Global roadmap for research and development of tuberculosis vaccines

About EDCTP

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public–public partnership between 14 European and 16 African countries, supported by the European Union.

EDCTP's vision is to reduce the individual, social and economic burden of poverty-related infectious diseases affecting sub-Saharan Africa.

EDCTP's mission is to accelerate the development of new or improved medicinal products for the identification, treatment and prevention of infectious diseases, including emerging and re-emerging diseases, through pre- and post-registration clinical studies, with emphasis on phase II and III clinical trials. Our approach integrates conduct of research with development of African clinical research capacity and networking.

The second EDCTP programme is implemented by the EDCTP Association supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation.

About AIGHD

The Amsterdam Institute for Global Health & Development (AIGHD) is a collaborative institute of the University of Amsterdam and the VU University Amsterdam. Combining biomedical science with social science, economics and legal science, it addresses challenges in global health and development by conducting interdisciplinary research, generating insights and solutions, and educating the next generation of global health leaders.

Contents

Executive summary

With an estimated 10 million new cases and 1.4 million deaths per year, tuberculosis (TB) is one of 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 Organisation's (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 lists short-term objectives and long-term strategic objectives for global TB vaccine research and development (R&D). It is designed to provide global stakeholders, including researchers, funders, industry, regulatory authorities and policy decision-makers, with actionable priorities to guide their activities. It **focuses on developing and delivering effective and affordable vaccines for use in low- and middle-income countries,** where the vast majority of people affected by TB are found.

The roadmap describes the actions needed to achieve 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.
3. A therapeutic vaccine to improve TB treatment outcomes.

The proposed actions focus on R&D, as well as the enabling conditions needed to enhance this R&D and ensure uptake of new TB vaccines. The R&D actions are grouped into three categories: **diversifying the pipeline**, **accelerating clinical development** and **ensuring public health impact**. The enabling considerations focus on **funding**, **open science** and **stakeholder engagement**. For each of these categories, the major barriers to the development of new TB vaccines are identified, along with the actions required to overcome these barriers, their timing and, where relevant, their interdependencies.

The **process for developing this roadmap** included a desk review and stakeholder mapping, in-depth interviews with selected stakeholders, a stakeholder workshop and various rounds of consultation on draft versions of the roadmap. These rounds of consultation included both targeted requests for feedback from selected stakeholders and an open public consultation. Each step of the process involved close collaboration with the WHO's Immunization, Vaccines and Biologicals department and its Global TB Programme.

The roadmap identifies a 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 current approach to vaccine development is considered too narrow. In addition, vaccine development has focused on a limited set of candidate TB antigens, which are all *M. tuberculosis* virulence factors. Expanded basic and translational science is required, focusing on mechanisms and biomarkers of protection, new approaches to vaccine discovery, and improving vaccine formulation and delivery. Use of controlled human infection models also needs to be considered.

There are two key barriers to **accelerating clinical development** of new TB vaccines. The first barrier, lack of validated preclinical models that predict infection and disease in humans, makes it hard to identify the most appropriate candidates for clinical evaluation. It can be addressed by developing and optimising diverse "fit for purpose" animal models that can predict/replicate findings in humans. TB vaccine candidates also need to be compared within and across animal models.

The second barrier, difficulties in generating the evidence needed to support decision-making on progression of candidates through the clinical development pipeline, reflects the lack of agreed laboratory correlates of protection for use in clinical trials. This necessitates large and long phase II/III trials with prevention of disease as the clinical efficacy endpoint. Alternative efficacy endpoints – prevention of infection and prevention of recurrence – have been proposed for proof-of-principle studies but the extent to which these endpoints predict prevention of disease is not clear. This barrier

needs to be addressed by defining meaningful trial endpoints, identifying validated correlates of protection, and standardising and improving the efficiency of TB vaccine trials. TB vaccine trial capacity also needs to be strengthened.

Key barriers to **ensuring public health impact** are: (1) limited understanding of countries' likely demand for a new TB vaccine and how it would be integrated into national immunisation programmes, especially for a vaccine to be used in adults and adolescents; (2) uncertainty on how vaccine implementation would be integrated with ongoing TB prevention efforts and how a vaccine would be used in vulnerable groups; and (3) a lack of data on likely national and global demand to stimulate manufacturers to enter the market.

To address these barriers, key epidemiological and health economic metrics need to be quantified, and vaccine effectiveness and impact evaluated post-licensure. In addition, user preferences and implementation requirements for new TB vaccines need to be better understood.

Key **funding** barriers include low global investment in TB vaccine R&D, a lack of diversity in current funding sources, and limited coordination of R&D funding. Actions to overcome these barriers include attracting new investments in TB vaccine R&D, developing innovative financing mechanisms, and creating mechanisms to reduce financial risk.

With regard to **open science,** barriers include failure to publish pre-clinical and clinical study findings (or delayed publication), and lack of effective sharing of datasets and specimens. Actions identified to address these barriers include promoting timely and open access to data and specimens, and creating mechanisms to coordinate open science.

Finally, key barriers in the area of **stakeholder engagement** include limited engagement of industry vaccine developers, low levels of political commitment to new TB vaccines, slow decision-making for vaccine implementation, as well as stigma, vaccine hesitancy and other factors that could affect vaccine take up in communities. Required actions in this area include creating a supportive environment for TB vaccine development and use, overcoming barriers to delivery and uptake, and promoting TB vaccine and research literacy.

The roadmap ends with a section that pulls together actions related to **commercialisation of vaccine development and manufacturing, and access to new TB vaccines when licensed**. The proposed approach is a combination of push mechanisms, pull mechanisms and technology transfer.

Foreword

World Health Organization

With the End-TB Strategy the World Health Organization and the global tuberculosis (TB) community have set ambitious targets to end the TB epidemic by achieving 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015, and by eliminating the catastrophic expenses caused by TB, in line with the Sustainable Development Goals (SDG). The political declaration of the 2018 High-Level Meeting of the General Assembly on the fight against TB, and the World Health Assembly resolution WHA73.3 on the global strategy for TB research and innovation have renewed these commitments. These efforts have borne fruit: global solidarity has saved at least 63 million lives in the past two decades. Despite this success, TB remains one of the top infectious disease killers globally. In 2019 alone, 10 million people fell ill from TB and 1.4 million people died from the disease. Drug-resistant forms of TB remain a public health crisis and a health security threat. The world has committed to end the TB epidemic by 2030, but currently does not have the tools that are urgently needed to accelerate the global TB incidence decline. At the same time, efforts to end TB are experiencing setbacks due to lack of sufficient financing for both TB response and TB research. In addition, due to the COVID-19 pandemic, the gap between the estimated number of people developing TB and the number of people officially reported as diagnosed with TB has significantly widened in 2020.

The bacille Calmette–Guérin vaccine, first used in the 1920s, provides partial protection against severe forms of TB in infants and young children (averting thousands of paediatric deaths annually), but fails to stop transmission of pulmonary tuberculosis in adults. More effective vaccines that provide protection against all forms of TB in all age groups are urgently needed to accelerate the decline in TB incidence globally. Recognizing this, member states during the United Nations General Assembly high level meeting on TB, held in New York in 2018, have committed to increase investment in and accelerate research for the development of more effective TB vaccines, placing prevention as a cornerstone of the global response.

Between 2018 and 2022, the TB response could cost nations an estimated US$12.4 billion per year. Drug-resistant TB is the leading contributor to deaths from antimicrobial resistance (AMR), accounting for one fourth of all AMR-related deaths. This burden constitutes an overwhelmingly compelling case for new TB vaccine research and development, which is currently chronically under-funded.

In 2021, we find ourselves at a particularly delicate juncture in the fight against TB. In addition to plateauing of resources for vaccine research, TB control programmes are experiencing significant setbacks because of diverted resources related to the COVID-19 pandemic. The risk of losing the gains made in the past decade is real and we must take immediate action. Alignment on research priorities, increased funding for vaccine R&D and closer collaboration of stakeholders across the product development-to-uptake process are needed to shorten the time to the availability and impact of effective vaccines.

To this end, WHO's department of Immunization, Vaccines & Biologicals (IVB) and the Global TB Programme (GTB) have been privileged to collaborate with the Amsterdam Institute of Global Health and Development (AIGHD), and the European & Developing Countries Clinical Trials Partnership (EDCTP) in the development of this first *Global roadmap for research and development for tuberculosis vaccines*. This strategic guidance document informs researchers, vaccine developers, manufacturers, funders, regulators and policy makers on the key priorities that must

be addressed to meaningfully advance the development of more effective TB vaccines.

The priorities highlighted in this roadmap chart the way forward, in technical areas ranging from the stages of discovery and early clinical development through to licensure with a line of sight to global deployment.

The effort to sustainably develop and implement new TB vaccines will be accelerated by early consideration of the needs of late-stage stakeholders, such as policy-makers, end users, commercial manufacturers, and financing and procurement agencies. WHO, AIGHD and EDCTP therefore plan to continue

their collaboration to develop a complementary '*Roadmap for Early Adoption, Commercialization and Implementation of TB Vaccines*'. The over-arching goal of the roadmap published today and the second, planned roadmap is to provide strategic guidance for the development, delivery and introduction of effective TB vaccines that are affordable and accessible by all countries that need them.

WHO remains committed to work with all partners and civil society, to advance the TB vaccine field with the urgency and solidarity it demands.

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Purpose, process and scope

Purpose of the roadmap

The purpose of the Global roadmap for research and development (R&D) of tuberculosis (TB) vaccines is to provide global stakeholders – researchers, funders, industry, regulatory authorities, policy decision-makers and civil society – with actionable priorities to guide their activities. The roadmap primarily focuses on developing and delivering affordable and effective vaccines for use in low- and middle-income countries with a high incidence of TB, in line with the World Health Organisation (WHO) goals outlined below. However, such vaccines may also be useful to protect high-risk populations or groups in high-income/low-incidence countries.

The roadmap integrates and aligns strategic planning and innovation 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.

Process of developing the roadmap

The European & Developing Countries Clinical Trials Partnership (EDCTP) commissioned the Amsterdam Institute of Global Health and Development (AIGHD) to develop a Global roadmap for R&D of TB vaccines. The roadmap is based on several rounds of consultation with experts and key stakeholders.

Interviews: Interviews were held with 22 stakeholders from academia, public health authorities, national TB programmes, immunisation programmes, civil society, agencies funding research or programme implementation, NGOs involved in TB care and control or immunisation, regulators, and industry, to gather perspectives on: the current TB vaccine clinical development pipeline; the development goals as outlined in the WHO Preferred Product Characteristics for three types of TB vaccine; and barriers to achieving these goals.

Stakeholder workshop: A meeting was held in March 2020 in Amsterdam, The Netherlands, bringing together 34 experts and stakeholders to discuss the outcomes of the interviews and to define priorities and actions.

Roadmap drafting: A draft of the roadmap was prepared based on the outcomes of the interviews and the stakeholder workshop.

Consultation: The draft roadmap was reviewed by WHO's Product Development for Vaccines Advisory Committee and EDCTP's Scientific Advisory Committee, and was then opened for public consultation. Comments were reviewed and incorporated into the final version.

Development of this roadmap coincided with the COVID-19 pandemic. The unprecedented speed and scale of COVID-19 vaccine development has provided much information that can potentially be leveraged to accelerate the development of TB vaccines. Although the pandemic was still unfolding as this roadmap was finalised, attempts have been made to incorporate lessons learned from COVID-19 vaccine development.

Scope of the roadmap

The roadmap focuses on the actions required to achieve the WHO's three TB vaccine development goals:

1. 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 arising from reactivation of latent infections.[1]

2. 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 better and longer protection than that generated by Bacillus Calmette–Guérin (BCG). It should also be safe when administered to infants with HIV infections or other causes of immune suppression. Improved manufacturing to ensure sustainable supply would represent an additional advantage.

3. A **therapeutic vaccine to improve TB treatment outcomes**. A therapeutic TB vaccine 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 treatment duration and the 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 goals involves end-to-end development of TB vaccines, going beyond licensure to include delivery to populations at risk.

Roadmap actions in pursuit of these goals have been 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, underpinned by three key enabling conditions (see figure 1).

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1   WHO. WHO Preferred Product Characteristics for New Tuberculosis Vaccines. 2018. Geneva: WHO. Available at: *https://www.who.int/immunization/documents/who_ivb_18.06/en/*
2   WHO. WHO Preferred Product Characteristics for Therapeutic Vaccines to Improve Tuberculosis Treatment Outcomes. 2019. Geneva: WHO. Available at: *https://apps.who.int/iris/handle/10665/330448*

Tuberculosis vaccine R&D roadmap

THEMES			
I Diversifying the pipeline	**II** Accelerating clinical development	**III** Ensuring public health impact	

R&D ACTION LINES				
Basic and translational science	**Animal models**	**Clinical trials**	**Epidemiology and modelling**	**Research to ensure optimal implementation**
1 1.1 Mechanisms and biomarkers of protection 1.2 New approaches to vaccine discovery 1.3 Improved vaccine formulation and delivery 1.4 Controlled human infection model	**2** 2.1 Optimised animal models 2.2 Comparison of vaccine candidates within and across animal models	**3** 3.1 Trial endpoints 3.2 Correlates of protection 3.3 Trial harmonisation and design 3.4 Trial site capacity	**4** 4.1 Country-specific data and projections 4.2 Post-licensure studies	**5** 5.1 Health system conditions for vaccine introduction 5.2 Barriers and enablers of vaccine uptake

KEY ENABLING CONDITIONS

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, philanthropy and donors
- Attract new entrants

A2 Develop innovative financing mechanisms for TB vaccine R&D
- Establish partnerships for joint funding of trials
- Customise calls to the clinical development pathway

A3 Create mechanisms that attract investment in early stages of development
- Market shaping to reduce commercial uncertainty
- 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 systems and procedures

c — Stakeholder engagement

C1 Create a supportive environment for TB vaccines
- Increase political commitment
- Advocate for development and uptake
- Harmonise and fast-track regulatory review
- Create innovative incentives

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

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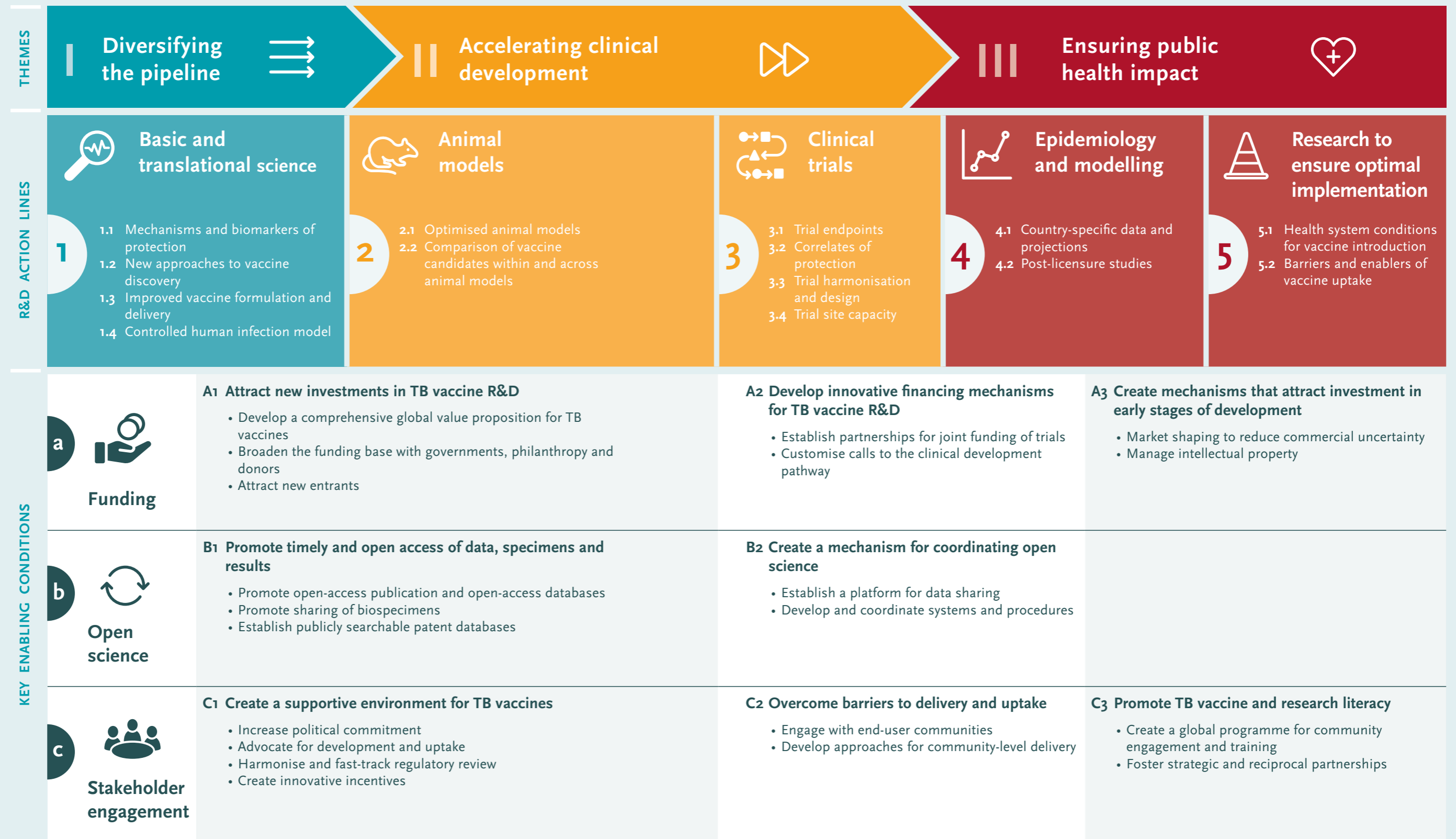- Foster strategic and reciprocal partnerships

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 sections summarise the current state of play for the three themes, as well as the challenges that need to be addressed if the WHO goals are to be achieved. For each of the five R&D action lines, current knowledge gaps and proposed actions to address these gaps are described. Actions are categorised as short-term (2 years), medium-term (5 years) and long-term (10+ years) priorities. These timelines relate to when the results should be achieved; work on many medium- and long-term priorities needs to begin immediately. Specific supportive actions are also identified for each of the three key enabling conditions.

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

3   Available at *http://www.edctp.org/web/app/uploads/2021/04/TB-Vaccine-Roadmap-Background-document.pdf*.

Roadmap action lines

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Theme 1
Diversifying the pipeline

The TB vaccine pipeline has 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 Mtb antigens are currently considered and they may be suboptimal in eliciting protection. Emphasis is put on stimulating classical, CD4+ T-helper-1 (Th1) cells, which may be essential but will probably not be sufficient to generate an optimal protective response, and on antigens that are known Mtb virulence factors. There is a need to diversify the pipeline, in particular by (1) exploring vaccine candidates that generate immunity beyond CD4+ Th1 cells, (2) assessing new routes of vaccine administration, and (3) promoting new antigen discovery. A strategy to promote diversity in the TB vaccine pipeline should be favoured over one focused on a limited set of selected TB candidates.

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

There is currently a poor understanding of the human immune responses that a vaccine needs to induce to protect against initial Mtb infection, sustained Mtb infection and TB disease. Mechanisms of disease and protection are incompletely understood across all phases of the natural history of TB infection. More in-depth knowledge is required of the biology of infection and immune responses during latent TB infection, incipient TB, subclinical TB[4] and clinically apparent TB disease. There is a need to identify drivers of transition in either direction along this spectrum, the drivers of clearance,[5] and potential intervention points for manipulation of the host response to Mtb infection. These investigations should also aim to identify new biomarkers and biosignatures that could be used as laboratory correlates of vaccine-induced protection and to differentiate vaccine-induced responses from those associated with Mtb infection.

While Th1 cell-mediated responses 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, spanning cellular and antibody responses. New insight is also needed into the role of innate immune responses in early clearance of mycobacteria, and how protective innate responses can be stimulated by vaccination.

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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 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.

There is limited understanding of how immune responses are influenced by route of delivery, vaccine platform, adjuvant, antigen type, Mtb genotype or *M. bovis* BCG strain, or how they contribute to the non-specific effects of vaccines.[6] Such modifiers should be explored to identify potential ways to improve vaccine-induced protective responses. Potentially disruptive technologies from other disease fields should also be investigated. For example, aerosol delivery could facilitate universal administration of new TB vaccines in mass vaccination campaigns.

Finally, little is known about immune responses in the lungs and whether immune responses measured in blood are informative about those at the site of infection. This calls for an expansion of current clinical studies, including studies of mucosal immune responses and, potentially, controlled human infection models (CHIMs). CHIMs could also be important for down-selecting vaccine 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.	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 should include targeted approaches to detect cellular and/or humoral immune responses as well as unbiased approaches, such as transcriptional profiling of blood cells and mycobacterial growth inhibition assays.	short-term for 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 from systemic responses.	mid-term
Deploy genome-wide strategies for antigen discovery: identify Mtb proteins, peptides and non-protein antigens that can be recognised by the host immune system, applying IFN-γ- and non-IFN-γ-based screening approaches.	mid-term

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

1.3 Improved vaccine formulation and delivery	
Key actions	**Timing**
Study the effects on vaccination outcomes of different adjuvants, vaccine platforms and Mtb challenge strains, among others, through experimental medicine studies.	mid-term
Explore new routes of vaccine administration, including aerosol and intravenous delivery, 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 close gaps in basic knowledge and to facilitate proof-of-principle studies to inform down-selection of candidate vaccines, 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 will require bringing more candidates into the clinical pipeline, but also dropping failing candidates at an early stage before they enter expensive, large-scale trials. Clinical development of TB vaccines is held back by: (1) lack of validated preclinical models that predict protection from infection and disease in humans; and (2) difficulties in generating evidence to support decision-making on progression through the clinical development pipeline, which limits effective "stage gating" – down-selection of candidates for clinical development.

The lack of consensus on immunological correlates of protection means that candidates have to be evaluated in long and expensive phase II and III trials with prevention of disease (PoD) as the clinical efficacy endpoint. Alternative efficacy endpoints, notably prevention of infection (PoI) and prevention of recurrence (PoR), are being used in proof-of-principle phase IIb trials as a stepping stone to phase III trials. In particular, PoR trials can be much shorter than PoD trials. However, the extent to which PoI or PoR endpoints predict PoD is uncertain, so it is not clear whether PoI or PoR trials can inform "go/no-go" decision-making and progression to a phase III PoD trial.

Accelerating and de-risking clinical development therefore requires improved preclinical models, as well as a better understanding of correlates of protection and alternative efficacy endpoints. While animal models are important, results from small-animal or non-human primate models should not on their own inhibit progression to clinical evaluation.

In overcoming these challenges, interdependencies between required R&D actions need to be considered. Both improving animal models (action line 2) and identifying correlates of protection (action line 3) require "back-translation" of results from trials that show an efficacy signal. This has only recently become possible, with the successes of the phase IIb PoD trial of the M72/AS01$_E$ candidate[7] and the phase IIb trial that showed PoI efficacy for BCG re-vaccination.[8] It implies an iterative process in which stepwise improvements in vaccine design lead to new efficacy signals, which then underpin the development of better animal models and the discovery of better correlates of protection. This must be considered in the timing and planning of R&D activities, including the collection and biobanking of samples within vaccine trials and making these accessible for use by related studies (see enabling conditions).

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

Animal models are key for preclinical candidate screening for safety, immunogenicity and protection against an Mtb challenge.[9] However, there is currently no single, harmonised animal model to support clear go/no-go decision-making for candidate TB vaccines. Neither

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7   Tait DR *et al*. Final Analysis of a Trial of M72/AS01 $_E$ Vaccine to Prevent Tuberculosis. *N Engl J Med*. 2019;381(25):2429-2439. doi: 10.1056/NEJMoa1909953

8   Nemes E *et al*. Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination. *N Engl J Med*. 2018;379(2):138-149. doi: 10.1056/NEJMoa1714021.

9   Because of the critical role animal models play in vaccine development, animal models in this roadmap are addressed under theme 2: Accelerating clinical development. However, animal models are also important for scientific discovery (theme 1: Diversify the pipeline), and the actions relating to animal models are also relevant for those applications.

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 sufficiently reflect safety, immunogenicity and protection in specific populations, such as infants, older people and immunocompromised individuals. This poses major challenges to the selection of candidates for human trials, and to the demonstration of a biological signal that can unlock funding for further studies.

Protection in small-animal models is not well defined, and there is no established functional readout for protective efficacy. Although much work has recently been done in this respect, a greater degree of harmonisation and standardisation of experimental methods is needed, including challenge strain selection, use of imaging, scoring of gross pathology and prioritisation of future experimental directions.

The utility of different 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 a need to develop models of resistance to infection and clearance.

A systematic approach to candidate selection for progression along the pipeline needs to be defined, based on stage-gating criteria that include protection against Mtb challenge in defined animal models and, potentially, induction of non-conventional immune responses.[10]

Comparative head-to-head testing of vaccine candidates in the same animal models in separate, independent laboratories can help to prioritise the most promising vaccine candidates for clinical development. Some head-to-head comparisons are being carried out[10] and this approach should be applied more broadly.

A further issue is that not all animal data are published, particularly negative results, and it is often not clear in which animal models a vaccine candidate has been tested (see enabling conditions, open science).

Key actions and priorities

2.1 Optimised animal models	
Key actions	**Timing**
Develop fit-for-purpose animal models: back-translate the findings from adolescent/adult and paediatric trials, and from clinical studies of disease progression and subclinical disease, into animal models of immunogenicity, infection and disease, ideally using the same product as in humans.	short-term (based on recent trials); mid- to long-term based on future human trials/ studies
Develop animal models to provide insight into the relationship between PoI and 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 animal models the results from trials and clinical studies that include infants, older people and immune-compromised people, e.g. people living with HIV/AIDS, diabetes and iatrogenic immune suppression.	long-term

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10 The TB Vaccine Development Pathway, developed by TBVI and IAVI on behalf of the Global TB Vaccine Partnership, has proposed a systematic approach to candidate selection for pipeline progression. It defines a set of stage gates which specify the criteria for progression at each stage of TB vaccine development, from discovery through to licensure. The stage-gate criteria make experiments in small animals an explicit part of TB vaccine candidate development (*https://www.tbvacpathway.com/*).

2.2 Comparison of vaccine candidates within and across animal models	
Key actions	**Timing**
Standardise and harmonise animal models, such as challenge strain selection and definition of protection outcomes, including the use of imaging and scoring of gross pathology. Identify priorities for standardisation and harmonisation of future experimental directions, e.g. assessing aerosol vaccine delivery.	short-term
Perform head-to-head testing of candidate vaccines in independent laboratories using standardised models that best predict protection in humans.	mid-term

Action line 3: Clinical trials

Objective: To define meaningful trial endpoints, improve the efficiency and standardisation of TB vaccine trials, and build trial capacity

The WHO Preferred Product Characteristics provide clear objectives and conditions for new TB vaccines, including the need for efficacy trial data based on PoD endpoints. However, knowledge gaps remain that limit extrapolation of results from trial populations. Critical questions include: (1) Does protective efficacy established among those latently infected ("post-exposure" or "post-infection" protection – that is, among individuals with positive interferon-gamma release assay [IGRA] results) – reflect protective efficacy among IGRA-negative individuals ("pre-exposure" or "pre-infection" protection)?[11] (2) To what extent can protective efficacy established among the general population be extrapolated to groups with increased risk of TB disease, such as people living with HIV and/or with type 2 diabetes, older people and people who use/smoke tobacco? (3) To what extent can protective efficacy established in one geographic area (e.g. sub-Saharan Africa) be extrapolated to other geographic areas (e.g. Asia, the Americas), for example because of different distributions of Mtb lineages?

Better PoD endpoints are needed for populations in which bacteriological confirmation of TB disease has low sensitivity, such as infants, children, and people living with HIV. Better assays for extrapulmonary TB could be used to develop a composite endpoint that incorporates this disease category. A better understanding of correlates of protection could potentially shorten trials, but it is unlikely that a single correlate of protection will be a sufficient 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. However, the search for correlates of protection should not hold back clinical development, and biospecimens should be collected in trials to support identification of correlates of protection. As trials with a PoI endpoint are being considered 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.

To accelerate clinical development, important target populations for TB vaccines should be included in phase I–II trials. This will generate safety and immunogenicity data to inform the design of later-phase clinical trials.[12] In addition, given the poor predictive value of animal models, testing of promising TB vaccine candidates in phase I studies should be accelerated. The scope of phase I studies should be expanded, for example to assess local cellular and humoral responses to vaccine antigen.

Comparisons across trials would be facilitated by standardisation of clinical endpoints, inclusion criteria and the measurements required at

11 In most countries, IGRA testing before vaccination would 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 to the population at large, i.e. irrespective of IGRA testing.

12 For instance, in phase I–II studies, safety and immunogenicity data should be gathered sequentially from BCG-unvaccinated/IGRA-negative, BCG-unvaccinated/IGRA-positive and BCG-vaccinated/IGRA-positive individuals. The latter population is important in endemic areas with a high burden of TB infection/disease.

different timepoints during the trial. People living with HIV should be included in trials; inclusion of other immunosuppressed individuals could be considered if safety is sufficiently guaranteed (e.g. with regard to live vaccines). TB preventive treatment is standard of care for these and other subpopulations and must be taken into account in the design and conduct of vaccine trials. PoD endpoints should also be clearly defined and standardised, including the number of positive and negative cultures required, and the role of molecular diagnostics.

Designs that increase the efficiency of PoD trials, such as studies in high-incidence populations, need to be explored. Lessons should be drawn from the accelerated clinical development of COVID-19 vaccines, including the potential for adaptive trial designs and trial phases conducted in parallel.

Clinical trial sites for phase II/III trials need to be developed, bearing in mind the need to consider heterogeneity in host and Mtb genetic background. Urgent actions should include development of sustainable capacity for late-stage trials. High staff turnover can hamper the mid- to long-term development of TB vaccines.

In addition to obtaining epidemiological data and building trial capacity, factors that could affect enrolment and retention in TB vaccine trials need to be explored at potential sites. Public engagement, drawing on lessons learnt from other vaccine trials in high-incidence settings, is also important, to prepare populations for the implementation of a new vaccine and to mobilise public support.

Key actions and priorities

3.1 Trial endpoints	
Key actions	Timing
Define and develop standardised PoD trial endpoints that better capture the various TB disease states in diverse target populations: standardise the definition of laboratory-confirmed pulmonary TB; develop clinical endpoints representative of subclinical TB; improve bacteriological confirmation of TB disease in neonates, infants and people living with HIV; improve bacteriological confirmation of extrapulmonary disease. Based on these actions, 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 responses.	mid-term
Quantify the clinical translation of PoI into PoD: analyse existing and new observational data; include secondary PoI endpoints in phase III PoD trials; take into account that this quantification may be different for different vaccine platform technologies.	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 to identify correlates of protection in ongoing and planned phase IIb and phase III trials.	short- to mid-term
Identify correlates of protection for TB disease from phase IIa and phase III trials that have shown protection: analyse data and putative correlates of protection from individual trials and, if possible, from meta-analyses of several trials.	short- to mid-term
Validate correlates of protection for TB disease: validate putative correlates of protection identified by back-translation of trial results (see action line 1) in immunogenicity studies, new trials with a clinical PoD endpoint and, if feasible, controlled human infection models.	mid- to long-term

3.3 Trial harmonisation and design	
Key actions	**Timing**
Harmonise clinical trial protocols: define an agnostic trial "shell" of standardised outcomes (including secondary endpoints), inclusion criteria and measurements for clinical trials for different vaccine types; standardise inclusion criteria for people living with HIV infection or diabetes; and standardise measurement timepoints during the trial. Such harmonised protocols should take into account the need for preventive treatment of children, people living with HIV and potentially other groups.[13]	mid-term
Develop more efficient TB vaccine trial designs: Phase I: explore innovative trial designs that provide information on the lung mucosal immune response. Phase IIb/III: organise efficacy trials within contact investigations, active case-finding programmes and high-risk populations (e.g. miners, prisoners, if ethical issues can be resolved); organise epidemiological and demonstration studies in such settings and populations to establish their feasibility and external validity; explore adaptive trial designs for evaluating safety, immunogenicity and efficacy of different vaccine candidates. Learn from COVID-19 vaccine development.	mid-term

3.4 Trial site capacity	
Key actions	**Timing**
Create an inventory of clinical trial site capacity: identify potential new clinical trial sites; assess their quality and suitability in terms of technical capacity and laboratory infrastructure.	short-term, before phase III trials start
Collect epidemiological data at potential sites for phase II/III trials in various parts of the world, as a continuous process, including: age-stratified data on TB incidence and prevalence of latent TB infection; Mtb lineage distribution; and data on special populations such as people living with HIV. At sites considered for PoI or PoR trials: collect data on age-specific incidence of Mtb infection and the incidence of recurrent TB and reinfection.	short-term, before phase III trials start
Develop vaccine trial sites: develop infrastructure and human capacity, including mentorship and support of junior investigators. Capacity does not need to be TB-specific[14] but should be sustainable so that key staff can be retained, and skills and infrastructure maintained. Trial sites need to be developed in diverse geographic locations to take account of heterogeneity in host and Mtb genetic backgrounds.	short-term, before phase III trials start
Study potential barriers to trial acceptance: conduct social science research into barriers to participation and retention in TB vaccine trials, 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 and efficient conduct of clinical trials and collaborative partnerships between trial sites and communities, in line with Good Participatory Practice guidelines.[15] Community engagement should be part of all phase II and III studies, and sponsors and developers should plan community engagement activities before phase I studies start.	Short-term: plans for community engagement should be developed when products enter phase I

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13 Enrolment should be 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.

14 Many sites will not be sustainable for TB vaccine trials alone and they should have the capacity to evaluate other preventive interventions, including vaccines against other diseases, when not being involved in TB vaccine trials.

15 AERAS. Good Participatory Practice Principles for TB Vaccines Trials. 2017. New York: AVAC. Available at: *https://www.avac.org/resource/good-participatory-practice-guidelines-tb-vaccine-research-2017*.

Theme 3
Ensuring public health impact

New TB vaccines, including those for adolescents and adults, will need to be delivered programmatically. To achieve public health impact, it is critical to understand the drivers of countries' policy decision-making and to provide evidence to support this decision-making. These drivers include the extent of country demand for a new TB vaccine and considerations associated with its addition to national immunisation programmes.

Decision-making will be influenced by multiple factors, including: political prioritisation of TB; the country's TB burden and the expected impact of a vaccine; the relative effectiveness of alternative control strategies; the safety, efficacy and equity impact of a vaccine (in the general population as well as specific groups such as people living with HIV and older people); the availability of vaccine supply; a vaccine's cost, affordability and cost-effectiveness; and the capacity of the health system to successfully introduce and sustainably deliver a vaccine as part of an integrated disease control programme. Other potentially important factors include broader economic benefits around childhood development, changes in household behaviour and macro-economic indicators. Collectively, these elements 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 and/or type 2 diabetes, children, older people 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, which would not form part of a standard childhood immunisation programme. Until recently, few vaccines were routinely administered to people in these age groups, but the expected roll-out of COVID-19 vaccines among adults will provide important lessons. Specific needs for evidence include the optimal way to deliver the vaccine (e.g. through national campaigns; which age groups to target), the implications of vaccine attributes (e.g. number of doses required, cold-chain requirements and need for re-vaccination), ensuring equitable access (including whether pre-vaccination diagnostic testing is required) and vaccine acceptance.

Locally gathered evidence will inform country decision-making. It will also help countries prepare for introduction and scale-up of a new TB vaccine, and make better-informed decisions about target groups for vaccination. In addition, it will enable donors to plan investments (enabling condition A), and will be important for estimating national and global demand to encourage manufacturers to enter the market and scale-up vaccine production. The COVID-19 response suggests that vaccine manufacturing capacity is key for effective implementation and ensuring the public health impact of vaccination.

The market size for a vaccine will depend on its product profile (e.g. a vaccine that is only effective post-exposure will have a smaller market than one that is effective both pre- and post-exposure), but also on country decisions. Decision-making is made more challenging by inter-dependencies – for example, the price of a vaccine will depend on market volume, but this will depend on its cost and countries' perceptions of its affordability. Expanding use to additional target groups would increase costs, but potentially reduce price per vaccine dose by increasing market volumes. Global/national policy on target groups, expected impacts, willingness to pay, and cost of implementation will all affect cost–benefit analyses and decision-making.

The process by which this information gap is closed should be iterative and considered during the 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). Analyses may be further refined as post-introduction data on vaccine efficacy, safety and impact become available.

Action Line 4: Epidemiology and modelling

Objective: To quantify key epidemiological and health economic metrics to support vaccine introduction, and to evaluate vaccine effectiveness and impact post-licensure

Key to decision-making on vaccine introduction is an understanding of the costs and benefits of a new vaccine, and the willingness to pay of countries and donors to achieve vaccine-related health impacts. Cost and benefits will depend on a vaccine's characteristics (e.g. its effectiveness, expected duration of protection, dose regimen, cost-effectiveness).[16] To ensure evidence-based decision-making, it is important to consider the timelines and information needs of country decision-makers and global funding agencies such as Gavi (e.g. its 5-year Vaccine Investment Strategy).

Collecting country data on the burden of Mtb infection and TB disease, and on the drivers of the TB epidemic, is important to define the size of target populations, understand the optimum vaccine use case, and estimate potential market volumes.[17] Optimal vaccination strategies need to be identified by modelling of health and economic impacts, considering various strategies for delivery that take into account the number of doses required, route of administration and duration of protection, as well as risk group-targeted vaccination strategies. Health technology and economic assessments of new TB vaccines should adopt a life-course perspective, and consider equitable access and use.[18]

Surveillance systems, including laboratory capacity, should be strengthened before vaccine introduction to provide baseline epidemiologic data to facilitate assessment of post-introduction impact. Data from post-licensure studies are an important source of information for establishing vaccine effectiveness and safety in subgroups and geographically diverse populations, as well as impact on TB incidence and transmission. Collection of such data requires developing approaches for real-world studies of TB vaccine implementation and strengthening of surveillance systems for TB disease notification and for pharmacovigilance.

Country data on Mtb lineage diversity would be needed if a vaccine shows lineage-specific variation in protective efficacy, to provide a baseline for post-licensure surveillance for shifts in Mtb lineage distribution.

Post-licensure studies should also explore potential non-specific effects of new TB vaccines in infants and neonates in comparison to BCG, such as impacts on all-cause mortality.

Key actions and priorities

4.1 Country-specific data and projections[19]	
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 managing budgets, in different countries and across different 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 standardisation, 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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16 WHO. Principles and considerations for adding a vaccine to a national immunization programme. From decision to implementation and monitoring. 2014. Geneva: WHO. Available at: *https://www.who.int/immunization/programmes_systems/policies_strategies/vaccine_intro_resources/nvi_guidelines/en/*

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

18 WHO. Immunisation Agenda 2030. 2020. Geneva: WHO. Available at: *https://www.who.int/immunization/immunization_agenda_2030/en/*.

19 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 decision-making on introduction of new TB vaccines and market volumes: include estimates of national and subnational TB disease and infection prevalence, including in people living with HIV and older people; define the contribution of high-risk groups to TB transmission to identify potential target groups for vaccination; map Mtb genotypic variation based on a representative sample of strains from TB patients starting treatment.	Short-term, well before licensure of a new vaccine
Conduct modelling studies to define vaccine development investment cases and potential country-specific vaccine use cases: model implementation scenarios, epidemiological impact, cost-effectiveness and budget impact in consultation with countries to define the optimum target groups and delivery strategies (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 approaches for real-world vaccine scale-up studies: develop suitable designs and validated tools to collect and analyse real-world data in rigorous post-licensure studies to establish effectiveness, safety and public health impact; establish and/or support post-licensure registries, making use of existing expertise from earlier introduction of novel vaccines; strengthen surveillance systems for collection of baseline epidemiologic data.	mid-term, before licensure of a new vaccine
Conduct post-licensure evaluations of vaccine effectiveness, impact and safety: carry out real-world post-licensure studies and surveillance to demonstrate use of a vaccine as an affordable public health tool and to support post-licensure indication expansions; make use of existing expertise from introduction of novel vaccines outside childhood immunisation programmes. Establish effectiveness across different subpopulations, including people living with HIV or diabetes, children and older people, people who use/smoke tobacco; effectiveness against different Mtb lineages; effectiveness and safety when given concurrently with other vaccines; safety in various subpopulations (e.g. pregnant women); impact on TB disease incidence; and 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. 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 with the needs of policymakers, affected populations, donors and implementers in various countries and settings.

The emerging experience with COVID-19 vaccination of adults and human papillomavirus (HPV) vaccination of adolescents, especially in low- and middle-income settings, is a useful starting point, but the specific requirements for TB vaccines need to be considered. Implementation strategies will need to consider accessibility, equity and opportunity costs, and take into account technological factors, such as thermostability, cold-chain requirements, and the potential need for multidose schedules. A wide range of social aspects must also be taken into account, such as vaccine acceptability in different groups, access among vulnerable/high-risk populations, and gender-related considerations. A further important factor is whether a vaccine can be given to people with co-morbidities or other vulnerabilities such as HIV infection, diabetes, malnutrition, or multidrug-resistant TB.

It will also be important to assess ways to enhance acceptability of a TB vaccine among adolescents and adults. There is risk of poor acceptance by users and communities, and vaccine hesitancy may be a key bottleneck to the introduction of new TB vaccines. Trust in a vaccine might be undermined if it offers only limited protection or has adverse effects. In low-incidence countries, 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 to develop 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 necessary conditions for immunisation programmes to implement these strategies; the requirements for optimising 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. Draw lessons from the roll-out of COVID-19 vaccines. For a vaccine for neonates and infants: determine the fit with the Expanded Programme on Immunisation and required timing with regard to other vaccinations.	short- to mid-term, taking account of Gavi's 5-year Vaccine Investment Strategy
Conduct pre- and post-introduction assessments of country immunisation programmes: assess the pre-introduction country-specific readiness of immunisation programmes and health systems to handle, store and administer a new TB vaccine, potentially making use of data and experiences from recent vaccine introductions. Assess capacity for monitoring of vaccine coverage and adverse events, and communication strategies for adverse events. Plan and conduct post-introduction assessments to identify gaps and areas for improvement, as well as lessons learnt.	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: conduct social and behavioural research to determine the perceptions of national decision-makers, health workers and the public to new vaccines; gather data relating to dosing, safety/reactogenicity, religious and gender-related factors, use with other vaccines versus specialised programmes, and, for immunotherapeutic vaccines, integration with TB treatment; conduct these studies across countries and settings to capture social and cultural variability.	mid-term, before licensure of a new vaccine

Key enabling conditions

Progress in diversifying the TB vaccine pipeline, accelerating clinical development and ensuring public health impact of new TB vaccines will depend on three enabling conditions:

- **Increased funding**: Considering the high resource needs and limited investment to date, inadequate resourcing is the most important bottleneck for TB vaccine R&D across discovery, preclinical research and clinical development.

- **Open science**: The efficiency of TB vaccine R&D will be enhanced by additional sharing of results, datasets and specimens.

- **Stakeholder engagement/multisectoral collaboration**: 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.

Enabling condition A: Funding

Globally, TB control and elimination receive relatively limited funding, and TB vaccine research is a critically underfunded part of TB R&D. Vaccine research makes up only 13% of TB R&D and, measured against the 2018–2020 Global Plan targets, vaccine research funding has the largest deficit of any category[20]. A healthy R&D pipeline requires more funding for basic and clinical research, and additional talented scientists need to be attracted to the field. Promising vaccine candidates need to be moved more rapidly through phases of clinical development and be tested earlier in PoD trials, for which very limited funding is currently available.

Funding for TB vaccine R&D comes from only 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 are few incentives for industry engagement in TB vaccine R&D.

New funders should be brought on board, for example through use of funding targets for

TB R&D as a proportion of countries' gross domestic expenditure.[21] When developed appropriately, R&D funding targets can be an important political tool to hold governments and donors accountable for their commitments.

Coordination between funders through the Global TB Vaccine Partnership (GTBVP) has led to the TB Vaccine Development Pathway and other initiatives.[22] Stronger and more visible coordination would be beneficial, in particular to support phase III trials, which 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 the project has come to an end, funding for further clinical evaluation is highly uncertain. This uncertainty stems from the lack of funding mechanisms that allow a smooth transition from one stage of clinical development to the next, or the need to compete again for further funding. This uncertainty is an obstacle to long-term investment and commitment by R&D actors. Longer-term funding is important to incentivise researchers to enter and continue

20 Treatment Action Group (TAG). Tuberculosis Research Funding Trends 2005–2019. 2020. New York: TAG. Available at: *https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2020/*

21 WHO. A global strategy for TB research and innovation. 2020. Geneva: WHO. Available at: *https://www.who.int/publications/i/item/9789240010024*

22 *https://www.tbvacpathway.com/*

in the field, especially for basic and preclinical research.[23] Finally, the TB community needs a better understanding of existing coordination mechanisms so it can make best use of them.

Finally, it is crucial to provide secure funding for early vaccine production and manufacturing. Vaccine production is costly, and maintaining functioning vaccine manufacturing facilities

and associated personnel may be difficult when funding is uncertain.

The experience with COVID-19 has shown that large-scale funding for vaccine R&D can be mobilised and deployed effectively. The actions below need to be taken with the lessons from the rapid development of COVID-19 vaccines in mind.

Key actions

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

Key actions

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 perspective. Include potential indirect effects, such as protection against leprosy.

Broaden the funding base with governments, philanthropy and donors: mobilise domestic R&D funding from large countries; encourage donors to support downstream aspects of TB vaccine R&D; engage with the HIV and antimicrobial resistance communities. In addition to development of the comprehensive value proposition, discrete well-defined projects on the development pathway could be identified for funders to support.

Attract new entrants: TB vaccine R&D could benefit from contributions from actors not currently directly involved in TB vaccine research. Novel and alternative ideas, and leveraging lessons learned, technologies, models and knowledge from other research actors, 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.

a.2 Develop innovative financing mechanisms for TB vaccine R&D

Key actions

Establish collaborations or partnerships for joint funding of trials, for example through "roadmap funding", where countries, research funders, industry, other donors and individuals donate, allocate or pool funding to create incentives to reduce the lag time in bringing promising vaccines to the market at affordable prices. This requires independent and transparent decision-making and selection procedures that are both product- and country-agnostic, with clear goals, principles and timelines, and strict rules governing what funding will be used for and under what conditions. Funders should provide information on who is funding what in the TB vaccine R&D space, and share information on the proposals that are submitted (e.g. with regard to identifying correlates of protection and clinical endpoints). Collaborations/partnerships for joint funding could extend to vaccine launch and implementation (i.e. focus on end-to-end clinical development).

Customise calls to the clinical development pathway: Calls for proposals should be made more flexible, providing the potential for long-term funding (e.g. ten years, with intermediate go/no-go decision points). This would allow consortia to adopt a long-term perspective and, if milestones are achieved, have the security of funding for next stages of R&D.

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23 It is important to establish programmes to train and support the next generation of scientists studying Mtb. TB can be an unattractive area of study for early-career investigators, because of the requirements for BSL-3 access and the time needed to generate data due to the lifecycle of the pathogen and long timelines of the infection's natural history and host immunity.

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

Market shaping to reduce commercial uncertainty: incentivise stronger engagement from industry, biotech firms and other developers, for example through grant funding and advance market commitments.[24] This requires defining a clear path to commercialisation, including commercial partners taking up production of a successful candidate; demonstrating the market; and leveraging the potential of global financing mechanisms such as PEPFAR, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Gavi and Unitaid that act as a "pull" mechanism to incentivise innovation.

Manage intellectual property, to ensure that it is 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 (e.g. the World Intellectual Property Organization) and patent-licensing mechanisms (e.g. the Medicines Patent Pool) can complement TB vaccine R&D efforts by facilitating partnerships and the licensing of intellectual property among organisations.

Enabling condition B: Open science

Currently, results from pre-clinical and clinical studies are often not made public or publication is delayed, hampering progress in understanding the potential of vaccine approaches. This is particularly true for negative results, most notably from animal studies. Datasets from pre-clinical and clinical studies are often not shared, slowing down progress and leading to duplication of 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 correlates of protection. These scarce specimens should be used efficiently; access is also important for investigators that have innovative ideas and approaches but are not well known in the TB R&D field.

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

Finally, efforts to apply the principles of open science and open access require coordination and harmonisation. Existing mechanisms such as the EU-funded TBVAC2020 consortium and the Collaboration for TB Vaccine Discovery (CTVD), funded by the Bill and Melinda Gates Foundation, have made important progress, but further collaboration and harmonisation across funders is needed. Promoting open science should accelerate the delivery of TB vaccines without creating new barriers.

In general, transparency should be established as a norm and expectation, particularly for data originating from publicly funded research.

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, and data-sharing and posting in open-access databases as a 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 in a timely manner.

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24 Mechanisms need to be in place to ensure that advance market commitments achieve acceleration of R&D, competition among manufacturers, affordable pricing, adequate supply capacity and technology transfer to manufacturers in low-resource settings.

Promote sharing of biospecimens collected in clinical studies: biospecimens collected in clinical studies should be made available through a central or virtual biobank on the basis of peer review, overseen by a biospecimen access committee. Access to biospecimens should be granted on the basis of the potential value of proposed research rather than on a "first-come first-served" basis, and should also allow actors/ fields outside the "traditional circle" to come up with innovative ideas and approaches.[25]

Establish publicly searchable patent databases for TB vaccine research to promote the diffusion of knowledge. Similar databases exist for drugs.[26] A vaccine patent database should include broadly defined patent information (i.e. including antigens, adjuvants, platforms and processes).

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b.2 Create a mechanism for coordinating open science in TB vaccine R&D

Key actions

Establish a platform for TB vaccine-related data sharing, starting with vaccine clinical data. Develop guidelines for data sharing, for example: data must be accompanied by contextual information (e.g. the purpose for which data were collected); appropriate use should be safeguarded (e.g. ethical rules, privacy regulations); and original collectors/contributors of data should be acknowledged in secondary use and publication. Approaches adopted in TB drug development could be used as a basis.[27] In addition, advantage could be taken of existing public data-sharing platforms that currently include Mtb-specific data, as well as current efforts to establish key meta-data, controlled vocabularies, and ontologies for other infectious diseases.

Develop and coordinate systems and procedures for efficient data and specimen sharing across the field of TB research and 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 HIV/AIDS[28] and the response to COVID-19.[29]

Enabling condition C:
Stakeholder engagement/intersectoral collaboration

Slow clinical development of new TB vaccines also reflects the engagement of a limited number of vaccine developers, as a convincing business case is lacking. In addition, complex and lengthy regulatory approval procedures slow down the initiation and conduct of clinical trials.

Despite recent high-level political commitment to TB vaccines, including the WHO's End TB Strategy and a United Nations resolution on TB,[30] political commitment at the country level is still low. Advocacy campaigns are needed to prepare policymakers, implementers and the public for a TB vaccine, especially one suitable for adolescents and adults, and to ensure

successful implementation of vaccination at scale. Again, lessons can be learned from the introduction and scale-up of COVID-19 vaccination.

Preparations need to be made for delivery and uptake of vaccines, taking into account country context and country-specific epidemiological profiles. Decision-making for vaccine implementation tends to be slow, and a lack of clear country preferences and preparedness for TB vaccine introduction could exacerbate delays. Price and cost often pose a barrier to new vaccine introductions, and not all countries have advisory mechanisms such as National Immunisation Technical Advisory

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25 This can build on the experience of IAVI, which is providing banked samples from two TB vaccine trials to the groups that come up with the most innovative proposals to progress the TB vaccine field. Decision-making on sample distribution is devolved to a group of experts.

26 Medicines Patents and Licenses Database (https://www.medspal.org)

27 *https://www.tballiance.org/rd/innovations/critical-path-tb-drug-regimens-cptr*

28 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 standardised tools and common preclinical and clinical platforms that permit the evaluation and sharing of results, while preserving the independent research crucial to innovation.

29 The COVID-19 response efforts include sharing of data, positive samples, bioassays and study protocols within days, with publications made available on preprint servers.

30 *https://www.un.org/pga/73/event/fight-to-end-tuberculosis/*

Groups (NITAGs) that can recommend new vaccine introductions. Gaps between policy and implementation, including poor access, are a major risk 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 a wide spectrum of activities from high-level engagement at head-of-state level through to grassroot community engagement. Advocates at these different levels will require high levels of TB vaccine and research literacy.

Community engagement in TB vaccine R&D is essential. It will contribute to successful introduction and scale-up of new TB vaccines. In addition, it is an ethical imperative to engage communities at each stage of TB vaccine R&D, and as more than just clinical trial participants.[31] Meaningful community engagement should be a mandatory aspect of the clinical development of new TB vaccines.

For all stakeholder engagement, the use of social media platforms should be explored. These are powerful tools, widely used in low- and middle-income countries, and can be used for multiple purposes, including communication and fundraising.

Key actions

c.1 Create a supportive environment for TB vaccines
Key actions

Increase political commitment for new TB vaccines, to ensure new political commitment at country level and to sustain high-level commitments, making sure that existing commitments and defined targets are met. TB advocates need to clearly communicate the need for, efficacy and safety of new TB vaccines to policymakers, including risk–benefit analyses. They also need to organise political advocacy and high-level engagement.

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.

Harmonise and fast-track regulatory review and local approval of vaccine trial protocols based on the example of the African Vaccine Regulatory Forum (AVAREF).[32] Establish NITAGs in countries that do not have them and strengthen their capacity. Fast-track regulatory approval of TB vaccines, learning from the experience with COVID-19 vaccines.

Create innovative incentives: forecast country demand; engage with multilateral funders, including Gavi, the Global Fund, Unitaid and the Coalition for Epidemic Preparedness Innovations (CEPI), to develop novel financing mechanisms for TB vaccine development and deployment.

c.2 Overcome barriers to delivery and uptake
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 optimise communication of this rationale through multiple channels. Engage with end-user communities from the start of the research process. Build resilient information systems to counter vaccine-related misinformation and disinformation.

Develop approaches for 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.

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31 AERAS. Good Participatory Practice Principles for TB Vaccines Trials. 2017. New York: AVAC. Available at: https://www.avac.org/resource/good-participatory-practice-guidelines-tb-vaccine-research-2017.
32 *https://www.afro.who.int/health-topics/immunization/avaref*

c.3 Promote TB vaccine and research literacy

Key actions

Create a global programme for community engagement and training for new TB vaccines (as already exists for TB drugs). Develop mechanisms for engaging community representatives in TB vaccine development, for example by defining a role for community members in setting the research agenda, reviewing clinical trials protocols, consulting on trial procedures and conduct, and informing the dissemination of results. Build the capacity of community representatives so that they are better able to engage with policymakers, including parliamentarians and legislators, and can be effective advocates for investment 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.

Access and commercialisation

Throughout the roadmap, various actions relate to **commercialisation of vaccine development and manufacturing, and access to new TB vaccines when licensed**. This section lists the current market-related constraints for new TB vaccines, the options for dealing with these constraints and the specific roadmap actions relating to each option. It is not meant as a comprehensive overview of all aspects of access and commercialisation, but rather provides the framework for actions in this roadmap relating to these topics.

Given the global disparity in TB incidence, the greatest 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 small 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 an attractive return on investment. This offers little incentive for industry, mainly concentrated in high-income countries, to engage in expensive product R&D and places major constraints on TB vaccine development.

Experience with other vaccines suggests the following solutions to address these constraints:

- **Push mechanisms**: stimulate TB vaccine R&D by public-sector funding and coordination.
- **Pull mechanisms**: incentivise industry to engage in TB vaccine R&D, for example through advance market commitments and regulatory incentives.
- **Technology transfer**: enable manufacturers, especially in low- and middle-income countries, to produce licensed vaccines.
- **Tiered pricing**: develop differential prices for high-income versus low- and middle-income countries.

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

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, philanthropy and donors; attract new entrants).

- Enabling condition A, funding: a2. Develop innovative financing mechanisms for TB vaccine R&D (establish collaborations or partnerships for joint funding of trials; customise calls to the 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 the 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, brought together governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy, with the aim of providing equitable access to COVID-19 vaccines.

Importantly, while demand forecasts and value proposition statements are needed (see action line 4), these data alone will be insufficient to de-risk commercial investment. Companies and investors will want forecasts to be backed by

commitments in which not only donors but also recipient countries share risk.

Key actions in this roadmap related to pull mechanisms are listed under:

- Action line 4: epidemiology and modelling: 4.1. Country-specific data and projections (conduct in-depth country-specific value proposition analyses; use 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, passing on the know-how required to manufacture a specific vaccine, can 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 high-quality products. As production costs are generally lower than in high-income countries, the prices of vaccines will be lower 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 production-scale processes, including all associated technologies, to full local production. Most technology transfer initiatives for vaccines have been instigated by non-profit organisations and institutes.

While technology transfer can facilitate access if the market conditions are right, a range of commercial models likely need to be explored for TB vaccines. Given the lack of a robust high-income market, to remain interested in advancing TB vaccines through clinical development, companies need some mechanism that can provide a return on investment. Models are needed that provide innovators with sufficient incentive to remain in the market, while ensuring that commercial arrangements do not hinder access.

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 harmonisation is also important.

Key actions in this roadmap related to technology transfer 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; harmonise regulatory review).

Tiered pricing

Tiered pricing can improve access where there is segmentation of resource-poor and resource-rich vaccine markets. This is not likely to be a viable option for new vaccines for prevention of TB disease in adults and adolescents, because of limited demand for such vaccines in resource-rich, low TB-incidence countries. It may be an option for new vaccines for improving TB treatment outcomes.

Through these combined actions, new TB vaccines will become available to socially and economically deprived populations, and to vulnerable groups such as people living with HIV or type 2 diabetes, young children and older people. 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.
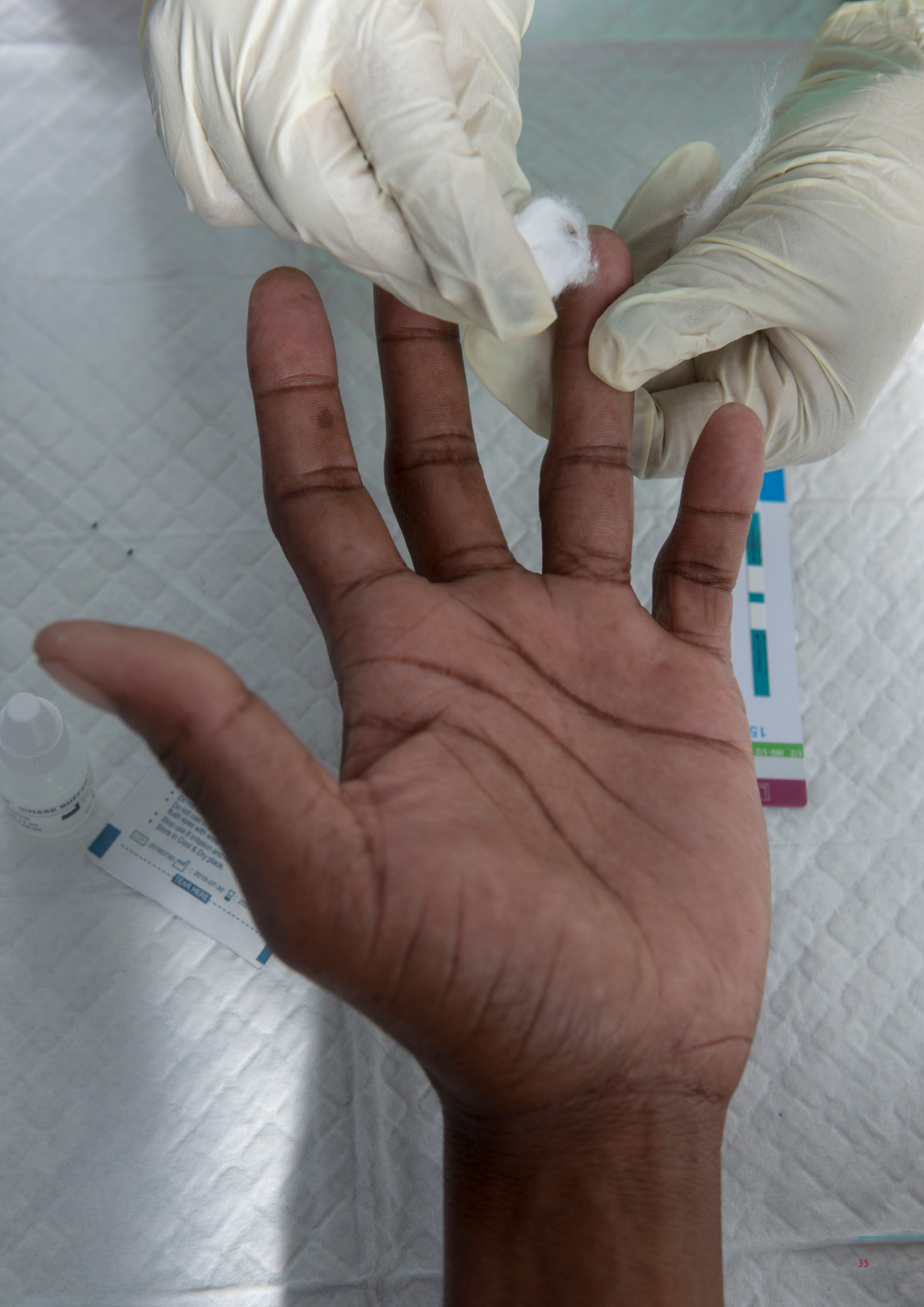
List of abbreviations

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 papillomavirus
IFN-γ	Interferon-gamma
IGRA	Interferon-gamma release assay
MAIT cells	Mucosal-associated invariant T lymphocytes
Mtb	*Mycobacterium tuberculosis*
NGO	Non-governmental organisation
NITAG	National Immunisation 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 Organisation

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- South African Tuberculosis Vaccine Initiative
- Statens Serum Institut
- The Union
- Treatment Action Group
- TuBerculosis Vaccine Initiative

- Unitaid
- United States Agency for International Development
- University of Geneva
- University of Leiden
- University of Oxford
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- University of Zaragoza
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Colophon

The power of sharing science