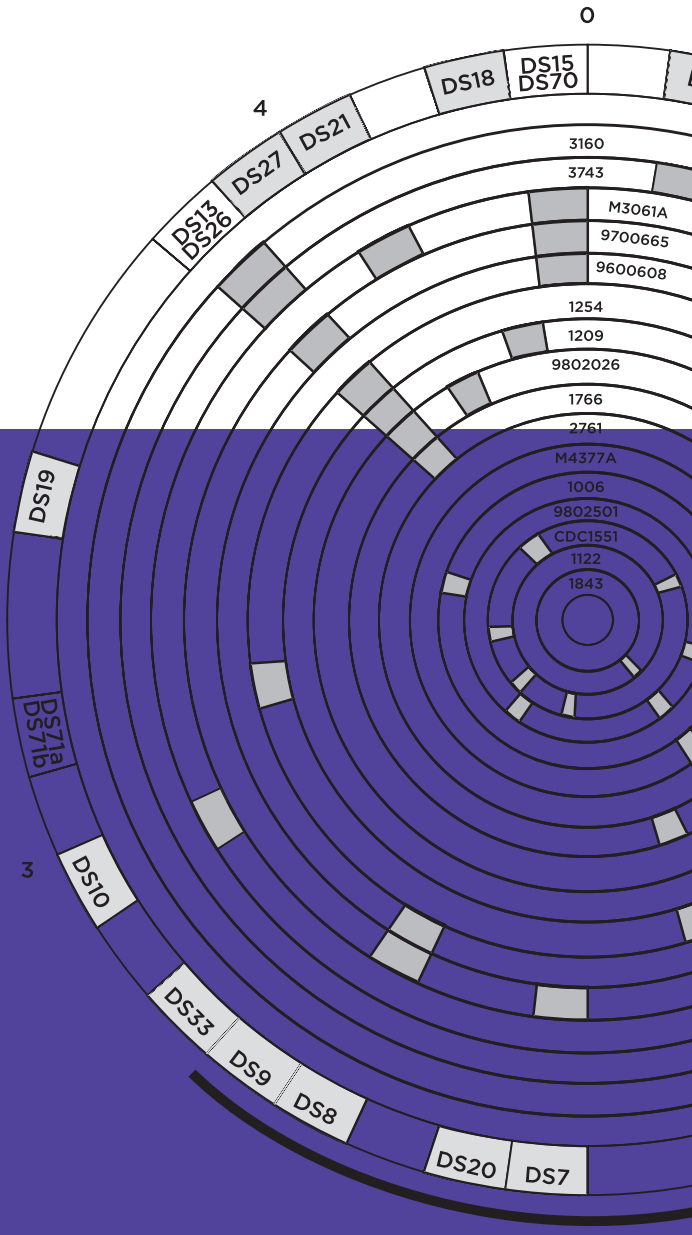
TAG
Treatment Action Group

Stop TB Partnership

TUBERCULOSIS RESEARCH
AND DEVELOPMENT:

2013 Report on Tuberculosis Research Funding Trends, 2005–2012



NOVEMBER 2013

TREATMENT ACTION GROUP

BY MIKE FRICK AND
ELEONORA JIMÉNEZ-LEVI

ACKNOWLEDGMENTS

Treatment Action Group (TAG) is grateful to all the participating TB R&D donors who made this report possible. We would also like to offer special thanks to the Stop TB Partnership for supporting TAG's TB/HIV Project and the writing of this report.

ABOUT TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive life-saving 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 AIDS.

TB/HIV PROJECT

Treatment Action Group's TB/HIV Project works to improve research, programs, and policy for people with TB and HIV.

Mike Frick is the TB/HIV project officer at TAG. He holds a bachelor's degree in international studies and Chinese from Kenyon College and a master of science degree in global health and population from the Harvard School of Public Health.

Eleonora Jiménez-Levi, formerly a senior researcher at TAG, led TAG's resource-tracking efforts on original-source funding for TB and HIV research and development from 2010 to 2013. She holds a bachelor's degree in political science from Barnard College and a master of science degree from the Harvard School of Public Health.

Contact TAG

Treatment Action Group
261 Fifth Avenue, Suite 2110
New York, NY 10016 USA
Tel 212 253 7922
Fax 212 253 7923

tag@treatmentactiongroup.org
www.treatmentactiongroup.org

ISBN # 978-0-9837221-9-9

Layout by Hollander Snow Studio

TUBERCULOSIS RESEARCH
AND DEVELOPMENT:

2013 Report on Tuberculosis Research Funding Trends, 2005–2012

NOVEMBER 2013

TREATMENT ACTION GROUP

BY MIKE FRICK AND
ELEONORA JIMÉNEZ-LEVI

EDITED BY MARK HARRINGTON

THIS REPORT IS DEDICATED TO:

Pavel and Oxana Rucsineanu and all who, like them, have to fight for TB treatment.

Oxana and Pavel fell in love and married while undergoing treatment for drug-resistant TB in a Moldovan hospital. But increasing drug resistance in Pavel's TB challenged the young couple's hopeful plans. Whereas Oxana was cured in 2010, Pavel remained in the hospital in treatment until he was finally sent home—not because his TB was cured, but because his doctors had nothing left with which to treat him.

Because Otsuka has refused to create a pre-approval expanded access plan for delamanid, and as Moldova has no legal provision for compassionate use to allow for access to bedaquiline, Pavel could not benefit from any of the new drugs in clinical trials for TB. Pfizer's linezolid, an existing drug that might have worked, was exorbitantly expensive.

Oxana's tenacious advocacy to save her husband finally resulted in Pavel's initiation on a linezolid-based regimen in August 2013. Her determination to ensure that others have similar opportunities for cure led her from their small town in Moldova to Washington, D.C., where she spoke to members of the U.S. Congress on the need to address MDR-TB.

Millions of men, women, and children around the world remain undiagnosed or receive drugs to which their TB disease is already resistant. In order to save people like Pavel and Oxana, we must couple research and development for new diagnostics, drugs, and vaccines with the regulatory changes required to quickly deliver new tools to patients in a way that is affordable and accessible. Only with a renewed commitment to innovation in research and regulation can the world uphold the promise to achieve zero TB deaths, new infections, and suffering.

Table of Contents

EXECUTIVE SUMMARY		**1**
1.	**INTRODUCTION**	**6**
1.1	RATIONALE	6
1.2	BACKGROUND	7
1.3	METHODOLOGY	8
1.4	LIMITATIONS	9
1.5	CORRECTIONS	10
2.	**RESULTS**	**11**
2.1	DONOR CATEGORIES	11
2.2	TRENDS IN TB RESEARCH BY CATEGORY	16
2.3	PRODUCT DEVELOPMENT PARTNERSHIPS AND RESEARCH CONSORTIA	26
2.4	TOP 10 FUNDERS OF TB R&D IN 2012	27
3.	**CONCLUSION**	**33**
4.	**RECOMMENDATIONS**	**35**

FIGURES

FIGURE 1. ANNUAL GLOBAL PLAN RESEARCH FUNDING TARGETS VERSUS 2012 INVESTMENTS

FIGURE 2. TOTAL TB R&D FUNDING, 2005–2012

FIGURE 3. TOTAL TB R&D FUNDING BY DONOR SECTOR, 2012

FIGURE 4. TOTAL TB R&D FUNDING BY DONOR SECTOR, 2005–2012

FIGURE 5. INVESTMENTS IN TB R&D BY RESEARCH CATEGORY, 2005–2012

FIGURE 6. TB R&D INVESTMENTS BY RESEARCH CATEGORY, 2012

FIGURE 7. BASIC SCIENCE: $129,623,072

FIGURE 8. TB DIAGNOSTICS: $42,429,160

FIGURE 9. TB DRUGS: $237,815,172

FIGURE 10. TB VACCINES: $86,558,192

FIGURE 11. OPERATIONAL RESEARCH: $77,128,668

FIGURE 12. TB R&D PDPS AND RESEARCH CONSORTIA, 2005–2012

TABLES

TABLE 1. 2012 TB R&D FUNDERS BY RANK

TABLE 2. 2005–2012 NIH FUNDING FOR SELECT INFECTIOUS DISEASES (IN MILLIONS)

TABLE 3. SUMMARY OF CHANGES IN TB R&D INVESTMENT, 2005–2012

Executive Summary

Over the last eight years, Treatment Action Group (TAG) has tracked annual spending on tuberculosis research and development (TB R&D) and compared investments in six areas of research with the corresponding annual funding targets called for by the Stop TB Partnership's *2011–2015 Global Plan to Stop TB* (*2011–2015 Global Plan*). For the first seven years, TAG observed slow and unsteady increases in funding signaling slow progress toward the new tools needed to end the global TB epidemic. This year, for the first time, TB R&D investors reported a drop in spending that threatens to undermine the tenuous gains made since 2005.

The insufficient year-to-year funding increases observed from 2005 to 2011 have now sputtered and reversed. The *2013 Report on Tuberculosis Research Funding Trends, 2005–2012* shows that funding for TB R&D dropped by $30.4 million in 2012 compared with 2011. With this setback, total spending of $627.4 million on TB R&D in 2012 now sits below the investment levels seen in 2011 and 2010, and pales in comparison with the $2 billion annual funding target outlined in the *2011–2015 Global Plan*.

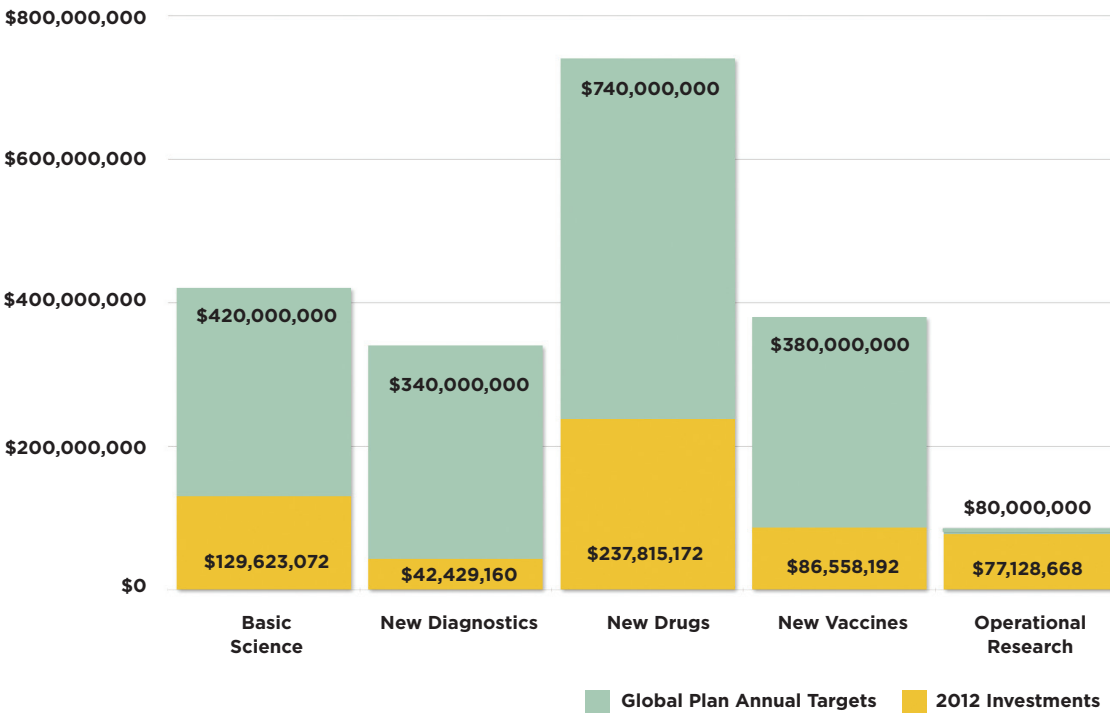
The $30.4 million drop in funding reflects an unprecedented pullback from the private sector, which reduced its investments by 22.1% in 2012 to supply 18% of total TB R&D spending. Some companies, such as Pfizer, withdrew from the TB R&D field entirely, while others, such as Otsuka, decreased their investments in drug discovery programs.

Even more troubling than the $30.4 million decline is that this drop occurred in 2012, before the implementation of sequestration-related funding cuts in the United States, home to many of the world's leading public-sector TB R&D donors. As in previous years, the public sector provided the greatest share of TB R&D funding in 2012, with 61 percent of the global total. Yet the drop in private-sector spending promises to place greater pressure on public institutions just as they become vulnerable to the shortsighted attacks of fiscal austerity measures in the United States and Europe. Philanthropic support, which remained relatively flat in 2012, with 20 percent of the global total, cannot close a gap created by the twin forces of public-sector budgetary woes and private-sector disinvestment.

Figure 1 of this report illustrates the donor community's stark failure to satisfy the funding targets established by the *2011–2015 Global Plan*. With the exception of basic science, where investments increased by 6.5% from 2011 to 2012, the gulf between actual and desired spending is widening in most research categories. Even this modest increase in basic-science funding leaves a gap of $290.4 million measured against the annual target. Diagnostics funding felt the biggest percentage decline, falling 23.4% to $42.4 million in 2012. Investments in diagnostics research will need to increase by $297.6 million in order to meet the *2011–2015 Global Plan* funding target. For the first time since 2005, funding for drug research decreased, falling 6.7% to $237.8 million. This leaves $502.2 million of the $740 million annual target unfunded. Investments in TB vaccines dropped 9.3% to $86.6 million, creating a shortfall of $293.4 million. After exceeding the *2011–2015 Global Plan* target in 2011, funding for operational research dropped back below this level in 2012, with total spending of $77.1 million—$2.9 million shy of the annual target.

FIGURE 1

Annual Global Plan Research Funding Targets versus 2012 Investments



TB R&D continues to suffer from a shallow sense of shared urgency and political will among government and corporate funders in high-, middle-, and low-income countries. In 2012, the top 10 donors disbursed 78% of the global total, and the top two donors—the National Institute of Allergy and Infectious Diseases at the U.S. National Institutes of Health, and the Bill & Melinda Gates Foundation—together accounted for 45% of total spending. Public and philanthropic institutions in the United States and the United Kingdom continue to underwrite the bulk of TB R&D spending. As table 1 of this report shows, the BRICS countries (Brazil, Russia, India, China, and South Africa) remain conspicuously absent from the top 10 donor list and are even underrepresented among the top 30 donors—despite having 40% of the world's notified TB cases and 60% of its estimated MDR-TB cases.

With an overall shortfall of $1.39 billion, TB R&D remains gravely underfunded and now, in the wake of private-sector disinvestment and public-sector fiscal instability, appears to be experiencing a reversal of the timid acceleration of the last seven years. Decreased funding will delay the development, approval, and implementation of the better diagnostic tests, new drug regimens, and more broadly protective vaccines that are urgently needed to fight TB. The pipelines for new TB diagnostics, drugs, and vaccines will remain anemic and subject to halting progress unless donors from all sectors in high-, middle-, and low-income countries recommit to meeting the funding levels required to accelerate TB R&D and ultimately end the global TB epidemic.

TABLE 1

2012 TB R&D Funders by Rank

2012 Rank	FUNDING ORGANIZATION	FUNDER TYPE	TOTAL
1	U.S. National Institute of Allergy and Infectious Diseases (NIAID)	P	$169,092,971
2	Bill & Melinda Gates Foundation (BMGF)	F	$111,601,679
3	Otsuka	C	$60,034,956
4	U.S. Other NIH Institutes and Centers (Other NIH ICs)	P	$36,646,883
5	European Commission (EC)	P	$27,260,036
6	Company X	C	$22,844,099
7	U.S. Centers for Disease Control and Prevention (CDC)	P	$18,481,592
8	U.K. Department for International Development (DFID)	P-D	$16,852,323
9	U.K. Medical Research Council (MRC)	P	$14,790,087
10	Wellcome Trust	F	$13,418,817
11	U.S. Agency for International Development (USAID)	P-D	$12,174,064
12	U.S. National Heart, Lung, and Blood Institute (NHLBI)	P	$11,831,219
13	AstraZeneca	C	$10,303,559
14	India (reported)	P	$8,684,341
15	U.S. President's Emergency Plan for AIDS Relief (PEPFAR)	P	$6,606,609
16	Dutch Ministry of Foreign Affairs Directorate-General of Development Cooperation (DGIS)	P-D	$6,195,582
17	Canadian Institutes of Health Research (CIHR)	P	$6,017,561
18	Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)	M	$6,000,000
19	German Federal Ministry of Education and Research (BMBF)	P	$5,232,441
20	Company Z	C	$5,178,920
21	Company W	C	$4,529,539
22	Company V	C	$4,297,934
23	Institut National de la Santé et de la Recherche Médicale (INSERM)	P	$4,173,870
24	Emergent Biosolutions	C	$4,157,360
25	Australian National Health and Medical Research Council (NHMRC)	P	$4,060,791
26	Sweden (reported)	P	$3,719,138
27	Korea (reported)	P	$3,279,378
28	Max Planck Institute for Infection Biology (MPIIB)	P	$2,950,000
29	Institut Pasteur	P	$2,553,445
30	Agence Nationale de la Recherches sur le Sida et les hépatites virales (ANRS)	P	$2,527,027
31	Carlos III Health Institute	P	$1,814,951
32	World Health Organization (WHO)	M	$1,707,923
33	Canadian International Development Agency (CIDA)	P-D	$1,684,379
34	Health Research Council of New Zealand (HRC)	P	$1,683,781
35	U.S. Food and Drug Administration (FDA)	P	$1,642,584

P = Public-sector R&D agency; C = Corporation/private sector; M = Multilateral; F = Foundation/philanthropy; P-D = Public-sector development agency

TABLE 1

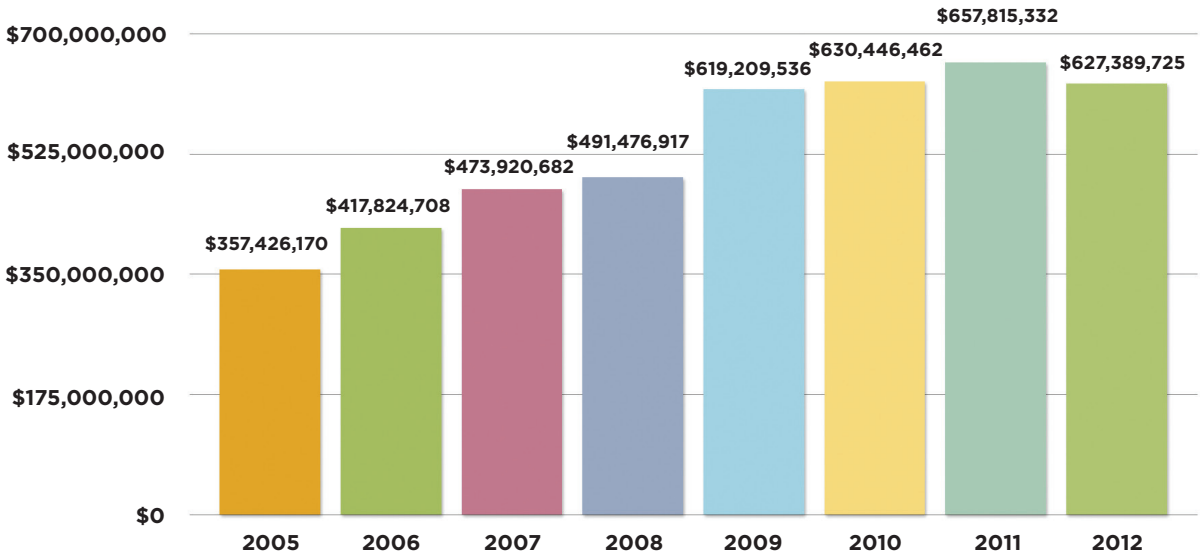
2012 TB R&D Funders by Rank (continued)

2012 Rank	FUNDING ORGANIZATION	FUNDER TYPE	TOTAL
38	Bloomberg Philanthropies	F	$1,500,000
40	Australian Research Council (ARC)	P	$1,412,237
41	Agence Nationale de la Recherche (ANR)	P	$1,385,878
42	Irish Aid	P-D	$1,284,370
43	South African Department of Science and Technology (DST)	P	$1,217,500
44	Swiss National Science Foundation (SNSF)	P	$824,473
45	Sequella	C	$642,350
46	UBS Optimus Foundation	F	$632,262
47	German Research Foundation (DFG)	P	$555,326
48	KNCV Tuberculosis Foundation (KNCV)	F	$499,817
49	Danish International Development Agency (DANIDA)	P-D	$323,250
50	OPEC Fund for International Development (OFID)	M	$279,810
51	Danish National Advanced Technology Foundation	P	$233,863
52	Departamento Administrativo de Ciencia, Tecnología e Innovación (Colciencias)	P	$220,000
53	Danish Council for Independent Research/Medical Sciences	P	$210,469
54	Company Y	C	$196,239
55	BioDuro	C	$180,000
57	Statens Serum Institut (SSI)	P	$153,252
59	Netherlands Organization for Health Research and Development (ZonMw)	P	$140,013
61	Gulbenkian	F	$122,055
62	WHO Stop TB Partnership	M	$112,500
68	GSK Biologicals	C	$63,298
69	Fondation Mérieux	F	$63,298
70	FIT Biotech	C	$63,298
71	Pfizer Laboratories Ltd	C	$56,566
77	Sandoz	C	$30,476
78	GlaxoSmithKline (GSK)	C	$29,123
79	Korea LG Life Sciences	C	$26,100
80	Thrasher Research Fund	F	$21,710
82	AP Møller Foundation	F	$7,663
83	Faber Daeufer Itrato & Cabot	C	$7,500
84	European Centre for Disease Prevention and Control (ECDC)	P	$4,113
85	Corporate Donors to TB Alliance	C	$1,680
	New Funders under $500K		$42,665
	Grand Total		**$627,389,725**

P = Public-sector R&D agency; C = Corporation/private sector; M = Multilateral; F = Foundation/philanthropy; P-D = Public-sector development agency

FIGURE 2

Total TB R&D Funding: 2005–2012



1. Introduction

For the eighth year, Treatment Action Group (TAG) publishes the latest data on global investments in tuberculosis research and development (TB R&D). The *2013 Report on Tuberculosis Research Funding Trends: 2005–2012* presents eight years of funding data to characterize annual investments by the world's leading donors to TB R&D. The report compares current spending in six areas of research with the corresponding R&D funding targets outlined in the Stop TB Partnership's *Global Plan to Stop TB 2011–2015* and shows how these levels of investment have changed over time since 2005, the baseline year. The analysis reveals that in all six research categories, actual spending falls far short of the investments required to develop and introduce new tools to fight TB. This is also the first year since TAG began reporting that the global funding total has decreased compared with the previous year—falling by $30.4 million. The $627.4 million spent on TB R&D in 2012 represents just 31.4% of the recommended $2 billion annual investment.

1.1 Rationale

Mycobacterium tuberculosis (MTB), the bacterium that causes human TB disease, is an old foe whose effect on health humanity has felt for at least 70,000 years, yet whose immunological workings remain scarce in detail.[1,2] The World Health Organization (WHO) estimates that one-third of the world's population is infected with MTB, which, when asymptomatic, is called latent tuberculosis infection (LTBI). Of the over two billion latently infected individuals, 10 percent will develop active disease at some point in their lifetimes. The WHO estimated that in 2011 there were 8.7 million new cases of active TB disease and 1.4 million TB deaths, including 500,000 deaths among women and 430,000 deaths among people with the human immunodeficiency virus (HIV).[3] Despite being preventable, treatable, and curable, TB remains the second leading cause of death from an infectious disease worldwide after HIV.[4]

These numbers of new TB infections and deaths remain stubbornly similar to those reported in 2005, the first year TAG collected comprehensive data on TB R&D spending, when an estimated 8.8 million people developed active TB disease and 1.6 million died.[5] New cases of TB fell at a rate of 2.2% between 2010 and 2011, but even this modest rate of decline masks wide disparities in progress across countries and regions.[6] Across the world, the rise of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) threatens to set back the tenuous progress made in the last decade. Unresponsive to standard first-line therapies, MDR-TB and XDR-TB require at least two years of treatment using highly toxic, often marginally effective drugs, which many patients cannot tolerate. The WHO reported 135,000 cases of MDR-TB among total *notified* TB cases in 2011 and estimated that the actual number of people with MDR-TB may exceed 600,000. According to the WHO, nine percent of new MDR-TB cases may actually be XDR-TB.[7]

Current strategies and tools will not end the epidemic alone; new strategies, better diagnostic tests, new drug regimens, and more broadly protective vaccines are all urgently needed. The technologies employed to prevent, diagnose, and treat TB remain stuck in the twentieth century even as the MTB pathogen itself continues to evolve and develop complex resistance patterns to the existing arsenal of drugs. Bacille Calmette-Guérin (BCG), the only licensed TB vaccine, was introduced in 1921 and offers no reproducible protection against pulmonary TB to adolescents and adults, who account for approximately 85% of MTB transmission and

TB-related morbidity and mortality.[8] The past 40 years witnessed the approval of just one new drug from a novel class—Janssen's bedaquiline—although access to the drug remains limited by slow regulatory approval in countries other than the United States, where the Food and Drug Administration (FDA) approved bedaquiline for the treatment of drug-resistant TB (DR-TB) in December 2012.[9] Despite recent advances in diagnostics, heralded by the introduction of Cepheid's GeneXpert MTB/RIF assay, there is still no point-of-care test capable of diagnosing people with TB and linking them to appropriate care in the timespan of a single clinical encounter.[10]

The clinical pipelines for new diagnostics, drugs, and vaccines each contain promising candidates, but each pipeline faces serious impediments to progress.

- **Diagnostics**: There is an urgent need to develop more rapid molecular tests for identifying drug-resistant strains of MTB; meanwhile, efforts to discover antibody or antigen targets to guide the development of point-of-care tests remain nascent and underfunded.[11]

- **Drugs**: Drug development has not kept pace with the muted optimism following bedaquiline's FDA approval. In July 2013, the European Medicines Agency (EMA) declined to approve the promising DR-TB drug delamanid, developed by Otsuka.[12] Separately, drug sponsor Pfizer closed its anti-infectives research division in 2012[13]—perhaps foreshadowing a fatigue with the TB drug market shared by almost all other major pharmaceutical companies. Few new drug candidates have entered the pipeline even as several existing compounds have lingered in phase I and phase IIa trials for years.

- **Vaccines**: The lack of identified biomarkers that correlate with protective immunity against TB has increased the cost, time, and uncertainty of advancing TB vaccine candidates through the pipeline. An incomplete understanding of host-pathogen interactions and continuing uncertainty about whether animal models—and if so, which ones—correlate with human TB disease also hinder progress.[14]

Our incomplete understanding of how MTB interacts with the human immune system stalls progress in all three of these R&D areas, demonstrating the need for robust investments in basic science. Ultimately, the development of new diagnostics, drugs, and vaccines hinges on political will and adequate funding, both in short supply. Without sufficient funding, promising new tools will languish in the pipeline, and others will never enter it, leaving patients with TB dependent on twentieth-century technologies to fight a disease that has evolved since its initial foray into humans millennia ago to embrace the pathogenic opportunities of a globalizing and urbanizing twenty-first-century society.

1.2 Background

In 2006, the Stop TB Partnership launched the *Global Plan to Stop TB 2006–2015* (the *2006–2015 Global Plan*), a ten-year strategy outlining the implementation and research required to achieve two primary goals: first, halving TB prevalence and deaths compared with 1990 levels by 2015; and second, eliminating TB as a public health threat by 2050. To achieve these objectives, the *2006–2015 Global Plan* called for R&D spending of $890 million per year to develop new diagnostics, drugs, and vaccines.

The Stop TB Partnership updated this strategy in 2010 by issuing the *Global Plan to Stop TB 2011–2015* (the *2011–2015 Global Plan*), which calls for annual R&D spending of $2 billion, or $9.8 billion over five years. The *2011–2015 Global Plan* added investment targets for basic-science and operational research—long advocated for by TAG—while updating the R&D targets for new diagnostics, drugs, and vaccines based on progress since 2006. The investment targets in the *2011–2015 Global Plan* form the basis of the *2013 Report on Tuberculosis Research Funding Trends: 2005–2012* (TB R&D Report).

Since 2006, TAG has tracked annual spending among leading TB R&D funders in order to measure progress against both the *2006–2015 Global Plan* and *2011–2015 Global Plan* spending targets. This year's report includes eight years of data showing year-to-year trends in TB R&D investments starting from the baseline year of 2005. The report serves as the leading reference on TB R&D investments among researchers, activists, civil-society organizations, and policy makers working to end TB.

1.3 Methodology

TAG generated original-source funding data through an electronic survey asking donors to report disbursements in TB R&D made in 2012 in the following six research categories:

- **Basic science**: Undirected, investigator-initiated research aiming to uncover fundamental knowledge about MTB and closely related organisms (e.g., *M. africanum* and *M. bovis* but not other mycobacteria).
- **Diagnostics**: Preclinical or clinical trials of diagnostic technologies and algorithms.
- **Drugs**: Preclinical or clinical research on treatments and treatment strategies for TB disease (including prophylaxis and treatment for both latent and active TB).
- **Vaccines**: Preclinical and clinical research on TB vaccines (including both preventive and immunotherapeutic vaccines).
- **Operational research**: Evaluations of new or existing TB control tools and strategies to guide their effective implementation in program settings. Operational research may include randomized trials, surveillance, and epidemiological and observational studies.
- **Infrastructure/unspecified**: Research specific to TB that the donor is unable to further characterize.

For this report, TAG collected data from 85 of 135 surveyed institutions.[I] Respondents include 39 public or national government institutions; 21 private-sector companies; 12 private foundations or philanthropic institutions; eight product development partnerships and research consortia; and five multilateral institutions. The report includes 11 new donors and one previous TB R&D donor not captured in last year's report. Of the 11 new donors, one invested over

I. Of the 67 organizations that completed the survey, seven reported that they did not fund TB R&D in 2012. Based on data from the 67 survey respondents, TAG uncovered disbursements from a total of 85 organizations.

$1 million in TB R&D in 2012, and the rest each disbursed under $500,000. Despite having made multiple requests, TAG did not receive data from seven institutions that reported in 2011. While TAG strives to collect comprehensive TB R&D investment data, we prioritized collecting data from the top 30 funders in 2011, who together comprised 94.2% of the 2011 TB R&D spending total. For this year's report, we secured data from 28 of the 30 top funders in 2011, yielding a 93 percent response rate from this core sample.

Several large funding bodies—including the U.S. National Institutes of Health (NIH)—did not report their 2012 TB R&D disbursements directly to TAG using our electronic survey. Instead, TAG collated data from these institutions using publicly available online databases.[II] Consistent with previous years, TAG aggregated public-sector funding for India, Korea, and Sweden.

We converted data reported in non-U.S. currency into U.S. dollars using the July 1, 2012, currency exchange rate provided by the OANDA Corporation: http://www.oanda.com/currency/converter. To avoid double-counting, TAG did not include disbursements made by product development partnerships such as Aeras, TB Alliance, or the Foundation for Innovative New Diagnostics (FIND) in total figures as these organizations function as funding recipients rather than original-source donors. All figures represent 2012 disbursements, or the actual transfer of funds made in 2012, rather than commitments or budgetary decisions to provide future funding.

1.4 Limitations

The accuracy of the data presented in this report depends on the percentage of eligible organizations that complete and return the electronic survey as well as the relative size of the reported versus nonreported investments. Organizational restructuring and staffing changes can limit our ability to collect comprehensive data, and staff turnover led to several nonresponses to our survey this year.

Several longtime survey participants did not complete this year's survey, including two top 30 donors from 2011: Company Y and the Government of Japan.

Although Company Y did not submit its data in time for this report, other organizations reported receiving funding from the company in 2012, and those investment amounts are reported here. TAG believes that the reported amounts of $196,239 significantly underestimate Company Y's total spending on TB R&D in 2012. Japanese public institutions, aggregated as "Government of Japan" and ranked 30th in 2011 with disbursements of $3.1 million, did not respond to several requests to complete the survey.

Outside of the top 30, another private company, Eli Lilly, submitted its survey after our database closed. Data from Eli Lilly will be included in the second edition of the report due for online release in March 2014. The National TB Program of the Brazilian Ministry of Health also did not report this year; in 2011, it contributed $291,258 to TB R&D.

The exclusion of these donors may partially account for the $30.4 million drop-in spending from 2011 to 2012, but it cannot explain the overall decline. Eli Lilly and the Brazilian Ministry of Health have not counted among the top 30 donors in reports from previous years, and

---

II. TAG collected NIH grant disbursements from the following website: http://report.nih.gov/categorical_spending_project_listing.aspx?FY=2012&ARRA=N&DCat=Tuberculosis.

Company Y and the Government of Japan together accounted for just under $7 million in 2011, or 1.06% of the global total. Even with their inclusion, we expect the overall picture of funding decline to remain qualitatively unchanged, although the gap might appear narrower.

TAG makes every effort to capture the most up-to-date investments in TB R&D and encourages new and existing donors not captured here to share their data and support the accuracy of this report. Please contact TAG at tbrdtracking@treatmentactiongroup.org if you have information or corrections to share.

1.5 Corrections

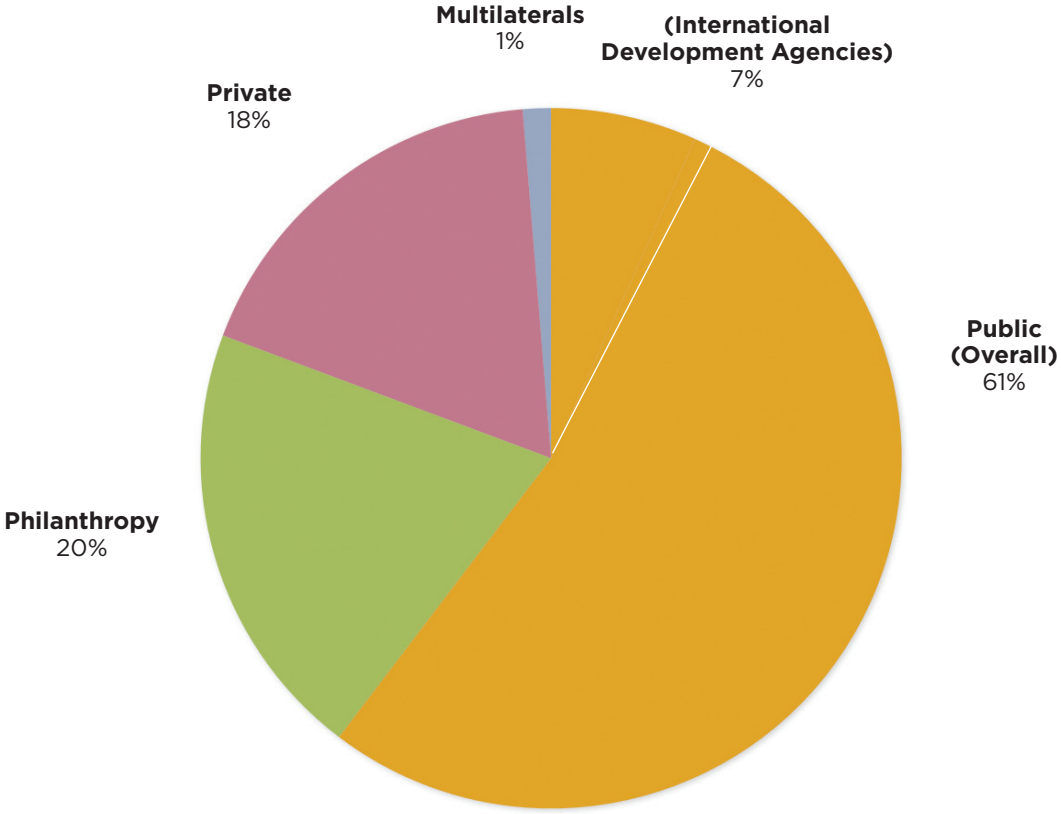
Since publishing the 2012 TB R&D Report, TAG received investment information from three donors who submitted data after that report went to press: the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), Company V and the Health Research Council of New Zealand. The Global Fund and the Health Research Council of New Zealand are previously reporting donors, while Company V is a newly reporting investor. Since receiving information from these sources, TAG updated the 2011 totals, which increased from $649,648,183 to $657,815,332—a 1.26% increase. All comparisons made between the 2011 and 2012 funding levels in this report reflect the corrected 2011 total.

2. Results

2.1 Donor Categories

FIGURE 3

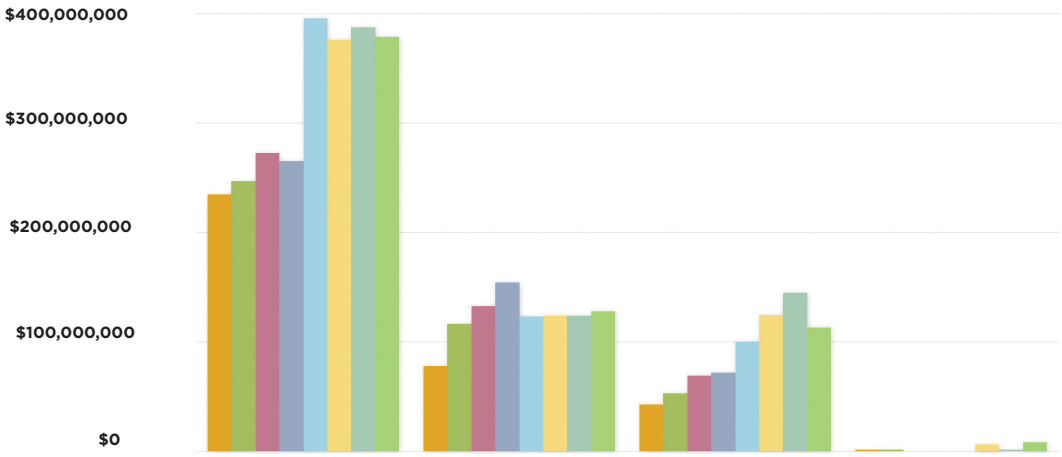
TB R&D Funding by Donor Sector: 2012
Total: $627,389,725



In 2012, 85 donors reported investing $627.4 million to support TB R&D, a 4.63% decrease from the $657.8 million invested in 2011 and a 0.50% decrease compared with funding in 2010. With this setback, total TB R&D investments for 2012 represent just 31.4% of the $2 billion annual funding target established by the *2011–2015 Global Plan*.

FIGURE 4

Total TB R&D Funding by Donor Sector: 2005–2012



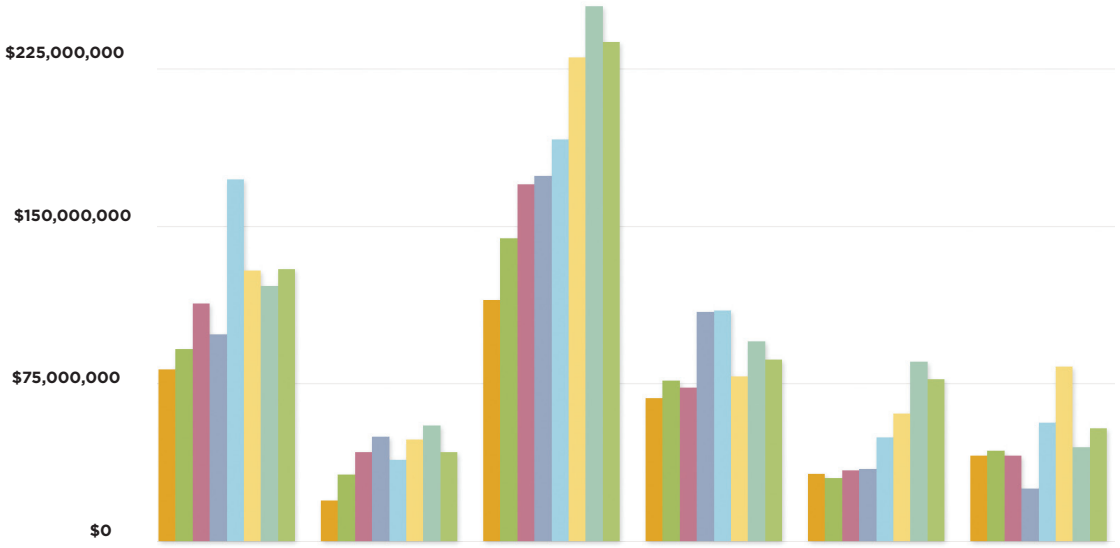
	Public*	Philanthropy	Private	Multilateral
2005	$234,503,645	$78,178,708	$43,095,353	$1,648,083
2006	$246,862,858	$116,289,274	$53,138,347	$1,534,259
2007	$272,404,317	$132,326,981	$69,387,383	NA
2008	$264,944,215	$154,513,987	$72,018,715	NA
2009	$395,326,911	$123,383,703	$99,973,537	$525,385
2010	$376,199,816	$123,974,117	$124,249,938	$6,022,590
2011	$387,307,078	$123,889,768	$144,972,421	$1,646,064
2012	$378,572,425	$127,730,076	$112,927,490	$8,159,734

* Includes funding from international development agencies
NA = Not available

Across research areas, TB R&D continues to rely heavily on ten funders, who in 2012 provided 78% of the global total. The TB R&D funders in this report represent a range of public, private, philanthropic, and multilateral institutions, and funding volumes vary significantly by donor type. Although it decreased slightly from 2011, public sector funding continued to comprise the largest share of the global total at 61%. Within this category, international development agencies supplied 7% of reported funding. The sharpest drop came from the 22.1% decrease in private-sector funding, reversing the gain in private investment observed in 2011. This marks the first year since 2005 that private-sector funding declined and may reflect wavering commitments to TB drug development among major pharmaceutical companies—a shift foretold by Pfizer's decision to close its anti-infectives research division. Philanthropic support grew by 3.1% over 2011 to supply 20% of total R&D spending in 2012. Support from multilateral institutions increased by $6.5 million, although total investments of $8.2 million from this category remain small in comparison to other donor types and comprise just 1% of global spending.

FIGURE 5

Investments in TB R&D by Research Category: 2005–2012

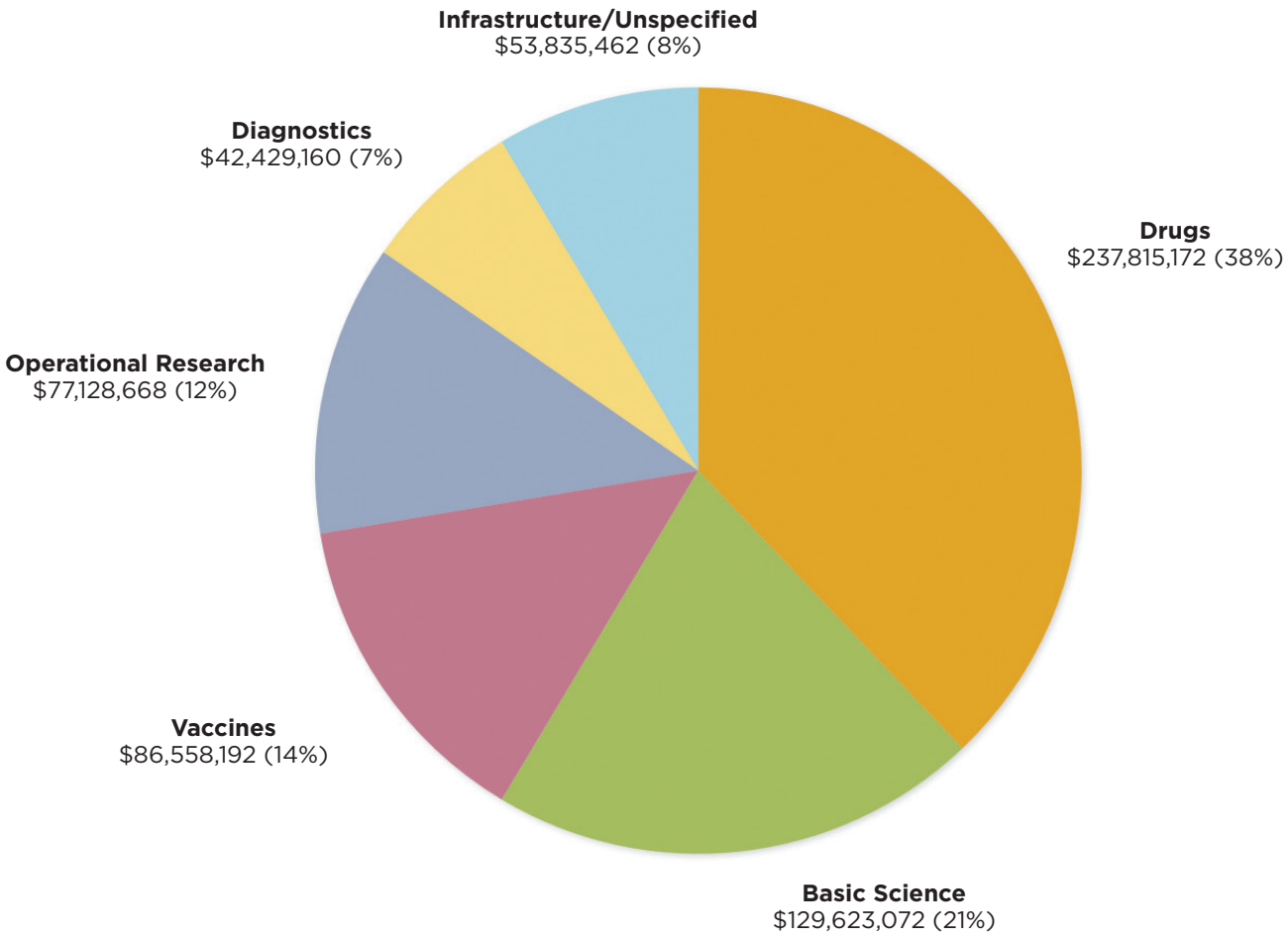


	Basic Science	Diagnostics	Drugs	Vaccines	Operational Research	Infrastructure/ Unspecified
2005	$81,892,167	$19,408,124	$114,862,738	$68,351,530	$32,170,084	$40,741,527
2006	$91,643,009	$31,890,329	$144,336,532	$76,555,111	$30,194,127	$43,205,600
2007	$113,325,202	$42,435,113	$170,233,497	$73,225,383	$33,967,288	$40,734,199
2008	$98,728,019	$49,788,950	$174,178,052	$109,337,224	$34,411,742	$25,032,930
2009	$172,447,841	$38,921,229	$191,483,304	$110,133,485	$49,536,760	$56,686,918
2010	$129,008,413	$48,410,889	$230,540,443	$78,446,298	$60,895,355	$83,145,063
2011	$121,723,565	$55,371,380	$254,842,733	$95,446,326	$85,540,175	$44,891,153
2012	$129,623,072	$42,429,160	$237,815,172	$86,558,192	$77,128,668	$53,835,462

Funding fell in four of six research areas and increased in two: basic science and infrastructure/unspecified. Money spent on infrastructure or unspecified research activities jumped 19.9% from $44.9 million in 2011 to $53.8 million in 2012. Basic-science spending increased by a modest 6.5%, from $121.7 million in 2011 to $129.6 million in 2012. Funding for operational research and for the development of new diagnostics, drugs, and vaccines all contracted. This marks the first year since 2005 that funding for drug research declined, falling 6.7% from $254.8 million in 2011 to $237.8 million in 2012. Diagnostics felt the biggest percentage decline in funding, falling 23.4% from a 2011 high of $55.4 million to $42.4 million in 2012. Investments in vaccines dropped 9.3% from $95.4 million invested in 2011 to a 2012 investment level of $86.6 million—well below the watershed amount of $110.1 million in 2009.

FIGURE 6

TB R&D Investments by Research Category: 2012
Total: $627,389,725



Disbursements in all six research areas fall short of the R&D funding targets outlined by the *2011–2015 Global Plan*. Incremental increases in funding since 2005, sometimes masked by year-to-year fluctuations, have not brought spending close to meeting the investment levels required to accomplish the Stop TB Partnership's TB R&D agenda. The gap between actual and required spending is largest for drug development at $502.2 million, while investments in operational research remain just $2.9 million short of recommended spending. However, this small gap in operational research spending does not merit celebration; in 2011, disbursements supporting operational research actually exceeded the *2011–2015 Global Plan* target, an achievement that funders did not maintain in 2012.

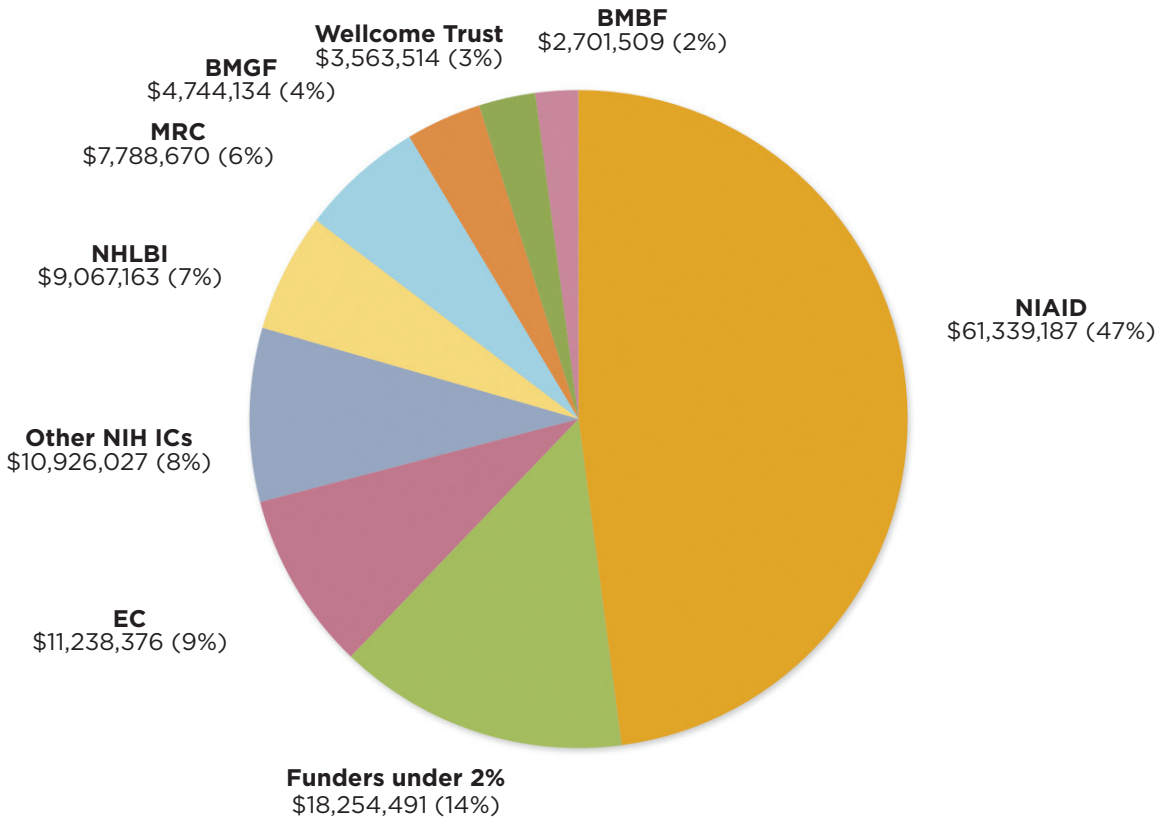
Figure 6 illustrates the proportion of the global total disbursed to each research area in 2012. As in previous years, drug development received the largest share of overall resources with 38%—the same percentage as 2011. Basic science accounted for the second largest percentage with 21%, perhaps owing to the modest increase in funding this category saw from 2011 to 2012. The shares of funding devoted to vaccines and operational research remained relatively stable compared with 2011, at 14% and 12%, respectively. Diagnostics emerged as the least funded research area, with only 7% of the overall total.

2.2 Trends in TB Research by Category

Basic Science

FIGURE 7

Basic Science: $129,623,072



Funders with Investments under 2%

Funder	Amount
CIHR	$2,324,367
Sweden (reported)	$1,993,916
NHMRC	$1,956,176
Institut Pasteur	$1,699,245
MPIIB	$1,450,000
HRC	$1,304,908
India (reported)	$1,235,547
ANR	$1,220,800

Funder	Amount
DST	$1,217,500
INSERM	$1,043,468
SNSF	$824,473
Carlos III Health Institute	$730,367
DFG	$555,326
ANRS	$329,957
ARC	$245,606
Korea (reported)	$122,835

Basic science forms the foundation on which the development of new diagnostics, drugs, and vaccines must build. Research into biomarkers that correlate with protective immunity against TB, serve as surrogate endpoints for TB drug trials, or provide molecular targets for drug susceptibility tests would greatly advance downstream clinical research pathways. A more comprehensive understanding of the immunological life cycle of MTB within the human body, and how this differs from the immunological mechanisms of MTB within animal models, would also advance clinical research efforts.

The *2011–2015 Global Plan* calls for annual investments of $420 million in basic science.[III] In 2012, donors invested a total of $129.6 million in these efforts, leaving a gap of $290.4 million—an amount twice as large as the actual investments. Although this is a significant shortfall, it is the second-highest level of basic-science funding observed since TAG began tracking R&D investments in 2006.

Overall funding for basic science grew by 6.5% from $121.7 million in 2011 to $129.6 million in 2012. The U.S. National Institute of Allergy and Infectious Diseases (NIAID) invested $61.3 million in basic-science research in 2012, or nearly half of the annual total. Almost the entire $7.9 million increase in basic-science spending came from NIAID, which raised its investments in this category by 9.2%, or $5.2 million. One of NIAID's sister institutions within the NIH, the National Heart, Lung, and Blood Institute (NHLBI), and other NIH institutes and centers (other NIH ICs) contributed $9.1 million and $10.9 million, respectively. Collectively, divisions of the NIH contributed 62.7% of total basic-science spending, or $81.3 million. This is the same proportion of the total supported by the NIH in 2011.

While NIAID continues to give the lion's share of financial support for basic science, investments made by the NHLBI and other NIH ICs are slightly surpassed by the $11.2 million contributed by the European Commission (EC; 9% of the total). Other European public institutions, principally the U.K. Medical Research Council (MRC) and the German Federal Ministry of Education and Research (BMBF), also provided considerable support for TB-related scientific research. In 2012, the MRC contributed 6% of the total at $7.8 million and the BMBF gave 2% of the total at $2.7 million.

The Bill & Melinda Gates Foundation (BMGF) led philanthropic investments in basic science, although at a lower level than in 2011. For the BMGF, the $4.7 million invested in 2012 represents a sharp decline from over $10 million invested in 2011, although this may reflect fluctuations resulting from BMGF's practice of not disbursing funding evenly across multi-year awards. The Wellcome Trust, a philanthropic organization based in the United Kingdom, provided $3.6 million in support for basic-science research on TB.

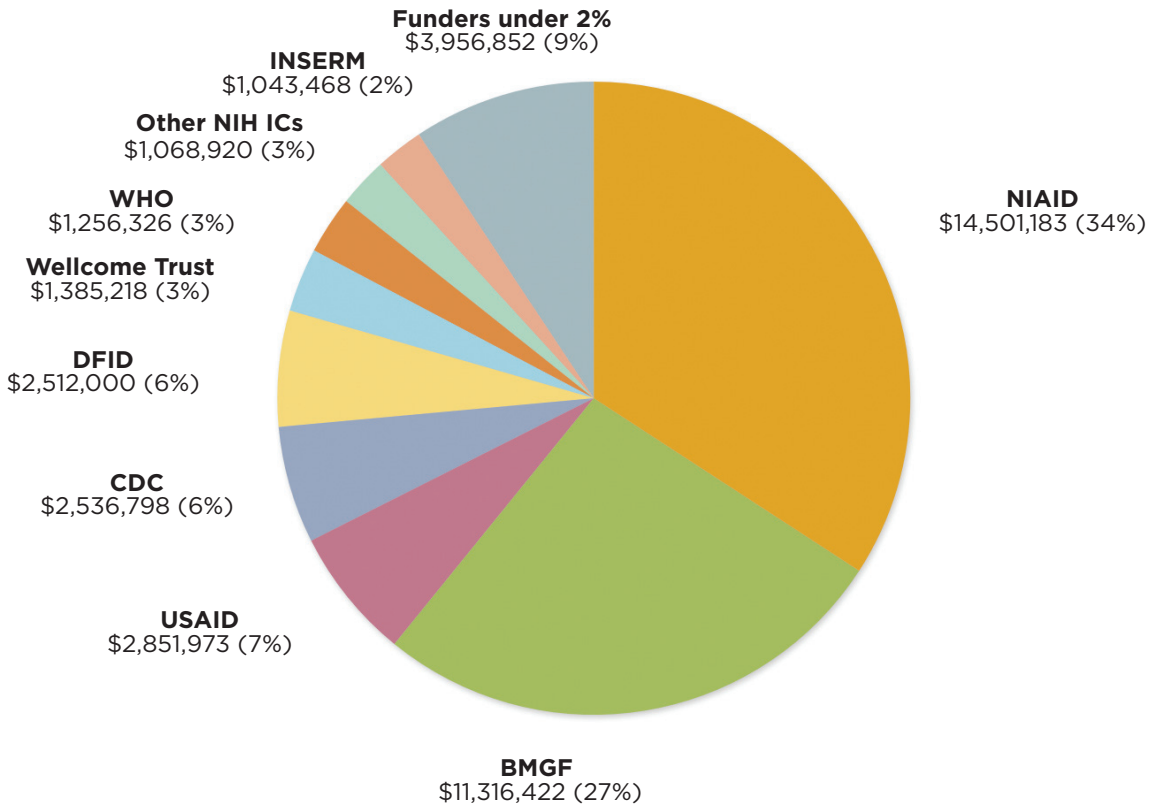
One new effort that did not report to TAG is the KwaZulu-Natal Research Institute on Tuberculosis and HIV (K-RITH), a joint venture of the Howard Hughes Medical Institute (HHMI) and the University of KwaZulu-Natal. Inaugurated in 2012, K-RITH has secured additional support from Germany's Max Planck Institute. HHMI provided several million dollars for K-RITH to build its new research unit in Durban, South Africa.[15] K-RITH primarily pursues investigator-driven basic science, but some of its research has application in diagnostic, drug, and vaccine development. TAG hopes to better quantify K-RITH's contribution to TB R&D in the second edition of this report, scheduled for release online in March 2014.

III The Stop TB Partnership and World Health Organization use the term "foundational science" to refer to "basic science."

TB Diagnostics

FIGURE 8

TB Diagnostics: $42,429,160



Funders with Investments under 2%

Funder	Amount
NHLBI	$740,071
DGIS	$608,744
BMBF	$412,509
UBS Optimus Foundation	$316,131
Korea (reported)	$247,950
NHMRC	$224,424
Company X	$210,000
Company Y	$195,000

Funder	Amount
Sweden (reported)	$187,681
ANRS	$163,894
HRC	$158,561
Institut Pasteur	$151,819
New funders under $500K	$148,985
ZonMw	$140,013
Thrasher Research Fund	$21,710
Otsuka	$16,570
MRC	$12,789

Despite the introduction of the GeneXpert MTB/RIF test and the advancement of "fast-follower" molecular diagnostic tests in its wake, there is still no point-of-care test capable of diagnosing TB disease and identifying drug resistance in the span of a single clinical encounter. With more than 50 companies and test developers working on TB diagnostics,[16] the R&D landscape appears more fragmented than other research areas.

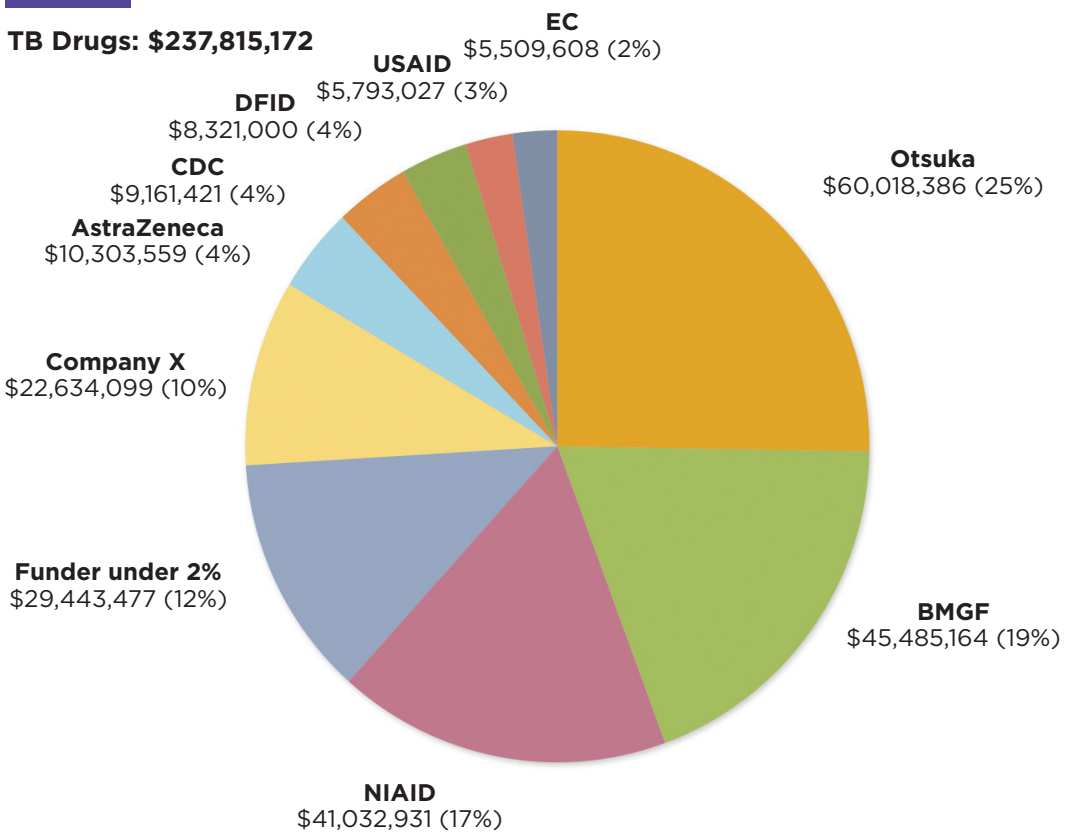
In 2012, donors invested $42.4 million in TB diagnostics research—a 23.4% decline from 2011 and the biggest percentage drop among research areas over the past year. With investments of $14.5 million, NIAID reclaimed the mantle of the largest diagnostics funder from the BMGF, which decreased its support from $13 million to $11.3 million in 2012. Together, NIAID and the BMGF contributed 61% of total spending for new TB diagnostics, with the remainder coming from international development agencies (U. S. Agency for International Development [USAID] and the U.K. Department for International Development [DFID]), normative health institutions (the WHO and the U.S. Centers for Disease Control and Prevention [CDC]), private foundations (Wellcome Trust), and a collection of private companies each with smaller investments under 2% of the total.

The total spending of $42.4 million on TB diagnostics represents just 12.5% of the $340 million annual investment outlined in the *2011–2015 Global Plan*. This abject failure to support diagnostics research at even a fraction of the required level has created a funding gap of $297.6 million and ensures that progress toward a true point-of-care test will remain slow and inconsistent.

Meanwhile, the marketplace for current TB diagnostics remains beset with the limitations of available technologies. The rollout of the GeneXpert MTB/RIF assay has suffered from the high cost of the cartridges and machines, limited in-country laboratory capacities, the machine's dependency on a stable supply of electricity, and impractical annual maintenance requirements. Manufacturers of interferon-gamma release assay (IGRA) tests have taken advantage of the confusing diagnostics landscape in some countries, most notably India, to market their tests under false claims that they can diagnose active TB disease.[17,18] Introduction of Alere's TB LAM test could create similar confusion among TB programs if not marketed carefully. The test performs best when diagnosing TB disease in people with HIV with CD4 T-cell counts less than 100 cells/mm^3—a boon for settings with high TB/HIV coinfection but less applicable to more general TB epidemics.[19]

TB Drugs

FIGURE 9



Funders with Investments under 2%

Funder	Amount
Company W	$4,529,539
Company V	$4,297,934
Other NIH ICs	$4,237,808
MRC	$2,534,051
CIHR	$2,094,966
ANRS	$1,850,788
Wellcome Trust	$1,546,996
FDA	$1,343,059
Irish Aid	$1,284,370
NHMRC	$1,071,099
INSERM	$1,043,468
Sequella	$642,350
ARC	$573,082
BMBF	$480,523

Funder	Amount
Institut Pasteur	$446,796
Carlos III Health Institute	$326,568
DGIS	$315,139
BioDuro	$180,000
NHLBI	$167,729
ANR	$165,079
Colciencias	$150,000
India (reported)	$47,904
Sweden (reported)	$43,311
Sandoz	$30,476
Korea (reported)	$27,150
Faber Daeufer Itrato & Cabot	$7,500
ECDC	$4,113
Corporate Donors to TB Alliance	$1,680

The year 2012 witnessed a major milestone in TB R&D: the first stringent regulatory authority approval of a new TB drug from a novel class in over 40 years. In December 2012, the FDA granted accelerated approval to Janssen's bedaquiline for the treatment of DR-TB. Unfortunately, the EMA issued the opposite ruling on Otsuka's new drug delamanid seven months later, declining to approve delamanid for DR-TB treatment in July 2013.

These historical decision points in TB drug development were not enough to increase or even sustain funding. Contrary to expectation, spending on TB drug R&D fell by 6.7% in 2012 to $237.8 million. Otsuka maintained its lead position among funders of TB drug research with investments of $60 million, a quarter of the global total. Bucking the overall trend, the BMGF increased funding for drug development by $20.2 million compared with 2011, jumping ahead of NIAID and Company X to become the second largest donor. NIAID increased its funding for drug research by $5.4 million, to supply 17% of the total. Company X moved in the opposite direction, cutting its financing by $8.2 million.

This paradoxical drop-in drug spending at a moment of unprecedented promise reflects disinvestment by the pharmaceutical industry. Pfizer, which contributed $6.3 million to TB drug research in 2011, recently announced the closure of its anti-infectives research division as the company reorients its efforts toward developing prophylactic vaccines.[20] Consequently, Pfizer reported zero investment in TB R&D in 2012. It sold its drug candidate sutezolid to Sequella,[21] a private biotech company that lacks the financial resources to launch the large medium-to-late-stage clinical trials required to move sutezolid beyond phase IIa and position it for regulatory review. Other pharmaceutical companies show few signs of intensifying their efforts in this area. AstraZeneca decreased funding for its candidate drug, AZD5847, by nearly $3 million between 2011 and 2012. The company has now taken over two years to complete a single phase IIa early bactericidal activity trial of AZD5847.[22]

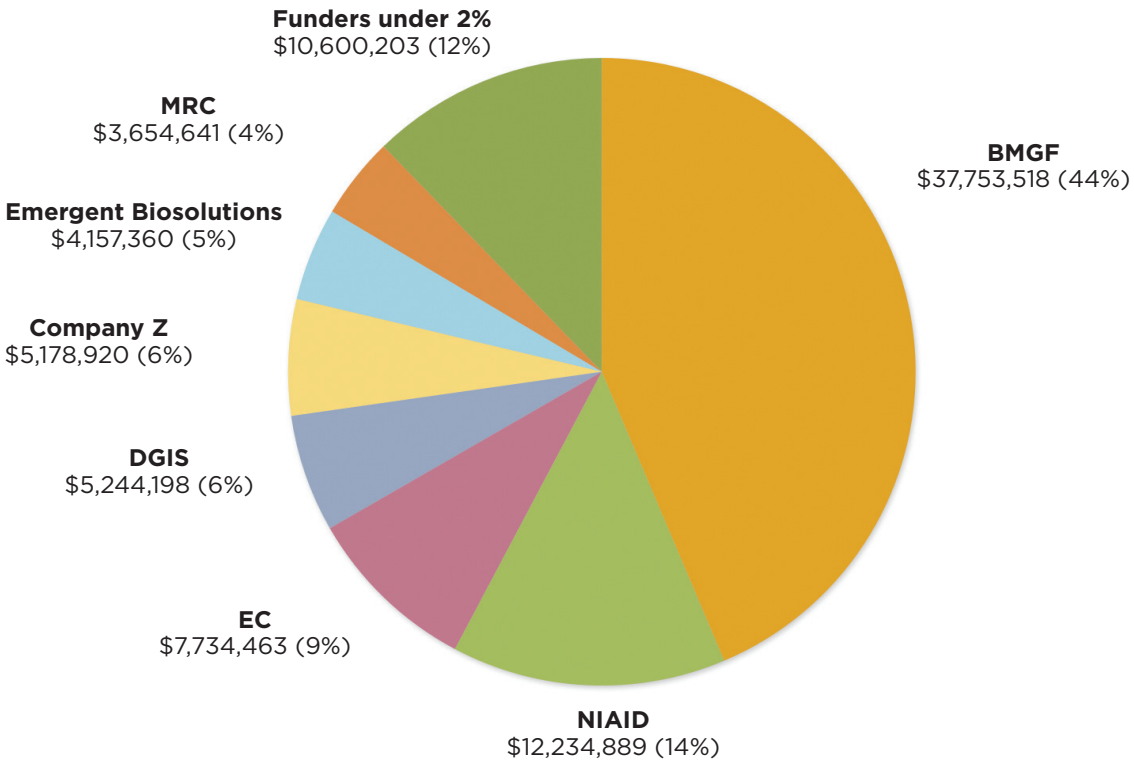
Lethargic private-sector investments in TB drug development mirror a much broader depletion of anti-infectives research among pharmaceutical companies. The Infectious Diseases Society of America and the WHO have both called attention to near-empty clinical pipelines for new antimicrobial agents with novel mechanisms of action.[23,24] Approvals of new antibacterial compounds by the FDA have dropped from 16 during 1983–87 to fewer than six between 2003 and 2007.[25] With just one new drug approval in the last four decades, TB faces even greater urgency to respond to growing drug resistance—a response that will be difficult to mount if more companies follow Pfizer's departure from the field.

TB drug development continues to receive more funding than any other research area, but it still falls $502.2 million short of reaching the *2011–2015 Global Plan*'s target of $740 million in annual spending. The excitement over the approval and near-approval of bedaquiline and delamanid, respectively, belies a barren early-stage clinical pipeline and halting progress among several candidates that have languished in phase I and IIa studies for years. TB drug development will continue to inch forward at a whisper of its potential speed as long as donors support barely a third of the investment called for by the Stop TB Partnership.

TB Vaccines

FIGURE 10

TB Vaccines: $86,558,192



Funders with Investments under 2%

Funder	Amount
DFID	$1,519,152
MPIIB	$1,500,00
BMBF	$1,329,258
INSERM	$1,043,468
Other NIH ICs	$657,365
CIHR	$550,109
Korea (reported)	$499,641
Wellcome Trust	$483,427
New funder under $500K	$475,828
NHLBI	$378,750
Carlos III Health Institute	$325,050
FDA	$299,525
Institut Pasteur	$255,585

Funder	Amount
Danish National Advanced Technology Foundation	$233,863
Danish Council for Independent Research/Medical Sciences	$210,469
Sweden (reported)	$194,900
SSI	$153,252
Gulbenkian	$122,055
WHO	$85,260
FIT Biotech	$63,298
Fondation Mérieux	$63,298
GSK Biologicals	$63,298
Pfizer Laboratories Ltd	$56,566
GSK	$29,123
AP Møller Foundation	$7,663

Declines in funding also hit the search for new TB vaccines designed to either replace or boost BCG. Investments in TB vaccines fell 9.3% to $86.6 million in 2012, $23.6 million less than the high point of $110.1 million reached in 2009. This leaves 77.2% of the *2011–2015 Global* Plan target for TB vaccines unfunded—a gap of $293.4 million. In other words, the funding gap for TB vaccines is over three times greater than actual spending.

This drop-in funding comes at a pivotal moment for TB vaccine research; the year 2012 marked many firsts for TB vaccine R&D, and not all were positive. Disappointing results from the first phase II efficacy trial of a TB vaccine in over 45 years dimmed the prospects of the leading TB vaccine candidate: MVA85A. Results from the trial indicated that MVA85A did not afford infants significant added protection against pulmonary TB when given as a boost to BCG.[26] An early look at immunogenicity data from a phase II trial of another advanced candidate, Crucell Ad35/Aeras-402, led investigators to dramatically reduce the size of the trial.[27] Despite these setbacks, the field continued to advance scientifically, with the first vaccine built using live, genetically attenuated MTB entering into clinical trials and with the initiation of the first trial to combine two novel TB vaccine candidates.[28]

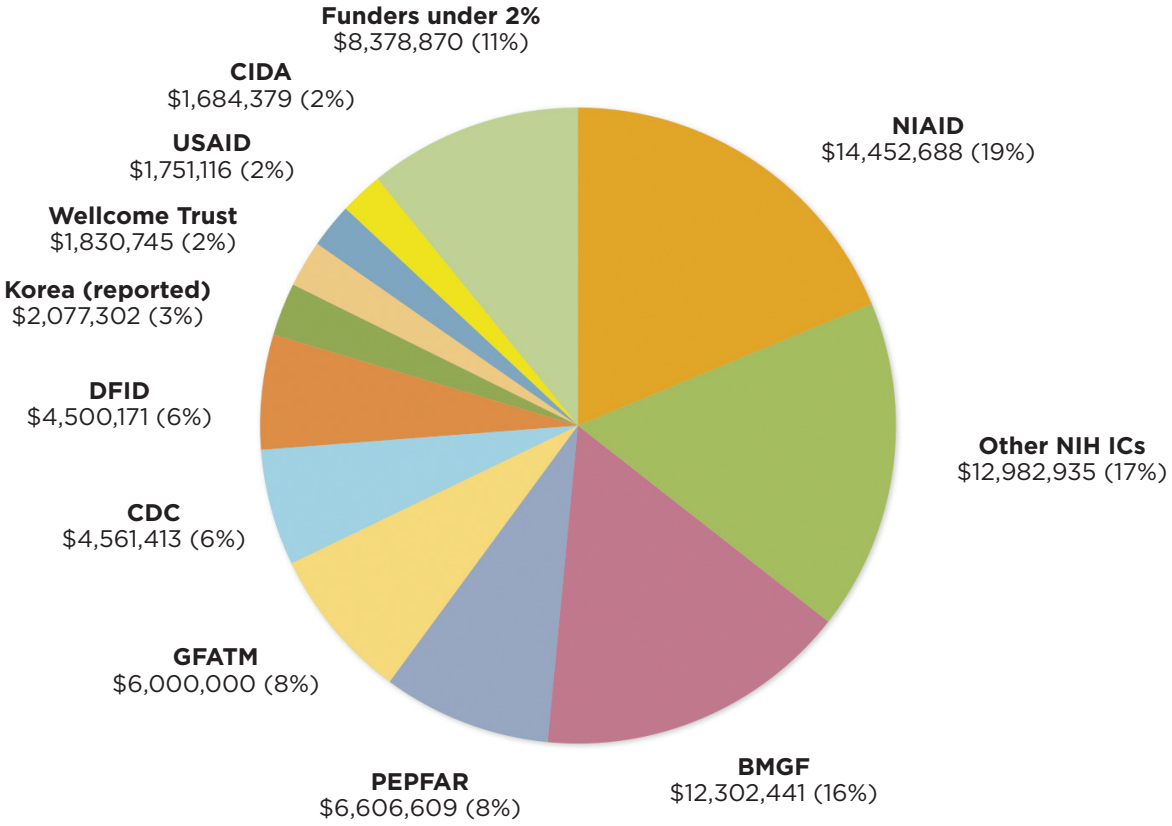
The BMGF remained the largest donor supporting the search for new TB vaccines, with 2012 contributions of $37.8 million, followed by NIAID with $12.2 million. Together, the BMGF and NIAID provided 58% of total 2012 support for TB vaccine research. The majority of BMGF support in this area went to product development partnerships (PDPs), including Aeras, a PDP based in Rockville, Maryland, which received $35.5 million from the BMGF in 2012, and the Tuberculosis Vaccines Initiative (TBVI), a PDP based in Lelystad, the Netherlands, which received $1.3 million. The EC and the European Union Directorate-General for International Cooperation followed in the third and fourth positions with 9% and 6% of the annual total, respectively.

Compared with other research areas, TB vaccine R&D has enjoyed less support from the private sector—a trend that shows no signs of reversing. In the wake of the MVA85A trial results, one private company, Emergent BioSolutions, announced its exit from the field. With an investment of $4.2 million, Emergent BioSolutions represents 5% of the TB vaccine R&D total for 2012; its departure will be seen in next year's TB R&D report. Oxford Emergent Tuberculosis Consortium, a PDP wholly supported by funding from Emergent BioSolutions and established to support the development of MVA85A, will feel this loss most acutely.

Operational Research

FIGURE 11

Operational Research: $77,128,668



Funders with Investments under 2%

Funder	Amount
Bloomberg Philanthropies	$1,500,000
Sweden (reported)	$1,227,145
CIHR	$966,231
NHLBI	$878,508
NHMRC	$809,092
MRC	$799,935
KNCV	$499,817
Carlos III Health Institute	$432,966

Funder	Amount
WHO	$366,337
DANIDA	$323,250
OFID	$279,810
New funder under $500K	$162,375
Colciencias	$70,000
India (reported)	$34,663
DGIS	$27,501
Company Y	$1,239

Where the clinical pipeline ends, operational research begins. When the pipelines for TB diagnostics, drugs, and vaccines produce new tools, operational research connects science to people by investigating the best ways to apply and scale these technologies in programmatic settings.

In 2011, spending in operational research exceeded the *2011–2015 Global Plan* target of $80 million per year—the first time that actual spending in any category of research met or exceeded global targets. This achievement, however, did not last: in 2012, funding in operational research fell 9.8% from $85.5 million to $77.1 million. Despite this decline, 96.4% of the operational research agenda remains funded, leaving a gap of just $2.9 million.

Much of the decline in operational research spending reflects sharply reduced support from USAID, which provided $9.0 million to this area in 2011 but less than $1.8 million in 2012. The BMGF also cut its investments in operational research in half, moving from $25.3 million in 2011 to $12.3 million in 2012—probably due in part to the end of the Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE). Against this backdrop of decline, NIAID and other NIH ICs emerged as the first- and second-largest donors to TB operational research, respectively contributing 19% ($14.5 million) and 17% ($12.9 million) of the yearly total.

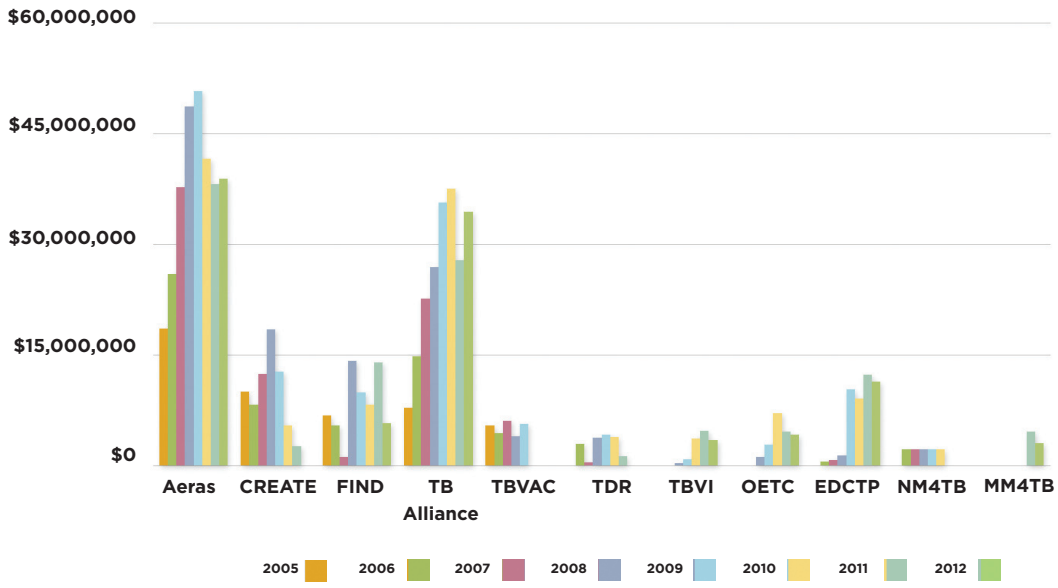
The Global Fund and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) remained key supporters of operational research, each contributing around 8% of the total.

Japan, traditionally a strong supporter of operational research, failed to return any data to TAG this year. In 2011, Japanese public institutions gave just over $2 million to TB-related operational research. It is possible that unreported Japanese support for operational research could close the funding gap in this area. However, the drop-in operational research spending primarily reflects dramatic drawbacks from several leading donors in this category, including USAID and the BMGF.

2.3 Product Development Partnerships and Research Consortia

FIGURE 12

TB R&D PDPs and Research Consortia: 2005–2012



	Aeras	CREATE	FIND	TB Alliance	TBVAC	TDR	TBVI	OETC	EDCTP	NM4TB	MM4TB
	$18,580,139	$10,000,000	$6,778,239	$7,874,983	$5,445,450	N/A	N/A	N/A	N/A	N/A	N/A
	$25,923,809	$8,298,826	$5,492,942	$14,808,362	$4,451,895	$2,995,748	N/A	N/A	$580,039	$2,214,000	N/A
	$37,704,051	$12,375,000	$1,145,409	$22,624,182	$6,091,335	$453,382	N/A	N/A	$805,625	$2,214,000	N/A
	$48,679,266	$18,493,585	$14,177,202	$26,885,734	$3,944,425	$3,817,352	$339,741	$1,196,000	$1,416,064	$2,214,000	N/A
	$50,792,515	$12,786,985	$9,975,320	$35,643,490	$5,634,040	$4,243,264	$841,333	$2,851,000	$10,343,479	$2,214,000	N/A
	$41,572,980	$5,410,545	$8,212,896	$37,538,794	Concluded	$3,900,000	$3,700,914	$7,142,159	$9,081,799	$2,214,000	N/A
	$38,166,117	$2,657,411	$13,938,587	$27,824,033	Concluded	$1,315,700	$4,731,422	$4,568,160	$12,313,115	Concluded	$4,644,099
	$38,904,315	Concluded	$5,726,157	$34,388,929	Concluded	NA	$3,434,338	$4,157,360	$11,393,907	Concluded	$3,086,837

TDR = WHO Special Programme for Research and Training in Tropical Diseases; OETC = Oxford-Emergent Tuberculosis Consortium; NM4TB = New Medicines for Tuberculosis
N/A = Not applicable; NA = Not available

As TB is a disease that disproportionately affects poor and marginalized people in low- and middle-income countries, TB R&D has long depended on PDPs to spearhead research for new diagnostics, drugs, and vaccines. Built on a nonprofit business model, PDPs combine resources from public, private, philanthropic, and academic partners to address diseases of high global importance but low commercial interest. Since PDPs function as funding recipients rather than original-source donors, TAG tracks their disbursements separately from the global total to avoid double counting.

In 2012, eight PDPs reported disbursing $101.1 million to support TB R&D, an 8.2% decline over 2011 levels. Part of this decrease may reflect the conclusion of certain PDP efforts such as the CREATE project, which disbursed $70 million from 2005 to 2011 to develop new public health strategies to reduce the incidence of TB in areas of high HIV prevalence. However, given that CREATE disbursed just $2.7 million in 2011, its closure does not account for the entire drop-in spending among PDPs globally.

Among PDPs, Aeras reported the largest disbursement, with $38.9 million to support TB vaccine research, followed by the TB Alliance, with $34.4 million for TB drug development. This represents stable disbursements by Aeras and a 23.6% increase for the TB Alliance. Smaller PDP initiatives reported disbursements ranging from $3.4 million (TBVI) to $11.4 million (the European and Developing Countries Clinical Trials Partnership (EDCTP)). The More Medicines for TB (MM4TB) project, supported under the EC Seventh Framework Programme, disbursed just over $3 million under its five-year project to support TB drug development.

PDPs continue to play an outsized role in TB vaccine R&D compared with other research areas. The vaccine candidates supported by either Aeras or TBVI constitute almost the entire clinical pipeline. While PDPs also make major contributions in other research areas—most notably, the TB Alliance in drug development and FIND in TB diagnostics research—the proportion of overall funding disbursed by PDPs appears highest in TB vaccine development. With a combined $42.4 million, Aeras and TBVI disbursed 49% of total monies spent on TB vaccine R&D in 2011.

2.4 Top 10 Funders of TB R&D in 2012

The top 10 donors spent $491,023,443, or 78% of the total $627,389,725 invested in TB R&D in 2012. Two organizations—NIAID and the BMGF—each spent over $100 million and together comprise 45% of the global total. Three U.S. government institutions appear among the top 10: NIAID, other NIH ICs, and the CDC. The United Kingdom also has three top 10 donors—one philanthropic institution (the Wellcome Trust) and two bodies of the U.K. government (the MRC and the U.K. Department for International Development). Two pharmaceutical companies in the top 10—Otsuka and Company X invested a combined $82.9 million. For the first time since TAG began reporting, USAID falls outside the top 10 donors.

Table 2

2005–2012 NIH Funding for Select Infectious Diseases (in Millions)

	2005	2006	2007	2008	2009*	2010*	2011	2012
HIV/AIDS	$2,921	$2,902	$2,906	$2,928	$3,338	$3,407	$3,059	$3,074
Smallpox	$187	$149	$142	$94	$98	$97	$41	$40
Anthrax	$183	$150	$160	$134	$115	$130	$87	$84
Tuberculosis	$158	$150	$188	$142	$216	$224	$209	$218
Malaria	$104	$98	$112	$142	$121	$148	$145	$152

* Includes ARRA stimulus funds

National Institutes of Health (U.S.). Estimates of funding for various research, condition, and disease categories. Available from: http://report.nih.gov/categorical_spending.aspx. (Accessed 2 October 2013)

1. The U.S. National Institute of Allergy and Infectious Diseases (NIAID)

The expiration of stimulus funding through the American Recovery and Reinvestment Act (ARRA) at the end of 2010 and the threat of federally mandated cuts under sequestration in 2013 serve as bookends for NIH investments in TB R&D in 2012. Despite a challenging fiscal climate, NIAID increased its investments from $157.6 to $169.1 million from 2011 to 2012. The $169.1 million estimate likely undercounts true NIAID spending on TB R&D, as it does not include TB research activities carried out by the AIDS Clinical Trials Group (ACTG) and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) network. For example, the ACTG and the IMPAACT network are evaluating rifapentine and isoniazid in a super-short-course treatment regimen for LTBI among people with HIV.[29] To enable more accurate reporting, TAG urges NIAID to work with disease-categorization specialists at the NIH to capture and quantify cross-network and cross-disease collaborative activities that contribute to TB R&D.

NIAID issued 482 awards to support TB-related research in 2012. With the exception of TB vaccines, NIAID spending increased across all research areas. As in previous years, NIAID committed the majority of its support to basic science, with $61.3 million in funding, a 9.2% increase. Funding for operational research and spending on infrastructure or unspecified projects each increased by around 25%, while spending on diagnostics and drugs increased by approximately 15% each. NIAID funding for TB vaccines declined by a staggering 41.6%, falling from $20.9 million in 2011 to $12.2 million in 2012. Vaccine development emerged as the least-funded research category under NIAID grant making for 2012.

Although increased over that in 2011, NIAID spending in 2012 still falls short of the watermark $224 million invested in 2010 at the peak of support from the ARRA stimulus package. NIAID has maintained robust investments in TB R&D in the wake of stimulus depletion, but federally mandated across-the-board budget reductions under sequestration threaten to stall progress for years. Sequestration will force the NIH to cut 5% ($1.55 billion) of its budget in fiscal year 2013; the cuts will apply evenly across all NIH institutes and centers.[30] Elias Zerhouni,

director of the NIH in 2002–2008, has warned that sequestration could set back medical science for a generation by making it more difficult for young scientists to establish research programs.[31] In a field that has struggled to attract scientific attention and talent for decades, sequestration-related cuts could eliminate critical opportunities for young investigators to build their scientific careers in TB R&D.

2. The Bill & Melinda Gates Foundation (BMGF)

In 2012, the BMGF invested $111.6 million in TB R&D, a slight 0.7% decrease from 2011. The BMGF did not display the same wavering commitment to TB drug development seen among pharmaceutical companies. In 2012, the BMGF increased funding for TB drug development by 79.6%, investing a total of $45.5 million in this category. Support for TB vaccine R&D remained steady at $37.7 million, while funding for diagnostics, basic science, and operational research declined by 13.3%, 54.6%, and 51.4%, respectively. The BMGF practice of not distributing money equally across multiyear awards may underlie some of these fluctuations.

While total funding from NIAID exceeds disbursements by the BMGF, the foundation remains the single largest contributor to TB vaccine development, and in 2012 it invested slightly more than NIAID in drug development. The BMGF's 2011–2016 strategy emphasizes the development of a new TB vaccine as the most direct path for decreasing TB incidence. The development of shorter, simpler treatment regimens is another focus area of the foundation's R&D investments.

Consistent with these priorities, the BMGF made significant contributions to PDPs, giving $35.5 million to Aeras for vaccine development and $32.8 million to the TB Alliance for the development of new drug regimens.

3. Otsuka

Otsuka is a Japanese pharmaceutical company developing the new MDR-TB drug delamanid (OPC-67683). Unlike Janssen's bedaquiline, delamanid has not yet received regulatory approval, but it is the most advanced new TB drug in terms of progression through the clinical pipeline. Enrollment for a phase III trial of delamanid began in 2012, with results expected by 2015.[32] According to its survey response to TAG, Otsuka also initiated a pediatric investigation program for delamanid that will culminate in an open-label trial evaluating the safety and pharmacokinetics of a pediatric formulation by 2017.

Despite the advanced stage of clinical trials for delamanid, Otsuka's first foray into the regulatory landscape did not turn out favorably. In July 2013, the Committee for Medicinal Products for Human Use (CHMP) of the EMA declined to approve delamanid for the treatment of MDR-TB, citing the short (two-month) duration of treatment with delamanid in Otsuka's phase IIb randomized controlled trial.[33] The CHMP also took issue with the open-label (nonrandomized) design of a second phase II trial showing that patients receiving delamanid over a background regimen of other MDR-TB drugs had a greater chance of survival than patients not taking delamanid.[34]

In 2012, Otsuka invested $60 million to support clinical trials and regulatory filings for delamanid, a 7.8% decrease over the previous year. Otsuka continues to lead investments among private-sector companies and remains the third largest funder to TB R&D globally. Still, the 7.8% drop-in funding seems perplexing for a company with a drug poised for approval before

two stringent regulatory authorities (the EMA and the Japan Pharmaceuticals and Medical Devices Agency), working to complete a phase III study, and preparing for future phase IV studies and smaller trials among special populations such as people who use drugs, children, and pregnant women.

4. Other U.S. NIH Institutes and Centers (Other NIH ICs)

The NIH includes 27 different research centers and institutes. Since 2006, TAG has tracked TB R&D research investments across three NIH institutional categories: NIAID, NHLBI, and other NIH ICs, which represent the remaining 25 research centers and institutes.

Other NIH ICs invested $36.6 million in TB R&D in 2012, an 8.9% drop from 2011. Despite this decrease, other NIH ICs collectively remained the fourth largest donor to TB R&D globally. Funding from other NIH ICs declined most precipitously for vaccines, which experienced a 60.6% drop equal to just over $1 million. Funding also decreased by half for drugs and by nearly a quarter for diagnostics. The other three research categories—basic science, operational research, and infrastructure/unspecified—all saw increases in funding. The sequestration cuts threatening NIAID also jeopardize the ability of other NIH ICs to remain leading supporters of TB R&D.

5. The European Commission (EC)

Several funding schemes under the EC support global health research: the Sixth and Seventh Framework Programmes, the Directorate-General Research and Innovation Division, and the European Research Council. In 2012, the EC invested $27.3 million in TB R&D, a 3.6% decrease over the previous year. Funding from the EC pivoted toward basic science in 2012, as illustrated by a 52% increase in this category for a total investment of $11.2 million. In contrast to the case in 2011, in 2012 the EC made no disbursements supporting diagnostics and decreased its spending on drugs by 22.2%. EC support for vaccine science held steady at just over $7.7 million. The EC reports that its activities place a special emphasis on new tools to address MDR-TB.

The initiation of Horizon 2020—a financing mechanism to spur research and innovation within Europe from 2014 to 2020—will hold major implications for the role of the EC in TB R&D. Horizon 2020 will combine all of the research funding currently parceled under different Framework Programmes for Innovation and Technical Development into a single funding instrument with an estimated budget of $88.6 billion. Approximately 10% of the Horizon 2020 budget will support health research, although the exact proportion of funds that will go toward TB research remains unclear.[35]

Horizon 2020 will also include renewed funding of $864.7 million for the EDCTP, with disbursements stretching from 2014 to 2024. The EDCTP supports phase II–IV clinical trials of new drugs, vaccines, microbicides, and diagnostics in sub-Saharan Africa while building research capacity and strengthening clinical trials infrastructure among partner countries. The second iteration of the EDCTP will maintain the original focus on HIV, TB, and malaria while also funding research on other "poverty-related diseases," particularly those that often present as coinfections with the core three.[36]

6. Company X

Company X is a pharmaceutical company that invested $22.8 million in TB drug development in 2012—a 26.7% decrease from 2011 levels. This decrease was large enough to drop Company X out of the top five donors.

7. The U.S. Centers for Disease Control and Prevention (CDC)

After narrowly making the top 10 list in 2011, the CDC climbed several spots in the 2012 rankings due to a 32.9% investment increase equal to $4.7 million. This increase restored CDC funding to just under the position it held before 2011, the year when an unprecedented funding decline of 29% dropped CDC disbursements to a record low of $14.2 million.

In total, the CDC spent $18.8 million on TB R&D in 2012, with most funds channeled through the research arm of the CDC Department of Tuberculosis Elimination (DTBE). The DTBE supports drug development through its flagship clinical trials network, the Tuberculosis Trials Consortium (TBTC), where it invested $9.2 million in 2012. Still, this remains under the peak of $10.4 million the DTBE spent on TB drug development in 2008. A second DTBE research network, the TB Epidemiological Studies Consortium (TBESC), received funds for an operational research project to determine the rate of progression from LTBI to active TB disease using IGRA diagnostic technologies (a use for which IGRAs do not work).

Although the 32.9% investment increase seems encouraging, fiscal austerity measures coupled with ongoing federal budget instability in the United States pose a grave threat to the CDC's ability to remain a key global player in TB R&D. Sequestration-related cuts enacted in 2013 have forced the DTBE to cut the TBTC budget by approximately 13%.[37] This new layer of cuts compounds problems created by the 10% funding drop the TBTC has weathered over the past three years. The consortium has already closed three clinical trials sites in Rio de Janeiro, Brazil; Durham, North Carolina; and Washington, D.C. Plans for a groundbreaking phase III trial evaluating the potential of rifapentine-based regimens to shorten treatment for drug-sensitive TB continue to progress, although at a slower-than-optimal pace, and remain vulnerable to future rounds of budgetary drawbacks.

8. The U.K. Department for International Development (DFID)

With funding of $16.9 million, investments from DFID dropped 18.8% from the $20.7 million it disbursed in 2011. As a result of this decline, DFID fell from seventh to eighth place in the top 10 rankings. Typical of other development agencies, DFID does not invest in basic-science research; the majority of DFID funding went toward drugs ($8.3 million) and operational research ($4.5 million). The amount spent on operational research reflects a 204.7% increase and is consistent with a TB clinical landscape that finally has new diagnostic tests and drugs awaiting implementation.

DFID funding for diagnostics remained stable at $2.5 million, but spending on vaccines declined by 75%. After investing $6.1 million in TB vaccine R&D in 2011, DFID spent only $1.5 million in this category in 2012. Still, this exceeds vaccine spending by any other national development agency. In August 2013, the Australian Agency for International Development announced a one-year grant of $2.6 million to support Aeras, signaling that other international development agencies may begin to support TB vaccine research.[38]

9. The U.K. Medical Research Council (MRC)

The MRC is the United Kingdom's leading government-funded research agency and an august and venerable sponsor of TB research. The MRC conducted the world's first randomized controlled trial evaluating streptomycin to treat TB in the 1940s and led many trials of BCG in Commonwealth countries in the postwar era. For the second year, the MRC ranks ninth among all donors to TB R&D.

In 2012, the MRC spent $14.8 million on TB R&D, a 12.2% drop from the $16.9 million disbursed in 2011. Most MRC funding supported basic-science research, although spending in this category decreased by 26.4% compared with 2011. While the MRC cut diagnostics and drugs spending, it increased funding for TB vaccine research from $324,949 in 2011 to over $3.6 million in 2012, a tenfold (1,024.7%) increase.

The MRC prioritizes global health research that addresses inequalities in health between developed and developing countries, although it does not single out TB research within this broader objective. According to the survey submitted to TAG, the MRC anticipates that future funding for TB R&D will remain stable.

10. The Wellcome Trust

The Wellcome Trust is a U.K.-based charity dedicated to supporting biomedical research and public understanding of science. In 2012, the Wellcome Trust provided $13.4 million to TB R&D, an 84.7% increase from 2011 and enough of a jump to enter the league of top 10 donors for the first time. The Wellcome Trust supported all six research areas in 2012, although it directed most of its TB funding toward basic science, which received $3.6 million. Compared with 2011, the Wellcome Trust increased its investments in basic science, diagnostics, drugs, and infrastructure/ unspecified projects while decreasing funding for vaccines and operational research.

While the Wellcome Trust does not set funding targets for specific diseases, research to understand the transmission and pathogenesis of TB falls under "combatting infectious diseases," one of the five challenge areas laid out in the institution's strategic plan.[39] The Wellcome Trust also maintains a strong commitment to building research capacity and supporting researchers in developing countries.

With a 2012 investment total of $12.2 million, USAID just narrowly missed joining the ranks of the top 10 TB R&D funders.[IV]

IV. USAID notes that the survey results it submitted to TAG, which received agency clearance, may undergo substantial revisions due to in-country data not available by the time our database closed. Any changes to USAID investment levels will be reflected in the March 2014 update to this report.

3. Conclusion

Table 3

Summary of Changes in TB R&D Investment, 2005–2012

Year	Total TB R&D Investment	Change over Previous Year	Change over Previous Year	Change over 2005	Change over 2005
2005	$357,426,121				
2006	$417,824,708	$60,398,587	16.9%	$60,398,587	16.9%
2007	$473,920,682	$56,095,974	13.4%	$116,494,561	32.6%
2008	$491,476,917	$17,556,235	3.7%	$134,050,796	37.5%
2009	$619,209,536	$127,732,619	26.0%	$261,783,415	73.2%
2010	$630,446,462	$11,236,926	1.8%	$273,020,341	76.4%
2011	$657,815,332	$27,368,870	4.3%	$300,389,211	84.0%
2012	$627,389,725	-$30,425,607	-4.6%	$269,963,604	75.5%

Global spending on TB R&D declined by $30.4 million from 2011 to 2012, the first year-to-year funding decrease since TAG began tracking investments in 2005. This 4.63% drop resulted in a $1.39 billion funding shortfall measured against the annual $2 billion target put forward by the *2011–2015 Global Plan*. The $627.4 million spent on TB R&D by 85 reporting donors in 2012 left funding gaps in every area of R&D.

The composition of donors also raises concern. In 2012, the top 10 donors disbursed 78% of the global total, indicating a shallow sense of shared urgency and political will globally. Judging by the top 10 list, TB R&D remains an endeavor financed primarily by public and philanthropic institutions in the United States and the United Kingdom: four of the top 10 donors are based in the United States, whereas three are in the United Kingdom. This confirms an independent estimation that donors in the United States and the United Kingdom accounted for 95% of TB R&D spending as recently as 2010.[40]

Notably absent from the top 10—and sorely underrepresented among the top 30 donors—are the BRICS countries (Brazil, Russia, India, China, and South Africa), which together account for 40% of the world's notified TB cases and 60% of its estimated MDR-TB cases.[41] Using 2010 data, David Walwyn showed that India, China, and South Africa devoted less than 0.05% of their total R&D spending to TB, despite the heavy burden of premature morbidity and mortality attributable to TB in those countries.[42]

In January 2013, ministers of health from the BRICS countries signed the Delhi Communiqué committing their nations to jointly address urgent public health problems, including MDR-TB. In the Delhi Communiqué, the BRICS countries resolved to collaborate on R&D for "new [TB] drugs, vaccines, diagnostics" through the "promotion of consortia of tuberculosis researchers."[43] It remains unclear whether this declaration will signal an actual increase in R&D investment from the BRICS nations or just another rhetorical acknowledgment of the growing MDR-TB crisis, the subject of both a Ministerial Meeting of High M/XDR-TB Burden Countries and a resolution at the 62nd World Health Assembly in 2009.[44,45] These earlier statements avowing the urgency of addressing MDR-TB did not translate into meaningful investment increases in R&D from the BRICS countries, which have never had a funding institution rank among the top 10.

Across all countries, the public sector continues to shoulder the bulk of TB R&D funding, with 61% of the global total, even as it fights the shortsighted attacks of fiscal austerity measures in the United States and Europe. Against this backdrop of public-sector instability, private-sector companies display wavering support to TB R&D. Some companies, such as Pfizer, have withdrawn from the TB R&D space completely, while others, including Otsuka and Company X, decreased their investments in 2012. Private-sector disinvestment in TB drug development parallels a larger pullback from anti-infectives research by pharmaceutical companies; this shift is occurring at a moment when antibiotic resistance poses a grave threat to our ability to respond to a host of infectious diseases.[46] Some areas of TB R&D—most notably vaccines—remain almost completely devoid of private-sector support. This retraction in funding has completely reversed the 13% private-sector gain observed in 2011.

Philanthropic support appears more stable and grew by a modest 3.1% in 2012. The BMGF continues to lead philanthropic investment, with 87.4% of the total in this category, although the Wellcome Trust also makes significant contributions to basic science. Multilateral investments saw the largest percentage increase in 2012, due in part to the inclusion of data from the Global Fund. At just over $8 million, however, multilateral spending remains dwarfed by other donor categories.

Of the six research areas tracked by TAG, drug development continues to receive the largest share of funding, although the $237.8 million invested in this area in 2012 leaves 67.9% of the *2011–2015 Global Plan* target unfunded. The donor community is just $2.9 million shy of reaching the operational research funding target, but is nowhere near target thresholds for diagnostics (87.5% unfunded), vaccines (77.2% unfunded), or basic science (69.1% unfunded).

4. Recommendations

Over eight years, the narrative arch of this report has seen hesitant progress stall and ultimately reverse: year after year, TAG reports annual spending data on TB R&D and finds large gaps between actual disbursements and the funding targets called for by the Stop TB Partnership. TB R&D remains gravely underfunded, and, in 2012, momentum reversed with investments dropping by $30.4 million compared with 2011. Promising scientific advances made over the last decade will require a substantial increase in funding in order to bring forth the new tools required to prevent, diagnose, and treat people at risk of or suffering from TB. The following recommendations outline what must be done to accelerate progress in each area of research:

- **Basic science**: Donors of all types must increase funding for basic science to unveil the dynamics of how the human immune system responds to MTB at different stages of infection and disease. An element of basic-science research should include concerted efforts to identify biomarkers correlating with risk of disease, protective immunity, and biological processes underlying drug efficacy such as sterilization and elimination of MTB postinfection. The discovery and validation of different biomarkers will offer unique insights into diagnostic, drug, and vaccine development. Ultimately, validated biomarkers will allow researchers to conduct shorter clinical trials, look for efficacy earlier, and improve the selection of candidates for late-stage trials—moves that stand to produce considerable cost savings over the current model.

- **Diagnostics**: Future efforts in TB diagnostics research should focus on developing an accurate, rapid, and user-friendly point-of-care test that can liberate patients and providers from the inaccuracy of sputum smear microscopy and the slowness of mycobacterial culture and shorten the time between diagnosis and start of treatment. In response to the MDR-TB crisis, donors must prioritize the development of rapid and decentralized drug-susceptibility tests for fluoroquinolones and other second-line drugs. Funders should also work together to develop open-access biobanks with genetically diverse samples from different diagnostic studies, including samples of resistant strains of TB. Regulatory agencies and normative bodies must also invest in developing stringent evidentiary standards for new diagnostic tests to ensure that new tools are marketed and used appropriately.

- **Drugs**: Drug discovery will not keep pace with the TB epidemic unless a raft of new compounds enters the pipeline and current candidates advance beyond small phase II studies. Private-sector drug developers could speed up the pipeline by making their compounds available to public research consortia and PDPs such as the TBTC, ACTG, and TB Alliance that wish to evaluate new and existing drugs in combination. Without cross-sector collaboration, many promising compounds will continue to progress along slow, isolated research trajectories. Sponsors should also collaborate on drug-drug interaction studies so that new compounds such as bedaquiline and delamanid may be used together safely. All funders must commit to studying TB drugs in special populations including children, pregnant women, people with HIV, people who use drugs, and people with hepatitis B and C. These efforts will not only require substantial increases in funding but also creative and innovative financing and licensing mechanisms to enable research collaborations across donor categories.

- **Vaccines**: Progress in TB vaccine research hinges on advancements in basic science, particularly in the search for biomarkers of protective immunity against TB. TB vaccine R&D would also benefit from improved animal models of TB infection and disease and from the

development of a human challenge model that would give researchers an earlier gauge into the efficacy of vaccine candidates in humans. Broadening the base of scientific partners to include more public-sector support from the BRICS countries would also boost efforts to develop new TB vaccines with developing-country settings in mind. In addition, the field urgently needs greater investments from private-sector partners who can leverage in-house compound libraries for preclinical discovery and marshal the financial resources required to launch large late-stage clinical trials.

- **Operational research**: Donors and high-burden countries should commit to conducting rigorous operational research to inform countries as they prepare to rollout new tools. Operational research efforts should characterize how new tools link both to each other and to the overall health system so that countries may produce locally relevant treatment cascades illustrating gaps in patient identification, retention, and care. Operational research should also proceed in lockstep with epidemiological surveillance so that countries first know their epidemics and, based on this knowledge, adapt implementation guidelines and strategies to meet national needs.

For the investments detailed in this report to bring the global TB epidemic closer to zero TB deaths, new infections, and suffering, a rigorous scientific research agenda must be met by improvements in clinical research capacity and regulatory systems.

- **Clinical research capacity**: Donors need to invest in raising the capacity of investigators and institutions in developing countries to engage in TB R&D as equal partners. Many late-stage drug and vaccine clinical trials will need to take place in high-burden countries with insufficient laboratory capacity and infrastructure to meet Good Clinical Practice standards. Donors should match investments in the technical capacity of clinical trial sites with commitments to fund the meaningful engagement of TB-affected communities in the design and implementation of clinical trials according to the *Good Participatory Practice Guidelines for TB Drug Trials*.[47]

- **Regulatory modernization**: Moving new tools from R&D to implementation will require modernizing the TB regulatory climate. The EMA's negative review of delamanid indicates that many regulatory authorities sit unprepared to parse innovation in TB R&D in light of the urgency of global health threats such as MDR-TB. Approval of technologies also lags between stringent regulatory authorities in the United States, Europe, and Japan and in developing countries where the burden of TB is greatest. Necessary changes to this outdated system include harmonizing regulatory guidelines and review across countries and within regions; expediting regulatory review of new drugs, drug regimens, and vaccines; and closing regulatory approval gaps between adult and pediatric drug formulations.[48]

For the first time in eight years, spending on TB R&D decreased compared with the previous year. Even more troubling than the $30.4 million decline is the fact that this drop is occurring before the implementation of sequestration-related funding cuts in the United States, home to many of the world's leading public-sector TB R&D donors. Wavering private-sector support is placing greater pressure on public institutions just as they begin to encounter unprecedented budgetary drawbacks. With chasm-sized funding gaps in nearly every area of research, TB R&D stakeholders and TB-affected communities are approaching the final years of the *2011–2015 Global Plan* with anemic pipelines for new TB drugs, diagnostics, and vaccines. Private, public, and philanthropic donors in high-, middle-, and low-income countries must recommit to meeting the funding levels required to accelerate progress toward the technologies that can end the global TB epidemic.

Endnotes

1. Comas I, Coscolla M, Luo T, et al. Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. Nature Genetics. 2013 Sept 1. doi:10.1038/ng.2744. [Epub ahead of print]

2. Walzl G, Ronacher K, Hanekom W, Scriba TJ, Zumla A. Immunological biomarkers of tuberculosis. Nat Rev Immunol. 2011 May;11(5):343–54. doi: 10.1371/journal/ppat.1002607.

3. World Health Organization. Global tuberculosis report 2012. Geneva: World Health Organization; 2012. Available from: http://www.who.int/tb/publications/global_report/en/. (Accessed 2013 September 3)

4. Ibid.

5. World Health Organization. Global tuberculosis report 2006. Geneva: World Health Organization; 2006. Available from: http://www.who.int/tb/publications/global_report/2006/en/. (Accessed 2013 September 3)

6. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annual Review of Public Health. 2013;34:271–86. doi: 10/1146/annurev-publhealth-031912-114431.

7. World Health Organization. Global tuberculosis report 2012.

8. McShane H. Tuberculosis vaccines: beyond bacilli Calmette-Guerin. Philos Trans R Soc Lond B Biol Sci. 2011 Oct 12;366(1579):2782–9. doi: 10.1098/rstb.2011.0097.

9. Lessem E. The TB treatment pipeline. In: Clayden P, Collins S, Daniels C, et al.; i-Base/Treatment Action Group. 2013 Pipeline Report. New York: Treatment Action Group; 2012. Available from: http://www.pipelinereport.org. (Accessed 2013 September 20)

10. Daniels C. The TB diagnostics pipeline. In: Clayden P, Collins S, Daniels C, et al.; i-Base/Treatment Action Group. 2013 Pipeline Report. New York: Treatment Action Group; 2012. Available from: http://www.pipelinereport.org. (Accessed 2013 September 20)

11. Harrington M. 2013 tuberculosis pipeline executive summary. In: Clayden P, Collins S, Daniels C, et al.; i-Base/Treatment Action Group. 2013 Pipeline Report. New York: Treatment Action Group; 2012. Available from: http://www.pipelinereport.org. (Accessed 2013 September 20)

12. Hallam K. Otstuka's drug-resistant TB treatment fails to win EMA nod. Bloomberg News [Internet]. 26 July 013 (cited 2013 September 20). Available from: http://www.bloomberg.com/news/2013-07-26/otsuka-s-drug-resistant-tb-treatment-fails-to-win-ema-nod.html.

13. Dandekar V. Pfizer draws curtain on anti-infective research; refocuses on next-generation vaccines. PharmAsia News [Internet]. 13 May 2013 (cited 2013 September 20). Available from: http://www.elsevierbi.com/publications/pharmasia-news/2013/5/13/pfizer-draws-curtain-on-antiinfective-research-refocuses-on-nextgen-vaccines.

14. Frick M. The TB vaccines pipeline. In: Clayden P, Collins S, Daniels C, et al.; i-Base/Treatment Action Group. 2013 Pipeline Report. New York: Treatment Action Group; 2012. Available from: http://www.pipelinereport.org. (Accessed 2013 September 20)

15. KwaZulu-Natal Research Institute for Tuberculosis and HIV (press release). K-RITH has officially opened. 2012 October 15. Available from: http://k-rith.org/news-updates/2012/has-officially-opened. (Accessed 2012 October 2)

16. Pai M. Tuberculosis diagnostics: test developers' FAQs. Int J Tuberc Lung Dis. 2013;17(5):570–1. doi: 0.5588/ijtld.13.0036.

17. Treatment Action Group, Global TB Community Advisory Board, India CAB (Open Letter). Marketing and use of QuantiFERON-TB Gold for active TB in India and high TB burden countries. 2013 May 14. Available from: http://www.tbonline.info/posts/2013/5/17/tag-tb-cab-india-cab-open-letter/. (Accessed 20 September 2013)

18. Treatment Action Group, Global TB Community Advisory Board (Open Letter). Marking and use of TB Platinum for active TB in India and high TB burden countries. 2013 July 2. Available from: http://www.tbonline.info/posts/2013/7/3/tag-tb-cab-india-cab-open-letter-immunoshop/. (Accessed 20 September 2013).

19. Minion J, Leung E, Talbot E, Dheda K, Pai M, Menzies D. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. Eur Respir J. 2011 Dec;38(6):1398–405. doi: 10.1183/09031936.00025711.

20. Dandekar V. Pfizer draws curtain on anti-infective research; refocuses on next-generation vaccines. PharmAsia News [Internet]. 13 May 2013 (cited 2013 September 20). Available from: http://www.elsevierbi.com/publications/pharmasia-news/2013/5/13/pfizer-draws-curtain-on-antiinfective-research-refocuses-on-nextgen-vaccines.

21. Sequella Incorporated (press release). Sequella acquires exclusive worldwide rights to Pfizer's sutezolid, currently in clinical development for tuberculosis. 2013 July 17. Available from: http://www.sequella.com/docs/Sutezolid%20press%20release.pdf. (Accessed 2013 September 20)

22. Lessem E. The TB treatment pipeline.

23. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2008;46:155–64. doi: 10.1086/524891.

24. Chan M. Combat drug resistance: no action today means no cure tomorrow. World Health Day 2011 statement by WHO Director-General Dr. Margaret Chan. 2011 April 6. Available from: http://www.who.int/mediacentre/news/statements/2011/whd_20110407/en/index.html. (Accessed 2013 October 2)

25. Spellberg B, et al. The epidemic of antibiotic-resistant infections.

26. Tameris M, Hatherhill M, Landry B, et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomized, placebo-controlled phase 2b trial. Lancet. 2013;381(9871):1021–8. doi: 10.1016/S0140-6736(13)60177-4.

27. Frick M. The TB vaccines pipeline.

28. Ibid.

29. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT01404312, Evaluating the safety and effectiveness of short-course rifapentine/isoniazid for the prevention of active tuberculosis in HIV-infected individuals with latent tuberculosis infection; 2011 July 26 (cited 2013 September 3). Available from: http://clinicaltrials.gov/ct2/show/NCT01404312?term=A5279&rank=1.

30. Fact sheet: impact of sequestration on the National Institutes of Health. http://www.nih.gov/news/health/jun2013/nih-03.htm

31. Former NIH director: the sequester will set back medical science for a generation. http://www.washingtonpost.com/blogs/wonkblog/wp/2013/02/21/former-nih-director-the-sequester-will-set-back-medical-science-for-a-generation/.

32. Lessem E. The TB treatment pipeline.

33. European Medicines Agency (E.U.). Refusal of the marketing authorization for delamanid (EMA/446276/2013). 2013 July 26. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002552/WC500146651.pdf. (Accessed 2013 October 3)

34. Ibid.

35. Voitzwinkler F. (Global Health Advocates, Brussels, Belgium). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2013 July 10.

36. European and Developing Countries Clinical Trials Partnership. Strategic business plan for the second phase of the European and Developing Countries Clinical Trials Partnership programme (EDCTP2, 2014–2024). 2013: The Hague, The Netherlands. Available from: http://www.edctp.org/Towards_EDCTP2.799.0.html. (Accessed 2013 September 24).

37. Quirk T. Tuberculosis trials, already struggling, hit hard by US sequester. Nature Medicine. 2013 July 8;19:798–99. doi: 10.1038/nm0713-798b.

38. Aeras (Press Release). AusAID pledges AUS$2.5M 'shot in the arm' for TB vaccine R&D. 2013 August 19. Available from: http://www.aeras.org/pressreleases. (Accessed 2013 September 24).

39. Wellcome Trust. Strategic plan 2010–20: extraordinary opportunities. London: Wellcome Trust; 2010. Available from: http://www.wellcome.ac.uk/About-us/Strategy/. (Accessed 2013 October 2)

40. Walwyn D. Determining quantitative targets for public funding of tuberculosis research and development. Health Research Policy and Systems. 2013 Mar 8;11(10): n.p. doi:10.1186/1478-4505-11-10.

41. World Health Organization. Global tuberculosis report 2012.

42. Walwyn D. Determining quantitative targets for public funding of tuberculosis research and development.

43. Ministry of Health and Family Welfare, Government of India. Delhi Communique. 12 January 2013. http://pib.nic.in/newsite/erelease.aspx?relid=91533.

44. World Health Organization. The Beijing 'call for action' on tuberculosis control and patient care: together addressing the global M/XDR-TB epidemic [Internet]. 3 April 2009 (cited 2013 October 2). http://www.who.int/tb_beijingmeeting/media/en_call_for_action.pdf.

45. Sixty-Second World Health Assembly. Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis (WHA61.15) [Internet]. 22 May 2009 (cite 2013 October 2). Available from http://apps.who.int/gb/ebwha/pdf_files/A62/A62_R15-en.pdf

46. U.S. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: U.S. CDC; 2013. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/. (Accessed 2013 October 2).

47. Critical Path to TB Drug Regimens. Good participatory practice guidelines for TB drug trials. Washington, D.C.: Critical Path to TB Drug Regimens; 2012. Available from: http://cptrinitiative.org/resources/gpp-tb-resource-document/. (Accessed 2013 October 2)

48. Clayden P, Harrington M. Seven ways to speed up the pipeline. In: Clayden P, Collins S, Daniels C, et al.; i-Base/Treatment Action Group. 2013 Pipeline Report. New York: Treatment Action Group; 2012. Available from: http://www.pipelinereport.org. (Accessed 2013 September 20)

Appendix 1

Table 4

2012 and 2011 Top Reporting TB R&D Funders

2012 Rank	2011 Rank	Funding Organization	Funder Type	Total
1	1	NIAID	P	$169,092,971
2	2	BMGF	F	$111,601,679
3	3	Otsuka	C	$60,034,956
4	4	Other NIH ICs	P	$36,646,883
5	6	EC	P	$27,260,036
6	5	Company X	C	$22,844,099
7	10	CDC	P	$18,481,592
8	7	DFID	P-D	$16,852,323
9	9	MRC	P	$14,790,087
10	15	Wellcome Trust	F	$13,418,817
11	8	USAID	P-D	$12,174,064
12	12	NHLBI	P	$11,831,219
13	11	AstraZeneca	C	$10,303,559
14	13	India (reported)	P	$8,684,341
15	27	PEPFAR	P	$6,606,609
16	14	DGIS	P-D	$6,195,582
17	17	CIHR	P	$6,017,561
18	**	GFATM	M	$6,000,000
19	19	BMBF	P	$5,232,441
20	31	Company Z	C	$5,178,920
21	20	Company W	C	$4,529,539
22	*	Company V	C	$4,297,934
23	**	INSERM	P	$4,173,870
24	18	Emergent Biosolutions	C	$4,157,360
25	25	NHMRC	P	$4,060,791
26	23	Sweden (reported)	P	$3,719,138
27	29	Korea (reported)	P	$3,279,378

* New TB R&D funder
** Previous TB R&D funder who did not report in 2011

Basic Science	Diagnostics	Drugs	Vaccines	Operational Research	Infrastructure/ Unspecified
$61,339,187	$41,032,931	$12,234,889	$14,452,688	$14,501,183	$25,532,093
$4,744,134	$45,485,164	$37,753,518	$12,302,441	$11,316,422	$0
$0	$60,018,386	$0	$0	$16,570	$0
$10,926,027	$4,237,808	$657,365	$12,982,935	$1,068,920	$6,773,828
$11,238,376	$5,509,608	$7,734,463	$0	$0	$2,777,588
$0	$22,634,099	$0	$0	$210,000	$0
$0	$9,161,421	$0	$4,561,413	$2,536,798	$2,221,960
$0	$8,321,000	$1,519,152	$4,500,171	$2,512,000	$0
$7,788,670	$2,534,051	$3,654,641	$799,935	$12,789	$0
$3,563,514	$1,546,996	$483,427	$1,830,745	$1,385,218	$4,608,917
$0	$5,793,027	$0	$1,751,116	$2,851,973	$1,777,948
$9,067,163	$167,729	$378,750	$878,508	$740,071	$598,998
$0	$10,303,559	$0	$0	$0	$0
$1,235,547	$47,904	$0	$34,663	$0	$7,366,227
$0	$0	$0	$6,606,609	$0	$0
$0	$315,139	$5,244,198	$27,501	$608,744	$0
$2,324,367	$2,094,966	$550,109	$966,231	$0	$81,888
$0	$0	$0	$6,000,000	$0	$0
$2,701,509	$480,523	$1,329,258	$0	$412,509	$308,641
$0	$0	$5,178,920	$0	$0	$0
$0	$4,529,539	$0	$0	$0	$0
$0	$4,297,934	$0	$0	$0	$0
$1,043,468	$1,043,468	$1,043,468	$0	$1,043,468	$0
$0	$0	$4,157,360	$0	$0	$0
$1,956,176	$1,071,099	$0	$809,092	$224,424	$0
$1,993,916	$43,311	$194,900	$1,227,145	$187,681	$72,185
$122,835	$27,150	$499,641	$2,077,302	$247,950	$304,500

P = Public-sector R&D agency; C = Corporation/private sector; M = Multilateral; F = Foundation/philanthropy; P-D = Public-sector development agency

Table 4

2012 and 2011 Top Reporting TB R&D Funders (continued)

2012 Rank	2011 Rank	Funding Organization	Funder Type	Total
28	33	MPIIB	P	$2,950,000
29	22	Institut Pasteur	P	$2,553,445
30	34	ANRS	P	$2,527,027
31	49	Carlos III Health Institute	P	$1,814,951
32	71	WHO	M	$1,707,923
33	37	CIDA	P-D	$1,684,379
34	**	HRC	P	$1,683,781
35	42	FDA	P	$1,642,584
38	35	Bloomberg Philanthropies	F	$1,500,000
40	54	ARC	P	$1,412,237
41	52	ANRS	P	$1,385,878
42	43	Irish Aid	P-D	$1,284,370
43	24	DST	P	$1,217,500
44	**	SNSF	P	$824,473
45	21	Sequella	C	$642,350
46	39	UBS Optimus Foundation	F	$632,262
47	44	DFG	P	$555,326
48	63	KNCV	F	$499,817
49	**	DANIDA	P-D	$323,250
50	70	OFID	M	$279,810
51	51	Danish National Advanced Technology Foundation	P	$233,863
52	78	Colciencias	P	$220,000
53	57	Danish Council for Independent Research/Medical Sciences	P	$210,469

* New TB R&D funder
** Previous TB R&D funder who did not report in 2011

Basic Science	Diagnostics	Drugs	Vaccines	Operational Research	Infrastructure/ Unspecified
$1,450,000	$0	$1,500,000	$0	$0	$0
$1,699,245	$446,796	$255,585	$0	$151,819	$0
$329,957	$1,850,788	$0	$0	$163,894	$182,389
$730,367	$326,568	$325,050	$432,966	$0	$0
$0	$0	$85,260	$366,337	$1,256,326	$0
$0	$0	$0	$1,684,379	$0	$0
$1,304,908	$0	$0	$0	$158,561	$220,311
$0	$1,343,059	$299,525	$0	$0	$0
$0	$0	$0	$1,500,000	$0	$0
$245,606	$573,082	$0	$0	$0	$593,549
$1,220,800	$165,079	$0	$0	$0	$0
$0	$1,284,370	$0	$0	$0	$0
$1,217,500	$0	$0	$0	$0	$0
$824,473	$0	$0	$0	$0	$0
$0	$642,350	$0	$0	$0	$0
$0	$0	$0	$0	$316,131	$316,131
$555,326	$0	$0	$0	$0	$0
$0	$0	$0	$499,817	$0	$0
$0	$0	$0	$323,250	$0	$0
$0	$0	$0	$279,810	$0	$0
$0	$0	$233,863	$0	$0	$0
$0	$150,000	$0	$70,000	$0	$0
$0	$0	$210,469	$0	$0	$0

P = Public-sector R&D agency; C = Corporation/private sector; M = Multilateral; F = Foundation/philanthropy; P-D = Public-sector development agency

Table 4

2012 and 2011 Top Reporting TB R&D Funders (continued)

2012 Rank	2011 Rank	Funding Organization	Funder Type	Total
54	26	Company Y	C	$196,239
55	61	BioDuro	C	$180,000
57	56	SSI	P	$153,252
59	58	ZonMw	P	$140,013
61	66	Gulbenkian	F	$122,055
62	60	WHO Stop TB Partnership	M	$112,500
68	59	GSK Biologicals	C	$63,298
69	65	Fondation Mérieux	F	$63,298
70	64	FIT Biotech	C	$63,298
71	*	Pfizer Laboratories Ltd	C	$56,566
77	41	Sandoz	C	$30,476
78	72	GSK	C	$29,123
79	76	Korea LG Life Sciences	C	$26,100
80	**	Thrasher Research Fund	F	$21,710
82	**	AP Møller Foundation	F	$7,663
83	80	Faber Daeufer Itrato & Cabot	C	$7,500
84	73	ECDC	P	$4,113
85	79	Corporate donors to TB Alliance	C	$1,680
		New funders under $500K		$42,665
		Grand Total		**$627,389,725**

* New TB R&D funder
** Previous TB R&D funder who did not report in 2011

Basic Science	Diagnostics	Drugs	Vaccines	Operational Research	Infrastructure/ Unspecified
$0	$0	$0	$1,239	$195,000	$0
$0	$180,000	$0	$0	$0	$0
$0	$0	$153,252	$0	$0	$0
$0	$0	$0	$0	$140,013	$0
$0	$0	$122,055	$0	$0	$0
$0	$112,500	$0	$0	$0	$0
$0	$0	$63,298	$0	$0	$0
$0	$0	$63,298	$0	$0	$0
$0	$0	$63,298	$0	$0	$0
$0	$0	$56,566	$0	$0	$0
$0	$30,476	$0	$0	$0	$0
$0	$0	$29,123	$0	$0	$0
$0	$0	$0	$0	$0	$26,100
$0	$0	$0	$0	$21,710	$0
$0	$0	$7,663	$0	$0	$0
$0	$7,500	$0	$0	$0	$0
$0	$4,113	$0	$0	$0	$0
$0	$1,680	$0	$0	$0	$0
$0	$13,293	$7,663	$0	$21,710	$0
$129,623,072	**$237,815,172**	**$86,558,192**	**$77,128,668**	**$42,429,160**	**$53,835,462**

P = Public-sector R&D agency; C = Corporation/private sector; M = Multilateral; F = Foundation/philanthropy; P-D = Public-sector development agency

Appendix 2

FIGURE 13

Historical Data on TB R&D Funders Ranked 1–12 that Invested above $500,000 in 2012

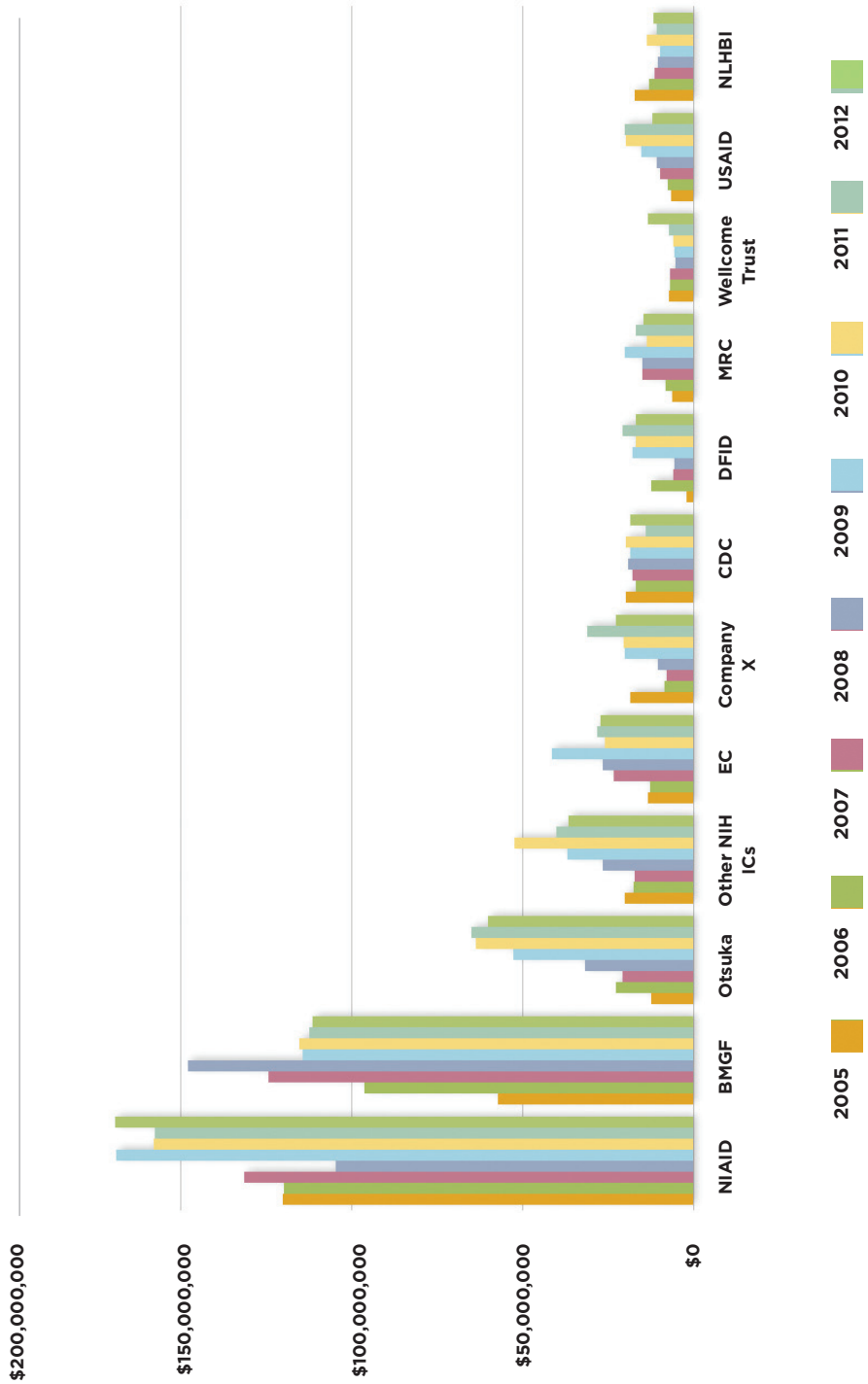


FIGURE 14

Historical Data on TB R&D Funders Ranked 13–24 that Invested above $500,000 in 2012

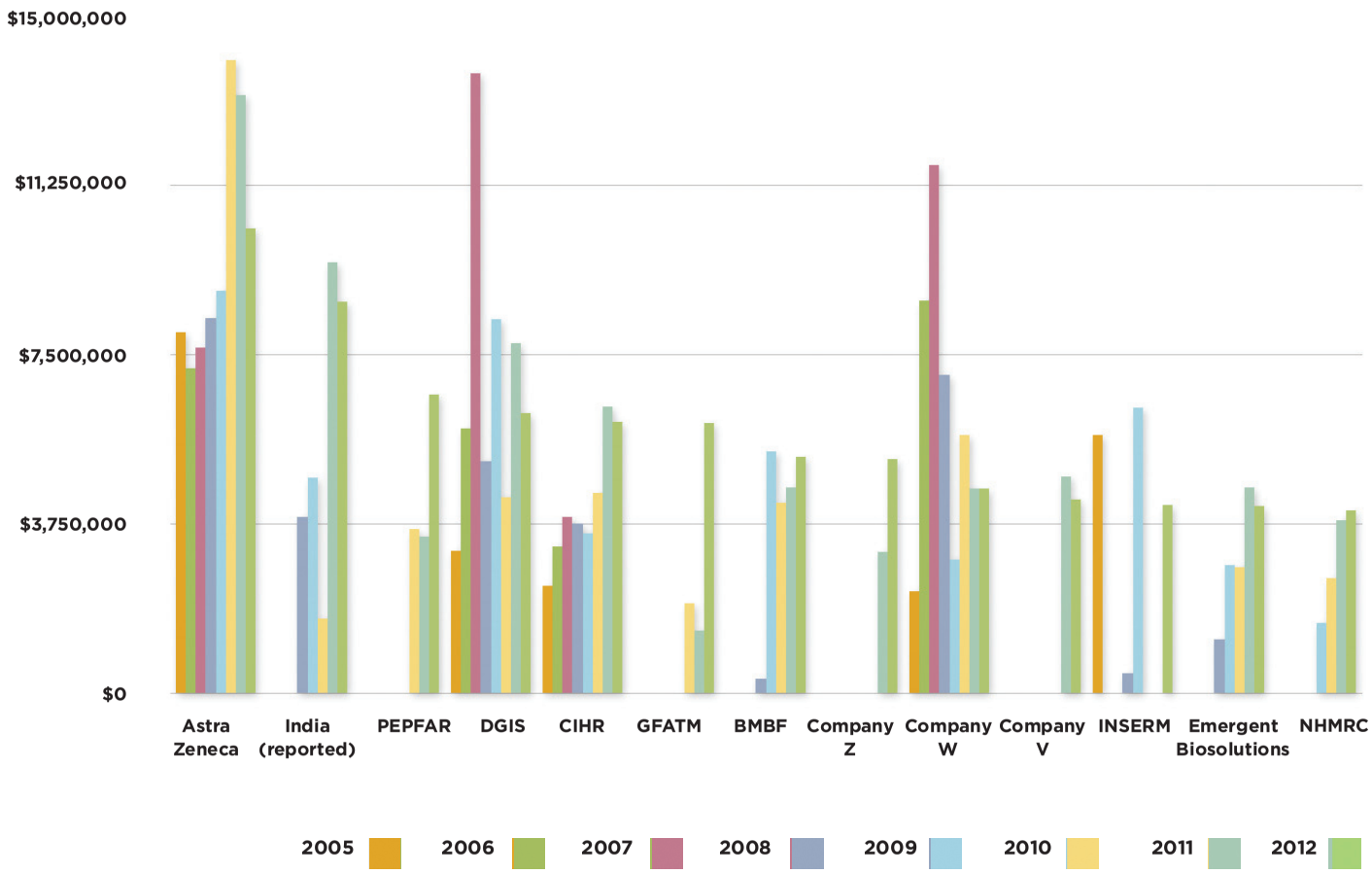


FIGURE 15

Historical Data on TB R&D Funders Ranked 25–35 that Invested above $500,000 in 2012

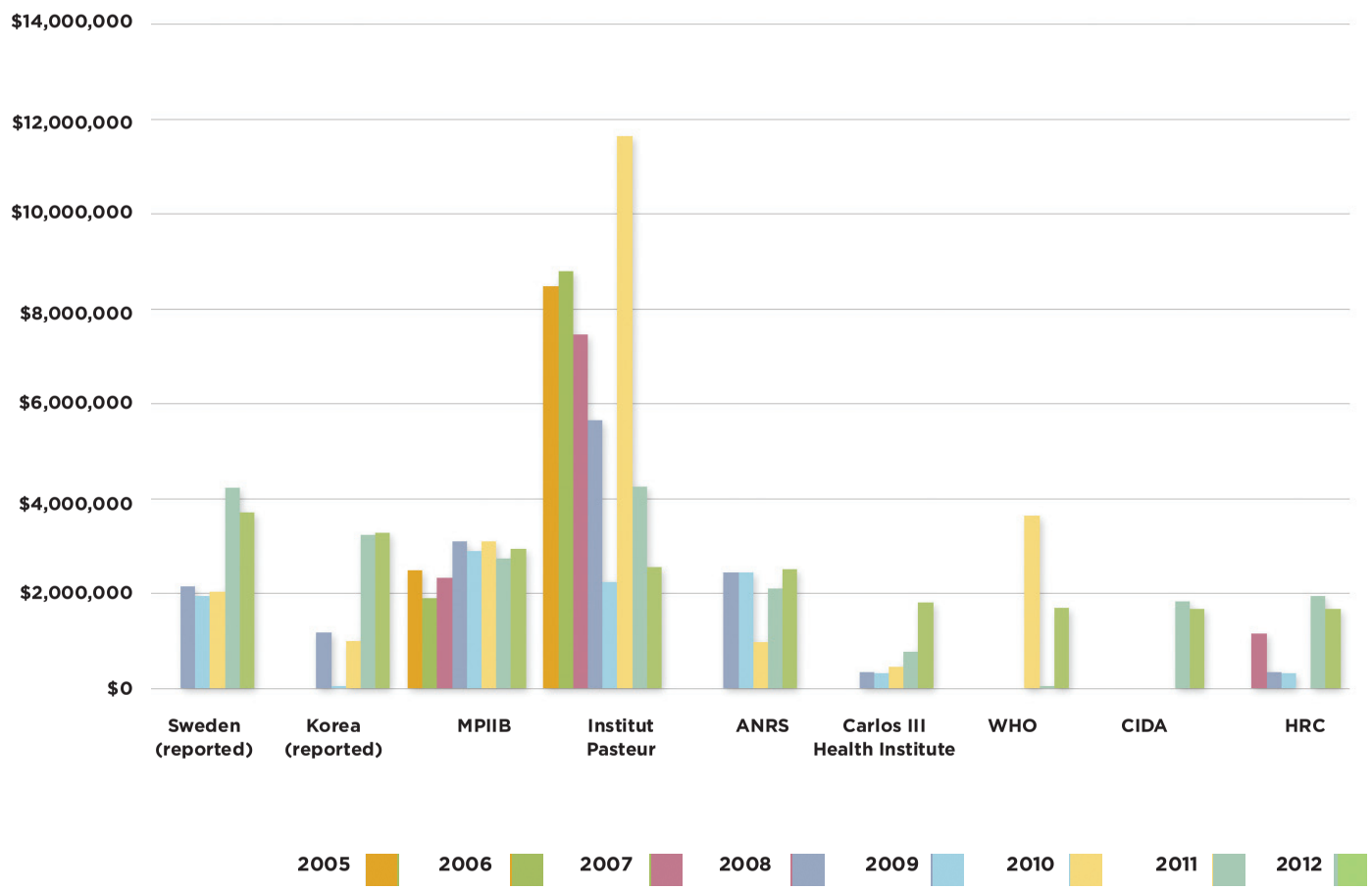


FIGURE 16

Historical Data on TB R&D Funders Ranked 36–49 that Invested above $500,000 in 2012

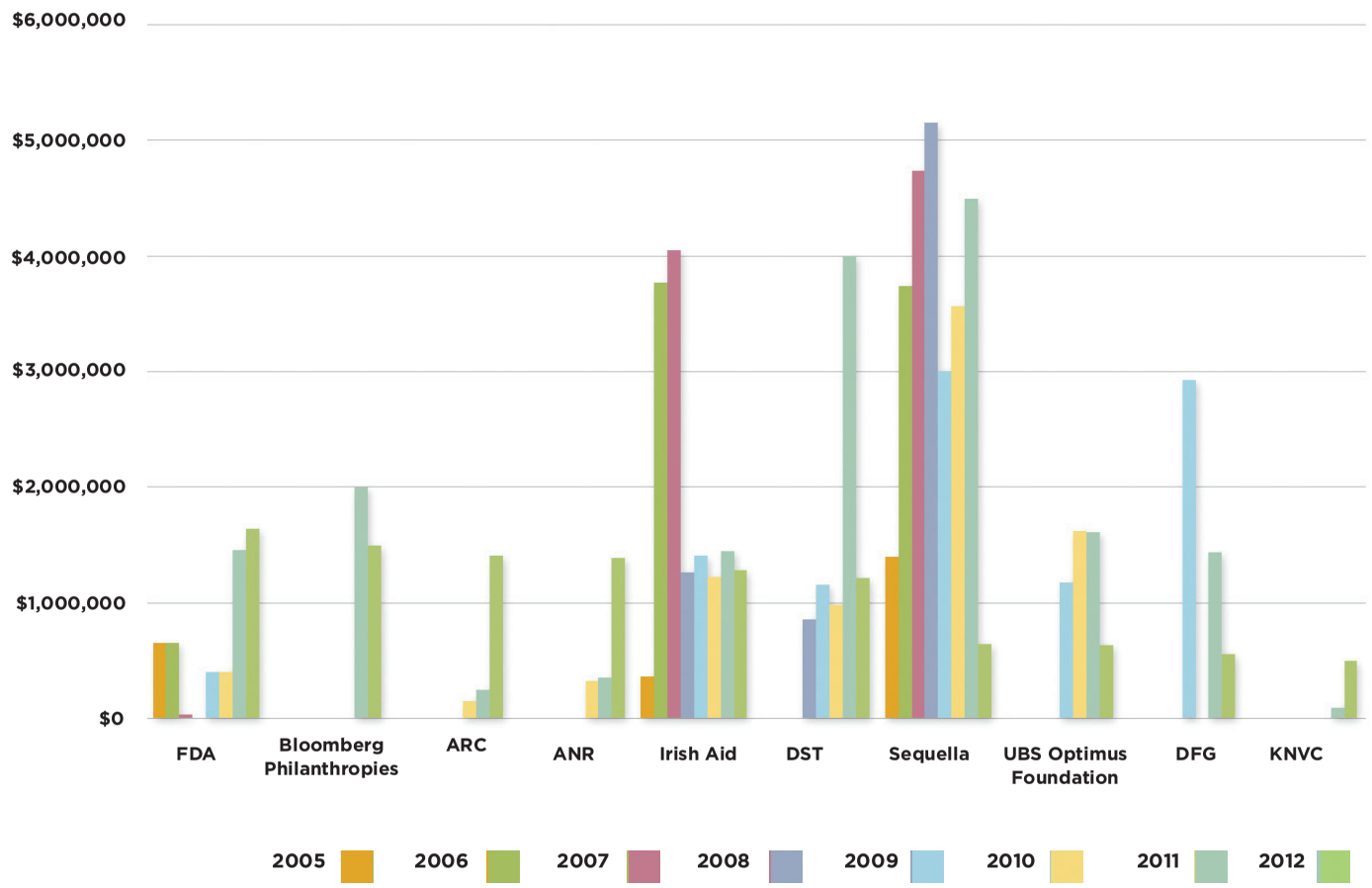


FIGURE 17

Historical Data on TB R&D Funders Ranked 50–62 that Invested Less than $500,000 in 2012

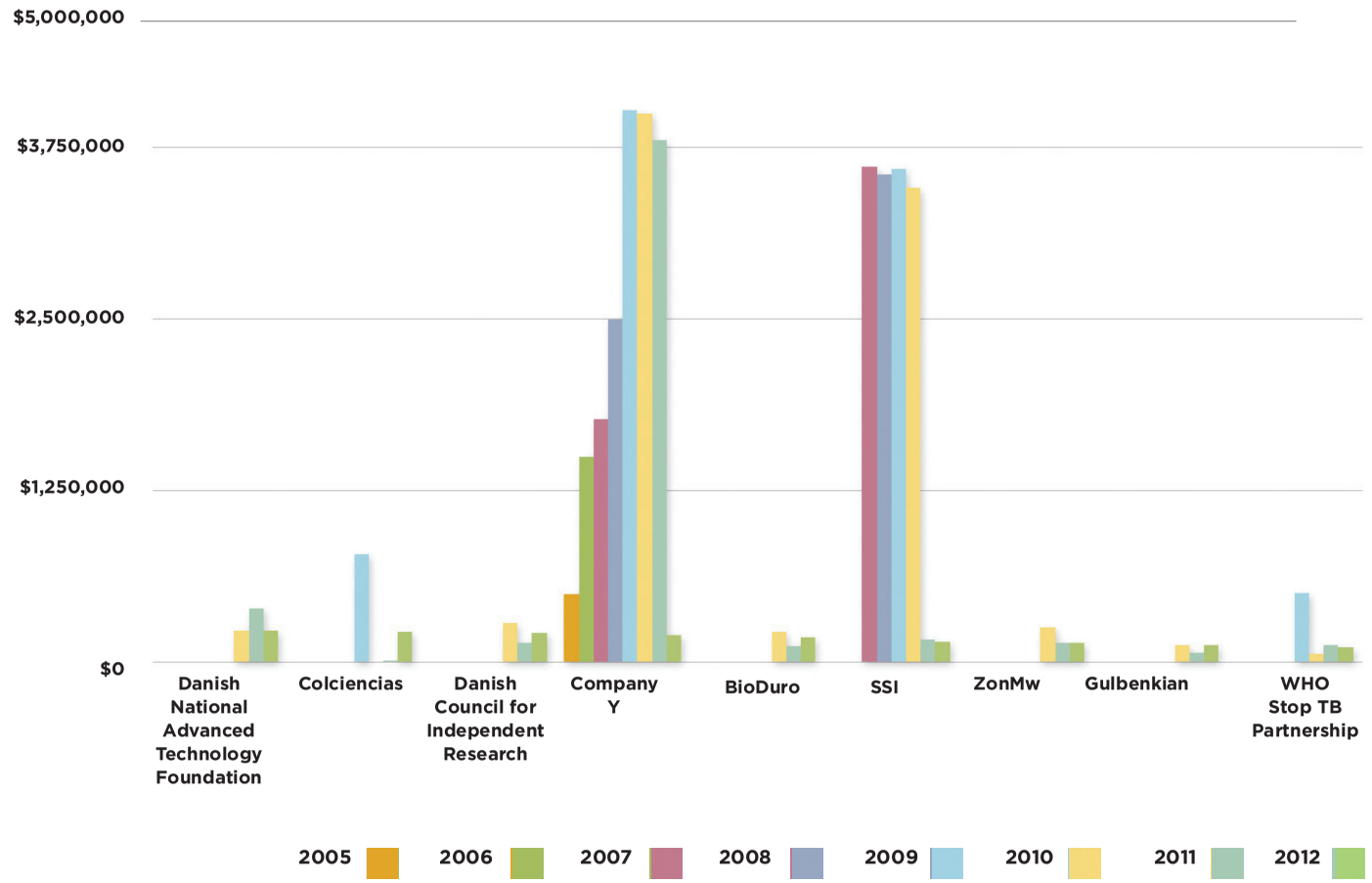


FIGURE 18

Historical Data on TB R&D Funders Ranked 63–79 that Invested Less than $500,000 in 2012

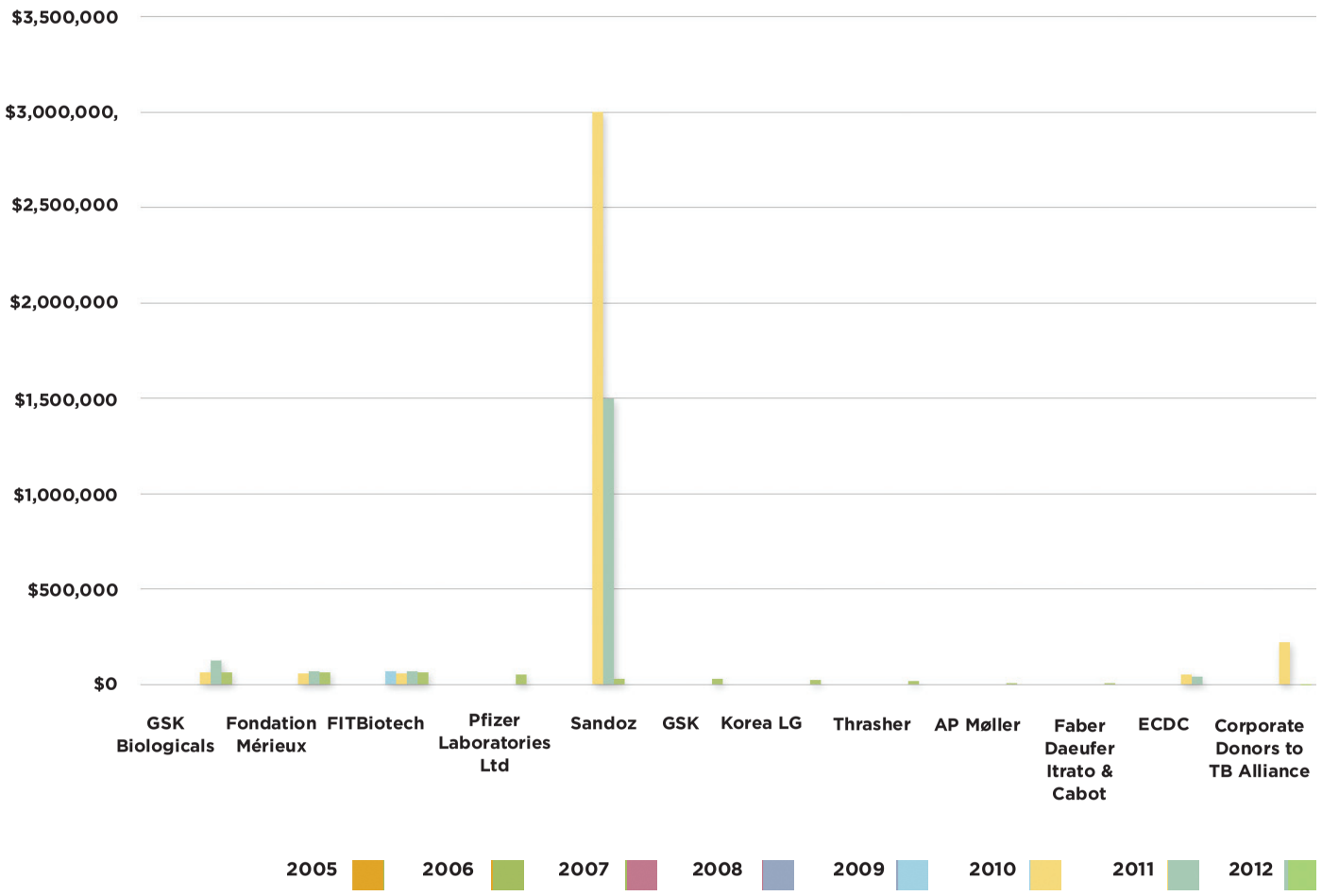


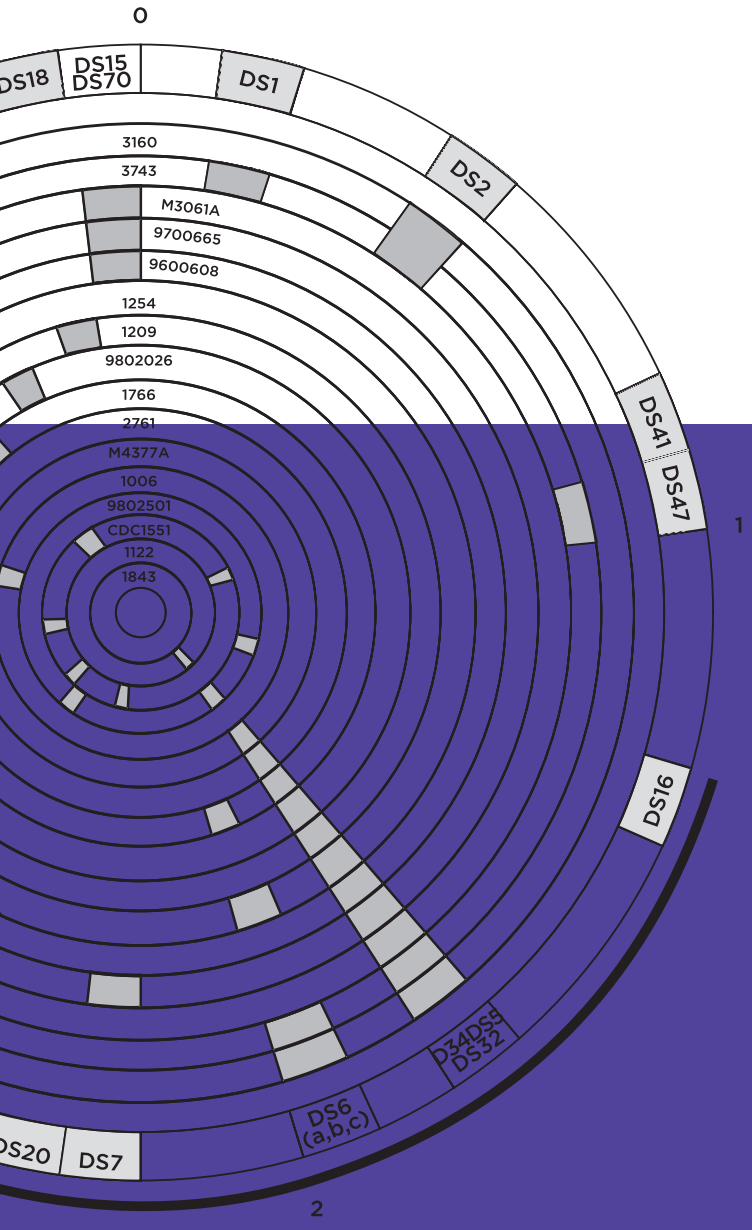
TABLE 5

TB R&D Funders Unresponsive in 2012

Anacor
Belgian Federal Science Policy Office
Brazilian Ministry of Health, National TB Program
Brazilian Ministry of Health, Department of Science and Technology
British Council
Canada University Health Network
Chinese Center for Disease Control and Prevention
Consejo Nacional de Ciencia y Tecnología
Dafra Pharma
Damien Foundation
Japan BCG Laboratory
Japan International Cooperation Agency
Japanese Ministry of Health, Labour and Welfare
Norwegian Ministry of Health and Care Services
PepsiCo
Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association
Rockefeller Foundation
South African Medical Research Council
Thailand National Science and Technology Development Agency
U.K. Department of Health
U.K. Health Protection Agency/National Institute for Health Research

Treatment Action Group
261 Fifth Avenue, Suite 2110
New York, NY 10016
Tel 212 253 7922
Fax 212 253 7923

tag@treatmentactiongroup.org
www.treatmentactiongroup.org



TAG
Treatment Action Group

ISBN 978-0-9837221-9-9