GLOBAL ROADMAP FOR RESEARCH AND DEVELOPMENT FOR TUBERCULOSIS VACCINES

(branding and organizational style to be included)

List of abbreviations

AVAREF	African Vaccine Regulatory Forum
BCG	Bacillus Calmette–Guérin
CD4+	T-lymphocytes expressing the Cluster of Differentiation 4 receptor
CD8+	T-lymphocytes expressing the Cluster of Differentiation 8 receptor
CEPI	Coalition for Epidemic Preparedness Innovations
CHIM	Controlled human infection model
CoP	Correlate of protection
CTVD	Collaboration for TB Vaccine Discovery
EDCTP	European Developing Countries Clinical Trials partnership
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GTBVP	Global TB Vaccine Platform
HPV	Human Papilloma Virus
IAVI	International AIDS Vaccine Initiative
IFN-γ	Interferon-gamma
IGRA	Interferon-gamma release assay
MAIT cells	Mucosal associated invariant T lymphocytes
Mtb	*Mycobacterium tuberculosis*
NGO	Non-governmental organization
NITAG	National Immunization Technical Advisory Group
PEPFAR	President's Emergency Plan for AIDS Relief
PoD	Prevention of disease
PoI	Prevention of infection
PoR	Prevention of recurrence
R&D	Research and development
TB	tuberculosis
TBVI	tuberculosis Vaccine Initiative
Th1 cells	T-helper lymphocytes, type 1
Th17 cells	T-helper lymphocytes, type 17
WHO	World Health Organization

Executive summary

This document proposes a Roadmap for research and development for tuberculosis (TB) vaccines. With an estimated 10 million new cases and 1.4 million deaths per year TB remains among the most devastating infectious diseases worldwide. The only available TB vaccine, Bacille Calmette-Guérin (BCG), has been used for decades to protect infants from severe TB disease but is not effective in preventing adult pulmonary TB, the major cause of morbidity, mortality and transmission. There is increasing consensus that the World Health Organization (WHO)'s End TB Strategy will not be able to meet its goal of eliminating TB as a global health problem by 2030 without a new TB vaccine.

This Roadmap aims to provide global stakeholders such as researchers, funders, industry, regulatory and policy decision makers with key actionable priorities to help guide their actions by listing the short-term objectives and the long-term strategic objectives for global TB vaccine development. It **focuses on developing and delivering affordable and effective vaccines for use in low- and middle-income countries** where the vast majority of people affected by TB are concentrated.

The Roadmap describes the actions needed to reach the **three development goals for TB vaccines set by the WHO**: (1) A safe, effective and affordable TB vaccine for adolescents and adults; (2) An affordable TB vaccine for neonates and infants with improved safety and efficacy; and (3) A therapeutic vaccine to improve TB treatment outcomes. These actions focus on the necessary research and development (R&D), and on the enabling conditions needed to enhance this R&D and ensure uptake of new TB vaccines once developed. The R&D actions are grouped into three categories, which are: diversifying the pipeline, accelerating clinical development, and ensuring public health impact. The enabling considerations are categorized along the following lines: funding, open science, and stakeholder engagement. For each of these categories the major barriers to developing new TB vaccines are indicated, along with the specific actions to overcome these barriers, their timing and, where relevant, their interdependencies.

The **process for developing this Roadmap** consisted of several steps, including desk review and stakeholder inventory, in-depth interviews with selected stakeholders, a consent workshop and various rounds of stakeholder consultation on the subsequent draft versions of the Roadmap. These rounds of consultation included both targeted requests for feedback to selected stakeholders and a public consultation. In each step of the process there was close collaboration with the WHO's Immunization, Vaccines and Biological Department and its Global TB Programme.

The Roadmap identifies a clear need to **diversify the TB vaccine pipeline**, as relatively few candidates are in preclinical and early clinical development. With its emphasis on stimulating classical CD4+ Th1 cells, the approach to vaccine development taken thus far is considered too narrow. In addition, only a limited set of candidate TB antigens are currently considered that are known *M. tuberculosis* virulence factors. Overcoming these barriers requires expanding basic and translational science, focused on mechanisms and biomarkers of protection; new approaches to vaccine discovery; improving vaccine formulation and delivery; and controlled human infection models.

There are two key barriers to **accelerating clinical development** of new TB vaccines: lack of relevant, validated preclinical models that predict infection and disease in humans, and lack of evidence to support decisions to move a candidate forward through the clinical development pipeline. The first limits effective selection of candidates for clinical development. It is to be addressed by developing, optimizing and using diverse "fit for purpose" animal models that can predict/replicate findings in humans. It also requires comparing TB vaccine candidates within and across animal models.

The second is related to a lack of agreed laboratory correlates of protection for use in clinical trials. It necessitates large phase II/III trials of long duration with *prevention of disease* as clinical efficacy endpoint. Alternative efficacy endpoints are being proposed for proof-of-principle: *prevention of infection* and *prevention of recurrence,* but it is unknown to what extent these endpoints predict prevention of disease. This barrier needs to be addressed by defining meaningful trial endpoints, identifying validated correlates of protection, improving the efficiency and standardization of TB vaccine trials, and building trial capacity.

Key barriers to **ensuring public health impact** of new TB vaccines are unmet needs (1) to understand countries' likely demand for a new TB vaccine and associated considerations when added to their national immunization programmes, especially for vaccine to be used in adults and adolescents; (2) for evidence on how to integrate vaccine implementation with ongoing TB prevention efforts and how to use the vaccine among vulnerable groups; and (3) for estimating the national and global demand to stimulate manufacturers to enter into the market and prepare and scale-up vaccine production. Two action lines are proposed to address these barriers. One is aimed at quantifying key epidemiological and health economic metrics to support vaccine introduction and evaluating vaccine effectiveness and impact post-licensure. The other focuses on understanding user preferences and implementation needs for new TB vaccines.

The key barriers with regard to **funding** include low investments in TB vaccine R&D, lack of diversity in the current funding sources and limited coordination of R&D funding. Actions to overcome these barriers are attracting new investments in TB vaccine R&D, innovating financing for TB vaccine R&D and creating mechanisms for reducing financial risk.

With regard to **open science** the barriers hampering TB vaccine R&D include late or no publication of pre-clinical and clinical study findings and lack of effective sharing of datasets and specimens. Actions identified to address these barriers are promoting timely and open access of data, specimens and results, and creating mechanisms for coordinating open science.

Finally, key barriers in the realm of **stakeholder engagement** are limited engagement of industry vaccine developers, still limited political commitment for new TB vaccines at country level, slow decision making for vaccine implementation, as well as stigma, vaccine hesitancy and other factors that may affect vaccine adherence by communities. Actions in this realm are creating a supportive environment for TB vaccines, overcoming barriers to delivery and uptake and promoting TB vaccine and research literacy.

The document ends with a brief section that outlines the framework for the various actions listed in the Roadmap related to **commercialization of vaccine development and manufacturing and access to new TB vaccines when licensed**. The proposed approach here is a combination of push mechanisms, pull mechanisms and technology transfer.

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1. PURPOSE, PROCESS AND SCOPE

Purpose of the Roadmap

The European Developing Countries Clinical Trials partnership (EDCTP) has assigned to the Amsterdam Institute of Global Health and Development (AIGHD) the development of a global roadmap for Research and Development (R&D) of Tuberculosis (TB) vaccines (hereafter referred to as "the Roadmap").

The purpose of the Roadmap is to provide global stakeholders – researchers, funders, industry, regulatory, policy decision makers and civil society – with key actionable priorities to guide their actions. The Roadmap will primarily focus on recommendations for developing and delivering affordable and effective vaccines for use in low- and middle-income countries with high incidence of TB, in line with the World Health Organization (WHO) goals outlined below. However, such vaccines may also be useful in high income/low incidence countries to protect high-risk populations or groups.

The Roadmap integrates and aligns strategic planning and innovation from the current situation towards a shared vision with associated short-, medium- and long-term priorities for global TB vaccine development. The Roadmap covers the entire R&D chain with an emphasis on late stage development and implementation research.

Process of developing the Roadmap

This Roadmap is based on several rounds of consultation with experts and key stakeholders.

Interviews. Interviews were held with 22 stakeholders from science, public health authorities, national TB programmes, immunization programmes, civil society, funding agencies of research and programme implementation, NGO's involved in TB care and control or immunization, regulators and industry, to gather perspectives on the current TB vaccine clinical development pipeline; the development goals expressed in the WHO Preferred Product Characteristics for three types/indications of TB vaccines; and barriers to achieving these goals. The barriers addressed filling the clinical development pipeline for TB vaccines, moving TB vaccine candidates through clinical development; and ensuring uptake and public health benefit for TB vaccines, following market introduction.
Consent meeting. A meeting was held early March 2020 in Amsterdam, the Netherlands, bringing together 34 experts and stakeholders from this broad variety of groups, to discuss the outcomes of the interviews and define priorities and actions. These related R&D to diversify the pipeline, accelerate clinical development and ensure public health impact, as well as to conditions to enable TB vaccine R&D, introduction and uptake.
Roadmap drafting. The draft of the Roadmap was prepared based on the outcomes of the interviews and the consent meeting, and on comments on an earlier version elicited from all experts and stakeholders involved in the previous two steps.
Consultation. Two rounds of consultation were done: one by WHO Product Development for Vaccines Advisory Committee and EDCTP's Scientific Advisory Board, followed by a public consultation through the internet. Comments were reviewed and incorporated in the final version.

It should be noted that the definition of priorities and actions, as well as their desired timing, reflected the situation shortly before the COVID-19 pandemic became a global health threat. The consequences of this pandemic for health services and systems, for R&D and for funding for these activities were evolving as this Roadmap was drafted and could be taken into account only to limited extent.

Scope of the Roadmap

The Roadmap takes the current state of the art in TB vaccine R&D as the starting point and focuses on recommendations for actions in support of reaching the desired state as formulated in the three overall WHO goals in TB-vaccine development:

1. Develop a **safe, effective and affordable TB vaccine for adolescents and adults**. The vaccine should be protective in people with or without evidence of previous *Mycobacterium tuberculosis* (Mtb) infection. It should prevent progression to TB disease following primary infection, or following a second or subsequent infection and should prevent TB disease from re-activation of latent infections.[1]

2. Develop an **affordable TB vaccine for neonates and infants with improved safety and efficacy**. A new TB vaccine intended for administration in early life, should provide a superior degree and longer duration of protection than the current Bacillus Calmette–Guérin (BCG) vaccines. It should also be safe when administered to infants with HIV infection or other causes of immune suppression. Improved manufacturing securing sustainable supply would represent an additional improvement.

3. Develop **therapeutic vaccines to improve TB treatment outcomes**. Therapeutic TB vaccines should reduce the rate of recurrence following completion of a full course of drug therapy in patients with active TB, and should increase the proportion of patients cured, and/or shorten the necessary treatment duration and number of drugs needed to achieve a cure. The vaccine should be effective for TB caused by drug-sensitive and drug-resistant Mtb strains.[2]

Each of these overall goals involves end-to-end development of TB vaccines through delivery to the populations at risk, going beyond licensure.

The Roadmap actions in pursuit of these goals are clustered into three themes:
   I.   Diversifying the pipeline;
   II. Accelerating clinical development;
   III. Ensuring public health impact.

Within these three themes, five interdependent R&D Action Lines are identified (1-5), underpinned by three key enabling conditions a, b and c (see figure 1).

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[1] WHO Preferred Product Characteristics for New Tuberculosis Vaccines, Geneva 2018
[2] WHO Preferred Product Characteristics for Therapeutic Vaccines to Improve Tuberculosis Treatment Outcomes, Geneva 2020
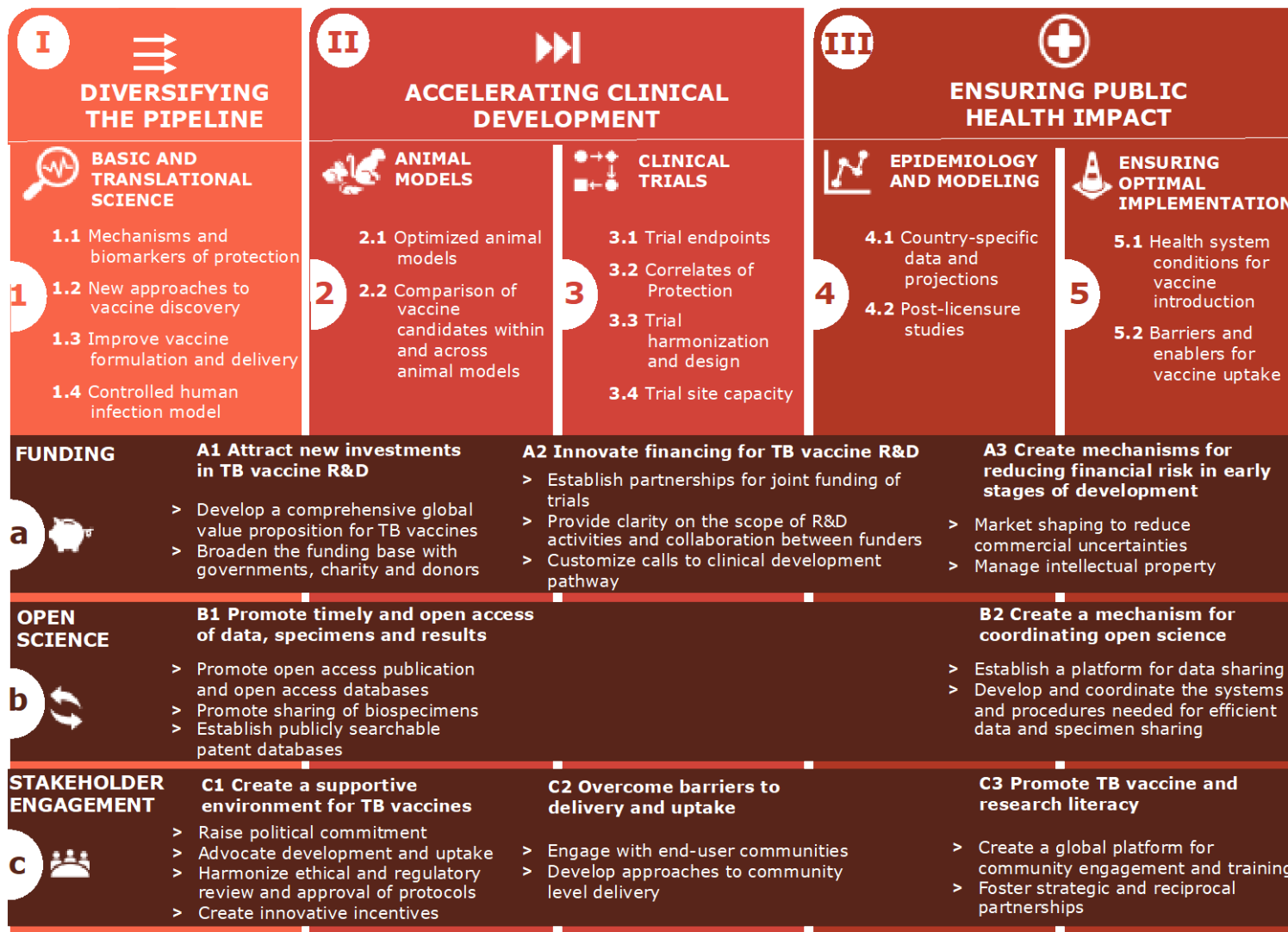
I — DIVERSIFYING THE PIPELINE

BASIC AND TRANSLATIONAL SCIENCE

1
- **1.1** Mechanisms and biomarkers of protection
- **1.2** New approaches to vaccine discovery
- **1.3** Improve vaccine formulation and delivery
- **1.4** Controlled human infection model

II — ACCELERATING CLINICAL DEVELOPMENT

ANIMAL MODELS

2
- **2.1** Optimized animal models
- **2.2** Comparison of vaccine candidates within and across animal models

CLINICAL TRIALS

3
- **3.1** Trial endpoints
- **3.2** Correlates of Protection
- **3.3** Trial harmonization and design
- **3.4** Trial site capacity

III — ENSURING PUBLIC HEALTH IMPACT

EPIDEMIOLOGY AND MODELING

4
- **4.1** Country-specific data and projections
- **4.2** Post-licensure studies

ENSURING OPTIMAL IMPLEMENTATION

5
- **5.1** Health system conditions for vaccine introduction
- **5.2** Barriers and enablers for vaccine uptake

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a — FUNDING

A1 Attract new investments in TB vaccine R&D
- Develop a comprehensive global value proposition for TB vaccines
- Broaden the funding base with governments, charity and donors

A2 Innovate financing for TB vaccine R&D
- Establish partnerships for joint funding of trials
- Provide clarity on the scope of R&D activities and collaboration between funders
- Customize calls to clinical development pathway

A3 Create mechanisms for reducing financial risk in early stages of development
- Market shaping to reduce commercial uncertainties
- Manage intellectual property

b — OPEN SCIENCE

B1 Promote timely and open access of data, specimens and results
- Promote open access publication and open access databases
- Promote sharing of biospecimens
- Establish publicly searchable patent databases

B2 Create a mechanism for coordinating open science
- Establish a platform for data sharing
- Develop and coordinate the systems and procedures needed for efficient data and specimen sharing

c — STAKEHOLDER ENGAGEMENT

C1 Create a supportive environment for TB vaccines
- Raise political commitment
- Advocate development and uptake
- Harmonize ethical and regulatory review and approval of protocols
- Create innovative incentives

C2 Overcome barriers to delivery and uptake
- Engage with end-user communities
- Develop approaches to community level delivery

C3 Promote TB vaccine and research literacy
- Create a global platform for community engagement and training
- Foster strategic and reciprocal partnerships

Figure 1: *TB roadmap with three main themes (I-III), five R&D action lines (1-5) and three key enabling conditions (a-c)*

The following paragraphs describe for each of the three themes the current state, as well as the challenges and needs to achieve the defined WHO goals. For each of the five R&D Action Lines the current knowledge gaps and the proposed actions to address these gaps are elaborated, with key actions and their priority indicated as short term (2 years), medium term (5 years) and long term (10+ years). These timelines relate to when the results should be achieved; work for many medium and long-term priorities can and often should start already in the short term. Supportive actions needed across all action lines are clustered in three key enabling conditions. The resulting global R&D roadmap for TB vaccine development is intended to guide integrated and strategic planning across all stakeholders.

The document ends with a brief section on commercialization and access, providing the framework for the various actions related to this topic listed in this Roadmap, and indicating where these can be found.

Background information on the WHO TB-vaccine development goals, the current clinical development pipeline and the state of the art is included in the online annex.[3]

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2. Roadmap action lines

Theme 1: Diversifying the pipeline

The TB vaccine pipeline currently shows relatively few candidates in preclinical and early clinical development. There is increasing consensus that the approach to vaccine development taken thus far is too narrow. Only a limited set of candidate TB antigens are currently considered which may have suboptimal activity in protection against TB. Emphasis is put on stimulating classical, CD4+ T-helper-1 (Th1) cells, which may be essential but will most likely not be sufficient to generate an optimal protective response, and on antigens that are known Mtb virulence factors. There is a need for diversifying the pipeline, in particular towards (i) exploring vaccine candidates that generate immunity beyond CD4+ Th1 T-cells, (ii) assessing new routes of vaccine administration, and (iii) antigen discovery.

Action Line 1: Basic and translational science
Objective: To further expand our knowledge of the human protective immune responses, identify biomarkers that correlate with protection and explore new approaches to TB vaccine discovery and vaccine delivery

The human immune responses that a vaccine needs to induce to be protective against Mtb infection, against sustained Mtb infection and/or against TB disease are poorly understood. Insights are lacking in mechanisms of protection and disease across all phases of the natural history of TB. More in-depth knowledge is required on the biology of infection and antigenicity of latent TB infection, incipient TB, subclinical TB[4] and clinically apparent TB disease. Drivers of transition in either direction along this spectrum, as well as the drivers of clearance[5] need to be identified, along with intervention points for manipulation of the host response to Mtb infection. These investigations should also aim to identify new biomarkers and biosignatures that improve our understanding of mechanisms of protection, and which can be used as laboratory correlates of vaccine-induced vaccine protection and to differentiate vaccine-induced response from Mtb infection.

While Th1 cell-mediated responses characterized by antigen-specific CD4+ T cells are critical for protective immunity in humans, they may not be sufficient to provide long-term protection against Mtb infection and/or TB disease. Other potential contributors to a protective immune response should be explored, including cellular responses as well as antibody responses. Moreover, insights are needed in innate immune responses in the early clearance of mycobacteria, and how protective innate responses can be stimulated by vaccination.

There is limited understanding of how the immune response is influenced by route of delivery, vaccine platform, antigen- or adjuvant-associated, non-specific effects of different vaccines[6], *M. tuberculosis* genotypic lineage and *M. bovis BCG* strain. Such modifiers should be further explored for improving

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[4] Incipient TB infection is an infection with viable *M. tuberculosis* bacteria that is likely to progress to active disease in the absence of further intervention but has not yet induced clinical symptoms, radiographic abnormalities, or microbiologic evidence consistent with active TB disease. Subclinical TB disease is disease due to viable *M. tuberculosis* bacteria that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays.

[5] The successful eradication of inhaled *M. tuberculosis* before an adaptive immune response develops. Clearance can be natural or vaccine-induced.

[6] (Partial) protection by TB vaccines against other pathogens, as studies have suggested for BCG.

vaccine-induced protective responses, also looking for potentially disruptive technologies from other disease fields.

Finally, we know little about human immune responses in the lungs and whether immune responses measured in blood are informative about those at the site of infection. This calls for expanding current approaches to experimenting in humans, such as designs for studying mucosal immune responses and evaluating the feasibility and utility of controlled human infection models (CHIMs) for Mtb. CHIMs would also be important for down-selecting (i.e. showing failure) of candidates, platforms or administration routes (see Theme 2).

Key actions and priorities

1.1 Mechanisms and biomarkers of protection	
Key actions	**Timing**
Conduct observational clinical studies combining pathogenesis and immunology, making use of systems biology, epidemiology and modelling: identify which components of the host-pathogen interaction are associated with clearance, progression to disease and subclinical disease; identify biomarkers and biosignatures of natural protection.	mid-term
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.*	mid-term
Identify biomarkers and biosignatures that correlate with vaccine-induced protection, based on data and biological samples from trials that have shown protection signals. This would include targeted approaches to detect cellular and/or humoral immune responses and unbiased approaches including transcriptional profiling of blood cells and mycobacterial growth inhibition assays.	short-term for the phase IIb trials that have shown protection signals; mid- to long-term to validate these biomarker candidates and/or identify additional candidates and validate them

1.2 New approaches to vaccine discovery	
Key actions	**Timing**
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.	mid-term
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.	mid-term
Deploy genome-wide strategies for antigen discovery: identify Mtb expressed proteins, peptides and non-protein antigens that can be recognized by the host immune system, applying IFN-γ as well as non-IFN-γ based screening approaches.	mid-term

1.3 Improve vaccine formulation and delivey	
Key actions	**Timing**

Study the effects on vaccination outcomes of adjuvants, vaccine platforms and lineage of the Mtb challenge strain, amongst others through experimental medicine studies.	mid-term
Explore new routes of vaccine administration, including aerosol and intravenous approaches, amongst others through experimental medicine studies.	mid-term
Study how vaccines can direct immune responses to the lungs, evaluating the capacity of different formulation and delivery platforms to induce mucosal immune responses.	mid-term

1.4	**Controlled human infection model**	
Key actions		**Timing**
Develop a controlled human infection model for immunobiology studies to inform basic knowledge gaps, as well as for proof-of-principle studies to inform down-selection of candidates, platforms and routes of administration. Controlled human infection models must ensure participant safety and adequate sensitivity; ethical issues will be critical to address.		long-term

Theme 2: Accelerating clinical development

Accelerating the clinical development of new TB vaccines requires bringing more candidates into the clinical pipeline, but also halting failing candidates in an early stage before they enter expensive, large-size trials. However, clinical development of TB vaccines is critically slowed down by (1) lack of relevant, validated preclinical models that predict protection from infection and disease in humans, and (2) lack of evidence to support decisions to either or not move a candidate forward through the clinical development pipeline. This limits effective stage gating, i.e. down-selection of candidates for clinical development. The lack of consensus on immunological correlates of protection (CoP), means that candidates have to be evaluated in expensive phase II and III trials of long duration with prevention of disease (PoD) as the clinical efficacy endpoint. Alternative efficacy endpoints that allow smaller-sized, less expensive trials are being used for proof-of-principle in phase IIb to move candidates forward to phase III, notably prevention of infection (PoI) and prevention of recurrence (PoR). In particular PoR trials can be done with much shorter duration than PoD trails. However, it is unknown to what extent PoI or PoR endpoints predict PoD, and whether success or failure of a PoI or PoR trial should be sufficient reason for (not) progressing a candidate to a phase III PoD trial. Accelerating and de-risking clinical development therefore requires better preclinical models as well as better (understanding of) alternative efficacy endpoints and correlates of protection.[7] Whilst animal models are important, results from animal models should not on their own inhibit progression to clinical research.

Overcoming these challenges requires consideration of interdependencies between the R&D steps that need to be taken. Both improving animal models (action line 2) and identifying correlates of protection (action line 3) require backtranslation of results from trials that showed an efficacy signal. This has become possible only recently with the successes of the phase IIb PoD trial of the M72/AS01$_E$ candidate and the phase IIb trial that showed efficacy for PoI of BCG re-vaccination. It implies an iterative process in which stepwise improvements lead to new efficacy signals which then lead to the development of better animal models and the discovery of better correlates. This must be considered in the timing and planning of R&D activities, including the collection and biobanking of samples within each vaccine trial and making these accessible for use by related studies (see Enabling Conditions).

Action Line 2: Animal models
Objective: To develop, optimize and use diverse "fit for purpose" animal models that predict/replicate aspects of findings in humans

Animal models are considered key for preclinical candidate screening for safety, immunogenicity and protection against a *M. tuberculosis* challenge.[8] However, there is currently no single, harmonized animal model that could be used for clear 'go/no-go' decisions for candidate TB vaccines. This poses major limitations for use of the current pre-clinical models for selecting candidates to progress to human trials as well as for the timelines before a biological signal is seen that can unlock funding for larger trials. Neither small animal nor non-human primate models have been validated as predictive for protective responses in humans. Moreover, it is unclear to what extent existing animal models

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[7] A systematic approach to selecting candidates for moving to the next stage in the pipeline is proposed by the TB Vaccine Development Pathway that defines an agreed set of stage gates. These stage gates specify the criteria for progression at each stage of TB vaccine development, from discovery through to licensure, and are updated by TBVI and Aeras/IAVI. The revised stage gate criteria make experiments in small animals an explicit part of TB vaccine candidate development (https://www.tbvacpathway.com/).

[8] Because of the critical role animal models play in vaccine development, animal models in this Roadmap are addressed under theme 2: Accelerating clinical development. Animal models are however also important for scientific discovery (theme 1: Diversify the pipeline), and the actions pertaining to animal models are relevant for those applications as well.

sufficiently reflect safety, immunogenicity and protection in specific human target populations, such as infants, elderly and immunocompromised individuals.

Protection in small animal models is not well defined, with no real functional readout for protective efficacy. Although recently much work has been done in this respect, a greater degree of harmonization and standardization of experimental methods is needed, including challenge strain selection, use of imaging, scoring gross pathology specimens and identifying priorities for future experimental directions.

The utility of animal models for preclinical candidate screening is not always clear. It is important to define what a particular animal model can deliver, distinguishing between immunogenicity models, challenge models and disease models. Different models are needed to reflect different stages in human infection; in particular there is need to develop models of resistance to infection/clearance.

A final challenge is that not all animal data, in particular negative results, are published and it is often not clear in which animal models a vaccine candidate has been tested.[9] Comparative head-to-head testing of vaccine candidates in the same animal models in separate, independent laboratories can help prioritize the most promising vaccine candidates for clinical development. Such head-to-head comparisons of current vaccine candidates are ongoing as part of the stage gating effort mentioned (in footnote 7) and should be applied more broadly.

Key actions and priorities

2.1 Optimized animal models	
Key actions	**Timing**
Develop *fit for purpose* animal models: 'back-translate' into immunogenicity, infection and disease animal models the results/findings from adolescent/adult and pediatric trials, ideally using the exact same product as in humans, and from clinical studies of disease progression and subclinical disease.	short-term (based on recent trials); mid-long term based on future human trials/studies
Develop animal models to provide insight into the relation between PoI for PoD: 'back-translate' results from trials with PoI and, ideally, both PoI and PoD endpoints, as well as from clinical studies of clearance and disease progression.	mid-term
Develop immune compromised animal models that can predict/replicate findings in specific human target populations: 'back-translate' into disease animal models the results that will emerge from trials and clinical studies including/among infants, elderly and immune compromised humans, e.g. people living with HIV/AIDS, diabetes, and iatrogenic immune suppression.	long-term
2.2 Comparison of vaccine candidates within and across animal models	
Key actions	**Timing**
Standardize and harmonize animal models, including harmonization and standardization of challenge strain selection; definition of protection outcomes, including the use of imaging and scoring gross pathology specimens. Identify priorities for future experimental directions, e.g. assessing aerosolized delivery of vaccines.	short-term
Perform head-to-head testing of candidate vaccines in independent laboratories using the standardized models that best predict protection in humans.	mid-term

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[9] An action to address this challenge is listed under Enabling Conditions, Open Science.
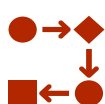
Action Line 3: Clinical trials
Objective: To define meaningful trial endpoints, improve the efficiency and standardization of TB vaccine trials and build trial capacity

The WHO Preferred Product Characteristics state clear objectives and conditions for new TB vaccines, including the need for efficacy trial data based on PoD endpoints. Knowledge gaps however remain that limit generalization of results from the trial target populations. Critical strategic questions include: (1) Does protective efficacy established among those latently infected ("post-exposure" or "post-infection" protection, i.e. among individuals with positive Interferon-gamma Release Assay [IGRA]) reflect protective efficacy among IGRA-negative individuals ("pre-exposure" or "pre-infection" protection)[10]? (2) To what extent can protective efficacy established among the general population be extrapolated to (sub)populations with increased risk of TB disease, such as people living with HIV, people living with type 2 diabetes, the elderly and people who use/smoke tobacco? (3) To what extent can protective efficacy established in a limited geographic area (e.g. sub-Saharan Africa) be extrapolated to other geographic areas (e.g. Asia, the Americas), e.g. related to different distribution of *M. tuberculosis* lineages?

Better PoD endpoints are needed for trial populations in which bacteriological confirmation of TB disease has low sensitivity, such as infants and children and people living with HIV. Better assays for extrapulmonary TB would allow use of this disease category as part of a composite endpoint. Better correlates of protection would potentially speed trials, but it is unlikely that a single CoP will suffice for use in trials as a basis for licensure. Rather, a set of correlates are needed that are reflective of vaccine-induced protection, vaccine failure and natural protection independent of vaccination. The search for CoP should however not hold back clinical development, but biospecimen collection needs to be planned and implemented in trials to help identify CoPs. As PoI is being to establish clinical proof-of-principle, the translation of this endpoint into PoD and its usefulness in the clinical development pathway need to be clarified. For PoI, the measure that might best correlate with PoD (e.g. IGRA conversion, sustained IGRA conversion) is unknown.

Comparisons across trials would be facilitated by standardization of clinical trial protocols with regard to definition of the clinical endpoints, definition of inclusion criteria and the required measurements over time. TB preventive treatment is standard of care for specific subpopulations and must be taken into account in the design and conduct of vaccine trials. Trial designs that increase the efficiency of PoD trials, such as trials in specific high-incidence populations and adaptive designs, need to be explored.
Standardization is also needed for exact definition of PoD endpoints, such as the number of positive and negative cultures required, and the role of molecular diagnostics.

Clinical trial sites for phase II/III trials need to be developed, considering the need for capturing heterogeneity in host and bacteriological genetic background. In addition to obtaining epidemiological data and building trial capacity this requires studying barriers to enrolment in TB vaccine trials and compliance with trial completion across sites being considered for TB vaccine trials.

Key actions and priorities

3.1 Trial endpoints	
Key actions	Timing

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[10] In most countries IGRA testing prior to vaccination will not be feasible or cost-effective. It is unclear how protective efficacy shown against disease in latently infected individuals would translate into public health impact and cost-effectiveness when the vaccine is given in the population at large, i.e. irrespective of IGRA testing.

Define and develop standardized PoD trial endpoints that better capture the various TB disease states in diverse target populations: standardize definition of laboratory-confirmed pulmonary TB; develop clinical endpoints representative of subclinical TB; improve bacteriological confirmation of TB disease in neonates and infants and PLH; improve bacteriological confirmation of extrapulmonary disease. Based on these, a set of efficacy endpoints should be defined through analyses of clinical trial experiences and clinical trial modelling.	mid-term
Define and develop better PoI trial endpoints: define an endpoint for Mtb infection for establishing PoI; this endpoint should differentiate Mtb infection from vaccine-induced immune response.	mid-term
Quantify the clinical translation of PoI into PoD: analyze existing and new observational data; include secondary PoI endpoints in phase III PoD trials; taking into account that this quantification may be different for different types of vaccines.	short-term for the phase IIb trials that have shown protection signals; mid- to long-term as new trial data emerge

3.2	**Correlates of Protection**	
Key actions		**Timing**
Collect biospecimens for identifying CoPs in planned and ongoing phase IIb and phase III trials.		short- to midterm
Identify CoPs for TB disease from phase IIa and phase III trials that have shown protection: analyze data and putative CoP values from individual trials and, if possible, from meta-analyses of several trials.		short- to midterm
Validate CoPs for TB disease: validate putative CoP identified by backtranslation of trial results (see Action line 1) in terms of vaccine-induced response and clinical protection in immunogenicity studies, new trials with a clinical PoD endpoint and, if feasible, controlled human infection models.		mid- to long-term

3.3	**Trial harmonization and design**	
Key actions		**Timing**
Harmonize clinical trial protocols: define an agnostic trial "shell" of standardized outcomes, inclusion criteria and measurements for clinical trials for different vaccine types. This would also address secondary endpoints; inclusion criteria for people living with HIV infection or diabetes; and standardized measurements over time. Such harmonized protocols should take into account the need for preventive treatment of children, people living with HIV and potentially other adults enrolled in PoD trials.[11]		mid-term
Develop new models for TB vaccine trials with increased efficiency: efficacy trials within contact investigations, active case finding programs and high-risk populations (e.g. miners, prisoners if ethical issues can be resolved); epidemiological and demonstration studies in such settings and populations to establish their feasibility and external validity; adaptive trial designs for evaluating safety, immunogenicity and efficacy of different vaccine types.		mid-term

3.4	**Trial site capacity**	
Key actions		**Timing**
Make inventory of clinical trial site capacity: identify potential sites well beyond the existing ones; assess quality and suitability in terms of existing technical and laboratory infrastructure.		short-term, before phase III trials start

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[11] Note the importance of making enrolment as inclusive as possible so that the social value and benefits of new TB technologies can accrue to diverse groups and those most at risk of TB, such as children, adolescents, pregnant women, people living with HIV, and people who smoke/use tobacco.

Collect epidemiological data in sites considered for phase II/III trials in various parts of the world, as a continuous process: age-stratified data on TB incidence; age-stratified data on prevalence of latent TB infection; *M. tuberculosis* lineage distribution. In sites considered for PoI or PoR trials: age-specific incidence of Mtb infection and of the incidence of recurrent TB and reinfection.	short-term, before phase III trials start
Develop vaccine trial sites: develop infrastructure and human capacity. Capacity does not need to be TB specific[12] but should be sustainable through trials on an ongoing basis so that key staff can be retained, and skills and infrastructure maintained.	short-term, before phase III trials start
Study potential barriers to trial acceptance: social science research of barriers to participating in TB vaccine trials and completing follow-up, including TB-associated stigma, other stigma, and social barriers; compile best practices from successful vaccine trial sites.	Short-term, before phase III trials start
Promote community engagement in TB vaccine trials to support ethical, efficient conduct of clinical trials and collaborative partnerships between trial sites and communities, in line with Good Participatory Practice guidelines.[13] Community engagement should be part of any phase II or phase III study, and sponsors and developers should start developing plans for community engagement when products enter phase I.	Short-term: plans for community engagement should be developed when products enter phase I

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[12] This is important because many sites will not be sustainable for tuberculosis vaccine trials alone and they should have the capacity to evaluate other preventive interventions, including vaccines against other diseases when not being used for TB vaccine trials.

[13] Good Participatory Practice Principles for TB Vaccines Trials (https://www.avac.org/resource/good-participatory-practice-guidelines-tb-vaccine-research-2017).

Theme 3: Ensuring public health impact

New TB vaccines, including for adolescents and adults, will need to be delivered programmatically. In order to achieve public health impact, it is critical to understand the drivers of countries' policy decisions and to provide information and evidence to support those decisions. These drivers include the likely demand for a new TB vaccine and associated considerations when added to national immunization programmes. These considerations may relate to the country's TB burden, its national political priority and expected impact on that burden; relative effectiveness of alternative strategies; safety, efficacy, and equity impact of the vaccine (in the general population as well as specific subgroups such as people living with HIV/Aids and the elderly); availability of vaccine supply; the vaccine's cost, affordability, and cost-effectiveness; and the capacity of the health system to successfully introduce and sustainably deliver the vaccine as part of an integrated disease control programme. In addition, these considerations involve broader economic benefits around childhood development, changes in household behavior and macro-economic indicators. Collectively these considerations make up the vaccine's value proposition.

Evidence is also needed on how to integrate vaccine implementation with ongoing TB prevention efforts (e.g. TB preventive therapy) and how to use the vaccine among vulnerable groups such as people living with HIV, people livening with type 2 diabetes, children, elderly and contacts of (drug-resistant) TB patients, as well as people in high-transmission settings such as slums and prisons. This is particularly important for a vaccine for adults and adolescents that would not fit in standard childhood immunization programmes and few, if any, other vaccines are routinely administered to persons in these age groups. Specific needs for evidence here include the optimal way of delivering the vaccine (e.g. national campaigns; age groups to target), vaccine attributes (e.g. number of doses required, cold-chain requirements and need for re-vaccination), equitable access (including whether pre-vaccination diagnostic testing is required) and vaccine acceptance.

Locally gathered evidence about these trade-offs will help countries prepare for introduction and scale-up of a new TB vaccine and make better informed decisions about target groups for vaccination, as well as enable donors to plan investments (enabling condition A). It is also important for estimating the national and global demand to stimulate manufacturers to enter into the market and prepare and scale-up vaccine production. Market size for a vaccine will be dependent on its product profile (e.g. a vaccine that is only effective post-exposure will not have as big a market as a vaccine that is effective both pre- and post-exposure), but also on country decisions. Decision making in this regard is faced with inter-dependencies, such as between price per vaccine dose and market volume; between market volume and global policy/country decisions on target groups; and between target groups and expected impact, willingness to pay, and cost of implementation. The process by which this information gap should be closed needs to be iterative and be considered in planning of data collection on country preferences (action line 5), implementation requirements and epidemiological metrics, and modelling of public health impact and cost-effectiveness (action line 4). This may be further refined as data on vaccine efficacy, safety and impact that are collected post-introduction become available.

Action Line 4: Epidemiology & modelling
Objective: To quantify key epidemiological and health economic metrics to support vaccine introduction, and evaluate vaccine effectiveness and impact post-licensure

Key to the choices to be made with regard to vaccine introduction is an understanding of the trade-offs and the willingness to pay of countries and donors to achieve vaccine-related health impacts, given particular vaccine characteristics (e.g. effectiveness, expected duration of protection, dose regimen, cost-effectiveness).[14] The priority should consider timelines and information needs of country decision makers and funding agencies, such as Gavi (e.g. the 5-year Vaccine Investment Strategy).

Collecting country data on the burden of TB disease and Mtb infection, and on the drivers of the TB epidemic, is important to define the size of target population(s), understand the optimum vaccine use case, and estimate potential market volumes[15]. Optimal vaccination strategies need to be identified through modelling the health- and economic impact including various strategies for delivery taking into account number of doses required, route of administration, duration of protection as well as risk group-targeted vaccination strategies. Health technology and economic assessments of new TB vaccines should consider a life-course perspective to vaccination, and equitable access and use[16]. Country data on Mtb lineage diversity would be needed for a vaccine that potentially displays lineage-specific variation in protective efficacy as a baseline for post-licensure surveillance.

Beyond post-marketing surveillance, data from post-licensure studies is an important source of information for establishing vaccine effectiveness and safety in subgroups and geographically diverse populations, as well as its impact on TB incidence and transmission. Collection of such data requires developing valid approaches for real-life studies of implementation of new TB vaccines and strengthening surveillance systems with regard to TB disease notification, shifts in Mtb lineage distribution and pharmacovigilance, among others. Post-licensure studies should also evaluate endpoints for non-specific effects[17] of new TB vaccines in infants and neonates in comparison to BCG, such as all-cause mortality.

Key actions and priorities

4.1	Country-specific data and projections[18]	
Key actions		**Timing**
Conduct in-depth country-specific value proposition analyses: assess value drivers for new TB vaccines among decision makers responsible for delivery of vaccines and budgets across different countries and stakeholders. Such in-depth value proposition analyses should take into account preferred delivery strategies; value drivers such as efficacy relative to better safety, process manufacturing, strain standardization, and price; willingness to pay for a vaccine with certain characteristics; and minimum price of TB vaccines and their cost of delivery.		Short-term, well before licensure of a new vaccine

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[14] Principles and considerations for adding a vaccine to a national immunization programme. From decision to implementation and monitoring. World Health Organization. Geneva, 2014.

[15] Refining this information for subgroups will be important, along with estimating their contribution to *M. tuberculosis* transmission, as this will allow identifying vaccination strategies that have most impact on TB incidence and/or are most cost-effective.

[16] Immunization Agenda 2030 (https://www.who.int/immunization/immunization_agenda_2030/en/).

[17] Several observational studies have suggested that BCG vaccination offers heterologous protection against infections by other micro-organisms.

[18] For larger countries; beyond those it may be sufficient to study a limited number of countries in a region that represent different contexts.

Collect epidemiological data at country and subnational level to inform economic and impact modelling related to country decisions on introduction of new TB vaccines and market volumes: include estimates of national and subnational TB disease and infection prevalence including people living with HIV and elderly; define the contribution of TB high risk groups to transmission to identify potential target groups for vaccination; map *M. tuberculosis* genotypic variation based on a representative sample of strains from TB patients starting treatment.	Short-term, well before licensure of a new vaccine
Modelling to define vaccine development investment cases and potential country-specific vaccine use cases: modelling of implementation scenarios, epidemiological impact, cost-effectiveness and budget impact in consultation with countries to define the optimum target groups and delivery pathways (e.g. routine vaccination, mass campaigns), for vaccines that are close to market introduction, using transmission and economic modelling as well as other quantitative approaches.	Short-term, well before licensure of a new vaccine

4.2	**Post-licensure studies**	
Key actions		**Timing**
Develop valid approaches for real-life vaccine scale-up studies: develop suitable designs and validated tools to assess and use real world data in rigorous ways as post licensure studies to establish real-world effectiveness, safety and public health impact; establish and/or support post-licensure registries making use of existing expertise from earlier introduction of other novel vaccines.		mid-term, before licensure of a new vaccine
Conduct post-licensure evaluations of vaccine effectiveness, impact and safety: real-world post-licensure studies and surveillance to demonstrate benefit for post-licensure indication expansions and use of the vaccine as an affordable public health tool, making use of existing expertise from introduction of other novel vaccines outside childhood immunization programmes. Establish effectiveness across different subpopulations including people living with HIV or diabetes, children and elderly, people who use/smoke tobacco; effectiveness against different *M. tuberculosis* lineages; effectiveness and safety in interaction with other vaccines given concurrently; safety in various sub-populations (e.g. pregnancy); impact on TB disease incidence; non-specific health effects for vaccines replacing BCG.		long-term, once a new vaccine is being introduced

Action Line 5: Research to ensure optimal implementation
Objective: To understand implementation requirements for new TB vaccines

The WHO Preferred Product Characteristics for TB vaccines have defined preferences with regard to TB vaccine attributes at a global level. However, the feasibility, acceptability and implementation requirements of strategies to deliver TB vaccines to adolescents and adults are largely unknown and require urgent study. Such strategies must be aligned to the needs of policy makers, affected populations, donors and implementers in various countries and settings.

The experience with (in particular) Human Papilloma Virus (HPV) vaccination of adolescents and seasonal influenza vaccination of elderly is a useful starting point, but the specific requirements for TB vaccines (e.g. possible need for repeated campaigns) need to be considered. Accessibility, equity and opportunity costs will be important, taking into account both technological (e.g. thermostability, cold chain requirements, multidose schedules) and social aspects (vaccine acceptability in different groups, access in vulnerable/high risk populations, gender considerations; can the vaccine be safely

and effectively used in people with comorbidities or other vulnerabilities such as HIV infection, diabetes, malnutrition, multidrug resistant TB).

Ways to enhance acceptability of a TB vaccine by adolescents and adults is also important to assess. Vaccine hesitancy may be a key bottleneck to introducing new TB vaccines. There is risk of poor acceptance by users and communities and trust in a vaccine might be undermined if the vaccine only offers limited protection or has adverse effects. In low-incidence countries, this may be true even for a vaccine that would confer very high levels of protection, since the balance of potential health gain due to a reduction in disease and health loss due to adverse effects will be different from that in high-incidence countries. There is also a need to understand the potential role of TB-associated stigma in undermining acceptance and uptake of a new TB vaccine, and of ways to address TB-associated stigma in relation to vaccination.

Key actions and priorities

5.1	**Health system conditions for vaccine introduction**	
Key actions		**Timing**
Define the generic public health system requirements to deliver a new TB vaccine. For a vaccine for adolescents and adults: determine in different countries the feasibility of various strategies including special vaccination campaigns tailored to country context; the conditions for immunization programs to implement these strategies; the requirements for optimizing access for different population groups; the integration of TB vaccination into the health system within and beyond national TB programmes); and approaches to measuring vaccine uptake in adolescents/adults. For a vaccine for neonates and infants: determine the fit in the Expanded Programme on Immunization and required timing with regard to other vaccinations.		short- to mid-term, taking account of Gavi's 5-year Vaccine Investment Strategy
Conduct pre-introduction assessments of country immunization programmes: assess the country-specific readiness of immunization programmes and health systems to handle, store and administer the new TB vaccine, considering its number of doses and schedule, storage space and cold-chain requirements and other specific characteristics, in particular for delivery to adolescents and adults, potentially making use of data and experience (from recent vaccine introductions. This also includes monitoring of vaccine coverage and adverse events, and communication approaches of adverse events.		mid-term, before licensure of a new vaccine
5.2	**Barriers and enablers of vaccine uptake**	
Key actions		**Timing**
Assess drivers of acceptability and uptake of new TB vaccines in various settings: social and behavioral research to determine across countries and settings (to capture social and cultural variability) national decision makers' and public and health workers' perceptions around new vaccines, related to amongst others dosing, safety/reactogenicity concerns, religious concerns, gender, use with other vaccines versus specialized programmes, and for immunotherapeutic vaccines, integration with TB treatment.		mid-term, before licensure of a new vaccine

3. Key Enabling conditions

We distinguish three enabling conditions for diversifying the TB vaccine pipeline, accelerating clinical development and ensuring public health impact of new TB vaccines: increased funding, open science and stakeholder engagement/multisectoral collaboration. Considering the high resource needs and limited investments, inadequate investment is the most important bottleneck for TB vaccine R&D across discovery, preclinical research and clinical development. There is a need for improving the success and efficiency of TB vaccine R&D through sharing of results, datasets and specimens. Stakeholder engagement is needed to accelerate clinical development of new vaccines, and to enhance delivery and uptake of new vaccines once they have been licensed. For each of the enabling conditions the main challenges are described as well as the key actions to overcome them which will be essential to successfully implement all action lines.

Enabling condition A: Funding

TB control and elimination receive relatively limited funding, and TB vaccine research is a critically underfunded part of TB R&D. A healthy R&D pipeline requires more funding for basic and clinical research, and to attract more talented scientists to the field. Promising vaccine candidates should move more quickly through the clinical development phases and be tested earlier in PoD trials for which very limited funding is currently available.

Funding for TB vaccine R&D comes from just a few sources, mostly public and philanthropic. Industry investments are very limited. While the potential market size for TB vaccines is large, the ability to pay for them is limited as the market is concentrated in low- and middle-income countries. As a consequence, there is a lack of financial models supportive of industry engagement in TB vaccine R&D.

Coordination between funders in the TB vaccine space through the Global TB Vaccine Partnership (GTBVP) has led to the TB Vaccine Development Pathway, amongst others.[19] Stronger and more visible coordination would be beneficial, in particular to support phase III trials that are large, of long duration and expensive and are difficult for a single funder to support. Funding should also be more sustainable.

Funding is usually awarded on a project-by-project basis, with fixed deliverables, timelines, budgets and applicant consortia. Once project deliverables have been met and the project has come to an end, renewal of funding for the next stages of the R&D phases for promising products is highly uncertain. This uncertainty either stems from the absence of additional new calls for proposals that allow a smooth transitioning from one stage to the next in de development path of a vaccine, or, if such calls are open, the uncertainty of having to compete again for renewal of funding. This uncertainty hampers necessary long-term investments and commitments to be made by R&D actors. In addition, especially for basic and preclinical research, longer-term funding is important to incentivize researchers to enter and continue in this field. Finally, the TB community needs a better understanding of the existing coordination mechanisms to understand how to best make use of them.

Key actions

a.1	**Attract new investments in TB vaccine R&D**
Key actions	

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[19] https://www.tbvacpathway.com/

Develop a comprehensive global value proposition for TB vaccines that encompasses vaccine characteristics, use case, societal value, business case, investment case, and health and micro/macro-economic impact assessment, including from a life-course vaccination perspective. Include potential indirect effects, such as protection against leprosy.

Broaden the funding base with governments, charity and donors: mobilize domestic R&D funding from large countries' governments; get specific donors involved that could contribute to funding downstream aspects of TB vaccine R&D; engage with the HIV and antimicrobial resistance communities. In addition to the comprehensive value proposition, discrete well-defined projects on the development pathway could be listed for funders to support.

Attract new entrants: R&D on TB vaccines could benefit from the contributions from actors outside of the direct field of TB vaccine research. Novel and alternative ideas, and leveraging lessons learned, technologies, models and knowledge from other research actors than those that have traditionally been working on TB vaccines could complement, accelerate and strengthen the search for novel vaccine strategies and supporting research. Funders should promote the involvement of new entrants in their funding programmes (e.g. in evaluations or even eligibility criteria).

a.2	**Innovate financing for TB vaccine R&D**

Key actions

Establish collaborations or partnerships for joint funding of trials e.g. through "roadmap funding" where countries, research funders, industry, other donors and individuals can donate, allocate or pool funding that will be used to create incentives required to reduce the lag time in bringing promising vaccines to the market at affordable price. This requires independent and transparent decision-making and selection procedures that are both product and country agnostic, with clear goals, principles and timelines set, and strict norms for what the funding will be used for and under which conditions. Funders should provide information on who is funding what in the TB vaccine R&D space; share information on the proposals that are submitted, e.g. with regard to finding correlates of protection and clinical endpoints. These collaborations/ partnerships for joint funding may also include vaccine launch and implementation, i.e. end-to-end.

Customize calls to clinical development pathway: Calls for proposals should be made more flexible, with regards to developing long term funding (e.g. ten years, with intermediate go/no-go's) allowing consortia to adopt a long-term perspective and – if performing as planned – having the security of funding for next stages of R&D.

a.3	**Create mechanisms that attract investment in early stages of development**

Key actions

Market shaping to reduce commercial uncertainty: incentivize stronger engagement from industry, biotech firms and other developers, such as through grant funding, regulatory incentives[20] and advance market commitments[21]. This requires defining a clear path to commercialization, including commercial partners to take up production of a successful candidate; demonstrating the market; and showing the potential of global financing mechanisms such as PEPFAR, the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM), Gavi and Unitaid that act as a "pull" mechanism to incentivize innovation by guaranteeing innovators a final market for their product.

Manage intellectual property, ensuring that intellectual property can be used efficiently, openly, and equitably to facilitate TB vaccine R&D in ways that promote collaboration among universities, biotech companies, pharmaceutical companies, and government funders. Initiatives (such as the World Intellectual Property Organization's) and patent licensing mechanisms (the Medicines Patent Pool) can complement TB vaccine R&D efforts by facilitating partnerships and the licensing of intellectual property among organizations.

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[20] Regulatory incentives should be consistent with other objectives in the Roadmap related to open science and equitable access.

[21] Mechanisms need to be in place to ensure that advanced market commitments achieve acceleration of R&D, competition among manufacturers, affordable pricing, adequate supply capacity and technology transfer to developing-country manufacturers.

Enabling condition B: Open science

Currently results of pre-clinical and clinical studies are often made public late or not at all. This relates in particular to negative results, most notably of animal studies, hampering progress in our understanding of the potential of various vaccine approaches. Datasets from pre-clinical and clinical studies are often not shared, slowing down progress and leading to duplication of often expensive data collection efforts. Specimen sharing from clinical trials and related studies is becoming highly important now that trials have shown protection signals allowing the identification of CoP. These scarce specimens should be used efficiently; access is important also for investigators and groups that have innovative ideas and approaches but are not well known in the TB R&D field.

The field should learn and benefit from the recent experience with COVID-19. Even though commercial incentives for TB vaccine R&D may be less than for COVID-19, data-sharing mechanisms and platforms created for drug and vaccine R&D for COVID-19 should be leveraged for TB vaccine R&D where possible.

Finally, efforts to improve open science and access require coordination and harmonization. Existing mechanisms such as the EU funded TBVAC2020 consortium and the Bill & Melinda Gates Foundation funded Collaboration for TB Vaccine Discovery (CTVD) have made important progress in this regard, but further collaboration and harmonization across funders would be needed. The efforts towards open science should accelerate the delivery of TB vaccines without creating new barriers.

In general, a norm and expectation should be established for transparency, particularly for data originating from research supported through public funding.

Key actions

b.1	Promote timely and open access of data, specimens and results
Key actions	
Promote open access publication and open access databases for pre-clinical, clinical and epidemiological studies: funders and product development partnerships should require registration of all animal and human studies, open access publication of both positive and negative results, data-sharing and posting in open access databases as condition for funding and/or consortium membership. Related costs should be eligible for funding. Trial registration database(s) should require that clinical trial results are uploaded by trial- and vaccine sponsors in a timely manner.	
Promote sharing of biospecimens collected in clinical studies: biospecimens collected in clinical studies should be made available on the basis of peer review, overseen by a bio specimen access committee. Access to biospecimens should not be granted on first-come first-serve basis but also allow actors/fields outside of the 'traditional circle' to come up with innovative ideas and approaches.	
Establish publicly searchable patent databases for TB vaccine research to promote the diffusion of knowledge by facilitating access to the information disclosed in a patent. Similar searchable patent databases exist for drugs[22]. A vaccine patent database should include patent information broadly defined i.e., inclusive of antigens, adjuvants, platforms, and processes.	
b.2	Create a mechanism for coordinating open science in TB D
Key actions	
Establish a platform for data sharing focused on TB-specific datasets starting with vaccine clinical data. Develop generic protocols for data sharing, e.g. data shared must be accompanied by contextual data (e.g. for what purpose was the data collected); proper use should be	

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[22] Medicines Patents and Licenses Database (https://www.medspal.org)

safeguarded (e.g. ethical rules, privacy regulations); and original collectors/contributors of the data in secondary use and publication acknowledged. Experiences for TB drug development could be used as a basis.[23]

Develop and coordinate the systems and procedures needed for efficient data and specimen sharing across the field of TB research and across TB research funders. The Global TB Vaccine Partnership, a mechanism for coordination of TB vaccine R&D funding, could take on this activity drawing on best practices and lessons learned from other fields such as vaccine development for AIDS[24] and emerging infectious diseases research response efforts[25].

Enabling condition C: Stakeholder engagement/intersectoral collaboration

The slow clinical development of new TB vaccines is currently also due to engagement from only a limited number of vaccine developers as a convincing business case is lacking. Complex and lengthy regulatory approval procedures slow down the initiation and conduct of clinical trials.

Despite recent high-level political commitment for TB vaccines, including the WHO's End TB Strategy and a United Nations resolution on TB,[26] political commitment at country level is still low. Advocacy campaigns are needed to prepare policy makers, implementers and the public for a TB vaccine, especially one that has to be given to adolescents and adults, and to successfully implement vaccinations at large scale.

Delivery and uptake of vaccines need to be prepared, considering country context and country-specific epidemiological profiles. Decision making for vaccine implementation tends to be slow, amongst others due to lack of clear country preferences and preparedness for TB vaccine introduction. Price and cost often pose a barrier to a positive discussion around new vaccine introduction and, in several countries, advisory mechanisms such as National Immunization Technical Advisory Groups (NITAGs) are non-existent. Gaps between policy and implementation, including poor access, are bound to arise and need to be pre-empted. Stigma, vaccine hesitancy and poor adherence to vaccination policies need to be addressed and overcome.

Stronger stakeholder engagement requires focused advocacy, encompassing the whole range from high level engagement at head of state level down to true grassroot community engagement. This requires TB vaccine and research literacy of advocates at these various levels.

Community engagement is essential. It is not only important for introduction and scale-up of new TB vaccines, but an (ethical) imperative in TB vaccine R&D communities have a role to play in each stage of R&D and as more than just clinical trial participants.[27] Meaningful community engagement should be a mandatory aspect of the clinical development of new TB vaccines.

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[23] https://www.tballiance.org/rd/innovations/critical-path-tb-drug-regimens-cptr

[24] The Collaboration for AIDS Vaccine Discovery fosters sharing of data, methods, reagents, and specimens in a collegial network of research consortia and central service facilities, using standardized tools and common preclinical and clinical platforms that permit the evaluation and sharing of results, while preserving the independent research crucial to innovation.

[25] The COVID-19 response efforts include sharing of data, positive samples, bioassays and study protocols within days and make publications available on preprint servers.

[26] https://www.un.org/pga/73/event/fight-to-end-tuberculosis/

[27] Good Participatory Practice Guidelines Principles for TB Vaccines Research (https://www.avac.org/resource/good-participatory-practice-guidelines-tb-vaccine-research-2017).

c.1	<u>**Create a supportive environment for TB vaccines**</u>

Key actions

Raise political commitment for new TB vaccines, to ensure new political commitment at country level and continue high level commitments making sure that existing commitments and defined targets are met. TB advocates need to provide clear communication about the need, efficacy and safety for new TB vaccines towards policy makers, including the risk-benefit analysis of a new TB vaccine. They also need to organize political advocacy and high-level engagement at country level to address price and cost of a new TB vaccine.

Advocate for development and uptake of new TB vaccines with vaccine developers as well as with the public through positive messaging about opportunities and actions in vaccine development.

Harmonize regulatory review and local approval of vaccine trial protocols based on the example of the African Vaccine Regulatory Forum (AVAREF).[28] Establish National Immunization Technical Advisory Groups (NITAG) in countries that do not have them and strengthen their capacity.

Create innovative incentives: forecast demands from countries; engage multilateral funders, including Gavi, GFATM, Unitaid and the Coalition for Epidemic Preparedness Innovations (CEPI) in offering novel financing mechanisms.

c.2	<u>**Overcome barriers to delivery and uptake**</u>

Key actions

Engage with end-user communities to address stigma, vaccine hesitancy and adherence. Provide a convincing rationale for (high-risk) target groups to be vaccinated and optimized communication of this rationale through various channels. Get end-user communities involved from the start in the research process. Build resilient information systems to counter vaccine related misinformation and disinformation.

Develop approaches to community level delivery (e.g. through community health workers) to address gaps in access to vaccination. Educate healthcare networks, the medical community and the general public about TB vaccine introduction through targeted, country-specific approaches.

c.3	<u>**Promote TB vaccine and research literacy**</u>

Key actions

Create a global program for community engagement and training for new TB vaccines (such as already exists for TB drugs). Develop mechanisms for engaging community representatives in TB vaccine development including through defining a role for community members in setting the research agenda, reviewing clinical trials protocols, consulting on trial procedures and conduct, and informing results dissemination. Engage and educate community representatives who can really speak to and meet with policy makers, including parliamentarians and legislators, to invest in the development and introduction of new vaccines. Provide funding to TB vaccine trial sites to support community advisory boards and other local community engagement activities as part of overall funding for clinical trials.

Foster strategic and reciprocal partnerships between vaccine scientists/sponsors and representatives of civil society and TB affected communities to support the involvement of all parties in advocacy for new TB vaccines.

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[28] https://www.afro.who.int/health-topics/immunization/avaref

4. Access and commercialization

Throughout the roadmap various actions are listed related to **commercialization of vaccine development and manufacturing and access to new TB vaccines when licensed**.
This section provides the framework and lists the current market-related constraints, the options for dealing with these constraints and the specific Roadmap action relating to that option.

Given the extreme global disparity in TB incidence, the bulk of the need for TB vaccines is in low- and middle-income countries. This is particularly true for TB vaccines for adolescents and adults, and for vaccines to replace BCG in neonates and infants. There may be a market in high-income countries for immunotherapeutic TB vaccines, although this will necessarily be limited in size due to the relatively low numbers of TB patients requiring treatment. New TB vaccines need to be affordable for low- and middle-income countries. These markets are neither sufficiently big nor sufficiently predictable to offer attractive return on investment. This offers little incentive for industry, mainly concentrated in high-income countries, to engage in expensive product R&D and poses major constraints to TB vaccine development.

Experience with other vaccines provides four solutions dealing with these constraints:
- Tiered pricing: differential prices for high-income vs low- and middle-income countries. Given the expected small size of the high-income market this is not a viable option for new TB vaccines.
- Push mechanisms: stimulate TB vaccine R&D by public-sector funding and coordination.
- Pull mechanisms: incentivize industry to engage in TB vaccine R&D through advanced market commitments and regulatory incentives.
- Technology transfer: enable manufacturers, especially in low- and middle-income countries, to produce licensed vaccines.

This Roadmap envisages a combination of push mechanisms, pull mechanisms and technology transfer to enhance TB vaccine R&D and access to new TB vaccines once licensed.

Push mechanisms
There are several models for push mechanisms for vaccine R&D. These include funding mechanisms (e.g. research grants, R&D prices and vaccine bonds), and coordination mechanisms to increase the effectiveness of R&D investments (e.g. product development partnerships and (pooled) roadmap funding). Push mechanisms can in particular boost discovery, preclinical and early-stage clinical development, but potentially also late-stage clinical development.
Key actions in this Roadmap related to push mechanisms are listed under:
- Enabling Condition A, Funding: a1. Attract new investments in TB vaccine R&D (Broaden the funding base with governments, charity and donors; Attract new entrants).
- Enabling Condition A, Funding: a2. Innovate financing for TB vaccine R&D (Establish collaborations or partnerships for joint funding of trials; Customize calls to clinical development pathway).

Pull mechanisms
Pull mechanisms include advance market commitments, by which donors guarantee to purchase a vaccine once licensed at a pre-agreed price and volume. Advance market commitments do not provide financial support for R&D as such, leaving the commercial risk with the manufacturer. However, they provide an incentive to industry by extending the range of profitable markets in which they can operate. A successful example has been Pneumococcal Advance Market Commitment launched by Gavi, the World Bank and donors in 2009. In 2020, COVAX, one of three pillars of the Access to COVID-19 Tools Accelerator, was initiated bringing together governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy, with the aim of providing innovative and equitable access to COVID-19 vaccines.
Additional pull mechanisms are regulatory incentives, such as priority review vouchers.
Key actions in this Roadmap related to pull mechanisms are listed under:

- Action Line 4: Epidemiology & modelling: 4.1. Country-specific data and projections (Conduct in-depth country-specific value proposition analyses; Modelling to define vaccine development investment cases and potential country-specific vaccine use cases).
- Enabling Condition A, Funding: a3. Create mechanisms that attract investment in early stages of development (Market shaping to reduce commercial uncertainty).
- Enabling condition C: Stakeholder engagement/intersectoral collaboration: c.1. Create a supportive environment for TB vaccines (Advocate for development and uptake; Create innovative incentives).

Technology transfer

Technology transfer relates to transferring the know-how for manufacturing of a specific vaccine. It is meant to enable manufacturers in low- and middle-income countries to produce licensed vaccines in accordance with regulatory and Good Manufacturing Practice requirements, thereby increasing access to good-quality products in low- and middle-income countries. As cost of production are generally lower than in high-income countries the prices of vaccines will reduce for countries and public health programmes. Technology transfer to multiple manufacturers may also reduce prices through market competition. Technology transfer may range from one-off transfer of the production scale process, including all associated technologies, to full local production. Most technology transfer for vaccines have come from non-profit organizations and institutes. Intellectual property arrangements need to be made. An example is the Medicines Patent Pool, a mechanism for the public health management of intellectual property through public-private partnerships set up for drug treatment of poverty diseases. Since a vaccine made in a new facility is treated as a new vaccine and has to undergo rigorous pre-clinical and clinical studies to be approved for use, regulatory harmonization is important as well.

Key actions in this Roadmap related to pull mechanisms are listed under:
- Enabling Condition A, Funding: a3. Create mechanisms that attract investment in early stages of development (Market shaping to reduce commercial uncertainty; Manage intellectual property).
- Enabling condition C: Stakeholder engagement/intersectoral collaboration: c.1. Create a supportive environment for TB vaccines (Advocate for development and uptake; Harmonize regulatory review).

Through these combined actions, new TB vaccines will become available to socially and economic deprived populations, and to people with vulnerable health including people living with HIV or type 2 diabetes, young children and the elderly. Access to new TB vaccines in these settings and for these populations is an ethical imperative and paramount to the public health impact of TB vaccine development.