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REVIEWER'S REPORT

Manuscript No.: IJAR-57682

Title: Advances, Challenges and Emerging therapies in Tuberculosis : A Comprehensive review of Global Tuberculosis Control and future Directions

Recommendation:
Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality		✔,		
Techn. Quality		✔,		
Clarity	✔,			
Significance	✔,			

Reviewer Name: Dr. Bilqees Hamza

Detailed Reviewer's Report

The manuscript titled **"Advances, Challenges, and Emerging Therapies in Tuberculosis: A Comprehensive Review of Global Tuberculosis Control and Future Directions"** provides a comprehensive and timely overview of the global public health challenge posed by *Mycobacterium tuberculosis* (MTB). The study successfully outlines the current global burden of the disease, noting the disruption caused by the COVID-19 pandemic, which halted a decade of consistent declines in incidence and caused a subsequent 3.6% increase in global case notifications between 2020 and 2023. The scope of the paper is well-defined and appropriately addresses the geographical distribution of the epidemic, detailing that 56% of global cases are concentrated across five high-burden nations: India, Indonesia, China, the Philippines, and Pakistan. The review covers transmission dynamics, host-pathogen immunology, current diagnostic advancements, and emerging therapeutic paradigms, making it highly relevant to clinical researchers and global public health stakeholders.

As a comprehensive review, the manuscript synthesizes recent literature, epidemiological reports from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), and recent clinical studies regarding drug-resistant strains. The authors present structured data, such as a country-by-country epidemiological breakdown (Table 1), which highlights that India accounts for 27% of global multi-drug resistant tuberculosis (MDR-TB) cases.

The key findings focus on the complex, stepwise genetic mutations (e.g., *katG* for isoniazid resistance and *rpoB* for rifampicin resistance) that drive the spread of MDR-TB and extensively drug-resistant TB (XDR-TB). The paper highlights a noticeable demographic imbalance, noting that males are two to three

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times more likely to develop drug-resistant strains. On a therapeutic level, the review summarizes the shift from toxic, long-term regimens toward novel, shorter, all-oral treatments involving newly licensed agents like bedaquiline, delamanid, and pretomanid. It also discusses emerging host-directed therapies, nanotechnology-driven drug delivery, and targeted bacteriophage applications.

The manuscript provides strong analytical depth by connecting molecular-level bacterial mechanisms with global macro-epidemiological patterns. The discussion regarding the genetic virulence of the Beijing genotype and its high prevalence among drug-resistant isolates in Northern India and China adds strong clinical value to the narrative.

[MOLECULAR RESISTANCE MUTATIONS]
(katG → Isoniazid | rpoB → Rifampicin)
▼
[SELECTION & CLONAL EXPANSION]
(e.g., Virulent Beijing Genotype)
▼
[MACRO-EPIDEMIOLOGICAL IMPACT]
Concentrated Regional Burdens (India 27%, Russia 7.4%, China 7.3%)

By consolidating recent diagnostic breakthroughs like Xpert MTB/RIF and line probe assays alongside futuristic tools like AI-driven precision medicine, the paper serves as a valuable resource for updated protocols. It effectively argues that eliminating tuberculosis requires more than just developing new antibiotics; it demands integrated diagnostics, equitable access, and a strong commitment to overcoming public health bottlenecks.

Suggestions for Improvement

- **Refine Table 1 Layout and Clear Artifacts:** In Table 1, the row containing Indonesia also lists "Namibia" and "Pakistan" vertically compressed within the same block, alongside an unformatted journal tag ("IJAR"). Reformat this section into distinct, individual rows for each country with separate data rows to ensure proper data presentation.
- **Expand on Host-Directed Therapies (HDT):** While HDTs are mentioned as a promising development, the text should explicitly name and discuss specific mechanisms or adjunctive agents currently under evaluation (e.g., metformin, statins, or matrix metalloproteinase inhibitors) to give readers more actionable insight.

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- **Elaborate on Nanotechnology Mechanics:** Provide a clearer explanation of how nanoparticle drug delivery systems bypass the protective, lipid-rich cell walls of MTB, explaining how these technologies improve drug bioavailability and reduce systemic toxicity.
- **Detail Bacteriophage Logistics:** Expand the section on bacteriophage therapy to address practical challenges, such as phage resistance, delivery methods directly to caseous lung cavities, and current regulatory hurdles preventing widespread clinical use.
- **Clarify the Pathogenesis Timeline:** In the section discussing pathogenesis, add a detailed flowchart or conceptual map that clearly outlines the immunological progression from initial inhalation and alveolar macrophage phagocytosis to granuloma formation, latent dormancy, and eventual caseous necrosis or cavitation.
- **Incorporate Diagnostic Limitations:** Balance the praise for rapid molecular assays like Xpert MTB/RIF by including a brief critical evaluation of their real-world implementation challenges, such as high maintenance costs, reliance on a stable power supply, and limited accessibility in rural healthcare centers.
- **Address the Overlap of Diabetes and HIV Comorbidities:** Give more attention to the metabolic and immunological interactions that occur during coinfections, explaining how diabetes and HIV directly compromise CD4+ and CD8+ T-cell responses and accelerate the reactivation of latent TB.
- **Fix Minor Text and Grammatical Errors:** Correct spelling and proofreading errors throughout the text, such as the repeated phrase "public hea health initiatives" in the abstract.
- **Discuss the Financial and Social Impacts of Treatment:** Add a short paragraph analyzing the financial toxicity and social stigma associated with prolonged MDR-TB and XDR-TB treatments, emphasizing why shorter, all-oral regimens are vital for patient compliance.
- **Standardize Citation Formatting:** Ensure all bibliographic references in the text match a consistent academic style guide (such as APA 7th edition or Vancouver), making sure that recent citations and older foundational references include verified volume numbers, page numbers, and active DOIs where available.

Recommendation for Publication

I recommend this manuscript for **publication with minor revision**. The review is highly thorough, well-structured, and successfully links molecular microbiology with international public health challenges. It addresses an urgent global health priority by examining the post-COVID resurgence of TB and the rising threat of drug resistance. Once the author fixes the layout issues in Table 1, addresses the minor text

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errors, and expands slightly on the specific mechanisms of emerging therapies like phages and nanotechnology, this article will serve as an excellent, up-to-date reference for international medical journals.