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Trained immunity in tuberculosis infection: a systematic review

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ABSTRACT

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Tuberculosis (TB) is considered a major contributor to death resulting from pathogenic bacteria; specifically, *Mycobacterium tuberculosis* (Mtb) spreads through droplets from individuals with active TB. Both the innate and adaptive immune systems collaborate to control the infection, with innate immunity potentially playing a role in eliminating Mtb. Vaccination, early diagnosis, and treatment can reduce the severity of the infection, but new strategies are still needed to address TB. Research suggests that trained immunity may assist in combating pathogens, including Mtb, and could open new opportunities for treatment. A systematic review was conducted following the eight-step Cochrane methodology and adhering to PRISMA guidelines. An initial automated search identified 157 articles published between 2020 and 2025. Following duplicate removal and evaluation of titles and abstracts, 92 articles remained. After further screening, 52 articles were excluded, and 40 articles were identified for in-depth review. As a result, 8 publications satisfied all eligibility standards and were incorporated into the systematic review. Vaccines (e.g., BCG and TB-MAPS) and adjuvants (e.g., β-glucan) exploit trained immunity to enhance protection. BCG reprograms hematopoietic stem cells (HSCs) via chromatin remodeling, inducing long-term functional alterations in neutrophils, monocytes, and macrophages through epigenetic modifications (e.g., H3K4me3). TB-MAPS generated strong, long-lasting T cell and antibody responses and protected against Mtb infection in both lungs and spleen, matching BCG efficacy. When combined with BCG, it showed synergistic effects, further lowering lung bacterial load. Protection relied partly on IL-12p40 signaling, with IFN-γ and IL-17A pathways driving systemic and lung immunity. β-glucan operates via IL-1 signaling, epigenetically upregulating IL-1 family genes and enhancing proinflammatory responses via the PI3K/Akt/mTOR pathway. These interventions boost myelopoiesis and strengthen both innate and adaptive immune memory, providing stronger protection against TB and opening avenues for new therapeutic approaches.

ABSTRAK

Tuberkulosis (TB) dianggap sebagai kontributor utama kematian akibat bakteri patogen, terutama *Mycobacterium tuberculosis* (Mtb), yang ditularkan melalui droplet dari penderita TB aktif. Sistem imun bawaan dan adaptif bekerja bersama untuk mengendalikan infeksi, dengan imunitas bawaan memiliki potensi untuk membantu menghilangkan Mtb. Vaksinasi, diagnosis yang cepat, dan pengobatan yang tepat dapat mengurangi keparahan infeksi, namun masih dibutuhkan strategi baru untuk mengatasi TB secara lebih efektif. Penelitian terkini menunjukkan bahwa *trained immunity* berperan dalam membersihkan patogen, termasuk Mtb, dan pemahaman lebih dalam mengenai mekanisme ini dapat membuka peluang baru dalam pengobatan TB. Sebuah tinjauan sistematis dilakukan dengan mengikuti metodologi delapan langkah Cochrane dan mematuhi pedoman PRISMA. Pencarian otomatis awal mengidentifikasi 157 artikel yang diterbitkan antara tahun 2020 dan 2025. Setelah menghapus duplikat dan menyaring judul serta abstrak, tersisa 92 artikel. Setelah proses penyaringan lebih lanjut, 52 artikel dikeluarkan, menyisakan 40 artikel untuk tinjauan teks lengkap. Akhirnya, 8 artikel memenuhi semua kriteria inklusi dan dimasukkan dalam tinjauan sistematis, sementara 32 artikel dikeluarkan. Vaksinasi (BCG dan TB-MAPS) serta adjuvan (β-glukan), dapat meningkatkan perlindungan melalui *trained immunity*. BCG memprogram ulang *hematopoietic stem cell* (HSC) melalui perombakan kromatin, sehingga memicu perubahan fungsi jangka

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panjang pada neutrofil, monosit, dan makrofag melalui modifikasi epigenetik (H3K4me3). TB-MAPS menghasilkan respons sel T dan antibodi yang kuat serta tahan lama, dan mampu memberikan perlindungan terhadap infeksi Mtb pada paru-paru dan limpa, dengan efektivitas setara BCG. Ketika dikombinasikan dengan BCG, efeknya bersifat sinergis sehingga semakin menurunkan jumlah bakteri di paru. Perlindungan sebagian bergantung pada sinyal IL-12p40, dengan jalur IFN-γ dan IL-17A yang mendorong kekebalan sistemik dan paru. β-glukan bekerja melalui sinyal IL-1, secara epigenetik meningkatkan ekspresi gen keluarga IL-1 dan memperkuat respons proinflamasi melalui jalur PI3K/Akt/mTOR. Intervensi ini meningkatkan mielopoiesis dan memperkuat memori imun bawaan serta adaptif, memberikan perlindungan yang lebih kuat terhadap TB dan membuka peluang untuk pendekatan terapeutik baru.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), is a leading cause of death from pathogenic bacteria.[1] Primarily affecting the lungs, Mtb spreads from the initial infection site to other organs via airborne droplets from active cases.[2,3] In 2021, the WHO reported 10.6 million cases (up 4.6% from 2020) and 1.6 million deaths, with Southeast Asia (44%), Africa (25%), and the Western Pacific (18%) being the most affected regions. Drug-resistant cases rose by 3%, including 450,000 rifampicin-resistant cases.[4] By 2023, Indonesia ranked second globally with 1,060,000 cases and 134,000 deaths.[5]

Multicellular organisms rely on innate and adaptive immunity for protection. Innate immunity forms the first line of defense against Mtb before host cell infiltration, while adaptive immunity, which works alongside it, recognizes non-self structures via humoral/cellular components.[6] Although adaptive immunity typically controls Mtb infection, innate systems can also eliminate it.[7]

Traditionally, innate immunity responds promptly but non-specifically, lacking memory cells to prevent reinfection. However, pattern recognition receptors (PRRs) enable recognition, and reinfection enhances responses in humans and other species, leading to "trained immunity".[6] Though adaptive immunity controls Mtb infection, innate mechanisms can eradicate the pathogen, as evidenced by Indonesian contacts who exhibited resolving innate responses and heightened heterologous cytokines production before IGRA conversion.[8] This involves innate immune memory developed via metabolic and epigenetic changes, which improve responses to secondary infections.[1,6]

Vaccination, early diagnosis, and treatment reduce TB severity, yet persistent infections demand new strategies. Despite advances in TB biology over the past decade, standard 6-month regimens (using 2-4 antibiotics), as well as the need for better vaccines and shorter therapies, remain critical since outcomes have not sufficiently improved.[7] Trained immunity plays a pivotal role in Mtb clearance and inflammation and the modulation of inflammation.[1] Deeper mechanistic insights could yield novel treatments. Thus, this review explores trained immunity within the innate immune system based on prior studies.[6]

MATERIAL AND METHODS

This study used a systematic review design. A systematic review is an approach for conducting research that incorporates an in-depth assessment of all relevant scientific literature related to the research topic in order to provide a comprehensive summary. The process of searching and writing this article adhered to the preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An extensive literature review was conducted utilizing various databases, including SCOPUS, PubMed, and Semantic Scholar. The database searches were performed between February to March 2025 to compile the most comprehensive list of relevant studies. We specifically focused on articles related to trained immunity in tuberculosis infection. Clear and spesific keywords string were applied at each stage of the search, including: (“Trained Immunity”) OR (“Mycobacterium Tuberculosis” AND “Tuberculosis Infection”) and (“Immunity” AND “Immunology”) OR (“Tuberculosis”). The inclusion criteria for this review encompassed articles that specifically addressed trained immunity in tuberculosis infection, were published in scientific journals as full papers, were open access, and written in English. Only studies published in the past five years (2020–2025) were considered. Gray literature or publications not meeting these criteria were excluded.

To ensure a rigorous and unbiased selection process, study screening was performed independently by two reviewers. The screening was conducted in two successive stages: title-and-abstract screening and full-text review. During the first stage, both revieweres independently screened the titles and abstracts of all identified records against the predefined eligibility criteria based on the PICO framework. Following the initial screening of titles and abstracts, potentially eligible articles were retrieved in full and independently assessed for final inclusion.

RESULT

Study selection

The selection and data extraction process followed the Cochrane eight-step methodology and adhered to PRISMA guidelines. An initial automated search identified 157 articles published between 2020 and 2025. Following duplicate removal and evaluation of titles and abstracts, 92 articles remained. Following a further screening process, 52 articles were excluded, leaving 40 articles for full-text review. As a result, 8 publications satisfied all eligibility standards and were incorporated into the systematic review, while 32 articles were excluded (FIGURE 1). Any discrepancies or disagreements between the two reviewers regarding study eligibility were resolved through collaborative discussion. In cases where a consensus could not be reached, an academic supervisor was consulted to make the final determination. This process was managed using Covidence to ensure inter-rater reliability throughout the study selection phase.

Our systematic review employed a rigorous multi-stage screening methodology to identify relevant literature for analysis. Beginning with an initial cohort of 157 publications retrieved through comprehensive database searches, we progressively refined our selection through structured identification and screening phases. Each record underwent careful evaluation against predefined inclusion and exclusion criteria, followed by detailed full-text assessment of potentially eligible studies. This meticulous process ultimately yielded 8 pertinent studies that met our stringent quality standards and relevance requirements, ensuring a focused and reliable evidence base for our synthesis.

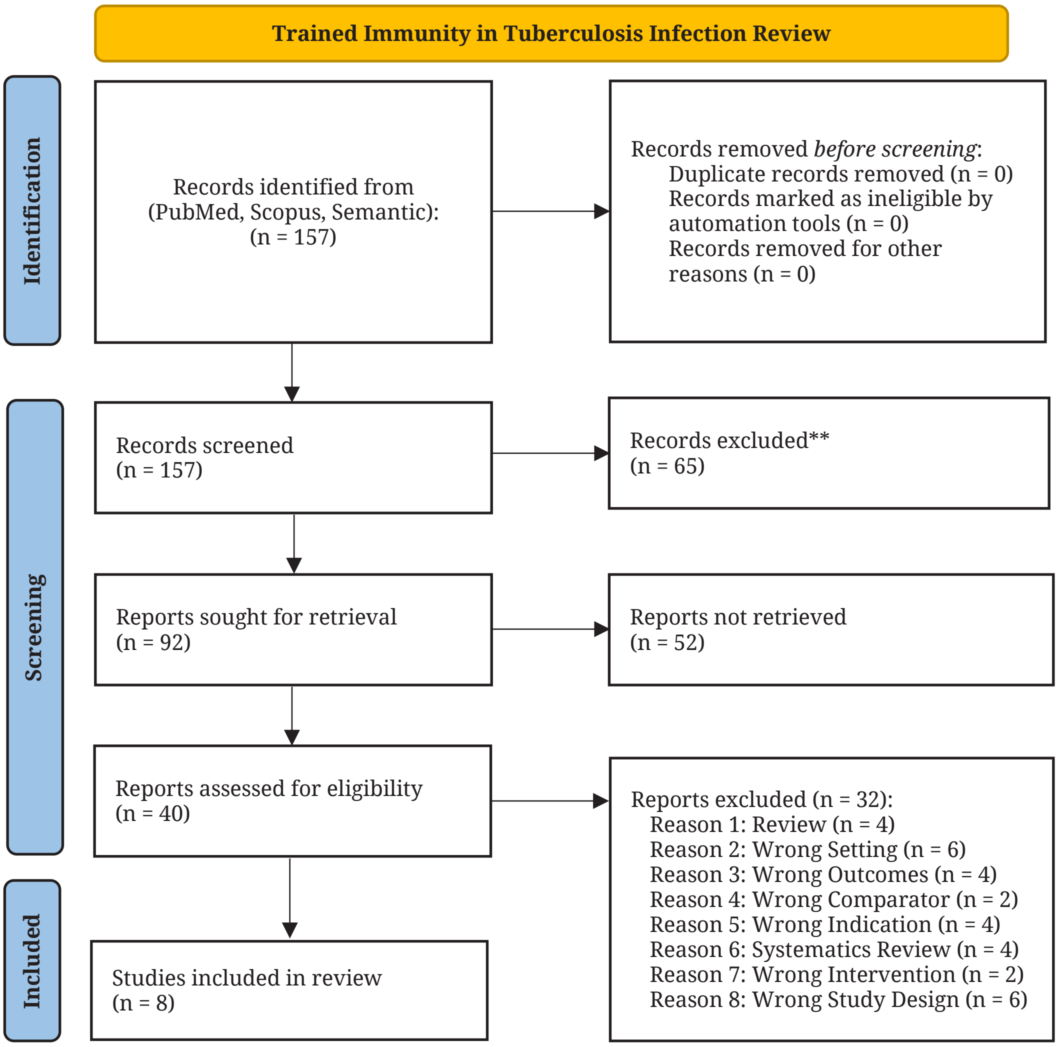

FIGURE 1. Method of Screening

TABLE 1. Summary of selected study (n = 8)

Author	Objective	Type of study	Subject	Result
Moorlag SJ *et.al.*,[9]	This study explores how β-glucan exposure reprograms monocytes and macrophages to enhance long-term antimicrobial defense against Mtb. Using human and mouse models, it investigates cytokine production, gene expression, and IL-1–mediated myelopoiesis as key mechanisms of trained immunity.	In vivo, In vitro	Human, Mice	β-glucan triggered epigenetic changes in monocytes, boosting IL-6, TNFα, and IL-1β production and reducing Mtb growth. In mice, it improved survival and lung protection by expanding myeloid progenitors. These effects depended on IL-1 signaling, proving its essential role in β-glucan–induced trained immunity.
Verrall AJ *et.al.*,[10]	This study investigates factors linked to early clearance of Mycobacterium tuberculosis (Mtb) among household contacts of TB patients in Indonesia.	In vivo	Human	About 25% of contacts showed early clearance by remaining IGRA negative. BCG vaccination significantly reduced infection risk, though its protection weakened with age and exposure. Higher hemoglobin, lymphocyte, and monocyte counts increased infection odds, while neutrophils had a slight protective effect, highlighting both immune and metabolic factors in TB resistance.

TABLE 1. Cont...

Author	Objective	Type of study	Subject	Result
Khan N *et.al.*,[11]	This study explores how Mycobacterium tuberculosis (Mtb) and BCG vaccination differently affect hematopoietic stem cells (HSCs) in the bone marrow. Using mouse models and RNA sequencing, it examines how each influences immune training, focusing on cytokine signaling, iron metabolism, and cell death pathways.	In vivo, In vitro	Mice	Mtb reprograms HSCs via a type I IFN/iron axis, suppressing myelopoiesis and trained immunity through RIPK3-dependent necroptosis. This impairs macrophage function and antimicrobial defense. In contrast, BCG promotes protective immunity via IFN-II and IL-1 pathways, highlighting Mtb's immune evasion strategy and BCG's long-term immune benefits.
Moorlag SJ *et.al.*,[12]	This study explores how the BCG vaccine, known for tuberculosis prevention, also induces long-term immune reprogramming in human neutrophils. Researchers assessed changes in neutrophil phenotype, function, metabolism, and epigenetics in vaccinated individuals over a 3-month period	In vivo, In vitro	Human, Mice	BCG vaccination led to enhanced neutrophil activation, greater pathogen-killing ability, increased cytokine and ROS production, and metabolic shifts (higher glycolysis). These effects were supported by epigenetic modifications (H3K4me3) and upregulation of lncRNAs, indicating trained immunity that strengthens neutrophil response to infections
Bickett TE *et.al.*,[13]	This study examines whether early, T cell-independent innate immunity contributes to BCG's protection against pulmonary tuberculosis. Using various mouse knockout models and cell depletion techniques, researchers assessed lung immune cell recruitment and cytokine responses after BCG vaccination.	In vivo	Mice	BCG reduced mycobacterial burden within 7 days, even without CD4/CD8 T cells or TNF-α, indicating innate-driven protection. Monocytes, macrophages, and neutrophils played key roles, with live BCG required for full efficacy. Protection was independent of NOD2 signaling, highlighting a unique, rapid innate immune mechanism.
O'Hara JM *et.al.*,[14]	This study introduces TB-MAPS, a multivalent TB vaccine combining Mtb protein antigens on biotinylated scaffolds. Researchers tested its ability alone and with BCG to induce broad, durable immune responses in mice, focusing on T cell diversity, antibody production, and memory across systemic and lung compartments.	In vivo	Mice	TB-MAPS generated strong, long-lasting T cell and antibody responses and protected against Mtb infection in both lungs and spleen, matching BCG efficacy. When combined with BCG, it showed synergistic effects, further lowering lung bacterial load. Protection relied partly on IL-12p40 signaling, with IFN-γ and IL-17A pathways driving systemic and lung immunity.
Sun SJ *et.al.*,[15]	This study analyzes how BCG vaccination affects human bone marrow at the epigenetic and transcriptional levels. Using scRNA-seq and scATAC-seq, researchers examined changes in hematopoietic stem and progenitor cells (HSPCs) from vaccinated individuals to understand how BCG drives long-term immune reprogramming.	In vivo	Human	BCG induced lasting gene expression and chromatin changes in HSPCs, especially in hematopoietic stem cells and megakaryocyte-erythroid progenitors. These changes favored immune and metabolic pathways, with over 13,000 epigenetic modifications linked to enhanced IL-1β and IL-6 secretion upon fungal challenge, indicating stronger innate immune responses.
Braian C *et.al.*,[16]	This study evaluates whether different β-glucans can train human macrophages to enhance their ability to control M. tuberculosis growth. Human monocytes were trained with β-glucans from various sources, and macrophage function, cytokine production, metabolism, and epigenetic changes were analyzed.	In vitro	Human	Training with curdlan and Alternaria-derived β-glucans improved macrophage control of M. tuberculosis, boosting IL-6 and IL-1β production. WGP dispersible β-glucan showed mixed responses among donors. Neutrophil co-culture enhanced mycobacterial control, independent of β-glucan type. Epigenetic analysis revealed β-glucan-induced changes in immune-related gene methylation, highlighting IL-6 as a key marker of improved mycobacterial defense.

Epigenetic reprogramming and immune activation by β-glucan

According to a study by Moorlag SJ *et al.*,[9] β-glucan “training” of human monocytes resulted in epigenetic modifications and the upregulation of genes involved in anti-mycobacterial defense, leading to increased production of IL-6, TNFα, and IL-1β, as well as the inhibition of Mtb growth upon exposure. In mice, β-glucan administration significantly reduced the pulmonary Mtb burden and improved survival rates. These protective effects were associated with the expansion of hematopoietic stem cells and myeloid progenitors in the bone marrow. Importantly, the protective benefits of β-glucan were lost in IL-1 receptor–deficient mice or after IL-1 inhibition, confirming the necessity of IL-1 signaling for trained immunity and protective myeloid cell development against Mtb infection.[9]

Braian C *et al.*,[16] evaluated whether different β-glucans can train human macrophages to enhance their ability to control M. tuberculosis growth. The study found that training macrophages with curdlan and Alternaria-derived β-glucans significantly improved macrophage control of M. tuberculosis growth compared to untrained controls, which correlated with increased production of IL-6 and IL-1β cytokines. WGP dispersible β-glucan showed variability among donors, dividing them into “responders” (with enhanced mycobacterial control and higher IL-6 release) and “non-responders.” The co-culture of neutrophils and macrophages further enhanced control of mycobacterial growth, although this effect was not dependent on the β-glucan stimulus. Epigenetic analysis revealed that β-glucan training led to differential methylation of genes linked to immune pathways, including interferon-gamma signaling in WGP responders and interleukin/cytokine signaling in curdlan- and Alternaria-trained cells. The study provides evidence that certain β-glucans can act as immune trainers, boosting macrophage responses against tuberculosis through functional and epigenetic reprogramming, with cytokine production (especially IL-6) emerging as a key correlate of improved anti-mycobacterial activity.[16]

Impact of BCG vaccination on IGRA positivity and infection risk

Among 1347 contacts of TB cases, 57.9% were IGRA positive and 36.3% were negative at baseline. After 14 weeks, 26.1% of initially negative contacts became IGRA converters, while 71.2% remained persistently negative and were classified as “early clearers.” Notably, BCG vaccination substantially reduced the likelihood of both baseline IGRA positivity and IGRA conversion after exposure, with the protective effect decreasing as both Mtb exposure and age increased. Early clearers, who accounted for about a quarter of all contacts had lower measures of exposure and tended to be younger. Higher hemoglobin concentration was associated with a greater risk of IGRA conversion. The findings highlight that BCG vaccination offers significant but variable protection against Mtb infection, influenced by the degree of exposure and age, underscoring the need for new vaccine strategies that enhance early clearance mechanisms.[10]

According to the findings reported by Moorlag SJ *et al*,[12] BCG vaccination led to enhanced neutrophil activation, greater pathogen-killing ability, increased cytokine and ROS production, and metabolic shifts (towards higher glycolysis). These effects were supported by epigenetic modifications (H3K4me3) and the upregulation of lncRNAs, indicating trained immunity that strengthens neutrophil response to infections.[12]

On the other hand a study by

Bickett TE *et al.*,[13] demonstrated that, BCG vaccination produced a significant reduction in Mycobacterium tuberculosis burden as early as 7 days post-vaccination, even in the absence of conventional T cells (CD4, CD8) or TNF-α, indicating strong, rapid innate immunity. Lung immune profiling revealed the recruitment of CD11b+F4/80+ monocytes/macrophages and an increase in neutrophils in vaccinated mice. Functional experiments showed that depletion of neutrophils prior to and during vaccination decreased the protective effect, confirming their role in establishing early immunity. Importantly, live BCG was required for maximal mycobacterial killing; γ-irradiated BCG, while still stimulating macrophage cytokine production, was less effective in reducing bacterial burden. Protective effects were not dependent on NOD2-mediated trained immunity or the vaccine's route of administration (except for low dose aerosol), emphasizing an alternative, unconventional mechanism where monocytes, macrophages, and neutrophils function together to induce rapid early mycobacterial clearance following BCG vaccination.[13]

The study by Sun SJ *et al.*,[14] found that BCG vaccination induces significant and lasting changes in both gene expression and chromatin accessibility within HSPCs. At the transcriptional level, the strongest effects appeared in the most uncommitted hematopoietic stem cells (HSCs) and megakaryocyte-erythroid progenitors (MEPs), with hundreds of differentially regulated genes detected 90 days post-vaccination. These genes were enriched in immune, metabolic, and proliferative pathways, with HSCs showing persistent rewiring suggestive of a myeloid lineage bias. At the epigenetic level, over 13,000 differentially accessible chromatin regions were identified, predominantly in more differentiated progenitors such as CMPs (common myeloid progenitors) and GMPs (granulocyte-monocyte progenitors). Importantly, transcription factor motifs enriched in these progenitors overlapped with transcription factors activated in HSCs, suggesting a cascade from stem cells to downstream lineages. Functionally, these molecular changes correlated strongly with increased secretion of IL-1β and IL-6 by PBMCs upon fungal challenge, indicating that BCG vaccination reprograms bone marrow stem cells in a way that enhances peripheral innate immune responses.[15]

Mtb-induced IFN-I signaling suppresses myelopoiesis in HSCs

A study by Khan N *et al.*,[10] demonstrates that, unlike BCG or β-glucan, Mtb reprograms hematopoietic stem cells (HSCs) through a type I interferon (IFN-I) signaling pathway, which suppresses myelopoiesis and disrupts the development of protective trained immunity. Mechanistically, Mtb-induced IFN-I signaling leads to dysregulation of iron metabolism, depolarization of mitochondrial membrane potential, and RIPK3-dependent necroptosis specifically in myeloid progenitors. This results in the depletion of myeloid progenitors, a failure to produce effective macrophages, and ultimately, a compromised innate immune response to Mtb infection in vivo. Both intravenous and physiological aerosol infection with Mtb led to rapid dissemination into the bone marrow, persistent alteration of HSC function, and long-term reduction of hematopoietic output for at least one year. These detrimental changes in HSC function are contrasted by the beneficial reprogramming and enhanced engraftment capacity observed with BCG vaccination, which biases hematopoiesis toward myelopoiesis and supports trained immunity. Loss of iron homeostasis further exacerbates susceptibility to Mtb infection, while

BCG or β-glucan imprinting is associated with preserved myelopoiesis and robust anti-TB immune responses.[16]

TB-MAPS: a promising adjunct for comprehensive tuberculosis vaccination strategies

TB-MAPS vaccination induced strong, long-lived antigen-specific antibody responses and a large repertoire of memory T cell subsets, including Th1, Th17, cytotoxic CD4+ and CD8+ cells, as well as functionally diverse γδ T cells and NKT cells in both systemic circulation and respiratory tissues. In mouse aerosol challenge models, TB-MAPS alone provided protection against both lung and spleen infection comparable to BCG, reducing bacterial loads by approximately 4- to 10-fold relative to controls. Importantly, concurrent or sequential administration of TB-MAPS with BCG produced synergistic effects, achieving up to an additional 8-fold reduction in lung bacterial burden compared to either vaccine alone while maintaining protection in the spleen. The vaccine's cellular responses were partially dependent on the IL-12p40 pathway, with IFN-γ-mediated (Th1) protection crucial for controlling dissemination, while IL-17A-associated lung protection involved both IL-23-dependent and -independent mechanisms (including γδ T and NKT cells).[14]

DISCUSSION

The collected evidence from the reviewed studies demonstrates that both Mycobacterium tuberculosis (Mtb) infection and Bacillus Calmette-Guérin (BCG) vaccination produce significant and durable effects on hematopoietic and innate immune reprogramming. BCG vaccination consistently activates hematopoietic stem and progenitor cells, leading to enhanced myelopoiesis, long-lasting trained immunity phenotypes in monocytes and neutrophils, and an improved capacity to control Mtb and unrelated pathogens, as shown in both experimental and clinical settings.[10-12,14-17] In contrast, Mtb infection subverts immunity by epigenetically and metabolically suppressing myeloid cell development and impairing the establishment of protective trained immunity, a process that exploits type I interferon signaling and iron metabolism, as described.[10] The introduction of innovative vaccine designs, including the MAPS platform, further expands the induction of systemic and tissue-resident cellular memory, yielding potent protection in preclinical models.[14] However, the predominantly preclinical nature of MAPS data, especially in murine models, still limits direct inference to human populations and highlights the need for cautious interpretation.

Together, these studies provide strong evidence that innate immune memory, or trained immunity, extends beyond monocytes to involve neutrophils and tissue-resident populations.[12,16] The findings from the INFECT study in Indonesia, highlight the real-world impact of early clearance and prevention of Mtb infection, which appears to be closely linked to mechanisms of innate protection stimulated by BCG.[10] Nonetheless, the human studies summarized in this review are often constrained by relatively small sample sizes and substantial inter-individual (donor) variability in immune responses, which may lead to overestimation or underestimation of effect sizes and limit generalizability to broader TBendemic populations. Mechanistic investigations of BCG and β-glucans converge on the discovery of epigenetic, metabolic, and transcriptional rewiring in innate immune cell lineages, providing an expanded view of vaccine-induced immunity across human and animal systems.[10,11,16]

In β-glucan studies in particular,

heterogeneity between donors, including genetic background, prior infections, and comorbidities, introduces additional noise that needs to be acknowledged as a source of potential bias when interpreting trained immunity readouts.

These articles are notable for their methodological strengths, such as the application of single-cell sequencing, longitudinal human vaccination protocols, and translational animal studies, yielding detailed insights into cell fate and gene expression signatures following BCG and Mtb exposure. However, certain limitations persist, including variability in individual immune responses, the challenge of differentiating durable from transient changes in stem cell populations, and the limited duration and sample sizes in many studies.[10,14,15] Small human cohorts and short followup periods are especially important constraints for drawing firm conclusions about long-term persistence and clinical relevance of trained immunity. The interpretation of field epidemiology data is complicated by confounders such as BCG scar misclassification or exposure intensity among participants, as highlighted by Verrall *et al.*,[10] and at a mechanistic level, there is a need for further clarification of the link between stem cell programming and adaptive immunity.[10,15] Moreover, the heavy reliance on murine models, while mechanistically informative, is intrinsically limited by speciesspecific differences in hematopoiesis, granulopoiesis, and TB pathogenesis, which may not fully recapitulate human disease. When considered together, these design features also raise the possibility of publication bias, where positive or mechanistically appealing findings are more likely to be reported than neutral or negative studies, potentially skewing the apparent strength of evidence in favor of trained immunitybased interventions.

Despite these challenges, the evidence strongly argues for the continued prioritization of BCG vaccination and the development of interventions that harness trained immunity for TB prevention. Demonstrations that β-glucans and novel subunit vaccines, such as MAPS, can induce similar protective profiles suggests new directions for TB immunotherapy. These strategies have the potential not only to reduce tuberculosis risk but also to improve host broadly protective immunity.[10,14,16] Translationally, these observations are particularly relevant for TB contact management, where trained immunity inducing approaches could, in principle, complement existing preventive strategies (such as TPT) to enhance early control of Mtb in recently exposed household and community contacts. At the programmatic level, integrating such strategies with national vaccine programs would require alignment with current BCG policies, consideration of booster or adjunct schedules, costeffectiveness in highburden settings, and compatibility with existing childhood and adult immunization platforms. For MAPSbased or βglucan–based interventions, issues of safety, route of administration, dosing, and manufacturability will be critical determinants of feasibility for largescale implementation in humans.

Mechanistic data reveal that trained immunity from BCG and β-glucans results from deep-layered epigenomic modifications, such as histone H3K4me3 methylation, metabolic shifts favoring glycolysis, and transcription factor activation, all of which shape the phenotype and function of both stem and mature innate immune cells.[9,12,15,16] In contrast, Mtb manipulates host immunity by suppressing myelopoiesis through the interferon and iron axis, resulting in programmed cell death of progenitors and failure to establish trained innate memory.[11] These mechanistic contrasts offer a biological rationale for prioritizing interventions that reinforce beneficial myelopoiesis and trained innate responses, but they still require validation in sufficiently powered human studies that reflect the diversity of TBexposed populations.

In summary, the integrated review of contemporary mechanistic and epidemiological research underscores the importance of innate immune reprogramming and trained immunity in defending against tuberculosis infection and disease. The future of TB prevention likely hinges on improved understanding of innate memory mechanisms, precision vaccine development, and their judicious application in vulnerable, high-burden populations.[10,11,14,16] Strengthening critical appraisal of study design limitations and more clearly articulating the translational pathway from experimental trained immunity to feasible, scalable tools for TB contact management and national vaccination programs will be essential to realize this potential. To elucidate the multifaceted mechanisms of trained immunity contributes to the prevention of tuberculosis infection, a comprehensive illustration is presented (FIGURE 2).

This schematic illustrates the proposed immune mechanisms induced by β-glucans, BCG and TB-MAPS vaccines against tuberculosis (TB) infection. The first panel depicts the β-glucan triggered epigenetic changes in monocytes, boosting IL-6, TNFα, and IL-1β production and reducing Mtb growth. In mice, it improved survival and lung protection by expanding myeloid progenitors. The second panel show BCG pathway, BCG vaccination activates hematopoietic stem and progenitor cells, leading to enhanced myelopoiesis, long-lasting trained immunity phenotypes in monocytes, macrophage and neutrophils. These molecular changes correlated strongly with increased secretion of IL-1β and IL-6. In contrast, the third panel shows TB-MAPS generated strong, long-lasting T cell and antibody responses and protected against Mtb infection in both lungs and spleen. This image was created with BioRender (https://biorender.com/)

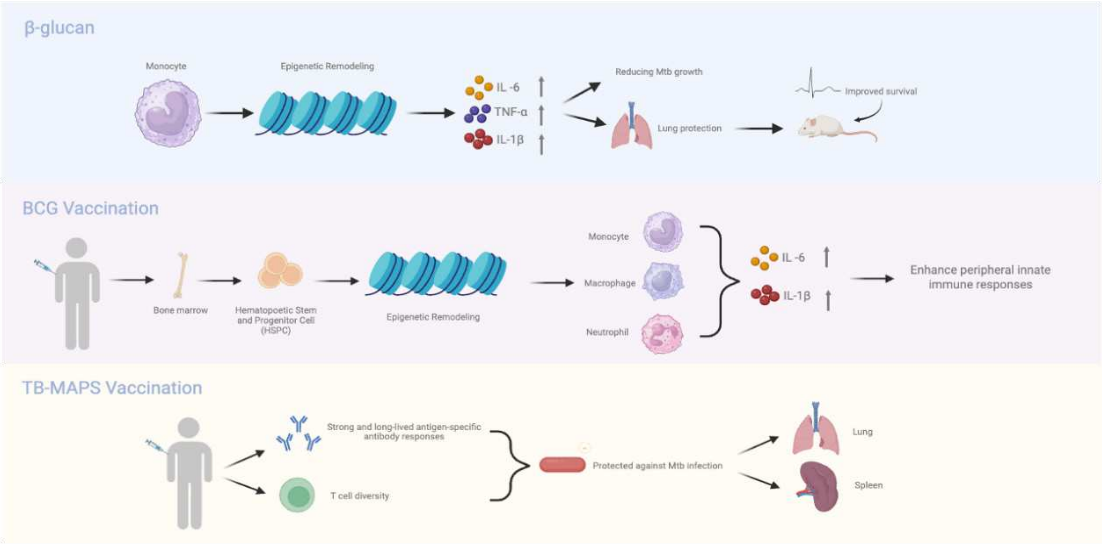

FIGURE 2. Summary of trained immunity mechanisms in tuberculosis infection.

This review has several limitations. Much of the evidence for TB MAPS is preclinical and derived from murine models, which restricts direct extrapolation to humans and requires cautious interpretation. Human studies are often based on small cohorts, short follow up, and substantial donor variability, particularly in β glucan studies, potentially biasing effect estimates and limiting generalizability to TB endemic populations. The heavy reliance on animal and in vitro models, combined with a likely publication bias favoring positive or mechanistically appealing results, may overstate the strength of support for trained immunity–based interventions. Finally, although mechanistic data provide a rationale for targeting trained immunity, key translational aspects including integration with TB contact management and national vaccination programs, as well as the practical feasibility of MAPS and β glucan–based strategies remain insufficiently validated in large, diverse human cohorts.

CONCLUSION

Mycobacterium tuberculosis (Mtb) can reprogram hematopoietic stem cells to suppress myelopoiesis and weaken trained immunity, thereby impairing antimicrobial defense and promoting pathogen persistence. In contrast, trained immunity, inducing interventions such as BCG and β-glucan can counter this effect by reprogramming innate immune responses through epigenetic and metabolic mechanisms. Among emerging candidates, TB-MAPS shows promise as a novel platform, particularly because of its protective immune responses and potential synergy with BCG. However, the current evidence remains largely preclinical. Further studies are needed to validate durability, mechanisms, biomarkers, and clinical relevance before these strategies can be translated into TB prevention programs.

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