Chapter 6: New Tools

SUMMARY

We cannot end the TB epidemic with the tools that we have today. Every day that the epidemic continues the human and economic costs rise. Increased investment in new diagnostics, treatment regimens and vaccines are urgently needed, along with greater investment in basic scientific research. Advancing operational research is also critical to introducing and scaling up access to new tools in the most efficient and effective way possible. To advance TB research and development (R&D), the world's governments have committed to increasing funding for TB R&D from roughly US$ 700 million annually to US$ 2 billion annually by 2022. Delaying this investment by even one year could result in 5 million additional people developing TB and 670,000 people dying from the disease, with an additional US$ 5.1 billion in TB treatment costs alone. Closing the R&D funding gap and creating a research-enabling environment is going to take concerted advocacy, with greater involvement of TB researchers, TB survivors and affected communities working together to hold governments accountable for fulfilling their commitments. Engaging communities affected by TB at all stages of the research process—including research that identifies and helps overcome the social, legal, political and economic hurdles in the way of developing and providing access to new tools—is vital to the ultimate success of any research initiative.

PRIORITY ACTIONS

Carrying out the following actions will require a collaborative effort on the part of national governments, public and private research institutions, biopharmaceutical companies, the philanthropic and financial sectors, and civil society and affected communities. Advocacy will remain critical to ensuring accountability for these actions.

1. Devote US$ 2 billion annually to TB R&D, which would close the $1.3 billion annual TB R&D funding gap. New funding should be used to increase support for research institutions, partnerships and collaborations including Product Development Partnerships (PDPs), the BRICS TB Research Network and innovative funding mechanisms and incentives.

2. Accelerate the development and use of new tools, including support for basic science and operational research. R&D priorities include:

- Diagnostics
  - Develop rapid and affordable non-sputum-based diagnostic tests
  - Develop accurate drug susceptibility tests for critical medicines
  - Improve tools for detecting TB infection and testing for risk of progression to active disease
- Medicines
  - Increase number of new candidates with novel mechanisms of action in the clinical pipeline
  - Advance development of new treatment regimens
  - Focus on treatment shortening strategies for both TB disease and TB infection
- Vaccines
  - Accelerate development of next-generation vaccine candidates, including late-stage evaluation of the M72/AS01$_E$ vaccine candidate, and work with

countries to prepare for successful licensure and roll-out
    - Evaluate novel TB vaccine concepts and mechanisms of vaccine-induced protection

3. Create an enabling environment for TB R&D by:

- Developing, funding and implementing national TB R&D strategies
- Increasing research center capacity for conducting clinical trials in high-TB-burden countries
- Ensuring an efficient and predictable regulatory and policy environment, such as by improving transparency in registration, building country capacity to evaluate new tools that have already been tested and shown safe in other countries, and other measures.
- Investing in and sustaining a talented field of TB researchers

4. Optimize access to new tools through comprehensive access strategies developed for new medicines, diagnostics and vaccines, aided by operational research that identifies and helps to overcome social, political, legal and economic barriers to access.

5. Advocate effectively, strengthen community systems and the meaningful engagement of affected TB communities in research, and include advocates and members of TB-affected communities in decision-making structures and scientific for a.

6A: Advancing the TB research agenda

When it comes to investing in TB research and development, we cannot afford business as usual. 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 die from the disease. Country governments can support TB R&D by developing and funding national plans for TB research, or by integrating TB into national health research agendas. R&D efforts should be needs-driven, evidence-based, and guided by the core principles of affordability, efficiency, equity and collaboration.

The following section lays out research frameworks and identifies priorities for essential investments in new TB tools, projected impacts of new investment, and highlights in R&D progress achieved in the last five years.

Strategic frameworks for the research and development of new TB tools
[NOTE: figures in research frameworks and off-the-shelf projects are in review and subject to revision]

New Medicines Strategic Framework 2018 – 2022

Vision: To develop shorter, more effective drug and regimens for all age groups and populations affected by TB			
Goals: Introduction of a new regimen with a shorter duration (2-4 months) and containing three or four new drugs without pre-existing resistance to treat both drug-susceptible and drug-resistant TB			
Objective	Milestone		Funding Required 2018 - 2022 (US$ Millions)
Sustaining the pipeline through basic discovery for TB drugs	New clinical candidates entering Phase 1	Accelerate screening and optimization of new chemical entities; validate biomarkers; develop animal models that are more predictive of clinical efficacy; identify new drug targets	1400
Maintaining trial site capacity	Increase number of GCP/GLP compliant sites available for TB drug trials	Identify, maintain and provide training at GCP/GLP-compliant sites	400

Developing a shorter regimen for DS-TB	Complete Phase III of a 2-4 month regimen for DS-TB	Conduct trials in pK studies, Phase 1, Phase II (EBA, SSCC, drug-interaction studies), and Phase III to advance two to three new shorter regimens	2000
Developing a safe, higher efficacy and shorter regimen for MDR-TB	Complete Phase III of a shorter regimen for MDR-TB	Conduct trials in pK studies, Phase I, Phase II, and Phase III to advance two to three new shorter regimens	800
Improving treatment for children in parallel to efforts in adults	Complete formulation and clinical testing in children in conjunction with any new regimen advancing in adults	Include children in trials early on for new regimens; develop safe, reliable and user-friendly regimens for all forms of TB in children early in the development process; conduct drug-interaction studies	200
Developing a safer, high-efficacy regimen for latent TB	Complete Phase III of a safer, high-efficacy regimen for latent TB	Conduct Phase III trials of new regimens for latent TB with the aim of a shorter duration of treatment	120
Ensuring adoption of new TB drugs and regimens at the country level	Patients access newly approved drugs and regimens, especially in high-burden countries	Include new drugs and regimens in national policies and guidelines; implement mechanisms to expedite regulatory processes in countries; engage key stakeholders; conduct extensive training of health providers	700

Engaging community and civil society in the entire process of drug development and access	Community and civil society are represented in all decision-making processes and forums along the drug discovery and development pipeline	Include community and civil society representatives in advisory committees, protocol and study design, scientific networks and other forums related to TB drug development.	90
TOTAL FUNDING REQUIRED			5710

New Diagnostics Strategic Framework 2018 – 2022

Vision: Achieve early and universal diagnosis of all people with all forms of TB to foster progress towards TB elimination, by making appropriate and affordable diagnostic solutions available at the right setting and ensuring that diagnostic results are linked to treatment and provide the basis for continuous drug resistance surveillance.			
Goals: Develop new diagnostic tools and accompanying solutions to: 1) Improve TB case detection through accurate tests, enabling patient-centred use at all levels of the health care system, for all populations, including children and those living with HIV, key populations including vulnerable groups, migrants, under-served groups as well as innovative diagnostic strategies that will ensure better outreach to people with TB. 2) Enable timely and effective treatment to reduce mortality and ongoing transmission, and prevent antimicrobial resistance by rapidly and simply detecting resistance to existing and future drugs. 3) Develop novel tests to enable rapid DST and treatment monitoring/test of cure to detect insufficient treatment sooner. 4) Reliably identify individuals at risk of progression from latent infection to active TB disease in order to introduce targeted preventive therapy and cut transmission.			
Objective	Milestone	Major Activities	Funding Required 2018 -2022 (US$ Millions)

Ensure that the critical knowledge enabling the development of new diagnostic tools and solutions is available	Undertake discovery science and build/improve capacity for such discovery research to identify and validate new markers	Support consortia on biomarker discovery using different platforms and approaches targeting: a. Detection of active TB at POC b. Identification and characterization of mutations c. Progression to active disease d. Treatment monitoring e. Validation of promising biomarkers f. Maintenance of a biomarker database	194.5
	Ensure increased access to clinical reference materials that are critical for the development and validation of new TB diagnostics	Specimen collection, maintenance and expansion of repositories, data management and QA/QC for: a. Specimen bank b. Strain bank c. Paediatric specimen bank d. Extrapulmonary TB specimen bank e. Specimen bank for treatment monitoring f. Data repository for chest X-ray images	32

	Support assessment of MTB genetic variants and clinical relevance to inform the development of molecular tests for the detection of drug resistant TB	Development and maintenance of a centralized repository of global genomic and clinically relevant data, review for quality and standardization a. Development of a database housing sequence and associated metadata from MTBC and use the data to validate mutations associated with resistance to anti-TB drugs b. Support contribution of relevant sequencing data by a large number of groups to ensure large geographical diversity c. Maintenance of the database to sustain effort	31.5
	Increase efficiency of early development pipeline and support decisions before large-scale trials	Conduct studies for evaluation/demonstration studies planned under objective 3 to assess potential impact and help plan those studies in the most effective way	25
	Undertake research and consultations to support development of e-Health solutions	Definition of patient charter/ethical criteria, and consensus-building on patient identifier	1.5
Total Objective 1 – Addressing knowledge gaps			284.5

Develop a portfolio of new diagnostic tools coupled with a package of accompanying solutions to ensure that results translate into patient treatment.	Develop tests and solutions for the diagnosis of active TB at the point-of-care level in all patient populations, including children and people living with HIV	Support test development, technical and clinical validation during development for: a. Smear-replacement tests and solutions b. Biomarker-based non-sputum tests and solutions c. Triage referral tests and solutions	127.5
	Develop tests and solutions for detection of drug resistance	Support test development, technical and clinical validation during development for: a. Next generation drug susceptibility testing at peripheral levels b. Drug susceptibility testing for new & repurposed drugs and new drug regimens including MIC testing where relevant c. Next generation sequencing directly from sputum	53.5
	Develop tests and solutions for prediction of the risk of disease progression	Endorsement and revision of TPPs. Test development, technical and clinical validation during development, including validation and qualification of immune activation biomarkers	30
	Develop tests to support syndromic approaches to help differentiate between pathogens and reduce antibiotic overtreatment	Validation and qualification of suitable biomarkers for syndromic tests for patients with respiratory symptoms on first visit to primary health care services to help differentiate between pathogens, providing a clinically actionable answer	23
	Develop tests and solutions for treatment monitoring/test of cure	Develop a TPP. Test development, technical and clinical validation during development, including molecular candidate as well as validation and qualification of suitable biomarkers.	6

	Develop e-Health and connectivity solutions to facilitate access by patients to tests listed above.	Endorsement and revision of TPPs. Integration of connectivity in diagnostic technologies, development of eHealth applications and aggregation platforms	5
Total Objective 2 – Development of a portfolio of new tests and solutions			245
Evaluate the portfolio of new diagnostic tools and solutions, including new detection strategies, approaches for optimized use, and innovative delivery mechanisms, demonstrate patient benefit and predict likely impact within the entire health system.	Conduct evaluation in clinical trials and demonstration studies for new tests and solutions identified above, as well as for syndromic approaches	a. Evaluation of tests for active TB and for drug susceptibility testing (MDR/XDR TB) b. Demonstration studies of TB tests and DST c. Demonstration studies of tests targeting paediatric TB d. Demonstration studies of tests targeting extrapulmonary TB e. Evaluation and demonstration of syndromic approaches f. Demonstration studies of e-Health solutions and platform for connected diagnostics	94.5
	Predict patient impact from the use of improved diagnostics on TB detection rate, transmission and mortality	a. Develop mathematical modeling b. Conduct impact and cost-effectiveness studies to evaluate new technologies and innovate strategies/approaches	70
	Conduct market analysis and estimate potential for new diagnostics	Update and expand existing market assessments	2
Total Objective 3 – Evaluation, demonstration and impact			166.5

Ensure that fully validated new diagnostic tools and solutions are widely available and appropriately used in endemic countries	Roll out of new tools and solutions	Procurement of devices and consumables for the roll-out of at least one new technology to support the detection of active TB in 90% of new cases and drug resistance in 100% of cases in high-risk groups	2300
	Strengthening laboratory capacity for appropriate scale-up of new tools	a. Training (coordination, development of tools, sessions, training supervisors, specimen transfer) b. QA and accompanying measures c. Ongoing assistance d. Training assistance for supply management aspects	228
	Patient-centered diagnosis and decentralization of testing	a. Dx referral system (sample transportation, results delivery to patients/clinic, follow-up with patients) b. m/e-Health solutions/transmission of results c. Incentive systems for patients to compensate for time required for diagnosis	77
	TB-HIV laboratory integration (TB testing in HIV settings) as well as screening for co-morbidities such as hepatitis	Demonstration projects and operational research on how the viral load test could be used a predictor to screen for TB	24
	Private sector integration	a. Incentive for private sector to use endorsed tools b. Laboratory strengthening and EQA for tools in use in the private sector c. Scale up of models such as IPAQT and JEET	23
	Maintain speed of national policy change and in-country regulation process	a. Harmonize regulatory processes in problematic countries: China, Russia, Brazil to some extent b. Supporting national policy change and adoption (local cost-effectiveness and validation studies)	33

	Sensitize stakeholders (NTPs, MoHs, technical, procurement and funding agencies, patient community representatives)	Coordinate with advocacy groups; organize workshops with NTPs, MoHs, technical procurement and funding agencies, and patient representatives	10
	Conduct operational research on how best to deliver diagnostic services in routine programmatic settings to ensure a patient-centered approach, and to estimate costs and resources used by NTPs	Conduct studies covering different test categories and scenarios, as well as different settings, i.e. low/high-MDR, low/high-HIV, different geographies, LTBI test & treat target groups, strategies for contact tracing	30
	Scale-up manufacturing and other market interventions to bring price down	Investment in commercialization and successful scale-up	75
	Introduction in countries of new drug DST and DST for additional group C drugs	Introduction of appropriate testing strategies and protocols, and EQA for phenotypic testing and molecular detection including DST for new drugs, revision of critical concentration when necessary and gathering the necessary knowledge to design and implement NGS-based targeted sequencing	34
	Expanded sequencing capacity in countries as of 2022	Implement capacity to perform NGS sequencing at reference lab level and provide training and support in data analysis. Establish a mechanism to use the supranational reference lab capacity as a main driver to provide this training and long term support	20

Total Objective 4 – Availability and appropriate use of new tests (inc. roll-out) Without roll-out	2854 73
TOTAL FUNDING REQUIRED	3623 (with roll-out) 769 (without roll-out)

New Vaccines Strategic Framework 2018 – 2022

Vision: To develop new, more effective vaccines that will directly and safely prevent TB in all age groups and populations.
Goals: 5) Prevent TB diseases and interrupt transmission through the development of new vaccines that would prevent infection, progression, reactivation and/or reinfection 6) Incorporate and consider access strategies throughout the TB vaccine development process 7) Strengthen community engagement in TB vaccine R&D

Objective	Milestone	Major Activities	Funding Required 2018 -2022 (US$
Continue to advance the clinical pipeline of TB vaccine candidates	Advance candidate and candidate concepts through clinical trials, utilizing portfolio management and common stage-gating criteria	Initiate Phase III trial of M72/AS01E vaccine candidate	1250
		Continue to support vaccine candidates through the clinical pipeline and initiate new Phase I/IIa/IIb trials on vaccine candidates that meet criteria	
	Explore and implement novel Phase II clinical trial designs to identify the most promising vaccines as early as possible in development and optimize use of resources	Conduct trials using prevention of infection and prevention of recurrence study designs	75
	Ensure sufficient capacity to support large-scale clinical trials	Scale up manufacturing to support large-scale (Phase IIb/III) clinical trials	500
		Expand clinical trial and laboratory capacity in different regions to conduct clinical trials at GCP standards	

	Conduct studies to assess prevalence and incidence of relevant TB vaccine trial endpoints in populations to be involved in clinical efficacy trials	Conduct incidence and prevalence of TB infection studies; incidence of disease studies; and cross-sectional prevalence of disease studies in multiple regions	25
Total Objective 1 – Clinical pipeline			1850
Enhance knowledge through experimental medicine	Develop and test a human challenge model to speed TB vaccine R&D	Support consortium to advance human challenge model through development and preclinical phase, and initiate clinical phase	40
	Complete human studies in parallel with NHP challenge in order to learn about protective immune responses	Conduct NHP challenge studies to determine correlates of protective immunity	150
		Compare results from these NHP studies with those in human efficacy trials (and back-translation for model verification)	
	Test key hypotheses about protective immune responses	Conduct multiple experimental medicine studies to test different hypotheses	100
Total Objective 2 – Experimental medicine			290
Increase emphasis on early-stage and discovery research	Identify immune correlates of protection and disease	Identify immune mechanisms and correlates, through preclinical comprehensive host response analysis	60
		Integrate biomarker discovery into all Phase IIb and Phase III studies	100
	Identify novel vaccine targets	Explore different mechanisms of protective immunity (e.g. mucosal, alternate cellular targets, innate immunity)	40
	Investigate new approaches to mount an effective response	• Conduct studies of unconventional immune cells • Improve formulation and antigen delivery, through adjuvant and vector development (Note: robust and scalable). • More optimal delivery, e.g. through exploring	100

		unconventional routes of vaccine delivery.	
Total Objective 3 – Early-stage and discovery research			300
Improve animal models	Develop and optimize fit for purpose animal models, to also allow assessment of vaccine efficacy in immunologically primed and/or latently infected individuals or under conditions of coinfection or comorbidity, to find signals of prevention of infection and/or recurrence of disease or blockade of natural transmission.	Enhance infrastructure and diversity the portfolio of modalities for preclinical stage and priority gating of candidates; qualify and verify models by benchmarking against clinical signals.	150
Total Objective 4 – Animal models			150
Improve preclinical and clinical readouts	Standardize reagents and harmonize assays and benchmark relevant signals by forward- as well as backward-translation/ verification between preclinic and clinic	Gather stakeholder input and come to consensus on path forward	1
		Continue and expand on programmes to provide reagents to laboratories and research facilities	30
		Develop necessary assays based on stakeholder consensus	40
Total Objective 5 – Reagents and assays			71
Lay the groundwork for adolescent and adult vaccination campaigns	Conduct strategic access and implementation research	Studies of cost-of goods, TB cost–effectiveness, full value proposition, health-economic assessment, country vaccine readiness, and vaccine landscape	12
Total Objective 6 – Conduct strategic access research			12
Engage communities in TB vaccine R&D	Strengthen community engagement in research	Clinical trials have community advisory/ engagement plans and involve community representatives in the design, conduct and dissemination of research	90
		Vaccine developers actively engage community stakeholders in the R&D process, from early-stage research to clinical trials and licensure	
Total Objective 7 – Community engagement			90
		Grand Total	**2763**

Box 6.1. The new 1HP regimen shortens TB preventive therapy to one month

No TB elimination scenario is realistic without a major advance in TB prevention. Yet, with

the notable exception of South Africa, TB prevention has been a persistently neglected aspect of TB care in high-burden countries. The neglect of TB prevention as a core strategy must end.

In addition to exciting advances in TB vaccine development, research on TB prevention has led to the recent development of effective regimens that are shorter in duration and easier for people living with TB infection to complete. The shortest prevention regimen available today is 1HP—a daily dose of rifapentine and isoniazid taken for four weeks. A phase III clinical trial involving 3000 participants over age 13, all of whom were living with HIV, found that 1HP performed just as well as nine months of isoniazid, which had long been the standard for TB preventive therapy.[1] One of the key challenges to overcome in scaling up access to shorter TB preventive regimens will entail ensuring the equitable availability and affordability of rifapentine in all countries.

Box 6.2. The potential of FujiLAM as a point-of-care diagnostic test

Fujifilm's SILVAMP TB LAM, or FujiLAM, is the first of a new generation of "LAM" tests for detecting TB. Testing is done using a urine sample, which is easy to collect from people of all ages. Lipoarabinomannan, or LAM, is a molecule that TB bacteria produce that helps them colonize the body by de-activating white blood cells produced by the immune system. FujiLAM is not the only diagnostic test that detects the presence of LAM, but it has been shown to be significantly better at detecting LAM than a LAM test previously recommended by WHO for diagnosing TB in PLHIV. In a comparison study published in 2019, FujiLAM was 70 percent effective at detecting LAM versus 42 percent for the previously recommended LAM test when both were compared to a reference standard using the sputum-based Xpert MTB/RIF test.[2] Test results take less than an hour, and can be used by healthcare workers with minimal training. No complex instruments are involved.

Further testing is needed to assess FujiLAM's potential as a point-of-care diagnostic test for TB. The test's greatest potential is in serving individuals who have difficulty producing sputum, particularly children, health facility inpatients and PLHIV who are more severely ill. Looking forward, the introduction of a LAM test that is just as sensitive as currently available sputum-based tests would be transformative for TB diagnosis.

Box 6.3. The M72 TB vaccine trial advances vaccine research

TB vaccine research is at its most promising stage in decades. Currently there is no TB vaccine approved for use in adults living with TB infection. But the M72/AS01$_E$ vaccine—known more commonly as M72—has been shown in the primary results of a phase IIB clinical trial to safely provide protection for 54 percent of 3,573 adults who were already infected with *M. tuberculosis*. In this case, protection means that the vaccine prevented those adults living with TB infection from developing active TB disease. Modeling shows a vaccine providing this level of protection has the potential to avert tens of millions of new TB cases and prevent millions of deaths. Further evaluation is needed to define the potential

[1] Swindells S, Ramchandani R, Gupta A, Benson C, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. N Engl J Med. 2019;380:1001-1011.

[2] Broger T, Sossen B, du Toit E., et al. Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study. The Lancet Inf Dis. 2019. 19;18:852-861.

impact with more precision. The trial results showed that it is possible to develop a new vaccine that improves the body's ability to control TB infection and prevent people from getting active TB disease.[3] Given the sheer numbers of people living with TB infection, such a vaccine has potential to provide a widespread public health benefit and be transformational in TB prevention.

The M72 phase IIb clinical trial was conducted in Kenya, South Africa and Zambia among HIV-negative adults. The study was sponsored by GSK and conducted in partnership with Aeras/IAVI with funding from the Bill & Melinda Gates Foundation, the Department for International Development (DFID) in the UK, the Directorate General for International Cooperation in the Netherlands, and the Australian Agency for International Development. Additional investment is needed to advance the M72 vaccine toward licensure and implementation through further research and testing.

BOX 6.4 The World Health Organization's Global Strategy for TB Research and Development

As this updated Global Plan goes to press, WHO is in the process of following through on the 71st World Health Assembly's call to develop a new Global Strategy for TB research and development. The strategy is intended to be an overarching guidance document with a set of evidence-based recommendations. Its main goal is to provide all UN Member States a framework of interventions they can make that will remove barriers in TB research and innovation. The strategy's target audience is primarily ministries of health, science and technology, finance and education. In the spirit of fast-tracking efforts to end TB, the strategy also makes the case for a unified and aligned response in which key relevant national and international partners and TB-affected communities undertake investments and partnerships necessary for accelerating innovation.

The strategy has four objectives:

1. Create an enabling environment for TB research and innovation
2. Increase financial investments in TB research and innovation
3. Promote and improve approaches to data sharing
4. Ensure equitable access to the benefits of research and innovation

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[TK2-page spread:] Priority "off the shelf" research projects

The Stop TB Partnership's Working Groups on New TB Vaccines, New TB Diagnostics, and New TB Drugs (together, the New Tools Working Groups) have identified the following "off the shelf" research projects that research funders can support. These projects are highlighted because they would significantly advance the state of TB R&D and could be initiated quickly.

[3] Tuberculosis research funding trends 2005–2017 New York: Treatment Action Group, Geneva: Stop TB Partnership. 2018. Online. http://www.treatmentactiongroup.org/content/tbrd2018?eType=EmailBlastContent&eId=7dac4161-dc99-43a2-9447-4d18aeb4c8ac#overlay-context=content/tbrd2018

Off-the-shelf research projects: diagnostics

Title: Decentralized next-generation sequencing (NGS) for affordable, scalable and rapid TB drug-susceptibility testing (DST)

Rationale: NGS refers to sequencing technologies that can rapidly process millions of DNA sequences in parallel, to decode the genome of a person or bacterium and find genetic mutations that are associated with drug resistance – which means that a comprehensive drug resistance profile can be effectively identified for accurate diagnosis and management of drug resistant TB. It is a technique that is already well-established to inform personalized treatment decisions in oncology.

The project: Decentralized NGS based solutions below the reference level i.e. bringing NGS workflows closer to the patient. This will involve late stage development of decentralized products/platforms or workflows along with validation and clinical evaluation.

Investigators: a team-based approach that integrates academia and industry

Estimated cost: US$40 M

Title: A test that predicts progression from infection to TB disease (incipient TB test)

Rationale: An ideal test of TB disease progression would differentiate the various stages from infection to active TB, and may detect the presence or absence of incipient TB (defined as the prolonged asymptomatic phase of early disease during which pathology evolves, prior to the clinical presentation of active disease). Current commercially available diagnostic tests—the tuberculin skin test and IFN-γ release assays—are insufficient in their ability to predict which infected individuals will progress to disease, due to the fact that they detect a memory immune response.

The project: a large clinical trial using a test aligned with the WHO TPP for incipient TB in an at risk population where trial participants are stratified for treatment based on incipient TB test score.

Investigators: clinical trial experts

Estimated cost: US$25 M

Title: A biomarker based test

Rationale: A more sensitive point-of-care non sputum-based test to replace smear microscopy for detecting pulmonary TB that is easy to perform and has limited operational requirements

The project: developing a next-generation biomarker based test for broader use in the general population independent of their HIV status, and for use in children.

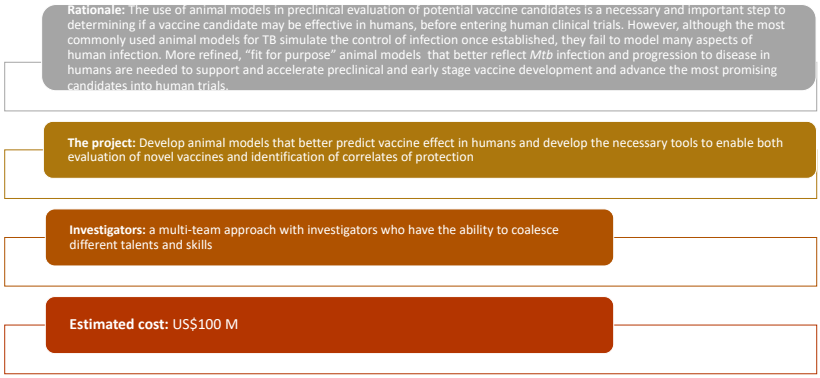
Investigators: product developers, academia and clinical trial experts

Estimated cost: US$10 M

Off-the-shelf research projects: medicines

212 ***[TK in development]***
213
214 ***Off-the-shelf research projects: vaccines***

Title: Develop and refine preclinical models that reflect the full spectrum of *Mtb* infection



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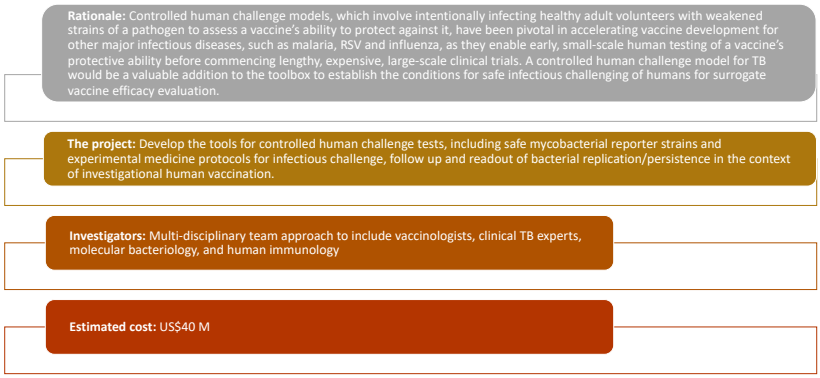
Title: Developing controlled human challenge models for TB vaccine efficacy evaluation



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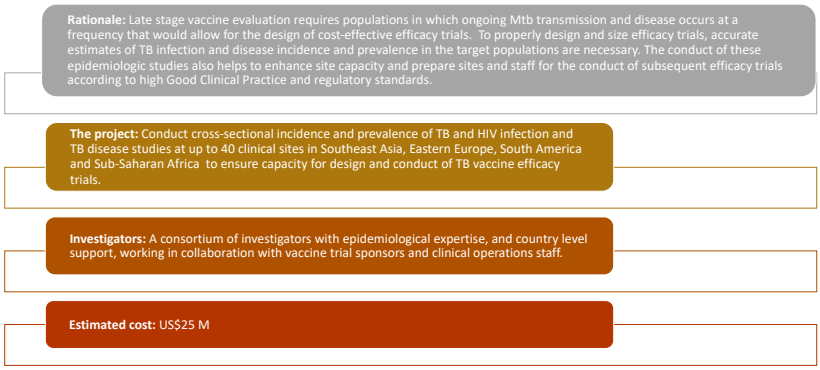
Title: Laying the epidemiological framework to prepare for late stage TB vaccine development



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Basic science

Mycobacterium tuberculosis is the pathogen that causes TB. The mechanisms by which *M. tuberculosis* causes human infection are still largely a mystery.[4] In order to understand the most promising approaches to discovering new TB diagnostics, medicines and vaccines, researchers would greatly benefit from understanding more about the TB bacillus, how it interacts with a living body, and how the body mobilizes a protective immune response. Some of the most urgent areas for basic science research include understanding more about how TB infection progresses to disease, how to predict the risk and stages of disease progression based on biomarkers,[5] and how to more reliably and easily know when a person has been cured through treatment. Advancing TB basic science also requires support for new infrastructure, including for what are known as biorepositories—physical facilities for storing, along with the means for collecting, processing and distributing, specimens that are used for scientific research. Basic science research is typically conducted by academic institutions and by public-private partnerships (PPPs), which rely in large part on public funding.

Pediatrics and key populations

Advancing a research agenda designed to meet the specific needs of children is critical to ending the pediatric TB epidemic. Research efforts focused on TB in children have focused mostly on finding out how to apply existing tools to diagnose, treat and prevent pediatric TB. But children have needs that differ from those of adults. For example, children have difficulty producing sputum, making them poor candidates for diagnosis using the rapid diagnostic test Xpert MTB/RIF, which tests sputum. The Stop TB Partnership Child & Adolescent TB Working Group and Treatment Action Group have laid out a detailed list of research priorities for child TB.[6] Priority investments in R&D include:

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

Diagnosis: Develop novel tests that are not invasive 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.

Additional research is needed to understand some of the basic characteristics of TB as it affects infants, children and adolescents, including the immune response to infection and associated biomarkers (regular changes that occur in the body that can be reliably measured and that indicate TB infection and TB disease) that can inform the development of new tools.

Pregnant women, children under 15 years old, and PLHIV make up approximately 20 percent

[4] Grundner C. To fight tuberculosis, fund basic research. PLoS Biol 2018. 16;9: e3000037. https://doi.org/10.1371/journal.pbio.3000037

[5] A biomarker is a measurable substance inside the body that reliably indicates the presence of TB infection and/or TB disease. LAM, discussed earlier in the chapter, is an example of a TB biomarker.

[6] Research Priorities for Paediatric Tuberculosis. Treatment Action Group, Stop TB Partnership Child & Adolescent TB Working Group. 2018. http://www.treatmentactiongroup.org/sites/default/files/Paediatric_TB_ResearchPriorities_10_8_18_Web.pdf

of all people who develop TB each year, yet people in these key populations are largely excluded from clinical trials research. This exclusion has led to suboptimal TB care and poor access to new tools. Including key populations in clinical research is critical to understanding how new tools will benefit people in these groups. There is both a scientific and an ethical rationale for including key populations in clinical research. While concerns surrounding the safety of new tools—particularly new medicines and vaccines—are understandable, any potential safety risks that new tools pose to individuals within key populations can be more easily evaluated in a clinical study setting.[7]

Other key populations for whom greater attention is necessary in TB innovation include those living with diabetes and pre-diabetes, the elderly and other immunocompromised persons, and high-risk groups such as healthcare workers, household contacts, mine workers and people who are incarcerated.

6B. Creating a research-enabling environment

Increase support for research institutions, partnerships and collaborations

It is critical that research institutions are supported to advance TB innovation. Below are three examples of institutions and initiatives that are key to accelerating the research and development of new TB tools. Each represents collaborations between the public and private sectors.

PDPs: Product Development Partnerships (PDPs) remain critical to advancing R&D for new TB tools. PDPs, a type of public-private partnership (PPP), are not-for-profit organizations 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 traditional market incentives are not powerful enough to drive innovation for TB.

Key TB research entities that operate through a PDP model include the TB Alliance (focused on advancing the research pipeline for new TB medicines), FIND (focused on innovative new diagnostics), IAVI and the Tuberculosis Vaccine Initiative (TBVI) (both focused on new vaccines), the European and Developing Countries Clinical Trials Partnership (EDCTP) (focused on new medicines, vaccines, microbicides and diagnostics) and the TB Trials Consortium (focused on clinical research for diagnosing, treating and preventing TB). While not a PDP, the Critical Path Institute is a public-private-partnership that aims to accelerate the pace and reduce the costs of developing new medical products, including through collaborations such as TB-PACTS—a data platform that curates TB clinical trial data, standardizes it, and makes it publicly available to qualified researchers.[8]

BRICS Tuberculosis Research Network: The BRICS have emerged as key global actors in TB innovation. Between 2007 and 2016, the average annual increase in TB research publications from the BRICS countries was nearly double the annual increase in TB research publications across all countries. By 2016, 31 percent of all TB research publications had a

[7] Gupta A, Hughes M, Garcia-Prats A, et al. Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. PLoS Med 2019; 16(8): e1002882.

[8] TB-Platform for Aggregation of Clinical TB Studies. Critical Path Institute. Online. https://c-path.org/programs/tb-pacts/

first author from a BRICS country.[9] The BRICS TB Research Network was established to further develop the base of TB R&D being carried out across Brazil, Russia, India, China and South Africa, including to accelerate the best use of both existing and new interventions in TB care and prevention. The international collaboration is building off of new national TB research initiatives, including India's TB Research Consortium, Brazil's National TB Research Strategy, and new TB activities being carried out by South Africa's Strategic Health Innovation Partnerships. With 38 percent of global TB deaths occurring in the five BRICS countries, the BRICS TB Research Network will need to play a growing role in the discovery and dissemination of new TB tools, both individually and as collaborators internationally.

The Life Prize: The Life Prize is a concept for collaborative research and development that, when applied to TB innovation, is designed to accelerate the introduction of new TB treatment options. The ultimate aim of The Life Prize is to identify a new TB treatment regimen that can be used to treat all forms of TB—including DR-TB—in one month or less. The Life Prize concept envisions licensing promising molecules from commercial manufacturers and other research institutions, and making that pool of molecules available to research institutions that will test them in treatment combinations. The Life Prize also envisions creating a new way of rewarding investment in TB R&D, by providing three types of funding and financial incentives:

- Prize funding for research institutions that enter new drug candidates that fulfill predefined criteria into clinical trials.
- Grant funding to finance the clinical testing of new treatment regimens with the potential to treat all forms of TB.
- Funding for the fair licensing of intellectual property and clinical data in order to permit open, collaborative research.

In this way, the Life Prize envisions reducing the risks and substantial costs that research institutions face compared with the traditional approach to R&D. To promote access, the concept model also provides a way to separate the cost of investment in R&D from the price and volume of medicines sales in order to facilitate equitable and affordable access. In the UN Political Declaration on the Fight against Tuberculosis, UN member states noted the Life Prize as a research platform through which research collaboration for TB can be strengthened.

Increase site capacity for conducting clinical trials

The most promising new tools for ending TB in low- and middle-income countries will be those that have been demonstrated to work well in those environments. This requires testing in the environments in which new tools need to be most widely used. The challenge for LMICs is that they typically have low capacity for conducting the necessary clinical trials. Barriers typically include a lack of financial and human capacity, ethical and regulatory system obstacles, lack of research environments including lack of physical research infrastructure, operational barriers and competing demands.[10]

To address these challenges, research funders should work to promote investigator-driven

[9] Global investments in tuberculosis research and development: past, present and future. Geneva: WHO. 2018. https://apps.who.int/iris/bitstream/handle/10665/259412/9789241513326-eng.pdf?sequence=1

[10] Alemayhu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries—a systematic review. Int J Equity Health. 2018;17:37.

research by local researchers in LMICs, while LMIC governments should invest in strengthening domestic research capacity. Stronger international collaboration is critical to create new systems for conducting clinical trials in LMICs.[11] Communities in which clinical trials will be conducted must be fully engaged, as laid out in the Good Participatory Practice Guidelines for TB Drug Trials and the Good Participatory Practice Guideline for TB Vaccine Research 2017.[12,13]

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. In the case of medicines, for example, there is often no forum for interaction or discussion between the drug sponsor applicant, regulatory authorities, and communities in the registration process. The present lack of regulatory harmonization has resulted in a staggered, country-by-country approval procedure 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. This process should be accompanied by WHO-issued guidance as a prelude to country policy setting and adoption. 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.

Sustain a talented field of TB researchers

Ensuring long-term success in TB R&D requires nurturing the field of TB research itself by incentivizing and strengthening the capacity of researchers to focus their efforts on TB innovation.

Partnerships like TDR—a joint effort by UNICEF, UNDP, the World Bank and WHO—support training for TB operational researchers working to improve TB care at the systems level in low- and middle-income countries. Through the Structured Operational Research and Training IniTiative (SORT IT)—a global operational research partnership led by TDR in collaboration with the International Union Against Tuberculosis and Lung Disease (The Union) and Médecins Sans Frontières (MSF)—researchers are trained to conduct operational research on their countries' priority challenges, build sustainable operational research capacity, and make evidence-informed decisions for improving TB program performance.[14] 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 in some cases develop a policy brief or presentation for policymakers and other stakeholders.[15]

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[11] Alemayhu, et al. 2018.

[12] Good Participatory Practice: Guidelines for TB Vaccine Research. 2017. Rockville: AERAS. Online. http://www.aeras.org/img/uploads/attachments/1015/good_participatory_practice_for_tb_vaccine_research.pdf

[13] Good Participatory Practice: Guidelines for TB Drug Trials. 2012. Dublin: Critical Path Institute. Online. https://www.cptrinitiative.org/downloads/resources/GPP-TB%20Oct1%202012%20FINAL.pdf

[14] SORT IT. Geneva: WHO. Online. https://www.who.int/tdr/capacity/strengthening/sort/en/

[15] Viney K, Bissell K, Hill P. Building operational research capacity in Papua New Guinea and the Pacific Islands. PHA. 2019; 9(S1): S3.

ADVANCE, a project supported by USAID, is a multi-partner research initiative that increases the involvement of African and Indian researchers in all stages of HIV vaccine research and development.[16] New initiatives along the lines of SORT IT and ADVANCE, applied to TB basic science research and clinical research, would help to ensure long-term capacity for innovation in all areas of TB research.

As part of this process it will be important to build the research literacy capacity of people with TB and TB survivors, ensuring that they inform, participate and respond to all aspects of the global TB research agenda.

Investing in new tools

TB R&D funding needs

Both public research institutions and commercial developers are investing too little in TB R&D, which is slowing the advancement of the new tools that are needed to end TB. In the UN Political Declaration on the Fight Against 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 overall global investments to US$ 2 billion in order to close the estimated US$ 1.3 billion gap in funding annually for tuberculosis research."*

Table 6.2 shows annual TB funding needs for the research and development of new TB medicines, diagnostics and vaccines from 2016-2022. Based on recent trends, the projected total funding gap for 2018-2022 is US$ 5.6 billion for new medicines development, US$ 807 million for new diagnostics and US$ 2.7 billion for new vaccines, totaling to US$ 9.1 billion for the five-year period, or US$ 1.8 billion annually. These figures do not include resources needed to roll out new tools, nor do they include resources needed for basic science or for operational research needed to help identify the most effective ways of implementing new tools within various national contexts.[17]

GERD framework

We could fill the TB R&D funding gap quickly if countries with the greatest capacity to invest and countries with the most benefit to gain from new TB tools were to devote to TB just a small fraction of each of their total gross domestic expenditure on research and development (GERD). In 2017 only three of the 32 countries reporting more than US$ 100,000 in TB R&D funding—South Africa, New Zealand and The Philippines—met their fair share of TB R&D funding, considered 0.1% of their overall GERD.[18] If 62 countries—those that make up the G20, plus countries that WHO classifies as having high TB burdens, plus a grouping of the world's wealthiest countries that are not included in either of those other groups—devote at least 0.1% of their GERD toward TB research and development,

[16] Accelerating the development of vaccines and new technologies to combat the AIDS epidemic (ADVANCE). Washington, DC: USAID. Undated. Online: https://www.usaid.gov/sites/default/files/documents/1864/USAID-ADVANCE-Brief2-508.pdf

[17] A fuller treatment of recent TB R&D funding trends—including analysis of funding for basic research, operational research, and pediatric TB research—is found in the annual *Tuberculosis Research Funding Trends* reports produced by Treatment Action Group and the Stop TB Partnership.

[18] Treatment Action Group, Stop TB Partnership, 2018.

they would close the annual funding gap for TB R&D.[19] These so-called fair share funding targets are considered a minimum of what countries should invest in TB R&D. The GERD framework is one proposal for fulfilling the UNHLM on TB political declaration commitment to close the TB R&D funding gap, "ensuring that all countries contribute appropriately to R&D."

Innovative financing approaches

In UN Member States' commitment to mobilize sufficient and sustainable funding for TB research and innovation, they committed to engaging innovative financing mechanisms as one means to mobilize new resources. Developing new, innovative sources of funding is critical to diversifying the funding base for TB R&D, as the funding currently available relies heavily on a small number of countries and funding agencies.[20]

In 2017 Unitaid became the world's third largest multilateral funder of TB R&D and the fifth largest funder overall.[21] Unitaid funds late-stage development with the main source of its funding coming through an innovative financing mechanism: a small tax on airline tickets purchased in ten countries.[22] UN Member States have also recognized the Life Prize as a promising innovative financing concept for TB R&D.

The Stop TB Partnership's Accelerator for Impact (a4i) is a public-sector blended finance impact investment fund to support the next generation of people-centered innovations for TB and global health. The fund will focus on:

- Pivoting the care model to become more digitalized, virtual and on-demand to make it as convenient as possible for people to access and receive quality and affordable care;
- Catalyze the rapid roll-out of new TB and global health innovations; and
- Unlock new funding and capital from both public and private sector investors.

Innovative financing mechanisms hold significant untapped potential for advancing TB R&D. It is now up to national governments, multilateral institutions, and the philanthropic, corporate and financial sectors to partner together and deliver new solutions that harness that potential.

The cost of inaction: What is the result of underfunding research and development?

One way to conceptualize the importance of upfront investment in new tools is to estimate the cost of inaction.[23] In other words, what will the negative consequences be if the world fails to fill the funding gap for TB research and development?

The total cost of inaction on TB R&D is estimated to be more than US$185 billion. These costs are expected to increase even further beyond 2030. Even a one-year delay in investment

[19] Treatment Action Group. Investing in R&D to end TB: a global priority. New York: Treatment Action Group; 2017. http:// treatmentactiongroup.org/sites/default/files/Funding%20target%20brief_final_31Oct.pdf

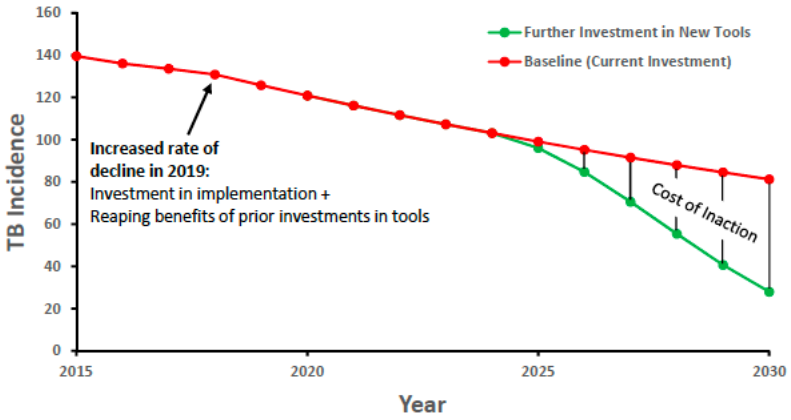
[20] Treatment Action Group, Stop TB Partnership, 2018. Cited in A Draft Global Strategy for TB Research and Innovation. Geneva: WHO; 2019. In press.

[21] Tuberculosis Research Funding Trends. New York: Treatment Action Group. Geneva: Stop TB Partnership. 2018. Online: http://www.treatmentactiongroup.org/sites/default/files/tb_funding_2018_final.pdf

[22] Cameroon, Chile, Congo, France, Guinea, Madagascar, Mali, Mauritius, Niger, Republic of Korea.

[23] This inaction is defined as the cost of future TB treatment and lost productivity that would accrue if the world achieved the 2020 milestones of the End TB Strategy by 2022, but failed to make the necessary investments in new tools between 2020 and 2025.

after 2020 would carry a tremendous cost: 4.8 million additional people having TB; 670,000 additional TB-related deaths; US$ 5.1 billion in added TB treatment costs (US$ 7.5 billion without discounting); 17.3 million additional DALYs (25.2 million without discounting); and an additional US$ 60 billion (US$ 87 billion without discounting) in lost productivity.



The cost of inaction assumes the following:

- The annual percentage declines in TB incidence and mortality that were achieved without new tools in order to reach the 2020 milestones by 2022 will continue through to 2030.

- Five years after the additional investment in new tools begins (in 2020), the decline in incidence and mortality will increase steadily and to a degree sufficient to achieve the 2030 milestones. The impact of new tools is therefore only slowly realized over time—with greater impact in 2030 than in 2025.

- The cost of TB treatment will not increase above 2018 levels.

- A 5% annual discount rate is applied to all costs and DALYs, thereby reducing the value of future savings in costs and productivity (although undiscounted costs and outcomes are also presented).

- Health utility losses from TB are assumed to scale with TB mortality, and a standardized conversion is made of 35 Years of Life Lost (YLL) per TB death and 0.35 Years of Life with Disability (YLD) per TB case (the ratios estimated by the 2017 Global Burden of Disease study).[24]

Despite the conservative nature of these assumptions, the estimated cost of inaction would be tremendous (TKFig. 6.X). By 2030, a five-year delay in investment in R&D for new tools is projected to result in:

- 13.9 million additional people becoming sick with TB
- 2.0 million addition TB deaths
- 49.8 million days suffered as a consequence of TB (75.1 million without discounting)

[24] Institute for Health Metrics and Evaluation. GBD Results Tool. Available at: http://ghdx.healthdata.org/gbd-results-tool. Accessed 1 Sept 2019.

- US$ 14.2 billion in additional costs for TB treatments alone (US$ 21.6 billion without discounting)
- US$ 172 billion in lost productivity (US$ 259 billion without discounting)[25]

Advocacy priorities

Accelerating the pace of TB innovation is going to take stronger, more coordinated advocacy. Using the Global Plan and the WHO Global Strategy for TB Research and Innovation, advocates—including TB researchers, civil society, affected communities and survivors—can join together in advocating for more resources and better policies that are needed to close the US$ 1.3 billion TB R&D funding gap, create an enabling environment for developing new tools, and ensuring equitable access to the benefits of TB research and innovation.

Advocacy is key to making an evidence-based case for governments to get more deeply involved in inherently risky research, to steer resources toward efforts that have the greatest potential for ending the epidemic within high-burden countries, for meeting the needs of patients and TB-affected communities, and for creating clear and reliable pathways for new tools to enter into widespread use. Government ministries and national legislatures remain the most important primary audiences for advocacy. The following actions will help to nurture a TB research advocacy coalition that is better prepared to engage them.

Provide more training and knowledge-sharing opportunities

Strengthening advocacy for new TB tools requires more routine knowledge-sharing and coordination between the TB research and advocacy communities. New research studies need to be routinely shared with advocates who can help translate findings and recommendations into advocacy messages and to share important studies with decision makers and the news media. Advocacy funders should consider additional grantmaking that supports strategic communications and advocacy training for TB researchers, as well as scientific literacy training for TB advocates and survivors.

Strengthen the research community's role in advocacy

Scientists can speak credibly about not only new research findings, but also about the barriers and opportunities they face in TB innovation. Scientists within communities of practice should more proactively work together—taking advantage of such forums as the Stop TB Partnership's New Tools Working Groups and the membership structure of the International Union Against Tuberculosis and Lung Disease, for example—to advocate for research funding and for policy change needed to create enabling environments for research. With larger cadres of advocacy-savvy TB researchers, advocacy organizations can find more opportunities for enrolling researchers in advocacy campaigns and policymaker outreach.

Engage TB survivors as partners in advocacy

Community-driven advocacy has become a important way to increase investment in scientific research, access to new tools, and to progress the advancement of human rights in the TB response, particularly for the most vulnerable, underserved and at-risk populations.

[25] Each Disability Adjusted Life Year is valued at per-capita GNI in this scenario.

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

One model for community advocates engagement in research is community-based participatory research (CBPR). It is grounded in principles of collaborative and equitable community engagement in research and shared ownership of research issues, processes, and products.

Global community networks (e.g., Global Coalition of TB Activists, TBpeople) and regional community networks (e.g., ACT! Asia Pacific, African Coalition on TB, DRAF TB, TBEC, We Are TB) have doubled since 2016. Their advocacy was instrumental in securing the targets and commitments within the UNHLM political declaration on TB, including commitments to mobilizing sufficient and sustainable financing for R&D and delivering as soon as possible new, safe and effective equitable, affordable, available vaccines, point of care and child-friendly diagnostics, drug susceptibility tests, and safer, shorter and more treatment regimens for adults, adolescents and children for all forms of tuberculosis and infection. TBpeople is partnering with the Stop TB Partnership and McGill University to demand TB innovation while exploring new ways to leading the way by demanding innovation in TB while re-imagining approaches to TB care for all.

Engage parliamentarians

Members of parliament—especially those sitting on relevant committees responsible for budgeting, health, regulatory, science and technology research, even national defense—must be better educated about the need for new TB tools and the commitments their governments have made to support TB research through the UN political declaration on TB. The Global TB Caucus provides the TB research and advocacy communities with an entry point to parliamentary engagement in more than 130 countries.

Expand advocacy efforts beyond ministries of health

Ministries outside of health, including finance, science and technology, labor and regulatory committees, are essential to creating budgetary space and creating the rules and regulations that create a research-enabling environment and should be routinely engaged by advocates.

Community engagement best practices

Meaningfully engaging TB-affected communities is essential to ensuring access to new TB tools. Research institutions should follow best practices 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.[26]

Engaging communities in research also fulfills a key guideline in WHO's *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."[27]

Community participants should be from the geographic area where research is being conducted. They can be a sub-population among the participants recruited, and can include groups within the broader society who have a stake in the outcomes of research. In the context of geographic areas are communities of people affected by TB—including people with TB, TB survivors and representatives of TB key affected populations such as urban poor, undocumented migrants, people living with HIV, people who use drugs, and people in prisons. These groups must be engaged and their capacity strengthened as a priority in all aspects of research activities, ensuring that this engagement is human rights-based, gender sensitive and people-centered.

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, with established modes of communication between researchers and community members.

There are several established models of effective community engagement in TB research. One of the most common ones involves the establishment of community advisory boards (CABs) by research networks and institutions.

Engaging with communities in all aspects of R&D also creates new groups of informed advocates who can effectively communicate the benefits of TB R&D to governments, regulatory authorities, funders and other institutions. 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.

[26] International Ethical Guidelines for Health-related Research Involving Humans. Geneva: CIOMS. Geneva: WHO. 2016. Online. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

[27] Ethics guidance for the implementation of the End TB Strategy. Geneva: World Health Organization. 2017. Online: https://apps.who.int/iris/bitstream/handle/10665/254820/9789241512114-eng.pdf;jsessionid=B7AE085FFA038B2A9CA419C423F2235F?sequence=1

6C: Rolling Out and Optimizing Access to New TB Tools

Any time lost between licensure of a new tool and getting it to people in need leads to unnecessary suffering and loss of life. With proper planning and a strategic, evidence-based approach to access and optimization of use, countries can get the most value and benefit from the use of 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.

Access strategies for new tools

New tools R&D and the delivery of those new tools need to be considered together from the outset in order to achieve maximum health impact. The following are approaches that national governments and health systems stakeholders should undertake in the course of introducing and scaling up access to new TB tools.

Access strategies for new TB medicines

Compassionate use programmes can provide early access to life-saving medicines even while they're still in the development stage. Supply chains in LMICs need to be strengthened in order to ensure successful distribution of new medicines once they've undergone licensing and registration. The Global Drug Facility (GDF) can help countries reliably access supplies of quality-assured medicines. At the same time, better forecasting and the use of strategic medicines stockpiles would further help to avoid stock-outs. The costs and energy associated with these aspects are often underestimated and need to be addressed in order to successfully introduce and scale up access to new medicines. Engaging local communities is critical to understanding and developing solutions to various factors that prevent access.

Access strategies for new TB diagnostics

Introducing and scaling up access to new diagnostic tools commonly requires optimizing product pricing and availability via procurement mechanisms such as pooled procurement, efficient demand forecasting and supply-chain management, technical assistance and training for product end-users; quality assurance; planning for uptake by private-sector health facilities; planning and budgeting for ongoing device maintenance and support; availability of digital health solutions to support supply chain monitoring and programmatic use of data from diagnostics. Health systems need to be able to access comprehensive support, including support for ministries of health to develop national guidelines and implementation plans for product access. Countries can also seek support from the GDF toward increasing access to TB diagnostics and laboratory supplies, as well as for technical assistance to support the uptake of innovative new tools.

Operational research is critical for guiding the implementation of person-centered use of new diagnostic tools. Program and systems improvements achieved by implementing recommendations informed by operational research will, in turn, reduce the product implementation risks for developers and encourage more innovation and investment. Finally, harmonized regulatory and registration frameworks for TB diagnostics are needed.

Access strategies for new TB vaccines

New TB vaccines targeted at adolescents and adults are most likely to have the greatest overall impact on the global epidemic of any new tool—but access presents a significant challenge. The kinds of new campaigns and programs that would be needed to roll out a new and widely used TB vaccine could take decades to implement, and the challenges surrounding widespread adolescent and adult vaccination are complex.

To assess and address program and systems gaps that could hinder the roll-out of a new vaccine requires comprehensive "strategic access" operational research. Various aspects of this research include evaluating cost-of-goods, pricing criteria, target product profile (TPP) cost-effectiveness, country vaccine readiness, and the vaccine landscape. It will also be important to understand the programmatic suitability for prequalification (PSPQ) early in the development process, so that licensed products will likely be preapproved for procurement by multilateral institutions like GAVI and UNICEF.

It will also be important to identify and advocate for programmatic approaches that could best reach adolescents and adults, such as potentially administering a TB vaccine using the same platform used for administering the human papillomavirus to young teenagers, and in line with a 'life course' vision of the future of immunization programs.

Global access to new TB vaccines must integrate evidence, technology, policy, funding, and politics—with end-users, communities, physicians and national TB programmes actively engaged in the process. These activities will help to ensure the alignment and smooth transition of new vaccines from R&D to worldwide markets in order to achieve maximum benefit for individuals and as well as optimized impact on the epidemic.

Operational research

Operational research involves a wide range of research activities that are used to investigate strategies, interventions, tools and knowledge that can improve the performance of health systems and programs.[28] Despite improvements in recent years, large implementation gaps still exist in the delivery of quality-assured, person-centered TB care. 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. Operational research is also necessary to understand how best to combine medical care with social-service support in order to achieve the best treatment outcomes and to better address the underlying factors that put people and communities at risk of TB.[29]

Research funders should allocate specific funding for operational research, directing it as a priority toward initiatives that will build the evidence base for closing implementation gaps in LMICs. Some key priorities for operational research include:

- Understanding 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.

- Understanding how to most efficiently and effectively conduct active case finding

[28] Zachariah R, Harries AD, Ishikawa N, et al. Operational research in low-income countries: what, why, and how? Lancet Infect Dis 2009; 9(11): 711–717.

[29] A Global Strategy for TB Research and Innovation. Geneva: WHO. In press.

(ACF), an approach by which health systems proactively reach out to persons at risk of TB and see that persons receive screening, diagnosis and appropriate care and support.

- Improving access to treatment, care and psycho-social support, including assessing, monitoring and overcoming social, legal, political and economic barriers to access, for both drug-susceptible and DR-TB.

- Understanding how public and private sectors can coordinate and collaborate to improve all aspects related to access and delivery of TB care and support.

- Optimizing TB infection control in order to reduce transmission.

- Improving methods for conducting disease surveillance, monitoring and evaluation of TB programs.[30]

- Understanding the role that TB affected communities and TB survivors can play throughout and beyond the TB cascade of care, including but not limited to TB service delivery.

To be sustainable, operational research capacity needs to be more routinely embedded within national TB control programs, with resources allocated through annual budgets.

Box 6.5 Building capacity for operational research in Papua New Guinea

Papua New Guinea (PNG) has one of the ten highest TB incidence rates in the world, one of the ten highest incidence rates of TB/HIV co-infection, and one of the ten highest incidence rates of MDR-TB.[31] In 2017-2018, SORT IT developed and implemented the first operational research capacity-building program for PNG. The program was funded by the Government of Australia and delivered by a coalition of researchers that included experts based at PNG research and training institutions. Twelve participants representing a third of PNG's districts were selected to the program and mentored over the course of a year in how to design an operational research study, analyze data, and publish in the peer-reviewed literature. The participants published a series of new operational research studies in 2019, with a focus on understanding and improving the capacity of the national TB program to identify, treat and care for people with DR-TB.[32] This research has helped to advance understanding in how the Xpert MTB/RIF diagnostic test has made an impact on capacity to address DR-TB;[33] outcomes of screening and care provided to people who have been exposed to TB in their households;[34] outcomes of the treatment of children;[35] effects of decentralization of

[30] Global investments in tuberculosis research and development: past, present, and future. Geneva: WHO. https://apps.who.int/iris/bitstream/handle/10665/259412/9789241513326-eng.pdf;jsessionid=B4395893955C977BDFAC5489FB9F9F20?sequence=1

[31] Global Tuberculosis Report 2019. Geneva: WHO. https://www.who.int/tb/publications/global_report/en/

[32] Aia P, Majumdar S, Pomat W, et al. The SORT IT model for building operational research capacity: the experience of TB service providers in PNG. PHA 2019; 9(S1):S1-S2.

[33] Lavu E, Johnson K, Banamu J, et al. Drug-resistsant tuberculosis diagnosis since Xpert® MTB/RIF introduction in Papua New Guinea, 2012-2017. PHA 2019; 9(S1): S12-S18.

[34] Honjepari A, Madiowi S, Madjus S, et al. Implementation of screening and management of household contacts of tuberculosis cases in Daru, Papua New Guinea. PHA 2019; 9(S1): S25-S31.

[35] Apis V, Landi M, Graham S, et al. Outcomes in children treated for tuberculosis with the new dispersible

services,[36] and other critical issues. Together, these studies are informing policy and the model of TB care within local TB programs.

Digital health and precision medicine

Digital health solutions have the potential to improve treatment support and the quality of TB care while reducing costs and ensuring that quality-assured TB care and support services are available, accessible and acceptable to all. Access to the Internet and smart phones are still relatively limited in many areas with high burdens of TB, but mobile phones with SMS capability are common.[37] New digital tools can help improve TB treatment adherence and support in a way that is less burdensome for people with TB and engage affected communities to monitor the TB response.

At the systems level, new digital tools—such as India's Nikshay platform—can help improve systems for patient registration and record-keeping, laboratory test orders, epidemiological surveillance and the movement of patient care from one health provider to another, among others. Other digital applications can help improve medicines forecasting and providing e-education for health professionals, people with TB and communities impacted by TB.[38]

The potential for improving TB care through digital technology, when used in the context of comprehensive care and support, is still largely untapped. However, one digital tool, the Stop TB Partnership's OneImpact, is facilitating community-based monitoring; an intervention that engages people affected by TB to report barriers to accessing quality and timely TB care and support services to strengthen the TB monitoring and evaluation system and response to people's needs. To promote the scale-up of digital tools for TB care, WHO has recently worked to collect evidence from digital health pilot projects, , develop target product profiles for digital tools, and provide recommendations regarding how best to implement and pay for digital health tools for the purpose of ending TB.[39,40]

Artificial intelligence (AI) is not new, but it has gained traction in healthcare in the last decade, due in part to advances in deep learning neural networks. Neural networks have been used for speech recognition with great success but have been increasingly used in the healthcare field for different applications in image recognition. AI for image recognition has a number of potential applications in TB, specifically for reading of chest x-rays (CXR) and other areas where reading has been done by humans. TB REACH has supported a significant number of the early studies using AI to read CXR. Recent developments include the published study of multiple deep-learning reading applications conducted at multiple sites. This study showed three different deep learning applications outperforming experienced human readers. There are multiple benefits of AI use to read CXR, including the ability to

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fixed-dose combinations in Port Moresby. PHA 2019; 9(S1): S32–S37

[36] Maha A, Majumdar S, Main S, et al. The effects of decentralisation of tuberculosis services in the East New Britain Province, Papua New Guinea. PHA 2019; 9(S1): S43–S49

[37] Yoeli E, Rathauser J, Bhanot S, Kimenya M, Masini E, Owiti P, Rand D. Digital health support in treatment for tuberculosis. N Eng J Med 2019. 381:986-987.

[38] Digital health in the TB response. WHO. 2015. Online: https://www.who.int/tb/publications/ehealth_TB.pdf?ua=1

[39] Digital health in TB care and control. WHO. 2019. Online: https://www.who.int/tb/areas-of-work/digital-health/en/

[40] Handbook for the use of digital technologies to support tuberculosis medication adherence. WHO. 2018. WHO/HTM/TB/2017.30 Online: https://www.who.int/tb/publications/2018/TB_medication_adherence_handbook_2018/en/

standardize scoring, saving large amounts of Xpert tests costs, and improving detection when using CXR as a triage test. AI for CXR can be especially helpful in places with a lack of trained human readers, with high screening throughputs.

AI can help classify other data as well, including sounds. Additional applications of AI that could help the TB response are being developed including electric remote cough monitors, automated reading of microscopic examinations, and using AI to identify 'hot spots' for TB screening campaigns or to help health care workers recognize people receiving TB treatment who may need specialized attention and support. The vast amount of data that are generated from TB programs will assist the development of new AI applications and uses in the TB response.

Table 6.1 Summary of Target Product Profiles for TB digital health tools[41]

Function	TPP: short description
Patient care	1. Video observed treatment (VOT) via mobiles
	2. eHealth portal for TB patients
Surveillance & monitoring	3. Graphic dashboards for TB
	4. eNotify TB
	5. ePV for TB
Laboratory information systems	6. TB diagnostic device connectivity
eLearning	7. Patient information platform on TB and smoking cessation
	8. Web-based training for health care professionals on TB and smoking cessation
	9. Clinical decision support systems for TB and tobacco care

As applications for digital health tools continue to expand, as access to information and communications technologies continue to grow in LMICs, and as artificial intelligence 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. Since concerns remain that digital technology has the potential to replace human contact and to even be misappropriated for uses that overstep the purposes of improving support and quality of care by violating the rights to privacy and autonomy, it will remain essential to seek input from people with TB and survivors in the course of designing digital health applications. Adhering to ethical standards will also remain critical in the course of navigating issues of privacy, oversight, accountability and public trust, data governance and management in the application of digital health tools.[42]

[41] Target product profiles and priority digital health products for TB. WHO. 2015. Online: https://www.who.int/tb/areas-of-work/digital-health/target-product-profiles/en/

[42] Effy V, Tobais H, Afua A, Alessandro B. Digital health: meeting the ethical and policy challenges. Swiss Med Wkly. 2018;148:w14571.

BOX 6.6: TB REACH DAT Projects

In Wave 6, TB REACH, with support from the Bill and Melinda Gates Foundation, funded 13 projects that focus on the use of digital adherence technologies (DAT) to enhance treatment support and improve treatment outcomes. These projects are being implemented in twelve countries, supporting various populations and settings, and using varying DAT tools such as 99DOTS, evriMED, SureAdhere (video observed technology, or VOT), and other locally developed technologies. The 13 TB REACH DAT projects provide a unique opportunity to understand the use and implementation of DATs for TB treatment across different settings and contexts. Lessons learned from these projects will add to the global evidence gap for understanding the impact that these tools can have on treatment outcomes, as well as any challenges and opportunities related to their use among people with TB, health care providers, and TB programs.

More information is available at:
http://www.stoptb.org/global/awards/tbreach/wave6DAT.asp
