8

ACCELERATING DEVELOPMENT OF NEW TB TOOLS

PRIORITY ACTIONS

- Invest, at minimum, US$ 4.22 billion annually to accelerate the R&D of new TB diagnostics, medicines and vaccines. Resources need to be mobilized from governments and philanthropies, increased engagement with the private sector, and new approaches to innovative and sustainable financing.
- Accelerate the development of new tools to prevent, diagnose and treat TB by identifying innovative product-development pathways and improving collaboration among actors in product development. Research goals include:
  - Vaccines:
    - Develop a new TB vaccine by 2025.
    - Diversify and broaden the pipeline of next-generation TB vaccine candidates by expanding research on Mtb immunology and basic mycobacteriology, and develop animal models that better reflect human infection and disease.
    - Provide resources and support to efficiently move a diverse range of vaccine concepts from the laboratory to the clinic.
    - Significantly accelerate clinical development of vaccine candidates and ensure sufficient financing, resources and capacity to advance multiple promising candidates through efficacy trials and licensure without delay.
    - Conduct research on correlates of vaccine-induced protection during vaccine efficacy trials to inform vaccine design and expedite clinical trials of future vaccine candidates.
    - Work with countries and affected communities to prepare for successful licensure and roll-out of new TB vaccines once licensed (see Chapter 4).
  - Diagnostics:
    - Develop rapid, affordable tests for diagnosis or triage that do not rely exclusively on sputum and are used at the point of care.
    - Develop accurate DST for critical medicines, including through sequencing-based tests and strategies for early detection of resistance to the medicines used in regimens.
    - Improve tools for detecting TB infection (i.e., latent TB) and subclinical TB, and testing for risk of progression to active disease.
    - Develop and harness AI and machine learning-based tests.
  - Medicines:
    - Increase and advance the number of novel drug candidates in the clinical pipeline.
    - Advance the development of new treatment regimens that will be superior to current regimens for drug-sensitive and drug-resistant forms of TB.
    - Focus on treatment-shortening strategies for both TB disease and TB infection.
- Invest at least US$ 800 million per year in basic science research.
- Expand the use of operational research.
- Develop and implement digital tools.
- Create an enabling environment for TB R&D.
- Apply best practices in community engagement throughout the R&D process.
- Apply access principles in rolling out and optimizing the use of new tools.
- Strengthen advocacy for TB R&D.

INVEST, AT MINIMUM, US$ 4.22 BILLION ANNUALLY TO ACCELERATE THE R&D OF NEW DIAGNOSTICS, MEDICINES AND VACCINES

Investments in science and technology are crucial to tackling any disease and are an absolute necessity to reach goals of elimination of disease. For TB, a disease that primarily affects the developing world, funding has always fallen short of meeting the basic required levels to support R&D needs.

Without new medicines, diagnostics and effective vaccines, we will not achieve the steep reductions in incidence and mortality that we need, and millions more people will get sick or die from the disease. After years of under-investment, developing these tools will require commitment and funding from governments, the private sector and philanthropic organisations that is on par with the urgent need for innovation. It will also require a radically transformed approach to accelerating promising medicine, diagnostic and vaccine candidates through the development pathway. R&D efforts should be needs-driven, evidence-based and guided by the core principles of affordability, efficiency, equity and collaboration.

In the **UN Political Declaration on TB**, UN Member States recognized the "lack of sufficient and sustainable financing" for TB research and innovation. In response, they committed to "mobilize sufficient and sustainable financing, with the aim of increasing global investments to US$ 2 billion per year in order to close the estimated US$ 1.3 billion gap in funding annually for tuberculosis research". For a few reasons, TB R&D resource needs have since increased to a minimum of US$ 4 billion annually.

First, investments in TB R&D have consistently fallen short of the need. In 2020, governments collectively invested only US$ 642 million in TB R&D (of a total US$ 915 million from all funding sources). Adjusted for inflation, total investment in TB R&D **was flat between 2018 and 2020**. The commercial pharmaceutical sector has also invested very little in TB R&D, including almost nothing for vaccines. In contrast to their support for a COVID-19 vaccine, multilateral funders such as Gavi and the Coalition for Epidemic Preparedness Innovations (CEPI), and the multilateral development banks have not yet contributed significant resources to support TB R&D. As a consequence, TB R&D continues to suffer from a lack of funding.

Second, funding needs are projected to increase as certain promising product candidates need to be tested in Phase III clinical trials, which are larger and more costly to implement than earlier phase trials. This is the first Global Plan to cost out Phase III vaccine trials.

Table 11 shows annual TB funding needs for the R&D of new TB medicines, diagnostics and vaccines from 2023 to 2030.

Table 11. Resources needed for TB R&D, 2023–2030

Tool	Investment needed (US$ billion)
Medicines	16.06
Diagnostics	7.72
Vaccines	10.00
Total	33.78

US$ 40.18 billion is needed to accelerate the R&D of new TB medicines and treatment regimens, diagnostics, and vaccines from 2023 to 2030. This includes US$ 800 million annually for basic science research.

While the figure includes R&D resource needs for new vaccines, the roll-out of a new vaccine is costed separately and expected to begin in 2026. (See Chapter 9 for a detailed discussion of TB financing. See Chapter 4 for details on vaccine implementation.) The Global Plan urges countries to increase investment in the operational research required to identify the most effective ways of implementing new tools in various national contexts.

A fuller treatment of recent TB R&D funding trends, including analysis of funding for basic research, operational research and paediatric TB research, is found in the annual **Tuberculosis research funding trends reports** produced by Treatment Action Group and the Stop TB Partnership.

The resource needs for TB R&D are greater than the US$ 2 billion funding needed in previous years. The increased need reflects the lack of investment in previous years and includes the costs of carrying out large-scale Phase III vaccine trials—a cost that reflects advances in vaccine R&D in recent years. Costed priorities are presented in the R&D strategic frameworks for diagnostics, medicines and vaccines below. (See Chapter 9 for a discussion of mobilizing resources for TB R&D.)

Apply lessons from the development and distribution of previous innovations

Investments, partnerships and global multisectoral efforts have translated into remarkable impact in creating effective therapies for HIV and, more recently, COVID-19. Advocacy, a sense of urgency, political will, and substantial public and private investments have proven critical to generating these impressive results. The TB R&D community has much to learn from these efforts.

Working together, governments, the private sector and philanthropic organisations identified new approaches and pathways to development, which enabled them to move quickly through the R&D and regulatory processes and introduce new products in record time. At the same time, the global community failed to ensure that new vaccines were distributed equitably around the world. High-income countries amassed large vaccine stocks and quickly achieved relatively high rates of vaccine coverage, while LICs faced challenges in acquiring vaccine stock and distributing vaccines efficiently, leading to relatively low rates of vaccine coverage during the same time period.

The urgency is even greater now than in the past, considering the pandemic's impact on TB R&D, which includes the diversion of resources (human, financial and infrastructural) and delays in TB research activities. With immense resources invested in COVID-19, scientists today have even less incentive to develop careers in TB research. New resources are critically needed to rebuild TB R&D capacity and safeguard TB innovation from potential future disruptions.

ACCELERATE THE DEVELOPMENT OF NEW TOOLS TO PREVENT, DIAGNOSE AND TREAT TB BY IDENTIFYING INNOVATIVE PRODUCT-DEVELOPMENT PATHWAYS AND INCREASING COLLABORATION AMONG KEY STAKEHOLDERS IN PRODUCT DEVELOPMENT

The following section lays out strategic frameworks for accelerating the R&D of new TB vaccines, diagnostics and medicines (see Tables 12a–e, Table 13).

New vaccines R&D

Vision: To develop new, more effective vaccines that will directly and safely prevent TB in all age groups and populations and are affordable and accessible to those who need them the most.

Goals:

1. Develop new TB vaccines that prevent TB infection, TB disease and/or recurrence of TB disease following successful treatment of TB, thereby interrupting TB transmission.
2. Incorporate the goal of equitable accessibility throughout the TB vaccine R&D process.
3. Strengthen community engagement in TB vaccine R&D.

Table 12a. Strategic framework adapted from the Roadmap for research and development of new TB vaccines, published by the European & Developing Countries Clinical Trials Partnership (EDCTP) and Amsterdam Institute for Global Health and Development (AIGHD), April 2021

Objective 1: Diversify the TB vaccine pipeline to increase probability of success in developing effective new TB vaccines			
Priority	**Key Actions**	**Comments**	**Funding Required (US$ million)**

Objective 1: Diversify the TB vaccine pipeline to increase probability of success in developing effective new TB vaccines			
Mechanisms and biomarkers of protection	Conduct observational clinical studies combining pathogenesis and immunology, making use of systems biology, epidemiology and modelling.	Identify components of the host–pathogen interaction associated with clearance, progression to disease and subclinical disease; identify biomarkers and biosignatures of natural protection.	1,000
	Study the role of non-conventional cellular immunity, antibody responses and trained innate immunity in natural and vaccine-induced protective responses.	Explore cellular responses through class-I restricted CD8+ T cells, Th17 cells and MAIT cells; B- cell and antibody responses including Fc-mediated antibody effector functions; and innate immune responses through unconventionally restricted T cells and epigenetic reprogramming of monocytes and natural killer cells. Investigate their role in human immune responses to Mtb	
	Identify biomarkers and biosignatures that correlate with vaccine-induced protection.	Based on data and biological samples from trials that have shown protection signals; through targeted approaches to detect cellular and/or humoral immune responses and unbiased approaches including transcriptional profiling of blood cells and mycobacterial growth inhibition assays	
Undertake novel approaches to vaccine discovery.	Develop new vaccine concepts that induce a broad diversity of potentially protective immune responses.	Explore candidates that generate non-conventional cellular immunity, protective antibody responses and trained innate immunity.	
	Study mucosal immune responses.	Understand the determinants of protective immune responses in the lung parenchyma and mucosa, and how these can be inferred by systemic responses.	
	Discover antigens that are protective in humans.	Identify Mtb expressed proteins, peptides and non-protein antigens that can be recognized by the human host immune system, applying IFN-γ and non-IFN-γ based screening approaches, including by genome-wide strategies.	
Develop and apply improved vaccine formulations and delivery platforms.	Study the effects on vaccination outcomes of adjuvants, vaccine platforms and lineage of the Mtb challenge strain.	Among other approaches, through experimental medicine studies	200
	Explore new routes of vaccine administration.	Including aerosol and intravenous approaches, among other approaches, through experimental medicine studies	
	Study how vaccines can direct immune responses to the lungs.	Evaluate the capacity of different formulations and delivery platforms to induce mucosal immune responses.	
Establish a controlled human infection model.	Develop a controlled human infection model for immunobiology studies.	To inform basic knowledge gaps, as well as for proof-of-principle studies to inform down-selection of candidates, platforms and routes of administration. Participant safety, sensitivity and ethical issues will be critical to address.	50
Advance promising vaccine candidates from early preclinical to clinical development.	Conduct the necessary studies for investigational new drug (IND) or equivalent regulatory submission.	To provide development partners, funders and regulators with sufficient evidence of safety (including necessary toxicology studies) and intended biological activity (e.g., immunogenicity; protection in preclinical challenge models) to support and enable advancement to Phase I clinical studies.	550

Table 12b. Priorities and actions to accelerate clinical development of new TB vaccines: animal models

Objective 2: Optimize and standardize animal models for understanding TB mechanisms of protection and accelerating vaccine development			
R&D Priority	**Key Actions**	**Comments**	**Funding Required (US$ million)**
Optimize animal models.	Develop fit-for-purpose animal models.	Back-translate the results/findings from adolescent/adult and paediatric trials into immunogenicity, infection and disease animal models, ideally using the same product as in humans, and from clinical studies of disease progression and subclinical disease.	735
	Develop animal models to provide insight into the relation between prevention of Mtb infection (PoI) and prevention of TB disease (PoD)	Leverage results from human trials with PoI, and ideally both PoI and PoD, end-points, as well as from clinical studies of clearance and disease progression to optimize animal models.	
	Develop immune-compromised animal models that can predict/replicate findings in specific human target populations.	Back-translate the results that emerge from clinical trials, including those in all age groups and immune-compromised humans, into disease animal models.	
Compare vaccine candidates within and across animal models.	Standardize and harmonize animal models.	Standardize and harmonize the selection of Mtb challenge strains; define protection outcomes, including the use of imaging and scoring gross pathology specimens. Identify priorities for future experimental directions, e.g., assessing aerosolized delivery of vaccines.	
	Perform head-to-head testing of candidate vaccines.	Perform these tests in independent laboratories using the standardized models that best predict protection in humans.	

Table 12c. Priorities and actions to accelerate clinical development of new TB vaccines: clinical trials

Priority 3: Advance candidates through clinical trials			
R&D Priority	**Key Actions**	**Comments**	**Funding required (US$ million**

Priority 3: Advance candidates through clinical trials			
Conduct clinical trials utilizing portfolio management and common stage-gating criteria.	Implement Phase III trials of vaccine candidates that meet criteria to advance to licensure and policy recommendations.		6500
	Continue to support vaccine candidates through the clinical pipeline and initiate new Phase I/IIa/IIb trials using PoI, PoR (prevention of relapse) and PoD end-points.	Prioritize the use of PoD end-points in adolescent/adult populations, considering the likely disproportionate effect on reducing the spread of Mtb (compared to PoI or PoR approaches or studies in infants and young children).	
	Include safety trials or safety assessments for PLHIV in clinical trial planning and implementation.		
Ensure adequate clinical trial site capacity in high TB burden regions to conduct global regulatory standard human trials of novel vaccines.	Conduct an inventory of clinical trial site capacity.	Identify additional sites; assess their quality and suitability in terms of existing technical and laboratory infrastructure.	
	Collect epidemiological data in sites considered for Phase II/III trials.	In various parts of the world, continuously collect age-stratified data on TB incidence; age-stratified incidence/prevalence of TB infection; Mtb lineage distribution; data on special populations such as PLHIV and other populations considered for vaccine trials.	
	Develop vaccine trial sites, including sustainable human resources capacity.	Develop infrastructure and human resources capacity, including mentorship and support for junior investigators, in diverse geographical locations to take account of potential variation in efficacy and safety due to heterogeneity in host and bacteriological genetic background.	
	Study potential barriers to trial acceptance.	Conduct social science research on barriers to participating in TB vaccine trials and completing follow-up, including TB-associated stigma, other stigma, and social barriers; compile best practices from successful vaccine trial sites.	
	Promote community engagement in TB vaccine trials.	Integrate community engagement into all Phase II or Phase III studies. Sponsors and developers should start developing plans for community engagement before Phase I studies start.	

Priority 3: Advance candidates through clinical trials			
Trial end-points	Define standardized PoD trial end-points that better capture the various TB disease states in diverse target populations.	Standardize the definition of laboratory-confirmed pulmonary TB; develop clinical end-points representative of subclinical TB if established as a substantial contributor to TB transmission; improve bacteriological confirmation of TB disease in neonates, infants and PLHIV; improve bacteriological confirmation of extrapulmonary TB.	8
	Define and develop better PoI trial end-points.	Define an end-point for Mtb infection for establishing PoI; this end-point should differentiate Mtb infection from vaccine-induced immune response.	
	Quantify the clinical translation of PoI into PoD.	Analyse existing and new observational data; include secondary PoI end-points in Phase III PoD trials, considering that this quantification may be different for different types of vaccines.	
Correlates of protection (CoPs)	Collect biospecimens for identifying CoPs.	In planned and ongoing Phase IIb and Phase III trials	800
	Identify CoPs for TB disease.	From Phase IIb and Phase III trials that have shown protection: analyse data and putative CoP values from individual trials and, if possible, from meta-analyses of several trials.	
	Validate CoPs for TB disease.	Validate putative CoPs identified by back-translation of trial results in terms of vaccine-induced response and clinical protection in immunogenicity studies, new trials with a clinical PoD end-point and potentially controlled human infection models. Validate identified CoPs in PLHIV to enable immuno-bridging studies.	
Trial harmonization and design	Harmonize clinical trial protocols.	Define an agnostic trial "shell" of standardized outcomes, inclusion criteria and measurements for clinical trials for different vaccine types. This would also address secondary end-points; inclusion criteria for people living with HIV infection or diabetes; and standardized measurements over time.	7
	Evaluate and develop new models for TB vaccine clinical trials with increased time- and cost-efficiency.	Phase I: explore innovative trial designs that provide information on the local human immune response. Phase IIb/III: efficacy trials within contact investigations, active case finding programmes and high-risk populations; adaptive trial designs for evaluating the safety, immunogenicity and efficacy of different vaccine types.	
Improve preclinical and clinical readouts.	Standardize reagents, harmonize assays and benchmark relevant signals by forward as well as back-translation/verification between preclinical and clinical.	Gather stakeholder input and come to a consensus on the path forward; continue to expand on programmes to provide reagents to laboratories and research facilities; develop necessary assays based on stakeholder consensus.	150

Table 12d. Priorities and actions to ensure public health impact: epidemiology and modelling

R&D Priority	Key Actions	Comments
Country-specific data and projections	Conduct in-depth country-specific value proposition analyses.	Assess value drivers for new TB vaccines across different countries and stakeholders, considering preferred delivery strategies; efficacy relative to safety; manufacturing, strain standardization and price; willingness to pay; and cost of delivery.
	Collect epidemiological data at country and subnational levels.	To inform economic and impact modelling related to country decisions on introduction of new TB vaccines and market volumes: collect data on prevalence of (sub)national TB disease and infection, including in specific risk groups; identify potential target groups for vaccination based on contribution to transmission; map *Mtb* genotypic variation.
	Conduct modelling to define vaccine development investment cases and country-specific vaccine use cases.	Model implementation scenarios, the epidemiological impact, cost-effectiveness and budget impact in consultation with countries for vaccines that are close to market introduction, using transmission and economic modelling as well as other quantitative approaches.
Post-licensure studies	Develop valid approaches for real-life vaccine scale-up studies.	Develop designs and validated tools for establishing real-world effectiveness, safety and public health impact following introduction; establish and/or support post-licensure registries making use of existing expertise from introduction of other vaccines; strengthen surveillance systems for collection of baseline epidemiological data.
	Conduct post-licensure evaluations of vaccine effectiveness, impact and safety.	Conduct real-world post-licensure studies and surveillance to establish effectiveness across various subpopulations (e.g., PLHIV) and Mtb lineages; effectiveness and safety when given concurrently with other vaccines; safety in subpopulations (e.g., pregnant women); impact on TB disease incidence; and non-specific health effects for vaccines replacing BCG.

Table 12e. Priorities and actions to ensure public health impact: research to ensure optimal implementation

R&D Priority	Key Actions	Comments
Health system conditions for vaccine introduction	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 vaccination campaigns; conditions for immunization programmes to implement these strategies; requirements for optimizing access for different population groups; integration of TB vaccination within and beyond NTPs; and approaches to measuring vaccine uptake in adolescents/adults. For a vaccine for neonates and infants: determine the fit within the Expanded Programme on Immunization and required timing with respect to other vaccinations.
	Conduct pre- and post-introduction assessments of country immunization programmes.	Assess the pre-introduction country-specific readiness of immunization programmes and health systems to handle, store and administer the new TB vaccine (considering its characteristics, particularly for delivery to adolescents and adults), to monitor vaccine coverage and adverse events, and to communicate adverse events.
Barriers and enablers of vaccine uptake	Assess drivers of acceptability and uptake of new TB vaccines in various settings.	Conduct social and behavioural research to determine across countries and settings the perceptions of decision-makers, the public and health workers on new vaccines, related to dosing, safety concerns, religious concerns, gender, use with other vaccines versus specialized programmes, and, for immunotherapeutic vaccines, integration with TB treatment.

Table 13. Priorities and actions with regard to enabling conditions for TB vaccine development

Enabling Priority	Actions
Funding	
Attract new investments in TB vaccine R&D.	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.
	Broaden the funding base with governments, charitable funders and donors. Mobilize domestic R&D funding from large countries' governments; get specific donors involved that could contribute to funding downstream aspects of TB vaccine R&D; engage with the HIV and AMR communities.
	Attract new entrants in TB vaccine R&D. Involve actors, technologies, models and knowledge from outside the TB vaccine research field; funders should promote such involvement in their funding programmes, e.g., in the specification of calls and eligibility criteria.
Innovate financing for TB vaccine R&D.	Create collaborations or partnerships for joint funding of trials with mechanisms for pooling resources between R&D funders, governments and industry; selection procedures that are product and country agnostic; and strict norms for what the funding will be used for and under what conditions.
	Customize calls to the clinical development pathway through options for flexible long-term funding (e.g., 10 years, with intermediate go/no-go decisions), enabling consortia to adopt a long-term R&D perspective for a specific candidate or approach.
Create mechanisms that attract investment in early stages of development.	Reduce commercial uncertainty by providing incentives for stronger engagement from industry and other vaccine developers through grant funding and advance market commitments with a clearly defined path to commercialization, including production of a successful candidate.
	Ensure that intellectual property can be used efficiently, openly and equitably to facilitate TB vaccine R&D in ways that promote collaboration among universities, biotech and pharmaceutical companies, and government funders.
Open science	
Promote timely and open access to data, specimens and results.	Funders and product-development partnerships (PDPs) should require registration of all animal and human studies, open access publication of both positive and negative results, data sharing and posting in open access databases as conditions for funding and/or consortium membership.
	Biospecimens collected in clinical studies should be made available based on peer review, overseen by an access committee. Access to biospecimens should not be granted on a first-come, first-served basis, but to researchers with the most innovative ideas and approaches.
	Establish publicly searchable patent databases for TB vaccine research (as exist for drug development) to promote the diffusion of knowledge by facilitating access to the information disclosed in a patent, including antigens, adjuvants, platforms and processes.
Create a mechanism for coordinating open science in TB.	Establish a platform for data sharing, starting with data from clinical studies, including generic protocols for contextual data (e.g., for what purpose the data were collected); proper use (e.g., ethical rules, privacy regulations); and acknowledgement of original collectors/contributors of the data in secondary use and publications.
	Develop and coordinate systems and procedures needed for efficient data and specimen-sharing across the field of TB research and across TB research funders.
Stakeholder engagement	

Enabling Priority	Actions
Create a supportive environment for TB vaccines.	Raise political commitment for new TB vaccines to ensure new political commitment at country level and continue high-level commitments, making sure that existing commitments and defined targets are met, based on clear communication to policy-makers about the need, efficacy and safety of new TB vaccines, including the risk–benefit and cost–benefit analyses of a new TB vaccine.
	Advocate for the development and uptake of new TB vaccines with vaccine developers and the public through positive messaging about opportunities and actions in vaccine development.
	Harmonize and fast-track regulatory review and local approval of vaccine trial protocols based on the example of AVAREF; establish National Immunization Technical Advisory Groups (NITAGs) in countries that do not have them and strengthen their capacity; fast-track regulatory approval of TB vaccines.
	Create innovative incentives by forecasting demand from countries and engaging multilateral funders, including Gavi, GFATM, Unitaid and CEPI, in offering novel financing mechanisms.
Overcome barriers to delivery and uptake.	Engage with end-user communities to address stigma, vaccine hesitancy and adherence; provide and communicate a convincing rationale for (high-risk) target groups to be vaccinated; involve end-user communities in the research process; build resilient information systems to counter vaccine-related misinformation and disinformation.
	Develop approaches to community-level delivery (e.g., through community health workers) to address gaps in access to vaccination; educate health care networks, the medical community and the general public about TB vaccine introduction through targeted, country-specific approaches.
Promote TB vaccine and research literacy.	Create a global programme for community engagement and training for new TB vaccines; develop mechanisms for engaging community representatives in TB vaccine development; engage and educate community representatives who can speak to policy-makers to invest in the development and introduction of new vaccines; support community engagement in TB vaccine 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.

The End TB Strategy calls for a new effective TB vaccine for use by 2025. It is likely that more than one vaccine will be necessary to meet the needs of different populations and different regions. This is possible if funding for new TB vaccine R&D is made available immediately, and if the scientific R&D process is fast-tracked using the same approaches used for COVID-19 vaccine development.

Scientific advances, particularly in the past five years, have demonstrated the feasibility of developing new vaccines to prevent TB infection and TB disease. These advances include positive results from two Phase IIb clinical trials. However, while these results were **published in 2018**, as of 2022 Phase III studies had not yet started, primarily due to chronically inadequate resources.

The successful development and licensure of at least one new TB vaccine by 2025 will require a transformation in the vaccine development pathway, including:

- accelerating clinical development pathways, including streamlining the design and reducing the duration of efficacy trials, while meeting regulatory requirements for licensure;
- developing animal models that reflect relevant human outcomes (i.e., resistance to infection) and are "fit-for-purpose" to prioritize vaccine candidates for human testing;
- evaluating novel vaccine technology platforms (e.g., mRNA) for TB and identifying human-protective antigens;
- developing innovative financing models and public–private partnerships that will enable the rapid development and deployment of vaccines once efficacy has been established;
- investing in scale-up of manufacturing and preparing the supply chain to ensure ample supply and rapid distribution of vaccines once licensed.

Roadmap for the R&D of new TB vaccines

In April 2021, the EDCTP and AIGHD launched a **Global roadmap for research and development of tuberculosis vaccines** (Global Roadmap). The Global Roadmap identifies key barriers to TB vaccine R&D and implementation, ways to overcome them, and a shared set of priorities to guide TB vaccine R&D activities. The Global Plan's strategic framework for TB vaccine R&D has been adapted to align with this Global Roadmap, and funding requirements were applied to these research priorities and activities. More details and information about these activities and priorities can be found in the Global Roadmap.

Recognizing that PLHIV are at high risk for TB infection and disease and that they tend to have a less robust immunological response to vaccination, a **Roadmap for developing TB vaccines for PLHIV** has been developed. This Roadmap seeks to accelerate development of TB vaccines for PLHIV by addressing gaps and unanswered questions regarding priority vaccine indications, clinical trial design, measures of safety, immunogenicity and efficacy considerations for PLHIV.

New diagnostics R&D

Vision: To ensure that all people with TB can access convenient, accurate and rapid TB diagnosis.

Goals:

1. Develop rapid, affordable tests for diagnosis or triage that do not rely on sputum and are used at the point of care.
2. Develop accurate DST for critical medicines, including through sequencing-based tests and strategies for early detection of resistance to the medicines used in regimens.
3. Improve tools for detecting TB infection (i.e., latent TB), subclinical TB and testing for risk of progression to active disease.
4. Develop and harness AI and machine learning-based tests.

Objectives:

1. Ensure expanded and equitable access to critical knowledge and resources that enable the development of new diagnostic tools.
2. Develop and evaluate a diverse portfolio of new tests and solutions.
3. Demonstrate patient benefit and predict impact within the entire health system.
4. Ensure that WHO-approved diagnostics are made available and appropriately used in relevant countries.

The last decade has seen a scaling up of automated diagnostic technologies that have been replacing sputum smear microscopy as the standard test in many parts of the world. The Global Plan calls for building on this progress to further develop and introduce the widespread use of diagnostics based on biomarkers such as urine, stool or blood that can work for all people (e.g., infants and children), for both pulmonary and extrapulmonary TB, and can be used wherever people seek and receive care (see Table 14).

To create a more enabling environment for implementing the new TB diagnostics strategic framework, in addition to new financing, developers need better access to biobanks, better access to data (including through open access arrangements), and stronger collaborations with academic research institutes. Public policy and regulatory environments that support the efficient approval and widespread uptake of new diagnostics would further help to create incentives for investment in new TB diagnostics R&D.

Table 14. R&D strategic framework for new TB diagnostics, 2023–2030

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
Objective 1			**417.15**
Ensure expanded and equitable access to critical knowledge and resources that enable the development of new diagnostic tools.	Increase access to reference materials and digital repositories that are critical for the discovery, development and validation of new TB diagnostics.	a. Facilitate sample storage and database maintenance within country of collection, reducing the need for import/export permits. b. Ensure that international biobanks and digital repositories collaborate and have centralized, open-access mechanisms and dashboards so requestors can obtain samples from anywhere. c. Promote the highest quality in biobanking and database curation to ensure global representativeness, relevance and integrity, in compliance with patient rights, data protection laws and FAIR Data Principles[1] .	62.54

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
	Integrate biomarker discovery and validation in well powered trials and studies collecting high-quality data.	Undertake research to identify and validate new non-sputum-based biomarkers and diagnostic concepts addressing high priority use cases, including paediatric TB, extrapulmonary TB, PLHIV, subclinical TB, preventing relapse, and to guide personalized medicine in TB.	316.40
	Support assessment of Mtb genetic variants to inform the development of molecular tests for the detection of DR-TB.	a. Expand the global knowledge base and repositories with genomic, phenotypic, and associated metadata from Mtb complex samples; review for quality and standardization. b. Support contributions of sequencing datasets by diverse groups (NTPs, academics, consortia, etc.) to expand and maintain a catalogue of mutations associated with resistance to anti-TB medicines that is updated periodically to ensure standardized and accurate interpretation of data.	16.00
	Undertake research and consultations to support the development of person-centred diagnostic tools and solutions.	a. Define patient charter/ethical criteria, and build consensus on appropriate patient data utilization and data protection protocols. b. Include end-users (people who have experienced TB, health workers, lab technicians, etc.) in the conceptualization, design, evaluation, and implementation of diagnostic tools and solutions, taking into account social and gender factors. c. Evaluate alternate, minimally invasive or non-invasive, easy-to-collect or self-collected specimen methods.	16.71
	Disseminate knowledge on diagnostic tools and solutions.	a. Develop clearer guidelines for validation studies for new diagnostics. b. Update target product profiles (TPPs). c. Develop and promote online country-specific platforms for knowledge-sharing on diagnostic development, ongoing accuracy trials, and implementation research, including massive online open courses (MOOCs) and in-country TB think tanks.	5.50
Objective 2			**1,6214.47**

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
Develop and evaluate a diverse portfolio of new tests and solutions.	Develop fit-for-purpose diagnostics for testing strategies addressing the major diagnostic gaps in TB.	Develop tests and solutions for the following: a. fast and affordable tests to determine risk of developing active TB disease in infected, at-risk populations; b. improved TB screening tools; c. simple and affordable POC diagnostics for TB detection in all people with TB, including those with extrapulmonary TB, PLHIV and children; d. new tools that are based on easy-to-obtain non-sputum samples; e. high-throughput centralized diagnostics; f. early detection of subclinical TB disease; g. detection of drug resistance, including both phenotypic DST and genotypic DST sequencing-based strategies; h. treatment monitoring and tests of cure; i. multi-disease platforms and tests to differentiate between pathogens, reduce antibiotic overuse, and improve self-isolation strategies; j. digital diagnostics for relevant use cases listed above.	848.93
	Conduct accuracy trials for new tests and evaluate their clinical performance in trials to guide global policy and country uptake.	Carry out accuracy trials and evaluation studies for tools a–j above.	612.54
	Ensure that any diagnostic is a connected diagnostic, so that surveillance, reporting and linkage to care is automated.	a. Support the development of standardized digital data collection tools suitable for multiple settings and transition away from paper-based data collection. b. Strengthen and centralize national TB surveillance systems using digital tools and applications. c. Incorporate connectivity elements such as digital readers/QR codes in the design of novel TB diagnostics to make the reporting of results digital. d. Improve the timeliness of reporting diagnostic results to patients using digital tools and applications.	160.00
Objective 3			**566.08**

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
Demonstrate patient benefit and predict impact within the entire health system.	Predict patient and health system impact from the use of new diagnostics and solutions to improve TB detection, reduce transmission and prevent mortality.	a. Demonstrate impact of new diagnostic tools on patient important outcomes, through pragmatic implementation trials in relevant countries and settings. b. Use diagnostic network optimization (DNO) and modelling to estimate the likely impact and cost-effectiveness of new technologies and innovative diagnostic strategies. c. Conduct qualitative studies on end-users' (people who have experienced TB, health workers, lab technicians, etc.) values and preferences, quality of care, and health system utilization.	549.08
	Conduct market analysis and estimate the potential of new diagnostics.	Update and expand existing market assessments.	4.00
	Work with companies and regulatory bodies to streamline the process of regulation, WHO prequalification, and national and international approval.	a. Conduct quality assurance and post-marketing surveillance. b. Support and streamline processes for WHO prequalification and national regulatory processes.	13.00
Objective 4			**5,115.12**
Ensure that WHO-approved diagnostics are made available and appropriately used in relevant countries.	Roll out tools and solutions, supporting transition away from smear microscopy for TB diagnosis.	Procure devices and consumables for the roll-out of WHO-approved molecular tools and innovative solutions (new and existing) for roll-out in high-burden countries.	4,158.00

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
	Effectively integrate diagnostic tools within the health system, including within the private sector.	a. Empower countries to develop fit-for-purpose models using DNO to optimize the placement and integration of diagnostic tools based on country contexts. b. Integrate TB diagnostic services with diagnostic services for communicable and non-communicable diseases. c. Incentivize the private sector, including pharmacies, medical clinics and hospitals, to use WHO-endorsed tools. d. Strengthen information technology (IT) capacity to implement more advanced diagnostic technologies that use AI. e. Strengthen laboratory capacity for appropriate scale-up of new tools via: i. training (coordination, development of tools, sessions, training supervisors, reference specimen transfer); ii. empowering in-country partners (e.g., supranational reference laboratories, centres of excellence) to support introduction of new tools in-country and promote operational research; iii. external quality assurance and accompanying measures for tools being used; iv. ongoing external and within-country assistance, including for supply management aspects.	526.50
	Ensure patient-centred diagnosis and decentralization of testing where appropriate.	a. Include people with TB in decision-making/policies regarding TB diagnostics. b. Develop patient-centred solutions for effective, rapid sample collection and transportation. c. Ensure that proper services are in place to link patients to care following their diagnosis.	48.00
	Support rapid policy change at the country level for implementation and facilitate in-country regulatory processes.	a. Support country-specific policy change and regulatory processes (local cost-effectiveness and validation studies). b. Harmonize regulatory processes in high-burden countries with stringent regulatory systems and with difficult markets to penetrate.	59.62

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
	Sensitize stakeholders on diagnostic uptake and national diagnostic algorithms.	Coordinate with advocacy groups and civil society to organize workshops with NTPs, ministries of health, technical procurement and funding agencies, medical associations (pharmacy, chest physicians etc.), and patient representatives.	35.00
	Scale up manufacturing and other market interventions to bring prices down.	a. Invest in commercialization and successful scale-up, including local diagnostic start-ups and companies to create lower cost, innovative diagnostic solutions. b. Support local manufacturers to improve scale-up. c. Conduct market interventions to reduce the price of diagnostic products (e.g., pool procurement mechanisms, advanced market commitment, volume guarantee, demand forecasting, demand generation, cost of goods sold [COGS], optimization, new channels, etc.).	264.00
	Expand next-generation sequencing (NGS) capacity in countries by 2030 and establish hubs for genomic drug resistance surveillance.	a. Build capacity and sustainable infrastructure, and provide training and support in genomics and bioinformatics to implement NGS approaches for genomic surveillance of DR-TB at the reference laboratory level. b. Reinforce the mechanism to use the supranational reference laboratory network and WHO collaborating centres as the main drivers to provide training, study guidance and long-term support.	24.00
TOTAL			**7,719.82**

New medicines R&D

Vision: Develop shorter, more effective, and safer medicines and regimens for all age groups and populations affected by TB.

Goals:

1. Introduce shorter treatment regimens (less than four months) for treating all forms of TB using three or four new medicines with no cross-resistance to existing medicines.
2. Introduce shorter regimens for TPT.

Objectives:

1. Sustain the pipeline through basic discovery for TB medicines.
2. Increase trial site capacity.
3. Introduce shorter regimens for DS-TB and, where appropriate, evaluate as potential universal regimens.
4. Develop a safe, higher efficacy and shorter (four-month) regimen for MDR-TB.
5. Improve TB treatment for children.
6. Develop a safer, high-efficacy regimen for TB infection.
7. Ensure adoption of new TB medicines and regimens at country level.
8. Engage community and civil society in the entire process of medicine development and access.

Currently available treatment regimens, while improved in recent years, still require several months of treatment with multiple antibiotics. Treatment regimens for active TB are long and complex both for people with TB and for health systems to administer. AMR is also a widespread challenge that is limiting the effectiveness of currently available regimens and will always be a looming risk factor for treatment regimens that are long and complex, as incomplete or inappropriate treatment accelerates the emergence of drug resistance.

To create a more enabling environment for implementing the new TB medicines strategic framework, developers need more financing mechanisms for advancing drug candidates from Phase I to Phase II trials without delays, more drug candidates brought together from diverse sources, and more consortia or collaborations that evaluate new regimens in late-stage clinical trials. Such consortia could play a key role in evaluating new regimens for their potential to serve as universal TB treatment regimens. Having better preclinical and translational models could help developers make better predictions about which early-stage drug candidates have the most potential for human benefit, reducing the time and costs of R&D by helping to better steer efforts towards the most promising candidates. Having more innovative financing mechanisms for funding distribution of new treatment regimens would help to create stronger incentives for investing in R&D for new TB medicines (see Table 15).

Table 15. New medicines R&D strategic framework

Objective	Milestone	Major Activities	Funding Required 2023–2030 (US$ million)
Sustain the pipeline through basic discovery for TB medicines.	Work towards one new clinical candidate entering Phase I each year.	Accelerate screening and optimization of new chemical entities; validate biomarkers of treatment outcomes; develop in vitro and animal models that are more predictive of clinical efficacy; identify new drug targets.	3,500
Increase trial site capacity.	Increase the number of Good Clinical Practice/Good Laboratory Practice (GCP/GLP) compliant sites available for TB drug trials.	Identify, maintain and develop new GCP/GLP compliant sites, including clinical trial sites, clinical laboratory, pharmacy, and biospecimen storage capacity.	900
Introduce shorter regimens for DS-TB and, where appropriate, evaluate as potential universal regimens.	Complete Phase III trials of a DS-TB regimen that is shorter than four months and assess regimens for all forms of active TB.	Conduct trials: pharmacokinetics studies, Phase I, Phase II (early bactericidal activity, serial sputum colony counting, drug-interaction studies), and Phase III to advance two to three new treatment-shortening regimens.	7,200
Develop a safe, higher efficacy and shorter (four-month) regimen for MDR-TB.	Complete Phase III trials of a shorter regimen for MDR-TB.	Conduct trials: pharmacokinetics studies, Phase I, Phase II, and Phase III to advance two to three new treatment-shortening regimens.	2,000
Improve TB treatment for children.	Complete formulation development and clinical testing in children.	Include children in trials as early as possible for new regimens; develop safe, reliable and user-friendly regimens for all forms of childhood TB early in the development process; conduct drug-interaction studies.	430
Develop a safer, high-efficacy regimen for TB infection.	Complete Phase III of a safer, high-efficacy regimen for TB infection.	Conduct Phase III trials of new regimens for TB infection with the aim of a shorter duration of treatment with high efficacy and safety.	330
Ensure adoption of new TB medicines and regimens at country level.	Enhance patient access to newly approved medicines and regimens, especially in high-burden countries.	Include new medicines and regimens in national policies and guidelines; implement mechanisms to expedite regulatory processes in countries; engage key stakeholders; conduct extensive training of health providers.	1,500
Engage community and civil society in the entire process of medicine development and access.	Recruit TB-affected community and civil society members to all decision-making processes and forums along the medicine discovery and development pipeline.	Include TB-affected community and civil society representatives, and specifically key and vulnerable populations, in advisory committees, protocol and study design, scientific networks and other forums related to TB drug development to ensure adequate medicine access.	200
TOTAL FUNDING REQUIRED			**16,060**

Meeting the unique needs of children and adolescents

Research efforts directed towards TB in children and adolescents have focused mostly on finding out how to better apply existing tools. However, children and adolescents have needs that differ from those of adults. For example, children have a hard time producing sputum, making them poor candidates for diagnosis using tests that require sputum collection (e.g., the rapid diagnostic test Xpert MTB/RIF).

Treatment Action Group and the Stop TB Partnership Child & Adolescent TB Working Group have laid out **a detailed agenda for child and adolescent TB R&D**. Priorities include the following:

Prevention: Identify new, shorter and simpler preventive regimens; develop a new vaccine for infants, children and adolescents that improves on the current BCG vaccine.

Diagnosis: Develop novel tests that are not invasive, do not rely on sputum, and can be used at the point of care.

Treatment: Evaluate the safety and efficacy of new TB medicines in children and adolescents to determine optimal dosing; identify treatment regimens that are shorter and simpler than those currently available; and ensure that TB treatment regimens are available in child-friendly formulations.

Basic science research: Research is needed to better understand how TB affects infants, children and adolescents, including the immune response to infection and associated biomarkers that can inform the development of new tools.

---

1. Guiding principles that make data findable, accessible, interoperable and reusable (FAIR Data Principles)

INVEST AT LEAST US$ 800 MILLION ANNUALLY IN BASIC SCIENCE RESEARCH

Scientists still **do not fully understand** how *M. tuberculosis* causes infection.. Gaining this understanding would help drive innovation and enhance the ability to develop new tools to prevent, diagnose and treat TB.

Basic science research is typically conducted by academic institutions, industry and public–private partnerships, which rely largely on public funding. At least US$ 800 million is needed annually to advance TB basic science research. This is in addition to the US$ 4.18 billion needed annually to advance TB R&D pipelines. Investments in basic science research should be used for priorities such as:

- undertaking research to understand:
  - how TB infection progresses to disease
  - how to predict the risk and stages of disease progression based on biomarkers[1]
- how to more easily and reliably know when a person has been cured through treatment;
- R&D infrastructure, including biorepositories (i.e., facilities for collecting, storing, processing and distributing specimens used for scientific research);
- developing and sustaining a larger field of TB researchers;
- improving collaboration between researchers and research centres.

---

1. LAM, discussed earlier in the chapter, is an example of a TB biomarker.

EXPAND THE USE OF OPERATIONAL RESEARCH

Operational research involves a wide range of research activities used to investigate strategies, interventions, tools and knowledge that can improve the performance of health systems and programmes. Despite improvements in recent years, large implementation gaps still exist in the delivery of TB care that is quality-assured and people-centred. Scaling up country-level capacity for operational research is essential to close those gaps and to reach universal access to TB prevention, diagnosis and treatment.

According to the WHO **Global strategy for tuberculosis research and innovation**, operational research is also necessary to understand how best to introduce and scale up new tools within various populations, and how best to combine medical care with social-service support in order to achieve the best treatment outcomes and better address the underlying factors that put people and communities at risk of TB.

Research funders should allocate specific funding for operational research, directing it as a priority towards initiatives that will build the evidence base for informing decisions that can close implementation gaps in LICs and MICs.

To be sustainable, operational research capacity needs to be more routinely embedded within NTPs, with dedicated operational research professionals and resources allocated through annual budgets.

Key priorities for operational research:

1. Understand how TB tools are used in local contexts, informing early-stage planning for the introduction of new tools in order to reduce delays between licensure and effective use.
2. Understand how to most efficiently and effectively conduct active case finding, an approach through which health systems proactively reach out to people at risk of TB and see that people receive screening, diagnosis, and appropriate care and support.
3. Improve access to treatment, care and psychosocial support, including assessing, monitoring and overcoming social, legal, political and economic barriers to access, for both DS- and DR-TB.
4. Improve access and equity for hard-to-reach populations in LICs and MICs, which is critical to achieving UHC.
5. Understand how public and private sectors can coordinate and collaborate to improve all aspects of accessing and delivering TB care and support.
6. Optimize TB infection control in order to reduce transmission.
7. Improve methods for conducting disease surveillance (including real-time digital surveillance), monitoring and evaluation of TB programmes.
8. Understand the role that TB-affected communities and TB survivors can play throughout and beyond the TB cascade of care, including in TB service delivery.
9. Improve understanding of approaches for strengthening community-level knowledge of TB and its underlying risk factors.

SORT IT

TDR—a joint effort by the United Nations Children's Fund (UNICEF), United Nations Development Programme (UNDP), the World Bank and WHO—provides a model for supporting the training of TB researchers who are working to improve TB care at the health systems level in LICs and MICs. Through the **Structured Operational Research and Training Initiative** (SORT IT)—a global operational research partnership led by TDR and implemented with over 60 partners—researchers are trained to conduct operational research according to country priorities (see, for example, impacts on operational research capacity **in Papua New Guinea and the Pacific Islands**), build sustainable operational research capacity, and make evidence-informed decisions for improving TB programme performance[1] . Participants perform classroom work, develop a research protocol and application for ethics review, receive training in data management and analysis, design a data analysis plan, write and submit a paper to a peer-reviewed journal, and acquire the skills and **tools for improved communication** of research findings (for research uptake) to policy-makers and stakeholders.

---

1. SORT IT [website]. Geneva: World Health Organization **https://tdr.who.int/activities/tackling-antimicrobial-resistance/sort-it-operational-research-and-training**

DEVELOP AND IMPLEMENT DIGITAL TOOLS

Digital health refers to using a mix of digital technologies and software applications to transform health services. These tools can be applied to a wide range of health care issues, processes and functions in order to improve physical and mental well-being at the individual and population levels (see Table 16).

Scale up the use of digital health tools

Scaling up digital health has many potential benefits, including:

- making health services more efficient;
- reducing capacity constraints in the health workforce;
- reducing costs for health systems and for people;
- improving people's access to the health system;
- reducing health inequities;
- improving health outcomes and well-being.

Scaling up digital health, especially in LICs and MICs, would help to address staffing and resource constraints that have historically made it difficult both to deliver and to access TB care. Although access to the Internet, smartphones and other forms of technology is still relatively limited in LICs, mobile "feature" phones (i.e., phones that lack the advanced functionality of smartphones, but can make calls, send text messages, and access some simple Internet features through a text-based interface) are extremely common. These phones can be used for digital health.

COMMON TYPES OF DIGITAL HEALTH TOOLS

- **Electronic health records (EHR), also known as electronic patient records (EPR):** These are software solutions that replace paper records with digital records. They can also facilitate digital transactions.
- **Telecare, also known as telehealth:** This refers to the remote delivery of health care (e.g., consultation, treatment monitoring and support) using telecommunications technology.
- **Digital medical electronics:** These include a wide range of devices that can be used inside or outside of a person's body. Common applications include medical imaging (e.g., digital chest X-rays) and electronic sensors (including sensors that can be ingested or implanted to monitor bodily functions).
- **Mobile devices, services and apps:** These are solutions that monitor and share health information using mobile technology. Devices are wearable. Apps appear on mobile phones.
- **Health analytics and bioinformatics:** These use powerful computing technology to analyse large amounts of data. Health analytics tends to focus on helping health programme managers understand trends in real-time, which helps them make better decisions to improve health care delivery and better manage disease in a population. Bioinformatics uses technology to collect and analyse large quantities of biological data, such as genomic information.
- **Digital adherence tools:** These are digital tools that support people with TB to complete a full course of appropriate treatment in a people-centred way. Video chat can be used where video communication technology is available, and can be appropriately organized and operated by health care providers and people receiving care. Mobile technology can also be used, including text messages or telephone calls, to provide ongoing treatment adherence support.

If scaled up, the digital health tools that would be especially helpful for ending TB include:

- **Computer-aided detection**: CAD is an image-based diagnostic tool. CAD is powered by software that uses AI to read chest X-rays for signs of TB and provides an output that can be used for screening and triage.
- **Diagnostics connectivity solutions:** Diagnostics connectivity provides the ability for diagnostic instruments to remotely share data, enabling instant reporting of results to clinicians and databases, real-time epidemiological surveillance, and real-time monitoring of diagnostic supplies.
- **Telemedicine** connects TB specialists with people who need care for remote consultations and treatment monitoring and support.
- **Remote adherence technologies** support people with TB to complete treatment.

Table 16. Applications of digital health solutions at different levels of the health system.

<table>
<tr><th>Health system level</th><th colspan="3">Applications</th></tr>
<tr><td>Population health</td><td colspan="3">Disease surveillance and forecasting
Population health risk management
Intervention selection and targeting
Communicating health information to the public or key populations
Incentivizing people to seek health services</td></tr>
<tr><td rowspan="3">Individual health</td><td>Diagnosis</td><td>Treatment</td><td>Prevention</td></tr>
<tr><td>Image-based diagnosis
Whole genome sequencing
Screening and triage, including self-screening
Monitoring health or diagnostics data, including self-monitoring</td><td>Digital adherence support
Drug 3D printing
Personalized treatment
Telehealth</td><td>Identifying vaccine candidates
Predicting risk of disease progression</td></tr>
<tr><td colspan="3">Managing referrals between points of service
Providing health education content to people with TB and families</td></tr>
<tr><td>Health system</td><td colspan="3">Real-world, real-time data collection
Transmitting data/medical information to health care providers
Detecting drug resistance
Providing training content to health care providers
Capacity planning and management
Quality assurance Delivering supplies by drone</td></tr>
<tr><td>Pharmaceutical and insurance industries</td><td colspan="3">Drug discovery
Supply chain management
Monitoring inventories
Real-world evidence collection and analysis
Adaptive trial design
Remotely monitoring clinical trials</td></tr>
</table>

Provide guidance for scaling up implementation of digital health tools

TB programmes need to know what tools to procure and implement, where and how. They need to know how to prioritize, how to operationalize and how to optimize solutions. This is a complex undertaking that poses numerous challenges. Governments and technical agencies need to provide clear, up-to-date guidance for innovators, implementers and policy-makers to aid them in developing, operationalizing and providing an enabling environment for digital health.

As applications for digital health tools continue to expand, as access to information and communication technologies continue to grow in LICs and MICs, and as AI becomes more capable, operational research will continue to be essential in order to understand how best to apply digital tools to support people with TB and improve the quality of care. Concerns remain that digital technology has the potential to replace human contact, or even be misappropriated for uses that overstep the purposes of improving support and quality of care by violating people's rights to privacy and autonomy. Therefore, it will remain essential to seek input from people with TB and survivors in designing digital health applications. Adhering to ethical standards will also remain critical in navigating issues of privacy, oversight, accountability, public trust, data governance and management in the application of digital health tools.

Develop strategies for integrating digital health tools into NTPs

With effective guidance, NTPs would be better positioned to develop strategies for integrating digital health into their TB elimination efforts. These strategies are essential for prioritizing which tools to invest in and where, and for coordinating governments, innovators, implementers and end-users in the integration process.

Countries will have more technical resources that can be used for strategy development as WHO works to strengthen the evidence base for digital health in the fight against TB, evolves its guidance in line with advancements in digital health tools, provides technical assistance to countries, and supports digital health policy development.

CREATE A RESEARCH-ENABLING ENVIRONMENT

Accelerating TB R&D requires changes in the surrounding research environment that can enable major leaps in innovation. Enabling TB R&D requires improving:

- support and incentive structures for researchers, including in LICs and MICs;
- data-, information-, and sample/material-sharing practices;
- support for research centres and research collaborations;
- capacity to conduct clinical trials, especially in LICs and MICs;
- regulations and policies that underpin R&D and product approval;
- strengthening advocacy for TB innovation.

Develop and sustain a talented field of TB researchers

Ensuring long-term success in TB R&D will require nurturing and incentivizing researchers to focus their efforts on TB innovation, from basic science through to translational research and clinical trials.

Training the next generation of scientific investigators is a priority that has traditionally been supported by mechanisms such as Wellcome Trust fellowships, National Institutes of Health (NIH) support at the pre- and post-doctoral levels, and European Union funding. These initiatives are critical but insufficient to fill the void.

Both governmental and nongovernmental funders must recognize the urgent need to train and sustain the next generation of researchers, and special effort should be made to support and strengthen the capacity of researchers in high TB burden LICs and MICs. Support should include financial investment, proactive career support and career development activities, as well as additional opportunities for training, networking and presenting research in local, regional and global forums. These efforts should be particularly aimed at graduate, post-graduate (doctoral), and junior faculty early-career researchers. Two model initiatives are SORT IT for operational research (see Box above) and ADVANCE for HIV research (see Box below).

The COVID-19 pandemic has had multiple impacts on this collective investment in early-career TB researchers. First, resources in the form of grants and early research opportunities, which previously focused on TB and other infectious diseases, have been diverted to prioritize COVID-19 research. Many TB scientists were diverted to assist with COVID-19 solutions using TB research infrastructure, including access to human cohorts and nonhuman primates, clinical operations, supply chain for laboratory reagents, and biosafety level 3 facilities. Students considering careers in infectious disease research have also been attracted to study COVID-19 by its higher profile and the enormous resources since devoted to coronavirus research, making it even more challenging—and necessary—to recruit early trainees to study TB.

The lockdowns and travel restrictions imposed by COVID-19 and inequitable global vaccine access have also dramatically decreased access to conferences and networking opportunities for early-career investigators, impacting their ability to showcase their work to other investigators in the field, which would previously have led to collaborations and opportunities for employment and career advancement. The focus now should shift towards repurposing the expanded COVID-19 research infrastructure for other infectious diseases, particularly a high-priority respiratory disease such as TB.

ADVANCE

Supported by the United States Agency for International Development (USAID), ADVANCE (Accelerating the Development of Vaccines and New Technologies to Combat the AIDS Epidemic) is a multi-partner research initiative that increases the involvement of African and Indian researchers in all stages of HIV vaccine R&D[1] . New initiatives along the lines of SORT IT and ADVANCE, applied to TB basic science research and clinical research, would help to ensure the long-term capacity for innovation in all areas of TB research.

Support open science and information sharing

The **Global roadmap for research and development of tuberculosis vaccines** and the WHO **Global strategy for tuberculosis research and innovation** identify the importance of open science and information to the R&D process. The WHO Global Strategy notes that "Sharing high-quality data... fosters scientific progress, promotes discovery..., improves future data collection methods... and allows for the analysis of similar data from multiple sources, which can subsequently inform national and global policy-making in a cost-effective and timely manner". Key actions to promote open science identified in the Global Roadmap are outlined in Table 13.

Increase collaboration in the development of new tools

Table 17 provides examples of institutions, partnerships and collaborations that are key to accelerating the R&D of new TB tools. Each entity carries out its work through multisectoral collaboration. PDPs remain critical to advancing R&D for new TB tools. PDPs, a type of public–private partnership, are not-for-profit organisations that work through collaborations with private-sector manufacturers, governments, NGOs and academia, and typically pool resources and technical expertise to develop and commercialize new tools. PDPs are especially important for developing new TB tools because they combine the expertise and resources from multiple sectors and help to overcome weak market incentives for developing new tools.

Table 17. Key TB R&D entities

Entity	Model	Focus
TB Alliance	PDP	medicines/treatment regimens R&D
Foundation for Innovative New Diagnostics (**FIND**)	PDP	diagnostics R&D
International AIDS Vaccine Initiative (**IAVI**)	PDP	vaccines R&D
TB Vaccines Initiative (**TBVI**)	PDP	vaccines R&D
TB Trials Consortium	government consortium	clinical, laboratory, epidemiological research
AIDS Clinical Trials Group (**ACTG**)	network	TB-HIV clinical trials
Medicines Patent Pool	UN-associated organisation	licensing
BRICS TB Research Network	government network	basic research, R&D, clinical trials, operational research
EDCTP	partnership between non-profit, government and private sectors	R&D
UNITE4TB	government-sponsored consortium	treatment regimens Phase II clinical research
European Regimen Accelerator for TB (**ERA4TB**)	public–private partnership	medicines/treatment regimens R&D
Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (**PanACEA**)	government and EDCTP-sponsored consortium	treatment regimens clinical research

Entity	Model	Focus
PAN-TB	philanthropic–nonprofit–private-sector consortium	medicines/treatment regimens R&D
EU-PEARL	public–private partnership	clinical research platforms

Increase site capacity for conducting clinical trials in LICs and MICs

The most promising new tools for ending TB will be those that have been demonstrated to work well in countries and settings with the highest burden of TB. This requires the testing of new tools in the environments where they will be most widely used and will have the greatest impact. As new diagnostics, medicines and vaccines enter late-stage trials, investment in the development of trial site and laboratory capacity is becoming increasingly urgent. This includes investing in physical infrastructure to ensure that appropriate laboratory capacity is available for large-scale trials, and in human capacity and training to ensure that trials are conducted in accordance with **GCP, GLP** and **Good Participatory Practice** standards.

Clinical trial capacity must be developed and enhanced in multiple regions, as the efficacy of any new tool might vary across different populations and regions. A new tool's licensure and acceptance for use can also be affected by where it was tested.

Existing clinical trial sites should be used for TB research wherever possible. Sites should be developed with the aim of sustaining their capacity over the long term, providing continued opportunities for trained staff, and utilizing the developed infrastructure for other disease areas.

Barriers to conducting trials in LICs and MICs include:

- a lack of financial and human resources
- ethical and regulatory system obstacles
- lack of physical research infrastructure
- operational barriers
- competing demands.

Addressing these challenges requires steps to be taken together:

- LIC and MIC governments should invest in strengthening domestic research capacities.
- All partners should work together to strengthen international collaboration with the aim of improving or creating new systems for conducting clinical trials in LICs and MICs.
- Research funders should promote investigator-driven research by local researchers in LICs and MICs.
- Research organisations should strengthen their engagement of affected communities in trial design and execution as laid out in the **Good Participatory Practice: guidelines for TB drug trials** and the **Good Participatory Practice: guidelines for TB vaccine research 2017**.

Ensure an efficient and predictable regulatory and policy environment

A frequent obstacle to accessing new tools is the lack of transparency in the national registration process. When registering medicines, for example, there is often no forum for interaction between the drug sponsor applicant, regulatory authorities, and communities. The present lack of regulatory harmonization has resulted in staggered, country-by-country approval procedures for new tools, resulting in deadly delays.

Country governments should build their capacity to evaluate new tools that have already been tested in other countries, allowing those that are shown to be safe and effective to be imported for use. WHO-issued guidance can support and expedite country policy-setting and adoption of new tools, particularly in countries without rapid regulatory processes. One other potential solution is to help expedite TB research by streamlining and harmonizing regulatory processes from clinical development to regulatory submission and regional approval.

---

1. Accelerating the development of vaccines and new technologies to combat the AIDS epidemic (ADVANCE). Washington, DC: USAID; 2016 **https://www.usaid.gov/sites/default/files/documents/1864/USAID-ADVANCE-Brief2-508.pdf**

APPLY ACCESS PRINCIPLES IN ROLLING OUT AND OPTIMIZING THE USE OF NEW TOOLS

Any time lost between the licensure of a new tool and people in need being able to use it leads to unnecessary suffering and loss of life. With proper planning and a strategic, evidence-based approach to access and optimization of use, people can get the most value and benefit from new tools. The following section lays out activities that national governments should undertake to scale up access and understand the most effective ways of deploying new tools within the health system.

The Universal Declaration of Human Rights, the **International Covenant on Economic, Social and Cultural Rights**, and the **Declaration of the Rights of People Affected by Tuberculosis** uphold the rights of people to enjoy the benefits of scientific progress and its applications. In keeping with these rights, the accessibility of new TB tools needs to be considered from the outset of the R&D process.

The accessibility of new tools is intimately tied to how R&D is financed and conducted, including incentive strategies, policies of research funders, governance of research institutions, and the values, norms and standards that guide R&D. As the **UN Political Declaration on TB** states, TB R&D should be "needs-driven, evidence-based, and guided by the principles of affordability, effectiveness, efficiency and equity". These principles should guide R&D from the earliest point in the process.

While there has been progress in important areas, TB R&D has long been underfunded. Given TB's public health significance as an airborne communicable disease that is responsible for more deaths than any other single infectious agent, where discrimination is both a cause and a consequence of the disease, and where large numbers of people in poor and marginalized populations are chiefly affected, states have an obligation to promote the development of new diagnostics, treatment regimens and vaccines, including through robust international cooperation, and to ensure access for all.

The **right to health** includes the **availability, accessibility, acceptability and quality** of health-related goods and services, where:

- availability requires making health goods and services available in sufficient quantity;
- accessibility involves four elements, all of which require attention to how goods and services impact key populations: non-discrimination, physical accessibility, affordability and access to information;
- acceptability requires all health facilities, goods and services to be respectful of medical ethics and culturally appropriate, sensitive to sex and lifecycle requirements, and designed to respect confidentiality, while improving the health status of people;
- quality requires goods and services to be scientifically and medically appropriate and of good quality.

It is essential that all stakeholders involved in promoting and carrying out TB R&D design and implement their activities in ways that respect, protect and ensure these rights-based principles at every stage of the R&D process, including the delivery of new tools.

APPLY BEST PRACTICES IN COMMUNITY ENGAGEMENT THROUGHOUT THE R&D PROCESS

Researchers and research institutions must embrace the involvement of communities as a standard part of the R&D process. Best practices should be followed for engaging TB-affected communities within all research activities and within decision-making bodies and forums. The **International ethical guidelines for health-related research involving humans** establishes universal principles for engaging communities in research activities, advising that:

"Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results."

Specifically related to TB, research institutions should consult the **Good Participatory Practice: guidelines for TB vaccine research** and **Good Participatory Practice: guidelines for TB drug trials**, which help to facilitate effective engagement with affected communities and stakeholders at all stages of the research process.

Engaging communities in research also fulfills a key guideline in the WHO **Ethics guidance for the implementation of the End TB Strategy**: "Community members should have the opportunity to participate in research beyond their role as potential trial participants. This participation should extend throughout each stage of the research process, from the design and conduct of studies to the dissemination of results."

Community participants should be from the geographical area where the research is being conducted. They can be a subpopulation among the participants recruited and can include groups within the broader society who have a stake in the outcomes of the research. Key and vulnerable populations are discussed in Chapter 7.

These groups must be engaged and their capacity strengthened as a priority in all aspects of research activities. Community engagement must be human rights-based, gender-sensitive and people-centred.

Communities should be consulted early in the research process, before a study is even initiated, to inform the research design. Community engagement should then remain ongoing through established modes of communication between researchers and community members.

Engaging with communities in all aspects of R&D also creates new groups of informed people who can advocate for TB R&D. People affected by TB, particularly TB survivors, must be engaged as experts in this space.

TB-affected communities can play a key role in monitoring the outputs of research, helping to ensure that the benefits of scientific progress are accessible to all people, free from stigma and discrimination, irrespective of how they individually identify or where they live. TB-affected communities can also champion enhanced research on the successes and benefits of TB community-based service delivery, advocacy and monitoring for social accountability.

Community advocates play a critical role in research. They are uniquely placed to document, monitor and analyse the intersectionality between social determinants of health and effective TB responses. Their increased engagement stems from community demands for self-determination and meaningful participation in the TB response.

MODELS OF COMMUNITY ENGAGEMENT IN RESEARCH

Community advisory boards (CABs): **Research entities can establish CABs** to ensure that community voices, needs and priorities are reflected at each stage of the research process, from designing studies and conducting trials to disseminating results and working to translate results into policy change.

Community-based participatory research (CBPR): In the CBPR model, community members and researchers collaborate on all aspects of a research project, and community members work with scientists as equal partners. The CBPR model is grounded in principles of collaborative and equitable community engagement in research and shared ownership of research issues, processes and products.

STRENGTHEN ADVOCACY FOR TB R&D

Implementing the priority actions above will only be possible with powerful advocacy. Informed by the Global Plan and the WHO Global Strategy for TB Research and Innovation, TB researchers, civil society, affected communities and survivors must work together to advocate for R&D funding, for the actions that contribute to a research-enabling environment, and for equitable access to the products and benefits created through innovation.

Priorities for strengthening advocacy for TB R&D include improving research literacy among the advocacy community, deepening the research community's involvement in advocacy, and strengthening collaboration between researchers and advocates.

Improve scientific literacy among the advocacy community

Research literacy means understanding and being able to effectively communicate key concepts, processes and goals being pursued in TB R&D. Wherever research literacy is lacking, TB advocates will be limited in their capacity to effect change.

Better research literacy training opportunities and supporting tools need to be developed and made accessible for advocates across civil society. These should support advocates in three areas:

- developing an understanding of key concepts in TB R&D, so they can effectively track developments in TB R&D;
- developing skills to communicate about TB R&D issues, so they can translate R&D priorities into effective messages;
- understanding the landscape of the TB R&D community (i.e., research institutions, policy-making processes, regulatory bodies), so they can identify and pursue effective advocacy strategies.

Deepen the research community's involvement in advocacy

Likewise, advocacy funders and research institutions should support initiatives that support researchers to become more effective advocates for the TB R&D agenda. Scientists can not only speak credibly on new research findings, but also have important insights into barriers and opportunities in TB innovation. There are challenges, however, that need to be overcome to involve researchers in advocacy, particularly when it comes to communications habits and the ability to navigate the advocacy landscape. Priorities for deepening the research community's involvement in advocacy include:

- providing more advocacy and strategic communications training opportunities for TB researchers;
- strengthening relationships with TB advocates and coalitions;
- elevating the visibility of TB research among key stakeholders.

Scientific researchers are typically trained to communicate with other scientists, creating challenges when it comes to communicating with advocates, policy-makers, the news media and other stakeholders who are not scientists. This communications gap can create a significant barrier for advocacy, undermining progress in TB R&D.

Research scientists have also typically not been trained in advocacy strategy and tactics and lack familiarity with the advocacy landscape. It can be difficult for members of the research community to know where or how to become involved in advocacy, even if they want to.

However, with larger cadres of advocacy-savvy TB researchers, advocacy organisations can find more opportunities to enroll researchers in advocacy campaigns and policy-maker outreach. Research studies and key insights from the research community can be routinely shared with advocates, who can help translate findings and recommendations into advocacy messages to share important studies with decision-makers and key influencers such as the news media.

Better advocacy training opportunities and supporting tools need to be developed and made accessible for members of the R&D community. These should support researchers in four areas:

- developing knowledge of common advocacy strategies and tactics;
- building strategic communications skills, such as media training, op-ed writing and public speaking;
- translating research findings and insights into action and impact;
- building collaborative relationships with professional TB advocates and advocacy coalitions.

Strengthen collaboration between researchers and advocates

Researchers and advocates can both become more effective when they work together. When advocates build science-literacy skills and when researchers develop strong advocacy skills, it equips both to communicate with each other and work more effectively together.

Advocates are well placed to help build greater visibility around important research studies and scientific advances, because advocates maintain relationships with journalists, policy-makers and organizational leaders. Likewise, researchers can add value to advocacy efforts by providing expert scientific perspectives that complement the policy knowledge and lived experience of advocates and affected communities.

To work together effectively, researchers and advocates need to communicate early and often. When researchers communicate proactively with advocates about their work—such as by alerting advocates in advance of new studies being published—they provide advocates with new information they can use to earn media coverage, publish op-eds, engage grassroots campaign networks, or secure meetings with decision-makers—all of which are essential to advocating for resources and policies needed to accelerate the development of new TB tools. To enable regular communication, advocates and members of affected communities should be included in research decision-making structures and scientific forums.