MTB/RIF and Xpert MTB/RIF Ultra were recommended for initial TB and RIF testing [3,4]. The Xpert MTB/RIF Ultra usage was indicated specifically for CSF, lymph node aspirates, and lymph node biopsy owing to its paucibacillary status. In PL-HIV adults and children with disseminated TB, Xpert MTB/RIF may be used on blood samples as the initial diagnostic test, thereby improving diagnosis in these individuals [4].

In 2020, moderate-complexity NAATs including RealTime MTB and RealTime MTB RIF/INH (Abbott, Chicago, IL, USA), BD Max MDR/TB (BD Lifesciences, Franklin Lakes, NJ, USA), Cobas MTB and Cobas MTB-RIF-INH (Roche, Munich, Germany), as well as Fluorotype MTBDR and MTB (Hains Lifesciences/Bruker, Nehren, Germany), which are all fairly automated, were recommended as initial diagnostic tests with their use in settings where high load testing is feasible [4]. Further, the WHO recommended loop-mediated isothermal amplification (LAMP) and the lateral flow urine lipoarabinomannan (LAM) assay as initial diagnostic tests for TB [3]. In 2015, the Alere Determine TB LAM Ag test, developed by Abbott, Palantine, USA, was recommended as the initial diagnostic test for the detection of pulmonary TB in adults with HIV. These strip tests on urine have limited sensitivity as an overall initial test while offering superior detection in HIV-infected

individuals, particularly seriously ill patients, or those having low CD4 counts [14,15]. The LAMP assay, developed by Eiken Chemical, Tokyo, Japan, diagnosed TB in one hour with the help of UV light. In 2016, the LAMP assay was recommended as the initial diagnostic test replacing smear microscopy for pulmonary TB diagnosis in adults. Additionally, LAMP can be used as a follow-on test to smear microscopy when the smear is negative in adults with presumptive TB [16]. Improved molecular testing as an initial diagnostic test offers improved bacteriological confirmation and increased RIF testing. The bacteriologically confirmed TB was 57% in 2019 but has risen to 62% with the offer of molecular tests as the initial diagnostic testing for TB. Among the 48 high-burden countries, only 18 have reported using molecular tests as the initial diagnostic test. While 33% of newly diagnosed cases were tested with rapid molecular tests in 2020, this percentage had increased to 48% by 2024 but is significantly way behind the expected use for initial diagnosis of TB [10,11]. Among the bacteriologically confirmed cases, only 61% were tested for RIF resistance in 2019, though the number had increased by 79% in 2024 [10,11]. In 2019, 206,030 people with MDR/RR-TB were detected while there were 188,666 RR/MDR-TB cases in 2023, including pre-XDR and XDR-TB [10,11]. Overall, global data indicate that although many molecular tests are approved and endorsed by the WHO, there is a need for improved usage of molecular tests as initial diagnostic tests. The currently available predominant molecular tests offer RIF testing in the same sample and should be strictly adhered to for better drug susceptibility testing (DST).

2.2. Follow-On Testing for Additional Resistance and Newer Definitions of Drug Resistance

With the initial diagnostic test indicating the detection of TB, follow-up tests are required for the assessment of additional drug resistance. While low- and moderate-complexity NAATs can detect resistance to RIF and/or isoniazid (INH), follow-on testing is required for fluoroquinolones (FQs) and second-line injectable drugs (SLIDs). Initially, line probe assay (LPA), which is a strip-based technology, was largely used as a follow-on test. Hains first-line LPA (FL-LPA) MTBDRplus ver1.0 and 2.0 (improved sensitivity for INH) and NTM+MDRTB II developed by Nipro (Tokyo, Japan) used probes for the detection of RIF and INH. All these FL-LPA kits were recommended on sputum smear-positive sputum samples from adults and children. However, LPAs were not evaluated for use in other respiratory or extrapulmonary samples as a preferred test over phenotypic DST, though, in practice, it is routinely used in smear-positive specimens as well as in culture [3,4]. Second-line LPA (SL-LPA) kits commercially developed by Hains were available as MTBDR*sl* ver 1.0 and ver 2.0. Hains MTBDR*sl* ver 1.0 detected resistance to FQs by *gyrA*, SLIDs by *rrs*, and ethambutol by *embB* genes on smear-positive sputum specimens from confirmed pulmonary TB patients. MTBDR*sl* ver 2.0 was updated to include the *gyrA* and *gyrB* genes for FQ detection, and the *rrs*, and *eis* genes for SLIDs, which could be used in both sputum-smear-positive and -negative cases. The use of SL-LPA on other respiratory and extrapulmonary samples is yet to be evaluated [3,4]. In 2021, the WHO endorsed the use of a high-complexity NAAT, Genoscholar PZA-TB II (Nipro), for detecting resistance to PZA using probes for the *pncA* gene. The test is recommended for testing on Mtb culture isolates, with studies from sputum samples insufficient to support diagnostic accuracy [3,4].

Although many kits have been commercially developed as follow-on tests, they necessitate the collection and transport of second specimens to higher level/more sophisticated laboratories in case of moderately complex NAATs, thus hindering prompt DST using molecular methods. To overcome this, low-complexity NAAT like Xpert MTB/XDR was developed for the detection of resistance to INH, ETH, FQs, and SLIDs, offering the possibility of using the same sample. In 2021, the WHO's TAG analyzed the use of 10-color optics technology for MTB/RIF or MTB/RIF Ultra, which was a requisite for the use of

Xpert MTB/XDR. Both 6- and 10-color optics technology was found suitable for testing using MTB/RIF or MTB/RIF Ultra. The WHO recommended the use of 10-color optics for MTB/XDR with the same reagent system and used in sputum samples where MTB and/or rifampicin resistance is detected [4,17]. ETH resistance detection by MTB/XDR is preferred over NGS technology of sequencing the *inhA* promoter. In addition, amikacin detection by MTB/XDR is preferred over phenotypic DST [4].

Until 2021, XDR-TB was referred to RR/MDR-TB cases with additional resistance to fluoroquinolones and SLID. However, in 2021, the WHO released a statement defining drug resistance in TB, which indicated that XDR-TB encompasses RR/MDR-TB cases with resistance to any FQs and at least one additional group A drug [18]. Hence, the emphasis went to the testing of drugs beyond FQs and SLIDs. Group A drugs included FQs, linezolid (LZD), and bedaquiline (BDQ), where no POC or NAAT testing was available for LZD and BDQ and relied on phenotypic DST. In 2023, the WHO endorsed the use of tNGS which uses the amplification of multiple targets in a single test. For bacteriologically confirmed TB cases, tNGS could be used on respiratory samples for the detection of resistance to RIF, INH, FQ, PZA, and EMB. For respiratory samples with RIF resistance detected in patients, tNGS could be used for the detection of resistance to drugs, as stated above, and, in addition, LZD, BDQ, clofazimine (CFZ), amikacin, and streptomycin. Deeplex Myc-TB (Genoscreen, Lille, France), AmPORE-TB (Oxford Nanopore Diagnostics, Oxford, UK), and TBseq (Hangzhou ShengTing Medical Technology Co., Hangzhou, China) are products endorsed by the WHO for tNGS. However, tNGS could be used to ensure rapid comprehensive DST for patients at risk of drugs in RR/MDR-TB treatment, pre-XDR patients, and treatment non-responders, but cannot be used as a replacement for phenotypic DST [4,19]. Improved testing using tNGS requires training and refined data interpretation for drug resistance prediction. tNGS can be implemented in a programmatic setting with proper planning and the use of simple NGS platforms for running the tests in medium labs, with data interpretation performed in higher-level labs [20].

2.3. Alternative Samples for TB Testing and Concept of Improved Diagnostic Yield

Despite rapid molecular testing being used as an initial diagnostic test, replacing smear microscopy and a battery of molecular testing-based follow-up tests for drug resistance up to tNGS, effective routine TB testing has not yet been achieved. One possible reason is specimen unavailability in key populations like children and PL-HIV who fail to produce sputum, people with EP-TB, and subclinical TB. The diagnosis of EP-TB is still challenging and requires specialized diagnostic techniques, which are limited in high-TB-burden countries with low-resource settings. Sputum induction is laborious and requires time and expertise to collect a good sample. However, the WHO recommends the use of samples like stools, nasopharyngeal aspirate, and bronchoalveolar lavage as an alternative to sputum in children. Similarly, urine is used for PL-HIV to test for LAM, and in the case of miliary TB in PL-HIV, blood samples can be used in Xpert MTB-RIF [3]. Tuberculosis tests with an average sensitivity will give higher positivity when a more feasible specimen is used than a highly sensitive test that works with a sputum sample. The diagnostic yield of a TB test is a valuable tool that identifies the proportion of people in whom TB was detected among the people in whom testing was attempted. Diagnostic yield considers the superior specificity of a test over its sensitivity and explores the option of an alternative and more feasible sample for testing. The diagnostic yield concept in TB testing can improve effective population coverage for TB screening, bridging the gap currently observed by using molecular tests only for sputum samples [21]. Non-sputum specimens like saliva, throat swabs, oral swabs, tongue swabs, face mask sampling, exhaled breath, dental plaque, and even cough aerosols are considered as alternative options for TB testing. Several kits are

currently in the pipeline, developed to assist with non-sputum testing and thus promising better TB detection in addition to existing diagnostic methods [22,23].

3. Clinical Challenges in TB Treatment

3.1. Introduction of Newer Anti-TB Drugs

In 2016, levofloxacin, moxifloxacin, and gatifloxacin were classified as Group A drugs; the SLIDs amikacin, kanamycin, and capreomycin as Group B drugs; and ETH, LZD, cycloserine (CS), and CFZ as Group C drugs, while BDQ and DLM belonged to group D2 [24]. Until 2018, the treatment guidelines for RR/MDR-TB prompted the use of FQs and SLIDs in shorter and longer regimens whereas ETH or CS/PAS were used in longer regimens. In 2018, isoniazid-resistant TB with documented sensitivity to RIF was classified as Hr-TB and treated with RIF, ETH, and PZA (REZ) with or without INH. Observational studies included FQs along with REZ for 6 months during this period [25]. The introduction of newer drugs like BDQ in 2012 and delamanid in 2014, approved by the WHO for the treatment of DR-TB, have prompted clinical trials with these drugs to be included in the treatment of RR- or MDR-TB [15]. The critical concentration for phenotypic DST was established for BDQ and DLM in 2017 [26]. In 2018, FQs, BDQ, and LZD were classified as Group A agents; CS and CFZ as Group B agents; and the rest, except for RIF and INH, belonged to Group C. The shorter regimen for RR/MDR-TB included 9–12 months with the inclusion of FQs and SLIDs. Pregnancy, severe forms of EP-TB like CNS or disseminated TB, and EP-TB in PL-HIV were excluded from the regimen. The longer oral regimen included three drugs from Group A and one drug from Group B, with BDQ included from age 6 years and DLM from age 3 years. Amikacin or streptomycin can be included in the longer MDR regimen based on susceptibility [25]. Except for Hr-TB, the compliance of patients in RR/MDR-TB was poor due to the longer duration and the use of injectable drugs, highlighting the need for better treatment options.

3.2. All-Oral Treatment Regimens for RR/MDR-TB

BDQ containing a long oral regimen with Group A and B drugs initiated the phase of an all-oral regimen for DR-TB. The shorter oral and BPaL regimens were an additional all-oral regimen that started in 2020 for RR/MDR-TB patients with BDQ in the intensive phase. A shorter oral regimen had BDQ for 6 months with LFX-ETH-EMB-INH^{h}, PZA, and CFZ for 4 months. All RR/MDR-TB patients without FQ resistance, INH resistance either due to *katG* or *inhA* genes but not both, and no extensive pulmonary disease or severe forms of EP-TB were eligible for 9–11 months of treatment [5]. The WHO recommended the use of BPaL which included BDQ, PTM, and LZD in an operational research mode (as part of the NIX-TB trial where the dose of LZD was 1200 mg) for RR/MDR-TB patients with additional FQ resistance [5]. Pretomanid was approved as a TB drug in 2019, with a critical concentration for phenotypic DST yet to be validated. Also, DST for CS, ETH, EMB, imipenem/meropenem, and PAS is unreliable for DST [6]. In 2022, the WHO recommended using the BPaLM regimen (LZD at 600 mg) for RR/MDR-TB patients > 14 years of age as the first choice of regimen. Patients with severe forms of EP-TB, pregnant and breastfeeding women, anemic individuals, and those with known resistance to drugs in the regimen can be excluded. When FQ resistance is detected, MFX is omitted and continued as BPaL [6]. By 2023, 58 countries (41 countries in 2022) globally had adopted the 6-month all-oral BPaLM or BPaL regimen for the treatment of RR/MDR-TB or pre-XDR-TB. The 9-month, shorter oral regimen has been adopted in 100 countries worldwide [16]. The treatment success rate for DR-TB was 68% in 2021 (outcome declared), compared to 60% in 2019 (GTB report 2024). With the ease of fixed-dose combination in BPaLM and BPaL, and a shorter all-oral regimen, better TB prognosis and treatment outcome can be expected in the coming years.

The limited access to the new drugs, which are active on MDR and XDR-TB in most of the high-TB-burden countries, poses additional challenges for TB management.

4. Challenges in TB Preventive Therapy

4.1. Definition of Population for LTBI Testing and Preventive Therapy

The population infected with TB rather than producing an active disease should be monitored and provided with preventive therapy to avoid progression into active TB disease. Once infected, people with LTBI have a 5–10% chance of progressing to TB disease in their lifetime [27]. The implementation of the WHO guidelines over the past 5 years has successfully identified the population for LTBI testing. Accordingly, people with HIV, household contacts of TB, risk populations who are undergoing anti-TNF treatment or dialysis, transplantation patients, and people with silicosis are offered testing for LTBI and preventive treatment. LTBI testing may be extended to prisoners, immigrants, the homeless, and people with drug abuse. Although LTBI testing is important for the risk group, TB disease should be ruled out [28]. In this case, combination of symptom checks (four symptoms like cough for more than 2 weeks, night sweats, fever, and weight loss), C-reactive protein (CRP) testing, chest X-ray, and molecular diagnosis should be used [7,8].

4.2. Improved Diagnosis of LTBI Cases

Once the population is identified for LTBI testing, they are tested for Mtb infection. Previously, tuberculin skin testing (TST) and immunoglobulin release assay (IGRA) were used, but in 2022, TB antigen-based skin testing (TBST) was added to this list for LTBI testing [7,8,29]. While TBST is superior to TST, it requires trained staff to administer it and interpret the results; it also needs a cold supply and vials should be properly maintained for multiple doses. In comparison, IGRA testing is expensive and requires extensive laboratory services including venipuncture and sophisticated equipment. TST is less cumbersome but, like TBST, it requires multiple visits and manual interpretation. The operational feasibility of the three methods is considered while performing the testing as all of them are indirect, depend on the immune response of individuals, and are considered unrelated to the history of childhood BCG vaccination [8,29]. Apart from TST, three products for IGRA testing, namely, QuantiFERON Gold (Qiagen, Germantown, MD, USA), QuantiFERON-TB Gold In-Tube (Qiagen), and T-SPOT.TB assays (Oxford Immunotec, Abingdon, Oxfordshire, UK), are available [8]. Three kits available for TBST are Cy-Tb (Serum Institute of India Pvt. Ltd., Pune, India), C-TST (Anhui Zhifei Longcom Biopharmaceutical, Chongqing, China), and Diaskintest (Generium Pharmaceuticals, Moscow, Russia) for Mycobacterium antigen skin testing [8,29].

4.3. TB Preventive Treatment Regimen

The classical TB preventive therapy (TPT) ded a 6-month INH (6H) regimen which showed a reduction in TB incidence in positive TST individuals. Another regimen used in TPT is 3HR where 3 months of INH and RIF were given, and which showed lesser adverse effects and better adherence. The 3HP regimen is a relatively short once-weekly dose of INH and Rifapentine for 3 months, and studies showed similar TB incidence as the 6H therapy. The 4R regimen, which is daily RIF therapy for 4 months and 1HP consisting of 1 month of Rifapentine and INH daily, was also given as TPT. Overall, 3HR was preferred in individuals <15 years of age and 4R in high-burden settings. While 1HP was considered non-inferior to 6H, 3HP was given under direct observation during the trials, warranting an operational barrier under the field settings (WHO TPT 2020, 2022, and 2024). In 2019, before the COVID-19 pandemic, 4.1 million people were offered TPT, a rise from 2.2 million people in 2018. Among the 0.53 million household contacts offered TPT, 81% were children

less than 5 years of age. In 2023, 4.7 million people were offered TPT with a considerable increase in HHC, which accounted for 2.7 million people.

4.4. Vaccination for TB Prevention

In 2019, BCG was the only licensed vaccine and was included as childhood vaccine coverage in 153 countries. There were 14 vaccine candidates in different phases of clinical trials, with M27/AS01E (developed by the Gates Medical Research Institute) showing promising results in phase IIb [15]. In the post-COVID-19 era, in 2023, there were 15 vaccine candidates in different phases of clinical trials. BCG continues to be the only licensed vaccine, with M27/AS01E being in a phase III clinical trial. BCG vaccination coverage was 89% in 2019 and 88% in 2023, thus maintaining a steady coverage across the pandemic [16].

5. Operational Challenges in Achieving EndTB-2035

5.1. Disruptions in TB Testing Due to COVID-19 Pandemic

The global burden of TB in 2019 was 7.1 million people newly diagnosed with TB and a death rate of 1.2 million [15]. Among the new cases, 58% were men, 34% women, and 8% children. With the COVID-19 pandemic, new TB case notification was reduced in 2020 to 5.8 million, which is an 18% decline from the previous year of notification. In addition, 1.4 million TB deaths were estimated, which was high due to reduced TB notification. Sixteen countries contributed to 93% of this reduction, with India (41%), Indonesia (14%), and the Philippines (12%) leading the list. The gap was probably due to the lack of supply and demand for TB testing [30]. Poor TB testing could be attributed to less access to health care facilities due to lockdown restrictions, symptoms prompting COVID-19 testing rather than TB, the availability of technicians to carry out the TB testing as many health care professionals were routed out to COVID-19 testing, and NAAT facilities in high-burden countries being mobilized for COVID-19 testing. Over the years, TB testing and reporting systems have increased, overcoming the COVID-19-related derangement. In 2023, there were 8.2 million new cases of TB with a reduction in TB deaths to 1.25 million compared to 1.32 and 1.42 million in 2022 and 2021, respectively, during the COVID-19 era. In total, 55% of people diagnosed were men, 33% were women, and 12% were children, indicating an improvement in pediatric TB testing [16]. In 2019, TB was the leading cause of death among infectious diseases due to single pathogen, which was superseded by COVID-19 until 2023, when TB returned to the top of the list [15,16]. Regarding the EndTB milestones on the reduction in TB incidence, 9% was achieved by 2019, which was reduced to 8.3% in 2023, while the corresponding reduction in deaths was 14% in 2019 and 23% in 2024, though the EndTB milestone was 75% reduction in 2025 compared to 35% in 2020. Globally, only one-third of the target is achieved, though the African (42%) and European (38%) regions have made great progress in reducing TB deaths [9,15,16]. With the era of the COVID-19 pandemic probably coming to an end and improved diagnosis and treatment modalities available for TB, we expect to meet these targets soon.

5.2. Role of Social Determinants in TB Testing

From the pre-COVID-19 era to the present, five risk factors, namely, malnutrition, HIV, diabetes, smoking, and alcohol abuse, have contributed to new TB cases. All these factors are considered social determinants, with data collected globally to offer comprehensive social protection [15,16]. Recent emphasis is laid on the additional vulnerable populations, as a trend analysis over 7 years (2015–2022) has indicated the need to address them to achieve the EndTB-2035 goal. Populations affected by forced displacement and homelessness showed an increased trend in undernutrition, highlighting the need for commitment to these population groups. The forced displacement of communities contributes to the

TB burden in terms of poor treatment outcomes or mortality due to a lack of awareness, social stigma, less access to health facilities owing to distance and cost, interruptions in diagnosis or treatment, and the loss of medical records, thereby making the EndTB milestones unachievable on time [31]. In 2023, the WHO recommended the supplementation of micronutrients like Vitamin A, E, D, iron, zinc, and selenium among children and pregnant and breastfeeding women. Calcium needs to be supplemented in low-calcium settings as part of antenatal care in addition to macronutrient supplements for adults and children with active TB [32,33]. The recent WHO report has emphasized offering comprehensive care to people in vulnerable situations like PL-HIV, children, older people, pregnant and lactating women, individuals with TB disease-associated disabilities, refugees, migrants, displaced people, and prisoners. This includes nutrition, palliative care, rehabilitation, and social, mental, and psychological support, as required by different people [16].

5.3. Need to Strengthen Universal Health Coverage (UHC)

Apart from the prominent EndTB milestones of reduced TB incidence (90%) and reduced death rate (95%), the third milestone is set to achieve 0% of TB-affected people facing catastrophic cost [9]. To achieve this, there is a need to strengthen UHC, which ensures that all TB patients have access to health services and such access does not incur any financial burden. Equity in access to quality health services, safe, effective, and affordable TB testing of good quality, and TB medicines and vaccines is essential. UHC is measured by two indicators, namely, the service coverage index (SCI) and catastrophic cost globally. The SCI increased from 45 to 68 (out of 100) between 2000 and 2019, with the increase observed among all the six WHO regions and, more specifically, in 30 high-burden countries [15,16]. When a TB patient incurs 10% or more of household expenditure towards TB care, this is defined as a catastrophic cost. Unfortunately, financial protection has worsened and catastrophic costs rose from 11.4% in 2010 to 13.5% in 2019 [16]. A global survey from 35 countries on catastrophic costs was consolidated in 2024, which included data from 18 of the 30 high-TB-burden countries. According to this report, the pooled average for the percentage of people facing catastrophic costs was 49%, which rose to 82% when it was calculated for DR-TB patients. The political commitment to EndTB has stepped up and high-level meetings were conducted in 2018 and 2023 to mobilize funds globally to achieve the milestones of EndTB-2035 were established. The funding of USD 35 million in 2023 was approved to provide UHC along with TB prevention, vaccines, diagnosis, treatment, and comprehensive care. A target of 100% is set in 2027 for rapid molecular testing, 90% for prevention, and 90% for treatment coverage [16].

5.4. Economic Evaluation and Improving Finance for TB Management

From the nation-level TB management perspective, government bodies and policymakers need to realize that issues in TB management should be paralleled with the overall health care challenges of their nation, necessitating an economic evaluation and ways to improve finance, particularly in resource-limited countries to improve TB care coverage. A recent study provided insights into the financial profile of TB management in many countries during the financial years 2006–2021. This WHO report-based study analyzed various financial sources like domestic funding, global funding, and grants across 131 countries in the Americas, Europe, Asia, Africa, and Oceania (Australia), and estimated the year-wise financial burden for TB management [34]. Accordingly, the overall domestic funding was 3.75 times more than global funding and 17 times more than the grants between the years 2006 and 2021, peaking particularly in the years 2010–2013. Domestic funding for TB management was highest in all countries across all continents, except Africa where global funding was higher, probably due to global attention, since Africa hosts nearly half of

the high-TB-burden countries globally, as listed by the WHO [34]. Countries with a high TB burden, such as India, have ramped up efforts on the commitment of central to local stakeholders/government bodies to effective TB management [35]. In countries with a high TB burden, such as India, Indonesia, and China, the national TB program contributes to TB management as part of their routine health care services and financing system. In these countries, either a private–public partnership or largely the public sector remains as the key for TB management, primarily offering symptom checks and radiology, and then ensuring treatment adherence once TB is diagnosed and treatment started. Geographical inaccessibility; a lack of knowledge, proper incentives, and supervision; high out-of-pocket expenses; the limited coverage of diagnostics and drugs; the non-coverage of health insurance for outpatient services, a lack of multi-sector engagement; social and cultural stigmatism towards TB; and the health-seeking behavior of individuals are beyond those vertically driven programs mentioned previously [27,36].

In several TB-endemic countries, domestic funding is a major contributor to the cost of TB management, with promises for further increase through resource mobilization, planning budget cycles, and efficient resource tracking [36]. Apart from the exclusive vertical approach through funding for TB, the involvement of primary health centers and the private–public partnership approach are documented to improve TB management. Importantly, the primary health care (PHC) setting can provide equitable access to quality and affordable health services, followed by effective referral to the next level and continuity of care wherever required. Furthermore, the WHO has underpinned the adoption of PHC to achieve the standard of UHC by offering community-based health services along with social protection [37]. In countries with large private sectors, the private and informal sectors become the point of care for about 60–80% of health-seeking behaviors among women and the ill; however, the disengagement of such private/informal sectors from national TB programs in high-TB-burden settings is alarming for the overall TB management strategies. Indeed, epidemiological studies conducted in countries experiencing a good public–private mix (PPM) have demonstrated better TB detection and treatment outcomes [38,39].

Studies have shown a positive correlation between a country's GDP and spending per incident TB case globally. In addition, the GDP has increased in recent years among several high-TB-burden countries, including India and China, which also resonates in their corresponding spending per incident TB case. However, the average spending per incident TB case was lower in the low- and middle-income countries (LMICs), compared to the upper- and middle-income countries (MICs), with government spending more on managing TB care among other infectious diseases, which are already short-funded [40,41]. Among the WHO's list of indicators for sustainable development growth (SDG), the GDP per capita was included with a recommendation of sustaining the per capita growth according to national agreements and increasing GDP growth by 7% at least in the least developed countries [16].

6. Conclusions

Both active and latent TB are a significant global public health concern due to their associated morbidity and mortality. In June 2013, the WHO's Strategic and Technical Advisory Group for TB endorsed the global targets to achieve regarding EndTB after the strategy was consolidated in line with national TB management in high-TB-burden countries. According to the EndTB strategy, a goal to reduce TB deaths by 95%, incidence by 90%, and catastrophic cost to 0% was aimed to be achieved by 2035. There has been immense progress in the areas of diagnosis, treatment, and prevention of TB, particularly active pulmonary TB, though it still seems challenging to reach the target of EndTB-2035. With the identification of potential challenges and opportunities, global targets for TB

elimination that are currently facing a setback may be achievable by 2035, as declared by the WHO.

This perspective analyzes the challenges and potential solutions in the following areas of TB management:

(a). In 2020, WHO endorsed the use of rapid molecular tests as the initial diagnostic test for the confirmation of TB, replacing smear microscopy. Low- and moderate-complexity NAATs were recommended for respiratory samples from pulmonary TB along with the detection of RIF resistance or RIF and INH, thus enhancing the rate of bacteriological confirmation of TB.

(b). For paucibacillary samples like smear-negative ones and samples from PL-HIV, children, and EP-TB patients, Xpert MTB/RIF Ultra was superior to Xpert MTB/RIF. Besides sputum, alternative samples like stools, nasopharyngeal aspirate, and gastric lavage could be used to test pulmonary TB. For PL-HIV patients, urine testing was performed using LAM and a blood sample in Xpert MTB/RIF. With molecular tests, the bacteriological confirmation of TB continued to improve.

(c). Line probe assays (Hains and Nipro) were performed for RIF, INH, ETH, FQs, SLID, and PZA recommended on respiratory samples (Mtb culture for PZA) for additional drug resistance. However, the collection and transport of a second sample caused delays and the failure of additional testing in many cases. The introduction of Xpert MTB/XDR (which detects INH, FQs, SLID, and ETH) as a low-complexity NAAT which can be used with the same buffer system as MTB/RIF or MTB/RIF Ultra optimized rapid DR-TB diagnosis.

(d). Additionally, the introduction of tNGS from respiratory samples with higher bacillary loads promises rapid DST for a fair share of pulmonary TB patients with access to the facility. tNGS can be used in different platforms across medium- and high-end/advanced labs offering flexibility for rapid DR-TB diagnosis over phenotypic DST, particularly for newer drugs.

(e). Despite the advances in DR-TB diagnosis, only 48% of new cases were diagnosed using molecular tests for initial diagnosis. This emphasizes that patients lack access to health care due to intricate reasons that need to be addressed.

(f). Initial TB treatment regimens were longer with SLIDs, contributing to lower adherence and patient compliance. The importance of HR-TB was recognized, and an all-oral, 6-month regimen was introduced in 2018. Also, newer drugs like BDQ, DLM, and PTM were introduced for the RR/MDR-TB regimen in the past 10–15 years, effecting a huge change in treating TB.

(g). In 2020, all-oral shorter regimens were introduced for RR/MDR-TB, with an additional BPaL regimen in operational research mode and further inclusion of BPaLM in 2022. These shortened the treatment and oral medication, and promised better patient compliance. However, only 75% of treatment coverage was attained in 2023, which fails to reflect the advantages of the newer regimen, indicating the need for an improved initiation of treatment after diagnosis.

(h). BCG is the only approved vaccine to prevent TB with 88% coverage globally, but there are 15 vaccine candidates in different phases of clinical trials offering promise for better vaccination.

(i). LTBI testing has improved with TST, IGRA, and TBST approved for selected populations based on the operational feasibility of use. Different TPT regimens are available that can be chosen, with improved coverage of household contacts reported in 2023 compared to previous years.

(j). The COVID-19 pandemic worsened TB diagnosis and access to health care between 2019 and 2021, but this improved in 2022 and 2023. NAATs were directed to COVID-19

testing in many countries, causing an interruption in TB testing. In 2023, there was an increased trend in the diagnosis and treatment of TB cases.

(k). Risk factors including diabetes, malnutrition, HIV, smoking, and alcohol abuse were considered for TB. However, additional vulnerable populations like pregnant and breastfeeding women, refugees, homeless people, prisoners, migrants, and displaced people are known to contribute to poor TB management. There is a need for the implementation of comprehensive domestic medical screening for LTBI among migrants or refugees when they arrive, in particular into low-TB-burden countries, such as the USA.

(l). UHC is advocated in terms of service coverage and reducing catastrophic costs. Strengthening UHC with political commitment and proportionating funds for TB management is globally planned for enhanced TB management.

(m). Economic evaluation with increased financial profiling is required for improved TB management, particularly in resource-limited countries. Domestic funding contributes to the majority of national TB management costs, with additional scope for resource mobilization and disease tracking as well as planned budgeting. In addition to the vertical national TB program, private–public partnerships and the role of PHC are vital for effective TB management.

In summary, a considerable improvement has been seen globally among the different lines of TB management strategies, such as diagnosis, treatment, and prevention (Figure 1).

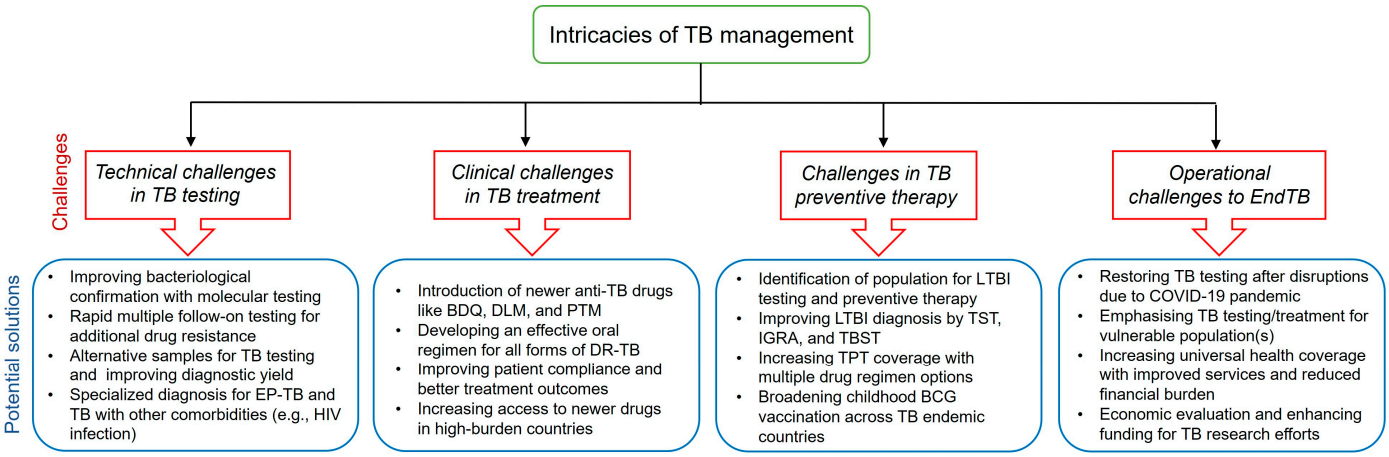

Figure 1. Intricate challenges and potential solutions for effective TB management towards EndTB. TB—Tuberculosis; EP-TB—Extrapulmonary TB; BDQ—Bedaquiline; DLM—Delamanid; PTM—Pretomanid; DR-TB—Drug-resistant TB; LTBI—Latent TB infection; TST—Tuberculin skin testing; IGRA—Immunoglobulin release assay; TBST—TB antigen-based skin testing; TPT—TB preventive therapy; BCG—Bacillus Calmette-Guerin.

Over the years, TB diagnosis has been progressively shifting away from conventional smear microscopy towards more rapid molecular tests, including the most advanced sequencing techniques, particularly in high-TB-burden countries such as India, China, and South Africa. However, diagnosis is very challenging for EP-TB, and TB among children, and in individuals with underlying health conditions, including HIV infection and diabetes, owing to the paucibacillary status and/or difficulty in sample collection. To overcome these hurdles, alternatives to sputum samples, such as urine and feces, are considered for TB diagnosis, along with specialized techniques for multi-modal diagnosis. In addition to the improvements in diagnosis, TB treatment has made significant progress recently with an oral regimen with a shortened duration for DR-TB, thus promising better patient compliance. Though BCG is still the only vaccine approved by the WHO, several candidate

TB vaccines are in the pipeline and are being evaluated for their safety and/or efficacy in clinical trials. Advancement has also been made in identifying LTBI cases, with a wide choice of TB preventive therapy for a broader coverage of contacts and high-risk groups. Similarly, nationwide UHC with increased service coverage and reduced catastrophic costs to patients is planned to be achieved with better funding. Economic evaluation among high-TB-burden countries indicates increasing contribution by domestic funds, which can be improved by international resource mobilization and funding from developed countries through the various United Nations health programs. The efficacy of TB management in routine health care can be improved using a multisector approach over a vertical line, thereby including PHC as well as private–public partnerships, as elaborated in a recent publication [35]. By addressing the gaps and challenges in TB management discussed thus far, the END-TB goal as set by the WHO may be achieved by 2035.

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