



EDCTP

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AMSTERDAM INSTITUTE FOR
GLOBAL HEALTH & DEVELOPMENT

Global roadmap for research and development of tuberculosis vaccines



Summary

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About EDCTP



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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.

Global roadmap for research and development of tuberculosis vaccines

Development of the Global roadmap for research and development of tuberculosis vaccines was supported by EDCTP through a grant to the Amsterdam Institute of Global Health and Development (AIGHD). The project was carried out in close collaboration with WHO.

The roadmap and supporting documents can be found at: www.edctp.org.

Global TB vaccine R&D roadmap

The Global roadmap for research and development of tuberculosis vaccines identifies a set of priorities to coordinate global action to accelerate the development and implementation of new TB vaccines.

Responsible for more than 1.4 million deaths a year, TB is a major global public health challenge. Ambitious global TB control goals have been established, but it is widely recognised that these will not be achieved without safe and effective vaccines.

WHO has identified a need for three distinct types of TB vaccine:

- A safe, effective and affordable TB vaccine for adolescents and adults.
- An affordable vaccine for infants that is superior to BCG.
- A therapeutic vaccine to improve treatment outcomes.

TB is a disease of poverty and is found primarily in low- and middle-income countries. Despite the huge global burden of disease,

there is little commercial incentive to develop new TB vaccines – no new vaccine has been introduced since BCG in the 1920s. Addressing this gap will require coordinated cross-sectoral partnerships and a focus on “end-to-end” clinical development, from early-stage discovery research through to programmatic implementation.

This roadmap has been developed through an iterative global consultative process designed to identify the key barriers to TB vaccine R&D and implementation, and potential ways in which they might be overcome. It is intended to provide a shared set of priorities to guide the activities of all stakeholders with an interest in TB vaccine development and use.



Key themes

The roadmap consultation identified three priority areas:

- Diversifying the pipeline.
- Accelerating clinical development.
- Ensuring public health impact.

Three cross-cutting enablers were also identified: funding, open science and stakeholder engagement.

Diversifying the pipeline

The TB vaccine pipeline is not well-stocked and lacks diversity. Early-stage R&D has focused on a limited number of *Mycobacterium tuberculosis* (Mtb) antigens and on a very specific type of immune response (induction of Th1 cells). There is a need to:

- Increase the diversity of the pipeline by focusing on a wider range of antigens, immune responses and delivery mechanisms.
- Improve understanding of correlates of protection and identify biosignatures that correlate with vaccine-induced protection.
- Improve understanding of mucosal immune responses in the lung and how they relate to systemic responses.
- Explore the potential use of controlled human infection models.

Accelerating clinical development

Clinical evaluation of TB vaccines is slow, high-risk and costly. In part, this reflects the fact that efficacy in animal models is not a good predictor of efficacy in people, making it difficult to prioritise candidates for clinical evaluation.

A further important barrier is the lack of well-defined correlates of protection or proxy measures of efficacy. Demonstration of efficacy therefore requires large trials with prevention of disease as the primary endpoint.

To address these and other clinical development barriers there is a need to:

- Optimise animal models by “back-translating” findings from successful clinical trials.
- Optimise alternative endpoints, by establishing the relationship between

prevention of disease and other possible endpoints (particularly prevention of infection and prevention of recurrence).

- Harmonise and standardise trial protocols, and explore innovative trial designs to improve efficiency.
- Build clinical trial capacity in high-burden countries.

Ensuring public health impact

Licensing approval is a key milestone in new product development, but does not by itself deliver public health benefit. Multiple barriers may hamper the timely implementation of a newly licensed TB vaccine.

Key challenges include limited understanding of how a new vaccine would be used within different countries, as well as the lack of investment cases to support national and global decision-making on procurement and implementation. Complex questions arise, including which populations should be targeted, how a vaccine would be distributed, and how impact would be assessed. Since a TB vaccine could be used in age groups not normally targeted for immunisation, implementation could also present significant logistical challenges.

In addition, cost–benefit analyses are challenging given multiple interdependencies – for example, prices depend on production volumes and therefore country demand, but demand will depend on pricing.

To address these issues there is a need to:

- Collect epidemiological and other data to model potential impacts of vaccine use.
- Use modelling to develop country-use scenarios and investment cases.
- Undertake activities to prepare countries for evaluation of newly licensed vaccines and rapid implementation once recommended locally.
- Identify and develop strategies to address potential barriers to implementation, including community resistance to TB vaccination.
- Plan post-licensure studies to establish vaccine effectiveness, safety and health impact when vaccination is scaled up.

Enablers

Funding: TB research is underfunded globally and, within TB, vaccine research is particularly poorly resourced. Efforts are needed to increase funders' interest in TB vaccine R&D and to attract additional funders. Greater coordination across funders could help to increase R&D productivity and accelerate clinical evaluation.

Innovative funding and other “push” mechanisms needs to be combined with market-shaping “pull” approaches, such as advance market commitments, to catalyse greater commercial interest in TB vaccine R&D.

Open science: A failure to publish data, particularly negative results, can lead to unnecessary duplication of efforts and research

being carried out on approaches unlikely to be successful. Global efforts are required to encourage greater sharing of data and specimens, with biobanks and data platforms established to facilitate sharing.

Stakeholder engagement: It will be important to engage with a wide range of stakeholders, including global agencies, industry, regulatory authorities, national decision-makers and communities. Goals of stakeholder engagement include advocacy for additional investment in TB vaccine R&D, awareness raising of the need for and possibilities presented by new TB vaccines, and mobilisation of community support for TB vaccination.

Conclusion

There remains an urgent need for TB vaccines to fulfill multiple roles in TB control. Although promising results have been obtained in recent trials, there is still a need to build a stronger and more diverse TB vaccine pipeline. It is equally important to begin preparing the ground now for the introduction of new TB vaccines.

Although licensing is seen as a key milestone in new product development, it is only one step in the pathway to public health impact. An end-to-end perspective needs to be adopted so that clinical development is informed by a sound understanding of national decision-making and implementation constraints, and licensing is swiftly followed by efficient programmatic implementation.

Progress will be accelerated if all stakeholders collectively and collaboratively focus on the priorities identified in this roadmap. The unprecedented speed at which COVID-19 vaccines have been developed holds important lessons that can be applied to speed the development and equitable implementation of new TB vaccines. One hundred years after BCG, there is real hope that disadvantaged populations around the world can finally gain the benefits of TB prevention and cure through the use of vaccination.

Tuberculosis vaccine R&D roadmap

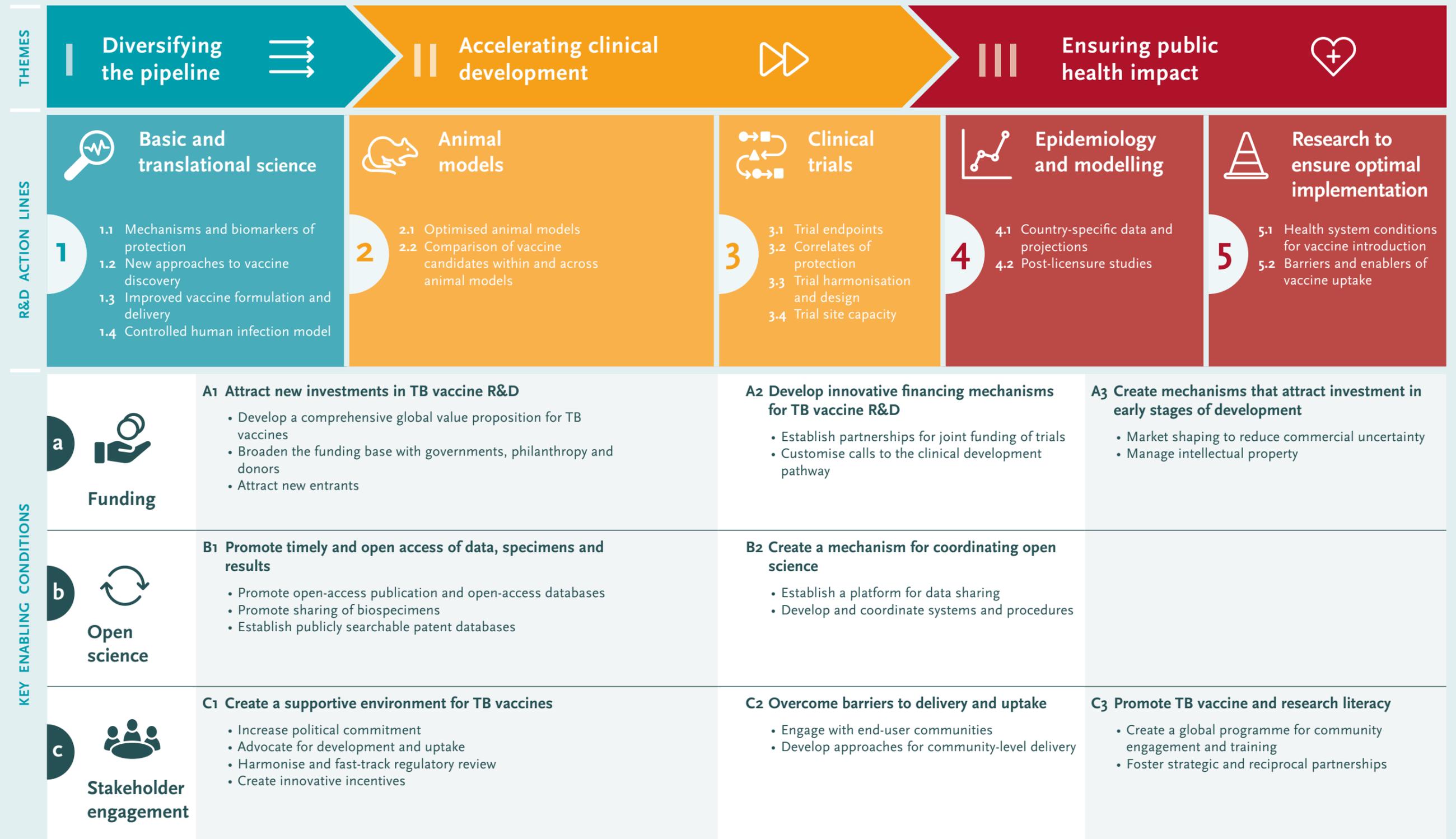


Figure 1: TB roadmap with three main themes (I–III), five R&D action lines (1–5) and three key enabling conditions (a–c)

Colophon

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