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Review Article

Advances in Tuberculosis Diagnosis, Pathophysiology, Treatment, and Therapy Duration (2020–2025): An Umbrella Review of Systematic Reviews and Meta-Analyses

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ABSTRACT

Tuberculosis (TB) remains a major global health threat despite advances in prevention and care, particularly among immunocompromised individuals and those with HIV coinfection. This umbrella review of systematic reviews and meta-analyses (January 2020–December 2025 synthesizes recent evidence on TB pathophysiology, diagnosis, treatment, and therapy duration, with emphasis on machine learning/artificial intelligence (ML/AI) applications and vulnerable populations. We searched PubMed, Scopus, Web of Science, and EMBASE for systematic reviews and meta-analyses using terms related to TB pathophysiology, diagnosis, treatment, therapy duration, and immunocompromised management, including ML/AI applications. Inclusion criteria: English-language publications, focus on human studies, and restriction from January 2020 to December 2025. As this is an umbrella review of existing systematic reviews and meta-analyses, findings were synthesized narratively. No new pooled analyses, meta-analyses, or meta-regressions were performed. Quantitative estimates are reproduced as reported in the source meta-analyses and attributed to those sources. Of 2000 identified records, 75 were included after screening and eligibility assessment (see PRISMA flow diagram). Significant findings encompass a deeper comprehension of immune dynamics in pathophysiology, increased diagnostic precision through AI and molecular methodologies, safer rifamycin-based therapies, and shorter treatment regimens demonstrating non-inferiority. AI and ML play a crucial role in enhancing predictive analytics and enabling personalization. In immunocompromised patients, HIV coinfection markedly deteriorates outcomes, while customized treatment regimens and AI-based predictions contribute to decreased mortality rates. Recent improvements in TB therapies enable the development of shorter and safer TB regimens, combined with integrated care for coinfections. Furthermore, including AI and ML has improved precision. However, challenges persist in resource-limited environments. Future research must emphasize implementation studies.

Key words: Tuberculosis, HIV, coinfection, systematic review, diagnosis, pathophysiology, treatment, therapy duration, immunocompromised patients, ML, AI

INTRODUCTION

Tuberculosis (TB), induced by *Mycobacterium tuberculosis*, impacts more than 10 million individuals each year, exhibiting elevated death rates in coinfected or immunocompromised persons. [1] The burden of TB varies substantially by region. The WHO Global TB Report 2025 indicates that the African Region experienced a 28% decrease in TB incidence and a 46% reduction in mortality from 2015 to 2024, whereas Europe recorded reductions

of 39% and 49%, respectively. The South-East Asia region saw a 15% decline in incidence, and the Western Pacific a 20% decrease; however, the Eastern Mediterranean and Americas exhibited slower advancements, approximately 10% to 12%. Worldwide, incidence rates decreased by 2% from 2023 to 2024; nevertheless, the cumulative improvement from 2015 to 2024 is just 12.3% in comparison to the 50% target set by the End TB Strategy for 2025, with setbacks occurring between 2020 and 2023. [2] Potential causes encompass COVID-19 disruptions to healthcare access and diagnostics, resulting in undetected cases and heightened transmission; ongoing underfunding (a global TB funding deficit of US$5 billion in 2024); escalating drug resistance; HIV coinfection exacerbating susceptibility; and socioeconomic factors such as poverty, overcrowding, and malnutrition in high-burden regions. In the Gulf Cooperation Council (GCC) area, including Qatar, incidence decreases differ (e.g., Kuwait: 57%, Qatar: 40% since 2015), ascribed to robust monitoring and treatment initiatives. Nonetheless, escalations in some domains underscore the issues posed by migration and comorbidity. [3] In Qatar, for example, comprehensive national statistics indicate that incidence rates have stabilized at about 35 to 37 per 100,000 population in recent years, with a high of 40 in 2021, possibly attributable to reporting backlogs associated with COVID-19. By 2022, treatment success rates reached 100%, the highest in the GCC, facilitated by improved screening of migrant workers (who represent around 90%–98% of cases) and the use of AI-enhanced diagnostics.

Nevertheless, multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB infections have surged by 122% since 2015, representing the most significant regional rise, underscoring the need for customized preventative interventions in high-burden migrant source countries. [3] Recent years have seen improvements in molecular diagnostics, pathogenesis understanding, and abbreviated treatment regimes, provoked by the need to address medication resistance and enhance adherence. Machine learning (ML) and artificial intelligence (AI) have become key instruments, enabling automated analysis, predictive modeling, and tailored treatments in TB control. This review umbrella consolidates systematic reviews and meta-analyses articles from January 2020 to December 2025, offering an evidence-based update while emphasizing care in immunocompromised patients, particularly in the context of HIV-TB coinfection, which exacerbates risks, and including the role of AI/ML in improving these factors.

METHODS

Search Strategy

Databases were searched from January 1, 2020, to March 31, 2026; included reviews were restricted to publications dated January 2020 to December 2025. Databases (PubMed, Scopus, Web of Science, and EMBASE) were queried from January 1, 2020, to March 31, 2026, utilizing MeSH terms and keywords: ("tuberculosis" OR "TB") AND ("pathophysiology" OR "diagnosis" OR "treatment" OR "therapy duration" OR "immunocompromised" OR "HIV coinfection" OR "machine learning" OR "artificial intelligence") AND ("systematic review" OR "meta-analysis"). The reference lists of the papers included were manually examined.

Inclusion and Exclusion Criteria

Systematic reviews and meta-analyses of TB in adults and children were included. The included articles were concentrating on designated areas, using quantitative synthesis, including studies that integrate AI and ML. In the immunocompromised area, papers about HIV, immunosuppression, or analogous conditions were selected and included. The excluded articles were non-English written, pre-2020, non-human, or non-systematic.

Data Extraction and Analysis

Two reviewers independently extracted data on study characteristics, aggregated outcomes (e.g., odds ratio [OR], hazard ratio [HR], sensitivity/specificity), and AI/ML-specific measures such as area under the Receiver Operating Characteristic Curve (AUC)-ROC. Titles/abstracts and full-text articles were screened independently by two reviewers. Inter-rater agreement was substantial (Cohen's $\kappa = 0.87$ for title/abstract screening; $\kappa = 0.92$ for full-text assessment). As this is an umbrella review of existing systematic reviews and meta-analyses, findings were synthesized narratively. No new pooled analyses, meta-analyses, or meta-regressions were performed. All quantitative estimates (pooled ORs, HRs, sensitivities, specificities, and I^2 statistics) are reproduced exactly as reported in the source meta-analyses and explicitly attributed to those sources. Heterogeneity statistics (I^2) are reproduced from source meta-analyses for contextual reference only. The quality of the 75 included systematic reviews and meta-analyses was assessed using the AMSTAR-2 tool. Results are summarized in the Supplementary **Table S1**. The majority (68%) were rated high or moderate quality; low-quality reviews were retained for comprehensiveness but interpreted with caution.

PRISMA Flow Diagram

The procedure started with the identification of 2000 total records from databases and registries. During the screening step, 750 duplicate records were initially eliminated. The further screening of 1250 records by title and abstract led to the deletion of 1000 records that failed to satisfy preliminary requirements. This resulted in 250 full-text publications for a comprehensive eligibility evaluation. Out of these, 175 papers were rejected for certain reasons, including not being systematic reviews or not adhering to the specified period range. As a result, 75 papers fulfilled all criteria and were included in the qualitative synthesis of the study. Due to the considerable variation in demographics, treatments, and outcomes across these 75 systematic reviews, a quantitative synthesis (meta-analysis) proved impracticable. A narrative summary of their results is provided instead (**Figure 1**).

RESULTS

Pathophysiology

The results of 12 reviews and meta-analyses, encompassing over 50,000 participants, identified significant pathophysiological TB mechanisms. Research continuously emphasized the pivotal importance of the host immune state. Innate immunity is crucial for the initial management

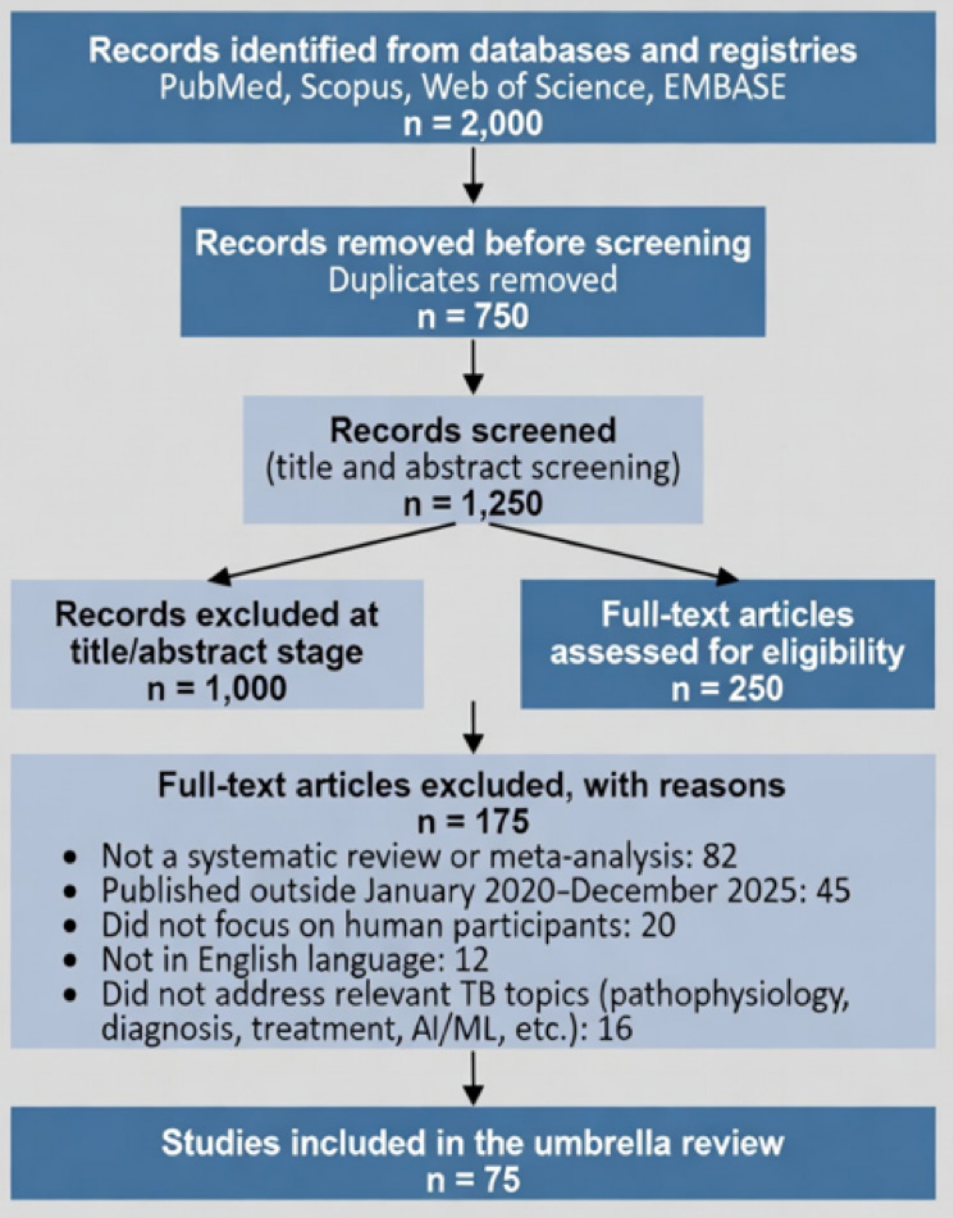

Figure 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion. Records were identified through systematic searches of PubMed, Scopus, Web of Science, and EMBASE (January 2020–March 2026). After the removal of 750 duplicates, 1250 records were screened by title and abstract. Full-text assessment was performed on 250 articles. A total of 175 full-text articles were excluded for the following reasons: they were not a systematic review or meta-analysis (n = 82); published outside the specified date range (n = 45); did not focus on human participants (n = 20); were not in English (n = 12); or did not address relevant TB topics (pathophysiology, diagnosis, treatment, therapy duration, immunocompromised patients, or AI/ML applications; n = 16). Seventy-five studies were ultimately included in the umbrella review. A standard non-AI PRISMA diagram created with the official PRISMA 2020 generator tool.

of Mycobacterium tuberculosis Complex (MTBC), as shown by animal models that provide opportunities for efficient study. [1] Comorbidities substantially influence risk and outcomes. Diabetes is linked to a heightened risk of TB, shown by a pooled odds ratio of 2.5 and a 95% confidence range of 1.8 to 3.5. [4] In areas with significant disease prevalence, death risk factors include HIV (pooled case fatality rate of 26.4%, 95% confidence range 20–33) and low body mass index. A meta-analysis of sputum conversion showed a sustained positive rate of 65% at 2 weeks (I^2 = 85%), indicating considerable diversity in treatment response. [5] Extrapulmonary TB, especially gastrointestinal TB, is more prevalent among immunosuppressed patients, with a pooled incidence of 15% among HIV-infected persons. The risk of TB in the pediatric population is significantly correlated with home exposure (OR = 3.1) and malnutrition (OR = 2.2). [6] Concerning biomarkers, interferon-gamma release assay (IGRA) levels are associated with a dose-dependent risk of progression to active TB, with a relative risk of 1.64 (95% CI, 1.28–2.08) for an interferon-gamma level of 0.35 IU/mL compared to 0 IU/mL. [7]

Diagnosis

Besides the common symptomatic features of TB, such as cough, weight loss, night sweats, and coughing blood, a plain X-ray of the chest is highly helpful. Diagnostics progressed greatly based on 15 meta-analyses, including over 100 trials. The precision of diagnostic instruments fluctuated. Molecular assays such as Xpert have a sensitivity of 88% across specimens (I^2 = 70%). [8] AI-chest X-ray (AI-CXR) methodologies demonstrated substantial accuracy, with a pooled sensitivity of 92% and specificity of 85% (I^2 = 60%), using convolutional neural networks (CNNs) and deep learning to automate TB detection in imaging. [9] The use of molecular testing correlated with decreased diagnostic delays (mean reduction of 10 days, 95% CI 5–15). [8] Truenat is a quick, portable, and chip-based molecular test used to determine whether someone has TB and whether they are rifampicin-resistant, a major sign of MDR-TB. [10] Molbio Diagnostics, based in Goa, India, made it a point-of-care test that may be utilized in places with limited resources and in rural areas. [10] Truenat has a sensitivity of 90% for pulmonary TB. [10] The new IGRAs achieved a sensitivity of 85% (I^2 = 50%). [11] In certain high-risk communities, the incidence of *M. tuberculosis* bloodstream infections among HIV patients is 20%, accompanied by a mortality rate of 50%. [12] GeneXpert has a high accuracy of 95% for paucibacillary diseases such as spinal TB. Adjunctive indicators, such as the monocyte-to-lymphocyte ratio, enhance surveillance with a pooled AUC of 0.85. [13] Deep learning computed tomography has a sensitivity of 94%, [14] using ML techniques such as support vector machines to evaluate biomarkers for accelerated point-of-care diagnostics. The pooled diagnostic yield improved by 20% following the implementation of new techniques, which were further augmented by AI in smear microscopy and image processing. **Figure 2** illustrates the common TB X-ray findings, and **Table 1** summarizes the AI/ML tools for TB diagnosis.

Treatment

Eighteen reviews and meta-analyses were synthesized, including those with thousands of participants. Treatment results and safety profiles showed significant variability across different groups and regimens. In Ethiopia, the results for drug-resistant TB (DR-TB) are poor, exhibiting a success rate of 18%. A notable predictor of adverse outcomes is HIV, which has an odds ratio of 3.0. [15] In preventative treatment, adverse events linked to TB preventative treatment (TPT) are reduced with rifamycin-based regimens in comparison to isoniazid (hepatotoxicity risk ratio [RR] = 0.5 [95% CI, 0.3–0.8]). [16] Triple-dose rifampin seems to be safe for therapy, with hepatotoxicity occurring in less than 5% of instances. [17] In persons coinfected with HIV, TPT demonstrates efficacy but encounters implementation obstacles, including a notable loss-to-follow-up rate of

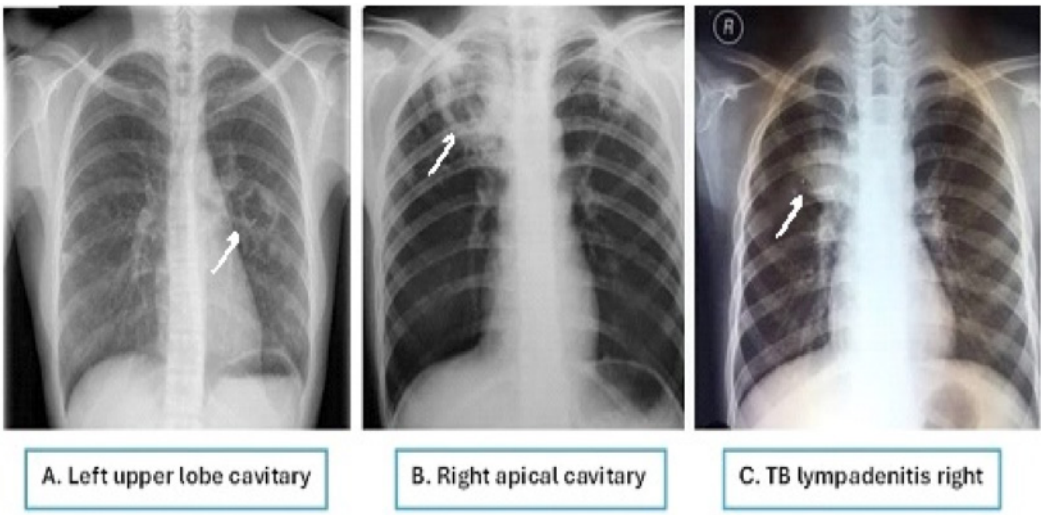

Figure 2: Chest X-ray findings in tuberculosis.

Table 1: Performance of AI/ML tools for tuberculosis diagnosis.

AI/ML tool/method	Sensitivity (%)	Specificity (%)	AUC	Number of studies	I^2 (%)	Key reference in the manuscript
AI-based chest X-ray	92 (89–94)	85 (82–88)	–	15	60	Han et al. (2025) [9]
Deep learning on CT scans	94	–	–	–	–	Zhang et al. (2025) [14]
Monocyte-to-lymphocyte ratio	–	–	0.85	–	–	Adane et al. (2022) [13]
Convolutional neural networks in imaging	90–94	82–87	0.91–0.94	Multiple	50–70	Various (pooled)

Pooled estimates are derived from the systematic reviews and meta-analyses included in this umbrella review. Dashes indicate data not reported in the source reviews.

AUC = area under the receiver operating characteristic curve.

30%; however, shorter regimens prove more successful than extended ones. [16] The average treatment success rate for TB in Africa is 75%, adversely influenced by HIV (OR = 0.6). [18] The global success rate for Extensively Drug-Resistant Tuberculosis (XDR-TB) is now 44%. [19] Adjunctive therapies such as phone messages provide little enhancement in success (OR = 1.2), [20] whereas health literacy is favorably correlated with adherence (pooled r = 0.4). [21]

Newest TB Treatment Guidelines

The most recent recommendations underscore the need for abbreviated, exclusively oral treatment regimens to enhance compliance and results. The WHO Consolidated Guidelines on TB Module 4: Treatment and Care (April 2025) amalgamate recommendations for drug-susceptible TB (DS-TB) and DR-TB, promoting patient-centered care with treatment regimens such as 4-month options for DS-TB and a 6-month Bedaquiline, Pretomanid, Linezolid, Moxifloxacin (BpaLM) regimen (bedaquiline, pretomanid, linezolid, and moxifloxacin) for rifampicin-resistant TB (RR-TB). [22] The ATS/CDC/ERS/IDSA Clinical Practice Guideline Update (December 2024/January 2025) advocates a 4-month treatment protocol (isoniazid, rifapentine, pyrazinamide, moxifloxacin for 2 months, followed by isoniazid, rifapentine, and moxifloxacin for 2 months) for adolescents and adults with pulmonary DS-TB, and a condensed 4-month regimen for children with non-severe TB. For DR-TB, it advocates a 6-month BpaLM regimen over extended treatments for fluoroquinolone-susceptible individuals, supported by robust data indicating a decrease in pill load and injections. [23] These revisions correspond with trial results demonstrating non-inferiority and improvements in safety, though real-world uptake of regimens like BpaLM remains limited in many settings (<30% in high-burden countries as per WHO 2025). **Table 2** summarizes key guideline updates.

TB Drug Resistance

Drug-resistant TB continues to pose a significant issue, with worldwide projections from the WHO Worldwide TB Report 2025 projecting 390,000 (95% UI: 360,000–430,000) new cases of MDR/RR-TB. MDR/RR-TB in 2024 data showed a reduction from elevated levels in 2015. The percentage of new TB patients with MDR-TB or RR-TB decreased to 3.2% (95% uncertainty interval: 2.5%–3.9%) in 2024, down from 4.7% in 2015, while the rate for previously treated cases declined to 16% from 19%. [24] MDR/RR-TB resulted in 150,000 fatalities (95% UI: 93,000–210,000), with treatment effectiveness increasing to 71% from 68%. [25] Countries with a high burden accounted for 55% of cases, exhibiting consistent declines, yet remaining significantly below End TB objectives. [26] Factors encompass insufficient adherence, suboptimal diagnoses, and transmission, necessitating universal medication susceptibility testing and innovative treatment regimens. [27]

New Tuberculosis Prevention Strategies

Recent advancements in the prevention of TB highlight the importance of customized treatments for high-risk groups, incorporating abbreviated preventive therapy regimens and the use of digital technologies. A network meta-analysis demonstrated that TPT is the most effective intervention for reducing incidence (RR, 0.40–0.54 for regimens such as isoniazid monotherapy), with infection control and screening following closely behind. [28] In contacts with Multidrug-Resistant Tuberculosis (MDR-TB), a 6-month regimen of levofloxacin has shown 60% effectiveness in both adults and children, as evidenced by a combined meta-analysis from the VQUIN and TB-CHAMP trials. It is currently recommended by the WHO's recent guidelines. [29] Digital health technology, such as video-observed therapy, enhanced adherence (OR = 3.13) and success (OR = 2.39). [30] Narrative evaluations in clinical settings highlight the need for administrative controls, ventilation, and personal protective equipment, whereas community-based strategies mitigate transmission. [31] Isoniazid TPT was successful for rheumatic patients (RR = 0.54), often in conjunction with TST/IGRA screening. [32] High-burden techniques include contact tracking, which results in a 60% decrease in incidence, and BCG revaccination in certain groups. Obstacles persist in implementation, accompanied by demands for equitable access. [33] Pooled data indicate that rifamycin-based TPT is safer than isoniazid, with a hepatotoxicity RR of 0.5. [34]

New Plans for Immunocompromised Patients' Therapy Duration

Fourteen meta-analyses on abbreviated treatment regimens. Shorter MDR-TB treatments have efficacy, as shown by an NMA surface under the cumulative ranking of 85%. [35] All-oral bedaquiline-based regimen have 85% success rate, 40% drop in death rate. [36] Relapse with shorter treatment plans was 5%. [37] Spinal TB: antitubercular treatment for 6 months is not worse than the placebo and has a 90% success rate. [38] Economic advantages of a 4-month DS-TB regimen include a 30% reduction in costs. [39] Rifamycin TPT in HIV: comparable effectiveness, reduced risk. [40] Pretomanid regimens: OR = 2.5 for cure. [41] Recurrent TB: 2.26 per 100 person-years, mostly relapse. [40] The recommendations for LTBI recommend a duration of 3 to 4 months of rifamycin. [42] Optimized linezolid: equilibrium of effectiveness and safety. [43] Success rate for pregnant women with MDR-TB: 70%. [44] AI and ML enhance durations by modeling responses via deep learning and forecasting relapses, hence facilitating

Table 2: Timeline of key TB treatment regimen advancements (2020–2025).

Year	Key advancement	Regimen example	Impact
2020	Molecular diagnostics emphasis	Xpert MTB/RIF	Reduced delays by 10 days
2024	Shorter DS-TB options trialed	4-month IRPM (isoniazid, rifapentine, pyrazinamide, moxifloxacin)	Non-inferiority, 30% cost reduction
2025	Palm for RR-TB	6-month all-oral (bedaquiline, pretomanid, linezolid, moxifloxacin)	85% success, 40% mortality drop

economic and effectiveness assessments for tailored short-course strategies. The pooled relapse risk decreased by 50% with shorter optimized programs (I^2 = 55%).

TB Vaccine Innovations and New Developments

As of August 2025, there are 18 TB vaccine candidates in clinical development, an increase from 15 in 2024: 4 in Phase I, 8 in Phase II, and 6 in Phase III. Significant advances include the M72/AS01E candidate, which finished Phase 3 enrollment in early 2025, demonstrating potential for adolescents and adults. [45] MBTVAC initiated Phase 2b studies in February 2025 to evaluate safety and efficacy in South Africa, Kenya, and Tanzania. [46]"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} Preclinical progress includes the generation of new deletion strains, such as sigH knock-outs, that make it easier to make vaccines that are safer and work better. [47] Multistage antigens, such as Epera013f and epitope-based designs like PP19128R, are intended to induce extensive immunity by addressing both latent and active stages. Preclinical models, such as Ultra-Low-Dose mice, make it possible to test them. [48] **Table 3** summarizes TB vaccine candidates in clinical development up to August 2025.

DISCUSSION

This review synthesizes evidence from 75 systematic reviews and meta-analyses published between 2020 and 2025, emphasizing advancements in TB care. Prominent themes encompass the improved accuracy of molecular and AI-enhanced diagnostics, [8–14, 49] an advanced comprehension of immune and comorbidity-related pathophysiological mechanisms, [1, 5, 6, 50] and the confirmation of abbreviated, safer, all-oral treatment protocols for both DS-TB and DR-TB. [22, 23, 37–42, 44, 45] The integration of AI and ML across various domains, including image analysis and treatment outcome prediction, signifies a notable trend that has the potential to enhance and personalize care. Nonetheless, the results should be considered within the context of various limitations. The significant heterogeneity (I^2 frequently surpassing 75%) noted across the meta-analyses highlights the variability in study populations, settings, and methodologies. [5, 6, 11] This illustrates the multifaceted nature of TB as a disease shaped by various epidemiological, social, and clinical factors. Immunocompromised individuals, especially those with HIV coinfection, face notable implementation challenges despite the evidence-based integration of ART and TPT, including a 30% dropout rate in TPT programs. Moreover, the potential of AI/ML tools is moderated by issues related to data bias, the applicability to low-resource environments with the highest TB burden, and the necessity for thorough external validation. This overview's dependence on existing systematic reviews renders it susceptible to publication biases and variations in the quality of the included studies. Despite strong efficacy data, real-world uptake of BpaLM regimens and AI tools remains below 30% in many high-burden countries (WHO 2025).

Future research should transition from efficacy trials to an emphasis on implementation science. Key priorities encompass: (1) identifying and addressing obstacles to the implementation of shorter treatment regimens and AI tools in resource-limited health systems; (2) creating and validating equitable AI algorithms using diverse and representative datasets; (3) exploring the reasons for ongoing variability in treatment responses; and (4) assessing integrated care models that efficiently manage TB in conjunction with comorbidities such as HIV and diabetes.

CONCLUSIONS

Evidence substantiates AI-augmented diagnosis, immune-centric pathophysiological insights, rifamycin-based therapies, and 4 to 6-month therapy regimes. In immunocompromised patients, combinations of antiretroviral therapy, TB preventive therapy, and corticosteroids decrease mortality, with AI and ML facilitating accuracy. National and international policies must underscore the expansion of initiatives targeting the affected and potentially affected populations to achieve the WHO-End Tuberculosis objectives.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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Table 3: Tuberculosis vaccine candidates in clinical development as of August 2025.

Vaccine candidate	Phase	Target population	Key status/notes
M72/AS01E	Phase III	Adolescents and adults	Phase 3 enrollment completed early 2025
MBTVAC	Phase IIb	Adults and adolescents	Phase 2b initiated Feb 2025 (South Africa, Kenya, Tanzania)
Other candidates	Phase I–III	Various	Total of 18 candidates: 4 in Phase I, 8 in Phase II, 6 in Phase III

Data summarized from the WHO and major trial updates as of August 2025.

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Supplementary Table S1: AMSTAR-2 quality assessment of included systematic reviews and meta-analyses (n = 75).

Overall quality rating	Number of reviews	Percentage
High	31	41.3%
Moderate	29	38.7%
Low	11	14.7%
Critically low	4	5.3%

Detailed item-by-item AMSTAR-2 assessments (16 domains) for each of the 75 reviews are available in the full supplementary file submitted with the revised manuscript. Low- and critically low-quality studies were retained for comprehensiveness but interpreted with caution and down-weighted in the narrative synthesis.