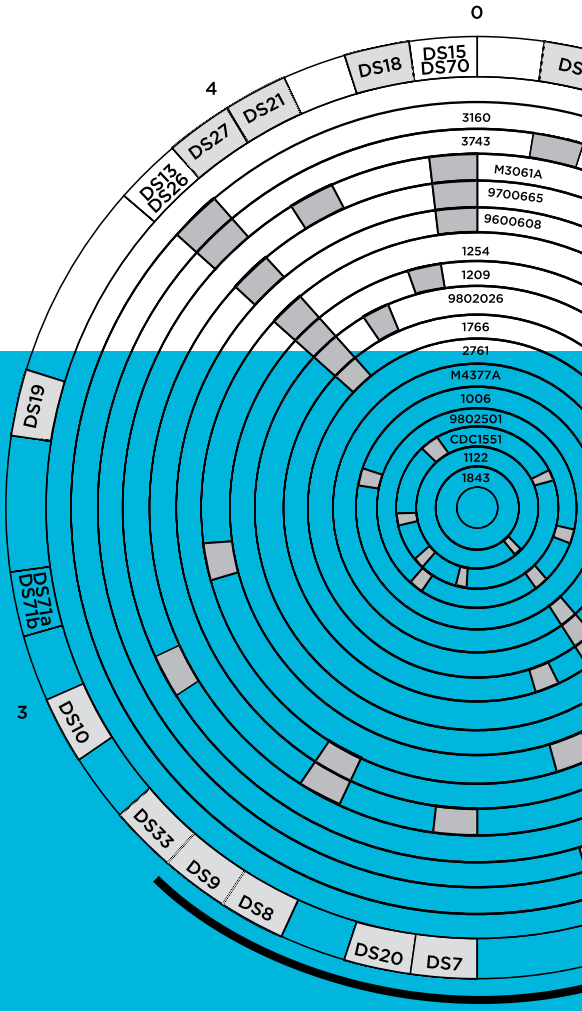
TAG
Treatment Action Group

TUBERCULOSIS RESEARCH
& DEVELOPMENT:

A Critical Analysis of Funding Trends, 2005–2007: An Update



SECOND PRINTING
MAY 2009

BY NEHA AGARWAL

EDITED BY JAVID SYED &
MARK HARRINGTON

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Executive Summary

For the third year, Treatment Action Group (TAG) analyzes and reports on the annual funding of tuberculosis (TB) research and development (R&D). The top 40 TB research funding institutions were surveyed for actual disbursements made for TB R&D in fiscal years 2005, 2006, and now 2007. The three-year data reveal trends in funding and demonstrates an alarming shortfall in the growth of TB R&D during the initial years covered by *The Global Plan to Stop TB: 2006–2015*.

In 2007, overall funding for TB R&D increased by $53 million over 2006, a 12.4% increase from $429 million in 2006 to $482 million. In 2006, funding increased by $61 million (16%) from $368 million in 2005 to $429 million. Thus, reported TB R&D investment appears to be increasing in a linear fashion with no evidence of acceleration and the disturbing possibility of deceleration. Given biomedical inflation and the weakened U.S. dollar during this period, a 12.4% annual increase does not reflect meaningful growth. In the first two years covered by *The Global Plan*, just $537 million was reported spent on research and development of new tools—diagnostics, drugs, and vaccines—for TB, which is just 6% of the $9 billion that *The Global Plan* recommended be spent on new tools development from 2006–2015.At the current anemic growth rate, achievement of *Global Plan* R&D targets—let alone the more ambitious TAG recommendation that $20 billion be spent, including basic science, new tools R&D, and operational research—appears most unlikely.

- In 2007, governments remained the largest funders of TB research, contributing 56.5% of the total. Philanthropic institutions contributed 29.2%. The private sector contributed 14.4%. Among the top 13 donors giving $10 million or more per year, the U.S. National Institutes of Health (NIH; all institutes in aggregate) has increased its support for TB R&D by 15% since 2005, while the Bill & Melinda Gates Foundation increased its support by 116%. The European Commission (EC) increased its investment by 75% and Otsuka Pharmaceuticals by 69%. The Netherlands Foreign Ministry, Novartis, the Eli Lilly Foundation, and USAID increased support by 334%, 419%, 9,094%, and 49%, respectively. Four of the major donors have reduced contributions since 2005.

- Of the six categories of research addressed in the analysis, TB drugs continue to receive the highest levels of funding ($170 million), followed by basic

science ($121 million) and vaccine research ($71.2 million). Diagnostic research funding remains grossly insufficient at $41.9 million, as does operational research at $36.8 million.

- Investment in new TB diagnostics, drugs, and vaccines increased from $209 million in 2005 to $253 million in 2006 and $284 million in 2007. This falls far short of the *Global Plan*'s recommendation to spend at least $900 million per year on R&D for new tools for the diagnosis, treatment, and prevention of TB.

- Aside from lack of funding, survey respondents attributed a lack of knowledge surrounding TB pathogenesis and the lack of appropriate biomarkers as the top barriers to accelerating and improving TB R&D. This highlights the importance of increased investment in the basic science of TB biology, immunology, and pathogenesis.

- Overall, 24 institutions increased overall TB R&D spending between 2005 and 2007, while 13 institutions decreased their investment. Five institutions reported in 2007 for the first time.

- Seven institutions that reported on 2005 or 2006 funding did not report for 2007, among them important donors such as the India TB Research Center ($6.3 million in 2006) and France's INSERM ($5.7 million in 2005). Obtaining data from these institutions as well as others who play a role in TB R&D is essential for maintaining the comprehensiveness and accuracy of these reports and crucial for developing trend analyses. It is kindly requested that these institutions submit TB R&D portfolios as soon as possible. To submit or obtain survey information, please email javid.syed@treatmentactiongroup.org.

- Thirty-one institutions have reported data for each of the three years tracked from 2005 to 2007. Of these, 15 showed increased TB R&D investment over the three years while 16 reduced spending. This suggests that TB R&D funders are becoming less diversified and that the field remains dominated by a small number of large funding institutions—not a healthy situation for any scientific field.

The 2007 data shows that TB R&D spending is increasing at a level far too low to achieve *Global Plan* targets, let alone the more ambitious $2 billion per year from 2006 to 2016 recommended by TAG, which includes the *Global Plan*'s $9 billion for new tools research plus an additional $11 billion for basic science, infrastructure, and operational research.

2. Introduction

2.1 The Importance of TB R&D

The most frequently used TB diagnostic, the sputum smear test, routinely fails to diagnose at least 50% of cases. TB treatment needs to be taken for 6–8 months for drug-susceptible TB and for nearly twice that duration for multidrug-resistant TB. Furthermore, TB treatments are difficult to take with some HIV medication. The BCG vaccine for TB loses its protection over time and doesn't prevent any form of TB disease in adults. It is clear that new tools to diagnose, treat, and prevent TB are needed to meet the Stop TB Partnership and World Health Organization (WHO) goals to reduce TB incidence and death by 50% in 2015 relative to 1990 levels, and to eliminate TB as a public health threat by 2050. Massive scale-up is needed in basic, applied, and operational research and in development of better tools to prevent, diagnose, and cure TB.

2.2 Background

In the spring of 2006, TAG began a resource-mapping exercise to establish a baseline for TB R&D funding disbursed in 2005 against which future funding trends could be analyzed. The findings were published in *Tuberculosis R&D Investments: A Preliminary Assessment* in August 2006. The final edition of the report, *Tuberculosis Research & Development: A Critical Analysis*, published in October 2006, presented a more comprehensive set of 2005 TB R&D data. In the following report, published in November 2007, TAG provided data on reported TB R&D funding in 2006, and compared 2006 with 2005 spending levels. The updated edition of this report, *Tuberculosis R&D: A Critical Analysis of Funding Trends, 2005–2006: An Update*, published in July 2008, included revised and corrected baseline and trend data for 2005 and 2006.

The 2006 TAG report *Tuberculosis Research & Development: A Critical Analysis* identified $393 million invested by forty donors in TB R&D in 2005. Though we now know that this number was inflated due to a discrepancy in reporting and should have been $363 million,[1] the report had a significant impact on raising

1. As noted in the July 2008 report, "In 2005 the MRC [UK] was incorrectly ranked number three with a total donation of $31 million. The correct amount invested by the MRC was $6.2 million, which knocks its ranking down to number 14. . . . The inaccurate account of MRC's contribution of $31 million in 2005 was due to the bundling of a five-year award that should have been annualized to represent spending in 2005. . . . The MRC error is a good illustration of the perils and pitfalls of R&D tracking. It is also an apt example of the need for explicit and standardized annual accounting on the part of R&D donors of all neglected diseases" (Feuer 2008, p. 12).

awareness about the dismal state of investment in TB research. The report's findings were used widely by researchers and policy makers, and the results were presented as a late-breaker at the 37th IUATLD World Conference on Lung Health in Paris in November 2006. Stefan Kaufmann and Shreemanta Parida cited the report in the special TB issue of *Nature Medicine* in March 2007. Neil Schluger of Columbia University cited it as the most important TB paper of 2006 at the March 2007 Keystone TB pathogenesis meeting in Vancouver.

TAG presented its results at the Stop TB Partnership Coordinating Board meeting in Jakarta, Indonesia, and at the NIH National Institute of Allergy and Infectious Diseases (NIAID) Advisory Council special meeting on MDR- and XDR-TB in May 2007. The Foundation for Innovative New Diagnostics (FIND), Médecins sans Frontières, the WHO, and other organizations have cited TAG's data.

2.3 Objectives

By tracking spending trends and highlighting underfunded areas of research, this publication aims to drive advocacy for research on new TB diagnostics, treatment, and prevention tools; for expanded basic science research, which provides the basis for new tools discovery; and for increased operational research, which demonstrates how new and existing tools can be optimized for effectiveness in real-world programmatic conditions.

Forty-nine donors reported for at least one year. Of these, ten did not report in 2005, ten in 2006, and seven in 2007. There was, however, variation in nonreporting. Thus, the data in this report are not complete; some public funders (notably from China, France, and India) did not provide complete data for 2007, nor did most industry funders. Nevertheless, most major sponsors of TB R&D are likely included here.

2.4 Methodology

A list of 128 potential TB research funders was generated using information from the Stop TB Partnership website; reports by Aeras, FIND, and the Global Alliance for TB Drug Development; from Internet research; and from contacts garnered from the last three years' TB R&D survey respondents. Key informants in the TB research community were consulted to assist in confirming a core list of significant donors.

TAG used an e-mail survey to solicit information from funders and recipients about actual annual disbursements (not commitments or awards) for TB research for 2007. The survey also collected information about future commitments; the amount of funding an institution disbursed or received; grant portfolios describing the research; and qualitative responses about priorities and obstacles in TB research.

All efforts were made to follow institutions tracked in 2005 and in 2006 to allow for three-year trend data. Unfortunately, seven previously reporting institutions did not provide data for 2007.

Several new institutions have been identified during the process, expanding the list to 49 surveyed institutions from 2005 to 2007. New to the list in 2007 are the Statens Serum Institute, the New Zealand Health Research Council, the Mexico National Institute of Public Health, Dafra Pharmaceutical Ltd., and the Korean Institute of Tuberculosis.

2.5 Limitations of the Data

The lack of accuracy in resource tracking continues to be a challenge. Several features contribute to this:

1. Certain funders decline to provide data, preventing us from thoroughly tracking existing funding levels and multiyear trends.

2. Funders often do not clearly categorize investments and lack a rigorous understanding about where their money is going, in some cases due to provision of block funds and in others due to a lack of clarity about how their investments will be used.

3. Certain funders have difficulty in separating commitments from disbursements or in apportioning multiyear grants into single years. In some cases funders operate on a two-year fiscal cycle. Some funders ask that their multiyear grants simply be divided by the number of years they cover, though this does not always correlate with actual disbursements.

4. Most companies surveyed declined to reveal the amounts of their investments, though TAG encouraged them to do so by allowing them to remain unnamed in the report. We salute the ten companies that provided data for 2007, eight by name and two who chose to remain anonymous.

TAG urges funders to be more rigorous in tracking their TB R&D investments each year by award and research category so they can measure what they are doing and how it changes over time.

Of the 128 potential research donors or recipients queried, 49 reported on at least one year, but only 30 provided data for each of the years 2005, 2006, and 2007. Thus, this report provides a complete three-year analysis of 30 TB R&D funders.

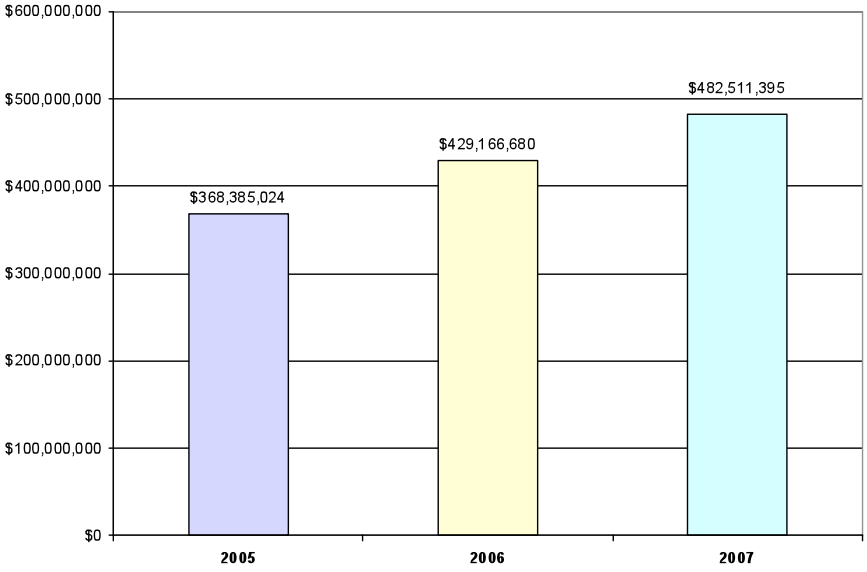
The top 16 donors in 2007 have been tracked in all three years, 2005, 2006, and 2007.

All efforts were made to follow up with nine previously reporting nonrespondents for 2007 that represented $18 million of spending in 2006. It is difficult to estimate what contribution these institutions would have made in 2007. However, even if $18 million were added to the 2007 grant total, TB R&D would have been just $500 million, still starkly below the $900 million recommended in the *Global Plan*.

3. Results

FIGURE 1

Total TB Research & Development Funding: 2005–2007



TAG's R&D funding reports aim to lay the groundwork for global agencies to undertake R&D resource tracking. In 2008 the Stop TB Partnership was to begin tracking national investments in TB R&D and report on investments for 2007, though these plans are currently on hold. The Gates Foundation–funded initiative, the G-FINDER at the George Institute for International Health in Sydney, Australia, started an R&D resource-tracking project for TB along with HIV, malaria, and ten neglected diseases, and produced its first report in February 2009. The G-FINDER used a different survey methodology, conducted its own coding of U.S. NIH grants (rather than relying on NIH program staff to provide data, as TAG did), and did not collect data about investments in operational research. TAG provided the G-FINDER with fully cross-checked data that they could use to verify their datasets, the G-FINDER shared with TAG the surveys it had collected online, and attempts were made to coordinate data collection to prevent duplication of effort. It is encouraging to note that the numbers provided by G-FINDER and by TAG for 2007 are relatively close, given these differences in methodology and scope.

TABLE 1

2007 TB R&D Spending Reported to G-FINDER and to TAG

	G-FINDER**		TAG		(T-G)
Basic Research	$132.4	32.3%	$121.4	25.2%	-11.0
Diagnostics	$35.0	8.5%	$40.6	8.4%	+6.9
Drugs	$145.1	35.3%	$170.2	35.3%	+35.1
Vaccines	$82.3	20.0%	$71.6	14.8%	-10.7
Unspecified	$15.6	3.1%	$36.8	7.6%	+21.2
Operational	N/A	0	$41.9	8.7%	+41.9
2007 total	$410.4	100%	$483.8	100%	+73.4*

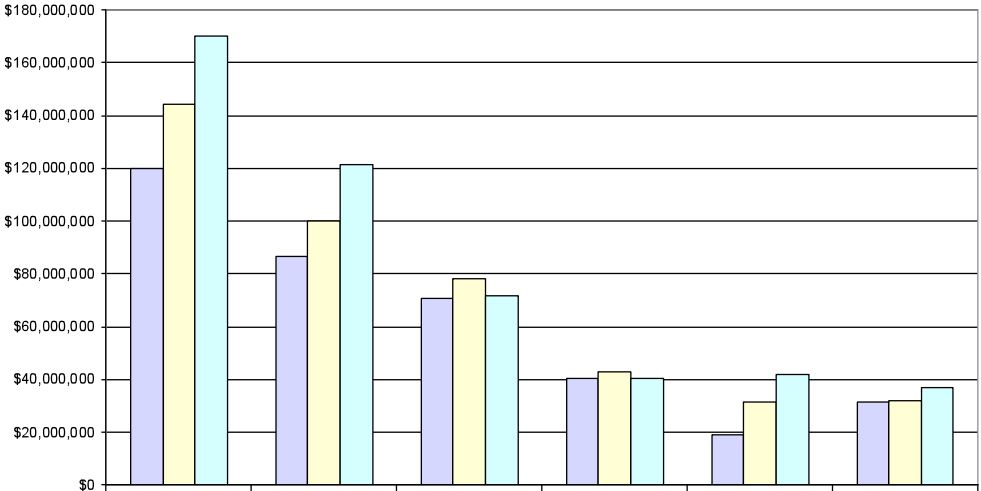
millions of U.S. dollars

* Difference is $31.5 million when operational research is omitted per G-FINDER's scope and methodology.

** Moran M, Guzman J, Ropars AL, McDonald A, Sturm T, Jameson N, Wu L, Ryan S, Omune B. Neglected disease research and development: how much are we really spending? The George Institute for International Health. p. 18. February 2009. www.thegeorgeinstitute.org/shadomx/apps/fms/fmsdownload.cfm?file_uuid=409D1EFD-BF15-8C94-E71C-288DE35DD0B2&siteName=iih, accessed 13 March 2009. See also Moran M, Guzman J, Ropars A-L, et al. Neglected disease research and development: how much are we really spending? PloS Medicine, February 2009, 6:2;e100030.

FIGURE 2

Investment in TB R&D by Research Category in 2005, 2006, and 2007

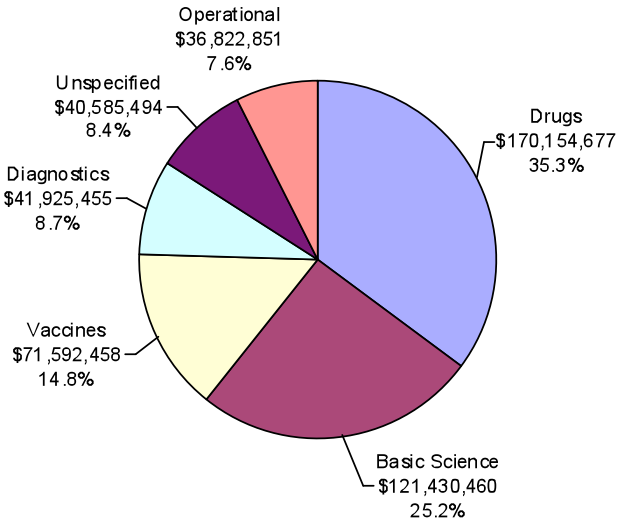


	Drugs	Basic Science	Vaccines	Unspecified	Diagnostics	Operational
2005	$120,119,362	$86,413,880	$70,584,582	$40,608,898	$19,216,467	$31,441,835
2006	$144,264,486	$100,218,236	$78,092,104	$43,069,677	$31,424,479	$32,097,698
2007	$170,154,677	$121,430,460	$71,592,458	$40,585,494	$41,925,455	$36,822,851

3.1 Research Investment Categories

FIGURE 3

TB R&D Investment by Category (2007)
$482,511,395



Scientific grants and research programs focusing on *Mycobacterium tuberculosis (MTb)* and tuberculosis (TB) disease are categorized according to the descriptions below. We do not cover research on other mycobacteria such as *M. avium* or *M. leprae*; however, *M. africanum* and *M. bovis* are considered, as genetically they are part of the *MTb* lineage.

- **Basic research**: undirected, investigator-initiated research that aims to uncover fundamental knowledge about Mycobacterium tuberculosis and other closely related organisms.

- **Applied, preclinical, infrastructure, or otherwise unspecified**: research that the donor or funder was unable to further categorize.

• **Diagnostics**: preclinical or clinical trials of diagnostic technologies and algorithms.

• **Drugs**: preclinical or clinical research on treatments and treatment strategies for tuberculosis disease (including prophylaxis and latent and active TB).

• **Vaccines**: preclinical or clinical research on TB vaccines.

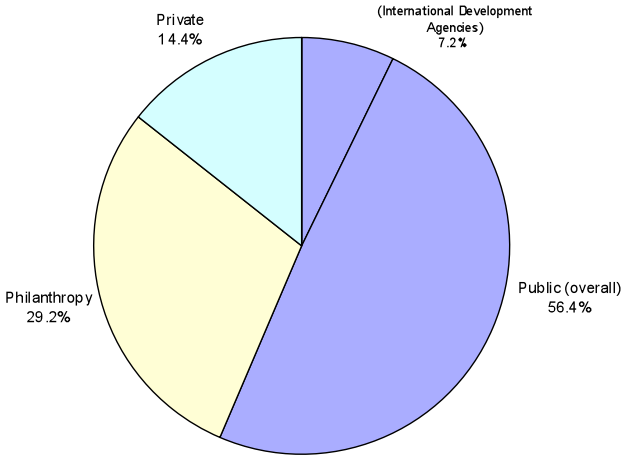
• **Operational research**: includes randomized controlled studies of existing interventions within routine program settings, or targeted evaluation of new or existing interventions to improve TB program performance and reduce TB rates.

Treatment Action Group's three-year collection of data provides an unprecedented picture of reported TB R&D spending from 2005 to 2007, with extensive data on individual donors and trends by research category and by donor category, and provides a unique overview of the world's progress—or more accurately, lack of progress—toward meeting the ambitious R&D targets of the *Global Plan* and the even more ambitious targets set by TAG in 2006.

3.2 Donor Categories

FIGURE 4

TB R&D Funding by Donor Sector (2007)



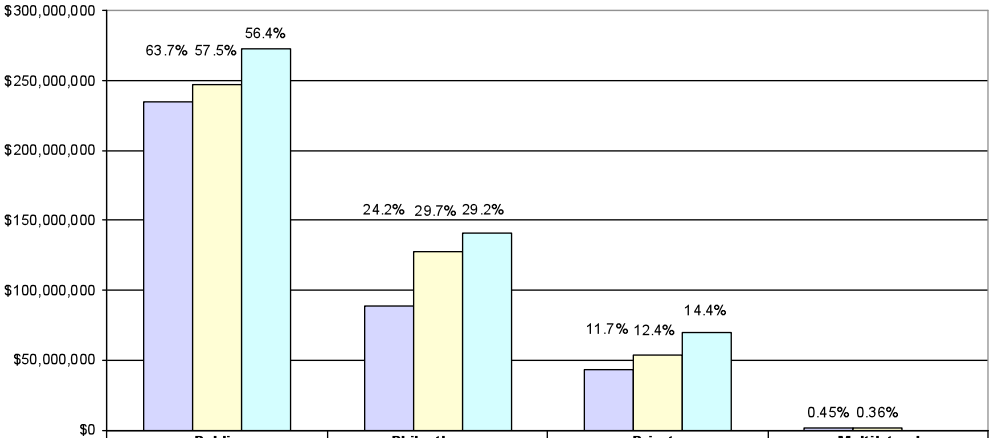
Of the $482 million reported to TAG by the 49 investors in TB R&D in 2007, $272.4 million (56.4%) came from the public sector, $140.9 million (29.2%) from the philanthropic sector, and $69.4 million (14.4%) from industry.

To avoid double counting, TAG did not include disbursements by product development partnerships (PDPs), such as Aeras, FIND, and the TB Alliance, or by other research consortia such as CREATE, TBVAC, or the WHO TDR, since their source funding is reported as a disbursement of the originator institution. Together these PDPs and consortia spent $97.2 million in 2007.

Public-sector investment decreased from 63.6% of total investment in 2005 to 56.5% in 2007. Philanthropies substantially increased the amount disbursed, with the proportion of their investment growing from 24% to 29% of the total between 2005 and 2007. Industry investment rose as a proportion of the total from 11.7% in 2005 to 14.4% in 2007, mostly reflecting investments in drug and diagnostics R&D.

FIGURE 5

Amounts and Proportion of Total TB R&D Funding by Donor Sector, 2005, 2006, and 2007



	Public	Philanthropy	Private	Multilateral
2005	$234,503,645	$89,137,611	$43,095,353	1,648,083
2006	$246,862,858	$127,631,216	$53,138,347	$1,534,259
2007	$272,404,317	$140,917,694	$69,387,383	0

4. Top 10 Funders of TB R&D

4.1 National Institute of Allergies and Infectious Diseases (NIAID), National Institutes of Health (NIH)

The U.S. National Institutes of Health (NIH), the world leader in health research spending, continues to be the largest funder of TB research for the third consecutive year. In 2007, the NIH, which comprises the National Institute of Allergy and Infectious Diseases (NIAID, rank 1), the National Heart, Lung, and Blood Institute (NHLBI, rank 11), and all other NIH institutes and centers (ICs, rank 6), disbursed a total of $160 million in grants and contracts targeted for TB R&D.

In 2007, the NIH was virtually paralyzed by an inability to mount ambitious new initiatives due to frozen funding levels. Due to the poor budget situation and to the NIH's inherent slowness in adapting to emerging needs, 2007 saw only a slight uptick in support for TB R&D, though it was the year immediately following the much-publicized outbreak of extensively drug-resistant tuberculosis (XDR-TB) in South Africa.

Although NIAID's 2007 TB R&D funds increased by $12 million (10%) from 2005, TB spending at the NHLBI declined from $17 million in 2005 to just $11.6 million in 2007. The overall NIH budget has been essentially flat since 2004, actually declining in constant dollars when biomedical inflation is considered. The NIAID supported 82% of the NIH's TB R&D and 27% of all TB R&D reported to TAG for 2007. Of NIAID's $131 million, $61 million went to basic research, a 20% increase from 2006. TB diagnostics and drugs increased at more modest rates of 11% and 13%, respectively. NIAID's investment in TB vaccine research decreased by 25%.

The immediate prospect for the NIH budget has recently brightened with the passage of the American Recovery and Reinvestment Act of 2009, but most of the $10.8 billion appropriated under this act—intended to be distributed among all of NIH's institutes and centers—must be spent within two years. It is unclear whether these stimulus funds will end up benefiting TB R&D. The fiscal year 2009 NIH budget is expected to be $30.3 billion plus the one-time stimulus investment of $10 billion.

4.2 The Bill and Melinda Gates Foundation

The Bill & Melinda Gates Foundation is the world's largest private philanthropic organization, with a total endowment of $29.0 billion at the start of 2009 (previously it was higher, but it has lost value in the recent economic crisis). The Gates Foundation disbursed $124 million for TB R&D in 2007, up 29% from the $96 million disbursed in 2006 and up 116% from the $57 million disbursed in 2005. The majority of the 2007 increase can be attributed to increases in drug development costs. In 2007, $51 million was spent on drug development, nearly a threefold increase from the previous year. Diagnostics research increased from $15 million in 2006 to $21 million in 2007. Operational research also increased from $9.5 million to $18 million since 2006. However, in 2007, basic science and vaccines funding decreased to 2005 levels.

For the first time in 2007, Gates Foundation support for TB R&D outpaced that of NIAID for all categories other than basic research.

The foundation's largest 2007 TB disbursement ($29.7 million) was made to the AERAS Global TB Vaccine Foundation. The Global Alliance for TB Drug Development received $29.3 million, followed by CREATE and FIND, which received $17.8 million and $16.1 million, respectively.

Recent economic setbacks have reduced the Gates Foundation's endowment to $29 billion at the start of 2009, but the Foundation has pledged to meet all of its commitments to existing projects. Nonetheless, as early-stage product development increasingly gives way to later-stage phase II and III trials of new TB drugs and vaccines, costs will mount, and it is unclear whether the public sector will step in to support this research as it should. Another concern is that generous Gates funding for TB R&D may deter other donors from remaining active. Circumstantially, this may explain the withdrawal of the Ellison and Rockefeller Foundations from TB funding. Despite the impact of the Gates Foundation on TB R&D, its activity must not excuse the public and private sectors from continued and increased investment.

4.3 The European Commission's Sixth and Seventh Frameworks

The European Commission's Sixth Framework Programme (FP6) is aimed at integrating European efforts toward small-scale, phase I clinical trials for new TB vaccines and to establish production technologies for lead compounds for

new anti-TB drugs. The Sixth Framework contributed $13 million to TB R&D in 2006. Of this, $7 million went to preclinical vaccine studies, $2.7 million to basic science, and $2.7 million to preclinical drug studies. The Sixth Framework ended in 2006 and was replaced by the Seventh Framework Programme, which runs from 2007 to 2013.

In 2007, the European Commission contributed $23 million to TB R&D, an 81% increase from 2006. This increase was partially unintentional as disbursements from the Sixth Framework were still being made in 2007 alongside new disbursements granted through the Seventh Framework. Future EC funding is expected to flatten out to near 2006 levels.

4.4 Otsuka Pharmaceutical Company

The Otsuka Pharmaceutical Company in Japan is developing the novel nitro-imidazo-oxazole compound OPC-67683, one in a new class of drugs with potent anti-TB activity. The compound is currently in a global, multicenter, randomized, phase II study for treatment of multidrug-resistant (MDR) TB. In 2006 Otsuka rose to become the third largest funder of TB R&D simply by putting OPC-67683 into early bactericidal activity (EBA) studies, an intermediate phase between phases I and II in drug development. In 2007 Otsuka occupies the fourth rank, and is the largest industry donor to TB R&D. We salute the Otsuka company for undertaking its development efforts with this promising new drug, and hope that it will pursue the drug through phase III and to licensure. Companies such as Otsuka and Tibotec are paving the way for a new generation of TB drug trials focused on dire unmet medical needs, such as for people with MDR TB. We hope that other companies will follow their lead and enter the drug development space as well. Nevertheless, the lack of evident public-sector support for large, pivotal phase III efficacy trials for OPC-67683 and other promising new TB drugs remains a concern.

4.5 U.S. Centers for Disease Control & Prevention (CDC)

CDC funding for TB fell from $20 million in 2005 to $17 million in 2006 and only increased by 5% in 2007. From 2006 to 2007, TB drugs received a 14% boost from $8.2 to $9.3 million and infrastructure/unspecified research increased by 15% from $2.8 to $3.2 million. Though individual categories of research have fluctuated, overall CDC TB R&D funding remains unchanged at around $18 million. In 2007, 87% of TB funding from the CDC went to the Tuberculosis Trials Consortium (TBTC) and the TB Epidemiologic Studies Consortium (TBESC).

4.6 Other NIH Institutes & Centers

In addition to larger and more focused NIH efforts at NIAID and the NHLBI, which are listed separately, an additional 14 of the NIH's 27 institutes and centers contributed $17.2 million in 2007. This amount declined from $20 million in 2005.

4.7 The Wellcome Trust

The Wellcome Trust is a UK-based private philanthropy that runs a diverse range of grant programs supporting biomedical research, as well as activities in medical humanities, technology transfer, and public engagement with science.

The Wellcome Trust is the second largest philanthropic investor and the seventh largest overall funder of TB R&D in 2007. Wellcome's overall spending decreased from $18.4 million in 2006 to $15.4 million in 2007. Vaccine research took the hardest hit, with a total disbursement of $319,000, a mere 9% of the 2006 amount. The other two areas of research funded by the Wellcome Trust, basic science and operational research, remained level.

The Wellcome Trust is primarily a response-mode funder. As such, the trust has not earmarked future funds for research into TB or other specific disease areas. However, the trust provides vital support for a range of TB researchers and for strengthening scientific infrastructure in developing countries, particularly Africa. The trust is also showing new interest in some platform technologies for potential new diagnostics (broader than TB alone). We encourage the Wellcome Trust to expand its contributions in all areas.

4.8 UK Medical Research Council (MRC)

Short-course curative TB chemotherapy was largely developed by the UK MRC in a series of groundbreaking trials carried out over the four decades from 1948 to 1986. With TB curable, TB research virtually shut down in the UK, at the U.S. NIH, and around the world. When TB research began to ramp up again after the outbreak of HIV-associated MDR-TB in New York City in the early 1990s, a whole generation of researchers had grown up without significant interest in TB R&D. Thus, the MRC's return to TB research more recently is welcome, and we hope that the MRC will once again step up to meet unfilled needs in TB research, including support not only for basic science but also for much needed clinical trials of new drugs and vaccines.

4.9 Netherlands Ministry of Foreign Affairs (DGIS)

The Netherlands Ministry of Foreign Affairs (DGIS) is a newcomer in the top 10 TB R&D funders. With an overall TB R&D spending of $13.7 million in 2007, DGIS jumped from the 17th largest donor in 2006 to the 9th largest donor in 2007. DGIS supports diagnostics, drugs, and vaccine research. The expansion in DGIS's portfolio is mainly reflected in the increased disbursement for vaccine research; $9.5 million was spent on vaccine development in 2007, representing 14% of total vaccine funding.

The Netherlands DGIS has shown an accelerated rate of TB R&D funding since 2005. This is due to political will by the government of the Netherlands, which in 2006 and 2007 made significant new contributions to TB R&D through the product development partnerships Aeras, FIND, and the TB Alliance.

Other European countries should take notice of the increasing Dutch contributions to TB R&D and should make similarly large, new, multiyear contributions to the field.

4.10 Novartis Institute for Tropical Diseases (NITD), Singapore

Rounding off the top ten TB research donors is the Novartis Institute for Tropical Diseases (NITD), which is focused on preclinical drug discovery. Novartis increased its investment from $8.7 million in 2006 to $11.7 million in 2007.

NITD represents a new model for industry R&D related to diseases of the developing world, in which a large pharmaceutical company sets up an institute to bring together researchers to discover new products to prevent and treat diseases of global concern.

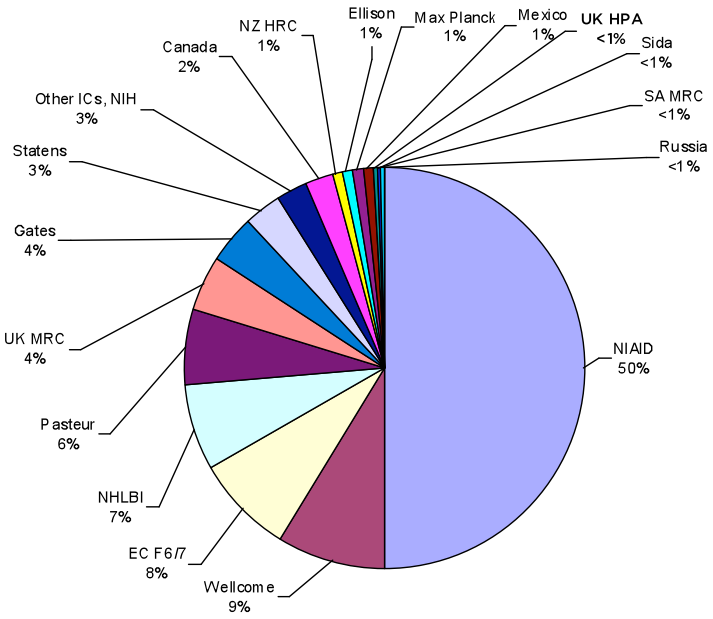
Given the paucity of new TB drugs in the clinic—just five new compounds as well as two older fluoroquinolones—we would encourage more companies to join Novartis, Eli Lilly, AstraZeneca, and GlaxoSmithKline in contributing to the preclinical discovery work carried out at institutions such as NITD.

5. Trends in TB Research by Category

5.1 Basic Science

FIGURE 6

Basic Science
$121,430,461



From the numbers alone, it appears as though basic science funding has experienced linear growth since 2005. From 2005 to 2006, such funding increased from $86 million to $100 million, representing a 16% increase. This growth rate was sustained as funding then increased from $100 million to $121.4 million in 2007. Basic science represents 25% of all TB research. However, it remains insufficient to the challenges posed by the need for a better

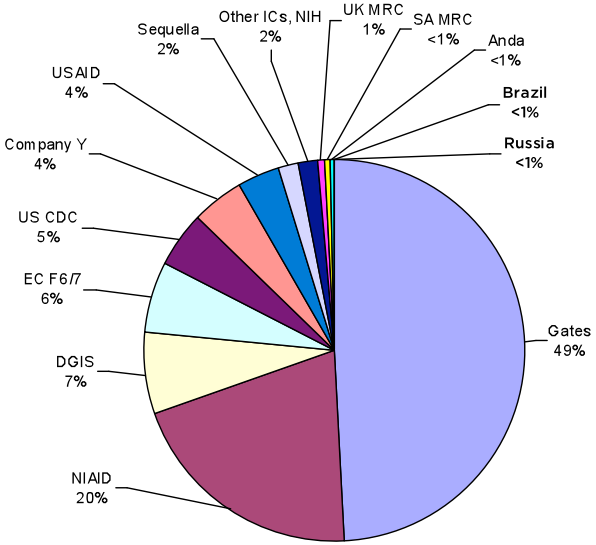
understanding of the *MTb* life cycle, host interactions, defense mechanisms, evolution, latency, and persistence. *MTb* is slow to grow, hard to identify in vivo until full-blown disease occurs, has imperfect animal models that do not fully recapitulate disease pathogenesis in humans, and is expensive and dangerous to handle, requiring biosafety level-3 laboratories in most developed countries. As a result, many researchers prefer to work with the attenuated *M. bovis* BCG organism which may be of limited relevance due to its extensive attenuation.

Much more resources are required if a new generation of scientists is to be attracted to spend its career in TB R&D. New molecular tools, systems biology, genomics and proteomics, and a variety of other new techniques desperately need to be applied to the study of TB pathogenesis and the quest for new and better interventions.

5.2 TB Diagnostics

FIGURE 7

TB Diagnostics
$41,925,455



The most commonly used TB diagnostic, the sputum smear test, routinely fails to detect 50% of TB cases. The failure of current TB diagnostic tools is a challenge for TB control efforts, and funding levels need to reflect the urgency of this area of research. In order to fulfill the *Global Plan*'s 2006 projected R&D needs, diagnostics research spending should double to at least $59 million.

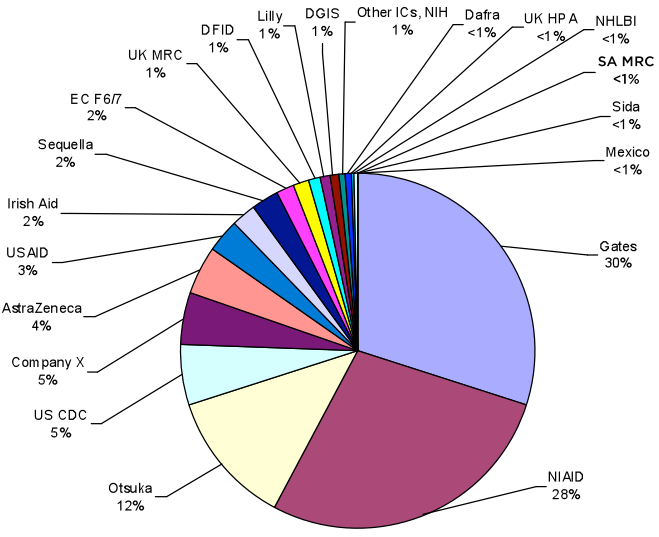
In 2006, diagnostics research represented the research category with the least amount of funding; in 2007, diagnostics ranks as the third lowest. The increase in diagnostics research funding is largely due to a boost in support from the Gates Foundation. At $42 million in 2007, diagnostics research comprises 8.9% of all TB R&D—an increase of 1.6% over 2006, but still grossly insufficient.

Gates Foundation support provided $20.6 million for diagnostics research, representing 49% of all diagnostic research funding in 2007, followed by NIAID at $8.5 million, DGIS at $2.9 million, and the EC at $2.6 million. Though the increase in diagnostics research funding is commended, three-year trend data suggests funding levels are tapering off. Between 2005 and 2006, funds increased by 64%. From 2006 to 2007, they decreased by 34%.

5.3 TB Drugs

FIGURE 8

TB Drugs
$170,154,676



Drug discovery and development is the big fish in the small pond of TB R&D. For the third year, drug development remains the largest funded category of TB R&D. Totaling $169 million, drug research makes up 35.8% of all TB R&D. Not only is drug research the largest funded, it also has the largest number of contributors. Twenty-seven of the forty-eight responding institutions provide drug research funding.

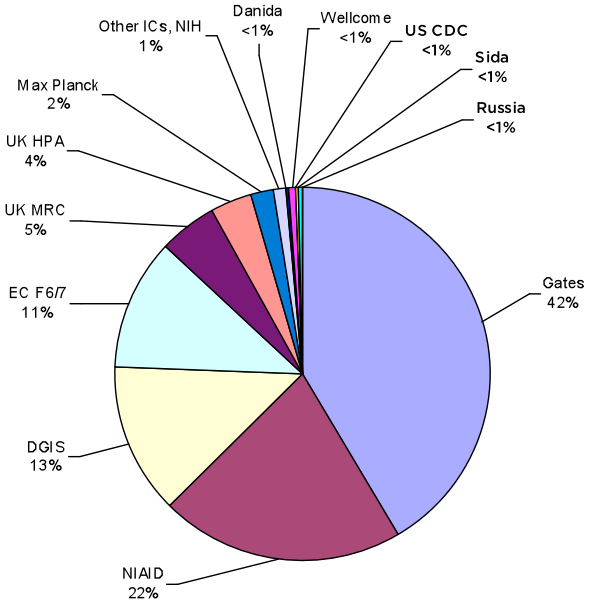
The Gates Foundation increased its drug research funding by $31 million, from $20 million in 2006 to $51 million in 2007; most of the increase was given to the TB Alliance and to the Accelerator program of smaller preclinical drug discovery grants. The Gates increase for drug development funding places NIAID in second rank, with a total of $47 million in 2007, up $5.5 million from the previous year. In third place is Otsuka Pharmaceuticals, the largest private contributor to TB R&D with $21 million directed to drug research in 2007.

With just four drugs in early phase trials—Sudoterb (phase I), SQ-109 (phase I), OPC-67683 (phase II), and TMC-207 (phase II)—and two drugs (gati- and moxifloxacin) in phase III trials, the clinical pipeline is alarmingly small. Failures are common during early phase drug development and may be anticipated among these candidates. The strength of the preclinical pipeline remains to be seen. Infrastructure for the large phase III trials required to gain regulatory approval is nonexistent. Infrastructure for phase IV postmarketing studies is also scant. The field is now challenged, not by a lack of drugs to test but by the lack of institutional commitment by any funder—including the U.S. NIH—to subsidize trials that the industry may be reluctant to undertake.

5.4 TB Vaccines

FIGURE 9

Vaccines
$71,592,458

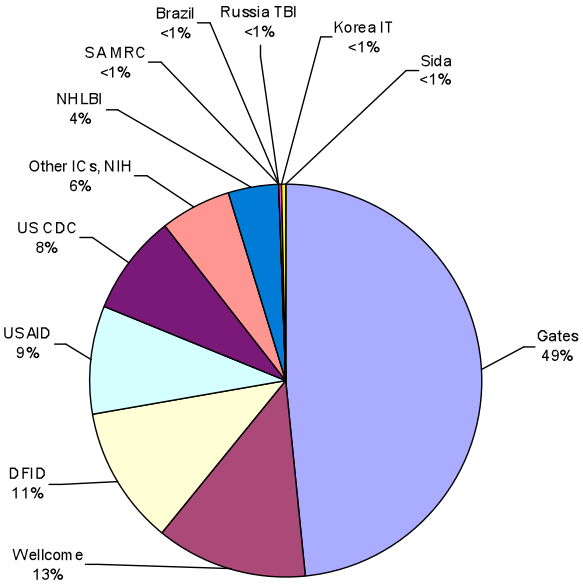


Of the six categories assessed in this report, vaccine research shows the most troubling trend. With a grand total of $68 million in 2007 funding, it is the only category that has dipped below its 2005 level of funding. It rose slightly in 2006 and has now fallen back in 2007 to slightly below the 2005 baseline.

5.5 Operational Research

FIGURE 10

Operational Research
$36,822,851



In 2007, operational research increased to $37 million from $32 million in 2006. The Gates Foundation remains the largest donor in this category of research, with a contribution of $17.8 million. The Wellcome Trust ranks second with $4.6 million, and the UK Department for International Development (DFID) is third with $4.2 million.

TB operational research remains deeply underfunded. If and when any new tools reach approval, the infrastructure to validate their effectiveness in the field under routine program conditions remains unbuilt.

6. Conclusions & Recommendations

6.1 Conclusions

Although TB is the most common curable infectious cause of death worldwide, TB R&D remains an underresourced backwater, with only sluggish growth registering in the years from 2005 to 2007. Despite the release of *The Global Plan to Stop TB 2006–2015* and the outbreak of XDR-TB in KwaZulu-Natal in 2006, the world's leading public research funding agencies have been slow to increase their investments in TB R&D. It is to be expected that public agencies would be slow to increase spending (and there is a danger that the current economic climate will further blunt growth), yet the world's leading public research funding agencies have also not risen to the challenge of massively increasing support for TB R&D.

Though public R&D funding has not increased substantially, some public international development agencies, such as the EC Frameworks 6 and 7, the Netherlands DGIS, USAID, and Irish Aid, have made substantial new investments in TB R&D. The overall performance by the rich Organization for Economic Co-operation and Development countries, however, remains disappointingly inadequate.

We have found some developing countries increasing their support for TB R&D, but reporting is patchy and inconsistent. We hope that this area will be one of major growth in the coming years, particularly as China, India, Russia, Brazil, Thailand, and South Africa report new TB R&D activity.

The Gates Foundation and the Wellcome Trust remain the only significant philanthropic supporters of TB R&D, with growth in the Gates Foundation's support largely responsible for the overall increase in TB R&D spending since 2005. However, as noted above, there may be a disturbing trend in play if the presence of a single large funder tends to displace or discourage other foundation support. It would ultimately be unhealthy for TB research if too few players take responsibility while too many turn away.

Some industry entities are now making a significant effort in TB, particularly in drug discovery. The much greater involvement of Otsuka, Novartis, Eli Lilly, AstraZeneca, Sequella, Statens Serum Institute, Company X, and Company Y provides a ray of hope that more companies will enter this space of unmet medical need with the potential to save millions of lives.

6.2 Recommendations

TAG remains committed to our original goal of encouraging research funders to increase their investments in TB R&D fourfold, to $2 billion per year, as the minimum necessary to underwrite the science that will lead to TB no longer being a significant public health threat by the year 2050. At current rates this goal is not one of science but of science fiction. The continuing failure to fund TB R&D at adequate levels, along with the continuing inadequacy of TB control programs worldwide, condemns tens of millions of people to unnecessary suffering and death over the next four decades. It is time to change that.

* * *

Appendix A: Top Reporting TB R&D Funders in 2007

2007 Rank	2006 Rank	Institute	Total	Donor Sector
1	1	US NIAID, NIH	131,378,370	P
2	2	Bill & Melinda Gates Foundation (BMGF)	124,213,521	F
3	8	European Commission Framework 6/7	23,366,617	P
4	3	Otsuka Pharmaceutical Company	20,766,495	C
5	6	US Centers for Disease Control & Prevention (CDC)	17,874,795	P
6	5	US other institutes & centers, NIH	17,257,593	P
7	4	Wellcome Trust	15,448,553	F
8	13	UK Medical Research Council (MRC)	15,021,383	P
9	17	Netherlands Minisitry of Foreign Affairs (DGIS)	13,735,741	P - D
10	11	Novartis Institute for Tropical Diseases	11,700,000	C
11	7	US NHLBI, NIH	11,579,120	P
12	40	Eli Lilly Foundation	10,450,000	C
13	14	USAID	10,000,000	P - D
14	12	Company X	7,900,000	C
15	15	AstraZeneca	7,650,000	C
16	10	Institut Pasteur	7,468,821	P
17	9	UK Department for International Development (DFID)	6,006,379	P - D
18	20	Sequella, Inc	4,735,000	C
19	19	Irish Aid	4,050,000	P - D
20	22	Canadian Institute of Health Research	3,917,387	P
21	21	UK Health Protection Agency (HPA)	3,907,664	P
22		Statens Serum Institute	3,611,407	C
23	24	Germany, Max Planck Institute for Infectious Biology	2,336,000	P
24	27	Company Y	1,770,000	C
25		New Zealand, Health Research Council	1,160,335	P
26	31	South Africa Medical Research Council (SA MRC)	1,096,987	P
27	25	Ellison Medical Foundation	1,020,900	F
28		Mexico National Institute of Public Health	814,746	P
29		Dafra Pharma International Ltd.	673,770	C
30	28	Swedish International Development Cooperation (Sida)	572,337	P - D
31	35	Denmark Ministry of Foreign Affairs (Danida)	353,246	P - D
32	18	Brazil (amalgamated)	321,481	P
33	36	Anda Biologicals	130,711	C
34	23	Russian TB Institutes	120,316	P
35	39	KNCV Tuberculosis Foundation	36,720	F
36	32	US FDA	35,000	P
37		Korean Institute of Tuberculosis	30,000	
	37	Ireland Health Research Board	0	
	16	India ICMR/TB Research Center (TRC)	0	
	26	Global Fund to fight AIDS, Tuberculosis and Malaria	0	
	29	Research Institute of Tuberculosis, Japan Anti-TB Association	0	
	30	All India Institute of Medical Sciences (AIIMS)	0	
	33	China CDC National Tuberculosis Reference Laboratory	0	
	34	Rockefeller Foundation	0	
	38	Thailand Ministry of Public Health	0	
	41	France Ministry of Foreign Affairs Coöperation Française	0	
	42	Swiss Agency for Development and Cooperation	0	
			482,511,395	

P = public sector R&D agency
P-D = public sector development agency
F = foundation / philanthropy
C = corporate / private sector

Basic Science	Infra/Unspec.	Diagnostics	Drugs	Vaccines	Operational
60,601,039	0	8,490,213	47,302,720	14,984,398	0
4,900,000	13,521	20,600,000	51,200,000	29,700,000	17,800,000
9,885,526	0	2,560,326	2,929,552	7,991,213	0
0	0	0	20,766,495	0	0
0	3,187,761	2,065,772	9,343,443	217,000	3,060,819
3,084,249	9,471,586	660,871	1,178,814	704,969	2,157,104
10,567,887	0	0	0	318,561	4,562,105
5,279,677	3,658,475	256,311	2,230,164	3,596,756	0
0	0	2,897,211	1,350,501	9,488,029	0
0	11,700,000	0	0	0	0
8,360,449	1,173,996	0	532,682	0	1,511,993
0	9,000,000	0	1,450,000	0	0
0	0	1,608,334	5,118,333	0	3,273,333
0	0	0	7,900,000	0	0
0	0	0	7,650,000	0	0
7,468,821	0	0	0	0	0
0	0	0	1,803,537	0	4,202,842
0	0	700,000	4,035,000	0	0
0	0	0	4,050,000	0	0
2,533,617	1,383,770	0	0	0	0
601,179	0	0	601,179	2,705,306	0
3,611,407	0	0	0	0	0
1,000,000	0	0	0	1,336,000	0
0	0	1,770,000	0	0	0
1,160,335	0	0	0	0	0
202,520	718,400	160,450	13,770	0	1,846
1,020,900	0	0	0	0	0
803,168	0	0	11,579	0	0
0	0	0	673,770	0	0
347,996	0	0	13,138	183,410	27,793
0	0	0	0	353,246	0
0	206,265	24,858	0	0	90,358
0	0	130,711	0	0	0
1,690	0	398	0	13,570	104,658
0	36,720	0	0	0	0
0	35,000	0	0	0	0
0	0	0	0	0	30,000
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
121,430,461	**40,585,494**	**41,925,455**	**170,154,676**	**71,592,458**	**36,822,851**

Category columns may not sum correctly due to fractional rounding

Appendix B: TB R&D Funders in 2007, 2006, and 2005

2007 Rank	Institute	Total	2007 Rank	2006 Total
1	US NIAID, NIH	131,378,370	1	119,771,818
2	Bill & Melinda Gates Foundation (BMGF)	124,213,521	2	96,466,861
3	European Commission Framework 6/7	23,366,617	3	12,844,807
4	Otsuka Pharmaceutical Company	20,766,495	4	22,900,000
5	US Centers for Disease Control & Prevention (CDC)	17,874,795	5	17,057,774
6	US other institutes & centers, NIH	17,257,593	6	17,579,000
7	Wellcome Trust	15,448,553	7	18,380,741
8	UK Medical Research Council (MRC)	15,021,383	8	8,111,736
9	Netherlands Ministry of Foreign Affairs (DGIS)	13,735,741	9	5,864,942
10	Novartis Institute for Tropical Diseases	11,700,000	10	8,700,000
11	US NHLBI, NIH	11,579,120	11	13,139,592
12	Eli Lilly Foundation	10,450,000	12	140,000
13	USAID	10,000,000	13	7,700,000
14	Company X	7,900,000	14	8,700,000
15	AstraZeneca	7,650,000	15	7,200,000
16	Institut Pasteur	7,468,821	16	8,785,490
17	UK Department for International Development (DFID)	6,006,379	18	12,576,339
18	Sequella, Inc	4,735,000	19	3,743,000
19	Irish Aid	4,050,000	20	3,765,210
20	Canadian Institute of Health Research	3,917,387	21	3,257,764
21	UK Health Protection Agency (HPA)*	3,907,664	22	3,689,954
22	Statens Serum Institute	3,611,407	23	**
23	Germany, Max Planck Institute for Infectious Biology	2,336,000	24	1,910,000
24	Company Y	1,770,000	25	1,500,000
25	New Zealand, Health Research Council	1,160,335	17	**
26	South Africa Medical Research Council (SA MRC)*	1,096,987	26	1,240,620
27	Ellison Medical Foundation	1,020,900	27	1,850,000
28	Mexico National Institute of Public Health	814,746	28	**
29	Dafra Pharma International Ltd.	673,770	29	**
30	Swedish International Development Cooperation (Sida)	572,337	30	1,415,691
31	Denmark Ministry of Foreign Affairs (Danida)	353,246	31	415,627
32	Brazil (amalgamated)	321,481	32	4,031,671
33	Anda Biologicals	130,711	33	395,347
34	Russian TB Institutes	120,316	34	2,772,000
35	KNCV Tuberculosis Foundation	36,720	35	199,556
36	US FDA	35,000	36	651,224
37	Korean Institute of Tuberculosis	30,000	37	**
N/A	Ireland Health Research Board	0	N/A	385,705
N/A	Research Institute of Tuberculosis, Japan Anti-TB Association	0	N/A	1,358,568
N/A	Rockefeller Foundation	0	N/A	450,000
N/A	Thailand Ministry of Public Health	0	N/A	226,463
N/A	Swiss Agency for Development and Cooperation	0	N/A	50,203
***	India ICMR/TB Research Center (TRC)	***	***	6,347,873
***	Global Fund to fight AIDS, Tuberculosis and Malaria	***	***	1,534,259
***	All India Institute of Medical Sciences (AIIMS)	***	***	1,299,004
***	China CDC National Tuberculosis Reference Laboratory*	***	***	626,059
***	France Ministry of Foreign Affairs Coöperation Française	***	***	131,782
***	Inserm	***	***	**
***	N.W.O. NL	***	***	**
	TOTAL	**482,511,395**		**429,166,680**

* Data not available for 2005; ** for 2006; *** for 2007

2006 Rank	2006–2007 % Change	2005 Rank	2005 Total	2005–2006 % Change	2005–2007% Change
1	9.7%	1	120,273,000	-0.4%	9.2%
2	28.8%	2	57,411,457	68.0%	116.4%
8	81.9%	8	13,322,711	-3.6%	75.4%
3	-9.3%	9	12,300,000	86.2%	68.8%
6	4.8%	4	19,903,000	-14.3%	-10.2%
5	-1.8%	3	20,334,300	-13.6%	-15.1%
4	-16.0%	6	18,081,399	1.7%	-14.6%
13		13	6,178,458	31.3%	
17	134.2%	17	3,168,488	85.1%	333.5%
11	34.5%	20	2,255,193	285.8%	418.8%
7	-11.9%	7	17,117,000	-23.2%	-32.4%
40	7364.3%	40	113,660	23.2%	9094.1%
14	29.9%	12	6,694,000	15.0%	49.4%
12	-9.2%	5	18,640,160	-53.3%	-57.6%
15	6.3%	11	8,000,000	-10.0%	-4.4%
10	-15.0%	10	8,472,800	3.7%	-11.8%
9	-52.2%	21	2,008,832	526.1%	199.0%
20	26.5%	27	1,400,000	167.4%	238.2%
19	7.6%	34	360,000	945.9%	1025.0%
22	20.2%	19	2,376,098	37.1%	64.9%
21	5.9%	*	*		
			*		
24	22.3%	18	2,500,000	-23.6%	-6.6%
27	18.0%	31	500,000	200.0%	254.0%
			*		
31	-11.6%	*	*		
25	-44.8%	24	1,650,000	12.1%	-38.1%
			*		
28	-59.6%	32	486,599	190.9%	17.6%
35	-15.0%	37	170,344	144.0%	107.4%
18	-92.0%	28	755,587	433.6%	-57.5%
36	-66.9%	*	*		
23	-95.7%	22	1,930,343	43.6%	-93.8%
39	-81.6%	38	170,666	16.9%	-78.5%
32		29	651,231	0.0%	
37	-100.0%	*	*		
29	-100.0%	26	1,487,961	-8.7%	-100.0%
34	-100.0%	23	1,750,000	-74.3%	-100.0%
38	-100.0%	33	430,957	-47.5%	-100.0%
42	-100.0%	36	195,099	-74.3%	-100.0%
16		15	5,313,133	19.5%	
26		25	1,648,083	-6.9%	
30		16	3,904,821	-66.7%	
33		*	*		
41		30	508,368	-74.1%	
		14	5,721,560		
		35	199,716		
			368,385,024		

References

Feuer C. Tuberculosis Research & Development: A Critical Analysis. Syed J, Harrington M, Huff B, eds. New York, Treatment Action Group, July 2008

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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 lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

TB/HIV PROJECT

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

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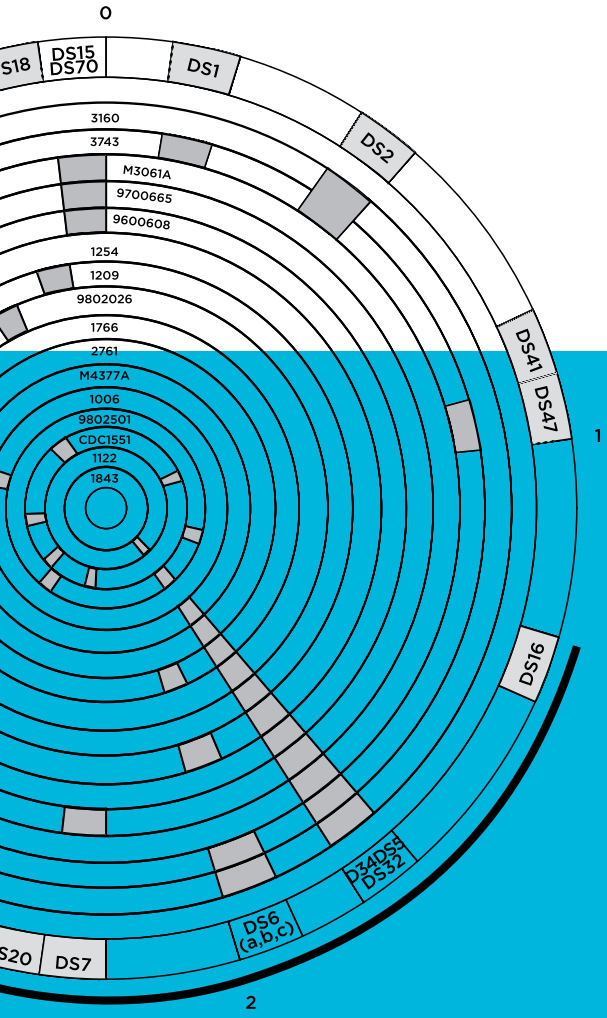

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