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Review

Toward tuberculosis elimination: An update on tuberculosis vaccines in clinical trials

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ABSTRACT

Despite major advances in diagnosis and treatment, tuberculosis (TB) control – and ultimately elimination – will remain unachieved without a vaccine capable of preventing pulmonary disease and transmission. Bacille Calmette–Guérin (BCG), a live attenuated vaccine derived from *Mycobacterium bovis* and the only licensed TB vaccine, has been widely implemented because of its proven efficacy against severe childhood TB. However, despite global coverage approaching 90%, BCG provides limited and inconsistent protection against pulmonary TB in adolescents and adults, the populations that sustain transmission.

In response, a diverse pipeline of novel TB vaccine candidates has emerged across multiple technological platforms. This review provides an updated overview of TB vaccines in clinical development. Currently, sixteen candidates are undergoing clinical evaluation, including four in active Phase 3 efficacy trials.

This review also offers critical insights into challenges shaping late-stage TB vaccine development. We argue that evolving understanding of *Mycobacterium tuberculosis* infection – including heterogeneity within latent infection, the contribution of subclinical disease, and limitations of binary IGRA-based classification – necessitates reassessment of current efficacy endpoints. By examining prevention-of-disease (PoD), prevention-of-infection (PoI), and prevention-of-recurrence (PoR) strategies, we highlight the need for closer alignment between biological insight, trial design, and policy objectives to ensure that new vaccines advance TB elimination.

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Tuberculosis (TB), one of the oldest diseases known to humankind, remains the leading cause of death from a single infectious agent worldwide. In 2024, an estimated 1.23 million people died from TB globally [1]. The current TB pandemic is strongly driven by low socioeconomic state, with undernutrition being the main risk factor. In the absence of treatment, approximately 50% of individuals who develop active TB disease will die [2]. Although TB is largely treatable with antibiotics, the global spread of drug-resistant strains threatens TB control and raises concerns about a return to a pre-antibiotic era. In response, the World Health Organization (WHO) included rifampicin-resistant TB in the highest ('critical') priority category of its 2024 Bacterial Priority Pathogens list for antimicrobial resistance [3].

Throughout the history of public health, few medical interventions have had an impact comparable to vaccination. Vaccines have prevented millions of deaths, dramatically reduced the burden of infectious diseases, and, eventually, led to their global eradication [4]. Beyond their direct protective effects, vaccination programs illustrate how scientific innovation, when combined with sustained political commitment and societal engagement, can fundamentally alter the trajectory of human disease [5,6].

Despite the continued global burden of TB, bacille Calmette–Guérin (BCG) remains the only licensed TB vaccine and has been in use for more than a century. Developed in 1921 from an attenuated strain of the cow pathogen *Mycobacterium bovis*, BCG has been widely implemented in national immunization programs, particularly in high-burden settings, because of its proven efficacy in preventing severe forms of TB in infants and young children, including TB meningitis and miliary disease. In contrast, protection against pulmonary TB – the main driver of transmission – has been highly variable across studies and geographic regions [7,8]. BCG is not a single, uniform vaccine but a group of related substrains that diverged during serial *in vitro* passage. Genomic analyses have revealed deletions, duplications, and regulatory differences that influence antigen expression, innate immune activation, and

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immunogenicity, potentially contributing to heterogeneity in vaccine efficacy [9,10]. Beyond TB-specific protection, accumulating epidemiological evidence suggests that BCG vaccination in early life is associated with reduced all-cause mortality, an effect likely mediated in part by heterologous protection against unrelated pathogens [11–14]. Following the administration of hundreds of millions of doses worldwide, global BCG coverage has reached approximately 90%, making it one of the most widely used vaccines in human history [15]. Nevertheless, BCG provides limited and inconsistent protection against pulmonary TB in adolescents and adults – the populations that sustain *Mycobacterium tuberculosis* transmission – highlighting the urgent need for next-generation TB vaccines capable of interrupting transmission and advancing TB elimination.

Advances in immunology and vaccine science in the late 1990s reinforced the feasibility of developing a new TB vaccine. This paradigm shift was explicitly recognized at the Madrid Conference held in March 1995 on the 'Definition of a coordinated strategy towards a new TB vaccine'. Convened under the auspices of the WHO and the International Union Against Tuberculosis and Lung Disease, this meeting articulated a coordinated international vision for TB vaccine development and marked a conceptual turning point by affirming that an improved TB vaccine was an achievable goal [16].

The observation that approximately 90% of individuals infected with *M. tuberculosis* never develop active disease in their lifetimes provides compelling evidence that effective natural protective mechanisms exist in humans (https://newtbvaccines.org/about-new-tb-vaccines/). Replicating this phenotype through vaccination – by mimicking infection without causing disease – would represent a major advance. When combined with early diagnosis and effective treatment for individuals who do develop TB, such a vaccine could enable sustainable disease control and ultimately contribute to TB elimination.

Progress toward WHO End TB goals has been enabled by sustained international investment and coordination, including European initiatives such as the Tuberculosis Vaccine Initiative (TBVI), U.S.-based organizations like the International AIDS Vaccine Initiative (IAVI), dedicated European funding programs and mechanisms such as the European & Developing Countries Clinical Trials Partnership (EDTP), and substantial philanthropic and public support from Open Philanthropy, the Gates Foundation through initiatives such as the Collaboration for TB Vaccine Discovery (CTVD), and the National Institutes of Health (NIH) between others.

Within the framework of the WHO End TB Strategy, which aims to drastically reduce TB incidence and mortality and ultimately achieve elimination, the limitations of BCG have reinforced the urgency of developing more effective vaccines. Achieving these ambitious targets will require vaccines capable not only of preventing severe disease in early life, but also of interrupting pulmonary TB and transmission across all age groups. Advances in bacterial genetics, immunology, systems biology, and vaccine technologies have enabled a more rational approach to TB vaccine design, targeting different stages of *M. tuberculosis* infection. Consequently, a diverse and increasingly mature pipeline of TB vaccine candidates has emerged, encompassing live attenuated mycobacterial vaccines, viral-vectored and protein subunit platforms, as well as innovative adjuvants and delivery routes. Many of these candidates have now progressed into clinical development, reflecting a strategic shift toward vaccines with the potential to accelerate progress toward TB elimination.

TB vaccine candidates from preclinical to clinical

At the turn of the millennium, TB vaccine development faced a critical bottleneck. Despite decades of intensive research and the generation of several hundred vaccine constructs at different preclinical stages [17,18], none had successfully progressed into clinical evaluation. This situation underscored a profound translational gap between experimental promise and human testing, reflecting both biological complexity and structural limitations in TB vaccine development [19,20].

This long-standing impasse began to shift in the early 2000s with the establishment of coordinated global initiatives aimed at strengthening the TB vaccine development pathway. Key advances included improved candidate selection strategies, systematic head-to-head comparisons of vaccine candidates in preclinical models [21], increased investment, and the expansion of clinical trial capacity in TB-endemic settings. Together, these efforts enabled a more structured and rational transition from preclinical research to clinical evaluation and laid the groundwork for a coherent TB vaccine pipeline [22].

Over the past two decades, unprecedented collaboration among academic institutions, public health organizations, product development partnerships, industry, and funders has further accelerated progress. International consortia have played a central role in prioritizing candidates, harmonizing preclinical and clinical evaluation frameworks, and supporting the infrastructure required to conduct vaccine trials in high-incidence settings. As a result, a diverse portfolio of TB vaccine candidates has successfully entered human trials, shaping the current clinical pipeline and providing a foundation for next-generation vaccines aimed at TB control and elimination [22,23].

Animal models – notably mice, guinea pigs and non-human primates – play an indispensable role in the proof of concept and preclinical development of TB vaccines [24–26]. However, none of them fully recapitulates the features of human TB, although non-human primates come closest to doing so. Efforts are underway to develop mouse models more relevant to the study of TB, such as the ultra-low dose infection [27] or the collaborative cross strains [28]. Nevertheless, progression from preclinical development into clinical evaluation remains particularly demanding for TB vaccines when compared with other infectious diseases. A central challenge is the absence of validated immune correlates of protection, which precludes the early identification of candidates most likely to be efficacious. Consequently, promising vaccines must advance through lengthy, complex, and resource-intensive clinical development pathways to demonstrate protective benefit [29].

Following the demonstration of safety and immunogenicity in early-phase trials involving tens of volunteers (Phase 1) and subsequently hundreds (Phase 2), TB vaccine candidates typically require evaluation in Phase 2b proof-of-concept studies and large Phase 3 efficacy trials [30]. These trials typically include thousands of participants and must be conducted in TB-endemic settings with high disease incidence to achieve sufficient statistical power (Figure 1). The need for such extensive clinical evaluation substantially increases the time, cost, and logistical complexity of TB vaccine development, underscoring both the challenges faced by the field and the significance of the progress achieved in advancing a diverse portfolio of candidates into the current clinical pipeline.

Recent milestones in TB vaccines: lessons learned from MVA85A and M72/AS01E clinical trials

Among the first new-generation TB vaccine candidates to advance into efficacy testing was MVA85A, a viral-vectored booster designed to enhance BCG-induced immunity. The Phase 2b efficacy trial of MVA85A in South African infants, published in 2013, evaluated a BCG-boosting strategy and showed no additional protection against pulmonary TB despite strong preclinical and early-phase immunogenicity data [21,31,32]. Although the vaccine induced robust Ag85A-specific $CD4^+$ T-cell responses, these responses did

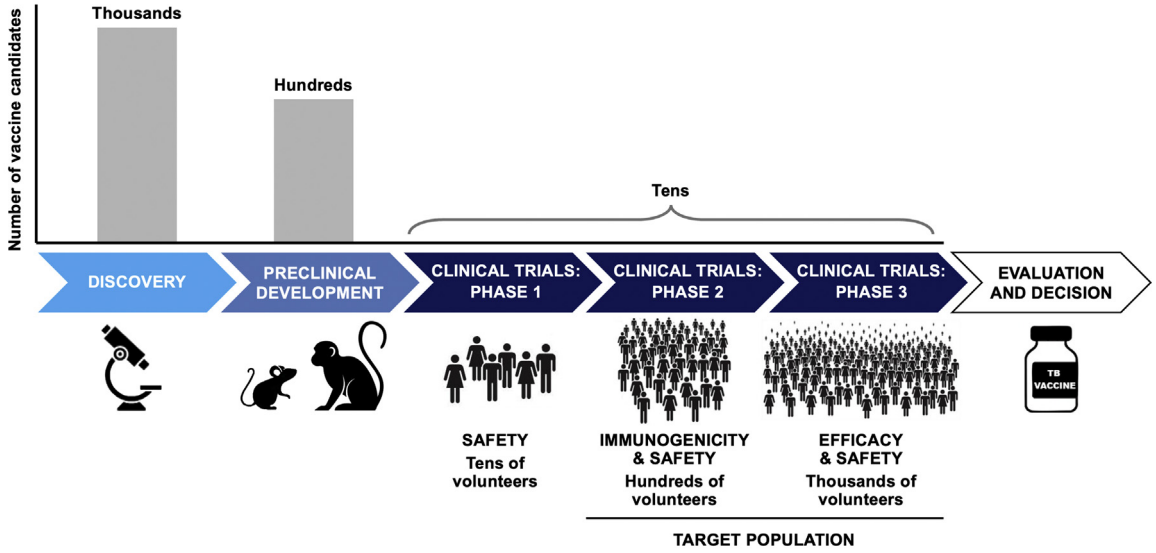

Figure 1. From discovery to efficacy trials: TB vaccine development bottleneck.
TB vaccine development involves a progressive reduction in candidate numbers as vaccines advance from discovery and preclinical stages into clinical evaluation, with increasing time, cost, and logistical complexity. Consequently, development timelines often exceed two decades, highlighting the need for sustained investment, expanded global trial capacity, and policy alignment to translate recent scientific advances into licensed vaccines and support the WHO End TB Strategy and TB elimination targets.

not translate into clinical efficacy, highlighting the absence of validated immune correlates of protection in TB vaccine development [21,32].

Despite its negative outcome, the MVA85A trial was a landmark study, representing the first modern TB vaccine efficacy trial conducted in a high-burden setting since BCG and establishing durable clinical trial infrastructure through South African Tuberculosis Vaccine Initiative (SATVI) [33]. Importantly, the lessons learned informed subsequent vaccine design and trial strategies, contributing to the successful advancement of later TB vaccine candidates.

This period of scepticism shifted with the Phase 2b trial of M72/AS01E, a recombinant protein subunit vaccine developed by GSK. Reported in 2018, the trial demonstrated approximately 50% efficacy against active pulmonary TB in IGRA-positive adults, with protection sustained for at least 3 years [34,35].

Together, the outcomes of MVA85A and M72/AS01E have shaped contemporary TB vaccine development. While MVA85A highlighted fundamental knowledge gaps and the limitations of immunogenicity-based selection, M72/AS01E provided proof that clinically meaningful protection is achievable. These experiences underpin current strategies emphasizing diversified vaccine platforms, improved biomarkers of protection, and clearly defined target populations as candidates advance through the clinical pipeline.

TB vaccine pipeline in clinical development: platform diversity

The current TB vaccine pipeline comprises a limited but conceptually diverse set of candidates undergoing clinical evaluation from Phase 1 to Phase 3, as summarized in Figure 2 and reported by the Stop TB Partnership (https://newtbvaccines.org/about-new-tb-vaccines/) and the WHO. These candidates span multiple technological platforms, including live attenuated mycobacterial vaccines, whole-cell inactivated mycobacterial preparations, protein subunit vaccines formulated with novel adjuvants, viral-vectored vaccines, and emerging nucleic acid–based approaches. The coexistence of these fundamentally different strategies reflects both the biological complexity of protective immunity against *M. tuberculosis* and the persistent absence of validated immune correlates of protection.

From an immunological perspective, subunit and viral-vectored vaccines emphasize defined antigen delivery, manufacturing consistency, and safety profiles, whereas whole-cell and live attenuated vaccines aim to induce broader and more physiologically relevant immune responses by presenting complex antigenic repertoires that more closely resemble natural infection. Following international consensus on the development of live mycobacterial vaccines – including the Geneva consensus on safety and clinical progression –, rationally attenuated *M. tuberculosis* strains and recombinant BCG derivatives have advanced into clinical development, supported by modern genetic tools and regulatory safeguards [36,37]. Although these approaches face higher safety and regulatory barriers, particularly for use in immunocompromised populations, they remain conceptually attractive for their potential to elicit durable and polyfunctional immunity.

The candidates currently represented in the clinical pipeline (Figure 2) illustrate this platform diversity. Protein subunit vaccines formulated with potent adjuvants include M72/AS01E [35,38], H107e/CAF10b [39], ID93/GLA-SE [40], AEC/BC02 [41], and GamTBvac [42]. Viral-vectored approaches are represented by MVA85A combined with ChAdOx1.85A (ChAdOx1–MVA85A) [43,44], AdAg85A [45], and TB/FLU-05E [46]. DAR-901 [47], RUTI® [48] and Immuvac (MIP) [49] vaccines are based on whole-cell inactivated or fragmented mycobacteria. Live mycobacterial candidates comprise BCG pre-travel vaccination, VPM1002 based on recombinant BCG [49,50], and MTBVAC based on attenuated *M. tuberculosis* [51–53].

Live attenuated mycobacterial vaccines remain firmly grounded in Pasteurian principles while incorporating modern recombinant DNA technologies to enhance safety and immunogenicity. MTBVAC, the only live attenuated *M. tuberculosis* vaccine currently in clinical development [54], exemplifies this approach. Reflecting its advanced position in the pipeline, four of the twelve TB vaccine clinical trials currently active involve MTBVAC (https://newtbvaccines.org/about-new-tb-vaccines/), spanning different populations and study designs.

Emerging platforms are beginning to enter clinical evaluation, exemplified by the mRNA-based candidates BNT164a1 and BNT164b1 [55]. Messenger RNA-based vaccines, which proved transformative during the COVID-19 pandemic, are now being ex-

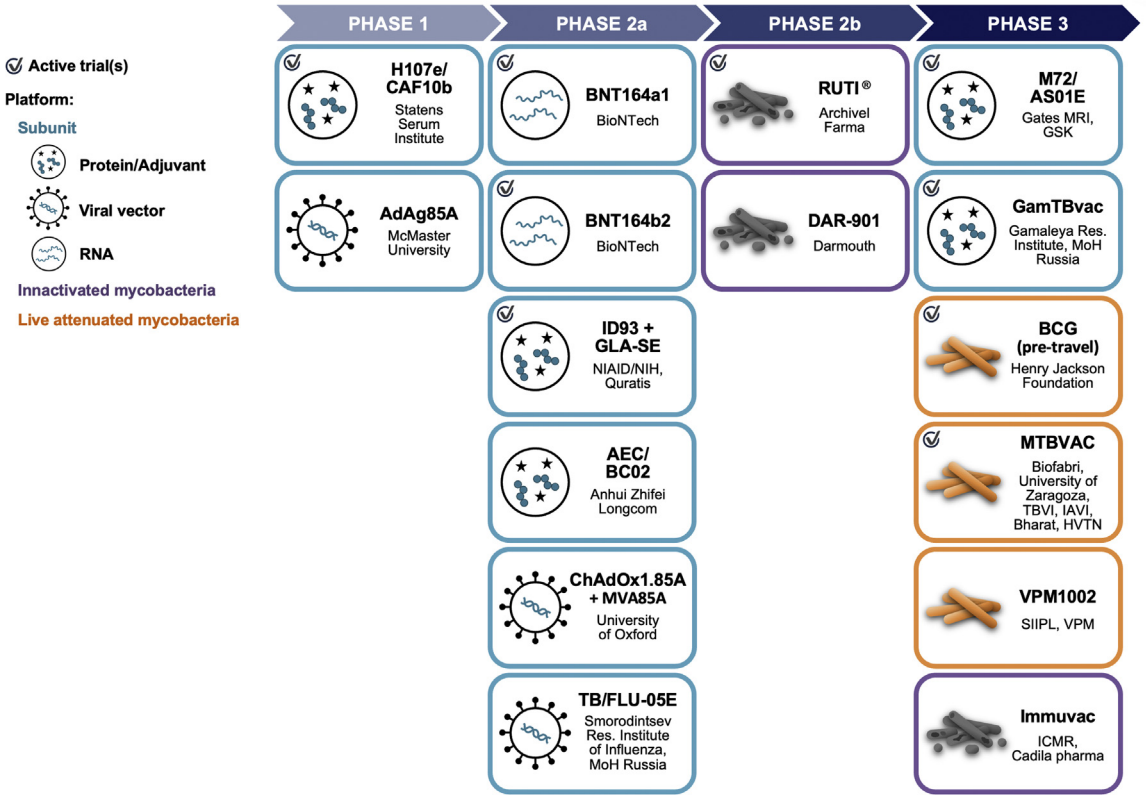

Figure 2. The current clinical pipeline of TB vaccine candidates.
TB vaccine pipeline comprises a limited but conceptually diverse group of candidates undergoing clinical evaluation from Phase 1 through Phase 3. As reported by the Stop TB Partnership and the WHO, these candidates span multiple technological platforms, including live attenuated and inactivated mycobacterial vaccines, protein subunit vaccines formulated with novel adjuvants, viral-vectored vaccines, and emerging nucleic acid–based approaches. The coexistence of these distinct strategies reflects the biological complexity of protective immunity against TB and the continued absence of validated immune correlates of protection, which necessitates large, lengthy, and costly clinical trials in TB-endemic settings.

plored for TB, offering rapid design, scalability, and precise antigen expression. Nanoparticle-based formulations and virus-like particles are under investigation to improve antigen presentation and immune targeting.

In parallel, innovative strategies are being explored to further optimize vaccine-induced protection, including alternative routes of administration such as aerosol delivery, aimed at enhancing mucosal immunity and improving protection against pulmonary disease [56].

Overall, this diversified clinical pipeline reflects both accumulated historical experience and evolving immunological insights. While no single platform has yet overcome the complex host–pathogen interactions characteristic of TB, the breadth of strategies currently under evaluation supports continued parallel development as an essential component of long-term TB control and elimination efforts.

How to accelerate TB vaccine clinical trials: implications for public health policy, regulation, and elimination strategies

In other infectious diseases, controlled human infection models have been used to accelerate vaccine development by enabling rapid proof-of-concept efficacy studies [57]. While similar approaches are being explored for TB, there are several hindrances that must be overcome before they can be used in clinical trials [58]. The capacity of *M. tuberculosis* for latent persistence, and the need for prolonged multidrug treatment impose major ethical and regulatory constraints. The development of an aerosol human infection model using BCG has been recently reported as a safer alternative [59]. However, despite providing unique insights into early immune responses in the human lung, the model may not fully recapitulate a virulent *M. tuberculosis* infection. As a result, human challenge models are unlikely to offer a safe or meaningful acceleration pathway for TB vaccine development in the near term, underscoring the importance of optimizing conventional trial designs aligned with TB elimination goals.

As TB vaccine development enters a phase increasingly defined by elimination-oriented goals, the selection of clinical trial endpoints has become not merely a technical consideration but a strategic decision with direct regulatory and public health consequences. How efficacy is defined and measured will largely determine which candidates advance, how quickly evidence is generated, and whether vaccines ultimately contribute to TB elimination rather than incremental disease control.

To date, prevention of TB disease (PoD) remains the only endpoint accepted for licensure, as it directly captures reductions in clinically and microbiologically confirmed disease. This endpoint is fully aligned with public health priorities but requires large, long, and costly trials conducted in high-incidence settings.

Alternative endpoints – prevention of infection (PoI) and prevention of recurrence (PoR) – have been pursued primarily as pragmatic strategies to accelerate early clinical evaluation. PoI trials, relying on sustained IGRA conversion as a surrogate for *M. tuberculosis* infection, initially appeared promising following the BCG revaccination study [60]. However, recently in a larger randomized trial BCG revaccination failed to demonstrate a consistent or statistically robust reduction in *M. tuberculosis* infection as measured by sustained IGRA conversion and do not

provide a reliable surrogate for protection against TB disease [61].

Similarly, PoR refers to vaccine strategies aimed at preventing the recurrence of active TB disease after successful completion of curative treatment, including both relapse from persistent infection and reinfection in high-transmission settings. Trials of the H56/IC31 subunit vaccine [62] have demonstrated acceptable safety and immunogenicity but have not translated into measurable reductions in recurrent TB.

Overall, accumulated evidence indicates that while PoI and PoR endpoints have played an important exploratory and enabling role – particularly by reducing costs and sustaining momentum in TB vaccine research –, they have not yet delivered a reliable proof of concept capable of supporting Phase 3 efficacy trials or regulatory approval. As TB vaccine development advances toward elimination-oriented goals, future progress will require either validated surrogate markers that reliably predict disease prevention or renewed commitment to large-scale PoD trials that can directly inform licensure, policy decisions, and global implementation.

A further limitation of current efficacy paradigms is their incomplete capture of the TB disease spectrum. Increasing evidence indicates that subclinical TB contributes to transmission and is associated with lung pathology and long-term sequelae, even in the absence of symptoms [63]. Yet most PoD trials rely on symptom-triggered case detection and therefore risk underestimating both true disease burden and vaccine impact. From an elimination perspective, vaccines that interrupt progression earlier along the infection disease continuum may deliver substantial population-level benefits that are not adequately reflected in conventional trial designs.

Taken together, these considerations argue for a recalibration of TB vaccine evaluation strategies. Progress toward elimination will require either the validation of surrogate endpoints that reliably predict disease prevention or renewed global commitment to adequately powered PoD trials, complemented by trial designs and modelling approaches that account for subclinical disease and transmission. Without such strategic alignment between science, regulation, and policy, promising TB vaccine candidates' risk being stalled by endpoints that are expedient but insufficient to support elimination-focused decision-making [63].

Rethinking QuantiFERON® (QFT)-based enrolment strategies in TB vaccine trials

A central and increasingly consequential question in TB vaccine development is whether efficacy trials should preferentially target individuals with evidence of prior *M. tuberculosis* exposure (QFT/IGRA-positive) or those without documented exposure (QFT-negative). This distinction has profound implications for biological plausibility, trial efficiency, interpretability of efficacy signals, and ultimately population-level impact, and is closely linked to the ongoing reappraisal of the concept of latent TB infection.

From a pragmatic trial-design perspective, QFT-positive populations have frequently been prioritised because of the higher incidence of TB in the short-term, enabling smaller sample sizes and shorter follow-up in prevention-of-disease trials. However, a positive QFT reflects immune sensitisation rather than persistent infection and provides no information on timing of exposure or bacillary viability. Longitudinal studies consistently show that the risk of progression to active TB is highest within the first months to 2 years after infection [64], after which progression becomes uncommon. As a result, many QFT-positive individuals – particularly in low- or declining-incidence settings – are likely to represent resolved infections with durable immunological memory rather than true latency [65,66].

Beyond binary QFT status, there is growing recognition that substantial biological heterogeneity exists within QFT-positive populations, reflecting different stages along the spectrum of *M. tuberculosis* infection. Recent transcriptomic and immunological studies have identified host-response signatures capable of distinguishing individuals with recent or incipient infection from those with long-standing, immunologically controlled infection, with markedly different risks of progression to disease. Incorporating such biomarkers into TB vaccine trials could enable stratification of 'early' versus 'late' QFT-positive individuals, improving biological interpretability of efficacy signals, refining endpoint selection, and enhancing the efficiency of elimination-oriented trial designs [67].

This reconceptualization complicates interpretation of vaccine efficacy in QFT-positive populations. Observed protection may reflect effects on reinfection, non-specific immune enhancement, or immunomodulation rather than prevention of reactivation of persistent infection. Inclusion of large proportions of QFT-positive individuals unlikely to harbour viable bacilli may dilute effect estimates, reduce statistical power, and obscure biological mechanisms, particularly for PoI or early-disease endpoints.

In contrast, targeting QFT-negative populations – especially adolescents and young adults who mostly contribute to transmission – offers greater biological clarity and potential public health impact. Vaccines designed to prevent infection, or early progression, are more likely to act on well-defined processes in individuals at genuine risk of TB acquisition. Although such trials require larger sample sizes and longer follow-up due to lower baseline incidence, recent modelling studies challenge the assumption that QFT-restricted enrolment is inherently more efficient [68]. In high-incidence settings, a substantial proportion – and in some age groups the majority – of incident TB arises among individuals who are QFT-negative at baseline, reflecting intense ongoing transmission and recent primary infection. Under these conditions, the efficiency advantages of QFT-restricted designs diminish or disappear, supporting mixed or IGRA-unrestricted enrolment strategies.

From a policy perspective, these considerations align with an evolving shift in WHO language – from individuals who 'are infected' to those who 'have been infected' – acknowledging that immunological sensitisation does not equate to persistent infection. Aligning TB vaccine strategies with this more nuanced understanding of TB natural history may help avoid over-medicalisation of low-risk populations and support more rational allocation of limited public health resources.

Importantly, real-world vaccine implementation is unlikely to accommodate systematic pre-vaccination QFT screening, which would add cost, complexity, and access barriers in high-burden settings. An optimal next-generation TB vaccine should therefore demonstrate acceptable safety and meaningful efficacy across both QFT-negative and QFT-positive populations. This has direct implications for late-stage development: whenever feasible, Phase 3 trials should include both exposure strata with pre-specified analyses to inform universal, targeted, or hybrid vaccination strategies.

Current late-stage programmes illustrate the diversity – and strategic uncertainty – of the field. M72/AS01E is being evaluated primarily in QFT-positive adults, reflecting its Phase 2b efficacy signal, whereas MTBVAC and VPM1002 are undergoing Phase 3 evaluation in neonates as pre-exposure strategies, with MTBVAC also being explored post-exposure in adolescents and adults.

Extending trial inclusion to populations at highest risk

Beyond infection status, accelerating TB vaccine development requires broader inclusion of populations that experience the highest TB burden. People deprived of liberty represent settings of intense transmission and extremely high incidence, offering potential gains in trial efficiency [69]. Although ethical, logistical,

and follow-up challenges are substantial, contemporary frameworks increasingly support inclusion under a paradigm of protection through research rather than protection from research, provided that robust safeguards, meaningful community engagement, and guarantees of post-trial access are in place.

People living with HIV (PLHIV) remain among the populations most severely affected by TB, which continues to be the leading cause of death in this group. In 2024, more than half a million PLHIV developed TB disease globally [1]. Despite their disproportionate burden, PLHIV have historically been under-represented in TB vaccine trials, largely due to concerns regarding safety, immunogenicity, and interpretability of immune responses in the context of immunosuppression.

Emerging evidence now indicates that subunit vaccines such as M72/AS01E are safe and immunogenic in adults with HIV receiving antiretroviral therapy, supporting their further evaluation in this population. Given the persistently high TB incidence and mortality among PLHIV – even in the era of effective antiretroviral therapy – systematic inclusion in safety, immunogenicity, and efficacy studies is essential to ensure that future TB vaccines deliver equitable impact. MTBVAC is undergoing Phase 2a clinical evaluation to assess safety and immunogenicity in adolescents and adults living with and without HIV (ClinicalTrials.gov: NCT05947890), reflecting the growing recognition that elimination-oriented vaccine strategies must generate robust evidence in populations at highest risk.

From efficacy to impact: translating TB vaccines into elimination

The eradication of smallpox illustrates a fundamental lesson for TB: vaccine discovery alone does not achieve elimination without effective global deployment. Although Edward Jenner developed the first smallpox vaccine in 1796, its population-level impact depended on large-scale distribution, exemplified by the Royal Philanthropic Vaccine Expedition (1803-1806) led by Francisco Javier de Balmis, which enabled vaccination of more than 500,000 individuals across the Americas and Asia [70]. This experience underscores that elimination requires not only scientific innovation, but also political commitment, logistical coordination, and equitable access – principles that remain directly relevant to TB.

Over the past two decades, TB vaccine development has progressed to the point where several candidates are approaching late-stage clinical evaluation. However, the public health impact of any new TB vaccine will depend as much on its translation into scalable, affordable, and widely accessible products as on its demonstrated safety and efficacy. Manufacturing capacity, regulatory approval, sustainable financing, and public trust will ultimately determine whether vaccines shift TB epidemiology or remain scientifically successful but programmatically marginal.

Regulatory and manufacturing pathways are therefore central to impact. WHO prequalification will be essential for global procurement and deployment, while early investment in manufacturing capacity will be required to ensure timely and affordable supply for high-burden countries. Experience from the COVID-19 pandemic has shown that regulatory timelines can be accelerated without compromising safety when political will and international coordination align – a lesson that should inform TB vaccine pathways.

Even after licensure, continued evaluation will be critical. Long-term follow-up and post-licensure surveillance will be needed to define durability of protection, effectiveness across epidemiological settings, and performance in key populations, including PLHIV. Equally important, transparent communication and community engagement will be essential to sustain public trust and vaccine uptake, particularly in settings vulnerable to misinformation and inequitable access.

Ultimately, equity will define success. TB disproportionately affects the poorest and most marginalized populations, and the true measure of a TB vaccine will be its ability to reach those at highest risk. International financing mechanisms, national political commitment, and sustained multilateral support will be required to ensure that access is driven by need rather than income or geography.

TB vaccine development has reached a uniquely pivotal and hopeful moment. For the first time in more than a century, vaccines capable of providing meaningful protection against pulmonary TB – and thus transmission – are within reach. If efficacy is confirmed, these vaccines must be positioned not as incremental additions to TB control, but as core instruments of the WHO End TB Strategy with genuine elimination potential. Converting efficacy into impact is therefore an urgent policy imperative. Delayed or fragmented action at this stage would risk confining new TB vaccines to disease control rather than elimination. With science, solidarity, and political commitment aligned, TB vaccination could become one of the most transformative public health interventions of the 21st century.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used ChatGPT in order to improve grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Ethical approval

Ethical approval was not required.

Author contributions

Conceptualization, C.M. and A.A.; Writing – original draft, C.M., J.G., N.A. and A.A.; Writing – review & editing, C.M., J.G., N.A. and A.A.; Funding acquisition, C.M.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: C.M., A.A., N.A. and J.G. are co-inventors on a patent on Tuberculosis Vaccine held by the University of Zaragoza and Biofabri. Biofabri is an industrial partner of University of Zaragoza and the exclusive licensee and industrial and clinical developer of MTBVAC. The authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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