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Review

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Faster, higher, stronger: the evolution of clinical perspectives on pan-TB

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Abstract

The landscape of tuberculosis (TB) treatment is evolving rapidly, especially in the face of drug-resistant strains. This review explores the historical and contemporary developments in drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB) therapies, with a focus on the emerging role of pan-TB strategies. Using a non-systematic literature review method, we analyzed peer-reviewed articles, clinical trial reports, and studies on DS-TB, MDR-TB, and pan-TB approaches published from January 2000 to December 2023. Our findings highlight significant advancements in TB therapies, including the WHO-endorsed four-month regimen for DS-TB and the all-oral BPaL/M regimen for MDR-TB. Pan-TB initiatives, such as the BPMZ regimen by TB Alliance and the Project to Accelerate New Treatments for Tuberculosis (PAN-TB), aim to develop universal regimens for both DS-TB and MDR-TB, showing promise in enhancing treatment efficacy and patient adherence. Continuous innovation and adaptable strategies are crucial in the fight against TB. Pan-TB approaches have the potential to effectively address both DS-TB and MDR-TB, and recent advancements underscore their importance. Future research should focus on extensive clinical trials to validate these strategies and explore innovative methods to improve treatment adherence and efficacy. This review provides valuable insights for clinicians and researchers, emphasizing the importance of developing and implementing effective, universally applicable pan-TB treatments, which are critical for improving patient outcomes and advancing global TB control efforts.

Keywords: Tuberculosis, drug-susceptible tuberculosis, multidrug-resistant tuberculosis, short-course, pan-TB

INTRODUCTION

The treatment landscape for tuberculosis (TB) has significantly evolved since its emergence as a major health concern in the 19th century[1]. This review critically examines the historical and modern advancements in the management of drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB).

Originally, TB treatments were elementary and largely ineffective. A landmark development occurred with the introduction of streptomycin in the mid-20th century[2-4], marking a significant shift in TB therapy. This was further advanced by the advent of oral medications such as isoniazid[5] and rifampicin[6]. The 1970s-1980s saw the standardization of a six-month treatment regimen, significantly enhancing patient outcomes and simplifying treatment methodologies[7-9].

The focus of the late 20th and early 21st centuries has been on optimizing TB therapy, aiming to reduce treatment duration and improve efficacy. Recent developments include new treatment regimens, strategies for preventing drug resistance, and more individualized patient approaches. Notably, the WHO's 2022 endorsement of a four-month treatment regimen[10,11] and studies like TRUNCATE-TB[12] represent significant progress in this area.

The rise of MDR-TB in the mid-1990s necessitated intensified research. The classical HRZE regimen faced challenges in the 1990s as the epidemic of drug-resistant tuberculosis (DR-TB) grew, primarily characterized by MDR-TB. In the absence of effective treatments for resistant strains, the typical approach has involved a regimen of 4-5 drugs over a duration of at least 18 months. Nevertheless, the success rate was only approximately 63%. The extensive duration of treatment imposes significant burdens on patients and raises issues on adherence. Since then, the treatment pathways for DS and MDR-TB have diverged and become more distinct, to the extent that they appear to be two different diseases rather than two forms of the same disease. This difficulty in MDR-TB treatment led to the continuing development of innovative short-course treatments and all-oral regimens. This review highlights pivotal studies and WHO guidelines that are reshaping the treatment of MDR-TB.

Moreover, this review emphasizes the importance of ongoing research efforts, such as the pan-TB initiative, in developing universal and effective TB treatment strategies. The concept of pan-TB first appeared in the WHO's 2016 Target Regimen Profiles (TRP) for TB Treatment, and serves as a complementary notion to DS-TB and MDR-TB. Here, "pan" denotes broad applicability. In 2023, the WHO further emphasized the importance of the pan-TB strategy in the TRP for Tuberculosis Treatment 2023 Update. The Project to Accelerate New Treatments for Tuberculosis (PAN-TB), established in 2021, is the first collaboration aiming at accelerating the identification of promising pan-TB regimens to offer improved safety and tolerability, a shorter duration, and greater simplicity compared to existing treatment options. In brief, PAN-TB is the name of a collaboration, while pan-TB represents a research direction and a therapeutic strategy, characterized by a set of design principles and target requirements but lacking a successful concrete treatment regimen thus far. The exploration of pan-TB may progress either through a breakthrough approach or gradually over time.

In summary, this review presents a thorough overview of the evolution of TB treatment, demonstrating a dynamic interplay between medical science, public health policy, and patient-centered care. It underscores the continuous pursuit of more efficient, shorter, and universally applicable treatment regimens, a journey that remains central to the global fight against TB.

METHODOLOGY

This mini-review was conducted through a non-systematic literature search. The primary source of information was PubMed, with additional data obtained from clinical trial registries and the authors' expertise. The review focused on TB treatments, including DS-TB and MDR-TB, with a special emphasis on pan-TB strategies. The literature search included peer-reviewed articles, clinical trial reports, and significant studies published from January 2000 to December 2023.

The search strategy involved searching databases such as PubMed, clinicaltrials.gov/, and www.newtbdrugs.org/pipeline/trials using search terms including "Tuberculosis treatment", "drug-susceptible TB", "multidrug-resistant TB", "pan-TB", "short-course TB treatment", and "TB clinical trials". The inclusion criteria were peer-reviewed articles, clinical trial reports, studies on DS-TB and MDR-TB treatment strategies, and pan-TB approaches published within the specified period. The exclusion criteria were non-peer-reviewed articles, editorials, and opinion pieces.

The selection process included an initial screening at the abstract level to identify relevant studies, followed by a detailed review of shortlisted articles to ensure their relevance and contribution to the field. Key findings from the included studies were then synthesized and discussed, with a focus on advancements, efficacy, limitations, and future trends in TB treatment. To provide a clear overview of the clinical evaluation pathway of pan-TB, Table 1 summarizes the key steps and considerations.

DRUG-SUSCEPTIBLE TUBERCULOSIS

Evolution of treatment for DS-TB [Table 1]

1. 19th to mid-20th century: TB emerged as a significant global health challenge during this period. The mid-1940s saw a pivotal change with the introduction of streptomycin[2-4], marking the first effective anti-TB drug. Its use, however, was constrained due to the necessity for injectable administration[13].

2. 1950s treatment revolution: the discovery of oral drugs, particularly isoniazid[5] and rifampicin[6], marked a transformative era in TB treatment. These drugs significantly improved treatment outcomes and facilitated patient-friendly administration.

3. 1970s-80s standard treatment regimen: the establishment of a standard six-month regimen, comprising isoniazid, rifampicin, pyrazinamide, and ethambutol, characterized this era[7-9].

4. Developments post-1980s: the latter half of the 20th century witnessed a decline in the use of injectables like streptomycin. Some studies have focused on shortening the duration of DS-TB treatment, but have ended in failure. Trials such as REMoxTB[14], RIFAQUIN[15], and OFLOTUB/Gatifloxacin[16] were instrumental in these endeavors.

5. 2022 WHO guidelines: the WHO endorsed a new four-month regimen (2HPMZ/2HPM) for patients over 12 years with DS-TB, which came from the Study 31/A5349 trial[10]. Additionally, a shortened regimen [2HRZ(E)/2HR] was recommended for children and adolescents aged 3-16 with drug-susceptible nonsevere smear-negative TB, which came from the SHINE trial[11].

6. TRUNCATE-TB study contributions[12]: this study introduced a novel 8-week treatment strategy for DS-TB, extendable to 12 weeks based on patient response. This regimen showed equivalency to the standard six-month course in efficacy and safety.

Table 1. Timeline of milestones in the treatment of drug-susceptible tuberculosis

Stage	Year	Event	Remarks 1	Remarks 2
Early research and discovery (1882-1940s)	1882	Discovery of *Mycobacterium tuberculosis* by Robert Koch	Foundation for TB treatment	
Discovery and early use of anti-tuberculosis drugs (1940s-1950s)	1943	Discovery of streptomycin	Beginning of chemical drugs for TB	
	1944	The first human trial of streptomycin	1946-1986: series of clinical trials leading to "short-course chemotherapy" for DS-TB	1949-1960s: China establishes TB control network; universal BCG vaccination
	1948	First large-scale clinical trial of streptomycin	Pioneering RCT era	
	1951	Development of isoniazid	Monotherapy is prone to drug resistance	
	1952	Development of pyrazinamide and cycloserine		
	1956	Development of ethionamide		
	1957	Development of rifampicin		
Formation of combination treatment regimen (1960s)	1962	Development of ethambutol		
	Late 1960s	Exploration of effective combination treatments		
Short-term chemotherapy regimens (1970s-1980s)	Early 1970s	Rifampicin shortened treatment duration study		China 1970s-1990s: promotion of DOTS strategy, early detection, and standardized treatment
	1980s	Identification of standard short-course chemotherapy regimen for DS-TB	High-developed countries like Europe and America control TB. Standard chemical treatment still in use today	
Emergence of drug-resistant TB (1990s)	Mid-1990s	Global outbreak of MDR-TB	Especially in countries where HIV is endemic	Treatment success rates for MDR-TB in China have long been below the global average
	1990s	Introduction of new drugs like clofazimine and moxifloxacin	In 2018, moxifloxacin is a group-A drug while clofazimine is a group-B drug for treating MDR-TB recommended by WHO	
Establishment of committees and response to XDR-TB (2000s)	2000	Establishment of the GLC	Aims to provide technical assistance to DOTS projects to promote rational use of second-line drugs globally	
	2006	Appearance of XDR-TB and global response	Strain resistant to both first-line and certain second-line drugs	
Era of short-course therapy	2014	REMoxTB, RIFAQUIN, and the OFLOTUB/Gatifloxacin studies	Failed to reduce treatment duration for DS-TB	
	2021	Study 31	Efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen	
	2022	SHINE study	Four months of antituberculosis treatment noninferior to 6 months in children with drug-susceptible nonsevere smear-negative TB	WHO endorsed new four-month treatment regimens for various age groups
	2023	TRUNCATE-TB	An 8-week bedaquiline-linezolid regimen was noninferior to standard treatment for TB with shorter duration	WHO Target regimen profiles for TB treatment updated in 2023

TB: Tuberculosis; DS-TB: drug-susceptible TB; BCG: bacillus Calmette-Guérin; RCT: randomized controlled trial; MDR-TB: multidrug-resistant TB; HIV: human immunodeficiency virus; WHO: World Health Organization; GLC: Green Light Committee; XDR-TB: extensively drug-resistant TB; DOTS: directly observed treatment, short-course.

7. Toward pan-TB (2012-2024): TB Alliance's research on pan-TB strategies has achieved significant advancements. This series of studies began with the NC001 study in 2011. Early trials demonstrated the efficacy of the BPaMZ combination in treating tuberculosis[17]. Subsequent studies highlighted its potential to shorten treatment duration[18]. Currently, it has advanced to a phase IIc trial, using a combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ). The ongoing SimpliciTB study

(NC008), expected to be completed in 2024, aims to validate the long-term efficacy and safety of BPaMZ for both DS-TB and DR-TB, marking a pioneering effort in this field. The SimpliciTB study, as its name suggests, seeks to simplify TB treatment by developing a universal therapy applicable to both DS-TB and DR-TB, with treatment durations of 4 months for DS-TB and 6 months for DR-TB. This pan-TB strategy offers a treatment option where pre-treatment drug resistance profiling is not required, which is particularly valuable in regions with limited healthcare resources and a high burden of tuberculosis.

Trends in short-course treatment of DS-TB

Recent advancements have rejuvenated research in shortening DS-TB treatment regimens. Key areas include the development of new regimens (e.g., 31/A5349[10], SimpliciTB[17,18]) and innovative strategies (e.g., SHINE[11], PredictTB[19], TRUNCATE-TB[12]). Key aspects include:

1. Introduction of new drugs: incorporation of fluoroquinolones and higher doses of rifamycins to enhance efficacy and safety.

2. Adapting treatment phases: modifying the intensive phase to improve initial outcomes, potentially shortening overall therapy duration.

3. Prevention of acquired drug resistance: addressing drug resistance emergence in DS-TB treatment is critical for maintaining treatment effectiveness.

4. Implementation of new strategies: for example, the TRUNCATE-TB trial customizes regimens based on patient response, shifting to a 6-month conventional treatment for those not responding within 2-3 months[12].

5. Pre-treatment stratification: trials like SHINE use pre-treatment stratification to identify patients for shortened courses, optimizing treatment duration without compromising efficacy[11].

6. pan-TB initiative: the pan-TB Initiative aims to develop universal therapies for all forms of tuberculosis, including MDR-TB, pre-extensively drug-resistant TB (pre-XDR-TB), and extensively drug-resistant TB (XDR-TB). Pre-XDR-TB refers to TB caused by Mycobacterium tuberculosis strains that meet the criteria for MDR-TB/rifampicin-resistant-TB (RR-TB) and are also resistant to any fluoroquinolone. Previously, XDR-TB was defined as TB resistant to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin) in addition to multidrug resistance. Since 2021, the definition of XDR-TB has been updated to include MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline, linezolid, or both. The key research areas of the pan-TB Initiative include investigating drug combinations, reducing treatment duration, and ensuring safety, tolerability, and global applicability[20-23].

Summary of key findings

Recent advancements in DS-TB treatments, such as the WHO's endorsement of a four-month regimen, have significantly reduced treatment duration while maintaining efficacy. Studies like TRUNCATE-TB demonstrate the potential for even shorter treatment regimens without compromising safety or effectiveness.

MULTIDRUG-RESISTANT TUBERCULOSIS

The global epidemic of MDR-TB [Table 2]

In the mid-1990s, MDR-TB emerged as a significant global health challenge, exacerbated in areas with high HIV prevalence. In China, the MDR-TB epidemic intensified existing TB challenges, influenced by various factors. During this period, the WHO began regular assessments of TB drug combinations, a pivotal step in combating MDR-TB.

The 1990s saw the introduction of new anti-TB drugs, notably clofazimine and fluoroquinolones. Originally an anti-leprosy medication, clofazimine was repurposed for TB treatment[24,25]. Fluoroquinolones, effective against a broad range of bacterial infections, showed promise in treating *Mycobacterium tuberculosis*[26,27].

In 1999, the WHO established a working group to address the MDR-TB crisis[28]. The Green Light Committee (GLC), formed in 2000, offered technical support for the Directly Observed Treatment, Short-course (DOTS) program[29]. The GLC's objective was to promote rational use of second-line drugs globally and improve access to affordable, high-quality medications.

Despite advancements, MDR-TB and XDR-TB remain significant public health issues in China. The treatment success rate for MDR-TB in China has consistently been lower than the global average[30].

The emergence of XDR-TB in 2006 further complicated the situation[31,32]. In response, WHO convened a global meeting on XDR-TB in October 2006, focusing on strengthening basic TB and HIV/AIDS control, as well as effective MDR-TB management[33,34].

Short-course treatment of MDR-TB

Recent years have witnessed significant changes in the treatment landscape for MDR-TB, with innovative regimens and evolving WHO guidelines [Table 2]. These developments reflect the ongoing evolution of patient-centric treatment strategies.

1. Bangladesh regimen (2010): a minimum 9-month course of amikacin, clofazimine, ethambutol, and pyrazinamide, supplemented by prothionamide, kanamycin, and high-dose isoniazid for the initial 4 months, achieved an 87.9% cure rate[35].

2. WHO guidelines (2011): WHO recommended a regimen including pyrazinamide, a fluoroquinolone, an injectable agent, ethionamide (or prothionamide), and either cycloserine or para-aminosalicylic acid[36].

3. STREAM stage 1 study (2012-2015): this study compared 9-11 month short-course and 20-month long-course regimens for rifampicin-resistant TB. Both groups showed approximately 79% favorable outcomes, but the short-course group experienced more serious adverse events[37].

4. Accelerated approval of bedaquiline (2012): bedaquiline received accelerated FDA approval in December 2012 based on Phase IIb trial data, marking a major advancement in MDR-TB treatment[38].

5. WHO interim guidance on bedaquiline (2013): this guidance highlighted bedaquiline's efficacy in MDR-TB treatment, followed by delamanid's approval in 2014, representing new anti-TB drug mechanisms after over 40 years[39,40].

6. Updated WHO guidelines (2016): in response to STREAM Stage 1 results, WHO endorsed a standardized 9-12 month short-course regimen with 7 drugs[41].

Table 2. Timeline of milestones in the treatment of multidrug-resistant tuberculosis

Stage	Year	Event	Remarks 1	Remarks 2
Emergence of drug-resistant TB (1990s)	Mid-1990s	Global outbreak of MDR-TB	Especially in countries where HIV is endemic	Treatment success rates for MDR-TB in China have long been below the global average
	1990s	Introduction of new drugs like clofazimine and moxifloxacin	In 2018, moxifloxacin is a group-A drug while clofazimine is a group-B drug for treating MDR-TB recommended by WHO	
Establishment of committees and response to XDR-TB (2000s)	2000	Establishment of the GLC	Aims to provide technical assistance to DOTS projects to promote rational use of second-line drugs globally	
	2006	Appearance of XDR-TB and global response	Strain resistant to both first-line and certain second-line drugs	
Era of empiric treatment	2008	Guidelines for the programmatic management of drug-resistant tuberculosis Emergency update 2008	The 2008 guidelines recommended using at least four anti-tuberculosis drugs with confirmed or likely effectiveness during the intensive treatment phase. For extensive disease or uncertain effectiveness, additional drugs were suggested. The regimen should include pyrazinamide and/or ethambutol, a fluoroquinolone, a parenteral agent, and second-line oral bacteriostatic drugs, with no specific preference. Ethambutol could be included if DST showed susceptibility. Group 5 drugs were advised only if needed to bring the total to four	
	2011	Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update	The 2011 guidelines advised including at least four second-line anti-tuberculosis drugs, along with pyrazinamide, during the intensive phase. It found no support for using more than four second-line drugs in extensive disease, unless drug effectiveness was uncertain. The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or PAS if cycloserine couldn't be used. Ethambutol was not part of the standard regimen but could be used. Group 5 drugs were also excluded from the standard regimen but could be used	
Era of short-course therapy (early 21st century to 2018)	2010	Introduction of the "Bangladesh regimen"	Shortened treatment duration of nine months.Significant shift in MDR-TB treatment approach	
	2012-2015	STREAM stage 1 study	Compared efficacy and safety of short-term (9-11 months) and long-term (20 months) treatment regimens for RR-TB	WHO updated MDR-TB treatment guidelines in 2016 based on STREAM stage 1 study results
	2012	Accelerated approval of bedaquiline	Bedaquiline received accelerated US-FDA approval for MDR-TB treatment based on the C208 Phase IIb clinical trial data in 2013. First new drug with an innovative mechanism in nearly 40 years	WHO interim guidelines on bedaquiline in 2013
	2014	Introduction of delamanid	Approved in Europe, Japan, and China	
	2016	WHO treatment guidelines for drug-resistant tuberculosis - 2016 update	Conditional recommendation for a shorter regimen of 9-12 months in specific patient groups (very low certainty). Updated regimen to include at least five effective drugs during the intensive phase, with specific groupings and additional strengthening recommendations (very low certainty)	
Era of short-course all-oral therapy (2018-2023)	2018	Lancet and WHO: large IPD-meta analysis	Highlighted the efficacy of linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline, and clofazimine	WHO updated MDR-TB treatment guidelines based on IPD-meta-analysis
	2015-2017	Nix-TB study	BPaL regimen achieved a 90% success rate with significant adverse effects	Pretomanid was approved in the form of BPaL regimen for marketing in 2019
	2017-2019	ZeNix study	Evaluated different doses of linezolid for safety and efficacy	
	2016-2020	STREAM stage 2 study	Showed superiority of 9-month oral regimen (with bedaquiline) over 9-month injectable regimen	
	2017-2022	TB-PRACTECAL study	Bedaquiline, protomanil and linezolid (BPaL) regimens and the addition of clofazimine (Cfz) or moxifloxacin (Mfx)	In 2022, WHO recommended BPaLM regimen for MDR-TB

2017-2023	endTB study	Compared five 9-month MDR/RR-TB regimens. Three regimens showed non-inferiority to conventional treatment
2023	WHO Target regimen profiles for tuberculosis treatment 2023 update	The minimal requirement is for the RR-TB regimen to have a duration less than or equal to the newly recommended shorter MDR-TB regimen (BPaLM). The optimal requirement is for the regimen to have a duration of 2 months or less

TB: Tuberculosis; MDR-TB: multidrug-resistant TB; HIV: human immunodeficiency virus; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB; GLC: Green Light Committee; DOTS: directly observed treatment, short-course; DST: drug susceptibility testing; PAS: para-aminosalicylic acid; RR-TB: rifampicin-resistant tuberculosis; IPD: individual patient data.

All-oral treatment of MDR-TB

The focus on all-oral regimens for MDR-TB treatment has significantly increased in recent years.

1. Individual patient data (IPD) meta-analysis (2018, The Lancet): this analysis highlighted the efficacy of linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline, and clofazimine. Optimal drug numbers for treatment phases were identified[42].

2. Update of guidelines (2018): the WHO guidelines advocated for an all-oral regimen for most MDR-TB patients, restructuring TB drug classification into three groups[43]. The ATS guidelines also recommend an effective all-oral regimen for MDR-TB[44].

3. Nix-TB trial (2015-2017): a 6-month regimen of bedaquiline, pretomanid, and linezolid achieved a 90% success rate but was associated with significant side effects. This led to the recommendation of the BPaL regimen in WHO guidelines[45]. Based on the BPaL regimen, various variants are being explored, including regimens in which delamanid is used instead of pretomanid [Table 3], which can provide more options and meet needs in different circumstances.

4. ZeNix trial (2017-2019): focused on optimizing linezolid use, finding a daily dose of 600 mg for 26 weeks as the most effective[46].

5. STREAM phase 2 study (2016-2020): showed the superiority of the 9-month oral regimen (including bedaquiline) and a 6-month regimen (with bedaquiline) over the 9-month injectable regimen[47].

6. TB-PRACTECAL study (2017-2022): evaluated various regimens, with the BPaLM regimen emerging as a promising option, leading WHO to recommend it for MDR-TB treatment[48].

7. Revision of WHO guidelines (December 2022): recommended a 6-month BPaLM regimen for MDR/RR-TB and pre-XDR-TB, and a 9-month fully oral regimen for MDR/RR-TB without fluoroquinolone resistance[49].

8. Results from the union conference (November 2023): the endTB study compared five 9-month MDR/RR-TB treatment regimens, including new drugs. Three regimens showed non-inferiority to conventional treatment, applicable to various patient groups[50].

Table 3. BPaL-based and BDeL-based regimens

Regimen	Study	Design	Participant	Notification
BPaL	Nix-TB, ZeNix; TB-PRACTICAL	Nix-TB: Single-arm ZeNix: RCT TB-PRACTICAL: RCT	Pre-XDR-TB, treatment-intolerant or non-responsive MDR-TB	In NC009 study, BPaL will be evaluated for DS-TB
BPaLM	TB-PRACTICAL	RCT	Pre-XDR-TB, MDR-TB. Regardless of resistance to fluoroquinolones	
BPaLC	TB-PRACTICAL	RCT	Pre-XDR-TB, MDR-TB. Regardless of resistance to fluoroquinolones	
BDeL	BDeLM-MDR[55]	Single-arm	Pre-XDR-TB	During recruitment
BDeLM	BDeLM-MDR[55]	Single-arm	MDR-TB	During recruitment.
BDeLC	BEAT-India[56]	Single-arm	Pre-XDR-TB, MDR-TB	Published

RCT: Randomized controlled trial; TB: tuberculosis; pre-XDR-TB: pre-extensively drug-resistant-TB; MDR-TB: multidrug-resistant-TB; DS-TB: drug-susceptible TB; WHO: World Health Organization.

pan-TB treatment [Table 4]

1. PAN-TB collaboration[22]: conducting a Phase 2b/c clinical trial to develop a simplified and shortened TB treatment regimen, potentially treatable without drug-resistance testing. It assesses the efficacy, safety, optimal duration, and pharmacokinetics of Delamanid, Bedaquiline, OPC-167832, and Sutezolid (DBOS) and Pretomanid, Bedaquiline, OPC-167832, and Sutezolid (PBOS).

2. NC009 study[23]: a phase 2 trial evaluating the safety and efficacy of three dose levels of TBAJ-876 combined with Pretomanid and Linezolid compared to standard DS-TB treatment (2HRZE) and WHO-recommended DR-TB BPaL regimen over 8 weeks.

Summary of key findings

Innovative short-course regimens, including the BPaL and BPaLM regimens, show promise in improving treatment outcomes and reducing adverse effects. The focus on all-oral treatment options has led to significant improvements in patient adherence and overall treatment success. The pan-TB initiative is paving the way for universally applicable TB treatments that could streamline care and enhance patient adherence globally. Early results from trials such as SimpliciTB indicate the potential for these strategies to significantly shorten treatment duration and simplify regimens.

TRENDS IN CLINICAL STUDY OF TUBERCULOSIS TREATMENT

WHO's TRP requirements[51]

1. Shorten treatment duration: efforts are ongoing to further reduce TB treatment courses, aiming for durations as short as 4 months or even 2 months. This is intended to enhance patient compliance and alleviate healthcare burdens.

2. Minimize acquired drug resistance and relapse: a central goal is to reduce the incidence of acquired drug resistance and relapse rates. This involves not only effective treatment regimens but also strategies for ensuring patient adherence and monitoring resistance patterns.

Randomized controlled trials *vs.* real-world studies in the context of TRP

1. Randomized controlled trials (RCTs): they provide high-quality evidence by minimizing bias and variability, crucial for evaluating the efficacy and safety of new treatment regimens. In the TRP context, RCTs test if regimens meet established efficacy standards.

Table 4. Timeline of milestones in pan-TB strategy

Study	Year	Design	Objective	Participants
SimpliciTB	2012-2024	Partial RCT	Evaluate the long-term efficacy and safety of the BPaMZ regimen for DS-TB and DR-TB	Patients with DS-TB and DR-TB
XBOS	2023	RCT	Assess the efficacy, safety, optimal duration, and pharmacokinetics (PK) of Delamanid, Bedaquiline, OPC-167832, and Sutezolid (DBOS) and Pretomanid, Bedaquiline, OPC-167832, and Sutezolid (PBOS)	Patients with DS-TB and RR/MDR-TB
NC009	2023	RCT	Evaluate the safety and efficacy of three dose levels of TBAJ-876 combined with Pretomanid and Linezolid compared to standard DS-TB treatment (2HRZE) and WHO-recommended DR-TB BPaL regimen over 8 weeks	Patients with DS-TB and DR-TB

TB: Tuberculosis; RCT: randomized controlled trial; DS-TB: drug-susceptible TB; DR-TB: drug-resistant TB; RR/MDR-TB: rifampicin/multidrug-resistant-TB.

2. Real-World Studies (RWS): RWS offer insights into regimen performance across diverse clinical settings and populations. They complement RCTs by providing data on treatment efficacy and safety in various demographic and geographic contexts, essential for evaluating tolerability, acceptability, and feasibility of program implementation.

3. Combination of RCT and RWS[52]: both methodologies are integral within the TRP framework. RCTs provide rigorous scientific evaluation, while RWS offer practical insights into real-world applications, together facilitating comprehensive assessments of new TB treatment regimens.

Exploratory and implementation research in parallel

Effectiveness research typically unfolds within RCT frameworks, focusing on intervention impacts under controlled conditions. For instance, the pan-TB initiative is centered on enhancing treatment universality, utilizing new and non-resistant drugs, rather than resistance detection capabilities. pan-TB aims to simplify and standardize TB treatment across populations and settings, developing regimens applicable irrespective of resistance profiles[20-23].

Implementation research, conversely, focuses on the practical application and implementation of interventions in real-world settings. It tackles the challenge of how interventions can be effectively implemented in real-world scenarios, often involving precision medicine-guided localized regimens tailored to specific populations or regions.

Clinical study based on local resources

In resource-rich environments, the focus is on conducting expansive, international multicenter RCTs. These settings allow for comprehensive data collection, fostering the development and testing of innovative treatments and new drugs. The emphasis is on discovering more effective and safer treatment regimens and facilitating international collaboration.

In contrast, resource-limited settings prioritize implementation research, adapting existing treatment methods to local contexts within healthcare system constraints. Such research is geared toward practical solutions, aiming to improve treatment outcomes through cost-effective strategies. Localized solutions, community involvement, and training of local health workers are emphasized to ensure relevance and sustainability.

An example is the MDR-Chin study[53,54], which demonstrates the application of clinical research based on local resources. The study reports high success rates in MDR-TB and pre-XDR-TB patients under three all-oral, short-course regimens. Tailored to China's context, the study considered drug costs and adverse

reactions, making treatments accessible to economically disadvantaged patients. It introduced a six-month efficacy indicator and explored slow phenotypic drug susceptibility testing (DST) in treatment outcomes, allowing flexible regimen adjustments.

RESEARCH GAPS AND CHALLENGES IN PAN-TB RESEARCH

Current challenges in pan-TB research

1. Diverse drug resistance patterns: the variability in drug resistance patterns among TB strains presents a significant challenge. Developing a universally effective regimen that can address multiple resistance profiles is complex and requires extensive research. Additionally, antibiotic resistance is an enduring issue. The currently effective pan-TB treatment regimen, once widely adopted, will inevitably lead to the emergence of new resistance. Our strategic goal is to break the cycle of antibiotic resistance and achieve the 2035 End TB target, rather than finding a treatment regimen that can permanently address the ever-evolving DR-TB.

2. Limited clinical trial data: despite recent advancements, there is still a paucity of robust clinical trial data specifically targeting pan-TB therapies. Many trials are ongoing, but comprehensive results are not yet available.

3. Adverse drug reactions and safety: ensuring the safety and tolerability of new drug regimens remains a critical concern. The potential for severe adverse reactions, particularly with newer drugs like bedaquiline and delamanid, needs further investigation.

4. Implementation in resource-limited settings: translating research findings into practical treatment protocols in resource-limited settings poses significant logistical and financial challenges. Ensuring access to new drugs and adherence to treatment regimens in these contexts is difficult.

5. Patient adherence and monitoring: maintaining high levels of patient adherence and effective monitoring during treatment is essential for the success of pan-TB regimens. Innovative approaches are needed to address these issues, especially in low-resource settings.

6. Integration with existing health systems: integrating new pan-TB treatment protocols within existing health systems requires careful planning and coordination. Ensuring that healthcare workers are adequately trained and that infrastructure is in place is crucial.

Research gaps

1. Long-term efficacy and relapse rates: there is a need for more long-term studies to evaluate the efficacy of pan-TB regimens in preventing relapse and managing chronic cases of TB.

2. Pediatric and special populations: research is lacking on the efficacy and safety of pan-TB regimens in pediatric populations and other special groups such as pregnant women and individuals with comorbidities.

3. Biomarkers for treatment response: identifying reliable biomarkers that can predict treatment response and guide personalized therapy is an area that requires further exploration.

4. Mechanisms of drug resistance: understanding the underlying mechanisms that lead to drug resistance in TB is crucial for developing effective pan-TB treatments. More basic research in this area is needed.

5. Socioeconomic and cultural factors: investigating the socioeconomic and cultural factors that influence TB treatment adherence and outcomes can provide insights for designing more effective intervention strategies.

Recommendations for future research

1. Expanded clinical trials: conduct more extensive and diverse clinical trials to gather comprehensive data on the efficacy and safety of pan-TB regimens across different populations and settings.

2. Focus on safety profiles: prioritize research on the safety profiles of new drugs, particularly in combination regimens, to mitigate adverse effects and improve patient outcomes.

3. Innovative delivery systems: develop innovative drug delivery systems and formulations that enhance patient adherence and reduce the burden of treatment.

4. Integrated healthcare models: explore integrated healthcare models that combine TB treatment with broader healthcare services to improve patient outcomes and system efficiency.

5. Community-based approaches: invest in community-based research and intervention strategies to ensure that pan-TB treatments are accessible and acceptable to all patient groups.

6. Global collaborative efforts: strengthen global collaborative efforts and partnerships to share knowledge, resources, and best practices in pan-TB research and treatment implementation.

CONCLUSION

The evolution of treatment for both DS-TB and MDR-TB underscores the significance of pan-TB research as a future trend. Key findings from this review indicate that recent advancements in TB treatment have the potential to significantly improve patient outcomes and reduce the burden on healthcare systems. The development of shorter, more effective treatment regimens, particularly through the pan-TB initiative, offers a promising path forward for global TB control efforts. Future research should focus on validating these findings through large-scale clinical trials and exploring innovative strategies to enhance treatment adherence and efficacy. Adapting these evolving treatment protocols to the unique healthcare landscapes, resource availabilities, and epidemiological profiles of each region is essential for the effective management and control of TB globally. This approach ensures that the promising developments in TB treatment are not only universally applicable but also practically implementable across diverse healthcare systems.

DECLARATIONS

Authors' contributions

Conceptualization of the study, literature review, data synthesis, initial drafting of the manuscript, critical revisions, and approval of the final version: Fu L

Literature review, data analysis, interpretation of findings, drafting sections of the manuscript, critical revisions, and approval of the final version: Deng G

Study design, supervision of the research process, providing expert insights, review and editing of the manuscript for important intellectual content, and approval of the final version: Lu H

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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