Response to Reviewer 1

Manuscript Title: *Comparison of Immune Evasion Mechanisms of MDR-Tuberculosis Mycobacteria vs Non-Tubercular Mycobacteria*

Authors:

Journal:

Reviewer Comment	Author Response
Abstract clarification: Distinguish mechanisms supported by direct experimental evidence in MDR-TB versus those extrapolated from drug-susceptible strains.	We thank the reviewer for this helpful suggestion. The abstract has been revised to clearly distinguish mechanisms supported by direct experimental evidence (LAM, SapM, Zmp1) from those extrapolated from drug-susceptible strains (ESX-1, PPE proteins).
Novelty statement: Define the novelty of this review compared to previous literature.	In response to the reviewer's request, the introduction (lines 56–63) now emphasizes the novelty of this review, highlighting its systematic comparison of MDR-TB and NTM, the distinction between validated and inferred mechanisms, and the linkage of immune evasion to translational barriers.
Drug resistance vs immune evasion: Clarify whether drug-resistance mutations directly influence immune evasion.	This point has been addressed by adding a discussion (lines 83–99) clarifying that katG and rpoB mutations primarily alter drug-target interactions, while immune evasion is mediated by virulence factors.
Species-specific examples in Table 1: Include species-specific examples and molecular mediators.	We appreciate this suggestion. Table 1 has been updated to include species-specific mediators such as GPL, PKS1, PtpA, and LAM for NTM, and SapM, PPE2, and Zmp1 for MDR-TB.
SapM validation: Clarify whether SapM mechanisms are validated in clinical MDR-TB isolates.	We acknowledge this important issue. Lines 151–167 now note that SapM activity has been validated in H37Rv

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	reference strains, with limited but suggestive evidence in clinical isolates.
PPE2 findings vs speculation: Distinguish established findings from speculative interpretations.	This concern has been addressed. Lines 183–195 now clearly separate confirmed nitric oxide suppression from speculative ROS inhibition.
Host DUBs in ubiquitination: Provide direct examples of host deubiquitinases.	We thank the reviewer for this valuable suggestion. Lines 221–237 now include USP10 and CYLD as experimentally validated host deubiquitinases exploited by MTB.
AIM2 lineage differences: Discuss lineage differences in AIM2 signaling and NTM evidence.	In response to this comment, lines 251–270 now highlight lineage-dependent AIM2 signaling in MTB and weaker contributions in NTM species.
NTM species diversity: Clarify whether SapM, PtpA, and LAM mechanisms are conserved across NTM species.	We appreciate the reviewer's observation. Lines 295–304 now emphasize diversity among NTM species, noting that SapM, PtpA, and LAM mechanisms are not universally conserved.
Biofilm regulatory pathways: Expand discussion of biofilm regulation.	This suggestion has been incorporated. Lines 338–355 now expand the discussion of biofilm regulation, comparing pathways in M. abscessus and M. avium.
Cytokine response conflicts: Discuss conflicting reports on cytokine responses.	We thank the reviewer for raising this issue. Lines 359–389 now critically evaluate conflicting reports on TNF-α, IL-12, IL-10, and TGF-β responses across NTM species and host cell types.
cGAS–STING in NTM: Address evidence of NTM interaction with cytosolic DNA-sensing pathways.	This point has been addressed. Lines 430–454 now refine the comparison, noting recent findings of NTM engagement with cGAS–STING.

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Vaccine candidates: Include current clinical vaccine candidates.	We appreciate the reviewer's suggestion. Lines 590–625 now summarize advanced vaccine platforms currently under clinical evaluation for TB and NTM.
Host-directed therapies: Critically evaluate clinical status and limitations.	In response to the reviewer's request, lines 636–640 now discuss translational challenges, safety concerns, and efficacy data of host-directed therapies.

Response to reviewer 2:

Reviewer Comment	Author Response
The manuscript provides a thorough description of resistance patterns and evasion techniques. It highlights virulence factors of M. tuberculosis and NTM, including lipoarabinomannan, biofilm development, shielding, and autophagy inhibition.	We thank the reviewer for recognizing the comprehensive coverage of immune evasion strategies. We retained these descriptions and expanded them with species-specific mediators (SapM, ESAT-6, PPE2, Zmp1 for MDR-TB; GPL, PKS1, PtpA, LAM for NTM) to strengthen the comparative analysis (Table 1).
Immune evasion mechanisms are discussed, such as blocking phagosome–lysosome fusion and evading the cGAS pathway for M. tuberculosis, and biofilm-mediated shielding for NTM.	We clarified which mechanisms are experimentally validated in MDR-TB versus extrapolated from drug-susceptible strains (Abstract, Section 3.2). For example, SapM-mediated PI3P depletion is validated in reference strains, while PPE2-mediated ROS suppression remains speculative. This distinction addresses the reviewer's request for clearer evidence attribution.
Significant gaps in knowledge were identified, including host genetic variation polymorphisms and the effects of host-directed therapies on immune evasion strategies.	We added explicit discussion of host genetic variation and its impact on immune responses (Section 5.3). We also critically evaluated host-directed therapies (rapamycin, metformin, IFN-γ, checkpoint inhibitors), noting early-phase trial data, safety concerns (immune overactivation, metabolic side effects, immune-related adverse events), and translational challenges.
Areas for expansion were noted, such as genetic screening to tailor treatment, the role of	We incorporated these suggestions into the Future Directions section. Specifically: genetic

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machine learning and AI in drug/vaccine development, and potential therapeutic targets.	screening and precision medicine approaches to tailor therapy; the role of AI/machine learning in accelerating drug discovery and vaccine design; and expanded discussion of therapeutic targets including biofilm inhibitors, efflux pump inhibitors, cytokine agonists, and metabolic modulators.
Overall, the manuscript is topical and interesting but could benefit from further development in these areas to enhance its clinical utility.	We have revised the manuscript to include all requested expansions and clarifications. The updated version now provides a clearer distinction between validated and extrapolated mechanisms, integrates species-specific examples, and critically evaluates clinical status and safety concerns of host-directed therapies. We believe these revisions enhance both the scientific rigor and clinical relevance of the review.