TAG
Treatment Action Group

From Fair Share to Fair Shot:
Capitalizing on Opportunities to Ensure Success of U.S.-Government-Funded TB Research

By Elizabeth Lovinger | Edited by Lindsay McKenna, Mike Frick, and Suraj Madoori | March 2020

In 2018, global funding for tuberculosis (TB) research and development (R&D) hit an all-time high of $906 million, and for the 14th year in a row the U.S. government remained the largest funder, investing a total of $371.6 million—more than every other government combined.[1] Increased investments in TB R&D have led to a resurgence of breakthroughs in TB treatment, prevention, and diagnosis, bringing us closer to a TB-free world than ever before. These advances mark the end of decades of scientific inattention to TB. After decades of stagnation, we now have multiple new drugs and all-oral regimens for drug-resistant TB; shorter and safer regimens for TB prevention; a promising vaccine candidate entering phase III clinical trials; and molecular and urine-based tests capable of bringing TB diagnosis closer to the point of care.

However, funding still lags far behind what is needed to end TB in our lifetimes. At the 2018 United Nations High-Level Meeting on TB, member states determined that it would take $2 billion in annual global R&D investments to develop the tools required to eliminate TB by 2030—more than double current funding levels.[2,3] Governments committed to closing this funding gap by contributing "appropriately" to R&D efforts and by approaching TB research as a "shared responsibility."[4] Concretely, this resolve to contribute appropriately has translated into a call for all governments to give their "fair share" to TB research, defined as using at least 0.1 percent of overall R&D spending on research to address TB.

For the United States, giving our fair share of global TB R&D investments means mobilizing an additional $72.9 million to bring the country's total TB R&D funding to $444.5 million.[5] Failing to do so puts existing investments at risk, limiting the prospect of accelerating TB research efforts to optimize existing tools and develop the next generation of technologies required to end TB. We need to invest our "fair share" in TB research—and hold other governments accountable for investing theirs—in order to ensure that scientists have a "fair shot" at ending TB.

THE HIDDEN COSTS OF AN UNDERFUNDED TB RESEARCH AGENDA

Adequate funding is critical to maintaining a robust research agenda, one capable of evolving with discoveries and delivering timely results to guide the introduction of innovative tools and interventions. Past experiences in TB research demonstrate the hidden costs exacted by lean funding. In the context of chronic underfunding, the urgency of the need relative to the amount of available funding can create a research environment in which so-called efficiency (i.e., the ability to do more with less) comes at the cost of scientific rigor (see Table 1).

One grave consequence of sustained underfunding for research across disease areas has been the increased reliance of regulators and policy makers on observational and other "real world" sources of data in place of large randomized controlled trials (RCTs). RCTs are considered the gold standard in clinical research but can be more expensive and logistically complicated than less rigorous means of collecting data. However, the investment in RCTs pays for itself by answering important research questions with minimal bias and uncertainty, thereby generating quality evidence to guide public health and clinical care. Data collected through other study types (e.g., observational studies, post-marketing evaluations) can make important contributions to the evidence base for a particular intervention but should supplement—not supplant—RCTs.

Investing the resources necessary to generate the highest attainable standard of evidence for new interventions is essential in TB or any medical field; safeguarding the health of the public demands that we act on proof, not proof of concept.

Increased funding for, and a renewed commitment to, high-quality science will be necessary to (1) accelerate the speed at which research can be conducted while preserving the evidentiary standards upon which regulatory and policy decisions are based; (2) ensure that research findings are broadly applicable, including to vulnerable populations that are commonly underrepresented in research; and (3) centralize community participation and consultation in the design and conduct of research, thereby ensuring that those most affected by TB—and the unique challenges they face—inform the resulting science and product development.

TABLE 1: EFFECTS OF UNDERFUNDING TB RESEARCH

Problem	Effect
Weak, underpowered trial designs with inappropriate internal comparators (or no comparators)	Increased uncertainty and risk of bias, ambiguous research results with narrow applications, and partial answers to important research questions. Leads to provider and patient skepticism, equivocal guidance, and slow uptake of new tools and interventions.
Poorly resourced clinical trials and scientific infrastructure	Limited geographic scope of research efforts and slow enrollment due to multiple "competing" studies at research sites. Leads to limited research capacity and lengthier research timelines.
Exclusion of vulnerable, high-need populations from research	Limited knowledge about the efficacy and safety of new TB tools in populations most vulnerable to TB. Leads to increased risks and disparities in access to the benefits of scientific progress.
Lack of community engagement in research agenda setting and conduct	Limited understanding of population needs. Leads to less ethical and effective research.

FIVE FUNDING PRIORITIES FOR TB RESEARCH

The National Institute of Allergy and Infectious Diseases (NIAID) Strategic Plan for Tuberculosis Research, released in 2018, lays out five priorities for TB research.[6] These priorities provide clear direction for the U.S. government to increase TB research funding in line with the "fair share" principle. Strategic investments made in FY 2021 across key U.S. agencies could expedite and expand ongoing and prospective research efforts to generate the high-quality public health tools needed to end TB. Based on the five priorities of NIAID's Strategic Plan, the following sections provide a vision for what increased U.S. government investments in TB R&D could accomplish.

Priority No. 1: Improving Fundamental Knowledge of TB

Although TB has existed for centuries, our basic understanding of TB biology and pathology remains incomplete. For example, researchers are still exploring the complexities of our innate immune response to TB and looking for biomarkers that can help identify people at increased risk of progressing from latent TB infection to active TB disease.

Basic science encompasses the fundamental knowledge that guides researchers seeking better ways to predict, prevent, diagnose, and treat disease. As the engine of all discovery and product development, basic science requires continuous, uninterrupted support—the more we invest, the greater chance we have of unlocking advances that can translate into a higher standard of care. The historical lack of resources for basic research has discouraged young investigators from building careers in TB and has depressed the creative, exploratory science that can lead to breakthrough discoveries. These factors limit potential returns on TB research investments from the very outset, as this foundational knowledge is necessary to inform effective diagnostic, prevention, and treatment strategies.

Moreover, greater investment in the basic understanding of TB can have important translational benefits for other areas of research. Research conducted in the 1960s and 1970s on retroviruses led to some of the most important discoveries in the fight against HIV decades later.[7] New antibiotics developed for TB could have utility against other diseases, bolstering the fight against antimicrobial resistance.

Recommendation: Congress should increase and direct USG research funding appropriated to the National Institutes of Health (NIH) to implementing the agency's core TB basic science agenda outlined in the NIAID Strategic Plan.

Priority No. 2: Advancing Research to Improve Diagnosis of TB

Eliminating TB requires closing global gaps in TB diagnosis. Of the estimated 10 million people who develop TB each year, only 7 million people are officially diagnosed and treated, leaving a gap of 3 million people who are either diagnosed and not reported, or who go undiagnosed and without treatment.[8] Closing the diagnostic gap requires tools that are rapid, accurate, and inexpensive; rely on easy-to-collect samples; and can be used at the point of care. Existing TB tests do not meet all of these criteria, though recent advances have brought rapid testing closer to the point of care.[9]

Improving TB diagnosis requires the discovery and validation of new biomarkers and their translation into point-of-care assays that can be administered at the community level. Scientists are exploring a number of new and promising biomarkers, yet few have progressed to a product-development phase in part because of insufficient funding.[10] NIAID has shown some leadership in this area already, but further investments are critically necessary.[11]

Recommendation: Congress should increase USG investment in R&D for novel TB biomarkers and their translation into rapid point-of-care diagnostic tests.

Priority No. 3: Accelerating Research to Improve TB Prevention

Currently, the only TB vaccine available, BCG, protects children against TB but offers little protection to adolescents and adults, the age groups that account for most TB transmission. A number of new TB vaccine candidates have shown positive protective signals in phase II trials and now require further evaluation in phase III. One such candidate is M72/AS01E, which in a phase IIb trial provided 50 percent protection against developing TB disease to adults with TB infection.[12] This positive protective effect must now be confirmed in a phase III study, an undertaking that will require hundreds of millions of dollars in investment—a sum substantially higher than the $109 million spent on TB vaccine R&D globally in 2018.

Additional funding could bring forward next-generation TB vaccine candidates—and novel component technologies, such as adjuvants that may have utility in vaccine development for many other diseases.

Recommendation: USG should examine its agencies' role in contributing to the development of promising TB vaccine candidates through phase III. This includes authorizing the Biomedical Advanced Research and Development Authority with additional resources to engage in TB product development, in collaboration with TB research agencies such as NIAID, the Centers for Disease Control and Prevention (CDC), and the U.S. Agency for International Development (USAID).

Priority No. 4: Supporting Research to Advance and Shorten Treatment of TB

Many exciting opportunities for shortened TB treatment regimens are on the horizon, but these require adequate investment through phases III and IV to ensure that we understand both the individual contributions of new medicines to treatment regimens and how new medicines should be optimally combined to shorten the duration of treatment and/or improve regimen safety and efficacy.

Additional resources will also be required to capitalize on lessons learned from failed attempts to shorten TB treatment, by evaluating treatment strategies tailored to address risk factors known to affect treatment outcomes, essentially applying the concept of "precision medicine" to TB. This type of programmatically relevant and cutting-edge research plays to the strategic advantage and mission of the CDC TB Trials Consortium (TBTC), which sits within the Division of TB Elimination (DTBE). TBTC trials are often conducted in collaboration with the NIH-funded AIDS Clinical Trials Group, which offers additional sites and scientific expertise in high-TB/HIV-burden settings.

Recommendation: Congress should fund DTBE to its full authorization level (or $195.7 million in FY 2021) and increase resources allocated to the NIH and USAID to support the next wave of collaborative treatment optimization and shortening studies.

Priority No. 5: Developing Tools and Resources to Advance TB Research

One factor limiting the pace of research is the paucity of tools available to measure the effectiveness of TB innovations—e.g., surrogate markers for longer-term clinical outcomes of interest such as relapse-free cure for treatment trials or correlates of immunity for TB vaccine trials. Increasing U.S. government investments in the discovery, validation, and development of reliable surrogate markers of clinically relevant outcomes has the potential to revolutionize the speed at which we can evaluate new TB innovations.

Other important research tools include biobanking initiatives, registries, and systems for data sharing. Insufficient funding can lead researchers to neglect the collection and storage of specimens in biobanks for future research and to defer setting up registries and systems for data sharing—particularly for key affected populations such as pregnant women. Registries have been crucial for monitoring the safety of antiretroviral treatments (ART) among HIV-positive pregnant women. Establishing a similar registry for TB medications would help researchers collect information—currently missing—that is important to optimizing TB treatment during pregnancy. The federal Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC) recommends the development of disease- and condition-specific registries (modeled after ART registries), but the infrastructure necessary to implement this recommendation will require funding.

Recommendation: Congress should invest in tools and initiatives capable of expediting TB research advancements and implement the recommendations of the PRGLAC Task Force by funding the Food and Drug Administration (FDA) to support the development and maintenance of a TB-specific pregnancy registry.

Table 2: U.S. Agency Funding Levels and Targets

(in $ millions)	Agency Role in TB R&D	FY 2018 Funding Levels	'Fair Share' Funding Targets
NIH – NIAID	Basic, translational, & clinical research	253.4	293.4
NIH – Other ICs	Basic, translational, & clinical research	43.9	57.8
USAID	Basic & applied diagnostic & drug research	36.7	48.9
CDC	Clinical & epidemiological research	17.6	26.7
Defense*	Basic, translational, & clinical research	12.9	8.9
PEPFAR*	Operational research	3.5	2.2
VA	Basic, translational, & clinical research	1.6	1.8
FDA	Clinical research & regulatory work	0.9	1.3
NSF	Basic & translational research	0.9	4.4
Total		371.6	444.5

ICs: Other Institutes & Centers; NSF: National Science Foundation; VA: Veterans Affairs

*Although DoD and PEPFAR met their targets for FY2018, further investments are still needed.

The figures in the far right column represent the amount of agency funding for TB R&D if the US met its fair share funding target. This breakdown is based on the proportion of current spending each agency contributes and imagines what this will look like under the fair share scenario.

TB research is very much a U.S. government enterprise, with multiple agencies playing unique and complementary roles in the research pipeline. Increasing FY 2021 funding to the level outlined as the U.S. government's fair share (see Table 2) would bring us closer to delivering on the commitments made at the 2018 UN High-Level Meeting on TB: to close the global funding gap for TB R&D; to support a robust, needs-driven TB research agenda; and to bring the world significantly closer to ending TB by 2030. Increased investments from the U.S. government would set an example for all other countries and would catalyze the global funding increases necessary to end TB through innovation.

RESOURCES

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