Tuberculosis Research & Development:
A Critical Analysis

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October 2006

ISBN 978-0-9791073-0-6
0-9791073-0-X

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:

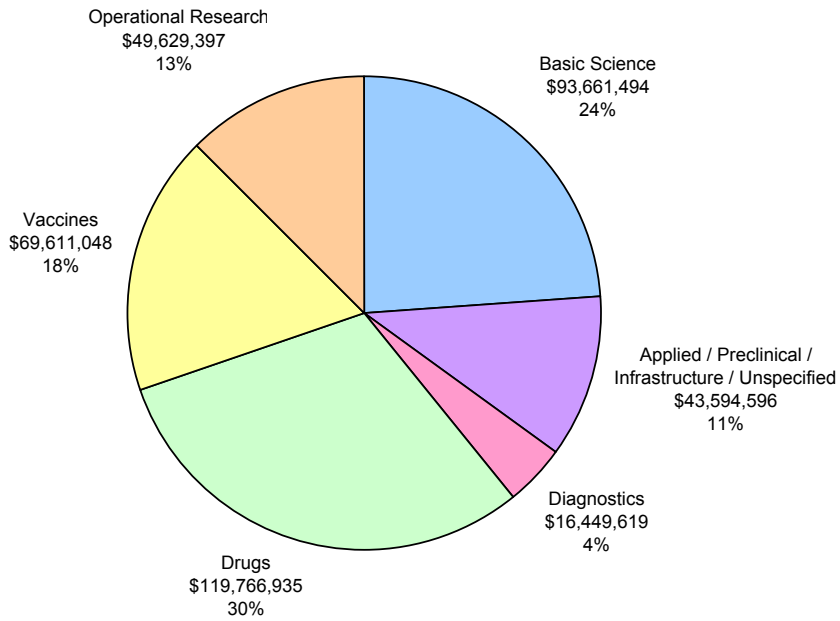
1. The top ten donors invested multimillion dollar amounts, ranging from $120 million (NIAID) to $12.3 million (Otsuka).

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.