Stop TB Partnership

TAG
Treatment Action Group

THE ASCENT BEGINS

Tuberculosis Research Funding Trends

2005–2016

ACKNOWLEDGMENTS

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ABOUT TAG

Treatment Action Group (TAG) is an independent, activist, and community-based research and policy think tank fighting for better treatment and prevention, a vaccine, and a cure for HIV, tuberculosis (TB), and hepatitis C virus (HCV).

TAG works to ensure that all people with HIV, TB, or HCV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end HIV, TB, and HCV.

TB/HIV PROJECT

Treatment Action Group's TB/HIV project works to create a policy, funding, and advocacy environment that is conducive to TB research, the uptake of evidence-based interventions, and the promotion of human rights of people affected by TB.

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The Ascent Begins: Tuberculosis Research Funding Trends, 2005–2016

NOVEMBER 2017

TREATMENT ACTION GROUP

BY MIKE FRICK

EDITED BY MARK HARRINGTON AND ERICA LESSEM

DEDICATION

In honor of Siya Trivedi

We dedicate this report to Siya Trivedi,* the brave young woman with extensively drug-resistant tuberculosis (XDR-TB) who sued a public Indian hospital for access to new drugs to treat her disease—and won.

First diagnosed with TB as an adolescent, Siya likely developed XDR-TB after years of clinical mismanagement.[1] After exhausting all other treatment options, and facing the end of her life, Siya and her father traveled from their home in Patna to Delhi seeking access to the new TB drugs bedaquiline and delamanid. There they discovered that delamanid had, at that time, not yet been registered in India by its developer, the Japanese pharmaceutical company Otsuka, despite over three years having passed since delamanid's regulatory filing in Europe. As such, delamanid was only available in India through compassionate use, which Siya's doctors at the Lala Ram Sarup TB Hospital in Delhi would not request on her behalf. Bedaquiline was only available through a small government clinical access program at six sites throughout the country, and only to people residing near the clinic sites. As Siya did not satisfy the domicile requirement for bedaquiline treatment under the program, the government denied her request to start using the drug.[2]

Determined to fight for herself and others, Siya urged her father to sue for access to bedaquiline. She won her case before the Delhi High Court, which ruled in January 2017 that the government could not determine bedaquiline eligibility based on domicile.[3] Siya was transferred to the esteemed Hinduja Hospital in Mumbai, where she received both bedaquiline and delamanid under compassionate use. In challenging the discriminatory domicile rule, Siya and her lawyers—the legendary Lawyers Collective—opened the door for many more patients with drug-resistant TB in India to access potentially life-saving new treatment options.[4]

Siya's fight illuminates the integral relationship between TB research and human rights, including the rights to health, life, nondiscrimination, and scientific progress. Research alone is not enough to save a life like Siya's; governments and product developers have an obligation to ensure that the results of research are disseminated equitably and expeditiously to those in need. All people with and at risk of TB have a right to enjoy the benefits of scientific progress.

Delamanid is now registered in India, and the Indian government has announced plans to scale up access to both delamanid and bedaquiline across the country. But a year and a half after its launch, only a few hundred patients have received bedaquiline through the public program in India. And Siya's fight against XDR-TB continues, as the drugs she needed came extremely late for her.

*Pseudonym used by request.

Table of Contents

PROLOGUE

"An ordinary young man was on his way from his hometown of Hamburg to Davos-Platz . . ."

The Magic Mountain, Thomas Mann

The opening sentence of Thomas Mann's 1924 novel *The Magic Mountain* begins with the protagonist on the road, traveling from Hamburg, Germany, to a tuberculosis (TB) sanatorium in Davos, Switzerland, where a temporary visit turns into a seven-year stay.[5] Mann could not have known that the geographic reference points of his opening scene would, nearly a hundred years later, orient a different kind of journey among those fighting TB. The TB sanitaria of Davos would empty their beds with the advent of antibiotic therapy in the 1950s and transform into the upscale lodges later hosting the World Economic Forum. There, in 2006, heads of state and other global elite rallied behind the *2006–2015 Global Plan to Stop TB*.[6] The *2006–2015 Global Plan* and its subsequent iterations called for $9 billion in funding for TB research and development (R&D) and expressed the urgency of introducing new diagnostic tests, drugs, and vaccines into the fight against TB and of expanding investments in basic science and operational research.[7]

Fast forward 11 years and return to Hamburg where leaders of the G20 nations met in July 2017. By the time the G20 leaders convened, the optimism of Davos in 2006 had yielded to sobriety in the face of the persistent lethality of the TB epidemic and its role as a driving force in the spread of antimicrobial resistance (AMR). In the years between Davos and Hamburg, TB overtook HIV as the world's leading cause of death from a single infectious agent; drug-resistant forms of TB accounted for a quarter of annual AMR deaths; and TB research struggled to secure even one-third of the targeted $9 billion in funding. Recognizing the growing threat of TB and AMR, the G20 heads of state "highlighted the importance of fostering R&D, in particular for priority pathogens as identified by the World Health Organization [WHO] and tuberculosis" in the declaration released from their meeting and called for "a new international R&D Collaboration Hub" to spur clinical research and product development.[8]

Following the G20 Summit, heads of state from the BRICS countries—Brazil, Russia, India, China, and South Africa—gathered in Xiamen, China, in September 2017 and voiced their support of "the decision to set up a Tuberculosis Research Network."[9] This and other proposals for increasing global funding for and coordination of TB research will be discussed at the WHO Global Ministerial Conference on Ending Tuberculosis, hosted by the Russian Federation in Moscow in November 2017. The political declaration to be endorsed by countries in Moscow will provide a blueprint for securing decisive commitments in support of TB R&D by country governments at the first-ever United Nations High-Level Meeting on Tuberculosis in New York in September 2018.

Tracing the connections between Davos, Hamburg, Xiamen, Moscow, and New York forms a map of the high-level forums where advocates for TB research and high-quality TB programs have pressed political leaders to back the science and innovation required to end the TB epidemic. Other maps could be drawn. One might start in and circle back to Cape Town, South Africa, where activists led by the Treatment Action Campaign marched in 2007 and then again in 2015 calling for greater investments in TB research and programs.[10] Under the rallying cry "*Invest so we can live!*" those marching in 2015 urged the BRICS countries to triple funding for TB R&D and challenged established donor nations such as the United States and United Kingdom to increase their own spending.[11]

One could also trace the journeys of individual patients with TB struggling to access accurate diagnosis and effective treatment against all odds while navigating broken health systems. Patient journeys show just how far TB research has come since the sanatorium era depicted in Mann's novel and just how far it still has to go before the TB epidemic can be brought to an end. *The Magic Mountain* unfolds against a backdrop of then–state-of-the-art TB care featuring X-rays, sputum collection, "quicksilver cigars" (thermometers), and

an elaborate schedule of rest and meals.[12] Today's standard of care is much more advanced but is available to far too few and carries many limitations that can only be resolved through additional research and much greater political commitment.

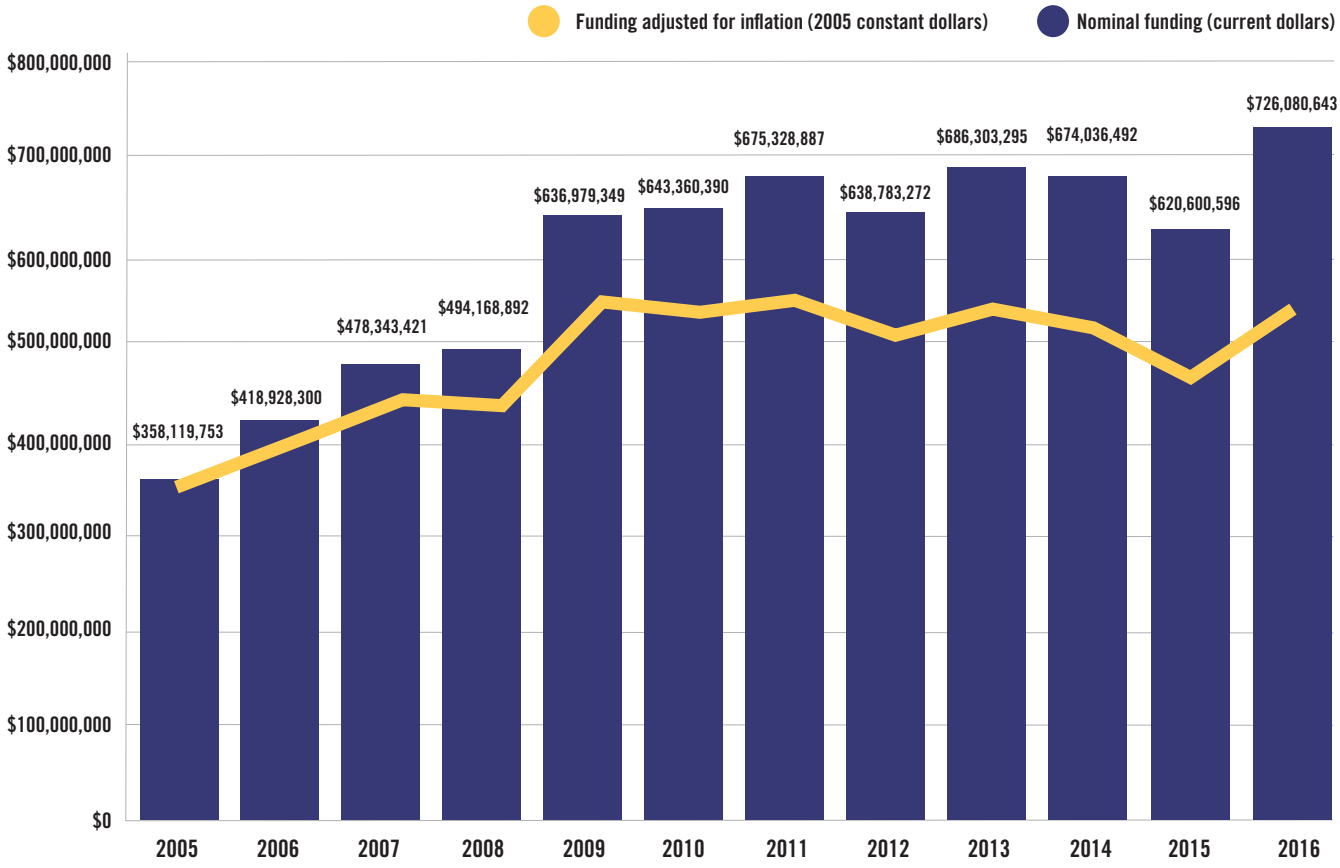
The strongest case for a renewed commitment to TB R&D by governments and other stakeholders comes from the personal testimonies of a growing cadre of TB survivors who are speaking out about the consequences of limited scientific progress. Diagnosed with TB at age 16, Deepti Chavan endured six years of treatment and ultimately lost a lung in her fight against drug-resistant TB (DR-TB). "We cannot risk the lives of TB patients by delaying diagnosis and putting them on the wrong treatment," said Chavan at a forum at McGill University in June 2017.[13] "Perhaps if my doctors had done drug resistance tests earlier, my lung could have been saved." Nandita Venkatesan beat DR-TB but lost her hearing, a side effect of treatment with the TB drug kanamycin. Speaking at the same forum as Chavan, Venkatesan emphasized the need to develop TB drugs with fewer toxicities and echoed the importance of drug susceptibility testing: "A test result to check drug resistance takes six weeks to come. But that time is enough to turn a patient's life upside down."[14]

The diagnostic challenges Deepti and Nandita identify as urgent research priorities are not altogether dissimilar from Mann's own experience with TB. Mann based his novel on a trip to Davos in 1912 to visit his wife, Katja, who was recovering from TB at a sanitarium in town. While in Davos, Mann himself received a TB diagnosis, but back home in Munich his doctor dismissed it and assured Mann he was TB free. Post-mortem exams suggest that Katja probably never had TB, while Mann's lungs showed scars indicative of tuberculosis.[15,16] TB will continue to elude detection for many, and the TB epidemic will evade all efforts to end it, unless the international community joins together to accelerate research and unlock the scientific progress needed to overcome TB. Davos, Hamburg, and Xiamen are in the past; now on its way to Moscow and New York, the TB community must ensure that the political leaders present at these gatherings match rhetoric in support of TB R&D with concrete financial commitments and action.

Executive Summary

FIGURE 1

Total TB R&D Funding, 2005–2016



This report, released just as the TB community gathers in Moscow for the Ministerial Conference and looks ahead to the 2018 U.N. High-Level Meeting in New York, presents 12 years of data on global funding for TB R&D collected by Treatment Action Group (TAG) with the goal of motivating heads of state, ministers of health and finance, stakeholders from the private and philanthropic sectors, and civil society to increase support for TB research. Global funding for TB R&D grew modestly from 2005–2008, but annual growth stalled after 2009, and available TB research dollars steadily lost purchasing power in the face of inflation (**Figure 1**).

The most recent figures on TB research funding, however, reveal a renewed momentum heading into Moscow and New York. In 2016, annual funding for TB R&D exceeded $700 million for the first time since TAG began tracking spending in 2005. Funding increased in all categories of TB research, although most of this growth came from public-sector sources, and a significant portion may reflect the upswing of grant payment cycles or more comprehensive reporting by major established donors. For the

"With the current amount of money, a flat line, and no more progress in funding, it is quite unlikely that we will be able to develop the new tools that everyone wants and needs to end TB."

Mario Raviglione, Director, World Health Organization Global TB Programme

> "Unless we see a sharp increase in funding, the momentum and hope of ending TB by 2030 will be delayed."
>
> **Lucica Ditiu, Executive Director, Stop TB Partnership**

fifth straight year, private sector spending on TB R&D decreased compared with the year before, with the pharmaceutical industry at its lowest level of investment since 2009. Increases in public, philanthropic, and multilateral spending made up for diminished industry expenditures.

The $726.1 million spent on TB research in 2016 now represents the baseline against which the long-term outcomes of Moscow and New York will be measured. Although higher than previous years, this figure is not yet large enough for TB advocates to retire the striking statistic that TB R&D receives only one-third of the nearly $2 billion in annual funding called for by the Stop TB Partnership.[17] New mechanisms for financing TB research—whether the R&D Collaboration Hub envisioned by the G20, the TB Research Network named by the BRICS leaders, or another platform to be proposed in Moscow or New York—will likely be required to substantially raise spending above this level. Actions taken in the next five years, by political leaders in office today, will determine the trajectory of TB research over the next two decades. This era will be judged against the ambitions of the United Nations Sustainable Development Goals (SDGs), a wide-ranging platform for action by all countries and stakeholders in "areas of critical importance for humanity and the planet;" ending the TB epidemic by 2030 is singled out as a specific target within this framework.[18]

The numerous targets of the SDGs represent a broad commitment by nations of the world to eradicate poverty in all of its forms and dimensions everywhere. TB, a disease described by Archbishop Desmond Tutu as "the child of poverty, and also its parent and provider," will stand as a bellwether of progress toward the successful attainment of this vision. As an integral part of the fight against TB, research must in turn become a higher priority for governments—a view echoed by all 12 of the TB scientists, policymakers, and activists interviewed by TAG for this report. In the assessment of Mario Raviglione, director of the WHO Global TB Programme, "with the current amount of money [for TB research], a flat line, and no more progress in funding, it is quite unlikely that we will be able to develop the new tools that everyone wants and needs to end TB." Lucica Ditiu, executive director of the Stop TB Partnership, concurred: "Unless we see a sharp increase in funding, the momentum and hope of ending TB by 2030 will be delayed." The increase in TB R&D funding this year should give the TB community the courage to set high expectations for the outcomes of the high-level political meetings in Moscow and New York.

Introduction

> "We now have some real critical momentum in the drugs, vaccines, and diagnostics fields, and it's absolutely critical we keep that momentum going. There are no easy wins in this. There are no quick solutions. We have to compensate for 50 years of complacency."
>
> **Helen McShane, Professor of Vaccinology, University of Oxford**

The report *Tuberculosis Research Funding Trends, 2005–2016* reviews 12 years of data on global funding for TB R&D and presents new data on TB research spending in fiscal year 2016. For the first time since TAG began tracking spending in 2005, funding for TB R&D crossed the $700 million mark. The total funding of $726.1 million in 2016 stands $105.5 million above the $620.6 million spent on TB research in 2015. However, overall funding for TB R&D remains woefully inadequate, especially when viewed against decades of underinvestment and ambitious global targets to end the TB epidemic within the next 15 years.

TAG is releasing this report to coincide with the opening of the First WHO Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era. Hosted by the Russian Federation in Moscow, this forum will bring together ministers of health from the 40 countries with the highest burdens of TB and DR-TB alongside stakeholders from multinational institutions, the private and philanthropic sectors, and civil society.[19] The meeting aims to accelerate progress toward achieving the End TB Strategy targets endorsed by the World Health Assembly and reflected within the SDGs: an 80 percent decrease in new TB cases and 90 percent decrease in TB deaths by 2030 compared with 2015 levels.[20]

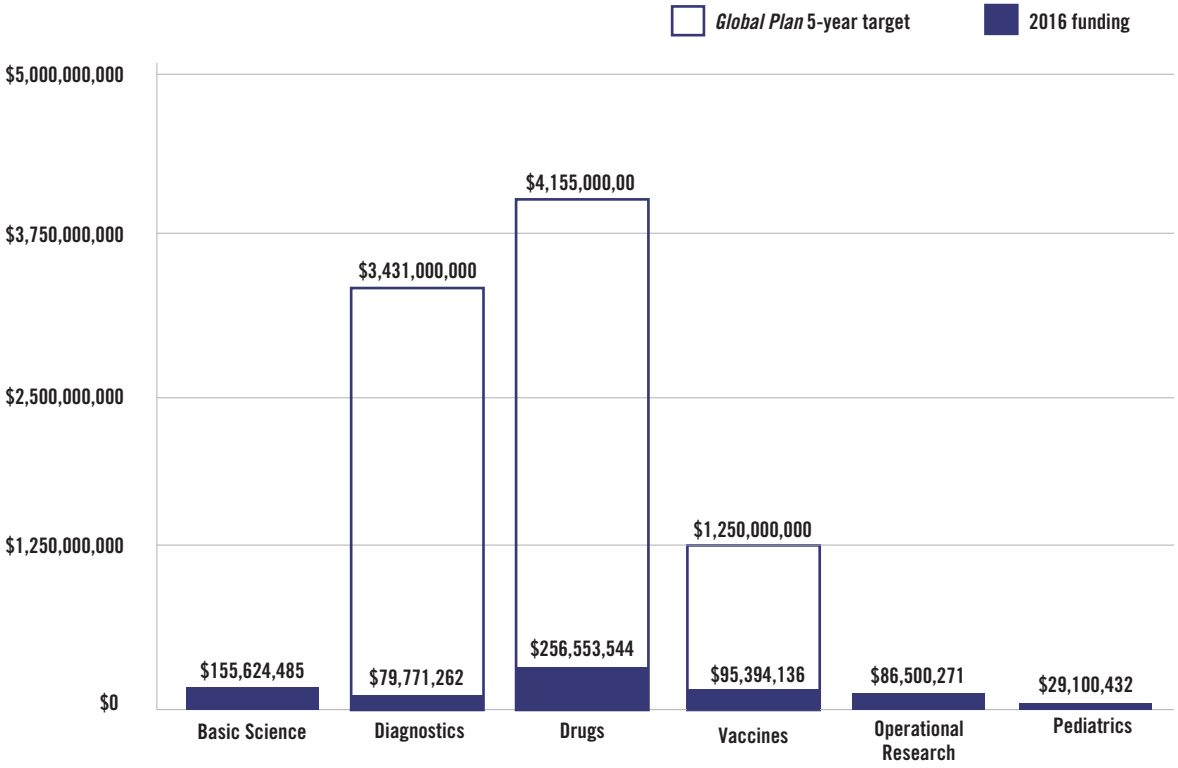
The epidemiologic modeling that informs the End TB Strategy shows that even universal access to available technologies will not produce the substantial reductions in TB incidence and mortality required to end the TB epidemic.[21] To achieve these targets, new tools to fight TB must be introduced no later than 2025. In particular, the End TB Strategy calls for a rapid point-of-care test for diagnosing TB and detecting drug resistance; safer, shorter, and more effective drug regimens for treating all forms of TB; and a new vaccine that can either improve upon or replace bacillus Calmette-Guérin (BCG), the existing TB vaccine.[22] In addition, a diagnostic test capable of identifying those individuals with latent tuberculosis infection (LTBI) most likely to progress to active, symptomatic, infectious disease would offer a powerful tool for driving down TB incidence through targeted preventive therapy.[23]

The Moscow Ministerial Conference will culminate in a signed declaration that will inform preparations for the U.N. High-Level Meeting on Tuberculosis, scheduled to take place in New York in September 2018. This will be the first High-Level Meeting on TB and only the fifth on a health issue, following earlier meetings on HIV, non-communicable diseases, Ebola, and AMR. Scientific research and innovation is one of the eight thematic areas of the Moscow Ministerial Conference and will appear on the U.N. High-Level Meeting agenda. The numbers on TB research funding reviewed in this report make clear that leaders at both meetings must commit to substantially increasing support for TB R&D if the world hopes to end the TB epidemic by 2030.

In the *Global Plan to End TB, 2016–2020: the Paradigm Shift,* the Stop TB Partnership estimated that the world must spend a combined $9 billion on TB diagnostic, drug, and vaccine R&D over the next five years to keep scientific progress on pace to satisfy the End TB Strategy's ambitions.[24] **Figure 2** shows funding to date in each of these areas in relation to the respective five-year target for that field. Already, one year into the *Global Plan to End TB*, funding in each area sits far below where it should be to reach the amounts called for by 2020.

FIGURE 2

Progress toward *Global Plan* 5-Year TB Research Funding Targets



The Global Plan to End TB did not set funding targets for TB basic science, operational research, or pediatric TB R&D.

"If we are to address TB seriously, our money needs to match what we say. There's definitely not enough money going into TB, and that's reflected in all aspects of the available tools we have and also in terms of the systems we have in place to address TB at the community and health system level. We need a lot more money going into [TB research] just to catch up to all the progress that could have been made the last 20–30 years if we had the same amount of money going into TB as we had going into HIV."

Jen Ho, Deputy Director, APCASO

Product development is not the only domain of TB research in urgent need of invigorated financial support. New funding must be made available for the full spectrum of TB research, from basic science insights into *Mycobacterium tuberculosis* (MTB), the causative agent of TB infection and disease, to operational research to optimize programmatic implementation of new strategies and interventions in diverse populations and settings.[25,26] Research related to pediatric TB also deserves more attention to overcome the historic neglect of the prevention, diagnosis, and treatment needs of children with and at risk of TB.[27,28] Although the *Global Plan to End TB* did not set specific targets for basic science, operational research, or pediatric TB, TAG will continue to track funding in these areas to produce the most complete picture possible of the health of the TB research field.

The slow pace of TB research highlighted by many of the individuals interviewed by TAG is not only a function of limited funding but also a consequence of the suboptimal way in which available money is organized and disbursed. As Soumya Swaminathan, outgoing director-general of the Indian Council of Medical Research (ICMR) and incoming deputy director general of programmes at the WHO, pointed out: "We could probably do more with the amount of funding that is currently available if there was a better way of targeting those funds to projects, groups, or ideas that are likely to deliver something. If there was

a global consensus on [how to] better target those funds—a mission mode program to develop a new vaccine, diagnostic, or drug regimen—then I think we would see more progress, even with the same amount of dollar funds."

In other words, how TB research is financed is just as important for political leaders to consider as the amount of money available. Deliberations in Moscow and New York, therefore, must encompass discussions of how best to raise, structure, and disburse TB research funding. Decisions on these points often shape who has access to the knowledge and tools that result from research.[29] With this concern in mind, Maurine Murenga, an organizer with the International Community of Women Living with HIV Eastern Africa, called on governments to "step up their legal obligations under the right to health, and reassess the TB R&D system in terms of how TB research is currently financed, conducted, and owned. Innovation must be developed and disbursed in a way that ensures all people with TB have access to TB research and its benefits." The TB scientists and activists quoted within this report offer many ideas for how to organize funding in ways that would encourage both transformative science and equitable access to the fruits of scientific advancement.

The overarching challenge for supporters of TB research heading into Moscow and New York is that the field not only must race forward in pursuit of future targets but also needs to make up for lost opportunities accrued over decades of inattention. Helen McShane, professor of vaccinology at the University of Oxford, put it this way: "We have had decades of neglect in TB—decades where TB was very under-resourced . . . We now have some real critical momentum in the drugs, vaccines, and diagnostics fields, and it's absolutely critical we keep that momentum going. There are no easy wins in this. There are no quick solutions. We have to compensate for 50 years of complacency."

This complacency has come at great cost to the individuals and communities that bear the heaviest burden of TB. TB is now the leading cause of death from a single infectious agent globally, and drug-resistant forms of TB (i.e., multidrug-resistant TB [MDR-TB] and extensively drug-resistant TB [XDR-TB]) form the leading edge of the advancing AMR threat, responsible for a quarter of annual AMR deaths.[30] The toll TB has taken on humanity over time is almost unfathomable. TB cut short an estimated two billion lives in the last two centuries alone and has plagued humanity for tens of thousands of years.[31,32] Confronting this staggering loss of life and human potential will require governments and other stakeholders to make a collective, decisive commitment to fully support R&D as an integral part of ending TB for good.

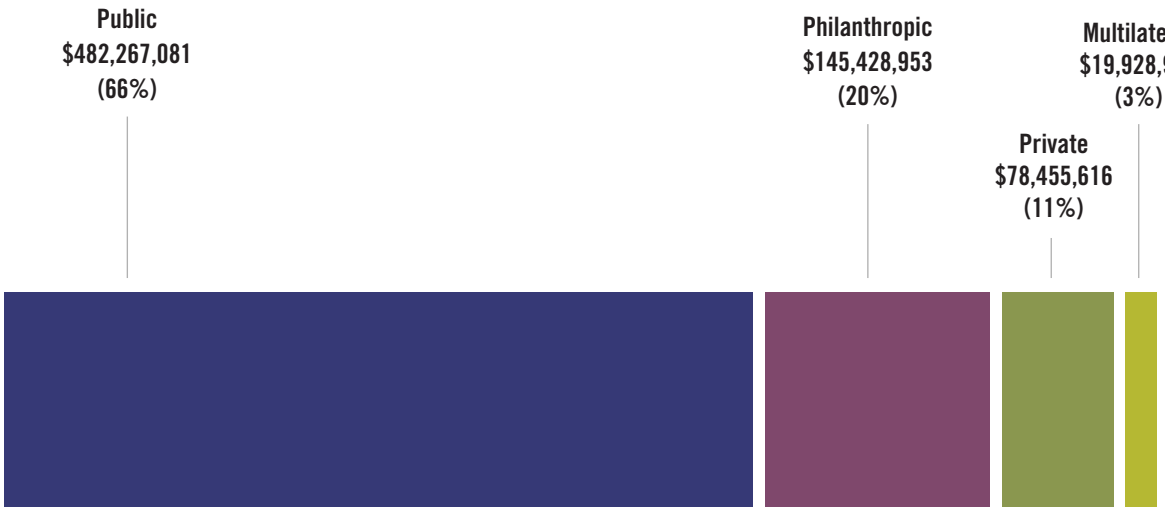
"While we can detect a renewed energy, focus, and momentum behind TB R&D over the past five years, this pales in comparison to the needs and also to the R&D environments in HIV and malaria. The status quo cannot continue if we are to achieve the SDG goal of ending the global TB epidemic and respond to the unmitigated threat of drug-resistant TB. Intensifying and invigorating R&D is vital to the TB response."

Suman Majumdar,
Co-Head of TB Elimination and Implementation Science,
Burnet Institute

Results

FIGURE 3

Total TB R&D Funding by Funder Category, 2016
Total: $726,080,643



In 2016, global funding for TB R&D totaled $726.1 million, an increase of $105.5 million over 2015 and the highest level of annual expenditure on TB research recorded by TAG since resource tracking began in 2005. This also marks the first time annual spending on TB research has exceeded $700 million. However, even this higher figure sits far distant from the estimated need. To reach the *Global Plan to End TB*'s five-year funding target of $9 billion, the world would need to spend an average of $1.8 billion per year between 2016 and 2020.[33]

Several factors underlie this jump in spending:

1. In 2015, many funders indicated to TAG either that they were between grant cycles or that major payments to existing projects would resume again in 2016. For example, Global Affairs Canada and the Dutch Directorate-General for International Cooperation (DGIS) reported no expenditures supporting TB R&D in 2015 but awards totaling $11.3 million and $7.6 million, respectively, in 2016.

2. TAG received more surveys this year than ever before, including some from TB research funders participating in the survey for the first time. The Chinese National Health and Family Planning Commission, Indian Council of Scientific and Industrial Research, and Innovative Medicines Initiative all made first-time reports to TAG.

3. More complete reporting by some institutions resulted in higher totals. A joint survey submission by the domestic and global TB divisions at the U.S. Centers for Disease Control and Prevention (CDC) produced a more comprehensive picture of CDC support for TB research. The same was true in South Korea, where the Korea Centers for Disease Control and Prevention coordinated a submission on behalf of several Korean public agencies.

4. Many funders spent more on TB research in 2016 than they did in 2015. The top two funders of TB research—the U.S. National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (Gates Foundation)—gave a respective $43 million and $9 million more than they did in 2015. The $43 million increase at the NIH would, on its own, rank among the five largest contributions to TB research in 2016. In addition, many smaller funders reported higher spending this year compared with last year.

Accounting for these factors, a large part of the observed increase in TB R&D funding in 2016 may reflect grant payment cycles, a wider survey reach, and more complete reporting, rather than an infusion of new resources. With the exception of Unitaid and the Global Health Innovative Technology Fund—the ninth and thirtieth largest contributors to TB R&D in 2016—the field has not witnessed the entry of deep-pocketed funders in recent years. TB research remains reliant on a handful of longtime major donors. Together, the NIH and Gates Foundation account for half of all money spent on TB research in 2016 and 53 percent since 2005. The five largest donors in 2016 comprise 61 percent of total funding for TB R&D, the top 10 make up 72 percent, and the top 30 over 90 percent. Moreover, 66 percent of TB R&D funding in 2016 came from public sources (**Figure 3**).

Although 2016 funding shows a sizeable increase in spending over 2015, this does not represent the biggest year-on-year increase recorded by TAG. That occurred when funding jumped from $494 million in 2008 to $637 million in 2009. The driving force behind that significant step-up in funding was the American Recovery and Reinvestment Act (ARRA), an $800 billion stimulus package signed into law by President Obama in response to the economic crisis.[34] Under the ARRA, the NIH received a one-time, two-year budget increase of $10.4 billion, which supported 21,581 grant-funded projects (75% of which were new awards).[35,36] In response, funding for TB research at the NIH jumped from $142 million in 2008 to $216 million in 2009 and has remained well above pre-ARRA levels ever since.

"Governments need to step up their legal obligations under the right to health, and reassess the TB R&D system in terms of how TB research is currently financed, conducted, and owned. Innovation must be developed and disbursed in a way that ensures all people with TB have access to TB research and its benefits."

Maurine Murenga, Organizer, International Community of Women Living with HIV Eastern Africa

Public money from the United States underwrites a large share of TB research

Unlike in 2009, there is no blockbuster legislative event that can easily explain higher TB research spending in 2016. But any significant increase in funding, whatever its source, raises the same question: can it be maintained over time? The additional $43 million in spending at the NIH alone accounts for 40 percent of the observed increase over 2015 spending levels. The CDC, U.S. Agency for International Development (USAID), U.S. National Science Foundation, and U.S. Department of Defense also reported higher TB R&D expenditures in 2016 than in 2015. The current political climate in the United States casts serious doubt over whether more robust funding from the U.S. public sector can be maintained into the future—especially for agencies other than the NIH, which has received particularly strong support from the U.S. Congress.

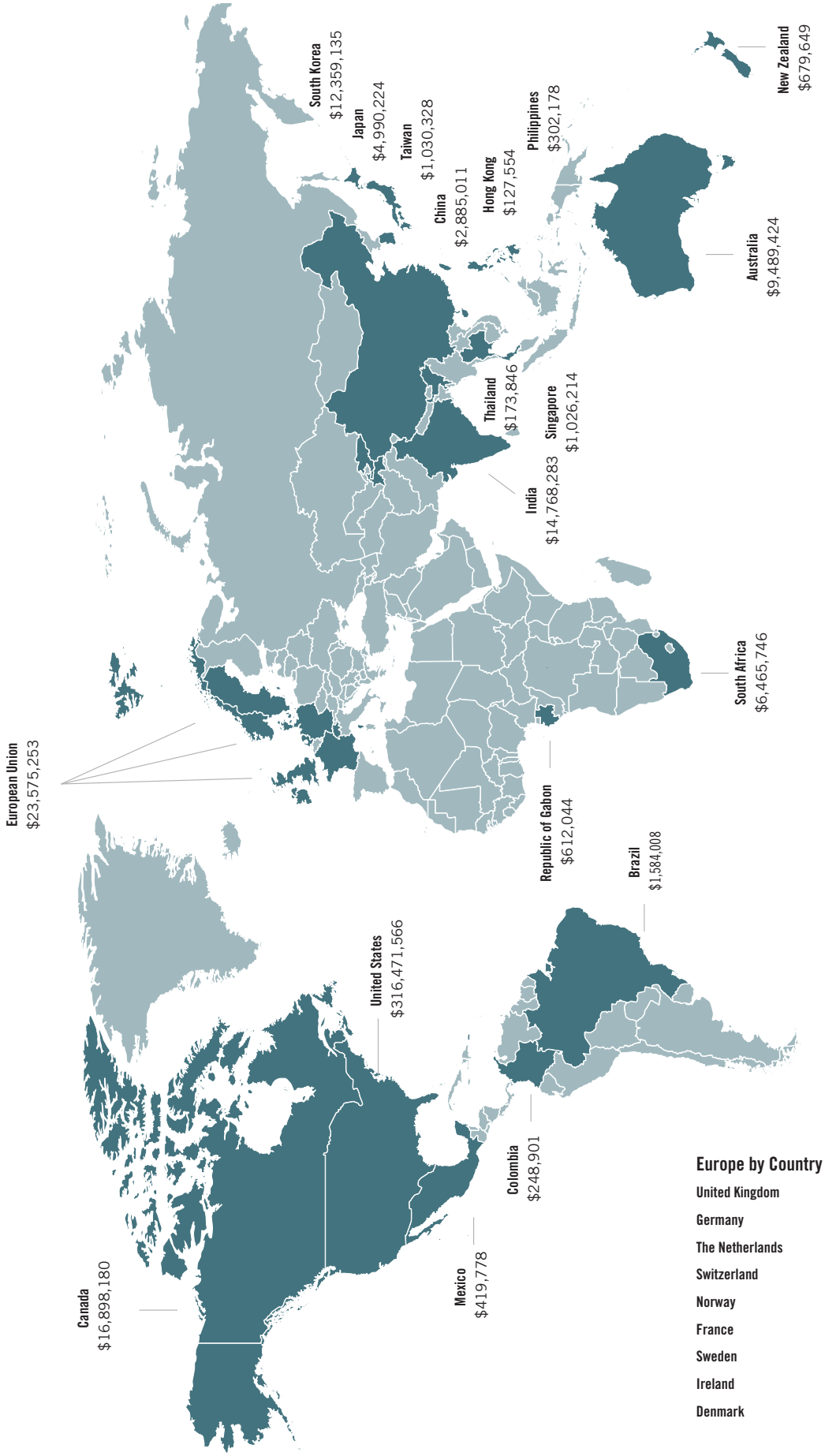
In his first budget proposal to Congress, President Trump asked for a $6 billion (18%) cut to NIH funding, including the outright elimination of the NIH Fogarty International Center (Fogarty), an important source of funding for TB operational research.[37] Thankfully, bipartisan congressional support for the NIH held, and the U.S. Senate countered the President's recommendation with a $2 billion increase to the NIH budget, including a modest increase for Fogarty.[38] Other U.S. government agencies that fund TB research do not enjoy the same depth of bipartisan support and may not fare as well in future budget cycles. Major proposed cuts to USAID and the CDC—the fourth and seventh largest funders of

"With the political environment in the U.S.—and such a dismal interest in science from the U.S. government administration right now—to have so much of the funding dependent on one country puts us in a very precarious position in terms of sustainability and pushing for greater investment. You can't depend on one single country to hold up most of your funding."

Jen Ho, Deputy Director, APCASO

FIGURE 4

Country Contributions to TB R&D, 2016



Europe by Country

United Kingdom	$27,575,390
Germany	$14,820,938
The Netherlands	$9,858,859
Switzerland	$5,938,196
Norway	$5,503,497
France	$1,689,104
Sweden	$1,606,583
Ireland	$1,110,380
Denmark	$56,730

TB research globally—have received more traction in Congress and could become a reality (although the Senate's decision to increase USAID's fiscal year 2018 TB budget by $20 million using unspent Ebola emergency response funds raises some hope that TB will escape large reductions in foreign aid).[39]

Political upheaval in the United States poses a grave risk to TB research given that U.S. public agencies contributed 44 percent ($316.5 million) of global funding for TB research in 2016. Jen Ho, deputy director of APCASO, summarized the danger this way: "With the political environment in the U.S.—and such a dismal interest in science from the U.S. government administration right now—to have so much of the funding dependent on one country puts us in a very precarious position in terms of sustainability and pushing for greater investment. You can't depend on one single country to hold up most of your funding." In 2016, the U.S. government spent over 10 times more on TB R&D than the country with the second-highest spending, the United Kingdom (**Figure 4**). A wider, more diverse funding base would help to ensure that TB research could continue to advance if political commitment in a particular nation wavers or if a leading donor suddenly shifts its priorities.

Funding from most high-TB-burden countries remains modest

The top five countries funding TB research in 2016 are all developed nations with low burdens of TB (**Table 1)**. Among the 30 countries with the highest TB burdens, only two rank among the top 10 funders of TB research: India and South Africa. South Korea, which has the highest TB incidence of Organization for Economic Co-operation and Development member states, also appears among the 10 largest funders. Overall, the vast majority of public funding for TB research comes from countries in the global North, and the United States gives more money than all other reporting countries combined.

Several TB activists interviewed by TAG framed the minimal investment in TB research by the BRICS and other high-TB-burden countries as a failure of governments to live up to their responsibility to respect, protect, and fulfill the human rights of their people. Ketholelie Angami, a TB activist with the Access to Rights and Knowledge Foundation in Nagaland, India, said: "The Indian government has to take full moral responsibility to invest in [TB] research and development rather than depend on international funders or multinational companies to come to the country and do the work. There should be a higher budget percentage from the Indian government [for TB research], and that would enable the government to take full responsibility and ownership of the situation and perform its moral responsibility to the right to health."

"The Indian government has to take full moral responsibility to invest in TB research and development rather than depend on international funders or multinational companies to come to the country and do the work. There should be a higher budget percentage from the Indian government [for TB research], and that would enable the government to take full responsibility and ownership of the situation and perform its moral responsibility to the right to health."

Ketholelie Angami, TB activist, Access to Rights and Knowledge Foundation

Some high-TB-burden countries, including India, have taken steps to increase their support for TB research. These efforts would have a more powerful effect if they led to greater coordination among different agencies and partners at the national and

TABLE 1

Country Funding for TB R&D as a Percentage of GDP and GERD

COUNTRY	TB R&D FUNDING 2016	TB R&D EXPENDITURE AS PERCENTAGE OF GDP RANK ORDER	TB R&D EXPENDITURE AS PERCENTAGE OF GERD RANK ORDER
United States	**$316,471,566**	**2**	**3**
United Kingdom	**$27,575,390**	**6**	**4**
European Union	$23,575,253	17	19
Canada	**$16,898,180**	**5**	**5**
Germany	$14,820,938	11	16
India	$14,768,283	10	12
South Korea	$12,359,135	8	14
The Netherlands	**$9,858,859**	**4**	**6**
Australia	$9,489,424	9	7
South Africa	**$6,465,746**	**1**	**1**
Switzerland	$5,938,196	7	8
Norway	**$5,503,497**	**3**	**2**
Japan	$4,990,224	18	24
China	$2,885,011	26	26
France	$1,689,104	22	25
Sweden	$1,606,583	15	18
Brazil	$1,584,088	20	21
Ireland	$1,110,380	12	11
Taiwan*	$1,030,328	16	13
Singapore	$1,026,214	14	17
New Zealand	$679,649	13	10
Mexico	$419,778	24	22
The Philippines	$302,178	19	9
Colombia	$248,901	21	15
Thailand	$173,846	23	23
Hong Kong	$127,554	25	20

GDP = Gross Domestic Product **GERD** = Gross Domestic Expenditure on Research and Development

Countries that appear in **bold** rank highly in terms of TB R&D spending as a percentage of both GDP and GERD.

* Data on GDP and GERD taken from the National Statistics Bureau of the Republic of China (Taiwan); all other GDP and GERD data are from the World Bank and UNESCO.

international levels. Soumya Swaminathan gave the example of the Indian TB Research Consortium, "which was established essentially to get over the problem of different funding agencies doing things that are not adding up to anything big." The Consortium brings together different Indian government ministries that fund TB research, external donors, private philanthropy, and corporate money to develop a unified approach to tackling short- and medium-term research priorities. The objective is to pool resources—not only funding, but also ideas and technical expertise—to shorten the time it takes to translate discoveries into interventions that benefit patients. Dr. Swaminathan highlighted the considerable excitement the Indian TB Research Consortium has already generated and outlined an ambitious vision for its future: "We are hoping that the government will invest a substantial amount in this program. We'll have to do the paperwork for that. And we're hoping to tie up with the BRICS network at some point, so that we can expand this network to even beyond India."

Between-country TB research collaborations of the type envisioned by Dr. Swaminathan are becoming more common. For example, the ministries of science and technology in India and South Africa entered into a bilateral Science and Technology Cooperation Agreement to create the Collaborative Research Programme on HIV/AIDS and TB. The program aims to foster the development of new products for responding to HIV and TB by building scientific capacity, advancing translational research, supporting technology transfer, and enhancing clinical trial site capacity.[40] Exchanges like this one will have a more sustainable impact if they establish a framework for the BRICS and other high-TB-burden countries to combine funding and invest in joint initiatives.

Countries at all income levels can afford to increase their support for TB research

Table 1 indicates that many countries with high gross domestic expenditures on R&D (GERD) spend relatively little on TB research. For example, South Korea and Japan each spend over three percent of their gross domestic product (GDP) on R&D but rank low compared with other countries in terms of the proportion of R&D expenditure that goes toward TB. South Africa stands out for ranking first among countries in terms of TB research funding as a proportion of both GDP and GERD. Other countries that rank high when TB research funding is measured as a percentage of both GDP and GERD include the United States, Norway, Canada, the United Kingdom, and The Netherlands—all high-income nations with low TB burdens.

All countries at all income levels can do more to support TB research. In 2016, an organization only needed to spend a little more than $11 million to rank among the 15 largest funders of TB research globally. Thus, even a modest starting investment or increase in spending could make a noticeable difference to the field. Greater country-level support for TB research could take a number of forms. Equally important to increasing funding is action by governments to create research-enabling environments by, for example, streamlining regulatory review of clinical trials and new products.

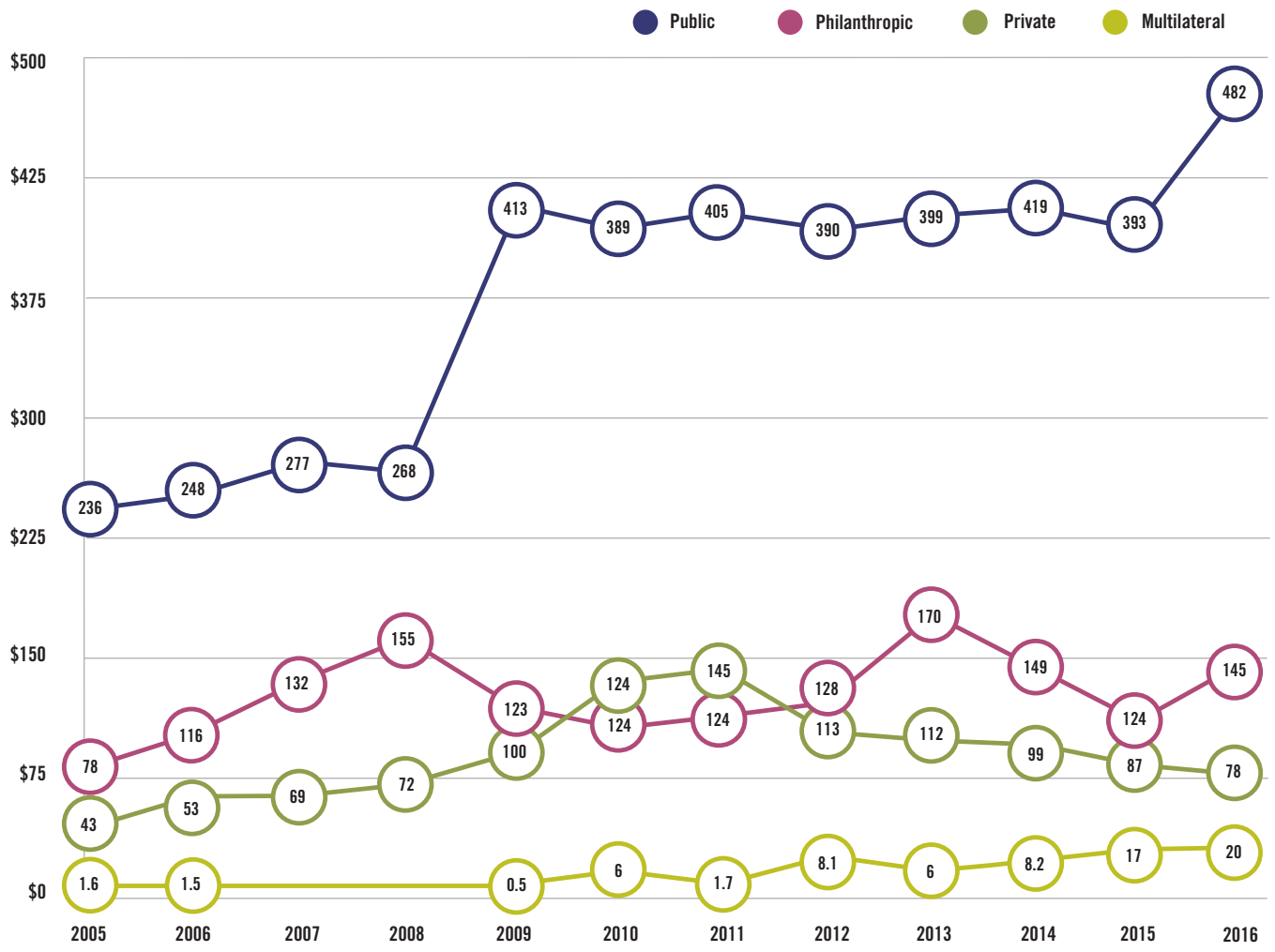
To these ends, the WHO *Global Action Framework for TB Research* (*Action Framework*) provides a blueprint for how stakeholders from different sectors can come together to promote TB research at the country level.[41] It encourages countries to form national TB research networks and develop national strategic plans for TB R&D. Thailand, Indonesia, and Vietnam have all started to develop national strategic plans for TB research under the aegis of the *Action Framework*. These nascent efforts build on more established examples such as the REDE-TB network in Brazil and the Tuberculosis Research Advisory Committee in Ethiopia.[42] Whether efforts to organize TB research at the national level lead to a measurable increase in funding will ultimately depend on the success these networks have in activating domestic research financing mechanisms.

Private sector spending on TB R&D continues to decline

The steady erosion of pharmaceutical industry spending on TB R&D continued in 2016. Private sector companies spent $78.5 million on TB R&D in 2016, the lowest level of expenditure since 2008 and 45 percent below peak industry spending of $145 million in 2011 (**Figure 5**). Part of this decline reflects the maturation

FIGURE 5

Total TB R&D Funding by Funder Category, 2005–2016 (in Millions)



of the clinical development program for the new DR-TB drug delamanid (developed by Otsuka), and the fact that primarily public resources are funding the further development of bedaquiline (developed through phase II by Janssen). The $28.9 million Otsuka spent on TB drug development in 2016 is less than half of the $65.1 million the company reported spending in 2011, when delamanid's phase III trial opened to enrollment. Spending by Otsuka may pick up again if its new compound in phase I (OPC-167832) advances into later-stage clinical trials, but no major pharmaceutical company shows signs of investing at the level Otsuka did between 2009 and 2014.

Many attribute the absence of robust industry engagement in TB research to the lack of a strong market incentive for investing in a disease that primarily affects poor people living in low- and middle-income countries. In the words of Mario Raviglione: "There are a couple of companies that invest in TB, but apart from those, the lack of interest is simply linked to the fact that there is no economic gain." The lack of a market incentive also applies to TB diagnostic and vaccine R&D. Claudia Denkinger, head of TB at the

product-development partnership FIND, remarked that "in diagnostics, we have seen the arrival of some bigger companies, but they are coming to the market on tiptoes. They are trying to test the waters and see what happens." Helen McShane described a similar dynamic among industry groups weighing involvement in TB vaccine development: "There aren't many private sector funders in TB research generally, let alone TB vaccine research. I think that's because the commercial return on investment is questionable. There are private sector companies that do invest, and that's to be applauded… Anything we can do to work together so that we help de-risk their investment is important."

The statement that there is no commercial incentive to invest in TB research is a kind of conventional wisdom—true in a general sense, but not an immutable truth or one that holds in all cases. This summary judgment also says as much about the prevailing business model of the pharmaceutical industry as it does about TB. Diseases like TB will garner little attention by for-profit industry as long as innovation occurs within a system in which developers recoup R&D costs through high product prices protected by patents and other intellectual property barriers. Within this system, there are many ways governments can de-risk industry investment in TB research. The policy options are numerous and range from priority review vouchers to taxation schemes to advance purchase commitments; the 2012 report of the WHO Consultative Expert Working Group on Research and Development provides an excellent overview of possible incentive strategies.[43]

Raviglione pointed to public-private partnerships as another way to bring industry groups into the field. Public and philanthropic dollars have a track record of signaling opportunities that attract industry interest to TB research. To take just one recent example, Otsuka will receive a grant for the development of OPC-167832 from the Gates Foundation, and funds to optimize delamanid's use and expand its indication beyond DR-TB have come from public sources—the NIH-funded AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescents AIDS Clinical Trials Network (IMPAACT) will open a large, household-randomized study of delamanid to prevent TB among household contacts of MDR-TB patients in early 2018.[44]

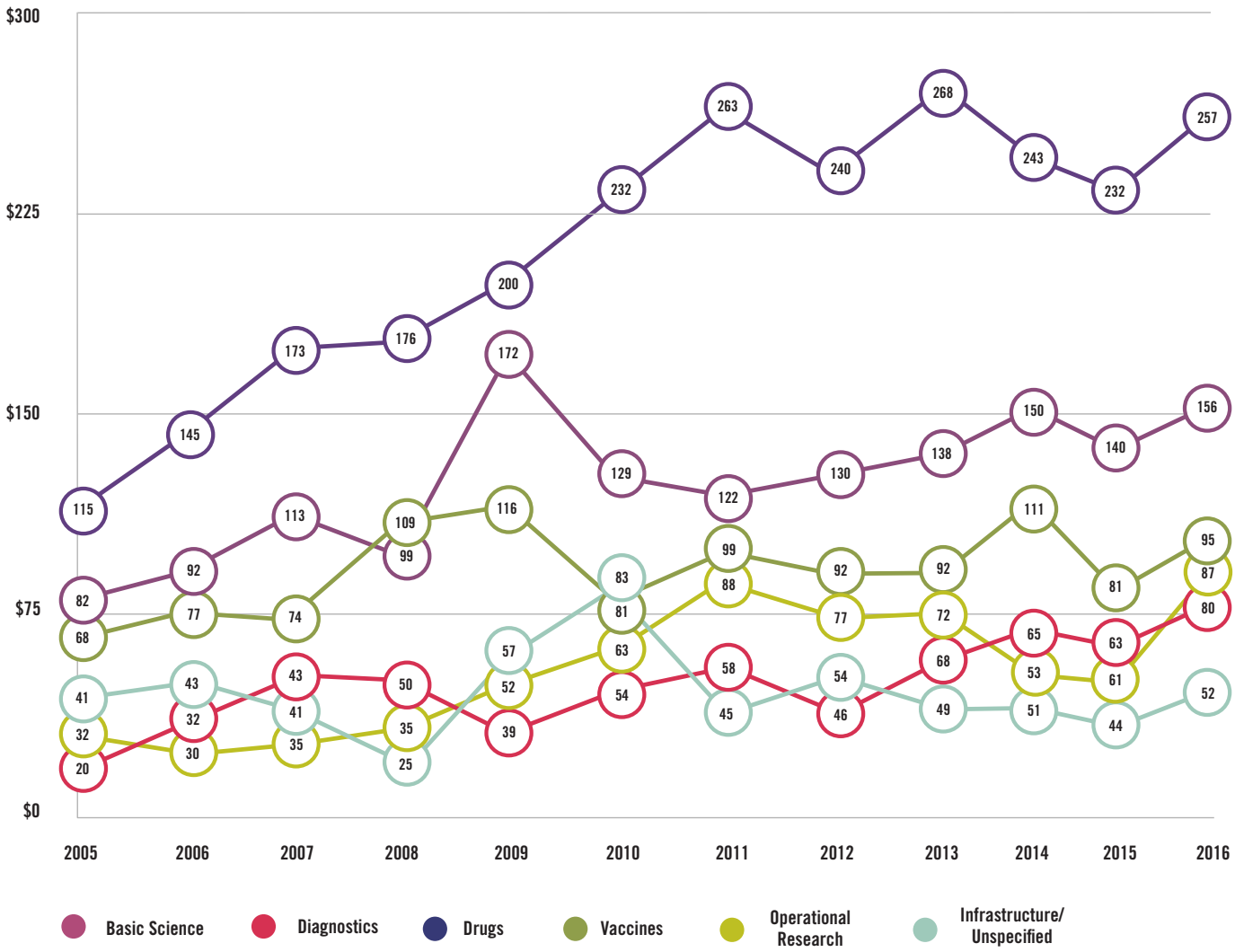
In situations where markets are small, fragmented, or not functioning properly, donor funding can catalyze innovation by shaping markets or correcting inefficiencies—the strategy behind Unitaid's investments in pediatric TB drug R&D. In addition, there may be attractive markets for specific interventions or products within the larger TB epidemic. For example, Raviglione hypothesized that "it's probably easier to develop an economic argument for prophylaxis because . . . a one-shot, or one-dose, prophylaxis, perhaps repeated two to three times over three months or so, becomes almost like the hepatitis vaccine. If I had that, then I would have a big market." Here, he pointed to the estimated 1.7 billion people alive today with LTBI who might be eligible for preventive therapy or vaccination, plus the billions more who will acquire MTB infection in the coming decades.[45]

More substantial reforms would involve de-linking the costs of research from product prices. The concept of de-linkage received prominent recognition in the political declaration of the U.N. High-Level Meeting on AMR. Starting with a statement of principles that "research and development efforts should be needs driven, evidence based, and guided by the principles of affordability, effectiveness, and efficiency and equity," U.N. member states went on to "acknowledge the importance of de-linking the cost of investment in R&D on AMR from the price and volume of sales so as to facilitate equitable and affordable access to new medicines." De-linkage also inspired extensive discussion in the final report of the U.N. Secretary-General's High-Level Panel on Access to Medicines, which contains many ideas for how governments can work with other stakeholders to "resolve the incoherence between market-driven approaches and public health needs."[46]

The private sector has an important role to play in the next five years of TB R&D and in the fight against AMR more generally. What this involvement should look like is hotly debated, but nearly all observers agree that the longstanding trend of pharmaceutical industry disinvestment from AMR research must halt and reverse for industry to make a serious, fair contribution to solving the crisis in TB and antibiotic R&D.

FIGURE 6

Total TB R&D Funding by Research Category, 2005–2016 (in Millions)



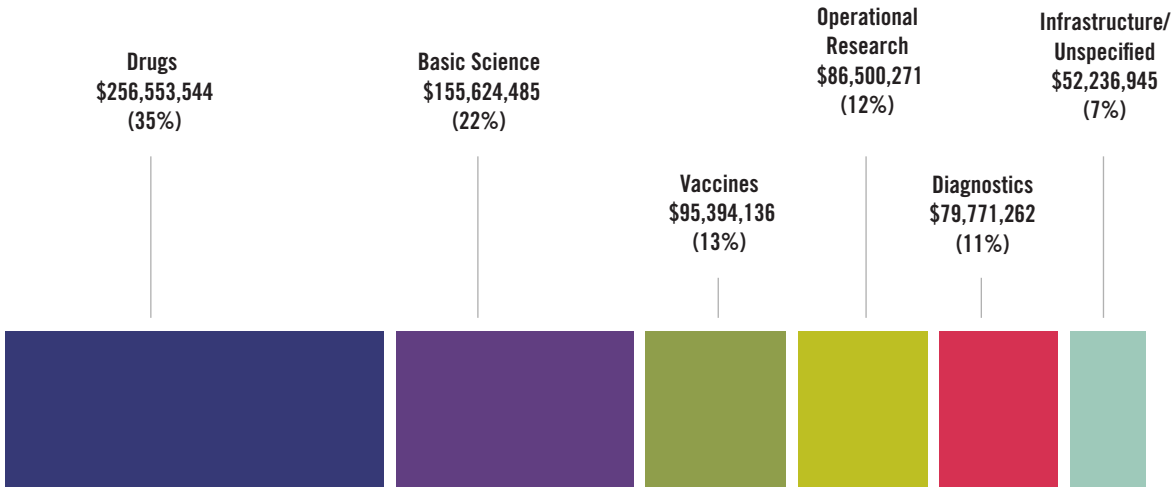
Funding increased in every area of TB research, but all areas remain underfunded

Figure 6 shows that funding increased in every area of TB research between 2015 and 2016. These increases are extremely modest—no more than 30 percent in any particular category, except for operational research—and all areas of TB research urgently need more funding. In some areas (vaccines, basic science, drugs), increased funding in 2016 merely made up for ground lost in 2015 when spending dropped across the board.

As in previous years, funders spent the most money on TB drug R&D, which comprised 35 percent of total funding (**Figure 7**). The sections that follow discuss funding for each research area in more detail, taking into account progress over the last decade and future research needs with an eye toward informing discussions at the Moscow Ministerial Conference and the U.N. High-Level Meeting in New York.

FIGURE 7

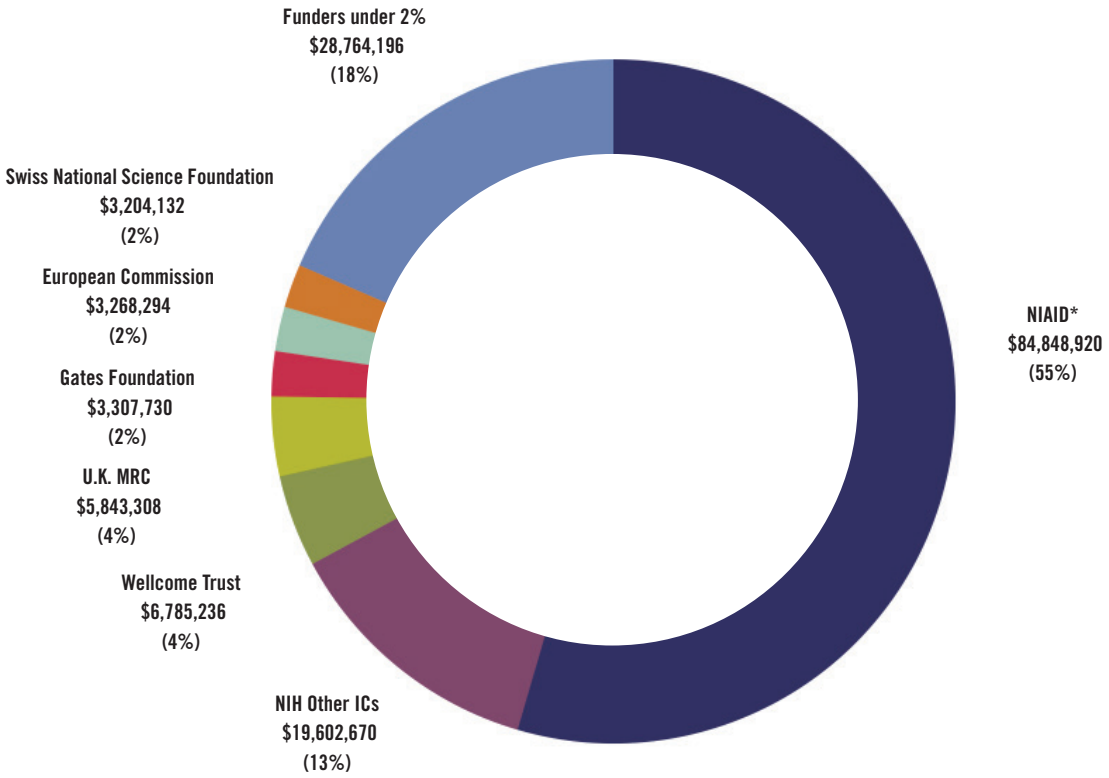
Total TB R&D Funding by Research Category, 2016
Total: $726,080,643



Basic Science

FIGURE 8

Basic Science: $155,624,485



Funders with investments under 2%

Canadian Institutes of Health Research	$2,477,030
Indian Council of Scientific and Industrial Research (CSIR)	$2,402,015
Australian National Health and Medical Research Council	$2,135,149
Institut Pasteur	$1,699,010
German Federal Ministry of Education and Research (BMBF)	$1,662,430
Max Planck Institute for Infection Biology	$1,610,000
Swedish Research Council	$1,400,613
Norwegian Agency for Development Cooperation (NORAD)	$1,304,343
South African Medical Research Council (SAMRC)	$1,214,299
South African Department of Science and Technology (DST)	$1,209,918
Korean Ministry of Science, ICT and Future Planning	$1,191,304
Swiss Federal Institute of Technology in Lausanne (EPFL)	$1,035,910
U.S. National Science Foundation	$924,307
National Research Foundation of South Africa	$755,295
South African Department of Health	$714,795
Japan Agency for Medical Research and Development (AMED)	$678,436
Korean Ministry of Health and Welfare	$628,696
German Research Foundation	$619,148
Republic of Gabon	$612,044
Public Health England	$517,796
French National Agency for Research (ANR)	$494,017
Foundation for Medical Research in France	$437,054
Health Research Council of New Zealand	$434,403
Indian Council of Medical Research (ICMR)	$356,509

Australian Research Council	$320,864
Brazilian Ministry of Science, Technology, Innovation and Communication	$311,728
SomaLogic	$245,285
Indian Ministry of Science and Technology	$221,173
Marsden Fund	$213,835
Japan BCG Laboratory	$164,258
Else Kröner-Fresenius Foundation	$130,000
Tata Education and Development Trust	$121,552
Howard Hughes Medical Institute	$100,000
Taiwan Centers for Disease Control	$58,030
Indian Ministry of Health and Family Welfare (MOHFW)	$55,400
French National Agency for AIDS Research (ANRS)	$52,604
Thailand National Science and Technology Development Agency	$46,219
Korean Institute of Tuberculosis	$38,270
Taiwan Ministry of Health and Welfare	$30,000
Taiwan Ministry of Science and Technology	$30,000
South African National Health Laboratory Service Research Trust	$27,024
Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association	$23,999
Indian Science and Engineering Research Board	$20,919
Thailand Ministry of Public Health	$18,219
Sidaction	$9,155
European Molecular Biology Organization	$6,048
Indian Defense Research and Development Organization	$5,093

* All acronyms and abbreviations of organization names are defined in Appendix 2.

> "I really think this is one of the most exciting times in history for tackling the problem of tuberculosis because of the tools and reagents we now have available."
>
> **Bill Jacobs, Professor of Microbiology and Immunology, Albert Einstein College of Medicine**

In 2016, the world spent $155.6 million on TB basic-science research. Sixty-eight percent of this funding came from the NIH, and within the NIH the National Institute of Allergy and Infectious Diseases (NIAID) gave over half of all money spent on TB basic science in 2016 (**Figure 8**). Since 2005, $1.5 billion has gone toward TB basic science, and 63 percent of this has come from the NIH.

In the view of Bill Jacobs, professor of microbiology and immunology at Albert Einstein College of Medicine in New York: "I really think this is one of the most exciting times in history for tackling the problem of tuberculosis because [of] the tools and reagents we now have available. When I started, we couldn't move genes around, and we're now at the point where we can knock out every gene of TB. You couple that with the ability to genetically manipulate mice and human stem cells. You add to that high-throughput sequencing—it's a truly incredible time."

The tools Jacobs referenced have allowed scientists to revise old concepts and investigate longstanding questions from new vantage points. To give just a few examples, scientists are employing positron emission tomography/computed tomography (PET/CT) imaging to view the intricate interactions between MTB and the human immune system at sites of infection in the lung; using genetic barcodes to track the behavior of individual TB bacteria to better understand infection dynamics; and refining the animal models used in TB research to learn more about the basic biology of TB and inform product development.[47] The prevailing excitement in TB basic science goes beyond technology. Compared with even a few years ago, there is a discernible emphasis on research that crosses disciplines, borrows ideas from other fields, or works iteratively between lab and clinic.[48]

However, Jacobs tempered his optimism with a hard truth: because MTB grows slowly, TB research invariably takes time and rarely moves as fast as funders expect. "The other aspect of this is how people view science," said Jacobs. "They want the big, cool discovery, and the problem is that there is a lot of fundamental work that needs to be done [in TB] to get those discoveries, and that's boring from the view of funding agencies. You are not going to get a big splash every three months from TB." Other scientists made a similar point about the time it takes to do good TB research and the importance of managing funders' expectations. "In the TB space, things take a lot longer, so you need a commitment to sustain funding," commented Stewart Cole, director of the Global Health Institute at the Swiss Federal Institute of Technology in Lausanne. "What takes five years in another field will take 10 years in TB, so if you only get a five-year commitment the funding is just too short. I think governments need to get that message."

Most funding in this area goes toward undirected, investigator-initiated science in which researchers answer open, competitive calls for proposals that are peer reviewed or scored by committees. Whether this system facilitates groundbreaking advances versus incremental steps forward is a contested question. "It's hard for committees to assess really, really innovative stuff because they've got nothing to benchmark it against, whereas if it's more of the same they know how to score it," said Cole.

Supporting TB basic science may require a mixture of funding models. Jacobs cited the Howard Hughes Medical Institute (HHMI) investigators program as an example of how funding bodies can support promising scientists over the span of an entire career rather than fund discrete projects: "One of the things that's good about this HHMI model of funding—and I can say this having been a Howard Hughes investigator for 28 years—is we don't fund projects, we fund individuals. We have to find people that are creative, innovative, willing to take risks—good scientists—and fund them." Jacobs lamented that HHMI has reduced its support for investigators working on infectious diseases over the years, a move that highlights the importance of bringing new funders into this space. (Despite repeated overtures, HHMI did not participate in this year's survey.)

> "In the TB space, things take a lot longer, so you need a commitment to sustain funding. What takes five years in another field will take 10 years in TB, so if you only get a five-year commitment the funding is just too short. I think governments need to get that message."
>
> **Stewart Cole, Director, Global Health Institute at the Swiss Federal Institute of Technology in Lausanne**

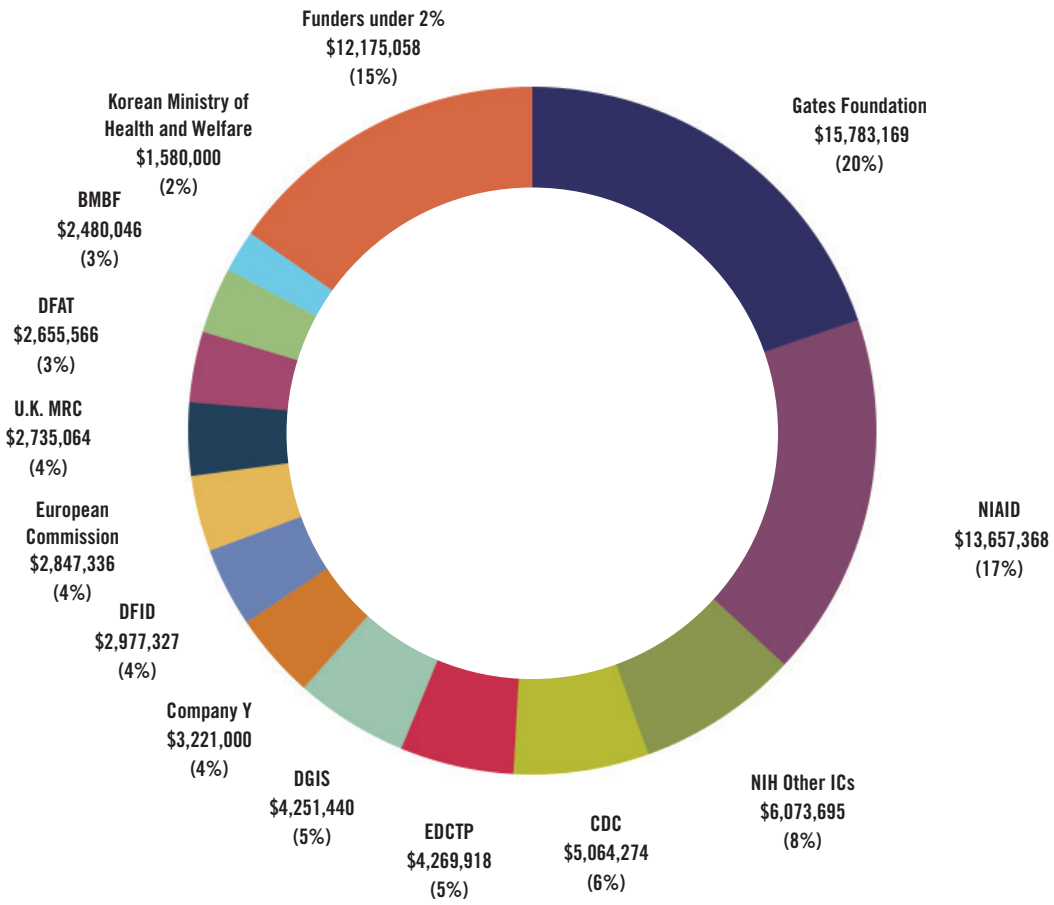
What funders should keep in mind, argued Jacobs, is that "the big breakthroughs are going to come from people doing serendipitous sorts of things, where they are doing something and they are going to make a serendipitous discovery that's going to open their minds to see things." If the history of HIV research is any guide, the discoveries that prove transformational for TB may come from unexpected quarters. For example, the advent of polymerase chain reaction in the early 1980s revolutionized the ability of scientists to quickly generate copies of recombinant DNA fragments and paved the way for HIV viral load testing.[49] Early work on retroviruses in the 1960s and 1970s, before the rise of the HIV epidemic, proved pivotal for creating protease inhibitors to treat HIV decades later.[50] Governments should recognize the undirected nature of basic-science research as an opportunity to invest two generations ahead. Investments in this area will pay dividends well beyond the expiry date of the End TB Strategy or even the TB epidemic itself.

Figuring out the best way to fund basic science is a question that transcends TB, but decisions in this regard will shape the future success of TB research. Basic science is the wellspring that nurtures the pipelines for new TB diagnostics, drugs, and vaccines. And it is the place product developers return to for answers and new ideas when clinical trials generate disappointing or surprising results. The health of the TB research field will depend on continued, robust support for research in this upstream space.

Diagnostics

FIGURE 9

Diagnostics: $79,771,262



Funders with investments under 2%

Longhorn Vaccines and Diagnostics	$1,570,000
Korean Ministry of Science, ICT and Future Planning	$1,375,652
Australian National Health and Medical Research Council	$1,349,546
Wellcome Trust	$1,099,317
Genedrive	$961,806
Norwegian Agency for Development Cooperation (NORAD)	$633,470
French National Agency for AIDS Research (ANRS)	$553,599
U.S. National Science Foundation	$495,832
Norway Regional Health Authorities	$481,874
Japan International Cooperation Agency (JICA)	$439,805
Taiwan Centers for Disease Control	$436,319
Médecins Sans Frontières (MSF)	$311,714
U.S. Department of Agriculture	$299,889
U.S. Department of Defense Medical Research and Development Program (DMRDP)	$280,368
Brazilian State Funding Agencies	$238,568
Cepheid	$200,000

Korea Health Industry Development Institute	$178,000
Institut Pasteur	$175,827
Japan Agency for Medical Research and Development (AMED)	$172,330
South African Department of Science and Technology (DST)	$167,680
Canadian Institutes of Health Research	$166,661
SK Telecom	$125,490
Thailand National Science and Technology Development Agency	$80,025
InSpace	$71,200
QuantaMatrix	$71,200
Korea Centers for Disease Control and Prevention	$57,850
Damien Foundation Belgium	$56,629
Indian Ministry of Science and Technology	$56,572
Hong Kong Health and Medical Research Fund	$51,538
Indian Council of Medical Research (ICMR)	$6,955
DuPont	$6,675
DMBio	$2,670

> "We need better messaging around diagnostics and how the link between diagnostics and treatment is so tight. Diagnostics are a companion to treatment, and neither can be seen in isolation. Particularly in tuberculosis, where even with all the drug innovations, we'll still have complex regimens. We need to get it right at the start. And that's where diagnostics help."
>
> **Claudia Denkinger, Head of TB, FIND**

In 2016, the world spent $79.8 million on TB diagnostics research (**Figure 9**). Since 2005, TB diagnostics R&D has received $618.3 million in funding. Unlike for other categories of TB R&D, no single donor accounts for more than 30 percent of annual funding for diagnostics. Instead, support for diagnostics research in 2016 came from a variety of philanthropic, public, and industry groups, led by the Gates Foundation with spending of $15.8 million.

The TB diagnostics field has brought several WHO-endorsed products to market over the past decade, including a rapid alternative to smear microscopy (Xpert MTB/RIF), a simple test for identifying TB in people with HIV who have very low CD4+ T-cell counts (TB LAM), and several options for detecting first- and second-line drug resistance faster than conventional culture (GenoType MTBDR*plus*, Nipro Assay, and MGIT). Even with these advances, the tragedy of TB diagnosis remains that 40 percent of people with TB are never diagnosed (or never have their diagnosis reported to a health system).[51] The four million people who 'go missing' from the official record of the TB response are, in their absence, a testament to the unfinished agenda in TB diagnostics R&D.

Claudia Denkinger, head of TB at FIND, described recent progress in TB diagnostics research as "incremental rather than transformational." In particular, she pointed to gaps in basic science—especially the absence of good biomarkers—as limiting faster progress. In a recent review of the diagnostics pipeline, TAG's Erica Lessem summarized the "meaningful—albeit incremental—advances" on the horizon, including "the launch of a more sensitive Xpert MTB/RIF Ultra assay for diagnosing TB and detecting drug resistance; a sputum lipoarabinomannan (LAM) assay that could revolutionize treatment monitoring; and several rapid tests inching toward market that could bring TB and rifampicin resistance testing closer to patients (GeneXpert Omni, TrueNAT) or expand susceptibility testing to more drugs (Xpert XDR, Realtime MTB RIF/INH,Fluorotype MDR)."[52]

Advancing diagnostics research beyond incremental improvements will require figuring out how to direct funding more strategically. Denkinger noted that a lot of the recent progress in TB diagnostics has centered on molecular technologies but that sequencing is likely to generate the most game-changing advances over the next five years. Whole-genome sequencing is already used for TB surveillance in some settings, and several companies are developing next-generation sequencing that is lower cost and easier to use. This raises the tantalizing possibility of achieving the dream of universal, culture-free DST. However, Denkinger pointed out that funders must be prepared to support the adaptation of these technologies to the developing country markets where TB is most common.

Funding must also be deployed to support the small- and medium-sized companies that are common in the TB diagnostics field. "The smaller companies, many of them don't make it to market . . . Many of them have gaps in their organizations where they constantly get thrown back," said Denkinger. Not only does this dynamic dissuade many companies from entering the field, it has also had a discernible impact on the pipeline of potential products. Overall, Denkinger characterized the pipeline as a "very centralized, heavy pipeline. It's a very early pipeline. And we unfortunately see lots of dropouts before [a test] makes it to WHO endorsement. And it's in part because the big players who would have the capabilities are tiptoeing and the small ones just simply have capacity gaps to meet the steps along the value chain that make it difficult for them to succeed."

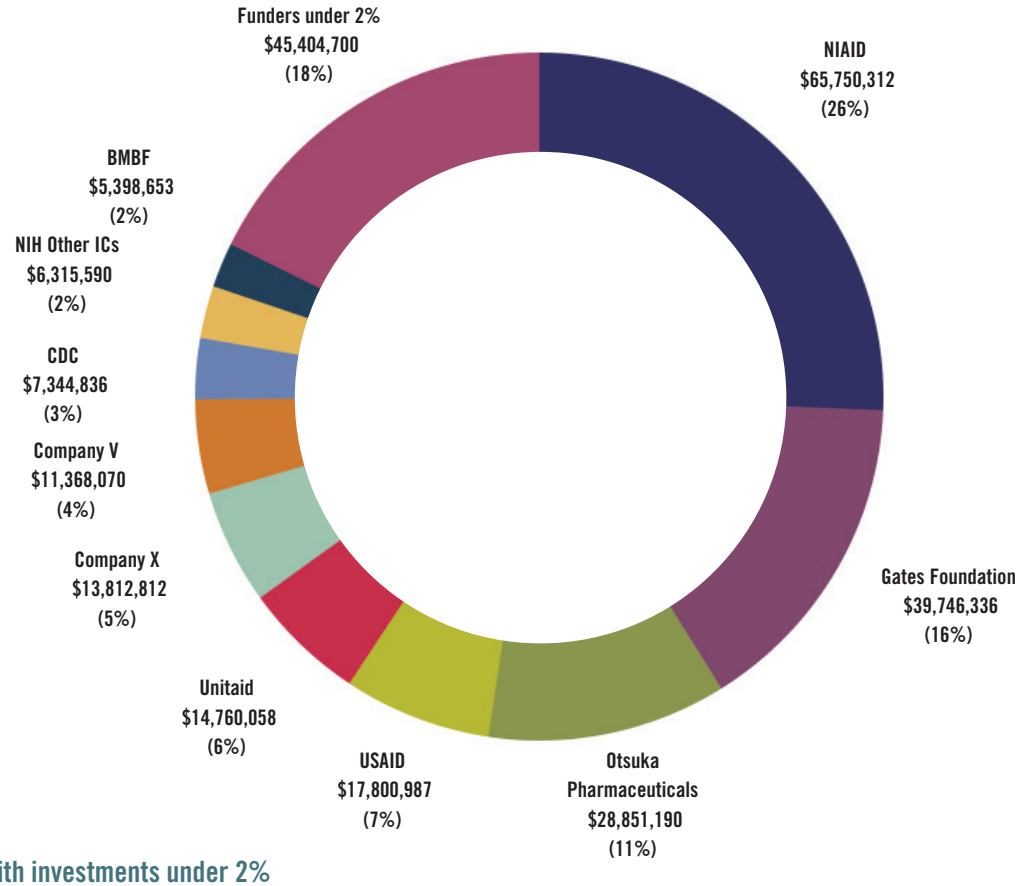
By "centralized, heavy," Denkinger is referring to the pipeline's concentration of products designed for use in reference laboratories or specialized tertiary care centers (e.g., large hospitals). The TB field already has several diagnostic options for use in these settings; the real breakthrough would be a rapid, point-of-care test simple enough to use in the primary health clinics where most people with TB first seek care. In addition, a test that could identify persons with LTBI most likely to progress to active TB disease would offer a powerful tool for targeting preventive therapy and, if deployed in combination with shorter prophylactic regimens or a more effective vaccine, would likely have the largest effect on bringing down TB incidence in line with the SDG and End TB Strategy targets.[53,54]

This last point is worth emphasizing: it is the *combination* of new diagnostics and new TB treatments that funders should keep in mind. Denkinger put it this way: "We need better messaging around diagnostics and how the link between diagnostics and treatment is so tight . . . Diagnostics are a companion to treatment, and neither can be seen in isolation. Particularly in TB, where even with all the drug innovations, we'll still have complex regimens. We need to get it right at the start. And that's where diagnostics help."

Drugs

FIGURE 10

Drugs: $256,553,544



Funders with investments under 2%

U.K. Medical Research Council (U.K. MRC)	$3,709,845
Dutch Directorate-General for International Cooperation (DGIS)	$3,397,763
Eli Lilly	$3,346,000
Innovative Medicines Initiative (IMI)	$3,282,029
Wellcome Trust	$2,802,355
Australian Department of Foreign Affairs and Trade (DFAT)	$2,655,566
U.K. Department for International Development (DFID)	$2,588,980
Korea Drug Development Fund	$2,225,000
Qurient	$2,225,000
Dutch National Postcode Lottery	$2,209,656
Korean Ministry of Science, ICT and Future Planning	$1,526,945
Global Health Innovative Technology Fund (GHIT)	$1,323,983
Irish Aid	$1,110,380
Macleods Pharmaceuticals	$1,000,000
European Commission	$976,008
Swiss Federal Institute of Technology in Lausanne (EPFL)	$888,811
Singapore National University Health System	$746,511
Company W	$740,100
South African Medical Research Council (SAMRC)	$639,906
Japan Agency for Medical Research and Development (AMED)	$634,900
Chinese National Health and Family Planning Commission	$630,152
French National Agency for AIDS Research (ANRS)	$569,917
Canadian Institutes of Health Research	$539,932
Company R	$536,018
Swiss National Science Foundation (SNSF)	$514,695

Company P	$500,000
Longhorn Vaccines and Diagnostics	$500,000
U.S. Food and Drug Administration (FDA)	$435,400
Institut Pasteur	$369,950
Médecins Sans Frontières (MSF)	$359,187
Foundation Jacqueline Beytout	$334,555
U.S. National Science Foundation	$275,000
Korean Ministry of Health and Welfare	$269,565
Brazilian Ministry of Science, Technology, Innovation and Communication	$229,025
Taiwan Centers for Disease Control	$212,556
Korean Ministry of Agriculture, Food and Rural Affairs	$165,217
South African Department of Health	$146,019
Indian Council of Scientific and Industrial Research (CSIR)	$133,665
Swedish Research Council	$118,589
United Nations Office for Project Services (UNOPS)	$116,760
Mexican National Council of Science and Technology	$111,255
Damien Foundation	$96,603
Hong Kong Health and Medical Research Fund	$76,016
Health Research Council of New Zealand	$31,412
Indian Ministry of Science and Technology	$24,028
Indian Council of Medical Research (ICMR)	$22,858
Individual donors to TB Alliance	$19,471
National Research Foundation of South Africa	$15,442
Indian Ministry of Health and Family Welfare (MOHFW)	$14,173
Faber Daeufer	$7,500

> "There's pretty good progress, especially in terms of basic science and in drug discovery. There are a significant number of interesting new compounds coming along. My only concern is that it will be difficult to find the cash to move these into preclinical development."
>
> **Stewart Cole, Director, Global Health Institute at the Swiss Federal Institute of Technology in Lausanne**

In 2016, the world spent $256.6 million on TB drug research, led by the NIAID with $66 million (**Figure 10**). Together, three organizations—the NIH, Gates Foundation, and Otsuka—account for 56 percent of the $2.5 billion spent on TB drug R&D since 2005.

A report published by WHO in September 2017 starkly illustrates the consequences of sparse funding for TB drug research. Released under the headline "The world is running out of antibiotics," *Antibacterial Agents in Clinical Development* names TB a "global priority for research and development" and calls out "the serious lack of new antibiotics under development to combat the growing threat of antimicrobial resistance." The report notes that the TB drug pipeline only contains seven candidates from four new chemical classes; four of these are in phase I and one is in phase III (pretomanid, developed by the TB Alliance, a product development partnership).

Assessing the strength of the TB drug clinical pipeline, Stewart Cole commented: "If any or a couple of these [compounds] fail, then we're not in good shape at all." In Cole's view, this precariousness has a lot to do with how funding is made available—or not—at certain pivotal stages. "There's pretty good progress, especially in terms of basic science and in drug discovery. There are a significant number of interesting new compounds coming along," said Cole. "My only concern is that it will be difficult to find the cash to move these into preclinical development."

Cole expressed particular concern about the lack of a dedicated funding stream for TB drug research within Horizon 2020, a seven-year, €80 billion research and innovation program run by the European Commission.[55] Dedicated funding for TB drug and diagnostics R&D under the European Commission framework programs that preceded Horizon 2020 led to the creation of several multi-country research networks of TB drug and diagnostics developers. "For me that was one of the major disappointments of Horizon 2020—that they basically pulled the funding plug on at least four networks [that] were operating well in the diagnostics and drug space," said Cole. European Commission funding for TB drug R&D has fallen from over $7 million in 2010 to less than $1 million in 2016.

Commenting on the overall health of the pipeline for new antibiotics, the WHO *Antibacterial Agents* report warned: "Most of the agents in the pipeline are modifications of existing antibiotic classes. They are only short-term solutions." In line with this assessment, a significant portion of TB drug development over the last 15 years focused on optimizing and repurposing existing compounds—many developed decades ago, and some initially approved for conditions other than TB. This work is important but more iterative than transformational, and it is a reflection of the incomplete research agenda in TB drug R&D resulting from years of neglect. Multiple clinical trials are seeking to shorten and simplify the duration of treatment for LTBI, drug-sensitive TB (DS-TB), and DR-TB using various combinations of existing drugs, sometimes paired with new agents such as bedaquiline or delamanid. Public money underwrites most of these efforts, notably work by the ACTG at the NIH, the Tuberculosis Trials Consortium at the CDC, and the PanACEA network, which receives support from the European and Developing Countries Clinical Trials Partnership and other European funders.

In addition to making headway on this long overdue work, TB drug developers reached a true milestone in the last decade: the first approvals of new drugs from novel classes to treat TB since the early 1970s. Bedaquiline (developed by Janssen) and delamanid (developed by Otsuka) each received conditional approval by stringent regulatory authorities based on phase IIb trial data.[56,57] Bedaquiline and delamanid were each developed and approved as add-ons to existing regimens; public and philanthropic funders—including Unitaid, USAID, the South African Medical Research Council, and the Gates Foundation—

> "If you look especially at making new TB treatment, you really need to have the different developers speaking with each other . . . But a vicious circle is created by the fact that there is so little money. There is huge competition and everyone runs for the same dollar, which is not really a dollar but only half a dollar."
>
> **Lucica Ditiu, Executive Director, Stop TB Partnership**

are now supporting trials that combine bedaquiline and delamanid with other DR-TB drugs in pursuit of shorter, all-oral regimens. Some of the most exciting data on this front are coming from a small study conducted by the TB Alliance treating XDR-TB patients with a six-month combination of bedaquiline, linezolid, and pretomanid (the Nix-TB regimen). Reflecting on interim results from this study, TB activist and co-technical lead of the Global TB Community Advisory Board Marcus Low recently wrote: "[Nix-TB]'s success in appearing to treat XDR- and pre-XDR TB with far fewer drugs in far less time than ever before represents a medical breakthrough," although he noted that the evidence in support of the Nix-TB regimen "is very limited and does not come from an randomized controlled trial."[58]

Although TB drug developers made meaningful progress repurposing existing compounds and brought two new drugs to market, what the TB field really needs is wholly new regimens. A breakthrough of this type may require introducing new, innovative ways to fund and conduct TB drug research. The Life Prize, hosted by the International Union Against TB and Lung Disease (The Union), is seeking to develop a one-month regimen that can treat all forms of TB everywhere.[59] To achieve this ambitious vision, the Life Prize intends to work collaboratively across different developers by using a combination of push, pull, and pool mechanisms: pull incentives in the form of cash prizes for compounds that meet predefined characteristics and enter phase I paired with push funding to support clinical trials of novel treatment combinations for groups that agree to pool the data and intellectual property behind their compounds.[60]

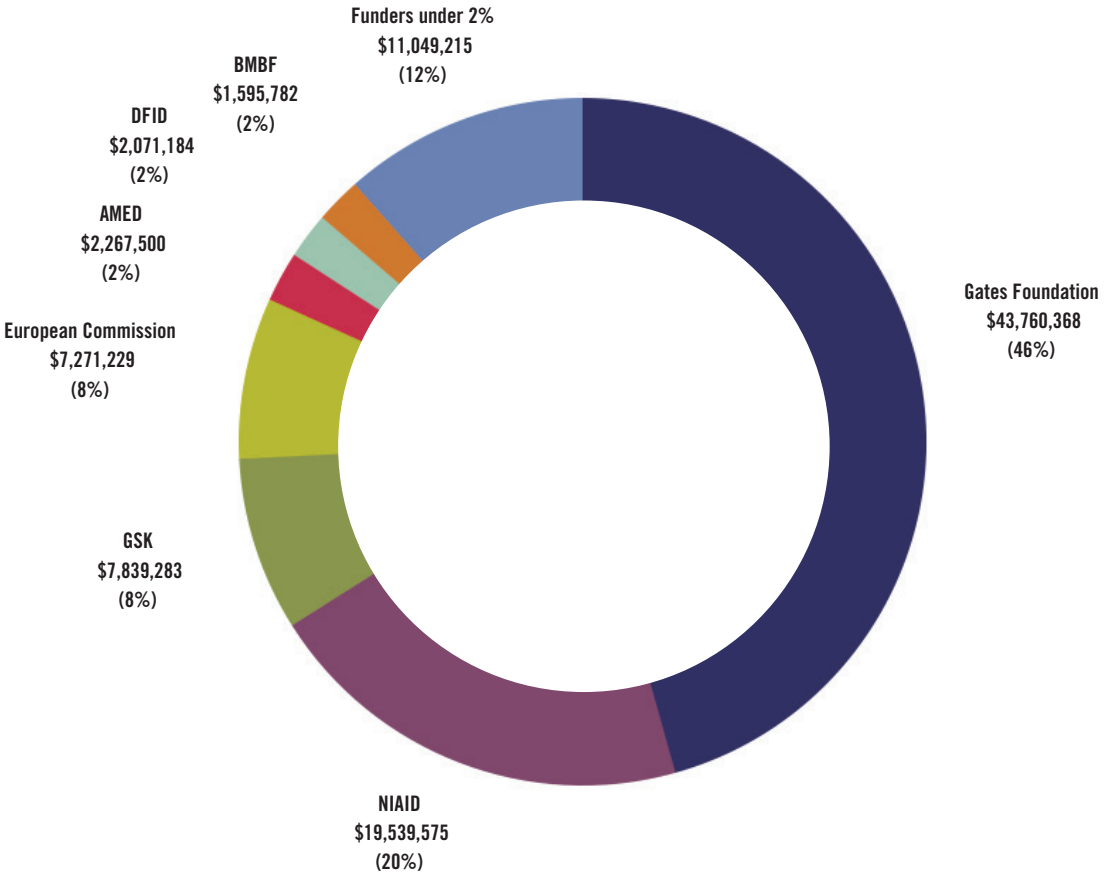
This approach to financing drug development is intended to assure the affordability of new medicines by de-linking R&D costs from market prices. Its system of rewards may also encourage healthy collaboration among TB drug developers in pursuit of a common goal. "If you look especially at making new TB treatment, you really need to have the different developers speaking with each other," said Lucica Ditiu. "But a vicious circle is created by the fact that there is so little money. There is huge competition and everyone runs for the same dollar, which is not really a dollar but only half a dollar."

Initiatives such as the Life Prize acknowledge that the technical availability of new treatment options is insufficient. TB drug developers must also ensure that the results of their research are made accessible to all people with TB in need. Ketholelie Angami noted this as one of the hard lessons learned from the slow, inequitable introduction of bedaquiline and delamanid: "These drugs [bedaquiline and delamanid] are being made available, but what is the point of making them available if they are not made accessible? . . . My point is that access to medicines should not be a luxury. So whatever the government and developers make, I generally see that they make a very good start, but they never make the good start a better end."

Vaccines

FIGURE 11

Vaccines: $95,394,136



Funders with investments under 2%

Norwegian Agency for Development Cooperation (NORAD)	$1,433,517
Korean Ministry of Health and Welfare	$1,413,043
Public Health England	$1,184,458
Max Planck Institute for Infection Biology	$1,150,000
U.S. National Institutes of Health, Other Institutes and Centers (NIH Other ICs)	$1,000,657
Global Health Innovative Technology Fund (GHIT)	$881,205
U.K. Medical Research Council (U.K. MRC)	$618,747
Wellcome Trust	$546,366
Company V	$490,840
Canadian Institutes of Health Research	$437,352
Institut Pasteur	$426,996

Biofabri	$254,685
Japan BCG Laboratory	$235,367
Korean Ministry of Science, ICT and Future Planning	$217,391
Australian National Health and Medical Research Council	$179,597
Swiss National Science Foundation (SNSF)	$125,967
Serum Institute of India	$109,167
Korean Ministry of Agriculture, Food and Rural Affairs	$100,000
U.K. Biotechnology and Biological Sciences Research Council	$90,000
Indian Council of Scientific and Industrial Research (CSIR)	$62,680
Danish Council for Independent Research	$44,771
Lundbeck Foundation	$34,449
Innovation Fund Denmark	$11,960

"It shouldn't be an either/or between TB vaccines, drugs, diagnostics. The reality is we need all of these things. We need a whole panel of new tools . . . And the way I think about this is, there are short-, medium-, and long-term goals, and a vaccine is definitely a long-term goal. But if we don't continue the investment now, we will never have an effective vaccine."

Helen McShane, Professor of Vaccinology, University of Oxford

In 2016, the world spent $95.4 million on TB vaccine research (**Figure 11**). Nearly half of this funding came from the Gates Foundation, which has given 40 percent of the $1.1 billion spent on TB vaccine R&D since 2005.

Despite limited funding from just a few major donors, the TB vaccine field has made considerable progress over the past 15 years. The pipeline grew from zero vaccine candidates under active clinical development in 2000 to 16 by 2017.[61] During this time, the field also completed the first efficacy trial of a TB vaccine since the 1960s. Although the phase IIb trial of MVA85A in South African newborns returned disappointing results, its successful execution constituted a landmark event in a field ascending from decades of inactivity.[62] Two additional trials are expected to report results in 2018, and several other vaccine candidates are either in or preparing to enter phase II studies. Helen McShane, the principal investigator of the MVA85A trial, described this progress as "enormous for a field where 17 years ago there were no vaccine candidates in clinical trials."

Results from the MVA85A trial sent many in the TB vaccine field "back to basics" to reexamine the hypotheses that steered developers during the field's revitalization.[63] McShane pointed out that in a relatively young field, one learns a lot from well-conducted clinical trials—even those that do not demonstrate efficacy. "In the MVA85A trial, although we didn't see enhanced efficacy, we demonstrated that it was possible to conduct a trial to the highest standards of Good Clinical Practice . . . This is a field where 10 years ago people were concerned it wouldn't be possible to even do that." In addition, data collected during the MVA85A trial continue to pay scientific dividends by offering, for example, insights into the role of TB immune marker interferon-gamma in infant TB, the diagnosis of TB in infants, and the search for correlates of risk to guide subsequent vaccine design.

Rebuilding the pipeline and developing the capacity to conduct large, adequately powered clinical trials represent the first steps toward reviving TB vaccine R&D. The next phase of TB vaccine research must focus on increasing the immunological diversity of vaccine candidates in order to pursue a variety of strategies and approaches.[64,65] "If you compare the pipeline today with the pipeline about five years ago, it looks very similar, so we have a fairly stagnant pipeline" commented McShane. To her point, most of the subunit vaccines in the pipeline are constructed from the same handful of MTB antigens in different combinations, and the majority of candidates have been designed to provoke cell-mediated immunity driven by CD4+ and CD8+ T cells.[66]

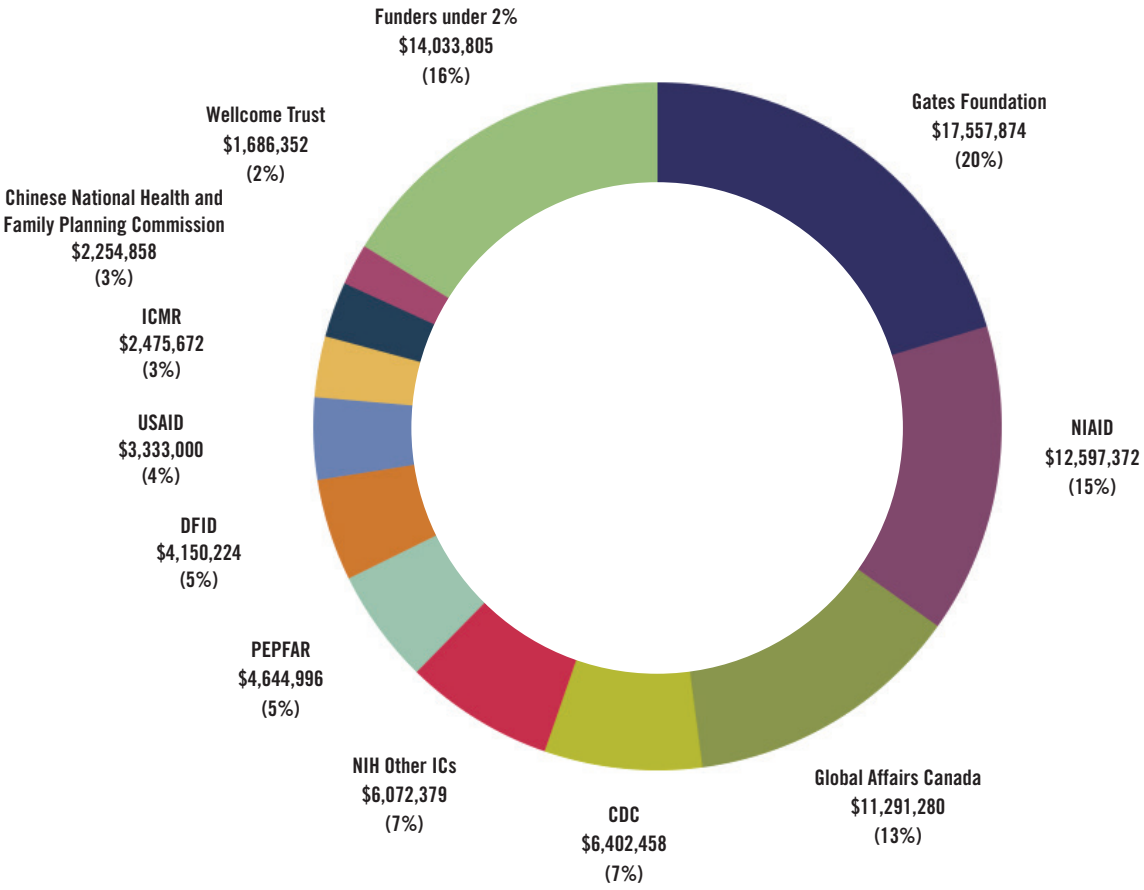
Advancing the pipeline will require funders to support clinical trials in lockstep with preclinical and basic research. "We need to do both," said McShane. "We need to push things forward into efficacy trials and design those efficacy trials in order that we learn as much as we can from them in parallel with doing basic science to inform the design of new TB vaccine candidates. And every vaccine candidate that we put forward should test a different hypothesis . . . I think we've got to keep pushing things through to human efficacy, be prepared to fail, and as long as we learn from everything we do, I can't see any other way to do this."

Given the complexity of the science, developing a new TB vaccine is a long-term endeavor. But governments must invest in vaccine research if they hope to end the TB epidemic by 2030.[67] Echoing a point made by Bill Jacobs and Stewart Cole in the context of basic science, McShane raised expectation management as an important part of nurturing sustained, long-term involvement by funders: "It's critical to manage expectations . . . One can just draw parallels with the malaria or HIV vaccine fields. In malaria there were 12 field efficacy studies before we got to the point where the first malaria vaccine is about to be licensed. And in HIV we've had five field efficacy trials and only one—the Thai trial—that potentially demonstrated a biological signal, which has yet to be replicated." According to the Resource Tracking for HIV Prevention R&D Working Group, HIV vaccine research received funding of $894 million in 2016—nine times what the world invested in TB vaccine R&D in the same year.[68] This comparison illustrates the serious degree to which TB vaccine R&D is underfunded in comparison to other global health threats.

Operational Research

FIGURE 12

Operational Research: $86,500,271



Funders with investments under 2%

Canadian Institutes of Health Research	$1,526,312
World Health Organization (WHO)	$1,504,453
Norwegian Agency for Development Cooperation (NORAD)	$1,503,592
South African Department of Health	$1,148,389
U.K. Medical Research Council (U.K. MRC)	$1,088,456
Global Health Innovative Technology Fund (GHIT)	$1,087,393
Korean Ministry of Health and Welfare	$1,043,484
European Commission	$832,737
Brazilian Ministry of Health	$629,818
Japan Agency for Medical Research and Development (AMED)	$380,940
Indian Ministry of Health and Family Welfare (MOHFW)	$310,616
Mexican National Council of Science and Technology	$308,524
Médecins Sans Frontières (MSF)	$287,913
Singapore Ministry of Health, National Medical Research Council	$279,703
Indian Ministry of Science and Technology	$273,655
Taiwan Centers for Disease Control	$263,423
Colombian Department of Science, Technology and Innovation	$211,601
Philippine Research Institute for Tropical Medicine	$185,042

Korea Health Industry Development Institute	$178,000
ELMA Foundation	$175,000
Swiss National Science Foundation (SNSF)	$168,681
United Nations Office for Project Services (UNOPS)	$105,141
Norwegian Public Health Association	$93,564
Foundation Mérieux	$77,727
International Centre for Genetic Engineering and Biotechnology (ICGEB)	$62,680
LHL International	$53,137
Korea Foundation for International Healthcare	$43,610
European and Developing Countries Clinical Trials Partnership (EDCTP)	$42,579
Colombian National Institute of Health	$37,300
Australian National Health and Medical Research Council	$32,976
Thailand Health Systems Research Institute	$29,383
CRDF Global	$22,135
Expertise France	$18,968
Individual donors to the Foundation for Medical Research in France	$15,670
Korean Institute of Tuberculosis	$8,900
Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association	$2,304

> "How do we deliver? We can talk all we want about the science, but at the end of the day, we also need to invest in how we make these tools available to the populations that are most in need. It would be great if we had a new vaccine one day, but if we don't have the mechanisms and infrastructure to deliver it, it's not a good return on investment."
>
> **Jen Ho, Deputy Director, APCASO**

In 2016, the world spent $86.5 million on TB operational research, a $25.5 million increase over 2015 (**Figure 12**). Since 2005, TB operational research has received funding of $685.5 million.

The importance of operational research, and its indelible connection to basic science and product development, enjoys wider recognition in the TB community than ever before. Suman Majumdar, co-head of TB elimination and implementation science at the Burnet Institute, described TB operational research as "gaining momentum, with program managers, countries, funders, and the affected community more aware of its role and value in the TB response." Majumdar defined operational research as "improving the efficiency, quality, and coverage of care delivery systems" and noted that "it is not expensive to conduct and provides significant value for money." Much operational research can grow out of routine surveillance or be embedded in programmatic service delivery, making it the low-hanging fruit of the TB research agenda.

Yet the TB response is riddled with signs that operational research remains underutilized and underfunded. In most countries, there are steep drop-offs in patient retention all along the cascade of TB care (a model for evaluating care delivery across the multiple steps of a health system people with TB must traverse).[69] In addition, the slow rollout of new tools ranging from Xpert MTB/RIF to the TB LAM test to bedaquiline stand as a testament to the ill-preparedness of TB programs to incorporate scientific advances into existing health systems.[70] Other TB programs struggle to take small operational research initiatives to scale and get mired in a never-ending succession of small pilot projects.[71]

Majumdar summarized the challenges to TB operational research as twofold. "First, a research-enabling environment in high-TB-burden countries is a prerequisite step. National TB programs, health workers, and, most importantly, the funders often do not see the value of operational research and do not provide the small investments needed to conduct it." Second, Majumdar highlighted the importance of building capacity to conduct operational research at the country level. One program that does this well is the Structured Operational Research and Training IniTiative, run by The Union and Médecins Sans Frontières in partnership with the WHO Special Programme for Research and Training in Tropical Diseases.[72] In the long run, shifting the mindset of TB program managers unaccustomed to seeing research as a core activity will depend on countries investing in capacity building and creating an environment that enables operational research to flourish as a central component of, rather than an optional addition to, good TB programs.

Funders must also take steps to encourage and support operational research in programmatic contexts. One of the challenges in tracking funding for operational research is that the two biggest supporters of this activity—the Global Fund to Fight AIDS, TB and Malaria (Global Fund) and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR)—face limitations in reporting how much money they give to operational research at the country level. The PEPFAR funding of $4.6 million in 2016 represents only activities funded by headquarters, not country programs, and the Global Fund can only provide its total spending on operational research over 2002–2016 ($145.9 million). The Global Fund TB team has shared its intention to explore ways to disaggregate this sum by country and year. Mohammed Yassin, Global Fund senior TB advisor, estimated that 10–15 countries account for 95 percent of Global Fund TB operational research funding. Surveying these country programs may yield a clearer picture of the Global Fund's role in the TB operational research landscape.[73] This information might also support advocacy encouraging countries to take advantage of Global Fund support for operational research, as this is widely understood to be an underutilized resource.[74]

Most reported funding for TB operational research comes from public funders in high-income, low-TB-burden countries. "We need a revolution in TB research, championed by high-burden countries who stand to benefit most from implementing new tools and strategies and, in particular, benefit from the efficiency gains provided by operational research," said Majumdar. "For too long, prioritizing and funding research alongside implementation in low- and middle-income countries has been seen as a non-essential activity." The fact that the Gates Foundation, the world's largest charity, was the biggest funder of operational research in 2016 is a further sign that governments are not investing enough in this area.

Noting that operational research received only around 10 percent of total TB R&D expenditures in 2016, Soumya Swaminathan called this share far too low for an activity "which could actually lead to the most short-term benefits for patients." She added that current and former TB patients often help to change policy and drive the uptake of innovations through advocacy. Informing policymaking to improve patient care is one of the greatest contributions operational research can make to the opening years of the End TB Strategy. For example, the government of India, the CDC, and the WHO have trained over 100 Indian TB professionals in operational research over the last six years. More than 60 research protocols have come out of this effort, and some have already led to meaningful policy changes at the state and national levels. Prominent changes include revising the national policy for directly observed therapy to include family observation for pediatric TB; implementing universal TB screening among severely malnourished children receiving care at Nutritional Rehabilitation Centers in five states; and instituting universal screening for TB among patients with diabetes in the state of Kerala.[75]

The absence of operational research can provide a disincentive for innovation in other areas if developers struggle to bring new technologies to market at scale. Jen Ho explained how implementation challenges can dilute developers' perceived return on investment: "How do we deliver? We can talk all we want about the science, but at the end of the day, we also need to invest in how we make these tools available to the populations that are most in need. It would be great if we had a new vaccine one day, but if we don't have the mechanisms and infrastructure to deliver it, it's not a good return on investment." This dynamic demonstrates the importance of funding the full spectrum of TB R&D, from basic science to product development to operational research. No research area is disconnected from another, and what happens in program settings can either encourage or discourage early-stage research efforts.

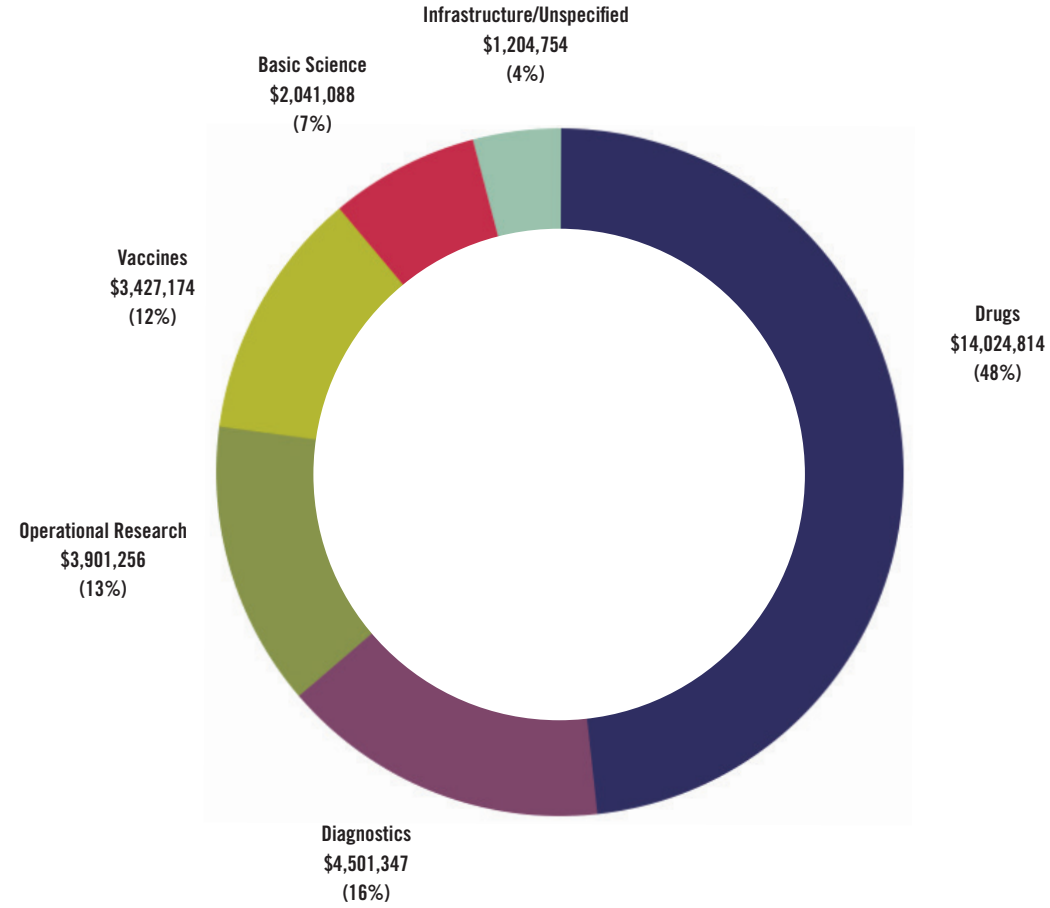
"We need a revolution in TB R&D, championed by high-burden countries that stand to benefit most from implementing new tools and strategies and, in particular, benefit from the efficiency gains provided by operational research. For too long, prioritizing and funding research alongside implementation in low- and middle-income countries has been seen as a non-essential activity."

Suman Majumdar, Co-head of TB Elimination and Implementation Science, Burnet Institute

Pediatric TB Research

FIGURE 13

Pediatric TB R&D Funding by Research Category, 2016
Total: $29,100,432



The worry voiced in last year's report—that funding for pediatric TB research is at risk of experiencing the same stagnation that applies to TB R&D funding overall—now appears to be true. In 2016, pediatric TB research received $29.1 million, an amount just slightly above the $25–26 million spent in each of the last three years (**Figure 13**). Nearly half of this money supported pediatric TB drug R&D, although this share decreased slightly, offset by funding increases for vaccine and operational research relevant to pediatric populations.

Steve Graham, professor of international child health at the University of Melbourne, described funding for pediatric TB research as "very limited," particularly in relation to the burden of TB in children: "Funding for pediatric research represents only three percent of total TB research funding—which is already inadequate—while children represent around 10 percent of the TB caseload globally."

> "There has been an increase in the quantity and quality of TB research in children, but this is still limited to a few research groups and populations. As a result, [this] research is not always relevant to resource-limited settings. There is a huge need for implementation research in different settings, and children should be included early in research for new drugs and diagnostics."
>
> **Steve Graham, Professor of International Child Health, University of Melbourne**

A better understanding of the burden of TB in children stands out as one of the most significant advances of the last decade. An estimated one million children develop TB each year, but 62 percent are never diagnosed or reported—a reflection of the inadequacy of currently available TB diagnostics for children.[76,77] In addition, TB is now recognized as a leading cause of childhood death, killing an estimated 191,000 children under five each year.[78] Shedding light on childhood TB's major piece of the global TB epidemic has strengthened the case for more research into pediatric TB, and the flat funding of recent years belies this need.

The introduction of the world's first appropriately dosed pediatric fixed-dose combinations (FDCs) of first-line TB drugs at the end of 2015 marks another milestone in pediatric TB research. The TB Alliance and Indian generic manufacturer Macleods developed these long-awaited products with funding from Unitaid. As often happens, solving one problem focuses attention on the recalcitrance of another, and the advent of pediatric first-line FDCs has highlighted the absence of equivalent second-line products for children. Only five of 14 second-line TB drugs are available in pediatric formulations, although Macleods has been working to address this gap. Financial support for Macleods to complete this work should be a priority for funders, as should work to develop diagnostic tests designed for children.

Much of the recent progress in pediatric TB R&D is owed to the IMPAACT network supported by NIAID and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the NIH. In 2016, IMPAACT spent $6.2 million on pediatric-related studies, or one-fifth of the global total. In addition to supporting specific clinical trials, IMPAACT has been influential in developing practices and standing protocols that encourage mainstreaming children and pregnant women with TB into the larger clinical trials landscape—for example, allowing for the enrollment of children with TB into trials of pediatric antiretroviral agents.[79]

Including funding for IMPAACT, the $14.2 million spent by the NIH on pediatric TB research in 2016 comprises nearly half of the global total (**Table 2**). "It's no surprise that the NIH is the leading funder of pediatric TB R&D," commented Lindsay McKenna, a senior TB/HIV project officer at TAG. "The investigator-initiated studies the NIH supports and the IMPAACT network are how we've been able to catch up as a field. In the last few years, NIH-funded projects have filled pediatric pharmacokinetic (PK) and safety data gaps for TB drugs that have been around for decades. A lot of people don't realize the role the NIH plays in helping to complete business shamefully left unfinished by TB drug sponsors, like PK and safety studies in HIV-positive children."

The pediatric TB research agenda represents more than an investment in child health. It symbolizes a commitment to equity in TB research that extends beyond children to include other vulnerable populations with unmet research needs. Ketholelie Angami explained: "I strongly feel that R&D has to broaden its scope. It has to broaden its scope and address research in pediatric diagnosis, treatment of TB in pregnant women, TB treatment in drug users, and other groups. These vulnerable populations should be taken into concern when research happens."

The recent push to promote the greater inclusion of pregnant women in TB drug trials is one example of how advocates and researchers are applying lessons learned during the last five years of pediatric R&D to advance research relevant to other vulnerable groups. TB is one of the leading non-obstetric causes of death in pregnant women, yet pregnant women remain almost systematically excluded from TB drug trials, a charge made by representatives of three community advisory boards that advise TB researchers in a recent position paper that discusses ways to include pregnant women in clinical trials.[80]

TABLE 2

Pediatric TB R&D Funders by Rank, 2016

2016 RANK	FUNDING ORGANIZATION	FUNDER TYPE	2016 PEDIATRIC TB R&D FUNDING	PERCENTAGE OF TOTAL 2016 PEDIATRIC TB R&D FUNDING
1	U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)	P	$9,806,869	33.70%
2	U.S. National Institutes of Health, Other Institutes and Centers (NIH Other ICs)	P	$4,442,441	15.27%
3	U.K. Medical Research Council (U.K. MRC)	P	$3,419,239	11.75%
4	Unitaid	M	$3,302,158	11.35%
5	U.S. President's Emergency Plan for AIDS Relief (PEPFAR)	P	$1,640,978	5.64%
6	Company X	C	$900,000	3.09%
7	Norwegian Agency for Development Cooperation (NORAD)	P	$849,372	2.92%
8	Company V	C	$724,020	2.49%
9	Global Health Innovative Technology Fund (GHIT)	M	$711,795	2.45%
10	Bill & Melinda Gates Foundation	F	$549,794	1.89%
11	Médecins Sans Frontières (MSF)	F	$494,569	1.70%
12	Norway Regional Health Authorities	P	$481,874	1.66%
13	Wellcome Trust	F	$481,288	1.65%
14	World Health Organization (WHO)	M	$385,000	1.32%
15	U.S. Agency for International Development (USAID)	P	$300,000	1.03%
16	South African Medical Research Council (SAMRC)	P	$133,408	0.46%
17	South African Department of Health	P	$127,056	0.44%
18	Serum Institute of India	C	$109,167	0.38%
19	Canadian Institutes of Health Research	P	$68,778	0.24%
20	South African Department of Science and Technology (DST)	P	$61,897	0.21%
21	Indian Ministry of Health and Family Welfare (MOHFW)	P	$44,660	0.15%
22	Damien Foundation Belgium	F	$33,311	0.11%
23	Indian Council of Medical Research (ICMR)	P	$19,606	0.07%
24	Japan Agency for Medical Research and Development (AMED)	P	$13,152	0.05%
	TOTAL		**$29,100,432**	

C = Corporation/Private Sector; F = Foundation/Philanthropy; M = Multilateral; P = Public-Sector R&D Agency

Otsuka Pharmaceuticals, which is completing its pharmacokinetic and safety study of delamanid in children, notified TAG that it cannot disaggregate pediatric expenditures from its overall spending on delamanid and is therefore not listed in the table.

In some sense, pregnant women at risk of TB are in a place similar to the one children and their advocates found themselves in a decade ago: fighting for representation in a research agenda that has overlooked their needs. TB activist Kate O'Brien developed DS-TB while pregnant and had to be treated with second-line drugs due to liver toxicity issues that are associated with some first-line drugs and are more common in pregnancy. "Despite having a common strain of a common illness that has been around for centuries, my baby and I were an experiment," said O'Brien, speaking before the U.S. Department of Health and Human Services Taskforce on Research Specific to Pregnant and Lactating Women. "Pregnancy isn't a 'complication' or 'condition', and it certainly shouldn't be an exclusion criterion for studies of medicines that women may need to take while pregnant. Most women are of childbearing age most of our lives. A drug isn't truly safe for women unless it's safe for pregnant women."

There will be no end to the TB epidemic without an end to TB among the groups most threatened by the disease. Funders must commit to supporting a TB research agenda that includes children, pregnant women, and other vulnerable groups.

"We've made incredible strides in terms of TB prevention and treatment research in children, but a lot of work remains, especially when it comes to diagnostics. There's been incremental progress in improving the sensitivity of existing TB tests, but we are still failing the 80 percent of children with TB [who] have culture-negative disease. We urgently need research to identify and validate gene signatures or biomarkers of TB that are reliable independent of age and sensitive enough to detect culture-negative TB."

Lindsay McKenna, Senior TB/HIV Project Officer, Treatment Action Group

TB Research Prepares for its Political Moment—How to Make the Most of Moscow and New York

"These two meetings are going to be absolutely important for people like me who are committed to the cause of TB. But the apprehension is that these kinds of meetings keep on happening and lots of resolutions will be discussed. The consistency of follow-up outside the meeting rooms is what is missing . . . Political action is what we need to start demanding now."

Ketholelie Angami, TB activist, Access to Rights and Knowledge Foundation

As the TB community gathers at the WHO Ministerial Conference in Moscow and prepares for the U.N. High-Level Meeting in New York, TAG asked the scientists, policymakers, and activists interviewed for this report what they hope to see come out of these meetings. What would success look like? What central messages should the TB research field convey to the political leaders in attendance at each event? Most answers returned to a few key points and themes, outlined below and told primarily using the words of interviewees themselves. Ketholelie Angami and Jen Ho, two activists who organize TB-affected communities, had particularly clear visions for what should be accomplished in Moscow and New York and are quoted at length.

Underlying many of the comments was a discernible mixture of aspiration and apprehension, expressed most clearly by Angami: "These two meetings are going to be absolutely important for people like me who are committed to the cause of TB. But the apprehension is that these kinds of meetings keep on happening and lots of resolutions will be discussed. The consistency of follow-up outside the meeting rooms is what is missing." To his point, **Table 3** shows the long list of declarations resulting from various political processes in recent years that have acknowledged the importance of TB research. "The challenges will lie with how to do the advocacy to bring about not only political commitment, but political action. Political action is what we need to start demanding now," added Angami.

1. A specific funding commitment backed by political action

"I would like to see a financial figure towards which heads of state say we will work towards filling this gap in research, either through working on the national level or through global commitments."

Lucica Ditiu, Executive Director, Stop TB Partnership

Nearly everyone agreed that the high-level meetings in Moscow and New York should push beyond rhetoric to reach specific commitments for TB research funding. Jen Ho phrased it most succinctly: "A real political commitment that's backed up by a real funding commitment—that would be a good starting point. Politicians are very good at putting words into declarations, and you could wordsmith forever negotiating the text. For me, it's having a real funding commitment by countries and strategies of how they plan on achieving their respective targets." For Lucica Ditiu, an ideal outcome would be "heads of state, hopefully from every country, commit to something—I would anchor it to a concrete figure . . . I would like to see a financial figure towards which heads of state say we will work towards filling this gap in research, either through working on the national level or through global commitments."

TABLE 3

Recent Political Declarations Highlighting TB R&D

2009 Beijing	A Ministerial Meeting of High M/XDR-TB Burden Countries	"We call for substantially increased investment by governments and all partners in R&D of new diagnostics, medicines, and vaccines to prevent and manage TB and M/XDR-TB. This requires coordinated action at the global level."
2012 New Delhi	Second BRICS Health Ministers Meeting	"Resolved to collaborate and cooperate for development of capacity and infrastructure to reduce the prevalence and incidence of TB through innovation for new drugs, vaccines, diagnostics, and promotion of consortia of TB researchers to collaborate on clinical trials of drugs and vaccines, strengthening access to affordable medicines and delivery of quality care."
2013 Cape Town	Third BRICS Health Ministers Meeting	"Resolved to collaborate and cooperate on . . . innovation for new drugs/vaccines, diagnostics and promotion of consortia of researchers to collaborate on clinical trials of drugs and vaccines as well as strengthening access to affordable, quality, efficacious and safe medicines and delivery of quality health care."
2014 Brasília	Fourth BRICS Health Ministers Meeting	Agreed to cooperate on research and innovation for TB, identifying technology sharing, manufacturing capacity, and TB financing as key priorities.
2015 Moscow	Fifth BRICS Health Ministers Meeting	"Resolved to continue collaboration on the goal of TB elimination in consonance with the WHO post 2015 Global TB strategy and Communiqué of the 4th BRICS Health Ministers' meeting, in which TB vaccine, medicines, and diagnostics research are important areas of cooperation."
2016 New Delhi	Sixth BRICS Health Ministers Meeting	Agreed to the setting up of a BRICS network on TB research and creation of a research and development consortium on TB, HIV and malaria including the possibility of international fund raising.
2017 Hamburg	G20 Summit	"We highlight the importance of fostering R&D, in particular for priority pathogens as identified by the WHO and TB . . . We call for a new international R&D Collaboration Hub to maximize the impact of existing and new anti-microbial basic and clinical research initiatives as well as product development."
2017 Xiamen	9th BRICS Summit	"We welcome the decision to set up the Tuberculosis Research Network, to be presented at the First WHO Global Ministerial Conference Ending Tuberculosis in the Sustainable Development Era: A Multisectoral Response, Moscow, Russian Federation, 16-17 November 2017."

2. A platform for coordinating and raising funding for TB research

Many interviewees suggested that fundraising should proceed through greater global coordination, and several introduced the idea of creating a common platform for financing TB research. Soumya Swaminathan, speaking in her former role as the director one of the top 15 funders of TB research, described the need for stakeholders to "put money on the table and commit certain amounts for joint programs." In referring to joint programs, she explained that fora bringing together TB research funders already exist but have sparked mostly dialogue and information sharing, rather than joint or coordinated funding. In her view, generating more tangible collaborations might be easier if the field started from "a grouping like the BRICS, because there's already a framework and government commitment to collaboration." These remarks allude to conversations among the BRICS nations to create a TB Research Network, a proposal mentioned in the Xiamen BRICS Leaders Declaration.

"A real political commitment that's backed up by a real funding commitment—that would be a good starting point. Politicians are very good at putting words into declarations, and you could wordsmith forever negotiating the text. For me, it's having a real funding commitment by countries and strategies of how they plan on achieving their respective targets."

Jen Ho, Deputy Director, APCASO

Importantly, a version of this proposal has also appeared in early drafts of the Moscow Ministerial Conference declaration. Mario Raviglione, referring to the draft available in early September, highlighted language "calling on WHO in collaboration with countries and research partners to establish a global platform for TB research and development." If this idea is carried forward, details about the platform's scope and structure will need to be worked out in Moscow and in the lead-up to the High-Level Meeting in New York. For one thing, it will need a name. Ideally, countries will see the platform as a mechanism to enhance coordination of research efforts, conduct joint fund raising, promote information sharing, and facilitate rapid scale-up of novel approaches and tools for TB prevention, diagnosis, and treatment.

Some observers have expressed skepticism about the potential of such a global platform to reconcile divergent funding priorities among a wide group of countries and institutions. Swaminathan countered this view by pointing out that "we are not saying everyone should abandon what they are doing, but that at least we should have a platform to come together on some things that we all agree are important, and that everybody should put some money into the pot to do that."

"What we need is major activation of the affected communities, activist communities, and the representatives of these communities. We need a much more united front . . . If we have this kind of united front, then there is the hope that we find people who will listen and act."

Mario Raviglione, Director, WHO Global TB Programme

Interviewees emphasized that participation in such a joint effort cannot be left to the BRICS nations or high-TB-burden countries. "I won't shy away from telling the rich countries that they need to invest in this," said Ho. Stewart Cole reiterated that "wealthy countries need to step up to the plate." And the responsibility should not fall on the public sector alone; advancing TB research will require multisectorial engagement by the pharmaceutical industry, philanthropies, and international institutions. Ho added that the TB field needs "much more strategic thinking about how we engage the private sector and get their interest." Overall, there was a strong feeling among interviewees that any new platform or mechanism called for by the declarations coming out of Moscow and New York should be founded on a true sense of global solidarity in which all countries and sectors of society contribute to funding TB R&D.

3. A framework for accountability managed by an empowered civil society

Many interviewees recognized the risk that a succession of high-level meetings will produce a series of mutually reinforcing declarations and little else. To build accountability around commitments made in Moscow and New York, Angami argued that "a clear strategic framework has to be formulated. Otherwise it's just thoughts and documents of references in the coming years, and what we are experiencing right now—in India, people dying continuously of TB everyday—will continue like this." In preparing for the U.N. High-Level Meeting, civil society coalitions have stressed that the meeting must result in a political declaration that includes an independent accountability framework for monitoring progress.

On this point, several interviewees emphasized the unique role that civil society and affected communities can play in promoting accountability. Yet these groups have traditionally received little support to engage in the TB response, particularly in the realm of TB research—something that must change for discussions in Moscow and New York to resonate as real change in the places where TB is fought. Ho reflected that civil society itself must begin paying more explicit attention to TB research: "When it comes to R&D . . . community involvement in setting the research agenda, that's something we as a community need to embark on more seriously and not just leave it to the people who are perceived to understand. How do we engage actual community members in these discussions?"

Angami agreed, saying that communities must first be empowered before they can hold leaders to account, and that this will require investing in their capacities: "To empower community, there needs to be a whole lot of investment in the community—training them, giving them exposure. Only then can activism be generated . . . But some global funders have not fully committed to really working with community groups. Honestly speaking, without any financial resources, things cannot happen. Community groups need to be funded." Ho also made a connection between investing in TB-affected communities and strengthening "overall community systems' capacities to respond to health threats." Approached this way, support for affected communities in the TB response may become an entry point for "communities to take ownership of their health—of their right to health."

4. A recognition that TB is central to the fight against AMR

Finally, many interviewees pointed to the swift ascent of AMR up the global political agenda as an object lesson for the TB community. In September 2016, the United Nations held a High-Level Meeting on AMR that culminated in a draft political declaration calling for joint action, including the need to resolve "the lack of investment in research and development." Many in the TB field see global attention to AMR as a tremendous opportunity, but one that TB risks missing out on without attentive advocacy. "While the hype on AMR is good, I'm worried that the focus is shifting away from TB funding, and that we'll see a

"While the hype on AMR is good, I'm worried that the focus is shifting away from TB funding, and that we'll see a decline rather than an increase over the next few years. We need to make sure that global policymakers don't bury TB as one of the key issues among AMR, but keep TB at the forefront of their thinking."

Claudia Denkinger, Head of TB, FIND

"The other thing [politicians] need to realize is that [if] we don't tackle TB, all the progress that has been made in HIV/AIDS will be rolled back because those individuals will be at risk of dying from TB. It's silly to tackle one problem, but not the one that causes the most deaths in the HIV/AIDS community."

Stewart Cole, Director, Global Health Institute at the Swiss Federal Institute of Technology in Lausanne

decline rather than an increase over the next few years," said Claudia Denkinger. "We need to make sure that global policymakers don't bury TB as one of the issues among AMR, but keep TB at the forefront of their thinking."

The case for making TB a centerpiece of the global fight against AMR is straightforward and compelling. Drug-resistant forms of TB are responsible for a quarter of all AMR deaths, and the *Review on Antimicrobial Resistance*, commissioned by the government of the United Kingdom, has said that TB will be one of the three biggest drivers of AMR's future economic toll, alongside malaria and *E. coli*.[81] The inclusion of TB as a "global R&D priority" in the WHO *Antibacterial Agents* report is an encouraging step toward representing TB drug development within AMR research priorities. Helen McShane pointed out that "the role of vaccination as a tool to prevent and treat AMR, including drug-resistant strains of TB, is currently underexploited and needs further exploration of potential." The same could be said of diagnostics. The rapid, point-of-care diagnostic tests; safer, shorter, more effective treatment regimens; and new, more effective TB vaccine called for by the End TB Strategy are all tools that would strengthen the global campaign against AMR.

In building on previous U.N. summits, the High-Level Meeting on TB will need to strike a delicate balance between ensuring that TB is addressed as a pressing health crisis in its own right while avoiding exceptionalizing TB and obscuring its overlap with allied causes. Several interviewees framed securing a place for TB on the AMR agenda as one piece of a bigger effort to position TB as a defining issue of global health security. Speakers cited the global response to Ebola hemorrhagic fever and Zika virus as moments when political leaders got half the equation right (swift and massive resource mobilization) but not the whole solution (the sustained financing required to make research a part of epidemic preparedness rather than an emergency response measure). Reflecting on global health security, Stewart Cole made a similar connection between TB and the fight against AIDS: "The other thing [politicians] need to realize is that if we don't tackle TB, all the progress that has been made in HIV/AIDS will be rolled back because those individuals will be at risk of dying from TB. It's silly to tackle one problem, but not the one that causes the most deaths in the HIV/AIDS community."

Conclusion

The $726.1 million spent on TB R&D in 2016 is a hopeful sign that the TB field is gathering the momentum necessary to overcome the last six years of inertia that kept funding flat and progress incremental. Although encouraging, a $105.5 million increase over the previous year is just a fraction of the massive step up in funding advocates for TB research should ask ministers and heads of state to commit to in Moscow and New York. A TB-free world will only be possible if the next decade of TB research travels farther than the last. Exceeding $700 million in annual funding for the first time marks a milestone, but an early one given the extent of unmet scientific need. To reach the *Global Plan to End TB*'s five-year funding target of $9 billion, the world must spend an additional $8.2 billion on TB research between now and 2020. The Moscow Ministerial Conference and the U.N. High-Level Meeting on TB in New York will be judged as successes if, one day, the world looks back in wonder that crossing such a low threshold was ever taken as an accomplishment. As the TB community convenes in Moscow and prepares to go to New York, it should set the following goal: let $700 million become not a high watermark, but the financial floor from which TB research ascends toward the scientific achievements that bring the TB epidemic to its end.

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Appendix 1: Methodology

TAG tracks global funding for TB R&D by surveying public, private, philanthropic, and multilateral organizations with known or potential investments in TB research**.** The survey asks recipients to report the amount of money spent on TB R&D in a given year and categorize spending into six research areas: basic science, diagnostics, drugs, vaccines, operational research, and infrastructure/unspecified projects. Survey recipients may report spending by individual projects or aggregate expenditures by research area. Within these categories, the survey asks recipients to indicate any funding that supported pediatric TB research. TAG surveyed 186 organizations for this year's report and received 118 surveys in return. From these, we identified 132 institutions funding TB research in 2016. Nine organizations that returned surveys reported spending no money on TB R&D in 2016, and four groups declined to participate.

The survey asks organizations to report TB research expenditures in local currencies, which TAG converts into U.S. dollars using the July 1, 2016, interbank exchange rates published by the OANDA Corporation. All dollar figures in the report are published as U.S. dollars unless otherwise noted and are rounded to the nearest dollar (all calculations, however, are performed on unrounded data). Dollar figures represent disbursements (i.e., the actual transfer of funds made in 2015) rather than commitments or budgetary allocations for future years.

TAG carefully reviews each returned survey for completeness, taking careful measures to avoid double-counting awards reported by more than one funder. Double counting can arise under several scenarios, including the fact that many organizations fund some projects while receiving outside money for others. To help minimize the risk of double counting, the survey asks recipients to note whether spending represents one of three categories: funding given to others, funding received from others, or self-funded research. Any awards listed by more than one survey enter our database as reported by the original-source donor. For collaborative projects supported by more than one organization, we ask funders to report only their share of the project, not total costs.

In addition to surveying funding institutions, TAG conducted 12 qualitative interviews with leading TB scientists, policymakers, and activists and asked each to reflect on the current state of TB research in relation to available versus required funding. TAG invited interviewees to express their hopes—or reservations—for the outcomes of the Moscow Ministerial Conference and U.N. High-Level Meeting with respect to TB research. Each interviewee received an embargoed copy of preliminary survey findings in early September 2017 with a list of open-ended questions. We interviewed nine individuals over the phone, and three submitted answers

RESEARCH AREAS TRACKED BY TAG:

1. Basic science: undirected, investigator-initiated research to discover fundamental knowledge about MTB and closely related mycobacterial organisms.
2. Diagnostics: preclinical and clinical trials of diagnostic technologies and algorithms.
3. Drugs: preclinical and clinical research on treatments and treatment strategies for MTB infection and TB disease.
4. Vaccines: preclinical and clinical research on TB vaccines, including both preventive and immunotherapeutic vaccines.
5. Operational research: evaluations of new or existing TB control strategies and tools to guide their implementation in program settings. Operational research may include randomized trials, surveillance, and epidemiological and observational studies.
6. Infrastructure/unspecified projects: TB research that the funder is unable to further classify.

in writing. Each phone interview was recorded and transcribed verbatim. We pulled quotations from the transcripts and written responses, grouped them into common themes, and selected the excerpts that appear within and alongside the text of this report. In some places, TAG edited quotations for length or clarity. TAG checked quotations drawn from phone interviews with speakers prior to publication.

Limitations to the data

The comprehensiveness of the data in this report depends on the proportion of institutions funding TB research that participate in the survey. This proportion cannot be calculated since the true number of TB research funders worldwide is unknown. TAG makes a considerable effort to ensure a wide survey reach and yield. The survey is available in six languages (English, French, Spanish, Russian, Chinese, and Portuguese). TAG routinely updates the survey frame by adding new organizations, most of which do not have known investments in TB R&D but either support health research generally or have a record of investing in related disease. Finally, TAG makes a particular effort to encourage the continued participation of the 30 largest funders from the previous year. The high degree of concentration of TB research funding means that the top 30 donors typically comprise over 90 percent of total spending, and the composition of this group has remained remarkably stable over time. This year, 29 of the top 30 funders from 2015 participated in the survey, and one (Qiagen) declined to participate.

PEDIATRIC TB RESEARCH RESOURCE TRACKING METHODOLOGY

TAG's survey asks all funders to delineate support for pediatric research and assign any relevant spending to one of the six core research areas tracked by the report. TAG further identifies research related to pediatric TB by conducting a keyword search of titles and abstracts contained in returned surveys using the following search terms: pediatric, paediatric, infant, child, kid, adolescent, and pregnant. While this methodology provides a reasonable estimate of pediatric TB research spending, it overlooks research that informs the development of pediatric products without enrolling children or studying MTB infection or TB disease in children directly. Some funders have notified TAG that they cannot disaggregate pediatric research funding from their overall expenditure on TB R&D. Otsuka, for example, did not report how much of the nearly $29 million it spent on TB drug development in 2016 went to pediatric studies of delamanid. Funders supporting clinical trials, cohort studies, and epidemiological surveys that include people of all age groups can rarely specify the proportion of funds devoted to younger age groups. TAG encourages all funders to develop ways of disaggregating pediatric TB research spending from within larger funding totals to support more accurate estimation here.

Several funders with known investments in TB research did not return surveys this year, including the Howard Hughes Medical Institute, the Singapore Agency for Science, Technology and Research (A*STAR), the French National Institute of Health and Medical Research (INSERM), Merck, QuantuMDx, Hain Lifescience, and the Irish Health Research Board. The U.K. National Institute for Health Research submitted its survey after the database locked; its reported expenditure of $2.0 million will enter next year's report as a correction. TAG received no information from entities in Russia, despite attempts to coordinate reporting with the Ministry of Health of the Russian Federation, the host of this year's Ministerial Conference on TB in Moscow. Understanding the funding landscape and trends over time is the first step toward securing stronger political commitments to TB research. TAG is hopeful that the Russian government will report its TB research funding at the Ministerial Conference.

TAG encourages donors not included here to participate in future report rounds. Please contact TAG at **tbrdtracking@treatmentactiongroup.org** if you have information or corrections to share. Any corrections submitted to TAG will enter print in next year's report.

This report would not be possible without considerable time and effort on the part of the dozens of funding officers and administrative staff who complete the survey each year. TAG is grateful to the 118 organizations across the world that participated in this year's survey. **Appendix 2** acknowledges organizations that have reported to TAG every year since 2005 with a dagger (†) appearing next to their names.

Appendix 2

TB R&D Funders by Rank, 2016

2016 RANK	FUNDING ORGANIZATION	FUNDER TYPE	TOTAL
1	U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)†	P	$212,333,119
2	Bill & Melinda Gates Foundation (Gates Foundation)†	F	$120,155,477
3	U.S. National Institutes of Health, Other Institutes and Centers (NIH Other ICs)†	P	$44,283,102
4	U.S. Agency for International Development (USAID)†	P	$33,687,987
5	Otsuka Pharmaceuticals†	C	$28,851,190
6	Wellcome Trust†	F	$19,910,189
7	U.S. Centers for Disease Control and Prevention (U.S. CDC)†	P	$18,811,568
8	European Commission†	P	$15,980,727
9	Unitaid	M	$14,760,058
10	U.K. Medical Research Council (U.K. MRC)†	P	$13,995,420
11	Company X†	C	$13,812,812
12	Company V	C	$11,858,910
13	U.K. Department for International Development (DFID)†	P	$11,787,715
14	German Federal Ministry of Education and Research (BMBF)	P	$11,441,790
15	Global Affairs Canada	P	$11,291,280
16	Indian Council of Medical Research (ICMR)	P	$11,052,862
17	GlaxoSmithKline (GSK)	C	$7,839,283
18	Dutch Directorate-General for International Cooperation (DGIS)†	P	$7,649,203
19	Australian Department of Foreign Affairs and Trade (DFAT)	P	$5,311,133
20	Canadian Institutes of Health Research†	P	$5,211,900
21	Korean Ministry of Health and Welfare	P	$4,934,788
22	Norwegian Agency for Development Cooperation (NORAD)	P	$4,874,922
23	U.S. President's Emergency Plan for AIDS Relief (PEPFAR)‡	P	$4,644,996
24	Japan Agency for Medical Research and Development (AMED)	P	$4,524,116
25	European and Developing Countries Clinical Trials Partnership (EDCTP)†	P	$4,312,497
26	Korean Ministry of Science, ICT and Future Planning	P	$4,311,292
27	Swiss National Science Foundation (SNSF)	P	$4,013,475
28	Australian National Health and Medical Research Council	P	$3,857,428
29	Eli Lilly	C	$3,346,000
30	Global Health Innovative Technology Fund (GHIT)	M	$3,292,582
31	Innovative Medicines Initiative (IMI)	P	$3,282,029
32	Company Y†	C	$3,221,000
33	Chinese National Health and Family Planning Commission*	P	$2,885,011

C = Corporation/Private Sector; F = Foundation/Philanthropy; M = Multilateral; P = Public-Sector R&D Agency

* New Funder; † Organization has reported to TAG each year since 2005

‡ PEPFAR's total only includes funding for operational research (implementation science) sponsored by PEPFAR agency headquarters and does not include country-level spending. As a result, this number likely significantly underestimates PEPFAR's support for TB research.

BASIC SCIENCE	DIAGNOSTICS	DRUGS	VACCINES	OPERATIONAL RESEARCH	INFRASTRUCTURE/ UNSPECIFIED
$84,848,920	$13,657,368	$65,750,312	$19,539,575	$12,597,372	$15,939,572
$3,307,730	$15,783,169	$39,746,336	$43,760,368	$17,557,874	$0
$19,602,670	$6,073,695	$6,315,590	$1,000,657	$6,072,379	$5,218,111
$0	$0	$17,800,987	$0	$3,333,000	$12,554,000
$0	$0	$28,851,190	$0	$0	$0
$6,785,236	$1,099,317	$2,802,355	$546,366	$1,686,352	$6,990,562
$0	$5,064,274	$7,344,836	$0	$6,402,458	$0
$3,268,294	$2,847,336	$976,008	$7,271,229	$832,737	$785,122
$0	$0	$14,760,058	$0	$0	$0
$5,843,308	$2,735,064	$3,709,845	$618,747	$1,088,456	$0
$0	$0	$13,812,812	$0	$0	$0
$0	$0	$11,368,070	$490,840	$0	$0
$0	$2,977,327	$2,588,980	$2,071,184	$4,150,224	$0
$1,662,430	$2,480,046	$5,398,653	$1,595,782	$0	$304,879
$0	$0	$0	$0	$11,291,280	$0
$356,509	$6,955	$22,858	$0	$2,475,672	$8,190,869
$0	$0	$0	$7,839,283	$0	$0
$0	$4,251,440	$3,397,763	$0	$0	$0
$0	$2,655,566	$2,655,566	$0	$0	$0
$2,477,030	$166,661	$539,932	$437,352	$1,526,312	$64,613
$628,696	$1,580,000	$269,565	$1,413,043	$1,043,484	$0
$1,304,343	$633,470	$0	$1,433,517	$1,503,592	$0
$0	$0	$0	$0	$4,644,996	$0
$678,436	$172,330	$634,900	$2,267,500	$380,940	$390,010
$0	$4,269,918	$0	$0	$42,579	$0
$1,191,304	$1,375,652	$1,526,945	$217,391	$0	$0
$3,204,132	$0	$514,695	$125,967	$168,681	$0
$2,135,149	$1,349,546	$0	$179,597	$32,976	$160,159
$0	$0	$3,346,000	$0	$0	$0
$0	$0	$1,323,983	$881,205	$1,087,393	$0
$0	$0	$3,282,029	$0	$0	$0
$0	$3,221,000	$0	$0	$0	$0
$0	$0	$630,152	$0	$2,254,858	$0

The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) informed TAG that it can only report its cumulative expenditure on TB operational research between 2002 and 2016, which totaled $145.9 million. The Global Fund is exploring ways to estimate its annual spending on TB operational research moving forward.

Organizations that reported no new spending on TB research in 2016: Alere; Danish International Development Agency (DANIDA); Firland Foundation; Dana Foundation; Netherlands Organization for Health Research and Development (ZonMw); and the World Bank.

Appendix 2

TB R&D Funders by Rank, 2016 (continued)

2016 RANK	FUNDING ORGANIZATION	FUNDER TYPE	TOTAL
34	Max Planck Institute for Infection Biology	P	$2,760,000
35	Institut Pasteur	F	$2,671,782
36	Indian Council of Scientific and Industrial Research (CSIR)	P	$2,598,360
37	South African Department of Health	P	$2,383,679
38	Korea Drug Development Fund	C	$2,225,000
39	Qurient	P	$2,225,000
40	Dutch National Postcode Lottery	P	$2,209,656
41	Longhorn Vaccines and Diagnostics*	C	$2,070,000
42	Swiss Federal Institute of Technology in Lausanne (EPFL)	P	$1,924,721
43	South African Medical Research Council (SAMRC)	P	$1,854,205
44	Public Health England	P	$1,702,254
45	U.S. National Science Foundation	P	$1,695,138
46	Swedish Research Council	P	$1,606,583
47	World Health Organization (WHO)	M	$1,504,453
48	South African Department of Science and Technology (DST)	P	$1,377,597
49	French National Agency for AIDS Research (ANRS)	P	$1,176,120
50	Irish Aid	P	$1,110,380
51	Macleods Pharmaceuticals	C	$1,000,000
52	Taiwan Centers for Disease Control	P	$970,328
53	Genedrive*	C	$961,806
54	Médecins Sans Frontières (MSF)	F	$958,813
55	National Research Foundation of South Africa	P	$823,240
56	Singapore National University Health System	P	$746,511
57	Company W	C	$740,100
58	Brazilian Ministry of Health	P	$629,818
59	German Research Foundation	P	$619,148
60	Republic of Gabon	P	$612,044
61	Indian Ministry of Science and Technology	P	$575,428
62	Brazilian Ministry of Science, Technology, Innovation and Communication	P	$540,753
63	Company R	C	$536,018
64	Company P	C	$500,000
65	French National Agency for Research (ANR)	P	$494,017
66	Norway Regional Health Authorities	P	$481,874

C = Corporation/Private Sector; F = Foundation/Philanthropy; M = Multilateral; P = Public-Sector R&D Agency

* New Funder; † Organization has reported to TAG each year since 2005

BASIC SCIENCE	DIAGNOSTICS	DRUGS	VACCINES	OPERATIONAL RESEARCH	INFRASTRUCTURE/ UNSPECIFIED
$1,610,000	$0	$0	$1,150,000	$0	$0
$1,699,010	$175,827	$369,950	$426,996	$0	$0
$2,402,015	$0	$133,665	$62,680	$0	$0
$714,795	$0	$146,019	$0	$1,148,389	$374,477
$0	$0	$2,225,000	$0	$0	$0
$0	$0	$2,225,000	$0	$0	$0
$0	$0	$2,209,656	$0	$0	$0
$0	$1,570,000	$500,000	$0	$0	$0
$1,035,910	$0	$888,811	$0	$0	$0
$1,214,299	$0	$639,906	$0	$0	$0
$517,796	$0	$0	$1,184,458	$0	$0
$924,307	$495,832	$275,000	$0	$0	$0
$1,400,613	$0	$118,589	$0	$0	$87,381
$0	$0	$0	$0	$1,504,453	$0
$1,209,918	$167,680	$0	$0	$0	$0
$52,604	$553,599	$569,917	$0	$0	$0
$0	$0	$1,110,380	$0	$0	$0
$0	$0	$1,000,000	$0	$0	$0
$58,030	$436,319	$212,556	$0	$263,423	$0
$0	$961,806	$0	$0	$0	$0
$0	$311,714	$359,187	$0	$287,913	$0
$755,295	$0	$15,442	$0	$0	$52,503
$0	$0	$746,511	$0	$0	$0
$0	$0	$740,100	$0	$0	$0
$0	$0	$0	$0	$629,818	$0
$619,148	$0	$0	$0	$0	$0
$612,044	$0	$0	$0	$0	$0
$221,173	$56,572	$24,028	$0	$273,655	$0
$311,728	$0	$229,025	$0	$0	$0
$0	$0	$536,018	$0	$0	$0
$0	$0	$500,000	$0	$0	$0
$494,017	$0	$0	$0	$0	$0
$0	$481,874	$0	$0	$0	$0

Appendix 2

TB R&D Funders by Rank, 2016 (continued)

2016 RANK	FUNDING ORGANIZATION	FUNDER TYPE	TOTAL
67	Health Research Council of New Zealand	P	$465,815
68	Indian Ministry of Health and Family Welfare (MOHFW)	P	$452,940
69	Japan International Cooperation Agency (JICA)	P	$439,805
70	Foundation for Medical Research in France*	F	$437,054
71	U.S. Food and Drug Administration (FDA)†	P	$435,400
72	Mexican National Council of Science and Technology*	P	$419,778
73	Japan BCG Laboratory	C	$399,624
74	Grand Challenges Canada	P	$395,000
75	Korea Health Industry Development Institute	P	$356,000
76	Foundation Jacqueline Beytout	F	$334,555
77	Australian Research Council	P	$320,864
78	U.S. Department of Agriculture*	P	$299,889
79	U.S. Department of Defense Medical Research and Development Program (DMRDP)	P	$280,368
80	Singapore Ministry of Health, National Medical Research Council	P	$279,703
81	Korean Ministry of Agriculture, Food and Rural Affairs*	P	$265,217
82	Biofabri	C	$254,685
83	SomaLogic	C	$245,285
84	Brazilian State Funding Agencies	P	$238,568
85	United Nations Office for Project Services (UNOPS)	M	$221,901
86	Korea Centers for Disease Control and Prevention	P	$219,668
87	Marsden Fund*	P	$213,835
88	Colombian Department of Science, Technology and Innovation	P	$211,601
89	Cepheid	C	$200,000
90	Philippine Research Institute for Tropical Medicine*	P	$185,042
91	ELMA Foundation*	F	$175,000
92	Brazilian Ministry of Education	P	$174,950
93	Damien Foundation Belgium	F	$153,232
94	APEC Support Fund*	M	$150,000
95	Else Kröner-Fresenius Foundation	F	$130,000
96	Hong Kong Health and Medical Research Fund	P	$127,554
97	Thailand National Science and Technology Development Agency	P	$126,245
98	SK Telecom	C	$125,490
99	Tata Education and Development Trust*	F	$121,552

C = Corporation/Private Sector; F = Foundation/Philanthropy; M = Multilateral; P = Public-Sector R&D Agency

* New Funder; † Organization has reported to TAG each year since 2005

BASIC SCIENCE	DIAGNOSTICS	DRUGS	VACCINES	OPERATIONAL RESEARCH	INFRASTRUCTURE/ UNSPECIFIED
$434,403	$0	$31,412	$0	$0	$0
$55,400	$0	$14,173	$0	$310,616	$72,751
$0	$439,805	$0	$0	$0	$0
$437,054	$0	$0	$0	$0	$0
$0	$0	$435,400	$0	$0	$0
$0	$0	$111,255	$0	$308,524	$0
$164,258	$0	$0	$235,367	$0	$0
$0	$0	$0	$0	$0	$395,000
$0	$178,000	$0	$0	$178,000	$0
$0	$0	$334,555	$0	$0	$0
$320,864	$0	$0	$0	$0	$0
$0	$299,889	$0	$0	$0	$0
$0	$280,368	$0	$0	$0	$0
$0	$0	$0	$0	$279,703	$0
$0	$0	$165,217	$100,000	$0	$0
$0	$0	$0	$254,685	$0	$0
$245,285	$0	$0	$0	$0	$0
$0	$238,568	$0	$0	$0	$0
$0	$0	$116,760	$0	$105,141	$0
$0	$57,850	$0	$0	$0	$161,818
$213,835	$0	$0	$0	$0	$0
$0	$0	$0	$0	$211,601	$0
$0	$200,000	$0	$0	$0	$0
$0	$0	$0	$0	$185,042	$0
$0	$0	$0	$0	$175,000	$0
$0	$0	$0	$0	$0	$174,950
$0	$56,629	$96,603	$0	$0	$0
$0	$0	$0	$0	$0	$150,000
$130,000	$0	$0	$0	$0	$0
$0	$51,538	$76,016	$0	$0	$0
$46,219	$80,025	$0	$0	$0	$0
$0	$125,490	$0	$0	$0	$0
$121,552	$0	$0	$0	$0	$0

Appendix 2

TB R&D Funders by Rank, 2016 (continued)

2016 RANK	FUNDING ORGANIZATION	FUNDER TYPE	TOTAL
100	Philippine Council for Health Research and Development*	P	$117,136
101	Serum Institute of India	C	$109,167
102	Howard Hughes Medical Institute	F	$100,000
103	Norwegian Public Health Association	P	$93,564
104	U.K. Biotechnology and Biological Sciences Research Council*	P	$90,000
105	Foundation Mérieux	F	$77,727
106	InSpace*	C	$71,200
107	QuantaMatrix	C	$71,200
108	International Centre for Genetic Engineering and Biotechnology (ICGEB)	P	$62,680
109	Sidaction*	F	$62,188
110	LHL International	P	$53,137
111	Korean Institute of Tuberculosis	P	$47,170
112	Danish Council for Independent Research	P	$44,771
113	Korea Foundation for International Healthcare*	F	$43,610
114	Colombian National Institute of Health	P	$37,300
115	Lundbeck Foundation	F	$34,449
116	Taiwan Ministry of Health and Welfare	P	$30,000
117	Taiwan Ministry of Science and Technology	P	$30,000
118	Thailand Health Systems Research Institute*	P	$29,383
119	South African National Health Laboratory Service Research Trust	P	$27,024
120	Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association	P	$26,303
121	CRDF Global*	F	$22,135
122	Indian Science and Engineering Research Board*	P	$20,919
123	Individual donors to TB Alliance	F	$19,471
124	Expertise France*	P	$18,968
125	Thailand Ministry of Public Health	P	$18,219
126	Individual donors to the Foundation for Medical Research in France	F	$15,670
127	Innovation Fund Denmark	P	$11,960
128	Faber Daeufer	C	$7,500
129	DuPont*	C	$6,675
130	European Molecular Biology Organization	F	$6,048
131	Indian Defense Research and Development Organization*	P	$5,093
132	DMBio	C	$2,670

C = Corporation/Private Sector; F = Foundation/Philanthropy; M = Multilateral; P = Public-Sector R&D Agency

* New Funder; † Organization has reported to TAG each year since 2005

BASIC SCIENCE	DIAGNOSTICS	DRUGS	VACCINES	OPERATIONAL RESEARCH	INFRASTRUCTURE/ UNSPECIFIED
$0	$0	$0	$0	$0	$117,136
$0	$0	$0	$109,167	$0	$0
$100,000	$0	$0	$0	$0	$0
$0	$0	$0	$0	$93,564	$0
$0	$0	$0	$90,000	$0	$0
$0	$0	$0	$0	$77,727	$0
$0	$71,200	$0	$0	$0	$0
$0	$71,200	$0	$0	$0	$0
$0	$0	$0	$0	$62,680	$0
$9,155	$0	$0	$0	$0	$53,033
$0	$0	$0	$0	$53,137	$0
$38,270	$0	$0	$0	$8,900	$0
$0	$0	$0	$44,771	$0	$0
$0	$0	$0	$0	$43,610	$0
$0	$0	$0	$0	$37,300	$0
$0	$0	$0	$34,449	$0	$0
$30,000	$0	$0	$0	$0	$0
$30,000	$0	$0	$0	$0	$0
$0	$0	$0	$0	$29,383	$0
$27,024	$0	$0	$0	$0	$0
$23,999	$0	$0	$0	$2,304	$0
$0	$0	$0	$0	$22,135	$0
$20,919	$0	$0	$0	$0	$0
$0	$0	$19,471	$0	$0	$0
$0	$0	$0	$0	$18,968	$0
$18,219	$0	$0	$0	$0	$0
$0	$0	$0	$0	$15,670	$0
$0	$0	$0	$11,960	$0	$0
$0	$0	$7,500	$0	$0	$0
$0	$6,675	$0	$0	$0	$0
$6,048	$0	$0	$0	$0	$0
$5,093	$0	$0	$0	$0	$0
$0	$2,670	$0	$0	$0	$0

Appendix 3

TB Experts Interviewed by TAG

1	Ketholelie Angami	TB activist, Access to Rights and Knowledge Foundation
2	Stewart Cole	Director, Global Health Institute, Swiss Federal Institute of Technology in Lausanne
3	Claudia Denkinger	Head of tuberculosis, FIND
4	Lucica Ditiu	Executive director, Stop TB Partnership
5	Steve Graham	Professor, international child health, University of Melbourne
6	Jen Ho	Deputy director, APCASO
7	Bill Jacobs	Professor, microbiology and immunology, Albert Einstein College of Medicine
8	Suman Majumdar	Co-head, TB elimination and implementation science, Burnet Institute
9	Helen McShane	Professor, vaccinology, University of Oxford
10	Maurine Murenga	Organizer, International Community of Women Living with HIV Eastern Africa
11	Mario Raviglione	Director, Global TB Programme, World Health Organization
12	Soumya Swaminathan	Director general, Indian Council of Medical Research (shortly after being interviewed, Dr. Swaminathan was appointed deputy director general of programmes at the World Health Organization)

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