Accelerating research and development of new vaccines against tuberculosis: a global roadmap

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To eliminate tuberculosis globally, a new, effective, and affordable vaccine is urgently needed, particularly for use in adults and adolescents in low-income and middle-income countries. We have created a roadmap that lists the actions needed to accelerate tuberculosis vaccine research and development using a participatory process. The vaccine pipeline needs more diverse immunological approaches, antigens, and platforms. Clinical development can be accelerated by validated preclinical models, agreed laboratory correlates of protection, efficient trial designs, and validated endpoints. Determining the public health impact of new tuberculosis vaccines requires understanding of a country's demand for a new tuberculosis vaccine, how to integrate vaccine implementation with ongoing tuberculosis prevention efforts, cost, and national and global demand to stimulate vaccine production. Investments in tuberculosis vaccine research and development need to be increased, with more diversity of funding sources and coordination between these funders. Open science is important to enhance the efficiency of tuberculosis vaccine research and development including early and freely available publication of study findings and effective mechanisms for sharing datasets and specimens. There is a need for increased engagement of industry vaccine developers, for increased political commitment for new tuberculosis vaccines, and to address stigma and vaccine hesitancy. The unprecedented speed by which COVID-19 vaccines have been developed and introduced provides important insight for tuberculosis vaccine research and development.

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Introduction

With an estimated 10 million new cases and 1·5 million deaths per year, tuberculosis is one of the most devastating infectious diseases worldwide.[1] The global elimination of tuberculosis requires innovative interventions, including safe and more effective vaccines.[2] The current vaccine, Bacille Calmette-Guérin (BCG), has low and inconsistent protective efficacy against pulmonary tuberculosis in adolescents and adults, who are the main source of transmission.[3] WHO has set three goals for the development of new tuberculosis vaccines: a safe, effective, and affordable tuberculosis vaccine for adolescents and adults; an affordable tuberculosis vaccine for neonates and infants with improved safety and efficacy compared with BCG; and a therapeutic vaccine to improve tuberculosis treatment outcomes.[4–6] A vaccine for adolescents and adults has the greatest potential to produce a rapid global health impact.[7,8]

The research and development of new tuberculosis vaccines has been slow, faced with scientific setbacks and poor funding.[9,10] Two phase 2b trials have shown protection signals against *Mycobacterium tuberculosis* infection for BCG revaccination and protection against tuberculosis disease for candidate M72/AS01$_E$.[11–13] With several tuberculosis vaccine candidates in the pipeline,[14] there is an urgent need to prioritise resources to research and development efforts and for a common vision of the knowledge and evidence required to guarantee the impact of new tuberculosis vaccines at the population and patient levels.

To address this need, we developed the *Global Roadmap for Research and Development of Tuberculosis Vaccines* through a participatory design process.[15] The aim of this roadmap is to create a shared vision among global stakeholders on the short-term, medium-term, and long-term priorities for global tuberculosis vaccine development, and to provide guidance on activities to accelerate the development and delivery of new tuberculosis vaccines. These stakeholders include researchers, funders, vaccine developers and manufacturers, regulatory authorities, policy makers, and civil society representatives, who are both the roadmap's intended audience and its co-creators. The roadmap takes WHO tuberculosis vaccine development goals and their associated preferred product characteristics as its starting point,[4] and is generic rather than product specific or vaccine candidate specific. Although new tuberculosis vaccines could also be useful to protect high-risk populations or groups in high-income, low-incidence countries, the focus is on vaccines for affordable and effective use in low-income and middle-income countries (LMICs) where tuberculosis incidence is high. The roadmap will be complemented by another for the global introduction of new tuberculosis vaccines, focusing on licensure, commercialisation, and implementation, which will be developed by WHO.

In this article we describe the process of creating this roadmap, the main research and development barriers and knowledge gaps for uptake, the activities that should be prioritised to address these issues, and the conditions needed to facilitate these activities and maximise their impact.

Roadmap development process

Initiated and funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), with additional support by WHO, the roadmap was developed between Sept 1, 2019, and Feb 28, 2021. We took a participatory approach to its creation, consisting of

Key messages

- The ambitious goal of global elimination for tuberculosis will probably not be achieved without safe and effective vaccines
- We designed a roadmap for the research and development of new tuberculosis vaccines through an iterative consultative process, intended to provide a shared set of priorities to guide the activities of all stakeholders with an interest in tuberculosis vaccine development and use
- Key barriers to tuberculosis vaccine research and development and implementation, and potential ways in which they might be overcome, are identified in three areas: diversifying the pipeline, accelerating clinical development, and ensuring public health impact; cross-cutting enablers are funding, open science, and stakeholder engagement
- Diversification of the tuberculosis vaccine pipeline requires discovery to focus on a wider range of antigens, immune responses, and delivery mechanisms, identifying correlates of vaccine-induced protection, improving our understanding of mucosal immune responses in the lung, and exploring the potential use of controlled human infection models
- Acceleration of clinical development calls for optimising animal models by back translating prevention of disease, infection, and recurrence; optimising clinical trial endpoints; harmonising and standardising trial protocols; exploring innovative trial designs; and building clinical trial capacity in high-incidence countries
- To ensure public health impact of new tuberculosis vaccines post-licensure, there is need for epidemiological and other data to model potential impacts of vaccine use, developing country-use scenarios and investment cases, preparing countries for rapid implementation once recommended locally, identifying potential barriers to implementation and developing strategies to address these, and planning post-licensure studies to establish vaccine effectiveness, safety, and health impact
- Funders' interest in tuberculosis vaccine research and development needs to be increased and new funders need to be attracted; coordination across funders should be improved; commercial interest in tuberculosis vaccine research and development should be catalysed through innovative funding and other push mechanisms combined with market-shaping pull approaches
- All tuberculosis vaccine research and development should be published, particularly negative results; global efforts are required to encourage greater sharing of data and specimens, with the establishment of biobanks and data platforms to facilitate sharing
- Engagement and advocacy is needed with a wide range of stakeholders, including global agencies, industry, regulatory authorities, national decision makers and communities; this should be aimed at additional investment in tuberculosis vaccine research and development, awareness raising of the need for and possibilities presented by new tuberculosis vaccines, and mobilisation of community support for tuberculosis vaccination

See Online for appendix

several steps that involved representatives of a broad group of stakeholders (appendix p 2). The process aimed to seek consensus, and no major controversies were encountered.

The first step consisted of semi-structured interviews with 22 stakeholders who were selected on the basis of their relevance to the roadmap. We gathered the stakeholders' perspectives on the current tuberculosis vaccine pipeline, the key barriers to achieving WHO vaccine goals, and possible solutions for overcoming them. These solutions considered scientific, technological, design-based, developmental, productive, strategic, and commercial perspectives. Respondents were sent the interview questions beforehand. Interviews took 30–60 min, were done in person or online, and were audiotaped and summarised thematically.

The second step consisted of a 2 day in-person workshop with 34 participants from many of the aforementioned stakeholders' organisations and communities. The workshop reviewed the interview responses and defined (1) the key barriers to tuberculosis vaccine development; (2) the knowledge gaps and the actions required to overcome these barriers; (3) the prioritisation, interdependencies, and timing of these actions; and (4) the enabling conditions needed to overcome the three major themes of diversifying the pipeline, accelerating clinical development, and ensuring public health impact.

Following several iterations of the draft roadmap based on the workshop's outcomes, and a round of invited comments from all persons who had been involved in the previous two steps, the resulting version was discussed and commented on by EDCTP's scientific advisory board and WHO's product development for vaccines advisory committee.

In the final step the draft roadmap was opened for public web-based consultation for 6 weeks, and was widely shared with stakeholders through the authors' networks and the global tuberculosis vaccine partnership. Comments received were categorised thematically and discussed individually by the authors. Incorporation of revisions and additions was based on their relevance and fit to the roadmap's aim, scope, and focus, the improvement of clarity, and support from other commentors.

The roadmap identifies, within the three research and development themes, five action lines: basic and translational science, animal models, clinical trials, epidemiology and modelling, and research to ensure optimal implementation (figure). In addition, it identifies three enabling conditions: funding, open science, and stakeholder engagement. Below we discuss for each of

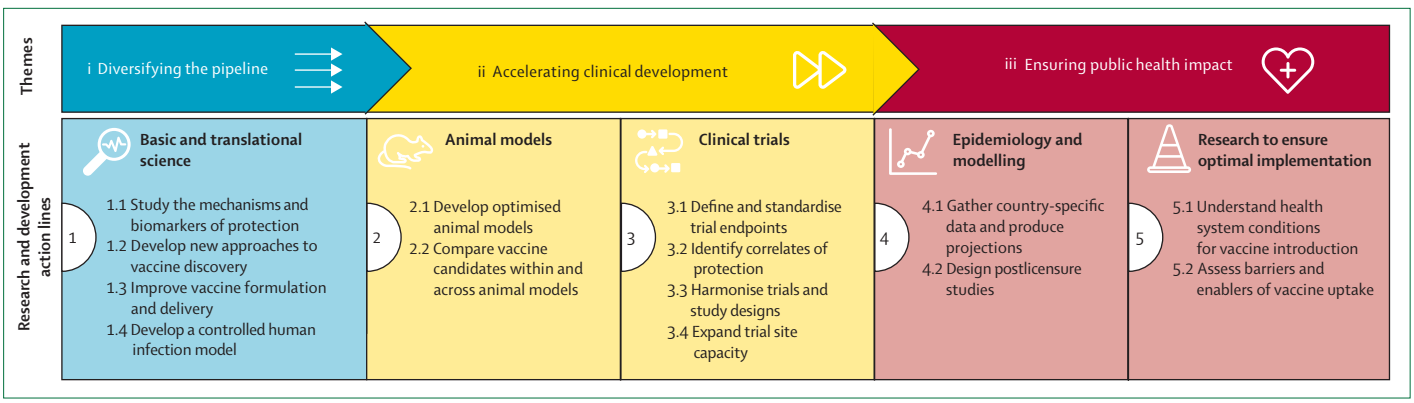

Figure: **Key themes and research and development action lines in the roadmap**
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these action lines and conditions, the associated barriers and knowledge gaps, and summarise the actions needed. For the timing of the various actions the reader should refer to the roadmap.[15] At the time of the launch of this roadmap there were no negative recommendations, but it is acknowledged that tuberculosis vaccine research and development is a rapidly evolving area with new lessons that can be taken from other diseases such as COVID-19.

Diversifying the vaccine pipeline

As vaccine candidates are often found to be unsafe or ineffective during clinical development, a healthy pipeline is characterised by multiple candidates in preclinical and early clinical development using diverse approaches. This is not sufficiently the case for tuberculosis vaccines.[16] Current approaches focus on the few antigens that are known *M tuberculosis* virulence factors and might not elicit optimal protection,[17] and on stimulating classic, $CD4^+$ T-helper-1 (Th1) cells. Th1 cell-mediated responses are crucial for protective immunity in humans but might not be sufficient for long-term protection.[18–20] In addition, there is little diversity in platforms: vaccine candidates currently in late-stage (phase 2b–3) clinical development are live attenuated, killed, and adjuvanted protein vaccines (appendix p 1).[14,21] By contrast, similar-stage and licensed COVID-19 vaccines also include non-replicating viral vector vaccines, DNA vaccines, and RNA vaccines.[22] Emerging biotechnologies used in other fields could be used to identify new targets and develop new vaccine candidates.

Basic and translational science

Priorities for basic and translational science include understanding the mechanisms and biomarkers of protection, generating new approaches to vaccine discovery, improving vaccine formulation and delivery, and developing a controlled human infection model (table 1).

Antigens used extensively in tuberculosis vaccine development include early secreted antigens such as the Ag85 family, ESAT-6, and CFP-10, all of which are highly immunogenic, have shown protection in animal models, and are associated with active bacterial replication.[23] Other antigens need to be considered that are associated with *M tuberculosis* dormancy, as vaccines based on these antigens could more specifically target latent tuberculosis infection.[24]

The role of non-conventional cellular immunity (eg, class I restricted $CD8^+$ T cells, IL-17-producing T cells, or mucosal-associated invariant T cells),[25–27] and antibody-dependent responses including Fc-mediated effector functions need to be clarified for the development of tuberculosis vaccines.[28–30] This requires a better understanding of these responses across the spectrum of human *M tuberculosis* infection. Studies of tuberculosis-exposed cohorts have shown that changes in immune markers,[31] metabolites,[32] and gene transcription profiles,[33] and the appearance of lesions on PET CT scans,[34] all occur from 6 to 12 months before the onset of clinically apparent tuberculosis disease. These signs indicate a clinically silent stage of inflammatory response to the multiplying *M tuberculosis*, which is now termed incipient tuberculosis.[35] In addition, tuberculosis prevalence surveys,[36] post-mortem studies,[37] and observational cohorts,[38] suggest the importance of a subclinical tuberculosis state in which the patient has chest radiographic abnormalities and positive diagnostic tests, but no typical or persistent tuberculosis symptoms.[35] Studies using PET CT imaging furthermore show marked heterogeneity in different lesions in the same individual.[39] Identifying the drivers of transition in either direction along this spectrum of clinical presentation might uncover intervention points where the host response to *M tuberculosis* infection can be manipulated. Similarly, there is a need to clarify the role of innate immune responses and trained innate immunity in early clearance of mycobacteria,[40–42] and how these can be stimulated by vaccination.[43–45] These studies should also aim to identify new biomarkers that can be used as laboratory correlates of vaccine-induced protection.[46–48]

	Comments
Mechanisms and biomarkers of protection	
Conduct observational clinical studies combining pathogenesis and immunology, making use of systems biology, epidemiology, and modelling	Identify components of the host–pathogen interaction associated with clearance, progression to disease, and subclinical disease; identify biomarkers and biosignatures of natural protection
Study the role of non-conventional, cellular immunity, antibody responses, and trained innate immunity in natural and vaccine-induced protective responses	Explore cellular responses through class-I restricted CD8 T cells, Th17 cells, and MAIT cells; B-cell and antibody responses including Fc-mediated antibody effector functions; and innate immune responses through unconventionally restricted T cells and epigenetic reprogramming of monocytes and natural killer cells; investigate their role in human immune responses to *M tuberculosis*
Identify biomarkers and biosignatures that correlate with vaccine-induced protection	Identify correlates of protection on the basis of data and biological samples from trials that have shown protection signals, through targeted approaches to detect cellular and humoral immune responses, and via unbiased approaches including transcriptional profiling of blood cells and mycobacterial growth inhibition assays.
New approaches to vaccine discovery	
Develop new vaccine concepts that can induce alternative immune responses	Explore candidates that generate non-conventional cellular immunity, protective antibody responses, and trained innate immunity
Study mucosal immune responses	Understand the determinants of protective immune responses in the lung parenchyma and mucosa, and how these can be inferred by systemic responses
Deploy genome-wide strategies for antigen discovery	Identify *M tuberculosis*-expressed proteins, peptides, and non-protein antigens that can be recognised by the host immune system, applying IFNγ and non-IFNγ based screening approaches
Improved vaccine formulation and delivery	
Study the effects on vaccination outcomes of adjuvants, vaccine platforms, and the lineage of the *M tuberculosis* challenge strain	Study these effects among others through experimental medicine studies
Explore new routes of vaccine administration	Explore routes including aerosol and intravenous approaches, among others, through experimental medicine studies
Study how vaccines can direct immune responses to the lungs	Evaluate the capacity of different formulations and delivery platforms to induce mucosal immune responses
Controlled human infection model	
Develop a controlled human infection model for immunobiology studies	Develop this model to inform basic knowledge gaps, and for proof-of-principle studies to inform down-selection of candidates, platforms, and routes of administration; addressing participant safety, sensitivity, and ethical issues will be crucial

Fc=fragment crystallisable (region). IFNγ=interferonγ. MAIT cells=mucosal-associated invariant T lymphocytes. *M tuberculosis*=*Mycobacterium tuberculosis*. Th17 cells=T helper 17 cells.

Table 1: **Research and development priorities and key actions to diversify the tuberculosis vaccine pipeline**

Furthermore, diversification of the pipeline requires an understanding of how immune responses are modified by the route of vaccine delivery, vaccine platform, and adjuvant and antigen type. In rhesus macaque models, intravenously administered BCG provided superior protection compared with BCG administered by intradermal or other routes,[49,50] and a cytomegalovirus-vectored recombinant protein (rhCMV/TB) vaccine showed a clinically significant reduction in tuberculosis disease 1 year following a low-dose *M tuberculosis* challenge.[51]

Finally, insight into immune responses at the site of infection in the lungs and how they correlate with responses measured in blood is poor.[52] This calls for studies of mucosal immune responses and, potentially, controlled human infection models.[53]

Accelerating clinical development

The acceleration of clinical development is limited by the effectiveness of stage gating, which is the process of moving promising vaccine candidates through the pipeline while removing those that are not likely to be efficacious at an early stage.[54]

There is an absence of validated preclinical models that adequately predict protection against tuberculosis disease in humans that can be used to guide the selection of candidates to enter clinical development, and of validated immunological correlates of protection that can be used to predict clinical efficacy in trials. These issues became acutely apparent a decade ago when BCG boosting by MVA85A, a candidate that had shown promising protection upon *M tuberculosis* challenge in a non-human primate model and adequate IFNγ responses in humans, provided no clinical protection against tuberculosis disease in a phase 2b trial among South African infants.[55–57]

Animal models are key for preclinical screening of vaccine candidates on immunogenicity, safety, and protection against *M tuberculosis* challenge, but there is currently no validated animal model to support selection for entering the clinical pipeline.[58,59] The correlation between protection in animals (mostly mice, guinea pigs, and non-human primates) and the prediction of protection in humans is weak. This poor correlation reflects differences in animal biology,[60] variability in outcomes,[61] and differences in infection challenge dose,[62] but also highlights the rarity thus far of protection signals of vaccine candidates in human studies by which these models can be validated.

Without validated immunological correlates of protection, licensure of a tuberculosis vaccine candidate for use in adolescents and adults requires demonstrating its efficacy for prevention of tuberculosis disease[63] by large, long (≥3–5 years), and extremely expensive trials. Alternative efficacy endpoints used in phase 2b trials are prevention of infection and prevention of recurrence;[11,64,65] both require smaller sample sizes and shorter follow-up.[9] In prevention of infection trials, individuals with negative IFNγ release assay (IGRA) results are randomly assigned to receive a vaccine or placebo, and followed up for initial or sustained IGRA conversion. In prevention of recurrence trials, people with tuberculosis who are cured after completing treatment are randomly assigned to either vaccine or placebo groups and followed for recurrence of tuberculosis disease (prevention of recurrence might be a licensure endpoint in its own). However, it is not certain that the efficacy observed for a prevention of infection or prevention of recurrence

endpoint predicts the efficacy for a prevention of tuberculosis disease endpoint in a subsequent phase 3 trial,[9] or, conversely, that an absence of an efficacy signal using such experimental approaches is associated with an absence of efficacy in a prevention of tuberculosis disease trial.

Animal models

The priorities are to develop optimised, fit-for-purpose animal models that can predict or replicate findings in humans, and to compare vaccine candidates within and across animal models (table 2). There is a need to establish a functional readout for protection in small laboratory animals and for a greater degree of standardisation of experimental methods. Different models are required to reflect the different stages in human infection, including models of resistance to infection and pathogen clearance. Different animal models might be needed to reflect the immunogenicity, safety, and protection of a vaccine in infants, older people, and individuals who are immunosuppressed.

A proposed systematic approach to candidate selection based on stage gating criteria needs to be refined and validated,[59] in terms of protection against *M tuberculosis* challenges, and conventional as well as non-conventional immune responses in defined models. Comparing multiple vaccine candidates against each other in the same animal models in independent laboratories can aid in prioritising the most promising candidates.

Clinical trials

The priorities for clinical trials relate to trial endpoints, correlates of protection, harmonisation of trials and study design, and trial site capacity (table 2). Prevention of tuberculosis disease endpoints need to be clearly defined and standardised, including the number of positive or negative cultures required and the role of molecular diagnostics. Better prevention of tuberculosis disease endpoints are needed for trials enrolling infants, children, and people living with HIV in whom sputum culture has low sensitivity; these trials should also have a composite endpoint that incorporates extrapulmonary tuberculosis. There is a need to clarify the usefulness of prevention of infection endpoints in the clinical development pathway and the prevention of infection measurements (IGRA conversion, sustained IGRA conversion)[11] that best correlate with prevention of tuberculosis disease. This might only be achieved by conducting a prevention of tuberculosis disease efficacy trial in a study population that has negative IGRA results at the time of vaccination.

Although immune correlates of protection can help shorten clinical development, it is unlikely that a single correlate will be sufficient basis for licensure. A set of correlates are needed that are associated with vaccine-induced protection, vaccine inefficacy, and natural protection independent of vaccination. Identifying correlates of protection and optimising animal models require the back translation of results from trials that show an efficacy signal through an iterative process in which stepwise improvements in vaccine design lead to new efficacy signals, which then enable the improvement of animal models and discovery of better correlates. These interdependencies must be considered in the planning of vaccine trials, including the collection and biobanking of samples within those trials.

The standardisation of clinical endpoints, inclusion criteria, and endpoint measurements is important to facilitate comparisons across trials. Tuberculosis vaccine trials should include people living with HIV, and potentially other individuals who are immunosuppressed, provided the expected benefit for these populations exceeds the potential risks and measures to mitigate such risks are in place. Tuberculosis preventive treatment is standard of care for these immunosuppressed populations and other subpopulations and must be considered in the design and conduct of vaccine trials.[66] Trial designs with increased efficiency should be explored, including adaptive designs and studies in high-incidence populations. Ways to accelerate the transition between clinical development phases should also be studied.

Clinical trial sites must be established in diverse geographical locations; trial site capacity does not need to be tuberculosis specific but should be sustainable through trials on an ongoing basis so that key staff can be retained, and skills and infrastructure maintained. Factors that could affect enrolment and retention in tuberculosis vaccine trials need to be explored, including a detailed understanding of local tuberculosis epidemiology, and community engagement in tuberculosis vaccine trials should be promoted.[67]

Ensuring public health impact

For a new tuberculosis vaccine to achieve a public health impact, it is crucial to understand the different factors for policy decisions at the country level about how it will be introduced, and to provide evidence to support these decisions. Such factors include (1) the national tuberculosis burden and its political prioritisation; (2) the safety, efficacy, and expected impact of the vaccine; (3) the vaccine's cost, supply, affordability, cost-effectiveness, and equity impact (eg, in vulnerable groups such as people living with HIV and older people); (4) the relative effectiveness of alternative control strategies; and (5) the capacity of the health system for its successful introduction and sustainable delivery.

In particular, for a vaccine for adolescent and adults, evidence would be needed on how to optimally deliver the vaccine (eg, through vaccination campaigns, which age groups to target), the number of doses required, cold-chain requirements and need for re-vaccination, how to ensure equitable access and vaccine acceptance,

	Comments
Optimised animal models	
Develop fit-for-purpose animal models	Back translate the findings from adult, adolescent, and paediatric trials into immunogenicity, infection, and disease animal models, ideally with the exact same product as in humans, and the findings of clinical studies of disease progression and subclinical disease
Develop animal models to provide insight into the relationship between prevention of infection and prevention of disease	Back translate the results from trials with prevention of infection and, ideally, both prevention of infection and prevention of disease endpoints, and from clinical studies of clearance and disease progression
Develop immune-compromised animal models that can predict or replicate findings in specific human target populations	Back translate the results that will emerge from trials and clinical studies including those that study infants, older people, and immunosupressed humans into disease animal models
Comparison of vaccine candidates within and across animal models	
Standardise and harmonise animal models	Include the harmonisation and standardisation of challenge strain selection, and definition of protection outcomes, including the use of imaging and scoring gross pathology specimens; identify priorities for future experimental directions—eg, assessing aerosolised delivery of vaccines
Perform comparative testing of candidate vaccines	Compare candidates in independent laboratories with the standardised models that best predict protection in humans
Clinical trial endpoints	
Define standardised prevention of disease trial endpoints that better capture the various tuberculosis disease states in diverse target populations	Standardise the definition of laboratory-confirmed pulmonary tuberculosis; develop clinical endpoints that are representative of subclinical tuberculosis; improve the bacteriological confirmation of tuberculosis disease in neonates and infants and people living with HIV; improve the bacteriological confirmation of extrapulmonary disease
Define and develop better prevention of infection trial endpoints	Define an endpoint for *M tuberculosis* infection for establishing prevention of infection; this endpoint should differentiate *M tuberculosis* infection from a vaccine-induced immune response
Quantify the clinical translation of prevention of infection into prevention of disease	Analyse existing and new observational data; include secondary prevention of infection endpoints in phase 3 prevention of disease trials, and consider that this quantification might be different for different types of vaccines
Correlates of protection	
Collect biospecimens for identifying correlates of protection	In planned and ongoing phase 2b and phase 3 trials
Identify correlates of protection for tuberculosis disease	From phase 2b and phase 3 trials that have shown protection: analyse data and putative correlates of protection values from individual trials and, if possible, from meta-analyses of several trials
Validate correlates of protection for tuberculosis disease	Validate the putative correlates of protection that were identified by back translation of trial results that reflect vaccine-induced response and clinical protection in immunogenicity studies, new trials with a clinical prevention of disease endpoint, and, potentially, controlled, human infection models
Trial harmonisation and design	
Harmonise clinical trial protocols	Define an agnostic trial shell of standardised outcomes, inclusion criteria, and measurements for clinical trials for different vaccine types, which should also address secondary endpoints, inclusion criteria for people living with HIV infection or diabetes, and standardised measurements over time
Develop new models for tuberculosis vaccine trials with increased efficiency	Phase 1: explore innovative trial designs that provide information on the local human immune response; phase 2b–3: efficacy trials within contact investigations, active case finding programmes, and high-risk populations, and adaptive trial designs for evaluating the safety, immunogenicity, and efficacy of different vaccine types
Trial site capacity	
Do an inventory of clinical trial site capacity	Identify potential sites beyond the existing ones, and assess the quality and suitability of existing technical and laboratory infrastructure
Collect epidemiological data in sites considered for phase 2–3 trials	Collect from various parts of the world, as a continuous process: age-stratified data for tuberculosis incidence, age-stratified prevalence and incidence of latent tuberculosis infection, *M tuberculosis* lineage distribution, data on special populations such as people living with HIV and other populations considered for vaccine trials
Develop vaccine trial sites	Develop infrastructure and human capacity in diverse geographical locations to take account of potential variation in efficacy and safety due to heterogeneity in host and bacteriological genetic background; should include mentorship and support of junior investigators
Study potential barriers to trial acceptance	Conduct social science research of barriers to participating in tuberculosis vaccine trials and completing follow-up, including tuberculosis-associated stigma, other stigma, and social barriers; compile best practices from successful vaccine trial sites
Promote community engagement in tuberculosis vaccine trials	Community engagement should be part of any phase 2 or phase 3 study, and sponsors and developers should start developing plans for community engagement before phase 1 studies start

M tuberculosis=Mycobacterium tuberculosis.

Table 2: **Research and development priorities and key actions to accelerate clinical development of new tuberculosis vaccines**

and how best to use the vaccine in vulnerable groups and in high-transmission settings such as slums and prisons.[68] Potential strategies must be aligned with the needs of policy makers, affected populations, donors, and implementers in various countries and settings. Vaccine hesitancy can undermine a new tuberculosis

vaccine's health impact, particularly if it offers only incomplete protection or has adverse effects.

This body of local information will support country decision making, enable donors to plan investments, and help with estimating national and global demand to encourage manufacturers to enter the market and scale up vaccine production. Global and national policies on vaccine target groups, expected impacts, willingness to pay, and cost of implementation will all affect cost–benefit analyses and thereby decision making.[69] This information gap needs to be closed through an iterative process of data collection on country preferences, implementation requirements and epidemiological metrics, and modelling of public health impact and cost-effectiveness. Analyses might be further refined as post-introduction data on vaccine efficacy, safety, and impact become available.

Epidemiology and modelling

Priorities relate to country-specific data and projections, and post-licensure studies (table 3). Key information for decision making is the cost and benefit of a new vaccine in relation to its protective efficacy in the target population, expected duration of protection and dosing regimen,[70] and countries' and donors' willingness to pay for the health impact it is to achieve.[71] Country-specific data need to be collected on the burden of *M tuberculosis* infection and tuberculosis disease, and on the size and accessibility of specific target populations, to inform the modelling of vaccination strategies,[72] taking into account strategies for specific risk groups, a life-course perspective, and equitable access and use.[73]

Before vaccine introduction, baseline epidemiological data need to be collected for health impact assessments, and postlicensure studies designed to establish the vaccine's effectiveness and safety when rolled out. Where needed, surveillance systems for tuberculosis disease notification and pharmacovigilance must be strengthened. If pre-licensure data suggest that a vaccine's protective efficacy is lineage dependent, data would be needed to provide a baseline for post-licensure surveillance of shifts in *M tuberculosis* lineage distribution. Postlicensure studies should also explore the potential non-specific effects of new tuberculosis vaccines in infants and neonates in comparison to BCG, such as the effects on all-cause mortality.

	Comments
Country-specific data and projections	
Conduct in-depth country-specific value proposition analyses	Assess value drivers for new tuberculosis vaccines across different countries and stakeholders considering preferred delivery strategies, efficacy relative to safety, manufacturing, strain standardisation and price, willingness to pay, and cost of delivery
Collect epidemiological data at country and subnational levels	Inform economic and impact modelling related to country decisions on the introduction of new tuberculosis vaccines and market volumes by ascertaining national (ideally subnational) tuberculosis disease and infection prevalence including in specific risk groups (eg people living with HIV and older people), identifying potential target groups for vaccination on the basis of contribution to transmission, and mapping *M tuberculosis* genotypic variation
Create models to define vaccine development investment cases and country-specific vaccine use cases	Create models of implementation scenarios, the epidemiological impact, cost-effectiveness, and budget impact in consultation with relevant countries for vaccines that are close to market introduction, by use of transmission modelling, economic modelling, and other quantitative approaches
Postlicensure studies	
Develop valid approaches for real-world vaccine scale-up studies	Develop designs and validated tools for establishing the real-world effectiveness, safety, and public health impact following introduction; establish and support post-licensure registries making use of existing expertise from the introduction of other vaccines; and strengthen surveillance systems for collection of baseline epidemiological data
Conduct postlicensure evaluations of vaccine effectiveness, impact, and safety	Real-world postlicensure studies and surveillance to establish effectiveness across various subpopulations (eg, people living with HIV) and *M tuberculosis* lineages, effectiveness and safety when given concurrently with other vaccines, safety in subpopulations (eg, pregnant women), impact on tuberculosis disease incidence, and non-specific health effects for vaccines replacing BCG
Health system conditions for vaccine introduction	
Define the generic public health system requirements to deliver a new tuberculosis vaccine	For a vaccine for adolescents and adults: determine in different countries the feasibility of various strategies including vaccination campaigns, conditions for immunisation programmes to implement these strategies, requirements for optimising access for different population groups, integration of tuberculosis vaccination within and beyond national tuberculosis programmes, and approaches to measuring vaccine uptake in adolescents and adults; for a vaccine for neonates and infants: determine the fit in the Expanded Programme on Immunization[70] and required timing considering other vaccinations
Conduct assessments of country immunisation programmes before and after introduction of a new tuberculosis vaccine	Assess the preintroduction country-specific readiness of immunisation programmes and health systems to handle, store, and administer the new tuberculosis vaccine (considering its characteristics, particularly for delivery to adolescents and adults), to monitor vaccine coverage and adverse events, and to communicate adverse events
Barriers and enablers of vaccine uptake	
Assess drivers of acceptability and uptake of new tuberculosis vaccines in various settings	Social and behavioural research to determine across countries and settings decision makers', public workers', and health workers' perceptions around new vaccines, related to dosing, safety concerns, religious concerns, gender, use with other vaccines versus specialised programmes, and, for immunotherapeutic vaccines, integration with tuberculosis treatment

M tuberculosis=Mycobacterium tuberculosis

Table 3: **Research and development priorities and key actions to ensure a public health impact**

Research to ensure optimal implementation

The priorities for investigation are health system conditions for vaccine introduction and barriers and enablers of vaccine uptake (table 3). There is an urgent need for data on the feasibility, public acceptance, and implementation requirements of strategies to deliver tuberculosis vaccines to adolescents and adults. These strategies can build on the emerging experience of LMICs with the COVID-19 vaccination of adults and human papillomavirus vaccination of adolescents while considering aspects that are specific to a tuberculosis vaccine. This experience includes health system (eg, accessibility, equity, opportunity costs), technological (eg, dosing schedule, thermostability, cold-chain requirements), social (eg, vaccine acceptance, access among vulnerable populations, gender-related considerations), and medical elements (safety and efficacy in people with co-morbidities or other vulnerabilities). Assessments of health system readiness and to identify gaps and areas

for improvement for vaccination implementation post-introduction are needed.

In addition, there is a need to enhance acceptance of a tuberculosis vaccine among adolescents and adults, which requires an understanding of the potential barriers to uptake including tuberculosis-associated stigma.

Enabling conditions

There are three conditions that are key to enabling a healthy tuberculosis vaccine pipeline, acceleration of clinical development, and a health impact with new tuberculosis vaccines: increased funding, open science, and stakeholder engagement and multisectoral collaboration (panel).

Panel: **Priorities and actions for enabling conditions for tuberculosis vaccine development**

Funding

Attract new investments in tuberculosis vaccine research and development

- Develop a comprehensive global value proposition for tuberculosis vaccines that encompasses vaccine characteristics, use case, societal value, business case, investment case, and health and microeconomic and macroeconomic impact assessment
- Broaden the funding base with governments, charitable funders, and donors; mobilise domestic research and development funding from large countries' governments; get specific donors involved that could contribute to funding downstream aspects of tuberculosis vaccine research and development; engage with the HIV and antimicrobial resistance communities
- Attract new entrants in tuberculosis vaccine research and development; involve actors, technologies, models, and knowledge from outside the tuberculosis vaccine research field; funders should promote such involvement in their funding programmes—eg, in the specification of calls and eligibility criteria

Innovate financing for tuberculosis vaccine research and development

- Create collaborations or partnerships for joint funding of trials with mechanisms for pooling resources between research and development funders, governments, and industry with selection procedures that are product and country neutral, and strict rules for what the funding will be used for and under which conditions
- Customise calls to the clinical development pathway through options for long-term funding (eg, 10 years, with intermediate go and no-go decisions) allowing consortia to adopt a long-term research and development perspective for a specific candidate or approach

Create mechanisms that attract investment in early stages of development

- Reduce commercial uncertainty by providing incentives for stronger engagement from industry and other vaccine developers through grant funding and advance market commitments with a clearly defined path to commercialisation, including production of a successful candidate
- Ensure that intellectual property can be used efficiently, openly, and equitably to facilitate tuberculosis vaccine research and development in ways that promote collaboration among universities, biotech and pharmaceutical companies, and government funders

Open science

Promote timely and open access of data, specimens, and results

- Funders and product development partnerships should require registration of all animal and human studies, open access publication of both positive and negative results, and data sharing and posting in open access databases as conditions for funding or consortium membership
- Biospecimens collected in clinical studies should be made available based on peer review, overseen by an access committee; access to biospecimens should not be granted in order of application but to researchers with the most innovative ideas and approaches
- Establish publicly searchable patent databases for tuberculosis vaccine research (as exists for drug development) to promote the diffusion of knowledge by facilitating access to the information disclosed in a patent including antigens, adjuvants, platforms, and processes

Create a mechanism for coordinating open science in tuberculosis

- Establish a platform for data sharing, starting with data from clinical studies, including generic protocols for contextual data (eg, for what purpose were the data collected); encourage proper use (eg, ethical rules, privacy regulations) and acknowledgement of original collectors or contributors of the data in secondary use and publications
- Develop and coordinate systems and procedures needed for efficient data and specimen sharing across the field of tuberculosis research and across tuberculosis research funders

Stakeholder engagement

Create a supportive environment for tuberculosis vaccines

- Raise political commitment for new tuberculosis vaccines at the country level making sure that existing commitments and defined targets are met, based on clear communication about the need, efficacy, and safety for new tuberculosis vaccines towards policy makers, including the risk–benefit and cost–benefit analysis of a new tuberculosis vaccine
- Advocate for the development and uptake of new tuberculosis vaccines with vaccine developers and the public through positive messaging about opportunities and actions in vaccine development

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- Harmonise and fast track regulatory review and local approval of vaccine trial protocols based on the example of AVAREF, establish national immunisation technical advisory groups in countries that do not have them and strengthen their capacity, and fast track the regulatory approval of tuberculosis vaccines
- Create innovative incentives by forecasting demands from countries and engaging multilateral funders, including Gavi the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Unitaid, and the Coalition for Epidemic Preparedness Innovations in offering novel financing mechanisms

Overcome barriers to delivery and uptake

- Engage with end-user communities to address stigma, vaccine hesitancy, and adherence; provide and communicate a convincing rationale for (high-risk) target groups to be vaccinated; involve end-user communities in the research process; build resilient information systems to counter vaccine-related misinformation and disinformation
- Develop approaches to community-level delivery (eg, through community health workers) to address gaps in access to vaccination; educate health-care networks, the medical community, and the public about tuberculosis vaccine introduction through targeted, country-specific approaches

Promote tuberculosis vaccine and research literacy

- Create a global programme for community engagement and training for new tuberculosis vaccines; develop mechanisms for engaging community representatives in tuberculosis vaccine development; engage and educate community representatives who can encourage policy makers to invest in the development and introduction of new vaccines; support community engagement in tuberculosis vaccine clinical trials
- Foster strategic and reciprocal partnerships between vaccine scientists or sponsors and representatives of civil society and tuberculosis-affected communities to support the involvement of all parties in advocacy for new tuberculosis vaccines

For more on **AVAREF** see https://www.afro.who.int/health-topics/immunization/avaref

Funding

The priorities are to attract new investments in and innovate financing for tuberculosis vaccine research and development and to create mechanisms that attract investments in early stages of development.

Inadequate funding is the single most important barrier to progress in the discovery, preclinical research, and clinical development of new tuberculosis vaccines. Globally, research funding for tuberculosis (at an estimated US $900 million in 2019) is US $2 billion below the target set in the Stop Tuberculosis Partnership's global plan to end tuberculosis 2018–2022. Tuberculosis vaccine research is severely underfunded, making up only 13% of tuberculosis research and development in 2019, which is the largest deficit in any category of tuberculosis research.[74]

Tuberculosis vaccine research and development funding comes from a small number of public and charitable sources, with little industry involvement, which probably reflects the poor incentives for industry to invest in tuberculosis vaccine research and development, because the market is concentrated in LMICs who have poor ability to pay. Engaging new funders is crucial and needs to be supported by a global value proposition for tuberculosis vaccines. Governments could be involved by agreeing on funding targets for tuberculosis research and development as a proportion of their domestic research and development expenditure.[75] Engaging vaccine manufacturers in LMICs is also important for guaranteeing global access.

Financing for tuberculosis vaccine research and development should be innovated by establishing partnerships for joint funding of trials—for example, through roadmap funding where countries, research funders, and industry and other donors pool resources to bring promising vaccine candidates to the market at an affordable price. This financing requires independent and transparent decision making with clear goals, principles, timelines, and norms, and strong coordination between funders—for example, through the global tuberculosis vaccine partnership. Rather than awarding research grants on a short-term, project-specific basis, funders should create pathway mechanisms that allow a smooth transition from one stage of clinical development to the next without the uncertainty of new competitive applications. This will be important to attract new actors to commit to tuberculosis vaccine research and development and incentivise basic researchers to enter and continue in the field. Commercial uncertainty for vaccine developers needs to be reduced by market shaping through grant funding and engaging global financing mechanisms such as the Global fund, Gavi the Vaccine Alliance, the US President's Emergency Plan for AIDS Relief, and Unitaid to act as incentive by guaranteeing innovators a market for their product. Mechanisms need to be in place to ensure that advance market commitments achieve the acceleration of research and development, competition among manufacturers, affordable pricing, adequate supply capacity, and technology transfer to LMIC vaccine manufacturers.

Finally, it will be important to manage intellectual property ensuring its efficient, open, and equitable use by facilitating partnerships and the licensing of intellectual property among organisations by building on existing initiatives and patent licensing mechanisms such as the medicines patent pool.[76]

Open science

The priorities regarding open science are to promote the timely and open access of data, specimens, and results,

and to create a mechanism for coordinating open science.

A key barrier to progress in tuberculosis vaccine research and development is that results from pre-clinical and clinical tuberculosis vaccine studies are often not made public, and when they are, it is very late. Negative results from animal studies tend to remain unpublished, and datasets from studies are often not shared. Open access publication, open access databases for pre-clinical, clinical, and epidemiological studies, and open access databases of tuberculosis vaccine patents should be the norm. This accessibility should be set by vaccine developers, research institutes, and funders and be cost-eligible in research grants.[77] A data-sharing platform should be created for tuberculosis vaccine data, building on the example from tuberculosis drug development,[78] to avoid duplication of data collection. Now that vaccine trials are showing protection signals, specimen sharing from clinical trials and related studies is crucial for identifying correlates of protection. Scarce specimens must be used as efficiently as possible, and access needs to be prioritised for the most innovative ideas and approaches, also if they come from outside the tuberculosis research field. Specimen sharing requires mechanisms for providing banked samples from tuberculosis vaccine trials.[11,13] Coordination between funders will be integral to creating mechanisms for efficient data and specimen sharing across the field of tuberculosis research and across tuberculosis research funders, as will be learning from vaccine development for HIV and COVID-19.

Stakeholder engagement and multisectoral collaboration

The priorities are to create a supportive environment for tuberculosis vaccines, overcome barriers to delivery, and promote knowledge about tuberculosis vaccines, research literacy, and uptake.

The clinical development of new tuberculosis vaccines is slowed down by low political commitment at the country level for supporting tuberculosis vaccine research and development and guaranteeing uptake post-licensure, low engagement of vaccine developers, and complex, lengthy regulatory approval procedures for clinical trials. Advocacy is needed to raise and sustain political commitment and to create support for tuberculosis vaccine development and uptake, among other things, by capitalising on positive efficacy signals from successful trials. Decision making for vaccine implementation tends to be slow, and the shortfall of clear country preferences and preparedness for tuberculosis vaccine introduction could exacerbate delays. National immunisation technical advisory groups can play a key role and should be established or strengthened.[79] The regulatory reviews of trial protocols should be harmonised and expedited, and the regulatory approval of new tuberculosis vaccines fast tracked. Innovative ways for incentivising vaccine developers to enter the tuberculosis space need to be explored. Any barriers to future uptake need to be overcome from early on, through engaging with end users to address stigma, vaccine hesitancy, adherence, and potential gaps in access, as well as through developing approaches to vaccine delivery in the community. The improvement of stakeholder engagement and multi-sectoral collaboration requires focused advocacy towards policy makers, vaccine developers, implementers, and the public. Tuberculosis vaccine and research literacy needs to be enhanced by creating a global programme for community engagement and training and fostering partnerships between scientists, civil society, and affected communities. Meaningful community engagement should be a mandatory aspect of the clinical development of new tuberculosis vaccines from the start of the research process.

Lessons from COVID-19

The unprecedented speed by which COVID-19 vaccines have been developed, licensed, and introduced provides an important example for tuberculosis vaccine research and development.[80] New platforms have been successfully deployed that might have useful applications for tuberculosis, in particular the mRNA technology with lipid nanoparticle delivery systems.[81] For COVID-19, the clinical development pathway was accelerated, among other factors, by early human trials and trial phases being conducted in parallel. Key success factors relevant for tuberculosis vaccine research and development are the mobilisation and effective deployment of large-scale funding, harmonisation of research and development efforts between industry and research institutes, deployment of comparative regional trials, use of efficient trial designs (such as adaptive platform trials and master protocols), early regulatory input in trial designs, accelerated regulatory review, and mechanisms for scientific exchange.[80] COVID-19 vaccine trials were further accelerated by the use of virtual platforms including online recruitment, web-based randomisation, and e-reporting of outcomes. Several of these elements can and should also be deployed for the clinical development and reduction of time to market for tuberculosis vaccines. Overlapping trial phases and large-scale manufacturing of candidates pre-licensure would, however, require funding several-fold the current amounts and advance purchase commitments. Moreover, the utility of adaptive trial designs could be restricted by differences between COVID-19 and tuberculosis in incubation periods and expected incidences.

Data-sharing mechanisms and platforms created for COVID-19 drug and vaccine research and development should be leveraged for tuberculosis vaccine research and development where possible, including rapid analysis, sharing of data, samples, bioassays, and study protocols, and making publications available on preprint servers.

As the primary target population are adults and adolescents, the rollout of COVID-19 vaccines is providing

Search strategy and selection criteria

References for this Review were identified through searching PubMed (articles in English) from Jan 1, 2010, to June 30, 2021, with combinations of the keywords "tuberculosis", "vaccine", "cellular immunity", "antibodies", "innate immunity", "clinical trials", "modelling", "cost-effectiveness", "implementation", and "funding". We reviewed and selected the references on the basis of their relevance for various roadmap action lines. In addition, we searched the websites of WHO, the Tuberculosis Vaccine Initiative, and Treatment Action Group for relevant reports.

lessons for tuberculosis vaccine introduction, such as the conditions required for vaccination campaigns to be effective,[82] coordinated pharmacovigilance and communication of adverse events,[83] and ways to address vaccine hesitancy and anti-vaxxer messaging.[84] Finally, the COVID-19 response suggests that vaccine manufacturing capacity and affordable and equitable availability in LMICs are key for effective implementation and ensuring the public health impact of vaccination.[82]

Conclusion

This research and development roadmap sets research priorities for the discovery, preclinical development, clinical development, preparation for introduction, and implementation of new tuberculosis vaccines. It brings together the views and visions of a broad range of stakeholders in the field that included researchers, end users, funders, regulators, and industry professionals. The overall call is for acceleration towards achieving health impact through new approaches in vaccine discovery, better validated animal models, more efficient clinical development, proactive mapping of postlicensure use and demand, and removing barriers to effective scale up. Tuberculosis vaccine research and development requires more funding and a more effective use of existing resources, open exchange of data, specimens, and results, and strong engagement with stakeholders at the political, commercial, public health, and community levels. The rapid development and deployment of COVID-19 vaccines provides several examples to build on. The next step is for the various actors to follow the roadmap.

Tuberculosis Vaccine Roadmap Stakeholder Group
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Contributors
FC led the roadmap development process and wrote the draft versions of the roadmap and this Review. BS, FD, and FC designed the roadmap structure and led the stakeholder consultations. MHe, ALW, and MM developed the scope of the roadmap and provided crucial input in the development steps. RKS and MHa provided technical input on the development process, design, and content. BS, FD, MHe, ALW, MM, RKS, and MHa reviewed and commented on draft versions of the roadmap and this Review. All group authors provided technical input on the roadmap and commented on one or more of its draft versions.

Declaration of interests
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