Tuberculosis Research & Development:
A Critical Analysis

by Cindra Feuer

edited by Javid Syed and Mark Harrington
with Bob Huff

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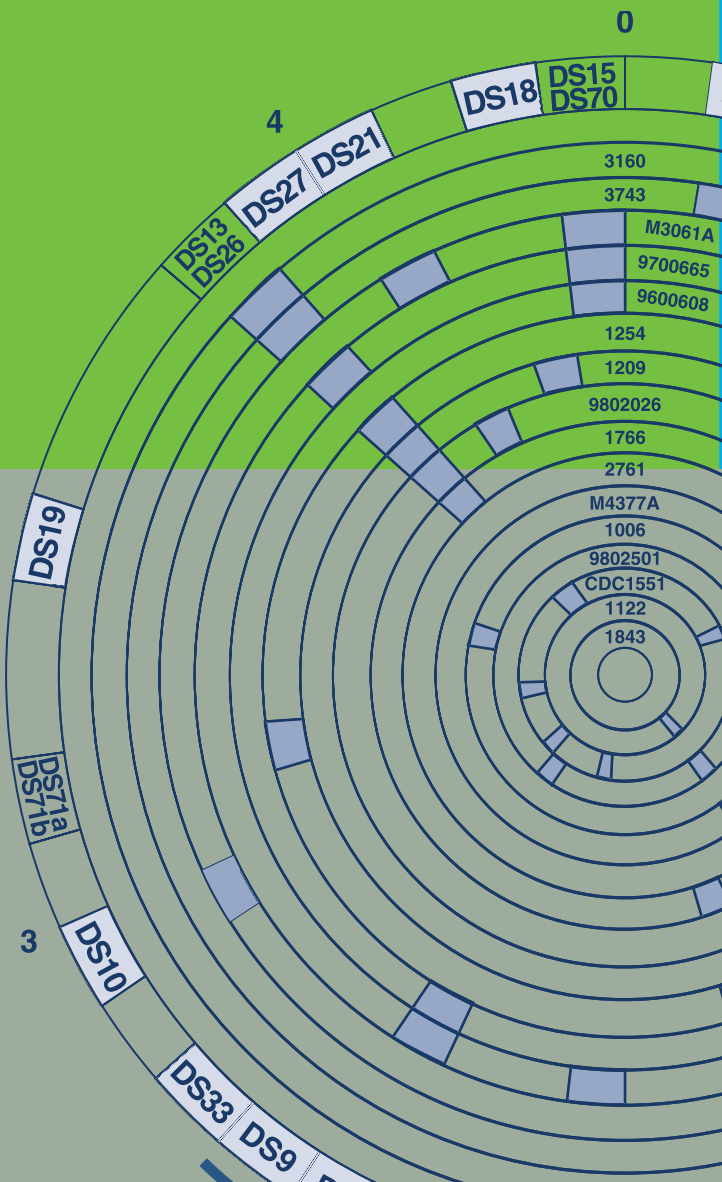

TAG
Treatment Action Group

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The content of this report and all opinions expressed are those of the Treatment Action Group.

“Extreme resistance signals that the current strategies [for TB control] are failing. If we stick to the previous model nothing is going to happen. The fire is burning now.”

—Martine Guillerm, Médecins sans Frontières

“If they can’t treat the people identified by microscopy, then why are they talking about fancy new diagnostics?”

—Helen Lee, Cambridge University

“The challenge with TB advocacy is to convince people with little funding who are already overwhelmed with work to get involved.”

—Ezio Távora dos Santos Filho, Brazilian TB/HIV activist

“We as a community—TB workers and investigators—have been for too long satisfied with an inadequate amount of resources dedicated to TB research.”

—Paul Zintl, Partners in Health

This report is dedicated to

Omololu Falobi
(1971–2006)

Founder
Journalists Against AIDS (JAAIDS), Nigeria

Nigerian AIDS activist, journalist,
father, & champion of justice

About TAG: The Treatment Action Group (TAG) is dedicated solely to advocating for larger and more efficient research efforts, both public and private, toward finding better treatments, a cure, and a vaccine for AIDS. TAG's TB/HIV Project works to combat TB/HIV coinfection through a combination of community-based advocacy, education, and mobilization strategies to achieve stronger and more comprehensive and coordinated efforts to combat TB/HIV through community participatory TB/HIV policy and research formulation, implementation, and evaluation. These efforts involve TB/HIV advocates in developed and developing countries.

If you are aware of TB research funding programs which are not captured in this assessment, or believe that TAG has not completely or accurately characterized TB research programs, please write to TAG directly and let us know so that we can ensure that TAG's website version of the report *Tuberculosis Research Funding: A Critical Analysis* is as complete and accurate as possible.

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Table of Contents

Foreword

by Mark Harrington

This report is the product of an effort by the Treatment Action Group (TAG) to ascertain the major funders of tuberculosis (TB) research and development (R&D) in 2005, what kinds of research activity they funded, and how much research activity is already taking place. This assessment will help policymakers, funders, researchers, and advocates understand the current state of research on TB, and it provides a baseline for understanding how much TB research funding will need to increase in order to bring TB under control over the next decade.

TAG's researcher/writer, Cindra Feuer, assisted by TB/HIV Project Director Javid Syed and I, contacted leading institutions worldwide to determine their TB R&D investments in 2005. Eighty institutions out of 100 provided information. We are grateful to all who provided useful data and responded to, in many cases, repeated queries. Here we are able to provide estimates of the total amount spent on TB R&D by the top 40 donors in 2005—$393 million—and estimates of the relative proportion spent on basic science; applied research on new TB tools including diagnostics, drugs, and vaccines; and operational research to optimize the use of existing interventions in routine program settings.

Though it is an inexact art, a recent bibliometric paper, which assessed outputs and expenditures on health research in eight disease areas, including TB from 1996–2001, estimated a similar level of investment, $350 million per year (Lewison 2004). It is likely that the bibliometric assessment picked up some operational research in high-burden countries which we did not quantify. Their assessment of industry investment, $28 million, was less than our assessment of $43 million, which counted only the six companies that reported figures to TAG.

The data indicate that investment in TB R&D lags far behind necessary levels. If new tools funding continues at its 2005 level of $206 million, just $2.06 billion will be available for new tools research over the next decade, whereas *The Global Plan to Stop TB: 2006–2015* estimates that $9 billion will be needed, revealing a new TB tools funding gap of $6.9 billion. Thus, TB R&D investment needs to increase nearly five-fold to meet *The Global Plan* targets. Still more is needed to expand basic science and operational research. All this will only come with worldwide political advocacy for a TB research movement with ambitious and comprehensive targets for investment in the basic, applied, and operational research that can make TB history.

To accomplish this, TAG recommends that investors in TB R&D worldwide urgently increase their investments fivefold, from less than $400 million per year, to $2 billion per year, with $1.05 billion directed towards new tools research and $950 million directed towards basic science, infrastructure development, and operational research each year, for a total investment of $20 billion in TB R&D over the coming decade. This will not take place without the creation of a global TB research movement that will coordinate research efforts and funding across various sectors as well as engage stakeholders to raise the political profile of tuberculosis.

Executive Summary

TAG surveyed 100 institutions involved in programming TB research and development funds in 2005. Globally, the top 40 donors in TB R&D reported investing $393 million in 2005. Whereas *The Global Plan to Stop TB 2006–2015* estimates a funding need for $9 billion in research on new TB tools (drugs, diagnostics, and vaccines), the top R&D investors spent only $206 million on this research in 2005. To achieve *Global Plan* objectives, new tools R&D investment needs to increase approximately five-fold, to $1.05 billion per year. In addition, *The Global Plan* did not budget for the basic science, infrastructure development, and operational research necessary to provide a foundation for and validate new TB tools. TAG found $188 million was invested in these critical research areas in 2005. Based on our findings and extrapolating from the five-fold increased investment needed in new tools research, TAG estimates that investment in basic science, infrastructure development, and operational research needs to increase five-fold to approximately $950 million per year. In total, over the next decade, TAG estimates $20 billion is needed to fully support TB R&D.

In 2005, public sector agencies accounted for 69% of TB R&D investments, philanthropies for 20%, 11% from industry (reporting incomplete because some companies declined to disclose), and multilateral agencies less than 0.4%. Among national governments, the leading funders were the US, the UK, France, the EU, and India. In 2005 the top institutional donors to TB research were the U.S. National Institutes of Health ($158 million), the Bill & Melinda Gates Foundation ($57 million), the U.K. Medical Research Council (MRC, $31 million), and U.S. Centers for Disease Control (CDC, $20 million).

Of the $206 million invested in new TB tools, new drugs received the most investment ($120 million), 31% of all TB R&D; followed by new vaccines ($70 million), 18% of all R&D; with new diagnostics receiving the least ($16.5 million), just 4% of all TB R&D.

$93.7 million was invested in basic research on TB, while applied/unspecified research received $43.6 million, and operational research received $49.6 million.

Recommendations

Research Agenda

1 A comprehensive, global TB R&D agenda is urgently needed. A TB R&D agenda needs to incorporate the entire spectrum of research that is needed to achieve the goals set forth in *The Global Plan to Stop TB*. This comprehensive research agenda should also address the need for major expansion of the basic and operational research foundation that would support new tool development. In addition, each of the Plan's New Tool Working Group used different (and in some cases incompletely documented) methods of calculating their ten year research needs. In particular the New Diagnostics Working Group estimate seems to be woefully short of the great need for investment in a breakthrough there, while the New Vaccines Working Group evidently lacks a detailed public workplan.

Research Coordination

2 TB R&D need to be better coordinated globally and nationally. TAG's analytic review demonstrates not only that TB R&D is severely underfunded, but that funders do not adequately coordinate their efforts globally, by research area, or in high burden countries. While philanthropic and public agencies were forthcoming with estimates for TB research, internal tracking systems were inconsistent and incomplete. Some funders did not code grants by specific disease, let alone research area or phase. TAG recommends the standardization of internal tracking systems according to disease (including the separation and coding of diseases that are studied in combination such as TB and HIV), research category, and research phase to enable more comprehensive annual tracking of R&D investments in all diseases of global health importance, including TB.

Research Funding Transparency

3 Pharmaceutical and biotechnology companies need to be transparent and open about their investments in TB R&D. The lack of transparency by some major players in the commercial sector prevents us from obtaining a clear understanding of the extent of private investment in TB R&D. Six of eighteen companies contacted provided detailed investment data for 2005 (two anonymously); four declined to provide any data; three did not respond; and five stated that they did not fund TB R&D. TAG recommends the private sector present its investments in TB R&D publicly. This will help inform efforts by policymakers, research funders, and TB control programmers worldwide to coordinate their investments in TB research.

Reporting Consistency

4 **Recording and reporting for TB R&D funding needs to be consistent and comprehensive**. TAG recommends that agencies responsible for tracking global R&D investments in TB create uniform and consistent criteria for tracking programs and for reporting on them annually. This work could be carried out by the Stop TB Partnership, if it were fully funded and staffed at an adequate and sustained level, with new expert staff dedicated to this work. It would be important for this research tracking effort to be seen as independent and unbiased. For this reason TAG suggests that the research tracking effort be carried out independent of the current New Tools Working Groups whose work will also be tracked. This will facilitate developing an accurate picture of R&D investments and needs forecasting specifically designed to measure progress toward achieving *The Global Plan* funding targets. In addition, R&D tracking needs to specify whether research is pre-clinical, clinical, or operational, to ensure that all phases of R&D and new tool development are adequately funded. For example, this report demonstrates that new drug development receives relatively greater investment than do other new tool areas, yet support for clinical trials for TB drug development remains anemic.

Recommendations to Donors, Researchers, Policymakers, and High Burden Countries

5 TB R&D investment must increase fivefold, from approximately $400 million per year to $2 billion per year for basic science, applied, and operational research in order to meet the ambitious R&D targets specified in *The Global Plan*.

6 Donors and developing-country policymakers must commit to global and national plans for health-related research.

7 Donors must support policies that strengthen healthcare systems in resource-constrained countries and high-burden countries.

8 Donors must recognize and support public-private product development partnerships (PDPs) for their work in catalyzing basic, translational and clinical research, particularly on new tools.

9 Donors must explore and support incentive mechanisms such as advanced market commitments to attract private industry to TB research.

10 Donors and research agencies must incorporate activists in the TB community into research program planning and execution.

11 Donors, research agencies, and high-burden countries must support community advocacy efforts to elevate TB's political profile and mobilize community to demand care, prevention, treatment, and research.

12 Donors, research agencies, and high-burden countries must demonstrate transparency and provide funding to allow for an ongoing and sustained effort to comprehensively map and annually update investments in TB R&D.

13 Donors, research agencies, and planners must support scientists from outside fields, such as HIV/AIDS, to integrate expertise from different disciplines. Researchers must recruit new scientists to the field and promote innovative approaches to TB research.

14 Regulatory agencies like the U.S. FDA, the EMEA, the South African Medicines Control Council (MCC), and others must commit to support guidelines to accelerate the study and licensure of new TB diagnostics, drugs, and vaccines.

15 Policymakers must ensure that new tools recommended for use by the national or regional regulatory authorities will be fully incorporated into TB programs.

Towards a Global TB Research Movement: Recommendations to Advocates

16 TB research advocates should articulate the need for high-level commitment to support TB research, using evidence of this and future tracking reports to expose failures of commitment.

17 TB research advocates should use economic and epidemiological data to engage ministries in donor countries and HBCs to allocate funding for TB research.

18 TB research advocates should demand support for affected communities to create TB visibility and awareness, and to elevate TB's profile among policymakers and other political leadership.

19 TB research advocates should build stronger linkages with the HIV community and other advocates, such as labor unions and poverty-reduction organizations working in at-risk or high-burden communities.

20 TB research advocates should continually assess accomplishments of current and planned TB-research project funding to determine whether the allocated funds are well placed and sufficient.

Executive Summary (continued)

Tuberculosis, an ancient scourge dating back to the time of the Pharaohs (Zink 2003; Donoghue 2004), has persisted as a global public health disaster with one in three of the world's population currently TB-infected. WHO estimates that there were nearly nine million new cases and almost two million deaths caused by TB in 2004, and that global incidence rose by 1% that year (WHO 2006).

After biomedical interventions and economic development had reduced TB incidence through much of the 20th century, degradation of health care systems and a dramatic spike in HIV infections in resource-poor countries in the 1990s allowed for a resurgence of the TB epidemic. The devastation of tuberculosis in the context of the HIV pandemic and the spread of multidrug-resistant (MDR) TB in the 1990s stimulated a global effort to scale up control through WHO's Direct Observed Therapy Short-course (DOTS) strategy. Despite this, it has become clear that our current tools are inadequate to control TB, and there has been increasing acknowledgment that investment in the discovery and development of new diagnostics, drugs, and vaccines will be required to eliminate TB as a public health problem in the 21st century.

The first five years of the new century have seen encouraging developments, including the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and the expansion of WHO's DOTS strategy into a new, more comprehensive Stop TB Strategy, which specifically includes TB/HIV, MDR-TB, and research and development (Raviglione 2006). But there is a paucity of comprehensive information about current levels of global research investment in tuberculosis.

TAG set out to map TB R&D investments and disbursements for the year 2005 in order to provide a baseline to inform advocacy efforts to mobilize greater resources for TB research. TAG surveyed an estimated 100 institutions believed to be the likeliest funders of TB research, gathered information from publicly available sources, followed up with those who did and did not respond, and conducted in-depth qualitative interviews with key informants.

Some notable potential major funders of TB research have not responded, particularly from public sector programs in some developed and developing countries. In addition, almost a quarter of the pharmaceutical and biotechnology companies contacted declined to provide R&D figures. We have included those that responded and noted those that declined to respond (*see Appendix B*).

TAG through this report identifies the need for a more comprehensive, and sustained effort to be undertaken to comprehensively map and annually update investments in TB R&D. This effort should include public, private, philanthropic, and multilateral

research programs from developed and developing countries, and should be accessible through a public database. It should apply consistently defined coding criteria to clarify the area (for example, basic, diagnostic, treatment, vaccine) and the phase (preclinical, clinical phases I, II, III, IV, and operational research).

This final analysis for TB R&D investments in 2005, builds on a preliminary analysis released at the Toronto International AIDS Conference (Feuer 2005a). It presents the results reported by 40 donors who provided $393 million for tuberculosis research in 2005 (*see Appendix A*). Broadly characterized, these donors fall into four categories and their donations into three strata.

The four main donor categories are public sector research and international development agencies (many from North America and the European Union, though we also received data from Brazil, India, Russia, and Thailand); philanthropic private foundations (most notably the Bill & Melinda Gates Foundation); pharmaceutical and biotechnology companies (industry); and the multilateral sector (the Global Fund).

The public sector provided $269 million or 68% of the total. The U.S. government alone provided $185 million or 47% of the total, with the National Institutes of Health (NIH) providing $157 million or 40% of the total. We salute India for making it into the top five public sector funders of TB research and acknowledge difficulties obtaining complete or comprehensive data from other high-burden countries (though Brazil, Russia, and Thailand also figure in this report).

Foundations provided $79 million (20% of total TB R&D), with the Gates Foundation providing $57.4 million (14.6%).

Six responding industry companies reported investing $43 million (11% of the total).

Multilateral agencies reported $1.7 million (0.4%).

NIH investment in TB research is impressive only when measured against a miserable worldwide total. Infused with new money to fight bioweapons, NIH spends more on smallpox and anthrax than it does on TB and malaria, two of the world's most lethal infectious diseases (*see Table 4*). To effect the revolution in TB required to address its terrible global toll, a nearly fivefold increase in funding for TB research will be needed. TB research should look to the lessons of HIV/AIDS activism, which mobilized political commitment that led to $30 billion invested in HIV/AIDS research by NIH alone over the past 25 years (Fauci 2006), with consequent, dramatic, and evident—though still insufficient—results (Walensky 2006).

Donors to TB research fell into three major strata:

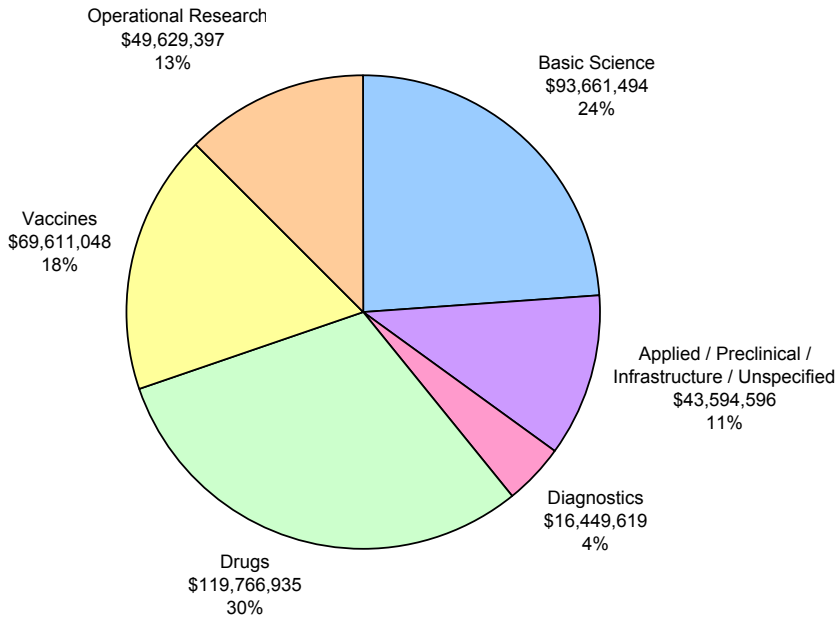
1. The top ten donors invested multimillion dollar amounts, ranging from $120 million (NIAID) to $12.3 million (Otsuka).

2. The top 27 investors each invested at least $1 million.

3. Thirteen donors spent less than $1 million, ranging from $500 thousand (Company Y) to a notably low cutoff for the top 40 donors at $114 thousand (Eli Lilly Foundation).

TAG asked donors to categorize their investments according to research area, including basic science, applied/preclinical and infrastructure development, diagnostics, drugs, vaccines, and operational research. Most donors were able to provide this information. Efforts to subcategorize within area—for example, by preclinical or clinical—were less consistent, as not all donors or recipients were able to specify the research phase. However, TAG is able to report that currently, only six new drugs and five potential vaccines are in clinical trials, most of them early-stage (Syed 2006).

Figure 1: 2005 TB Research: Investment by Category (Total = $392,713,089)



Of the $393 million reported to TAG, $94 million (24%) went to basic research, $44 million (11%) to applied or unspecified TB research, $16 million (4%) to diagnostics

research, $120 million (30%) to drugs research, $70 million (18%) to vaccine research, and $50 million (13%) to operational research.

The Stop TB Partnership's *Global Plan to Stop TB: 2006–2015* (henceforth *The Global Plan*) aims to cut TB incidence and death rates in half from 1990 levels by 2015, and ultimately rid the globe of TB by 2050. *The Global Plan* lays out cost projections for TB control and for research on new tools to control TB over the next ten years, including diagnostics, drugs, and vaccines, but not basic science or operational research. According to *The Global Plan*, the world needs to invest $9 billion in R&D over the next decade to discover, develop, evaluate, and disseminate effective new TB diagnostics, drugs, and vaccines.

While *The Global Plan* projects a $6.1 billion funding gap for new tools R&D over the next decade, the results of this review suggest that the baseline levels of funding at the beginning of 2006 for TB R&D are substantially lower than estimated in *The Global Plan*.

- Where *The Global Plan* states that $59 million is needed for new diagnostics research (preclinical and clinical) in 2006, respondents reported only $16 million was invested in this research in 2005.

- Where *The Global Plan* states that $418 million is needed for new drugs research (preclinical and clinical) in 2006, respondents reported spending only $120 million for this research in 2005.

- Where *The Global Plan* states that $291 million is needed for new vaccine research in 2006, respondents reported spending only $70 million for this research in 2005.

Thus, if the funding levels remain the same as in 2005, in 2006, year one of *The Global Plan*, the world is already falling short by $43 million for diagnostics research, $298 million for drugs research, and $221 million for vaccine research. (Some new money has become available—for instance, $104 million from the Gates Foundation to the TB Alliance for 2006 through 2011 and an expected $40 million over two years for a preclinical drug grant program, the TB Accelerator. On the other hand, CDC and NIH are slated for budget cuts in 2006 and 2007.)

To avoid double-counting, TAG analyzed contributions to and disbursements by public-private product development partnerships (PDPs)—such as the Aeras Global TB Vaccine Foundation, the Foundation for Innovative New Diagnostics (FIND), the Global Alliance for TB Drug Development—and those to and by multicenter funding consortia—such as the mainly EU-funded EDCTP and TB-VAC consortia—separately from major funders. In 2005 the PDPs and research consortia reported a total of $49

million in funding. TB vaccines received the largest investment, $33.4 million (68% of PDP/funding consortia investment), most of it to Aeras ($26.5 million). TB drugs received $6.4 million (13% of PDPs/funding consortia), and TB diagnostics $2.2 million (4.5% of PDPs).

It is obvious that investment in TB R&D by all sectors must increase substantially just to achieve baseline funding conditions specified in *The Global Plan*. Results of this assessment suggest that in the first year of *The Global Plan* we are not yet at the starting line in the race to achieve the 2015 targets. Of the $393 million reported by the 40 respondents whose R&D is summarized in this report, approximately $206 million is directly targeted at new diagnostics, drugs, and vaccines. This is just 2.3% of *The Global Plan*'s estimated $9 billion needed for new tools R&D funding over the coming decade, and *The Global Plan* does not specifically call for greater investment in basic science, which underpins all discovery efforts, nor does it fully account for the operational research needed to integrate new tools into health care systems.

The top challenges for this assessment were the lack of transparency from the commercial sector and the lack of standardized internal tracking systems for TB R&D in the public sector in the Group of Eight (G8) and high-TB-burden countries. Future resource tracking efforts would benefit from greater openness and from commonly applied and reported definitions of research category, phase, and focus. Despite the data limitations, TAG's assessment reveals severe underfunding of TB R&D at all stages, including new tool discovery and development as well as basic science and operational research. The progress of science depends directly on funding. While *The Global Plan* estimates that TB research needs to increase threefold over the coming decade, based on the shortfall identified herein, TAG estimates that an immediate increase of nearly fivefold is needed to win the battle against one of humanity's oldest and most prevalent pathogens.

1. Introduction

1.1 The Importance of TB R&D

"There were approximately 9 million TB cases and approximately 2 million TB deaths in 2004" (WHO 2006). The tuberculosis organism, *Mycobacterium tuberculosis* (MTB) has been with humans since an early period of our evolution. It infects one-third of the world's population, at least two billion people. While 90% of those with latent TB infection (LTBI) never progress to active disease, 5–10% of them develop TB disease during their lifetime. In people coinfected with HIV this risk increases to 5–10% per year.

MTB was discovered in 1882, and its presence in sputum from infected individuals, detected as acid-fast bacilli (AFB) by sputum smear microscopy, was part of Robert Koch's contribution to the field. Koch also introduced tuberculin skin testing (TST), the first method for detecting TB infection by measuring the magnitude of an immune response to a skin test. The Bacillus Calmette-Guérin (BCG) attenuated *M. bovis* strain has been used to vaccinate three billion infants and children for TB since the 1920s. Each year, over 100 million children receive BCG. Though BCG protects infants from the severest forms of TB, it fails to protect from pulmonary disease during adolescence and adulthood and may be dangerous in HIV-infected infants. Effective drug treatment for TB has been available since the 1940s and is used either as single-drug preventive treatment for latent TB infection (LTBI) with isoniazid (INH) or as short-course combination therapy for TB disease, most commonly with two months of isoniazid, rifampin (rifampicin), pyrazinamide, and ethambutol (known together as HRZE) followed by four months of isoniazid and rifampin (HR) or six months of ethambutol and isoniazid (EH), though the latter is less effective.

Close contact with people with infectious TB creates ideal conditions for its epidemic spread. In Europe during the Industrial Revolution in the 1800s TB was the leading infectious killer, especially among people who lived in closely crowded quarters with poor access to light, fresh air, sufficient food, and clean water. Similar conditions now promote TB's spread in resource-poor settings around the world. TB rates dropped in Western Europe and the U.S. even before the discovery of BCG or treatments because rising economic development had improved sanitation and living standards, making TB easier to contain (Dubos 1952). Some people who became sick with TB were able to overcome or contain the disease within their bodies as well. The factors for this are not clearly defined but likely include T-cell immunity mediated through interferon gamma and interleukin 12.

Improved public health, economic development, widespread BCG vaccination, the introduction of antituberculosis treatment (ATT), and isoniazid preventive therapy (IPT) for latent TB infection, resulted in dramatic global reductions in TB disease between 1940 and 1980. However, the success of short-term TB control using BCG, TB drugs, isoniazid preventive therapy, and antibiotics led to complacency and a decreasing interest in infectious disease research and control. From 1980 on, the U.S. government, the International Monetary Fund (IMF), the World Bank, and others supported policies that weakened health systems in developing countries and undermined their ability to effectively address any emerging epidemic (Breman 2001; Gandy 2003).

As the HIV pandemic spread through the 1980s, TB came roaring back. In 1991 an outbreak of HIV-related multidrug-resistant (MDR) TB in New York City cost over $1 billion to contain. That year the World Health Assembly (WHA) set global TB control targets of detecting 70% of smear-positive TB patients and curing 85% of them by

2000 (Resolution WHA 44.8). In 1993 WHO declared TB a global emergency and the World Bank issued an influential report stating that TB control was one of the most cost-effective health interventions (World Bank 1993). In 1994 WHO launched the new TB control framework, and branded it "DOTS" in 1995. Surveillance and monitoring systems were established in countries implementing the new approach. In the late 1990s the Stop TB Partnership was established as a public-private partnership of over 400 organizations to provide global leadership and coordination for TB control with its secretariat housed at WHO. Governments subscribed to the Amsterdam Declaration in 2000 and the Washington Commitment in 2001, a year that also saw the launch of the first *Global Plan to Stop TB* and of WHO's Stop TB Department. By the turn of the millennium several public-private product development partnerships (PDPs) had been formed to accelerate product development for new TB vaccines, drugs, and diagnostics, with support from the Rockefeller and Gates Foundations, among others.

Over the past decade DOTS coverage has increased worldwide and many countries are now scaling up their programs to reach 100% population coverage. Despite these advances, TB incidence and mortality rates continue to grow worldwide, fueled by HIV in Africa and by collapsing health systems leading to multidrug-resistant MDR-TB in Eastern Europe and extensively drug-resistant tuberculosis (XDR-TB) in Southern Africa. WHO has reported that global TB incidence rose 1% in 2004, while African TB incidence rose by 4% (WHO 2006).

Most of the existing tools to control TB—diagnosis through smear microscopy and TST, BCG vaccination, and combination chemotherapy—date from the years between 1880 and 1966, when the last new class of anti-TB drugs, the rifamycins, was discovered. In the 1940s and 1950s, which were considered a golden age of antibiotic drug discovery, TB was still a common killer disease in some industrialized nations, and therefore the pharmaceutical industry had incentives to invest in, test, and seek marketing approval for new drugs to fight TB.

But as TB incidence declined in the industrialized world, so did the profit motive for developing new tools. The recent resurgence in TB rates has sparked a renewed commitment—though not by industry—to discover more efficient tools to combat the disease. To date, the leading investment in TB R&D has come from public sector R&D agencies in the U.S., the U.K., and to a lesser extent the E.U., and from the Bill & Melinda Gates Foundation, which itself is the second largest contributor to TB research. The majority of private sector sources among the R&D-based pharmaceutical and biotechnology companies have either not stepped up to the challenges posed by TB or are unwilling to share publicly the details of their investments in TB product development. However, as this report will demonstrate, overall TB research investments remain insufficient to the need.

In the 1990s, WHA declared TB a global emergency and world governments committed to detect 70% of all infectious (smear-positive pulmonary) cases and to cure 85% of these by 2000 (WHO 1991), later changing the goal to 2005, and still later to 2015 (Stop TB 2006). Today, more people die of TB than of any other curable infectious disease (WHO 2006).

In 2000 the UN's Millennium Development Goals established a target of halting and beginning to reverse by 2015 the ravages of multiple infectious diseases including HIV, malaria, and—by implication if not explicitly—tuberculosis. The Stop TB Partnership set for itself an even more ambitious goal of cutting TB incidence and death rates in 2015 by half from 1990 levels. Since 1990 was just before HIV began cutting its incendiary swath through Africa and just before MDR-TB began spreading in Eastern Europe, the Partnership estimates it will be unable to achieve its goals for Africa and Eastern Europe by 2015 (Stop TB Partnership 2006). The Partnership further calls for the elimination of TB as a public health threat (meaning less than one case per million people) worldwide by the year 2050.

With current tools alone, the world is unlikely to reach the 2015 goals. Reaching the 2050 TB targets seems utterly impossible, especially in Eastern Europe and in sub-Saharan Africa, without a revolution in new TB diagnostics, drugs, and vaccines. Meeting such targets depends upon the successful discovery of novel and improved methods to diagnose, treat, and prevent one of the world's oldest scourges. As shown in this report, the world is already far from reaching its TB R&D investment targets in 2006, the base year from which *The Global Plan to Stop TB: 2006–2015* begins.

Today, investment lags behind the world's stated goals to curb and eventually eradicate TB. There are currently five vaccines, six drugs (four novel ones) in clinical trials, and a handful of new diagnostic technologies in pilot evaluation phases. These scientific advances demonstrate that progress is possible, albeit slow and unsteady, with current funding. However, according to *The Global Plan*, over the next ten years the world needs to invest $9 billion in R&D to discover, develop, evaluate, and disseminate effective new TB diagnostics, drugs, and vaccines, and to provide additional resources for operational research. According to Stop TB, approximately $2.9 billion in funding can be counted on, with a $6.1 billion gap in R&D funding for new TB tools over the next decade. *The Global Plan* does not include a target for basic science and does not set a comprehensive goal for operational research.

In spring 2006, TAG began a resource mapping exercise to establish a baseline for TB R&D funding. This would enable us to assess current spending, identify donors, analyze research gaps, and provide recommendations for improving TB R&D in order to meet the 2015 and 2050 goals. The results of the analysis, *Tuberculosis R&D Investments: A Preliminary Assessment* were released at Toronto in August 2006 and identified $348 million invested by the thirty top investors in TB R&D in 2005 (Feuer

2006a). This report, with TB R&D investigations through October 2006, presents updated results including ten new sources and brings the total reported R&D investments in 2005 to $393 million.

TAG surveyed 100 organizations believed likely to be significant funders of TB-related R&D. In this report we present results from the top forty funders of TB R&D who were willing to disclose details of their research investments. Six pharmaceutical or biotechnology companies provided details of their investments, four declined to provide data, three did not respond, and five stated that they did not invest in TB R&D (*see Appendix B*).

1.2 Limitations of Current TB Tools

The lack of a rapid and accurate point-of-care TB diagnostic test is impeding progress toward achieving improved TB case detection rates. According to the Foundation for Innovative New Diagnostics (FIND), just 19% of the world's cases of TB are detected by the most widely used test, sputum smear microscopy (Nantulya 2006). Technology must move beyond the standard sputum microscopy test discovered in the 1880s if diagnostic rates are to improve. This 19th-century TB test fails to detect over half of all active cases, can take several clinic visits to yield results, is labor-intensive for both patient and provider, and is nonspecific for *Mycobacterium tuberculosis*. Furthermore, as nearly two-thirds of those who are TB/HIV coinfected are smear-negative or have extrapulmonary TB, the test will not detect their infection. Its low sensitivity in HIV-positive and pediatric tuberculosis renders it even less effective in precisely those who are most likely to die from the disease.

WHO's Stop TB's Working Group for New Diagnostics calls for the development of new diagnostic tests that can detect pulmonary TB disease with high or low bacterial loads, extrapulmonary TB, pediatric TB, drug-resistant TB, and latent TB infection (Perkins 2006).

Similar to the outdated diagnostic method, TB therapeutics—the last approved class was discovered 40 years ago—do not meet the demands of the current epidemic. Specifically, there is an urgent need for shorter regimens that cure more rapidly. Existing multidrug regimens, while technically effective in treating drug-sensitive pulmonary TB, require six months of treatment, which can lead to difficulties in completing therapy. A shorter regimen would benefit adherence, resulting in higher cure rates. There's also a pressing need for drugs that can be safely taken concurrently with antiretroviral therapy used to treat HIV. Rifampin, for example, has potentially dangerous interactions with commonly used antiretroviral (ARV) drugs, such as nevirapine and several protease inhibitors. Novel drugs are also needed for difficult-to-treat TB cases and for MDR- and XDR-TB.

The live attenuated *M. bovis* Bacillus Calmette-Guérin (BCG) vaccine, discovered in 1921, is the world's most widely used vaccine and can reduce post-natal and early childhood TB mortality rates by 90%, according to some studies (Anderson 2006). Despite its value during childhood, the vaccine has little to no efficacy in preventing pulmonary TB, the most common and most infectious form of the disease among adolescents and adults. TB's resurgence in places where BCG vaccination is nearly universal indicates the vaccine's limits. Research using genetically modified BCG or MTB protein subunits is underway to develop a vaccine to prevent both new infections and reactivated TB disease (Lee 2006).

1.3 Objectives

TAG aims to highlight gaps in spending as well as in areas of scientific study by tracking major institutions that contributed to TB R&D. Findings from this unprecedented analysis will be used to advocate for strategic funding for new tools for TB diagnosis, treatment, and prevention, and for expanded basic and operational research efforts.

The focus year of TAG's analysis is 2005, the latest year for which complete data were available. This mapping of TB research provides an impression, not a comprehensive global tally of the year's research investments. It primarily documents contributions from G8 member nations' public research agencies, international development agencies, major nonprofit charitable foundations and trusts, pharmaceutical and biotechnology companies, and selected high-burden countries (HBC).

The figures presented in this report should not be interpreted as complete or absolute findings, due to lack of complete data available from industry as well as from some public funding institutions in the developed and developing world. Nevertheless, most of the major donors to TB R&D are likely included here.

1.4 Methodology

TAG used an e-mail survey to solicit information about actual annual disbursements (not commitments or awards) for TB research for 2004, 2005, and 2006; the amount of funds an institution received or disbursed; grant portfolios describing the research; and qualitative responses about priorities and obstacles in TB research.

Funding data were collected largely from original-source donors. In some cases recipients of funding were contacted if the source did not respond or if the recipient played an integral role in programming funding for TB research, as with WHO's Special Programme for Research and Training in Tropical Diseases (TDR). In addition to donors and researchers, TAG tracked public-private product development partnerships (PDPs)—funding managers that help expedite focused product-development research. Data were cross-referenced to avoid double counting.

Data were collated from public and private sector sources and were supplemented by interviews with a range of experts in the TB research community, including Stop TB Partnership secretariat staff and chairs of Stop TB's Working Groups for new TB diagnostics, drugs, and vaccines. Most of the information is based on self-reporting by recipients and representatives of the funding sources; some background information was garnered from donor web sites.

For TAG's preliminary tracking report, *Tuberculosis R&D Investments: A Preliminary Assessment*, TAG received a low-response rate from the private sector. For the second round of data collection, TAG emphasized the option of anonymous disclosure, which helped boost industry's response. The two companies wishing to conceal their identities appear in the text as "Company X" and "Company Y."

In addition to tracking total investments in 2005, TAG asked respondents to classify their TB R&D investments into five major research categories:

• Basic Science • Diagnostics • Drugs • Vaccines • Operational Research

TAG also requested respondents to classify their research by stage (preclinical or clinical), but this proved difficult for many respondents. The number of new agents in clinical trials is still quite small at the present time (six new drugs, five vaccines).

To ensure exchange-rate consistency, on the recommendation of WHO's Global TB Surveillance, Planning and Financing Project (Floyd 2006), TAG used the Oanda currency site (www.oanda.com/convert/classic) and selected 1 July 2005 as the date to convert foreign expenditures into U.S. dollars at interbank conversion rates. Among funders there are different fiscal years, and domestic investments are not converted, so purchasing power parity (PPP) conversion rates may be more appropriate in some cases (e.g., Brazil, India, Russia, Thailand).

TAG also interviewed key stakeholders and activists to inform the report's recommendations for how to improve TB R&D investment and to establish better resource tracking mechanisms and developing a global TB research movement to mobilize significant and sustained increases in funding for TB research.

1.5 Limitations of the Data

A list of potential TB research funders was generated using information from the Stop TB Partnership web site, reports by Aeras, FIND, and the TB Alliance, and from desktop research. Key informants in the TB research community were consulted to assist in confirming a core list of significant donors. Out of the approximately 100 potential research donors or recipients, eighty respondents provided 2005 investment data. Twenty-six respondents stated that they are not primary funders

of TB research. Thirteen entities did not respond. Six respondents—four from industry—declined to provide data (*see Appendix B*). Some of the surveyed sponsors did not have readily available data detailing research into new TB tools. In some cases, respondents cherry-picked information from disparate lines of funding, which produced incomplete data difficult to categorize, resulting in their placement in the catchall "unspecified" category. In addition to poor internal tracking, there are no commonly agreed upon standards defining research categories across the field of TB research.

Because it was difficult for many respondents to classify their TB R&D investments into research phases, there is a risk that the results reported here are too broad and will be misinterpreted. Without the clarification of the specific needs of each research area of new tool development such as basic science or clinical research, donors may believe that the funding of one institution that oversees one aspect of the R&D spectrum of activities will resolve all the needs for TB research funding for a particular tool. For example, funding NIH will only support basic science research, and will not lead to the clinical research needed.

Attempts to separate and gather data for TB research that is conducted in conjunction with other diseases such as HIV proved difficult. For example, donors may investigate TB and HIV together, but only code their studies as HIV research and therefore the financial investments would have gone undetected in TAG's survey. Again, NIH provides an example: attempts to gather TB/HIV data went unfulfilled because of lack of coding, and required the development of a common definition that would have facilitated data collection across all NIH institutes.

Some donors reported money awarded to research institutions that focus on infectious diseases but did not specify the amount apportioned to TB. In these cases, TAG relied on the recipient to report on spending activity; there may be discrepancies between stated donor funding and reports from the recipient agency. TAG deferred to donors' statements whenever possible. Funders and research organizations employ various means of recording grants—for example, commitments or awards made one year may be disbursed the following year. TAG tried to adhere as strictly as possible to counting actual money disbursed in fiscal year 2005.

Six of eighteen surveyed pharmaceutical and biotechnology companies disclosed financial information. Four declined, despite being given the option to have their totals be presented anonymously or only as an aggregate, and another three did not respond at all. Because the commercial sector is often unwilling to reveal investments or returns to the public, TAG is not able to quantify industry support for TB research in total. The six responding companies include the two that preferred to remain anonymous, and AstraZeneca, Novartis, Otsuka, and Sequella, all of whose commitments to TB R&D and to transparency are commended.

2. Results

Table 1: Top 40 Funders of TB R&D in 2005 Reported to TAG by October 2006
(*see Appendix A for investments by research category*)

Rank	Donor	Total
1	NIAID / NIH	120,273,000
2	Gates Foundation	57,411,457
3	Medical Research Council (UK)	30,887,839
4	Other Institutes & Centers / NIH	20,334,300
5	Centers for Disease Control	19,903,000
6	Company X	18,640,160
7	Wellcome Trust	18,081,359
8	NHLBI / NIH	17,117,000
9	European Commission 6th Framework	13,322,711
10	Otsuka	12,300,000
11	Institut Pasteur	8,472,800
12	AstraZeneca	8,000,000
13	USAID	6,694,000
14	Inserm	5,721,560
15	TB Research Center (ICMR), India	5,313,133
16	Ministry of Science and Technology, India	3,168,488
17	Netherlands Ministry of Foreign Affairs (DGIS)	3,168,488
18	Max Planck Institute	2,500,000
19	Canadian Inst. of Health Research	2,376,098
20	Novartis	2,255,193
21	Dept. for International Development (DFID)	2,008,832
22	Russian TB Institutes*	1,930,343
23	Rockefeller Foundation	1,750,000
24	Ellison Medical Foundation	1,650,000
25	Global Fund**	1,648,083
26	Research Institute for TB, Japan Anti-TB Association	1,487,961
27	Sequella***	1,400,000
28	Brazil (in aggregate)	755,587
29	Food and Drug Administration	651,231
30	Company Y	500,000
31	Swedish Int. Development Agency	486,599
32	Development Cooperation of Ireland	360,000
33	Ministry of Public Health, TB Cluster, Thailand	287,050
34	Netherlands Org. for Scientific Research (N.W.O.)	199,716
35	Swiss Agency for Development and Coop.	195,099
36	KNCV Tuberculosis Foundation	170,666
37	Danish International Development Agency (Danida)	170,344
38	All India Institute of Medical Sciences	154,821
39	Ministry of Foreign Affairs, France	127,092
40	Eli Lilly Foundation	113,660
	TOTAL	**$392,713,089**

* Aggregate spending of four Russian Federation TB institutes.
** Global Fund figures estimated based on their reported activities.
*** Sequella spent $3.5 million; $2.1 million from NIH not counted twice.

2.1 Donor Categories

Of the $393 million reported to TAG by the top forty investors in TB R&D in 2005, $269 million (68%) came from the public sector, $79 million (20%) from philanthropic foundations, $43 million (11%) from industry, and $1.6 million (0.4%) from the Global Fund. Product development partnerships (PDPs) and research consortia reported directing $49 million in TB R&D; although this was not included in the global total to avoid double counting.

2.2 Research Investment Categories

Scientific grants and research programs focusing on *Mycobacterium tuberculosis* (MTB) and tuberculosis (TB) disease are categorized according to the descriptions below and adapted from *Shots in the Dark: The Wayward Search for an AIDS Vaccine (Cohen 2001).*

Basic science research aims to uncover knowledge that may have no immediate, specific, practical application but may eventually directly benefit TB-control efforts by increasing the knowledge base, which will lead to new discoveries. Basic research includes cell biology, genetics, immunology, mycobacteriology, and animal models of transmission and pathogenesis.

Applied/preclinical research and infrastructure development involves targeted research which could not otherwise be categorized by the donor or recipient, including infrastructure or capacity building. This category includes data that TAG was unable to code because some funders were unable to subcategorize their research grants.

Diagnostics research is R&D targeted at the discovery, development, and testing of new diagnostic tests to detect latent TB infection, active TB disease (pulmonary and extrapulmonary), drug susceptibility and resistance, or biomarkers, which predict prognosis or response to therapy. Some operational research on existing diagnostic tests which are being studied in new settings (for example, BACTEC MGIT rapid liquid culture, ELISPOT, Quantiferon-Gold) may be included in this category.

Drug research includes early-stage lead-compound optimization, preclinical studies, and clinical trials in humans.

Vaccine research includes preclinical development, safety studies; capacity building of vaccine trial sites; and clinical trials in humans.

Operational research pursues the most effective methods of implementing new or existing products and helps answer broad questions that may impact on health

care delivery or policy. This includes program-related epidemiology, natural history, and surveillance; targeted program monitoring and evaluation; and health policy. TB operational research includes both rigorously designed studies, such as those funded by the CREATE consortium, as well as less academic investigations of new or existing interventions in routine program conditions. As such it tends both to overlap with earlier phases of testing and with TB control programs, while at the same time remaining a bit of a research orphan. The U.S. Office of the Global AIDS Coordinator (OGAC), which runs the President's Emergency Plan for AIDS Relief (PEPFAR), for example, refers to such research as "targeted evaluation."

2.3 TB R&D: Ten Major Funders

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

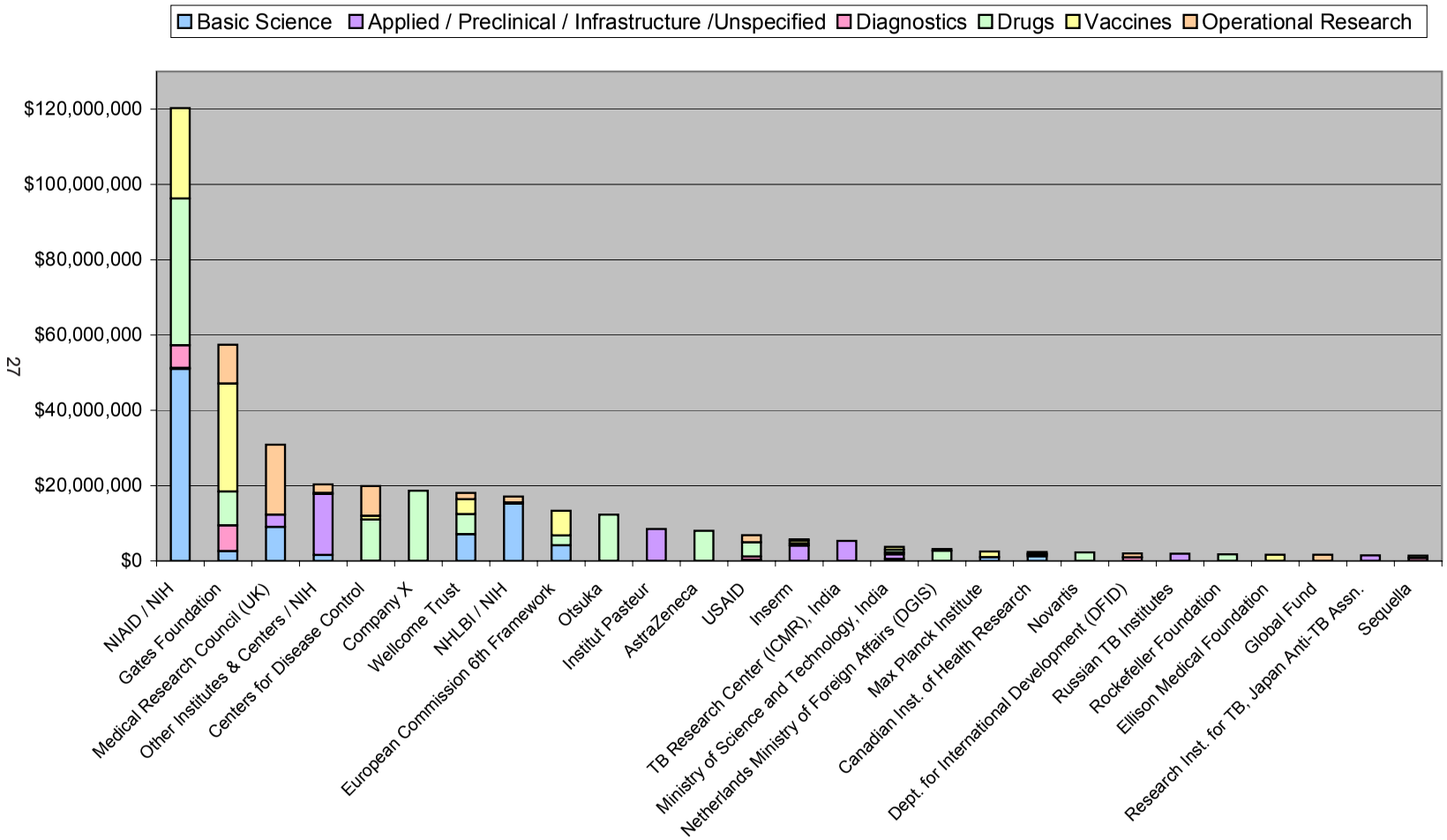
The U.S. National Institutes of Health (NIH), the world leader in health research spending, is the biggest funder of TB research. In 2005 NIH awarded $158 million in grants and contracts to study tuberculosis, which is 40% of all TB research reported.

Eight institutes, offices, and centers awarded over $1 million dollars to TB in 2005. Given the paltry overall state of investment in TB R&D, any one of those eight institutes would have made it into the top twenty-eight funders in our report (see Table 2).

We obtained detailed information on NIH TB spending from the Computer Retrieval of Information on Scientific Projects (CRISP, www.crisp.cit.nih.gov); from NIH's annual summary of spending on diseases and research areas (www.nih.gov/news/fundingresearchareas.htm); from key institute staff, such as Christine Sizemore at Division of Microbiology & Infectious Disease (DMID), NIAID, Barbara Laughon from the Division of AIDS (DAIDS), NIAID, and Hannah Peavy at the National Heart, Lung & Blood Institute (NHLBI); from the NIH budget office; and from individual institute and centers' communications offices, which in some cases responded to Freedom of Information Act requests.

Compared with many agencies, NIH is a model of transparency, with full grant information readily available on every award. However, NIH's dispersed structure, currently involving 27 different institutes and centers, and even more offices, along with the incomplete data available from the CRISP database, calls for an updated approach to resource tracking. Some holes remain in our analysis of NIH data; $12.8 million —mainly from institutes with smaller TB portfolios was coded as "unspecified." In addition, the NIH Office of AIDS Research, which maintains the AIDS Research Information System, a separate, more detailed database than CRISP, does not yet code for HIV/TB-related projects (such as AIDS clinical trials testing interventions for AIDS-related TB). Gathering information about HIV/TB related research requires

Figure 2: Top 27 Donors of TB Research (over $1 million in 2005)



that queries be sent to each NIH institute and center conducting HIV research to determine what proportion might be related to HIV/TB. Despite requesting this data, TAG was unable to obtain the information.

In 2005, NIH's budget, appropriated by Congress, for all health research totaled $28.6 billion. Of this, $158 million, or 0.55%, went for TB research—approximately 52 cents per U.S. resident.

Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) alone awarded $120 million to TB R&D, 31% of all expenditures reported to TAG. NIAID was the biggest contributor to TB R&D in 2005, spending more than twice that of the second major donor to TB research, the Bill & Melinda Gates Foundation.

Of NIAID's $120 million in TB R&D disbursements, $51 million went to basic research and $39 million, $24 million, and $6 million was apportioned for TB drug development, vaccines, and diagnostics, respectively.

NIAID provided 76% of NIH's TB funding. Part of NIAID's mission is to "support a comprehensive extramural research program, encouraging and funding all aspects of basic, translational, and applied research, leading to a better understanding of TB, as well as to the development of novel vaccines, drugs, and diagnostics" (Sizemore 2006).

Neither the president nor Congress currently supports increasing the NIH budget in the near future. As long as the overall NIH budget is flat, it will be very difficult for advocates to succeed in attracting increased funding for any disease, no matter how deadly. The entire NIH budget needs to once again be guaranteed many years of sustained, healthy multiyear growth as it was from 1994 to 2002. NIH estimates future levels of funding for TB R&D will remain flat at $158 million for fiscal years 2006 and 2007. TAG is concerned that in the face of the emerging epidemic of extensively drug-resistant (XDR) TB, budget cuts at NIAID are endangering some well-designed targeted research efforts such as the pre-clinical TB Antimicrobial Acquisition and Coordinating Facility drug screening contracts. It is ironic that while the Gates Foundation is planning to invest $40 million through its pre-clinical drug discovery TB Accelerator grants, similar NIH supported efforts are endangered.

2. The Bill & Melinda Gates Foundation (BMGF)

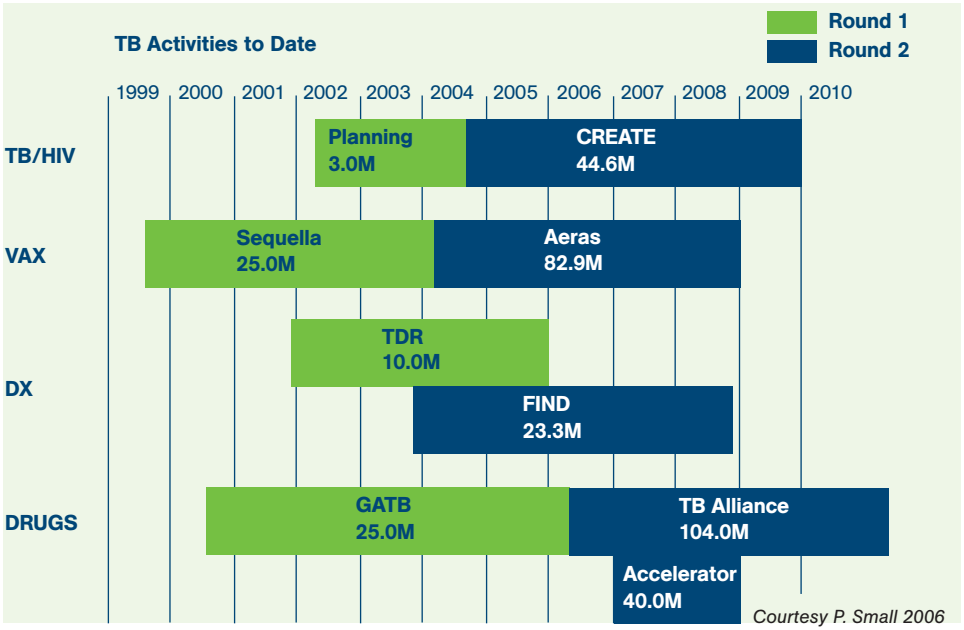
The Bill & Melinda Gates Foundation is the world's largest private philanthropic organization with an endowment at the end of 2005 of $29.2 billion. That year the Gates Foundation distributed a total of $1.36 billion, of which $844 million or 62%, went to the Global Health Program (Gates Foundation 2006). They disbursed $57.4 million in TB research grants in 2005, almost 15% of all TB research reported to TAG. In coming years a historic gift from investor and philanthropist Warren Buffet will

approximately double the Gates Foundation's annual spending.

At the launch of *The Global Plan to Stop TB* in Davos last January, Bill Gates pledged up to $900 million in TB R&D funding over the coming decade, meaning an average annual commitment of $90 million. In 2005 about half of Gates Foundation TB spending—$28.7 million—was on new vaccine research, with $2.6 million going to basic research, $6.8 million to new diagnostics, $9 million to new TB drugs, and $10.3 million to operational research. New initiatives not yet funded in 2005 include the preclinical drug discovery Accelerator package ($40 million over two years, due to start later in 2006) and a $104 million five-year grant expansion for the Global Alliance for TB Drug Development (with $15 million given in 2006).

The Gates Foundation's TB priorities are to prevent incidence and prevalence of disease by developing safe, effective, and affordable new tools, and by supporting the appropriate management of TB in regions with high HIV prevalence. To reach these goals, seven grant packages support the following work:

Figure 3: Evolution of Gates Foundation TB Funding



Aeras Global TB Vaccine Foundation received $26.7 million in 2004, $24.4 million in 2005, and is projected to receive $31.8 million in 2006. Its mission is to develop and license an improved TB vaccine for use in high-burden countries and to bring from one to three new vaccine candidates into early-phase testing.

Foundation for Innovative New Diagnostics (FIND) received $4.3 million in 2004 and $4.6 million in 2006. It is projected to receive another $5.3 million later this year. Its mission is to accelerate late-stage development of diagnostic tests for neglected infectious diseases including TB. Note: Because the first 2006 payment was committed as 2005 funding, we counted it in 2005, even though it was disbursed in 2006.

Tropical Diseases Research (TDR), housed at WHO, is a multipartner funding consortium focusing on neglected diseases of the developing world, including TB. In 2005 the Gates Foundation awarded TDR $2.3 million to support development of new TB diagnostics. TDR is formally known as the Special Progamme for Research and Training on Tropical Diseases.

Global Alliance for TB Drug Development (TB Alliance) received $5 million in 2005. Its mission is to develop new and effective anti-TB drugs that are affordable worldwide. This summer the Gates Foundation announced a new $104 million award to the TB Alliance, of which $15 million will be made available in 2006.

Consortium to Respond Effectively to the TB/HIV Epidemic (CREATE) received $9.3 million in 2004, $10.2 million in 2005, and is slated to receive $8.3 million in 2006. Its mission is to develop and validate novel, community-level intervention strategies to reduce rates of TB in populations with epidemic rates of HIV infection and escalating TB incidence.

Grand Challenges in Global Health (GCGH) is a set of large grants to "transform health in the world's poorest countries, and bring state-of-the-art solutions to people who need them most." Some of the projects are focused on adapting existing health tools, such as sophisticated laboratory tests, to novel technology platforms to make them practical for developing countries. Other projects seek to fundamentally redefine our understanding of how to prevent and treat disease, potentially leading to entirely new vaccines and drugs for diseases of the developing world. Many of the projects are applying cutting-edge technology that has never before been used to advance global health. After the 14 challenges were published in the journal *Science* in October 2003, scientists submitted more than 1,500 project ideas. From these, 43 projects involving collaborators in 33 countries were selected for funding, some of which are described below. The Grand Challenges initiative is supported by $450 million from the Gates Foundation, $27.1 million from the Wellcome Trust, and $4.5 million from the Canadian Institutes of Health Research (CIHR). Four of the grants focus on TB:

- **GC5: Determine how to design antigens for effective protective immunity** (four awards, one TB-related): Enhancing the immunogenicity and efficacy of vectored vaccines, Adrian Vivian Hill, Oxford, U.K.; $10 million over five years. Dr. Hill and colleagues will explore DNA and recombinant viral vector vaccines for HIV, TB, and malaria; $2 million per year over five years.

• **GC6: Learn which immunological responses provide protective immunity** (six awards, one TB-specific): Biomarkers of protective immunity against TB in the context of HIV/AIDS in Africa, Stefan H.E. Kaufmann, Max Planck Institute, Germany; $13.1 million over five years. Dr. Kaufmann will lead 15 institutions in Europe, Africa, and the U.S. to identify immune system differences between people exposed to TB who never become sick and those who develop serious disease, focusing particular attention on people with TB and HIV; $2.6 million per year.

• **GC11: Create therapies to cure latent infections** (one award): Drugs for treatment of latent TB infection, Douglas Young, Imperial College London, U.K.; $20 million over five years. Dr. Young will lead a collaboration among the U.K., the U.S., Singapore, Korea, and Mexico to investigate the fundamental biology of TB latency and use this to develop drugs effective against latent TB; $4 million per year.

• **GC12: Create immunological methods to cure latent infection** (four awards, one TB-specific): Preclinical and clinical evaluation of a post-exposure TB vaccine, Peter Anderson, Statens Serum Institute, Denmark; $11.3 million over five years. Dr. Andersen will lead a team in Europe, the U.S., and South Africa to study the MTB organism to identify mechanisms that allow it to escape from normal immune responses, which help some people keep TB under control for a lifetime, while others (particularly those with HIV) succumb to serious illness. The goal is to pursue information leading to a therapeutic vaccine that will enable people with latent TB infection to eliminate the infection; $2.2 million per year (Gates Foundation 2005; see also www.gcgh.org).

TB Accelerator will provide up to $40 million over two years (2006–2008) to accelerate the discovery of new TB drugs. Proposals were due on 30 April 2006 and are likely to be announced later in 2006 (www.gatesfoundation.org/GlobalHealth/Grantseekers/RFP/RFP_TB.htm).

3. Medical Research Council, UK

MRC is the U.K.'s publicly funded medical research agency. In 2005 its budget was approximately $943 million, 3% of which went for TB R&D. This $30.9 million made it the world's third largest TB research funding agency in 2005. MRC supports a broad biomedical research portfolio ranging from basic biology to medical practice. In 2005 the largest portion of MRC funding, $18.6 million, went to operational research, much of it at the long-established MRC research unit in the Gambia. MRC also spent $9 million on basic research and $3.3 million on applied preclinical research. In 2006 MRC funding for TB treatment research will increase, as it is supporting the

University College of London (UCL) to conduct the ReMox study of two moxifloxacin-containing regimens in comparison to standard TB treatment in Africa.

4. Other Institutes & Centers (ICs), National Institutes of Health (NIH)

Of the NIH's 27 institutes and centers, 12 contributed $20.3 million to TB research in 2005 in addition to the much larger and more focused programs from NIAID and NHLBI spending, which are listed among the top ten donors (numbers one and seven, respectively); $1.6 million went to basic research, $16.2 million to preclinical applied or unspecified, $70.2 thousand to new drugs, $205 thousand to vaccines, and $2.3 million to operational research. Noteworthy among these other TB programs are the international training grants provided by the Fogarty International Center (FIC), almost $4 million in 2005, which are highly effective and should be expanded.

Table 2: Other NIH Institutes & Centers TB Funding 2005

National Center for Research Resources (NCRR)	4,534,000
National Institute on Drug Abuse (NIDA)	4,196,000
Fogarty International Center (FIC)	3,977,000
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	2,000,000
Office of Director (OD)	1,612,000
NIH Roadmap initiatives	1,279,000
National Institute of Child Health and Human Development (NICHD)	846,000
National Institute of Alcohol Abuse & Alcoholism (NIAAA)	742,000
National Institute of Aging (NIA)	518,000
National Institute of Nursing Research (NINR)	240,000
National Center for Complementary and Alternative Medicine (NCCAM)	140,000
National Institute of Mental Health (NIMH)	129,000
National Institute of Dental & Craniofacial Research (NIDCR)	121,000
Total	**$20,334,300**

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

The CDC's Division of Tuberculosis Elimination (DTBE) works to prevent and control TB in the U.S. and internationally. As part of its mission, DTBE conducts behavioral, health systems, and clinical research. The CDC disbursed $20.9 million for TB R&D in 2005. The largest investments went to the Tuberculosis Trials Consortium (TBTC) for clinical trials of TB treatments, totaling $11 million. The Tuberculosis Epidemiologic Studies Consortium (TBESC) spent $7.8 million on epidemiology and operational research. Another $1 million was given to Aeras Global TB Vaccine Foundation.

CDC funding for TB is falling, as is the CDC budget as a whole. Recently the TB Trials Consortium suffered a 10% budget cut. Along with USAID, CDC is programming some funds from the Office of the Global AIDS Coordinator (OGAC), the State Department unit which oversees the President's Emergency Plan for AIDS Relief (PEPFAR). While PEPFAR is an HIV initiative focused on prevention and treatment, not research, it is funding some important TB/HIV-related work that is relevant here (PEPFAR calls it "targeted evaluation" rather than "operational research").

6. Company X

In 2005 "Company X"—which wishes to remain unidentified, and to which TAG agreed to provide anonymity in this report—invested $18.6 million on TB treatment research, the largest single investment by industry in TAG's survey.

7. Wellcome Trust

The U.K.'s Wellcome Trust—a private philanthropy whose size and importance grew in the mid-1990s after the sale of pharmaceutical maker Burroughs-Wellcome to Glaxo, now GlaxoSmithKline—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 was the second largest philanthropic investor, and the seventh largest overall, in TB R&D in 2005, contributing $18 million. Basic research received the largest sum, $7.1 million; preclinical drug research received $5.3 million; vaccine studies received $4 million; and operational research was awarded $1.7 million.

8. National Heart, Lung and Blood Institute (NHLBI), NIH

NHLBI funds mostly basic research relative to cardiac, lung, and circulatory health. Many of its TB projects investigate host immune responses in the lung during TB infection. Information gained by this research may help in the discovery and development of new diagnostics, drugs, and vaccines, but is fundamentally basic biological science, much of which is investigator initiated. In 2005, NHLBI disbursed $17.1 million in TB research grants, $15.2 million of which went to basic science.

9. European Commission 6th Framework Programme (FP6)

The European Commission's financial contribution to TB R&D has almost doubled since 2002, in part due to the formation of a coherent framework to develop treatments and vaccines for TB. FP6 aimed to integrate European efforts toward small-scale, phase I clinical trials for vaccines and to establish production technologies for lead compounds for new anti-TB drugs. FP6 grants are funded through consortia of

academic researchers across Europe, some working with mostly small biotechnology companies. The European Commission's 6th Framework Programme contributed a total of $13.3 million to TB R&D in 2005. Of this, $6.5 million went to preclinical vaccine studies, $4.2 million went to basic science, and $2.6 million went to preclinical drug studies (EC 2005).

10. Otsuka Pharmaceutical Co., Ltd.

Otsuka Pharmaceutical is a pharmaceutical company based in Japan, investing in TB drugs with a focus on new drug classes. It has one drug in early phase II/early bactericidal activity (EBA) clinical trials. In 2005 Otsuka spent $12.3 million on drug development.

2.4 Other TB R&D Funders

The middle rank of the top 40 investors in TB R&D in 2005 includes 17 investors who spent between $1 million and $10 million in 2005. These top 27 TB R&D funders make up the "TB research 27" and fund 99% of the reported research. They include:

- Eight public research agencies: #11, Institut Pasteur, France, $8.5 million; #14, Inserm, France, $5.7 million; #15, TB Research Centre (ICMR), India, $5.3 million; #16, Ministry of Science & Technology, India, $3.8 million; #18, Max Planck Institute for Infection Biology, Germany, $2.5 million; #19, Canadian Institutes of Health Research (CIHR), $2.4 million; #22, four Russian TB institutes, $1.9 million; and #26, The Research Institute of TB (RIT), Japanese Anti-TB Association (JATA), $1.5 million.

- Four drug companies: #12, AstraZeneca, $8 million; #20, Novartis, $2.3 million; and #27, the small but intrepid Sequella, $1.4 million.

- Three development agencies: #13, USAID, $6.8 million; #17, the Netherlands Ministry of Foreign Affairs (DGIS), $3.2 million; and #21, Department for International Development (DFID), U.K., $2 million.

- Two foundations: #23, Rockefeller, $1.8 million; and #24, Ellison, $1.7 million.

- One multilateral funding mechanism: #25, the Global Fund to Fight AIDS, TB & Malaria (GFATM), $1.6 million (mostly for operational research).

Thirteen additional funders who reported to TAG each spent less than $1 million on TB research in 2005 (*see Appendix A*).

2.5 Challenges Estimating Industry R&D Investment

Six of eighteen companies surveyed agreed to provide at least overall TB investment figures for 2005, four declined to disclose, five are not involved in TB research, and three did not respond at all to TAG's survey. Six companies that did respond reported a total of $43 million in 2005 TB R&D investments—11% of reported overall R&D—mostly on drugs with smaller amounts allocated to diagnostics and vaccines. Two responding companies accepted TAG's offer of anonymity in exchange for data.

It is difficult to estimate spending by the R&D pharmaceutical companies that declined to provide research investment figures. These include industrial behemoths such as Bayer, GlaxoSmithKline (GSK), and Roche. Some of these companies still enjoy steady, if not stellar, revenue streams from TB products. Others have recently touted their increasing involvement in TB research.

In some cases product development partnerships (PDPs) such as Aeras, FIND, and the TB Alliance reported investing in industry. It was not always clear whether a given company was also investing its own additional resources in these discovery and development ventures. It may be that industry is providing matching funds, staff, facilities, or intellectual property. In any case, greater transparency by industry in regard to its R&D investments in neglected diseases of great global public health importance is clearly overdue. Enhanced industry investment would also be welcome.

2.6 Funding Recipients: Product Development Partnerships (PDPs) and Research Consortia

The resurgence of TB as one of the world's leading killers, plus a paucity of effective control methods, gave rise at the turn of the millennium to a new generation of nonprofit organizations known as public-private partnerships (PPPs) or product development partnerships (PDPs). These funding managers provide linkages and collaborative mechanisms enabling industry, governments, private philanthropic organizations, academic institutions, and public health programs to collaborate on specialized research agendas. Their formation may have spurred increased commercial sector involvement in neglected areas of new tool R&D development that has not traditionally yielded profits. They have also created opportunities for researchers who usually labor in isolated spheres to work across disciplines.

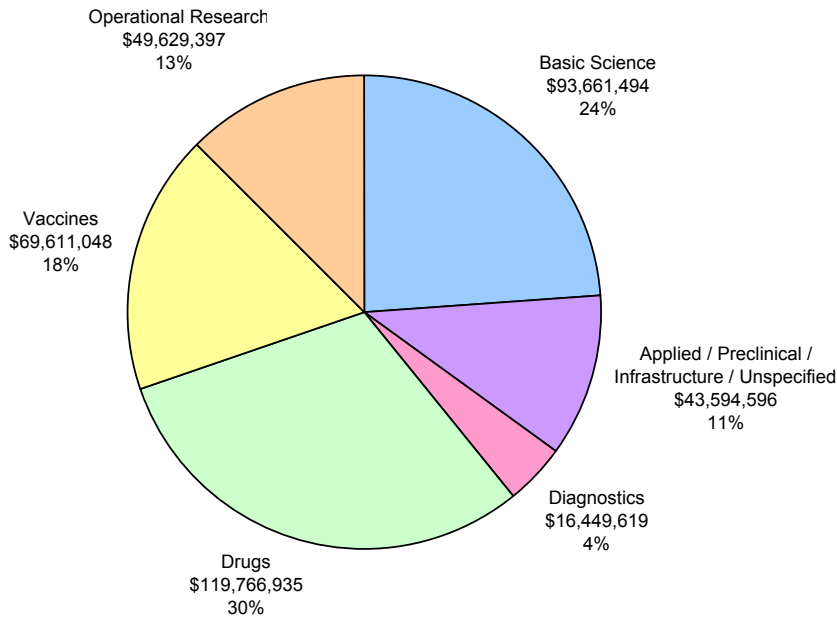
PDPs, along with other TB funding managers, such as research consortia and clinical trial networks, are not original funding sources. They both receive and disburse grants and therefore do not appear in this review's list of top TB R&D donors. The PDPs, along with other funding consortia were responsible for directing $49 million in R&D funds during 2005.

Table 3: Significant TB R&D PDPs and Research Consortia

PDP/Funding consortium	2005 TB spending (US dollars)
Aeras	26,526,253
TB-VAC	6,778,239
CREATE	5,816,005
Global Alliance for TB Drug Development	5,556,397
Foundation for Innovative New Diagnostics	2,193,605
TDR	1,400,000
EDCTP	580,039
WHO MDR-TB	156,045
PDP/Funding consortia subtotal	**$49,006,583**

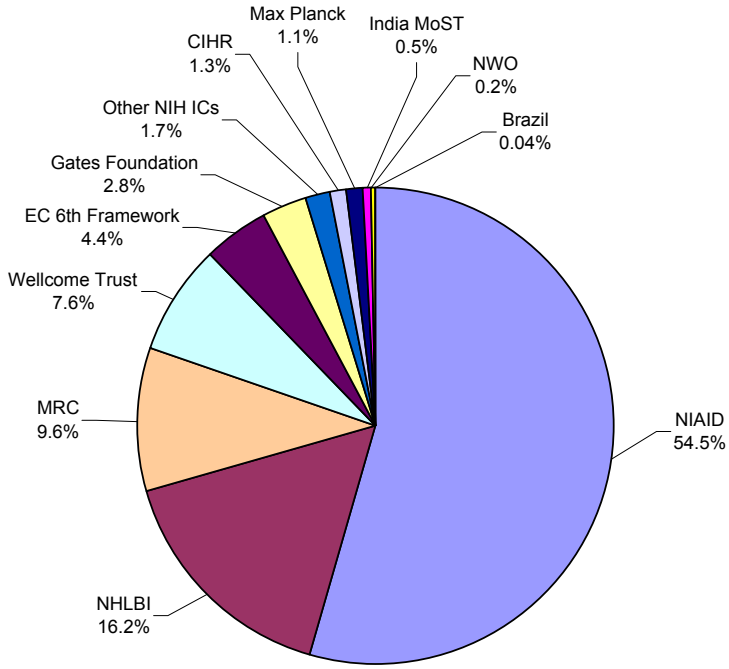
3. Tuberculosis R&D: A Close-up

Figure 1: 2005 TB Research: Investment by Category (Total = $392,713,089)



3.1 Basic Science

Figure 4: TB Basic Science (Total = $93,661,494)



Total reported funding allocated to basic science research on TB was $94 million in 2005. Of this, $51 million came from NIH's NIAID and $15 million from NIH's NHLBI; together they account for 71% of all basic R&D reported here. Besides NIH, the second and third largest donors were the U.K.'s Medical Research Council and the Wellcome Trust at $9 million and $7.1 million, respectively.

The Global Plan did not make specific recommendation for increasing basic science funding, although this area of investment needs to be continually supported for the new tools pipelines to remain robust. The example of HIV/AIDS research, where basic science received a substantial boost in the early 1990s with continuing benefit to this day, demonstrates that basic science investment must be increased early and substantially to support a healthy research field.

Basic Science Research Advocacy

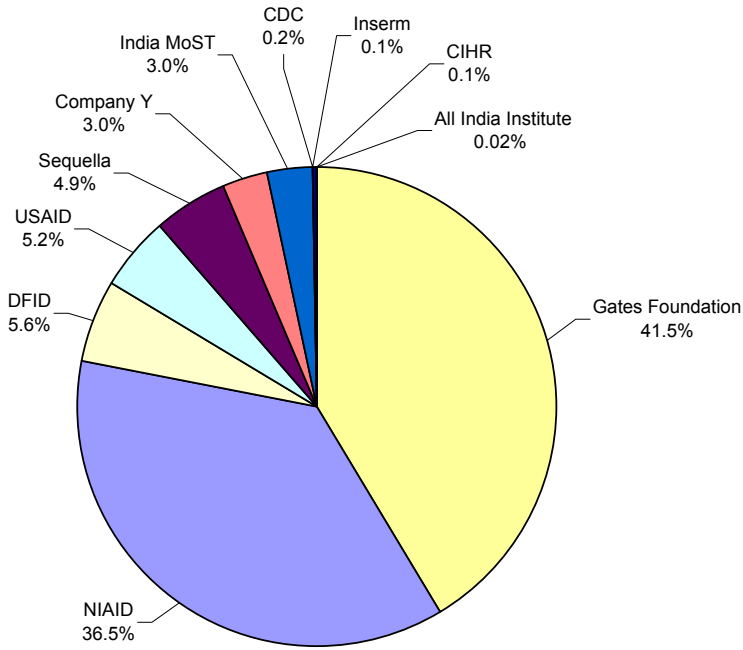
Two fundamental scientific unknowns continue to challenge the discovery of diagnostics and drugs. There is still a need to identify the best antigens for testing for TB. "No one has any idea of the ideal antigens," says Martine Guillerm, Laboratory Technical

Advisor with Médecins sans Frontières (MSF). "TB is provoking a very different answer from one patient to another and [research on the potential need to mix several] antigens is not happening." Similarly, in order to move drug discovery forward, there must be further understanding of the basics of the tuberculosis bacilli through exploration of the TB structure and genome for new targets.

Traditionally, the public sector funds basic science but these TB investment numbers testify to the anemic response of governments to the urgency of the problem. Advocates require both donor and high-burden country governments to support more basic science research on MTB, its bacteriology, genetics, immunology, and disease pathogenesis.

3.2 TB Diagnostics

Figure 5: TB Diagnostics Research (Total = $16,449,619)



According to TAG's review of investments, diagnostics research received $16 million in 2005, by far the least of all new tool areas and just 4% of all TB R&D. The largest single contributor was the Gates Foundation with $6.8 million–$4.6 million to FIND (awarded in 2005, disbursed in early 2006) and $2.3 million to WHO's Special Programme For Research and Training in Tropical Diseases (TDR) for the development of new diagnostics. This brings the Gates contribution to 41% of the total diag-

nostic research committed in 2005. NIAID provided $6 million in applied/preclinical funding for diagnostics.

Measured against the Stop TB Partnership's Global Plan to Stop TB, which aims to develop a toolbox of widely accessible diagnostic tests over the next decade, investments in diagnostic development fall far short of estimated needs. In order to fulfill *The Global Plan* 2006 projected R&D costs, diagnostic spending would have to increase almost fourfold to reach its 2006 budget requirement of $59 million.

TB Diagnostics Research Advocacy

TB control efforts urgently require new and improved assays to detect latent TB infection, TB disease among children and in people coinfected with HIV, and cases of MDR- and XDR-TB disease. These tests need to be cheap and appropriate for use in resource-constrained settings. Availability of appropriate diagnostic tools lags behind other new tools. Sputum smear microscopy, the standard diagnostic implement used in resource-poor settings where most of the TB burden lies, is over 100 years old. "People still feel OK with microscopy; it's difficult to believe it's still part of the game," MSF's Martine Guillerm commented to TAG. People coinfected with TB/HIV are needlessly dying from late diagnosis due to antiquated tests, which don't pick up extrapulmonary or sputum-smear negative TB.

Many activists are concerned that much of the investment in new diagnostic technology does not focus on resource-limited and point-of-care settings. "We have to ask, 'Where are the people with TB? Where are they getting care? And what is possible in those settings?" stated Gregg Gonsalves of AIDS and Rights Alliance for Southern Africa (ARASA), who is a member of Stop TB's New Diagnostics Working Group. "Then we need to build tests relative to those settings." He points to rusty equipment, lack of trained lab technicians, water, electricity, and refrigeration as limitations that need to be considered in developing new TB diagnostics. To address the problems with the current pipeline and make better use of existing tools, Gonsalves calls for a greater focus on customer specifications and requirements of a point-of-care test in high-burden countries, and the simultaneous building of lab capacity—both physical and human. Lydia Mungherera, activist with The AIDS Support Organization (TASO) of Uganda, testifies to the challenges of diagnostics in the context of poor infrastructure: "In government hospitals there are X-rays but they're usually not working, and people have to travel 50 kilometers to get an X-ray to begin with, and there's not even money for transport."

A practical device like a dipstick should be put out to bid, and financed according to milestones, recommends Gonsalves, and there should be guaranteed funding for field evaluation for new diagnostic tests. MSF has been working to connect clinicians with researchers and companies to help facilitate the development of diagnostic research

needs from the ground up. Their efforts have resulted in a shift of emphasis to more support for field requirements and basic science.

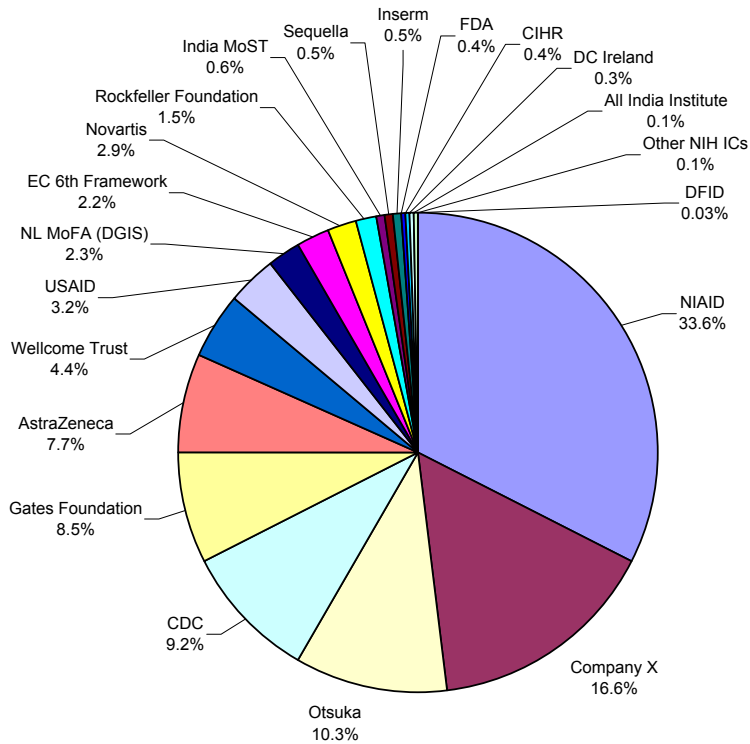
In response to activists' points, FIND stated that 61% of its resources for TB diagnostics research are focused on the development of point-of-care tests (Nantulya 2006b). One thing everyone can agree on is that at $16.4 million in 2005, a mere 4% of total TB R&D investments funding for TB diagnostics, research is woefully insufficient.

The discovery of novel diagnostics and improved access to more sophisticated procedures such as TB culture technology is important. But in the meantime, activists also want to see more community education concerning the volume of false negatives with microscopy. Activist Greg Manning with the Indian NGO Misbah says, "People need to know how unreliable these tests are. They need to know that the first time they go for a test shouldn't be their last." With the emergence of extensively drug-resistant (XDR) TB in high-HIV-burden areas such as South Africa, the need for rapid culture confirmation of smear positive disease, rapid culture to detect smear negative disease, and rapid drug susceptibility testing (DST) and drug resistance surveillance (DRS) is moving to the top of the global TB R&D agenda, along with the need for new anti-TB drugs active against MDR- and XDR-TB disease.

There is also a need for greater focus on developing regulatory mechanisms for oversight of diagnostics research and development in resource-constrained settings to ensure that improvements in diagnosis are linked with appropriate availability of high-quality, uninterrupted supplies of TB treatments, and on the potential use of new diagnostic tests as surrogate markers to accelerate regulatory review and approval of new TB drugs and vaccines. Currently, TB treatment trials must follow patients for 18 months post-treatment to ensure that they do not relapse, and new TB vaccine trials will have to follow immunized infants and children for 15 years to life to see if they develop TB disease.

3.3 TB Drugs

Figure 6: TB Drug Research
(Total = $119,766,935)



According to TAG's forty top respondents, investment in new TB drugs totaled $119.8 million in 2005. This amounts to 30% of all TB R&D reported, rendering this group the biggest recipient of new tools investments.

NIH's NIAID was the single leading donor, investing $39 million in applied/pre-clinical research. The CDC spent $11 million on clinical trials of TB drugs. The Gates Foundation contributed $9 million to TB treatment research, $5 million of it to the Global Alliance for TB Drug Development to develop novel therapies. The Imperial College of London was awarded $4 million in Grand Challenge money to improve treatment for latent tuberculosis. *The Global Plan's* 2006 budget for drug R&D is $418 million, almost a fourfold increase from 2005 spending. *The Global Plan* estimates that in order to achieve new, affordable TB drugs over the next ten years, $4.8 billion is needed, leaving a funding gap of $4.2 billion. This report reveals that investment for new TB drugs in the first year of *The Global Plan* is short $298 million. If funding stays at constant levels for the next decade the funding gap for new TB drugs will be $3.6 billion.

This is another area where greater disclosure by industry would have been welcome. "Company X," Otsuka, AstraZeneca, Novartis, and Sequella are to be commended for reporting investments of $18.6 million, $12.3 million, $8 million, $2.3 million, and $800,000 in new TB drugs, respectively. GlaxoSmithKline (GSK) recently announced a new drug discovery research facility in Tres Cantos, Spain, focusing on HIV, TB, and malaria; and Tibotec is moving forward with at least one new TB compound, TMC207, now in early bactericidal activity (early phase II) clinical trials.

TB Drug Research Advocacy

Although funding for new TB drugs is ahead of that for new diagnostics and new vaccines, it is still far from sufficient. Most notably, there is no funding available to build the extensive clinical trials infrastructure needed to carry out large-scale, long-term phase II/III efficacy and post-marketing phase IV studies of new TB agents and combinations. Funds for the CDC's TB Trials Consortium (TBTC) have been cut for two consecutive years; NIH's clinical trials budget is stagnant; and the TB Alliance's new $104 million from the Gates Foundation will support nine pre-clinical projects and identify the best of these compounds for clinical studies, and advance moxifloxacin into phase III trials. New TB drugs must address the challenges of current TB therapy by decreasing the duration and pill burden of first-line TB treatment; have manageable interactions with nevirapine and protease inhibitors; treat multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB; and treat pediatric TB disease (Syed 2006).

A concerted effort needs to be put into finding new bacterial targets. While there are six candidates in clinical trials, most candidate drugs are still in the preclinical phase. A lack of registered new drugs—the last new class (the rifamycins) was introduced forty years ago—has left a generation of biomedical researchers with virtually no experience in TB drug development.

Projected costs for clinical trials and their preparation far exceed what is currently in the coffers. Partners in Health (PIH) perceives a significant challenge to be the funding of new trial sites in high-burden areas. "The resources needed are not only those required for the actual trials, but also those required for the extensive multi-institutional planning processes and for readiness preparation of new field sites," says PIH's Paul Zintl.

Another challenge put forth by Zintl is that "the drug-susceptible and drug-resistant forms of the disease are often considered separately, despite the fact that they are part of a single problem for which new resources must be found urgently. This limited perspective can be found in both research and policy settings, and can result in unnecessarily competing constituencies."

Other activists approach research holistically, linking diagnosis with treatment. They argue that limited diagnostic tools, particularly for latent disease, will make clinical drug development difficult, especially when we begin to have multiple novel drug options that need to be studied in combination. Helen Lee, a diagnostic specialist at the University of Cambridge, emphasizes not only the importance of drug research but also of drug distribution. "If they can't treat the people identified by microscopy, then why are they talking about fancy new diagnostics?" she asks.

Because TB is mostly treatable with the current arsenal of drugs, the public sector has neglected the disease. However, this winter in South Africa we witnessed the worst outbreak to date of XDR-TB, a clear warning that time is not on our side. "Extreme resistance signals that the current strategies [for TB control] are failing," says MSF's Guillerm. "If we stick to the previous model nothing is going to happen. The fire is burning now."

Additional research challenges for TB drug development include the need to develop innovative trial designs—possibly using surrogate markers of drug efficacy—which could shorten the time to regulatory approval for drug-sensitive and drug-resistant disease. Regulatory authorities in both developed and developing countries need to be brought on board now to begin wrestling with these issues. Streamlining the uptake of potential breakthrough new drugs in resource-constrained, sometimes conservative TB program settings will be another challenge.

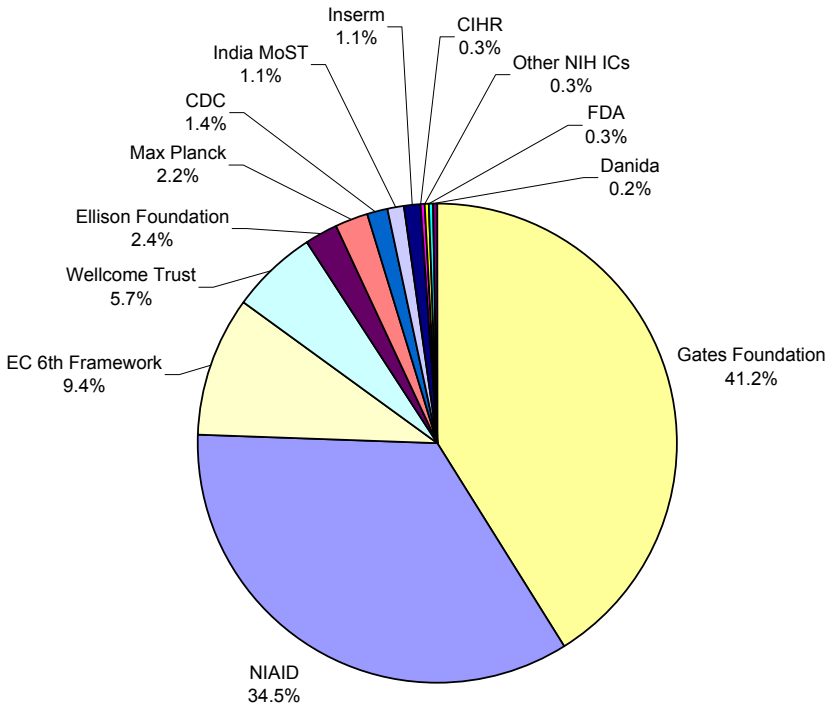
The private sector's sluggish response is a reaction to weak market incentives created by a disease of the poor. Activists need to hold both public and private sectors accountable for their forty years of failure and advocate to both spur market incentives and to support the funding of TB treatment research through innovative mechanisms such as product development partnerships (PDPs) like the TB Alliance.

3.4 TB Vaccines

Reported TB vaccine R&D spending was $69.6 million in 2005. The Gates Foundation was the leading benefactor supporting $28.7 million in TB vaccine R&D. Most of its funding was directed through the Aeras Global TB Vaccine Foundation. NIAID supported $24 million in vaccine research. The EC spent $6.5 million; the Wellcome Trust, $4 million; the Ellison Medical Foundation, $1.7 million; Germany's Max Planck Institute for Infection Biology, $1.5 million; and the CDC, $1 million on TB vaccine research in 2005.

The Global Plan estimated that $291 million is needed to support TB vaccine R&D in 2006, requiring a nearly fivefold increase from the approximately $70 million reported for 2005.

Figure 7: TB Vaccine Research
(Total = $69,611,048)



TB Vaccine Research Advocacy

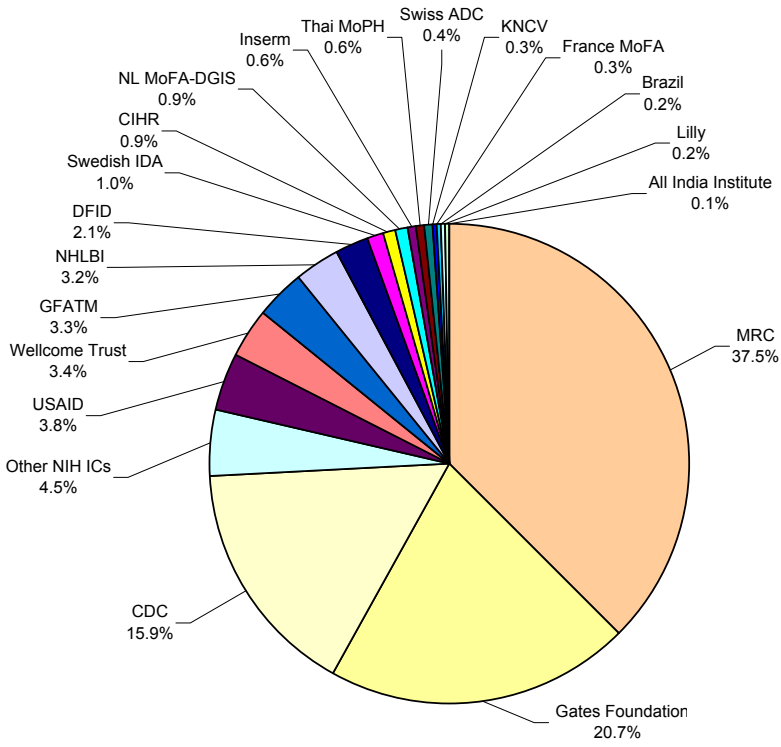
Improved understanding of host immunity to TB, the identification of genes as well as antigens, and the development of improved ways to stimulate immune response through adjuvants are all areas of exploration in developing a more effective TB vaccine.

There are currently five vaccines in clinical trials. In general, vaccine studies demand large-scale clinical sites and capacity building for multicentered trials of promising candidates.

The public sector has largely neglected TB vaccine research, because many authorities have regarded BCG as an effective and cost-effective vaccine. Because TB is a disease of poverty, there is little market incentive for the private sector to become involved. As noted in the drug section above, activists need to hold both public and private sectors accountable for their failure to adequately support research and help to both spur market incentives and to support expanded funding for the PDPs.

3.5 Operational Research

Figure 8: TB Operational Research (Total = $49,711,675)



In 2005, donors reported spending $49.6 million on operational research related to TB. The U.K. Medical Research Council was the largest investor in this area at $18.6 million. Much of its research was carried out in a long-standing research program in the Gambia.

The Gates Foundation invested $10.3 million in TB operational research, of which $10.2 million went to the Consortium to Respond Effectively to the TB/HIV Epidemic (CREATE), which is conducting three very large studies of interventions for TB and HIV in Brazil, South Africa, and Zambia. The Thibela-TB study is a randomized no treatment vs. treatment controlled study of isoniazid preventive therapy (IPT) among 70,000 South African gold miners, 35,000 of whom will be randomized (according to the mine shaft in which they work) to INH or no isoniazid preventive therapy (IPT). TB incidence in the South African mines is the world's highest at 4,000 per 100,000 per year. The ZAMSTAR study is a 24-community randomized study in South Africa and Zambia, investigating household TB/HIV integrated activities, intensified community-based TB case finding, strengthened DOTS, and clinic-based TB/HIV activities. The

THRio study is a phased implementation program applying TB screening and IPT for 15,000 HIV-infected clinic patients in Rio de Janeiro, Brazil.

In addition to these very large and well-controlled operational research studies, which should yield clear data and impact on future program design for TB and HIV worldwide, many sponsors are supporting smaller operational research programs that in some cases are nested within TB control programs. CDC is supporting Botswana's HIV scale-up program and they are jointly implementing IPT in Botswana; CDC is also supporting a variety of intensified TB case-finding activities in HIV programs in Africa, and HIV testing programs within TB programs. CDC spent $7.9 million on TB operational research in 2005. USAID reported $1.9 million invested on TB operational research programs in 2005.

TB Operational Research Advocacy

Operational research will help to ensure that new tools to control TB work in routine program conditions and build experience and programmatic support to ensure that once new TB products become available they are taken up in national TB programs.

Activists call for the public-sector funding of operational research that ensures an integrated approach to the delivery of effective diagnostics with treatment. This includes research on social support; outpatient and inpatient treatment; and optimal program design for TB detection, treatment, and cure for drug-sensitive and drug-resistant TB disease.

The Global Plan doesn't forecast the need for operational research. TAG recommends that funding for operational research reaches fivefold of what is available in 2005.

4. Funding for TB R&D In Context

4.1 TB R&D Relative to TB Control

The WHO-recommended Directly Observed Therapy Short course (DOTS) strategy contains the core elements of recent TB control efforts. The five elements which make up the DOTS strategy are:

- **Sustained political commitment**
- **Identification of infectious smear-positive cases of TB through sputum smear microscopy**
- **Standardized short-course TB treatment regimens given in conditions of direct observation**
- **Uninterrupted availability of treatments**
- **Monitoring and recording mechanisms that assure quality and outcomes**

Maintaining DOTS at the core, WHO's TB control strategy was expanded in 2006 to include five additional elements. These are to:

- **Address TB/HIV, MDR-TB and other challenges**
- **Contribute to health system strenghtening**
- **Engage all care providers**
- **Empower people with TB and communities**
- **Enable and promote research**

Based on decades-old principles and technology, DOTS was placed by WHO at the core of the global effort to scale up public TB control programs to reverse the epidemic's spread. Based on studies conducted by Karel Styblo in Tanzania, the DOTS strategy aimed to achieve 70% case detection of smear-positive pulmonary TB and 85% cure rates by 2000—and then, when that was not achieved, by 2005. In theory, detecting 70% of infectious cases and curing 85% of them would result in 6–7% decreases in TB incidence yearly, ultimately reducing disease prevalence. "The cost of TB control … including health system staff and infrastructure … [and National TB Program] budget requirements, is projected to be U.S. $1.6 billion in the 22 high-burden countries in 2006" (WHO 2006), with additional costs in the world's other 170 countries. This is four times the amount spent on TB R&D in 2005. Yet despite this investment TB incidence and mortality continue to increase.

The Global Plan estimates that $4.7 billion is needed each year (on average) over the next ten years; this figure is likely to be an underestimate due to the rampant increase in MDR-TB and HIV-related TB, and the underestimates in the current Plan for spending on such key elements as infection control, laboratory systems strengthening, and—as we demonstrate in this report—on research and development. Despite the past decade's progress in scaling up DOTS, Stop TB/WHO's goals of detecting at least 70% of sputum smear-positive pulmonary TB and curing 85% of reported TB cases were not achieved. Case detection rates of smear-positive TB for 2004 were just 53% (WHO 2006). "DOTS can only be the foundation for global tuberculosis control," wrote S.K. Sharma of the All India Institute of Medical Science and J.J. Liu of the Chinese Centers for Disease Control. "To truly contain the disease, much more is needed in the control of multidrug-resistant tuberculosis (MDR-TB) and the development of drugs, diagnostics, and vaccines" (Sharma 2006).

4.2 TB R&D Funding Relative to Other Diseases

HIV, TB, and malaria are the world's three most common lethal infectious pathogens today. Both TB and malaria are curable, while HIV is treatable but incurable to date. Yet research funding for these three killer infections is far from proportionate to the damage they wreak. Although TB carries a high disease burden, NIH spends more on smallpox and anthrax, which in recent years killed no one and just a few people,

respectively. TB and malaria together kill over three million people each year.

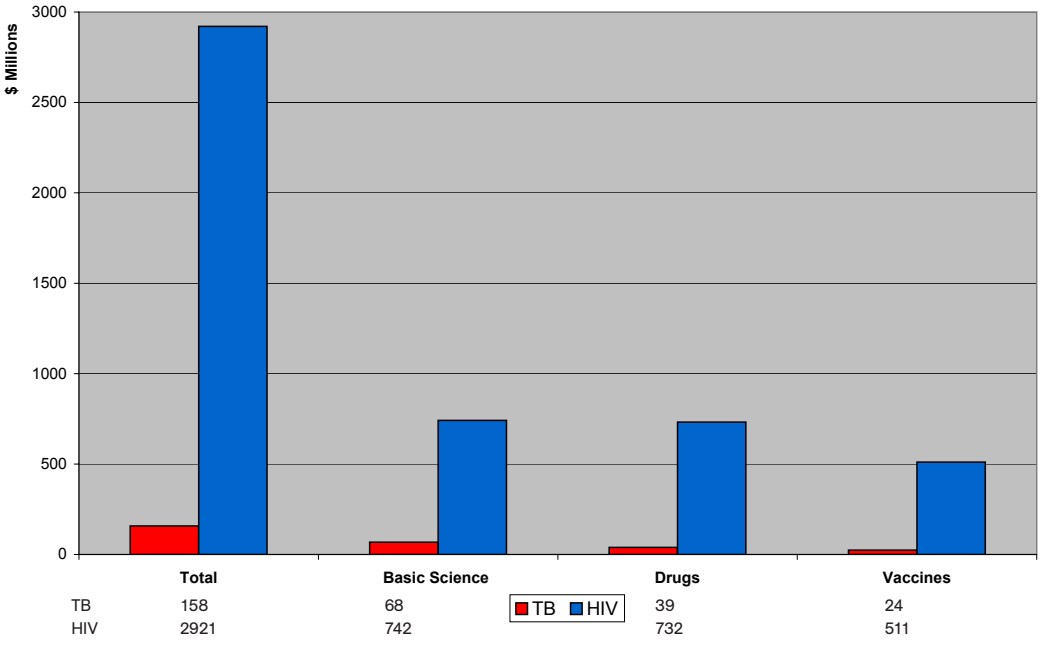
Table 4: NIH Spending on Selected Infectious Diseases in 2005

Infectious Disease	FY05 Actual (million $)
HIV/AIDS	2921
STDs/Herpes	252
Smallpox	187
Anthrax	183
Influenza	164
Tuberculosis	158
Pneumonia	154
Hepatitis C	121
Malaria	104

HIV/AIDS received the most funding of any specific infectious disease in 2005 at $2.9 billion. This global pandemic, only 25 years old, became a priority research area in the 1990s due to its recent appearance, rapid pandemic spread, high mortality rates, and the formidable AIDS activist movement, which placed unprecedented and historic pressure on the U.S. and other developed–and, later, developing–country governments to respond to this global emergency.

By contrast, and despite its worldwide toll and continuing advance, TB research receives far less than it is due.

Figure 9: NIH Investment: TB vs. HIV (2005)



5. Recommendations

Progress in biomedical research is directly linked to funding. Therefore, it is imperative to advocate for well-directed, adequate investments. To do so intelligently, a global assessment of baseline expenditures is needed, as well as a comprehensive scientific research agenda covering the entire field of TB research from basic to applied and preclinical research. This agenda should target research on essential new tools including diagnostics, drugs, and vaccines, well-funded and efficient clinical trials programs to validate these new tools in rigorous controlled trials, as well as operational research to fully understand their effectiveness in routine program conditions. Additionally, an accurate accounting of available and required resources to accomplish R&D targets will help drive a credible advocacy agenda.

How Much Funding is Available?

This analytic review indicates that approximately $393 million was available for TB R&D in 2005 from the forty top donors.

a. New Tools

In 2005, this report shows that $206 million was invested in research specifically directed toward discovery, development, and validation of new tools to better control TB, including new diagnostics, drugs, and vaccines. *The Global Plan to Stop TB: 2006–2015* indicates that $9 billion is needed over the coming decade for new tools research on TB, or $900 million per year. Based on the discrepancy between new tools investment identified for 2005 and *The Global Plan* targets, TAG estimates that investment in new tools must rise nearly fivefold, from $206 million to approximately $1.05 billion per year in order to achieve the targets of *The Global Plan*.

b. Basic Science, Infrastructure, & Operational Research

Investment in new tools depends on insights from basic science and validation through clinical and operational research; all of which require development of research infrastructure. Additional resources are necessary for basic science, infrastructure development, operational research. *The Global Plan* does not specify investment targets for the areas of basic science, infrastructure development and operational research. By extrapolating from the resource gap identified in our analysis for new tools research, TAG estimates that investment in basic science, infrastructure, and operational research must also increase approximately fivefold, for discovery and development of innovative new interventions to control TB. Thus from the baseline of approximately $188 million invested in these areas in 2005, TAG estimates that $950 million is needed per annum.

How Much Funding Is Needed?

The world must invest at least $2 billion per year—or $20 billion between 2006 and 2015—on TB R&D in order to lay the scientific foundation to eliminate TB as a public health threat by 2050.

Figure 10: How Much Funding Is Needed? (Dollars in Millions)

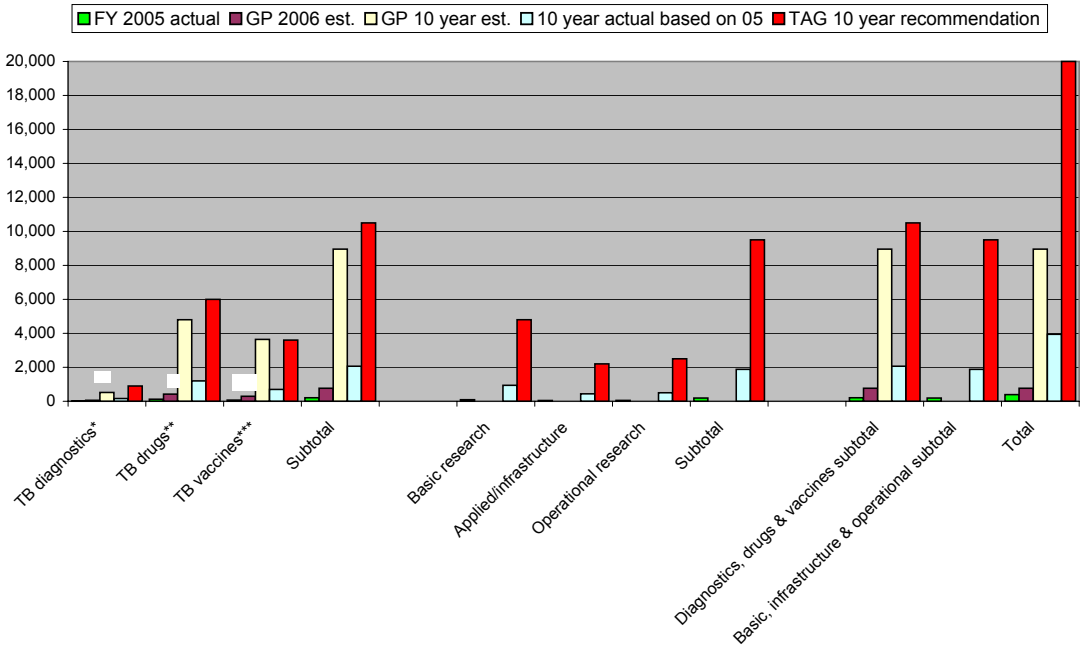


Table 5: How Much Funding Is Needed? (Dollars in Millions)

	FY 2005 actual	GP 2006 est.	GP 10 year est.	10 year actual based on 05	TAG 10 year recommendation
TB diagnostics	16	59	516	160	900
TB drugs	120	418	4800	1200	6000
TB vaccines	70	291	3641	700	3600
Subtotal	**206**	**768**	**8957**	**2060**	**10500**
Basic research	94	0	0	940	4800
Applied/infrastructure	44	0	0	440	2200
Operational research	50	0	0	500	2500
Subtotal	**188**	**0**	**0**	**1880**	**9500**
Diagnostics, drugs & vaccines subtotal	206	768	8957	2060	10500
Basic, infrastructure & operational subtotal	188	0	0	1880	9500
Total	**394**	**768**	**8967**	**3940**	**20000**

If a fivefold increase in funding research on a specific disease seems unrealistic, let us recall that in 1988 the NIH received just $500 million for AIDS research. That fall AIDS activists led by ACT UP demonstrated at the U.S. Food & Drug Administration (FDA) to demand faster approval of new drugs for AIDS. In 1990 ACT UP demonstrated on the NIH campus in Bethesda, MD, to demand that NIH speed up research on new treatments for HIV and its associated opportunistic infections, and for NIH to incorporate activists and people living with HIV into programs that were planning and executing clinical trials. Public demonstrations and activist meetings with scientists, policymakers, and politicians led Congress to propose massive increases in funding for HIV/AIDS research at the NIH. In 1993, responding to an early report by TAG (Gonsalves & Harrington1992), Congress passed and President Clinton signed legislation strengthening the NIH Office of AIDS Research (OAR), giving it the ability to plan, coordinate, and evaluate the entire NIH AIDS research budget across its multiple institutes. TAG's 1992 report also called for a doubling of the entire NIH budget in order to allow for healthy increases in AIDS research.

NIH convened an external group of scientists and activists to review its entire AIDS research program. The president and Congress increased the AIDS research budget to $1.3 billion in 1994. In the late 1990s both parties agreed that the entire NIH budget should be doubled by 2002. That year NIH received $23 billion and AIDS research received $2.5 billion. Much of the credit for this accomplishment goes to the AIDS activists who started demonstrating in the late 1980s to demand much greater federal investment in AIDS research.

By contrast there has been little organized demand by advocates for other diseases of global public health import for ramping up research on a massive scale. To achieve the health-related millennium development goals (MDGs), however, much greater investment in research on new tools and massive efforts to ramp up access to existing tools is urgently needed.

More recently, the NIH budget has leveled off at $28.6 billion per year and the AIDS research budget is beginning to drop slightly from the $2.9 billion appropriated for 2005. Grants to new investigators have fallen, programs are being cut, and there is a very real danger that young people interested in scientific careers will be deterred by the increasing difficulty of obtaining NIH funding. This poses a present and real threat to researchers and advocates who are determined to find solutions to deadly diseases like TB, malaria, and HIV/AIDS.

Since, according to TAG's data, the public sector funds 68% of TB R&D and the U.S. alone funds 47% of the total, clearly solutions will have to be found for the present stagnation of U.S. public sector investment in research by the NIH and the CDC. Both agencies and the extramural research community need to be placed on a track of steadily increasing resources over the next decade so that planners, researchers,

advocates, and policymakers can work to defeat lethal diseases such as AIDS, TB, and malaria.

Public sector research agencies in other countries need to increase their investment in biomedical research on global diseases, including TB and HIV, substantially as well. TAG was pleased that the U.K. Medical Research Council (MRC) with its historic record of funding breakthrough discoveries in TB research, including the first randomized streptomycin clinical trial in 1948, continues to be such an important presence. The MRC, the EU 7th Framework, and individual research agencies from G8 and other developed countries must substantially increase their investment in basic and applied research to control HIV, TB, and malaria, among other global pandemics.

Public sector investment by high burden and developing countries is also a major priority. Although our exploratory analysis was incomplete, TAG was pleased to be able to document that India's investment in TB R&D placed it among the top five national public sector investors in this area. While data are incomplete, we also found that Brazil, Russia, and Thailand are major players in TB research—particularly operational research. We call upon developing and high burden countries to substantially increase their investment in TB R&D in all phases, including basic science, and new tools discovery and development as well as operational research.

The philanthropic sector, and particularly the Gates Foundation, has been providing leadership in filling important gaps in TB R&D in the past half decade, with particular focus on later-stage discovery and clinical evaluation of potential new tools, including TB diagnostics, drugs, and vaccines. TB diagnostics remains an orphan area, with just 4% of overall TB research funding, even though current diagnostic procedures in TB programs around the world rely on 19th-century tests which cannot detect 40–60% of TB disease and which fail even more frequently among people living with HIV and among children.

A rapid point-of-care test for TB that does not depend on electricity or a cold chain and can be read by clinical officers and nurses in field settings will be a major breakthrough that will open the door to earlier diagnosis and appropraite treatment for millions of people each year. The Gates Foundation can further enhance its leadership position in this area by bringing together foundations to ensure that more of them invest in diseases of the poor—including TB—and that they work in concert to secure more investment from the public sector and from industry, and to ensure that their investments are optimized by being placed in the context of comprehensive global and national research agendas.

Investments in new TB drugs and vaccines are relatively healthier than in diagnostics. Currently, however, virtually no infrastructure exists for the large phase II/III

clinical studies that will be needed to validate these new interventions. The CDC-funded TB Trials Consortium (TBTC) is facing funding cuts; the European-Developing Countries Clinical Trials Program (EDCTP) is quite small; and sponsors such as Aeras, the TB Alliance, and industry are focusing on individual product development projects rather than on the collective development of sustained global clinical research infrastructure, which is properly the domain of the public sector. Therefore the public sector from both donor and developing countries will need to invest in the infrastructure necessary to carry out the later-stage clinical trials of new TB drugs and vaccines. This will require an investment of millions of dollars.

The Global Forum for Health Research (GFHR, www.globalforumhealth.org) has published a useful set of reports on the need both for greater harmonization of resource tracking by funders of health research around the world and for greater investment by developing countries in this research. TAG heartily endorses the efforts of the Global Forum and their call for greater harmonization in research tracking and for greater investment by developing countries in health research.

We have discussed above the problems with tracking investments by pharmaceutical and biotechnology companies in TB research. We salute those who did declare their investments and hope that more companies will be willing to do so in the future. To assure ongoing involvement by industry, investment by the public sector in basic science, clinical trials infrastructure, and operational research is essential. Collaboration among industry and the product-development partnerships (PDPs) can also play a useful role. Industry has not yet fully realized the promise of greater investment in diseases of the poor even in the HIV/AIDS field. Continuing conflicts between industry, developing country governments, and advocates demonstrate the difficulty of applying flexible regimens to achieve universal access, using a variety of mechanisms such as differential pricing, implementation of TRIPS flexibilities where needed, generic drug manufacturing, quality assurance, supply chain management, voluntary licenses, and free diagnostic, preventive, and treatment services to users at point of care. Industry involvement in HIV/AIDS research has been critical to progress in this area, and industry flight from other diseases of the poor including TB has had disastrous consequences. Thus industry involvement must increase, and advocates, donors, researchers, and industry must work together to overcome the barriers identified.

Multilateral agencies such as the Global Fund, WHO, and the World Bank will continue to be involved in various ways in supporting a scale-up of effective programs, including operational research, in diseases such as TB. However their roles vary and it is not clear that the Global Fund or the Bank will ever be major funders of research per se, or whether they should be. WHO has a critical role to play as the world's normative health agency providing guidelines and technical assistance to countries. However, WHO does not conduct much research itself, and it is unclear despite a recent World Health Assembly resolution endorsing greater involvement

in health research what the ultimate role of WHO will be. With respect to designing and implementing a global TB research agenda, WHO's role should be to assist in coordinating and establishing collaborations rather than planning to conduct most of the research itself. Its research unit at TDR is grossly underfunded and will be unable to significantly scale up its contribution to TB research anytime in the future.

As for tracking of global TB R&D investments over the life of *The Global Plan*, perhaps WHO's best role would be to facilitate the work of Stop TB and the over 400 members of the Partnership in order to develop a universal TB R&D tracking mechanism, which reports annually and comprehensively on TB research programs underway and progress toward meeting the investment goals and R&D outputs demanded in *The Global Plan*, and to focus global policy and research leadership on creating a truly comprehensive TB R&D agenda for the coming decade.

What is needed most of all is an understanding by advocates and affected communities worldwide—and this means by the people of all countries—that TB, like HIV/AIDS and malaria and other global pandemics, will not ever come under control unless there is massive new investment to provide universal access to the best interventions currently available and to significantly increase research to discover, develop, validate, and disseminate new and better tools.

In this compilation of investment information for TB R&D, TAG encountered major obstacles, including the lack of coordination among TB R&D investors globally and nationally, lack of transparency, particularly by industry, and the lack of consistent and comprehensive TB R&D recording and reporting systems.

Research Agenda

1 **A comprehensive, global TB R&D agenda is urgently needed**. A TB R&D agenda needs to incorporate the entire spectrum of research that is needed to achieve the goals set forth in *The Global Plan to Stop TB*. This comprehensive research agenda should also address the need for major expansion of the basic and operational research foundation that would support new tool development. In addition, each of the Plan's New Tool Working Group used different (and in some cases incompletely documented) methods of calculating their ten year research needs. In particular the New Diagnostics Working Group estimate seems to be woefully short of the great need for investment in a breakthrough there, while the New Vaccines Working Group evidently lacks a detailed public workplan.

Research Coordination

2 **TB R&D need to be better coordinated globally and nationally**. TAG's analytic review demonstrates not only that TB R&D is severely underfunded, but that funders

do not adequately coordinate their efforts globally, by research area, or in high burden countries. While philanthropic and public agencies were forthcoming with estimates for TB research, internal tracking systems were inconsistent and incomplete. Some funders did not code grants by specific disease, let alone research area or phase. TAG recommends the standardization of internal tracking systems according to disease (including the separation and coding of diseases that are studied in combination such as TB and HIV), research category, and research phase to enable more comprehensive annual tracking of R&D investments in all diseases of global health importance, including TB.

Research Funding Transparency

3 Pharmaceutical and biotechnology companies need to be transparent and open about their investments in TB R&D. The lack of transparency by some major players in the commercial sector prevents us from obtaining a clear understanding of the extent of private investment in TB R&D. Six of eighteen companies contacted provided detailed investment data for 2005 (two anonymously); four declined to provide any data; three did not respond; and five stated that they did not fund TB R&D. TAG recommends the private sector present its investments in TB R&D publicly. This will help inform efforts by policymakers, research funders, and TB control programmers worldwide to coordinate their investments in TB research.

Reporting Consistency

4 Recording and reporting for TB R&D funding needs to be consistent and comprehensive. TAG recommends that agencies responsible for tracking global R&D investments in TB create uniform and consistent criteria for tracking programs and for reporting on them annually. This work could be carried out by the Stop TB Partnership, if it were fully funded and staffed at an adequate and sustained level, with new expert staff dedicated to this work. It would be important for this research tracking effort to be seen as independent and unbiased. For this reason TAG suggests that the research tracking effort be carried out independent of the current New Tools Working Groups whose work will also be tracked. This will facilitate developing an accurate picture of R&D investments and needs forecasting specifically designed to measure progress toward achieving *The Global Plan* funding targets. In addition, R&D tracking needs to specify whether research is pre-clinical, clinical, or operational, to ensure that all phases of R&D and new tool development are adequately funded. For example, this report demonstrates that new drug development receives relatively greater investment than do other new tool areas, yet support for clinical trials for TB drug development remains anemic.

Figure 11: Who Should Pay?
(Dollars in Millions)

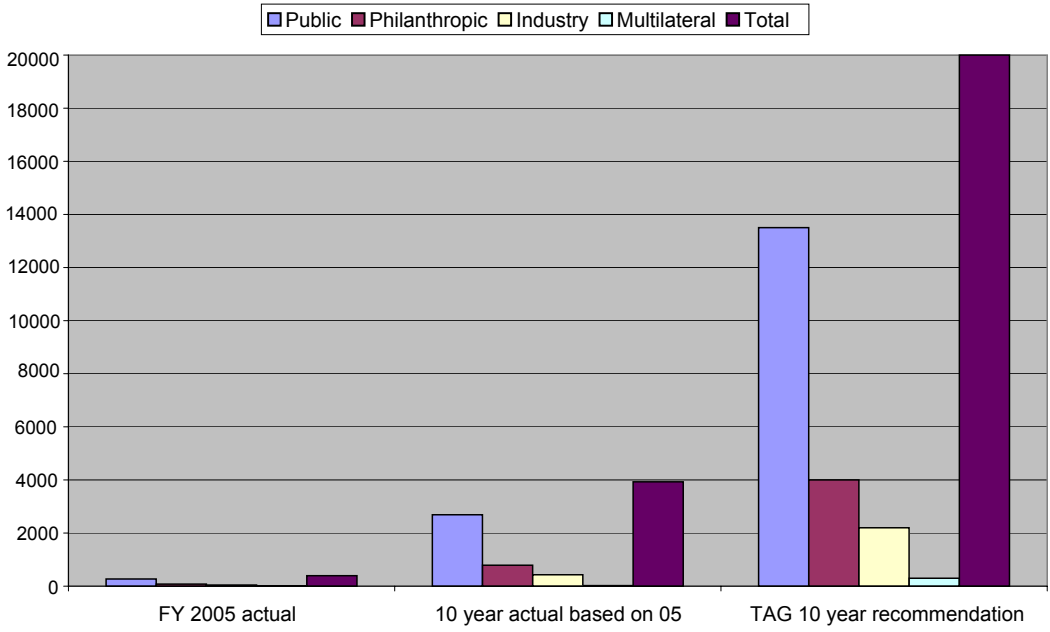


Table 6: Who Should Pay?
(Dollars in Millions)

	FY 2005 actual	10 year actual based on 05	TAG 10 year recommendation
Public	269	2690	13500
Philanthropic	79	790	4000
Industry	43	430	2200
Multilateral	2	20	300
Total	**393**	**3930**	**20000**

Recommendations to Donors, Researchers, Policymakers, and High Burden Countries

5 TB R&D investment must increase fivefold, from approximately $400 million per year to $2 billion per year for basic science, applied, and operational research in order to meet the ambitious R&D targets specified in *The Global Plan*.

6 Donors and developing-country policymakers must commit to global and national plans for health-related research.

7 Donors must support policies that strengthen healthcare systems in resource-constrained countries and high-burden countries.

8 Donors must recognize and support public-private product development partnerships (PDPs) for their work in catalyzing basic, translational and clinical research, particularly on new tools.

9 Donors must explore and support incentive mechanisms such as advanced market commitments to attract private industry to TB research.

10 Donors and research agencies must incorporate activists in the TB community into research program planning and execution.

11 Donors, research agencies, and high-burden countries must support community advocacy efforts to elevate TB's political profile and mobilize community to demand care, prevention, treatment, and research.

12 Donors, research agencies, and high-burden countries must demonstrate transparency and provide funding to allow for an ongoing and sustained effort to comprehensively map and annually update investments in TB R&D.

13 Donors, research agencies, and planners must support scientists from outside fields, such as HIV/AIDS, to integrate expertise from different disciplines. Researchers must recruit new scientists to the field and promote innovative approaches to TB research.

14 Regulatory agencies like the U.S. FDA, the EMEA, the South African Medicines Control Council (MCC), and others must commit to support guidelines to accelerate the study and licensure of new TB diagnostics, drugs, and vaccines.

15 Policymakers must ensure that new tools recommended for use by the WHO will be fully incorporated into TB programs or by national or regional regulatory authorities.

Towards a Global TB Research Movement: Recommendations for Activists

TB is not a priority to the traditional funders of biomedical science partly because there does not exist a cohesive movement to bring visibility to the disease and to place demands on policymakers. TB is a disease of the poor, where the few patient advocates involved are developing the necessary skills and resources, and there is little TB awareness among the general population. A TB research movement is further stymied by the conservative TB control programs and the public health community—compared to the HIV field—who holds steady to DOTS, despite its limitations, as the primary intervention strategy.

"If [the TB] community is not involved in demanding research is done, there will be less legitimacy for bringing more money into research," says Brazilian TB/HIV activist Ezio Távora dos Santos Filho. In order to raise TB's profile there needs to be outreach to affected communities, such as groups involved with HIV, prisoners, the homeless, sex workers, lesbians and gays, and advocates working on broader health issues. But to bring new advocates on board, there needs to be direct support for their work. "The challenge with TB advocacy is to convince people with little funding who are already overwhelmed with work to get involved," says Távora dos Santos Filho.

Greg Manning of India's Misbah organization says that because TB is a disease of the poor, it is inherently a disease of non-English speakers. "If you want TB advocates, they have to be resourced in other languages or you won't mobilize enough people to create a demand or build or a stronger base," he says.

Activists with access to epidemiological data can lobby their Ministries of Finance and Ministries of Research for funding allocations for TB R&D. Supplied with resource-tracking data they can also use reports, such as this, and future mapping data as substantiation that their local institutions need to step up their commitments to TB research funding.

Likewise, armed with proof of global investment figures, high-level funders such as the Group of Eight (G8) can also be exposed for failure to follow through on their promises. For example, in 2005 at the annual summit meeting in Gleneagles, the G8 committed to support of direct investment in research for new drugs, diagnostics, and vaccines for TB and malaria and to explore investment incentives such as advance market purchases. Again in 2006, in St. Petersburg, the G8 called for "a wider use of strategies and tools that promote investment in the research, development and production of vaccines, microbicides, and drugs for HIV, tuberculosis, malaria and other diseases, and that assist in scaling up access to these means of prevention and treatment through innovative clinical research programs, private-pubic partnerships and other innovative mechanisms."

16 TB research advocates should articulate the need for high-level commitment to support TB research, using evidence of this and future tracking reports to expose failures of commitment.

17 TB research advocates should use economic and epidemiological data to engage ministries in donor countries and HBCs to allocate funding for TB research.

18 TB research advocates should demand support for affected communities to create TB visibility and awareness, and to elevate TB's profile among policymakers and other political leadership.

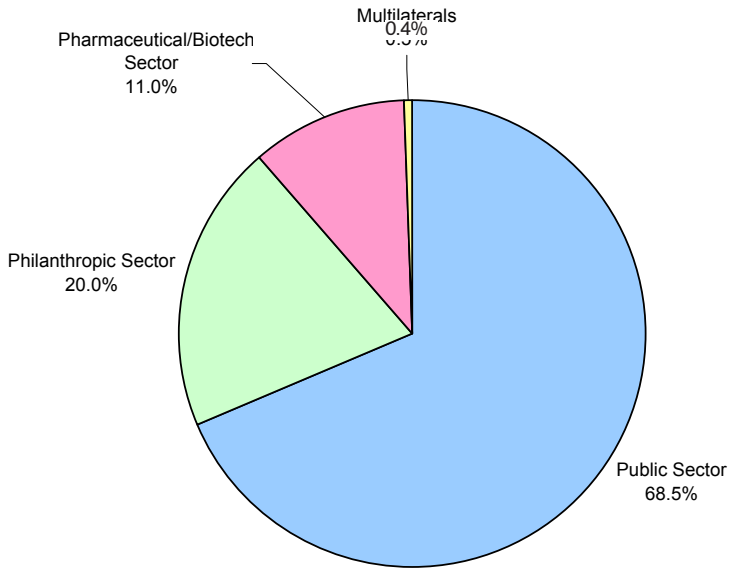
19 TB research advocates should build stronger linkages with the HIV community and other advocates, such as labor unions and poverty-reduction organizations working in at-risk or high-burden communities.

20 TB research advocates should continually assess accomplishments of current and planned TB-research project funding to determine whether the allocated funds are well placed and sufficient.

TB Research Funding: A Critical Analysis is the beginning, not the end, of holding global and regional institutions responsible to those living with and at risk for TB.

6. Conclusions

Figure 12: TB R&D Funding by Donor Category (2005)



This analytic review indicates that approximately $393 million was available for TB R&D in 2005 from the forty top donors.

In 2005, 68% of reported TB R&D funding was from governments, 20% from foundations, 11% from industry, and 0.4% from multilateral agencies.

TB research funding has increased in recent years, most notably through the creation and expansion of public-private product development partnerships (PDPs) focusing on discovery and development of new TB vaccines, drugs, and diagnostics. Much of this new product development effort has been funded by the Gates Foundation. However, given the disease burden and *The Global Plan* estimate that $9 billion is needed for research on new TB tools over the next decade, TAG's analytic review reveals that reported TB R&D spending in 2005 was a mere $393 million.

Of the $393 million, only $206 million was spent on new TB diagnostics, drugs, and vaccines research. More specifically, research on new tools came to just 16 million (4%) for new TB diagnostics, $120 million (30%) for new TB drugs, and $70 million (18%) for new TB vaccines. Another $94 million (24%) was categorized as basic science, $44 million (11%) as applied/unspecified, and $50 million (13%) as operational research. *The Global Plan to Stop TB: 2006–2015* indicates that $9 billion is needed

over the coming decade for new tools research on TB. Based on the discrepancy between new tools investment identified for 2005 and *The Global Plan* targets, TAG estimates that investment in new tools must rise nearly fivefold, from $206 million to approximately $1.05 billion per year in order to achieve the targets of *The Global Plan*.

Investment in new tools depends on insights from basic science and validation through infrastructure development and operational research. *The Global Plan* does not specify investment targets for these areas. By extrapolating from the resource gap identified in our analysis for new tools research, TAG estimates that investment in basic science, infrastructure, and operational research must also increase approximately fivefold, for discovery and development of innovative new interventions to control TB. Thus from the baseline of approximately $188 million invested in these areas in 2005, TAG estimates that $950 million is needed per annum.

In other words, the world must invest at least $2 billion per year on TB R&D in order to lay the scientific foundation to eliminate TB as a public health threat by 2050.

Meeting global targets to halve TB prevalence and death rates by 2015, and ultimately rid the world of TB by 2050, will only become reality if there is a momentous change in R&D funding.

This report, *Tuberculosis Investments: A Critical Analysis,* has been a work in progress. Doubtless, some funding sources remain unreported. Nonetheless, the results of this assessment are sufficient to make clear the case for dramatic and rapid increases in TB research funding worldwide.

7. Appendix A: Top 40 Reporting TB R&D Funders in 2005

Rank	Donor	Total
1	NIAID / NIH	120,273,000
2	Gates Foundation	57,411,457
3	Medical Research Council (UK)	30,887,839
4	Other Institutes & Centers / NIH	20,334,300
5	Centers for Disease Control	19,903,000
6	Company X	18,640,160
7	Wellcome Trust	18,081,359
8	NHLBI / NIH	17,117,000
9	European Commission 6th Framework	13,322,711
10	Otsuka	12,300,000
11	Institut Pasteur	8,472,800
12	AstraZeneca	8,000,000
13	USAID	6,837,907
14	Inserm	5,721,560
15	TB Research Center (ICMR), India	5,313,133
16	Ministry of Science and Technology, India	3,750,000
17	Netherlands Ministry of Foreign Affairs (DGIS)	3,168,488
18	Max Planck Institute	2,500,000
19	Canadian Inst. of Health Research	2,376,098
20	Novartis	2,255,193
21	Dept. for International Development (DFID)	2,008,832
22	Russian TB Institutes	1,930,343
23	Rockefeller Foundation	1,750,000
24	Ellison Medical Foundation	1,650,000
25	Global Fund	1,648,083
26	Research Institute for TB, Japan Anti-TB Association	1,487,961
27	Sequella	1,400,000
28	Brazil (in aggregate)	755,587
29	Food and Drug Administration	651,231
30	Company Y	500,000
31	Swedish Int. Development Agency	486,599
32	Development Cooperation of Ireland	360,000
33	Ministry of Public Health, TB Cluster, Thailand	287,050
34	Netherlands Org. for Scientific Research (N.W.O.)	199,716
35	Swiss Agency for Development and Coop.	195,099
36	KNCV Tuberculosis Foundation	170,666
37	Danish International Development Agency (Danida)	170,344
38	All India Institute of Medical Sciences	154,821
39	Ministry of Foreign Affairs, France	127,092
40	Eli Lilly Foundation	113,660
	TOTAL	$392,713,089
	% of total	100.00%

Basic Science	Applied / Preclinical / Infrastructure /Unspecified	Diagnostics	Drugs	Vaccines	Operational
51,000,000	273,000	6,000,000	39,000,000	24,000,000	
2,620,000		6,819,000	9,000,000	28,677,457	10,295,000
9,016,676	3,284,736				18,586,427
1,575,540	16,230,562		70,279	204,968	2,252,951
		25,000	10,975,000	1,000,000	7,903,000
			18,640,160		
7,115,258			5,326,924	3,958,080	1,681,097
15,207,488	330,931				1,578,581
4,150,905			2,631,410	6,540,396	
			12,300,000		
	8,472,800				
			8,000,000		
	320,000	860,000	3,780,000		1,877,907
	4,100,835	12,709	573,124	732,292	302,600
	5,313,133				
500,000	1,250,000	500,000	750,000	750,000	
			2,714,927		453,561
1,000,000				1,500,000	
1,240,797		10,816	440,091	229,511	454,883
			2,255,193		
		919,296	35,840		1,053,696
	1,930,343				
			1,750,000		
				1,650,000	
					1,648,083
	1,487,961				
		800,000	600,000		
35,114	600,295				120,178
			453,231	198,000	
		500,000			
					486,599
			360,000		
					287,050
199,716					
					195,099
					170,666
				170,344	
		2,798	110,756		41,267
					127,092
					113,660
$93,661,494	**$43,594,596**	**$16,449,619**	**$119,766,935**	**$69,611,048**	**$49,629,397**
23.85%	**11.10%**	**4.19%**	**30.50%**	**17.73%**	**12.64%**

8. Appendix B: Actual or Potential TB R&D Funders Not Reported On

Respondents not disclosing

Bayer
GlaxoSmithKline (GSK)
Health Protection Agency, U.K.
Howard Hughes Medical Institute
Roche
Sanofi-Aventis

Non-responders

Central TB Division, India
Crucell
Danish Agency for Science, Technology & Innovation
Japan International Cooperation Agency
Italian Ministry of Health
JALMA Institute of Leprosy & Other Mycobacterial Diseases
Japanese Ministry of Foreign Affairs
Japanese National Institutes of Infectious Diseases
Lupin Laboratories
Merck
Ministry of Health, France
Tianjin Centers for Disease Control and Prevention
U.S. Biotechnology Engagement Program, DHHS

Respondents stating they are not original sources of TB research funding

Abbott
BORSTEL
Bristol-Myers Squibb
Chiron
Doris Duke Charitable Foundation
Eli Lilly & Co.
Fiocruz/Foundation Oswaldo Cruz
German Technical Cooperation (GTZ)
German Ministry of Health (BMG)
German Ministry of Health and Cooperation (BMZ)
Karolinska Institute
International Union Against Tuberculosis and Lung Disease (IUATLD)
Istituto Superiore di Sanità
Japan Health Science Foundation
Médecins Sans Frontières (MSF)

National Tuberculosis Programme, Kenya
Norwegian Ministry of Foreign Affairs
Partners In Health (PIH)
Pfizer
Program for Appropriate Technology in Health (PATH)
Robert Koch Institute
South Africa Medical Research Council
Statens Serum Institute
Stop TB Partnership
Defense Advanced Research Projects (DARPA)
Walter Reed Army Institute of Research

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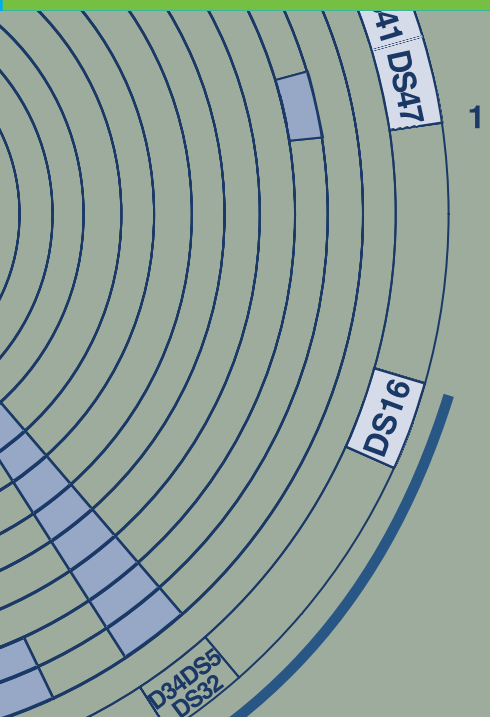

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