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REVIEW

Host Immune Response to *Mycobacterium tuberculosis* Infection: Implications for Vaccine Development

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Abstract: Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*) infection, including pulmonary tuberculosis and extrapulmonary tuberculosis. About a quarter of the people in the world are infected with TB, but only 5–10% of them will progress to active TB, posing a major challenge to the eradication of TB. The study of the host immune response to *Mtb* infection is a key aspect of the development of effective vaccines and immunotherapies to eradicate tuberculosis. In this review, we delve into the overview of animal models of TB infection and the host's innate and adaptive immune responses to *Mtb* infection. We discuss how *Mtb* is recognized and phagocytosed by macrophages, how it evades immune responses, the recruitment and mobilization of neutrophils and monocytes, the role of natural killer cells during the infection process, how dendritic cells initiate adaptive immunity, the important roles of $CD4^+$ T cells and their subtypes in TB infection, how $CD8^+$ T cells exert cytotoxic functions, and how B cells produce antibodies and exhibit memory characteristics to eliminate pathogens. Furthermore, we review the tuberculosis vaccines currently entering clinical trials, emphasizing that studying the host's immune responses following *Mtb* infection is crucial for the development of more effective vaccines, providing a theoretical foundation and direction for the treatment of tuberculosis.

Keywords: *Mycobacterium tuberculosis*, immune response, vaccine, infection

Introduction

Tuberculosis primarily affects the lungs which caused by *Mycobacterium tuberculosis* (*Mtb*) infection and is transmitted through airborne particles. According to the World Health Organization (WHO), a global total of 8.2 million people were reported as newly diagnosed with TB in 2023, up from 7.5 million in 2022 and 7.1 million in 2019 and far above the levels of 5.8 million in 2020 and 6.4 million in 2021.[1] *Mtb* is transmitted to the lungs through aerosol. Successful infection relies on various factors, such as the proximity and duration of contact with active tuberculosis (ATB) patients, and the immune function of the host.[2] Clinically, Mtb infection manifests as latent tuberculosis infection (LTBI), presenting significant challenges for tuberculosis eradication. Approximately one-quarter of the global population have latent *Mycobacterium tuberculosis* infection, but only 5–10% of these individuals progress to ATB,[3] which is characterized by persistent cough, sputum production, weight loss, fatigue, and night sweats. Investigating the host immune response to *Mtb* infection is a critical aspect of developing effective vaccines and immunotherapies for the eradication of tuberculosis. Innate immune cells in the lungs, primarily macrophages, neutrophils, monocytes, and dendritic cells (DCs), rapidly engulf *Mtb* and constitute the first line of defense against the pathogen.[4] Adaptive immune cells such as $CD4^+$

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T cells, $CD8^+$ T cells, and B cells, are involved in killing bacteria and inhibiting bacterial replication.[5] Despite the host immune system's pressure, *Mtb* has evolved various strategies to evade and disrupt immune responses, allowing it to persist within the host. The immune response to *Mtb* infection involves the participation of multiple innate and adaptive immune cells.[6] A thorough investigation of the complex interactions between *Mtb* and the host immune system will aid in identifying new therapeutic targets for tuberculosis and is also of great significance for its prevention.

Based on the animal model of *Mtb* infection, this review discusses the host innate and adaptive immune responses after *Mtb* infection, as well as the progress of existing tuberculosis vaccines, emphasizing that the study of host immune responses after *Mtb* infection is crucial for the development of more effective vaccines.

Application of Animal Models in *Mycobacterium tuberculosis* Infection Research

The study of immune responses to *Mycobacterium tuberculosis* has greatly benefited from the development of various animal models, including mice, rabbits, fish, and non-human primates (NHPs), each of which has distinct advantages and limitations.[7] Mice have been widely used to model the immune response of hosts to infections with clinical isolates of *Mtb*, including susceptible and *non-susceptible* mice, which exhibit differences in their immune responses following infection with *Mtb*.[8] Due to the similarities in brain development processes between humans and rabbits, such as neuronal development, myelination, and microglial function, rabbit models have been used to study meningeal and spinal tuberculosis.[9,10] However, rabbits exhibit resistance to *Mtb*, necessitating the use of large bacterial inocula or more virulent strains in model establishment.[11] The establishment of zebrafish models has provided new insights into the formation of *Mtb*-induced granulomas. The pathological process can be visually monitored, and subcellular imaging of infected phagocytes within live hosts is possible.[12] NHPs, such as rhesus or cynomolgus monkeys, can be infected via aerosol or bronchoscopy to the lungs, exhibiting many characteristic granulomas observed in humans and presenting clinical symptoms similar to those in humans. However, NHP models are often constrained by ethical considerations, high costs, and difficulties in genetic manipulation.[11] In conclusion, animal models of tuberculosis are crucial tools for studying the disease, as they can replicate the natural course of human tuberculosis and facilitate a better understanding of the infection process, pathogenesis, and immune responses to *Mtb*. These models enable the testing of new tuberculosis vaccines, evaluating their immunogenicity and protective efficacy, and providing a basis for the development of more effective vaccines.

However, it is important to note that animal models also have certain limitations. Although these models can screen for potentially effective vaccine components, they often fail to reliably reflect the true efficacy in humans when assessing the actual performance of the vaccine. There are significant differences in disease resistance/susceptibility among these models, and thus no single model can capture all aspects of the disease pathogenesis.[13] Therefore, during the vaccine development process, it is essential to combine various research methods to enhance the likelihood of clinical translation.

Innate Immunity in *Mycobacterium tuberculosis* Infection

The innate immune system serves as the body's first line of defense against *Mtb*, playing a crucial role in the early response to the pathogen. However, innate immune cells can also serve as niches for bacterial replication, with *Mtb* employing various strategies to undermine the innate immune response and establish chronic infection. Current research on host innate immunity focuses on several aspects: how *Mtb* is recognized and engulfed by macrophages, the mechanisms by which the bacteria evade immune responses, the recruitment and mobilization of neutrophils and monocytes, the role of natural killer (NK) cells during infection, and how DCs initiate adaptive immunity (Figure 1 and Table 1).

Pattern Recognition Receptors Recognize *Mycobacterium tuberculosis*

Pathogen associated molecular patterns (PAMPs) on *Mtb* include mannose-capped lipoarabinomannan (ManLAM), phosphatidylinositol mannoside (PIMs), phenolic glycolipids (PGLs), peptidoglycan, Trehalose diester mycolate (TDM), and Phthiocerol dimycocerosates (PDIM), which can be recognized by various cytoplasmic pattern recognition receptors (PRRs), such as C-type lectin receptors (CLRs) (eg, mannose receptor, DC-SIGN, Dectin-1, Dectin-2, Mincle),

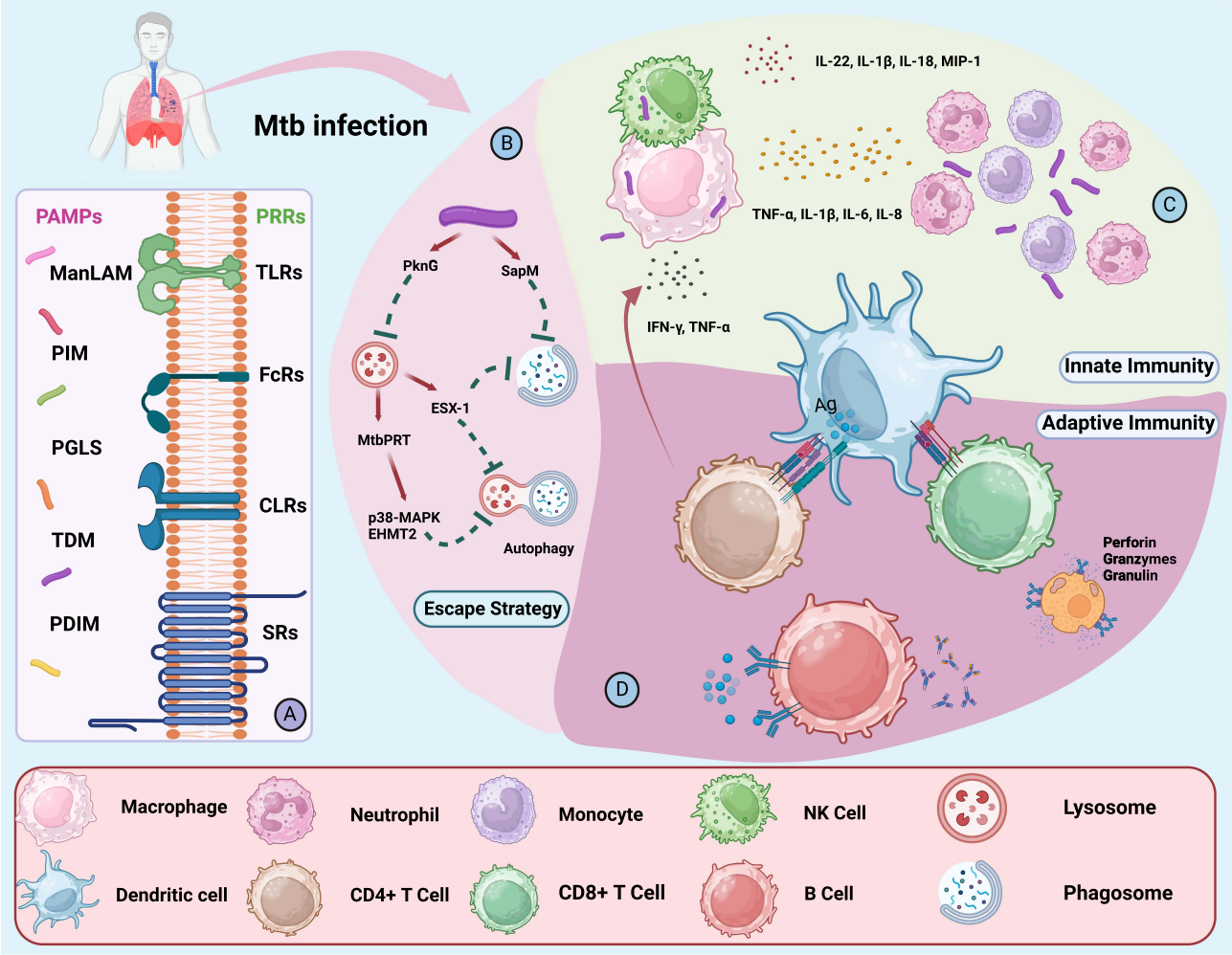

Figure 1 Host immune response after Mycobacterium tuberculosis infection. A) Pattern Recognition Receptors Recognize Mycobacterium tuberculosis; B) Mycobacterium tuberculosis evades the host immune response through various pathways; C) After infection with Mycobacterium tuberculosis, the host initiates innate immunity. Macrophages engulf Mycobacterium tuberculosis, release cytokines, and recruit neutrophils and monocytes. NK cells directly kill infected cells, release cytokines to enhance the immune response; D) Dendritic cells initiate adaptive immunity and reverse-regulate innate immunity. B cells release antibodies to eliminate Mycobacterium tuberculosis. Created with BioRender.com. https://BioRender.com/a29y964.

NOD-like receptors (eg, NOD2), complement receptors (eg, complement receptor 3), scavenger receptors (eg, MARCO, SR-A1, CD36, SR-B1), Fc receptors (eg, FcgR), and Toll-like receptors (TLRs) (TLR-2, TLR-4, TLR-9), thereby inducing the production of downstream cytokines and autophagy.[47] For instance, *Mtb* expresses various TLR ligands, and Toll-like receptors TLR-2, TLR-4, and TLR-9 are involved in host recognition of *Mtb*.[48] Studies have shown that

Table 1 Strategies of Host Immune Response After Mycobacterium Tuberculosis Infection

Immune Cells	Immune Response	References
Macrophages	PRRs mediate *Mtb* recognition and lysosomal LTPs and LPLA mediate lipid degradation	[14–16]
	Mediates the transcription of IL-1, TNF-α and IFN-γ, and forms and maintains tuberculous granulomas.	[16,17]
	Phagocytose apoptotic neutrophils and other *Mtb*-infected cells.	[16]
	T cells were activated using costimulatory molecules MHC I, II, CD80, and CD86.	[14,16,18,19]
	Excessive TNF-α production leads to apoptosis and necrosis of macrophages, resulting in the spread of *Mtb*.	[14–16]

(*Continued*)

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Table 1 (Continued).

Immune Cells		Immune Response	References
Neutrophils		Phagocytosis of *Mtb* releases ROS, proteolytic enzymes, and formation of cells to clear the pathogen. Release enzymes such as elastase, collagenase, and myeloperoxidase, which destroy *Mtb.* Presented the *Mtb* antigen to activate the macrophages and product Human neutrophil peptides as a-defensins. NETs can trap and kill microbes.	[20]
		Cytotoxic substances are released after death, which aggravate tissue damage and cause the spread of infection. Elastase, collagenase, and myeloperoxidase released are not specific and will simultaneously damage normal tissue.	[20,21] [14,20]
Monocytes	Classical (CD14++, CD16−)	Release ROS and proteolytic enzymes to eliminate *Mtb*. Mostly differentiated into dendritic cells.	[22] [22,23]
		Mycobacterium tuberculosis induce CD14++/CD16- monocytes to secrete IL-10, thereby reducing the production of pro-inflammatory cytokines. CCR2-dependent infiltration of monocytes mediates IFN-α secretion, leading to lung tissue injury.	[22,24,25] [26]
	Intermediate (CD14+, CD16+)	T cell proliferation and stimulation, MHC class II presentation and processing. Produce higher levels of TNF-a and lower levels of IL-10.	[22,27] [22,24]
	Non-classical (CD14+, CD16++)	Based on Fc receptor-mediated phagocytosis. Mostly differentiated into macrophages. Produce higher levels of TNF-a and lower levels of IL-10.	[22] [22,23] [22,24]
NK cells		NKp44 and TLR-2 were used to recognize *Mtb.* Secrete IL-22 and IFN-γ to interfere with the proliferation of *Mtb.* The NKp46 receptor and NKG2D mediate lysis of *Mtb*-infected monocyte and macrophages.	[28] [29,30] [31]
DCs		Recognizes antigens through macropinocytosis, Fc receptors and endocytosis. Presenting *Mtb* antigens through molecules, co-stimulatory molecules and chemokine receptor 7. Secrete proinflammatory cytokines IL-1 and IL-6 to recruit cells at the site of infection.	[17,32] [17,33] [17,34]
CD4 +T cells	Th1	Secrete IFN-γ, IL-2, and TNF-α, which in turn activate macrophages and recruit cells. Secrete IL-3 and GM-CSF to promote bone marrow stem cell differentiation.	[18,19,31,35] [36]
	Th2	Product IL-4 and IL-13 and promotes anti-inflammatory responses.	[37,38]
		Promote an anti-inflammatory response that hinders the clearance of *Mtb*	[38]
	Th17	Produce IL-17 to recruit IFN-γ-producing CD4+ T cells to the lungs.	[35,39,40]
		Excessive recruitment of CD4+ T cells results in extensive tissue damage.	[39,40]
	Tregs	Negatively regulates T cell responses to prevent hyperinflammatory responses.	[41]
		Mtb employs Tregs to mediate immunosuppression.	
CD8+ T cells		Secretes perforin, granzyme, and granulins to exert cytotoxic functions. Secrete IFN-γ and TNF-α.	[42] [43]
B cells		Product antibodies that specifically bind to Mtb. Kill *Mtb*-infected cells directly through ADCC. Activate CD4+ T cells by antigen presentation.	[44] [45] [46]

mice lacking the TLR adaptor protein myeloid differentiation factor 88 (MyD88) rapidly succumb to *Mtb* infection due to insufficient NOS2 expression in MyD88−/− mice, impaired activation of IL-1β or IL-1 receptor (IL-1R) pathways, diminished macrophage responsiveness to interferon-γ signaling,[49] and reduced IL-12 and TNF-α responses in macrophages and DCs.[50] MyD88 bridges TLR and IL-1 receptor family ligands to IL-1 receptor-associated kinases (IRAKs) in innate immunity, activating multiple downstream pathways including NF-κB, MAPK, and AP1. Investigating the interactions between PAMPs and PRRs and their downstream effects, as well as monitoring specific PAMP levels or PRR activation, may aid in the early detection and diagnosis of tuberculosis. Targeting PRRs or modulating PAMP recognition pathways could potentially lead to the development of more effective vaccines and immunoadjuvants.

Although host recognition of *Mtb* activates innate immunity, the pathogen has evolved strategies to evade PRR-mediated innate immune responses. *Mtb* can alter its cell wall components to inhibit host immune recognition and avoid detection by the host immune system. For instance, lipids such as ManLAM in the cell wall can bind to TLR2, activating mast cells to release exosomes and induce macrophage M2 polarization.[51] *Mtb* can also survive within the host by evading autophagy, an important host defense mechanism for eliminating intracellular pathogens. *Mtb* secretes ESX-1 associated proteins (EspL) to inhibit phagosome maturation and autophagy, thus promoting its survival.[52] Additionally, *Mtb* phosphoribosyl transferase (MtbPRT) inhibits autophagy independently by inducing high histone methylation (H3K9me2/3) on Atg5 and Atg7 promoters through activation of p38-MAPK and EHMT2 methyltransferase-dependent signaling pathways.[53] Feng et al found through a gene knockout mouse model that the absence of autophagy genes leads to acute susceptibility to high-dose *Mtb* infection.[54] Research has shown that conditional knockdown of the core autophagy component Atg5 in myeloid cells renders mice extremely susceptible to *Mtb*, while depletion of other autophagy factors does not affect the infection.[55] *Mtb* evades immune responses by blocking phagosome-lysosome fusion. For instance, *Mtb* can secrete PknG, which inhibits lysosome maturation by decreasing GlpK and ALD expression while increasing Ag85A and Ag85C expression, thereby enhancing bacterial infectivity, metabolism, growth rate, virulence, and drug resistance.[56] *Mtb* can also secrete proteins such as SapM, which interfere with phagosome maturation and acidification, thereby protecting the bacteria from host enzymatic destruction and enabling *Mtb* to survive and replicate within macrophages.[57] *Mtb* can also evade immune responses by inducing host cell apoptosis. For example, the lipoprotein ESAT-6 and another secreted protein, tuberculosis necrotizing toxin (TNT), induce necrotic apoptosis, which facilitates the proliferation and dissemination of the bacteria.[58] *Mtb* can evade detection by the immune system, which may make the diagnosis of latent or subclinical infections more difficult. Diagnostic tests for *Mtb* infection, such as the tuberculin skin test (TST) and interferon-γ release assay (IGRA), depend on the host's immune response.[59] However, if *Mtb* successfully suppresses this response, these tests may yield false-negative results, leading to missed or delayed diagnoses. *Mtb*'s immune evasion contributes to its persistent survival within the host, making complete eradication of the bacteria difficult even with prolonged treatment. This persistent survival is associated with an increased risk of drug-resistant tuberculosis, as prolonged antibiotic exposure can lead to the development of resistant mutations in *Mtb*,[60] including intermittent treatment and patient non-compliance with therapy.[61] The ability of *Mtb* to evade immune recognition poses a significant challenge to vaccine development. Traditional vaccines may fail to elicit a sufficiently strong immune response to provide protection, especially in populations with a high burden of latent tuberculosis. Studying *Mtb*'s immune evasion strategies is crucial for developing new vaccines that can elicit robust and durable immunity.

Macrophages Rely on Phagosomes to Defend Against *Mycobacterium tuberculosis*

Macrophages are the first immune cells to encounter *Mtb* during infection and serve as the primary replication niche for this bacterium. Macrophages recognize and engulf *Mtb*, utilizing lysosomes and phagosomes to eliminate the bacteria.[14] Intracellular signaling pathways triggered by PRR ligands induce actin polymerization to form early phagosomes. Research by Kolonko et al indicates that this process requires WASH-driven polymerization; disruption of WASH results in delayed phagosome maturation.[62] Within macrophages, phagosomes interact continuously with trans-Golgi transport vesicles, endosomes, and lysosomes, eventually fusing with lysosomes. This process, known as phagosome maturation,[63] is marked by acidification of the phagosome lumen mediated by the proton pump vacuolar ATPase (H^+-vATPase).[64] Ultimately, mature lysosomes mediate the degradation of lipid membranes through lysosomal lipid transfer proteins (LTPs) and lysosomal phospholipase A2 (LPLA2), leading to the clearance of *Mtb*.[15,16] Beyond their phagocytic function, macrophages also play a crucial role in regulating inflammatory responses during *Mtb*

infection. TLRs and CLRs recognize the bacteria and signal through NF-κB, mediating the transcription of cytokines IL-1 and TNF-α. TNF-α secreted by macrophages mediates T cell recruitment and granuloma maintenance following infection.[65] However, TNF-α exhibits a dual role in early tuberculosis infection: Clay et al induced TNF-α signaling deficiency in zebrafish, resulting in accelerated *Mtb* growth and significantly increased granuloma size.[66] Research by Roca et al indicates that excessive TNF-α triggers programmed cell death in infected macrophages by producing mitochondrial reactive oxygen species (ROS) and cyclosporin D.[67] IL-1 consists of IL-1α and IL-1β, both of which are predominantly secreted by mononuclear macrophages during tuberculosis immunity. A study involving IL-1α and IL-1β gene knockout mice revealed that single-gene knockout mice could still control acute *Mtb* infection, whereas double-gene knockout mice could not, indicating that both cytokines play a role in combating *Mtb* infection.[68] On the other hand, there are studies indicating that after infection with *Mtb*, the secretion of type I interferon (IFN-I) by macrophages is significantly increased, which exacerbates macrophage death.[69] Moreover, blocking IFN-I signaling enhances the efficacy of the frontline tuberculosis drug rifampicin in mice infected with *Mtb*.[70] At the same time, research by Saqib et al suggests that IFN-I inhibits the uptake of *Mtb* by neutrophils and drives the recruitment of CD101-negative neutrophils to the lungs, which promotes the extracellular persistence of *Mtb*, exacerbates epithelial damage, and impairs the production of surfactant.[71] During *Mtb* infection, the increased signaling of IFN-I can prevent T cell proliferation, directly leading to uncontrolled *Mtb* infection in neutrophils and alveolar macrophages.[72] Bacillus Calmette-Guerin (BCG) is currently used clinically for tuberculosis prevention. Recent studies show that hematopoietic stem cells cultured with BCG produce epigenetically modified macrophages, which exhibit significantly enhanced protection against severe *Mtb* infection compared to non-cultured macrophages.[73] This phenomenon, known as trained immunity, differs from adaptive immunity as it is mediated by innate immune cells such as monocytes, macrophages, and NK cells. It has shown beneficial effects against cancer, viral infections, and autoimmune diseases.[74] Although there are no current reports on whether trained immunity can fully control *Mtb* infection in humans, leveraging the modifiability of macrophages to enhance their immune response against *Mtb* remains a potential avenue for future tuberculosis prevention and treatment.

Recruitment of Neutrophils and Monocytes During *Mycobacterium tuberculosis* Infection

Following *Mtb* infection, the recruitment and mobilization of neutrophils constitute a crucial component of the immune response. Neutrophils exhibit a dual role. On one hand, host cells (eg, macrophages and DCs) recognize and engulf pathogens, subsequently releasing various cytokines, such as TNF-α, IL-1β, IL-6, and IL-8. These cytokines not only promote the inflammatory response at the local infection site but also enhance the recruitment and extravasation of neutrophils through the activation of endothelial cells.[75] Upon sensing chemokines secreted at the site of inflammation, neutrophils migrate to the infection site by upregulating the expression of chemokine receptors, such as CXCR1 and CXCR2. At the local microenvironment, they perform functions including pathogen phagocytosis and the release of neutrophil extracellular traps (NETs), thereby limiting the spread of *Mtb*.[20,21,76] However, some studies have shown that NETs can promote the extracellular growth of *Mtb* in mice infected with tuberculosis, leading to pulmonary lesions and inflammation.[77] Additionally, cit-H3, apart from being a marker of NETs, is also a potential marker of lung tissue damage induced by severe pulmonary tuberculosis.[78–80] On the other hand, excessive activation and persistent presence of neutrophils may lead to tissue damage. This is because the reactive oxygen species and proteases released by neutrophils not only exert lethal effects on pathogens but also damage host tissues. In chronic tuberculosis infections, the sustained recruitment and inflammatory response of neutrophils lead to the formation of localized necrosis and fibrosis, causing structural damage to the lungs and providing a niche environment conducive to *Mtb* survival.[81] A study found that, when comparing C57BL/6 mice resistant to *Mtb* infection with DBA/2 mice susceptible to it, neutrophils in DBA/2 mice were rapidly recruited to the bronchoalveolar regions and were more numerous. The prolonged clearance of neutrophils in DBA/2 mice at the early stage of infection extended their lifespan, suggesting that the rapid recruitment of neutrophils in genetically susceptible mice is pathogenic.[82] However, another study indicated that during the first four days post intravenous injection of *Mtb*, neutrophil depletion led to enhanced bacterial growth at extrapulmonary sites. This suggests

that the protective immunity conferred by neutrophils against *Mtb* may depend on the route of infection and the dynamics of the infection.[83] Due to the dual role of neutrophils in *Mtb* infection, regulating the recruitment and activation of neutrophils may represent a novel strategy for tuberculosis treatment, particularly in terms of preventing tissue damage and inflammation-related complications.

In addition to neutrophils, monocytes are also recruited to the site of *Mtb* infection. Based on the expression of surface markers CD14 and CD16, monocytes are primarily categorized into three subsets: classical monocytes ($CD14^{++}$, $CD16^{-}$), intermediate monocytes ($CD14^{+}$, $CD16^{+}$), and non-classical monocytes ($CD14^{+}$, $CD16^{++}$), each with distinct functions.[22] Classical monocytes primarily produce reactive oxygen species (ROS). Upon tissue infection or injury, they migrate to the affected tissue and secrete unique chemokines to activate other immune cells. Intermediate monocytes play a crucial role in antigen presentation as well as the secretion of cytokines and pro-inflammatory interleukins. A study indicates that after human infection with *Mtb*, CD16+ monocytes in peripheral blood are amplified during tuberculosis infection, and the disturbance of this subset determines the severity of the disease.[24] Meanwhile, anti-tuberculosis treatment in tuberculosis patients can reverse the amplification of CD16+ monocytes.[25] During severe infection, CD16+ monocytes in the peripheral blood of tuberculosis patients upregulate the expression of CC chemokine receptor type 2 (CCR2), aimed at enhancing their migratory capacity to the site of infection.[84] Following *Mtb* infection, monocytes differentiate into macrophages and DCs. Monocytes have been identified as the primary innate immune cell population producing iNOS in Mtb-infected mice.[23] Additionally, monocytes deliver *Mtb* to the pulmonary lymph nodes, where they coordinate with DCs to initiate $CD4^{+}$ T cell responses against *Mtb* infection.[27] However, monocyte recruitment following *Mtb* infection may also be detrimental to the host by creating an environment conducive to bacterial growth and replication. Antonelli et al demonstrated that treating *Mtb*-infected mice with polyinosinic-polycytidylic acid (polyIC) increased the severity and mortality of the infection through a CCR2-mediated mechanism.[26]

NK Cells in *Mycobacterium tuberculosis* Infection

NK cells are innate lymphocytes characterized by various surface markers, including CD56, CD16, CD94, NKG2D, and CD57. These cells do not rely on major histocompatibility complex (MHC) molecules to recognize target cells; instead, they identify potential infected cells by detecting "stress molecules" or "missing MHC molecules" on the surface of target cells.[85] Various components of the *Mtb* cell wall can directly bind to NKp44 on NK cells.[86] NK cells can also recognize stress molecules upregulated on the surface of *Mtb*-infected cells, leading to the direct killing of infected macrophages.[28] Additionally, NK cells can restrict intracellular bacterial replication through the secretion of IL-22[29] and IFN-γ.[30] IL-21-activated NK cells further enhance the immune response by increasing the production of IL-1β, IL-18, and MIP-1β. NK cells also lyse *Mtb*-infected macrophages and alveolar macrophages while upregulating $CD8^{+}$ T cell responses.[31] Interestingly, IL-21-dependent NK cell populations that emerge following BCG vaccination have been shown to expand after *Mtb* challenge,[87] suggesting that NK cells may exhibit some hallmark features of memory cells. Research by Choreño-Parra et al indicates that *Mtb* antigens stimulate $CXCR6^{+}$ NK cells in both mice and humans, although their activation mechanisms have not been further evaluated.[88] As mentioned previously, innate immune cells such as macrophages, neutrophils, and monocytes are crucial for the early response against *Mtb*, but they may also serve as niches for bacterial replication to some extent. However, NK cells do not serve as niches for *Mtb* and do not spread the pathogen. Due to the ability of *Mtb* to evade immune cell surveillance by suppressing the expression of MHC molecules, NK cells can recognize missing or aberrantly expressed MHC molecules. This characteristic makes them a potential vaccine target. Activating NK cells may help eliminate infected cells that lack MHC molecules, thus effectively controlling tuberculosis infection. Studies have shown that NK cells play an important role in defending against Mycobacterium tuberculosis infection.[89] Therefore, a deeper understanding of the recognition mechanisms and functions of NK cells will provide new ideas and strategies for the development of future vaccines.

Dendritic Cells Initiate Adaptive Immunity Against *Mycobacterium tuberculosis*

During *Mtb* infection, a critical function of innate immunity is to initiate the adaptive immune response. DCs are specialized antigen-presenting cells that initiate the adaptive immune response by presenting *Mtb* antigens through (MHC) molecules, co-stimulatory molecules (CD80, CD86, and CD40), and chemokine receptor 7 (CCR7).[17] DCs can

be categorized into monocyte-derived DCs (moDCs), conventional DCs (cDCs), and plasmacytoid DCs (pDCs) based on surface marker expression.[90] However, the functions of these subsets remain controversial and warrant further detailed investigation. Infected DCs migrate to the pulmonary draining lymph nodes, where they secrete soluble, unprocessed *Mtb* antigens and present them to T cells through MHC molecules. MHC molecules are divided into MHC class I and MHC class II, which present to $CD8^+$ and $CD4^+$ T cells, respectively.[91] DCs present antigens to $CD4^+$ T cells with bactericidal capabilities via MHC class II molecules, secreting IFN-γ to activate macrophages.[33] *Mtb*-infected DCs can promote a protective Th17 response against highly virulent *Mtb* infection by secreting IL-23, IL-6, and IL-1β.[34] Cytokines secreted by DCs help regulate the immune response, with surface co-stimulatory molecules binding to corresponding receptors on T cells, thereby activating T cell responses and initiating adaptive immunity. DCs are key participants in initiating the adaptive immune response against *Mtb* and determining the outcome of infection. Further research on DC cell populations may reveal that interventions or therapies aimed at improving DC function could benefit from enhanced interactions between DCs and antigen-specific T cells. This includes host-directed therapies, development of improved vaccines, and control strategies, which have significant implications for the treatment and prevention of tuberculosis.[32]

Adaptive Immunity in *Mycobacterium tuberculosis* Infection

Adaptive immunity refers to the part of the immune system that generates long-lasting, specific responses against particular pathogens. Specific T cells, through cytokine secretion and direct antimicrobial action, are central to the adaptive immune response against *Mtb* infection. T cells are classified based on surface markers and functions into several types: helper T cells (Th cells), which carry the CD4 molecule on their surface, primarily coordinate immune responses through cytokine secretion. These can be further subdivided into Th1, Th2, Th17, and regulatory T cells (Tregs), with each subset having unique functions based on their cytokine profiles.[92] Cytotoxic T cells (CTLs), which carry the CD8 molecule on their surface, directly kill virus-infected or tumor cells.[93] $CD4^+$ T cells, $CD8^+$ T cells, and B cells form the basis of humoral and cell-mediated immunity, providing specific responses to various *Mtb* antigens, which are typically presented by MHC class I and II molecules. However, adaptive immune responses can also have detrimental effects on the host by promoting excessive inflammation or chronic antigen exposure. The following sections will delve into the crucial roles of $CD4^+$ T cells and their subsets in tuberculosis infection, the mechanisms by which $CD8^+$ T cells exert cytotoxic functions, and how B cells produce antibodies and utilize memory characteristics to clear pathogens.

The Role of $CD4^+$ Cells in *Mycobacterium tuberculosis* Infection

$CD4^+$ T cells play a crucial protective role by secreting a range of cytokines (eg, IFN-γ and TNF-α). These cytokines attract other immune cells to the infection site and promote the differentiation of several $CD4^+$ T cell subsets into effector cells to eliminate *Mtb* infection.[94] Th1 cells activate macrophages by expressing membrane molecules such as CD40L and secreting cytokines like IFN-γ. This activation leads to increased expression of immune molecules such as CD80, CD86, and MHCII on macrophages, and the secretion of cytokines such as IL-12, which in turn enhances Th1 responses.[18,19] Additionally, in response to *Mtb* attack, IL-3 and GM-CSF produced by Th1 cells stimulate the differentiation of hematopoietic stem cells in the bone marrow into monocytes. Meanwhile, cytokines such as TNF-α, LTα, and MCP-1 induce endothelial cells to express more adhesion molecules.[36] This process not only facilitates the adhesion of monocytes and lymphocytes to endothelial cells but also assists these cells in traversing the vascular wall and migrating to the infection site. Thus, Th1 cells effectively activate and enhance macrophage function, and during the response to *Mtb*, they promote the recruitment and aggregation of macrophages and other immune cells, forming a robust immune defense network.[35] Th2 cells play a central role in humoral immunity by producing cytokines such as IL-4 and IL-13, which promote the development of anti-inflammatory responses.[95] *Mtb* can cause a shift in the host immune response from a Th1-dominated reaction to a Th2-dominated response.[37] A Th2-dominated response is insufficient to effectively control the growth of *Mtb* over the long term. Although the involvement of Th2 cells may partially alleviate inflammatory responses, it could also be a key factor contributing to the chronic persistence and difficulty in eradicating tuberculosis.[38] Th17 cells not only induce neutrophilic inflammation, which can potentially damage host tissues, but also play a significant role by producing IL-17.[35] IL-17 induces chemokines in the lungs during infection, which help recruit IFN-γ-producing $CD4^+$ T cells to the lungs, leading to extensive tissue necrosis and thereby enhancing the immune

response.[39] The depletion of Th17 cells is considered a potential mechanism for the transition of latent tuberculosis infection LTBI to ATB.[40] These findings highlight the dual role of Th17 cells in *Mtb* infection: on one hand, they may cause tissue damage, while on the other hand, they play a critical role in preventing pathogen spread and disease progression. Regulatory T cells (Tregs), a subset of $CD4^+$ T cells, play a crucial role in negatively regulating T cell responses to prevent excessive inflammatory reactions. In the context of *Mtb* infection, once *Mtb* within phagocytes migrates from the lesion to the lymph nodes, it activates and promotes the proliferation of *Mtb*-specific Tregs. Recent research by Wang et al[41] using single-cell RNA sequencing, has revealed an increase in Tregs in the lung lesions of tuberculosis patients. This proliferation significantly impacts the immune system of patients with ATB or LTBI, as *Mtb* can induce immunosuppression by increasing Treg cell numbers, thereby interfering with $CD4^+$ T cell function and control of the disease. Studying the immune response of $CD4^+$ T cells following *Mtb* infection and the balance among different cell subsets is crucial for understanding the immunopathogenesis of the disease, improving diagnostic methods, developing vaccines and therapies, and monitoring disease progression.

The Role of $CD8^+$ T Cells in *Mycobacterium tuberculosis* Infection

During the immune response to *Mtb* infection, $CD8^+$ T cells exert their cytotoxic function by secreting perforin, granzymes, and granulin, thereby directly killing *Mtb*-infected host cells.[42] Key cytokines produced by $CD8^+$ T cells, such as interferon-γ (IFN-γ) and TNF, play crucial roles in regulating immune responses and inflammation, extending beyond their direct cytotoxic capabilities.[43] $CD8^+$ T cells and their inherent cytotoxic mechanisms form pores by releasing perforin and other molecules, delivering cytotoxic molecules to target cells to directly kill or eliminate infected macrophages.[96] Recent advancements indicate that specific fragments of granzyme exhibit antimicrobial activity and can inhibit *Mtb* replication within host cells in vitro, further highlighting the multifaceted and complex roles of $CD8^+$ T cells in the host's defense against *Mtb* infection.[97] Recent studies using a mouse tuberculosis model[98] found that during the interaction between *Mtb* antigen TB10.4 and $CD8^+$ T cells, TB10.4-specific $CD8^+$ T cells failed to effectively recognize *Mtb*-infected macrophages. This suggests that the TB10.4 antigen may act as a decoy, masking the effective recognition and response to *Mtb*-infected macrophages. In contrast, specific $CD4^+$ T cells targeting major epitopes such as Ag85b or ESAT6 have demonstrated the ability to recognize and effectively inhibit the growth of *Mtb*-infected macrophages, highlighting different mechanisms of immune defense by $CD4^+$ T cells compared to $CD8^+$ T cells in Mtb infection. This difference in mechanisms may reflect specific strategies by *Mtb* to evade and disrupt host immune responses, thereby limiting the efficacy of $CD8^+$ T cells in host defense mechanisms. This finding not only deepens our understanding of the immune response mechanisms to *Mtb* infection but also provides valuable insights for future vaccine design and therapeutic strategy development.

B Cells in *Mycobacterium tuberculosis* Infection

While T cells are central to anti-tuberculosis immune responses, recent studies have highlighted the equally significant role of B cells in *Mtb* infections. B cells are a crucial component of the adaptive immune system, primarily responsible for antibody production and regulation to eliminate pathogens.[99] Although cellular immunity is the primary immune response in tuberculosis, studies have shown a significant increase in the production of specific IgG and IgA antibodies following *Mtb* infection, indicating the critical role of B cells in combating the infection.[100] After tuberculosis infection, B cells can differentiate into memory B cells, which rapidly produce antibodies upon re-exposure to the pathogen, thus enhancing the immune response. B cells are not only producers of antibodies but also secrete various cytokines, such as IL-10 and IL-6, which play crucial roles in regulating immune and inflammatory responses. B cells enhance the body's antibacterial capacity by producing antibodies that bind to *Mtb* and facilitate macrophage phagocytosis of the pathogen.[44] Additionally, B cells can directly kill infected cells through antibody-dependent cell-mediated cytotoxicity (ADCC).[45] The interaction between B cells and T cells is critical in tuberculosis infection. B cells can activate $CD4^+$ T cells through antigen presentation and provide auxiliary signals during the immune response, while cytokines secreted by T cells can also influence B cell activation and antibody production. In tuberculosis infections, B cells may also suppress excessive inflammatory responses by secreting immune-regulatory factors (eg, IL-10), thereby preventing damage to the host's own tissues.[46] The production of antibodies, cytokines, and memory characteristics by B cells is crucial for the response to

Mtb. Studying how B cells recognize and respond to this pathogen could lay the experimental foundation for developing vaccines that elicit strong humoral immune responses.

Vaccine Development and Challenges

The only vaccine currently approved for the prevention of tuberculosis is BCG, an attenuated strain of *Mycobacterium bovis* that provides protection against disseminated tuberculosis and tuberculous meningitis.[101] The protective benefit of BCG is based on the priming of antigen-specific naive B and T cells to generate memory B and T cells. When naive lymphocytes receive *Mtb* cognate antigens, they become activated and undergo clonal expansion, in which the transcriptional profiles of B and T cells are epigenetically regulated and differentiate into effector and memory cells,[102] Activated B cells undergo immunoglobulin class switching and somatic hypermutation to produce high-affinity antibodies with multiple effector functions. Most activated T cells express effector molecules such as perforin to exert immune effects,[103] and a small proportion of CD8+T cells can retain the epigenetic background for decades, rapidly proliferate and exert immune effects upon pathogen re-invasion[104] Training immunity is also an important way for BCG to exert its benefits. Studies have found that BCG mediates the reprogramming and differentiation of bone marrow stem cells, and enhances the ability of macrophages to resist *Mtb* infection by relying on IFN-γ,[105] This effect persists long after BCG is eliminated from the body.[73] However, BCG live vaccine can prevent the maturation of phagosomes by blocking expression of the lysosomal glycoprotein LAMP-1 in the phagosome exon.[106] However, its efficacy remains a subject of controversy. As of now, approximately 20 tuberculosis vaccine candidates are in clinical evaluation, with 15 of them undergoing clinical trials. These vaccines can be classified into attenuated live vaccines, inactivated vaccines, subunit vaccines, and recombinant live vaccines[107] (Table 2).

Table 2 Current Research Progress of Vaccines Entering Clinical Trials

Sort	Name	Location	Enrollment	Last Update Posted	Phage	Status	ClinicalTrials.gov ID
Attenuated vaccine	MTBVAC	South Africa	7120 (Estimated) 99 (Actual) 54 (Actual) 144 (Actual) 36 (Actual) 276 (Estimated)	Feb 2025 Jun 2023 May 2018 Feb 2023 Mar 2017 Nov 2024	III II I/II I/II I II	Recruiting Completed Completed Completed Completed Recruiting	NCT04975178 NCT03536117 NCT02729571 NCT02933281 NCT02013245 NCT05947890
		India	30 (Estimated)	Jun 2024	I	Active, not recruiting	NCT06438978
		Spain	4300 (Estimated)	Feb 2024	II	Not yet recruiting	NCT06272812
Inactivated vaccine	RUTI	Spain	24 (Actual)	May 2009	I	Completed	NCT00546273
		South Africa	95 (Actual)	Jan 2013	II	Completed	NCT01136161
		Ukraine	9 (Actual)	Jul 2022	II	Terminated	NCT02711735
		India	140 (Estimated)	May 2024	II	Active, not recruiting	NCT04919239
		Argentina	44 (Estimated)	Jan2024	II	Recruiting	NCT05455112
	DAR-901	Tanzania	625 (Actual) 1975 (Actual)	May 2021 Feb 2016	II II/III	Completed Completed	NCT02712424 NCT00052195
		United States	59 (Actual)	Aug 2016	I	Completed	NCT02063555
	Vaccae	China	10000 (Actual) 6800 (Estimated)	Jun 2018 Jun 2024	III IV	Completed Active, not recruiting	NCT01979900 NCT05680415
		Mongolia/Ukraine	152 (Actual)	Jul 2019	III	Completed	NCT01977768
		Ukraine	40 (Actual)	Oct 2013	II	Completed	NCT01380119
		Tanzania	1975 (Actual)	Feb 2016	II/III	Completed	NCT00052195

(*Continued*)

Table 2 (Continued).

Sort	Name	Location	Enrollment	Last Update Posted	Phage	Status	ClinicalTrials.gov ID
Subunit vaccine	M72/AS01E	South Africa	402 (Actual)	Jun 2023	II	Completed	NCT04556981
		Kenya/South Africa/ Zambia	3575 (Actual)	Dec 2019	II	Completed	NCT01755598
		Unknown	3253 (Actual)	Feb 2017	II	Completed	NCT02097095
	H56:IC31	South Africa/Tanzania	831 (Actual)	Feb 2024	II	Active, not recruiting	NCT03512249
		South Africa	25 (Actual) 84 (Actual) 22 (Actual) 98 (Actual)	Aug 2019 Nov 2019 Jul 2024 Dec 2019	I I I I/II	Completed Completed Completed Completed	NCT01967134 NCT02378207 NCT02375698 NCT01865487
	ID93+GLA-SE	United Kingdom	48 (Estimated)	Apr 2025	Not Applicable	Recruiting	NCT06670755
		United States	60 (Actual) 70 (Actual) 48 (Actual)	Sep 2017 Sep 2017 Jun 2023	I I I	Completed Completed Completed	NCT01599897 NCT02508376 NCT03722472
		South Africa	60 (Actual) 66 (Actual)	Mar 2019 Feb 2018	II I	Completed Completed	NCT02465216 NCT01927159
		Korea	36 (Actual) 107 (Actual) 144 (Estimated)	Jul 2019 May 2019 Dec 2024	I II I	Unknown Unknown Not yet recruiting	NCT03806699 NCT03806686 NCT06714513
		Unknown	1500 (Estimated)	Dec 2024	II	Not yet recruiting	NCT06205589
	GamTBvac	Russian Federation	60 (Actual) 180 (Actual) 7180 (Estimated)	Dec 2017 Jun 2020 Nov 2022	I II III	Completed Completed Recruiting	NCT03255278 NCT03878004 NCT04975737
	AEC/BC02	China	200 (Estimated) 25 (Actual) 30 (Actual)	Nov 2023 Mar 2022 Sep 2022	II I Ib	Suspended Completed Completed	NCT05284812 NCT03026972 NCT04239313
Recombinant live vaccine	VPM1002	Gabon/Kenya/South Africa/Tanzania/Uganda	6940 (Actual)	Sep 2025	III	Completed	NCT04351685
		South Africa	416 (Actual) 48 (Actual) 24 (Actual)	Apr 2018 Oct 2013 Nov 2011	II II I	Completed Completed Completed	NCT02391415 NCT01479972 NCT01113281
		Germany	80 (Actual)	May 2010	I	Completed	NCT00749034
		Bangladesh/India	2000 (Actual)	Apr 2024	II	Active, not recruiting	NCT03152903
	MVA85A	United Kingdom	30 (Actual) 37 (Actual) 40 (Actual)	Dec 2014 Jan 2016 Sep 2014	I I I	Completed Completed Completed	NCT01879163 NCT01954563 NCT01683773
		Senegal/South Africa	650 (Actual)	May 2016	II	Completed	NCT01151189
		Uganda	36 (Actual)	Jan 2015	II	Completed	NCT02178748
	ChAdOx185A	Uganda/United Kingdom	72 (Actual)	Aug 2022	I/II	Completed	NCT03681860
	Ad5Ag85A	Canada	36 (Actual) 24 (Actual)	Nov 2021 Sep 2017	I I	Completed Completed	NCT02337270 NCT00800670
	TB/Flu-04L	Unknown	44 (Actual)	Aug 2020	I	Completed	NCT02501421

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One example of an attenuated live vaccine is MTBVAC. Preclinical studies have highlighted that MTBVAC induces immunity against ESAT6 and CFP10, showing improved efficacy compared to BCG.[108] Phase II clinical trials conducted in South Africa in adults and newborns have also validated its immunogenicity, showing that MTBVAC vaccination induces sustained expression of antigen-specific Th1 cytokines in infants.[109] A Phase III clinical trial is underway to evaluate the safety, immunogenicity, and efficacy of MTBVAC in infants born to HIV-positive or HIV-negative mothers.[110]

Three inactivated vaccines currently known to be in clinical trials include RUTI, DAR-901, and Vaccae. Prabowo et al found that RUTI vaccination enhanced the inhibition of ex vivo Mycobacterium growth and induced a shift in the phenotype of murine monocytes, with a significant increase in non-classical monocytes.[111] Phase I clinical trials of RUTI assessed its safety and immunogenicity in healthy volunteers, showing that adverse events were positively correlated with dose.[112] A randomized, placebo-controlled Phase II clinical trial conducted in patients with latent tuberculosis evaluated the safety, tolerability, and immunogenicity of RUTI.[113] Phase I clinical trials of DAR-901 indicated that it has good tolerability and induces a robust $CD4^+$ T cell immune response compared to BCG.[114] When used as an adjunctive therapy, Vaccae has been shown to increase $CD4^+$ T cell counts.[115] A Phase III clinical trial evaluated the safety and efficacy of Vaccae in preventing tuberculosis, but the results have not yet been published.

Five subunit vaccines include M72/AS01E, H56:IC31, $ID93^+$GLA-SE, GamTBvac, and AEC/BC02. M72/AS01E has undergone a series of Phase II clinical trials in multiple regions, including India, South Africa, and Taiwan. Overall results indicate that M72/AS01E demonstrates good safety and immunogenicity across different populations.[116] Currently, the Bill & Melinda Gates Foundation and Wellcome Trust have announced a $550 million funding commitment to advance Phase III clinical trials of M72/AS01E. If successful, M72/AS01E could become the first new tuberculosis vaccine to be licensed in over a century.[117] Phase IIa clinical trial results for H56:IC31 show that it can induce persistent antigen-specific $CD4^+$ T cell responses in both *Mtb*-infected and uninfected adults, with good safety and tolerability.[118] Phase IIa clinical trial results for $ID93^+$ GLA-SE demonstrate that this vaccine induces specific multifunctional $CD4^+$ T cell responses and sustained antibody responses (including IgG1 and IgG3 subclasses). The adverse reactions observed were limited to mild indurations and erythema.[119] Phase I and II clinical trial results for GamTBVac conducted in Russia indicate that it has good safety and immunogenicity,[120] Phase III clinical trial is currently recruiting. Phase I clinical trials for AEC/BC02 have been completed, but results have not yet been published. Phase IIa trials are currently ongoing to assess the safety, tolerability, and immunogenicity of AEC/BC02 in patients aged 18 years and older with LTBI.[121]

Current recombinant live vaccines in clinical trials include VPM1002, MVA85A, ChAdOx185A, Ad5Ag85A, and TB/Flu-04L. VPM1002 was shown to have good safety and immunogenicity in healthy infants and adults in phase I and phase IIa clinical trials,[122] and the results of phase IIb clinical trials showed that it was safer than BCG for the prevention of *human immunodeficiency virus* (*HIV*) exposed and unexposed infants.[123] Phase III clinical trials evaluating VPM1002 are ongoing. Early trials of MVA85A demonstrated good safety and immunogenicity,[124] but Phase IIb trial results indicated a lack of evidence for vaccine efficacy.[125] Subsequent studies combined MVA85A with the simian adenovirus vaccine ChAdOx185A, revealing that both vaccines express the antigen Ag85A.[126] In a Phase I clinical trial of ChAdOx185A administered intramuscularly in adults previously vaccinated with BCG, the vaccine was used either alone or as part of a boost strategy with MVA85A.[127] Phase I clinical trials of Ad5Ag85A demonstrated good tolerability and immunogenicity in both BCG-vaccinated and non-vaccinated subjects, with stronger immune responses observed in volunteers previously vaccinated with BCG.[128] A Phase I clinical trial conducted in Kazakhstan in BCG-vaccinated, *Mtb* T-cell-negative healthy adults has validated the safety and immunogenicity of TB/Flu-04L.[129] Additionally, a Phase IIa clinical trial targeting LTBI populations is currently underway.[130]

In summary, following *Mtb* infection, the timely activation of both innate and adaptive immunity and the regulation of the balance between various immune cells and cytokines are crucial. *Mtb* is adept at disrupting the communication between innate and adaptive immunity. Understanding this mechanism is crucial for developing more effective vaccines and provides a theoretical foundation and direction for tuberculosis treatment.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no competing interests in this work.

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