

# **New tools for TB control: filling gaps, overcoming barriers**

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**6. References:** The development of this document involved a process of extensive consultation with a range of stakeholders engaged in promoting neglected disease research. The document was circulated widely for comment, including to all the members of the Stop TB Partnership's Working Groups on new tools to control TB (diagnostics, drugs and vaccines). The contribution of the following people is particularly acknowledged: Louise Baker (Stop TB Partnership Secretariat), Rachel Bauquerez (Stop TB Partnership Secretariat), Usha Balakrishnan (CARTHA), Martina Casenghi (Medecins Sans Frontieres), Dr. Ken Duncan (Global Alliance for TB Drug Development), Dr. Uli Fruth (WHO), Heather Ignatius (Global Alliance for TB Drug Development), Dr. Amina Jindani (St George's Hospital Medical School, London), Dr. Christian Leinhart (IUATLD), Dr Ikushi Onozaki, (Research Institute of TB, Japan), Dr. Mark Perkins (Foundation for Innovative New Diagnostics), Dr. Lee Reichman (New Jersey Medical School, USA), David Scales (Yale University), Dr. Neil Schluger (Columbia University).

## **Preface**

TB kills someone every 20 seconds, is a leading killer of people with HIV and remains a neglected disease. As an airborne infection transmitted simply through breathing, TB knows no barriers, as evidenced by recent reports of extensively drug-resistant TB. Achieving the goal of TB elimination by 2050 will depend not only on fully implementing all the currently available interventions to control TB but also on changing the political and scientific arena to increase the scope, scale and speed of TB research. The focus of this discussion paper is on the steps needed to fill gaps and overcome barriers in expediting Research and Development (R&D) for new tools.

The Stop TB Strategy, launched by the World Health Organization and adopted by the Stop TB Partnership in 2006, incorporates key elements to control TB. The DOTS strategy remains at the heart of the currently available interventions, with its emphasis on case detection and cure of patients with TB. Improved means of diagnosis and treatment hold out the promise of more rapid progress in attaining the Stop TB Partnership's goals to halve TB prevalence and deaths by 2015 (in comparison with the 1990 baseline). An improved vaccine is crucial to achieving the goal of TB elimination by 2050. The global challenges of HIV and anti-TB drug-resistance make the need for new diagnostics, drugs and vaccines even more pressing.

The profile of TB in the international and national political and funding arenas has in the past been low because the vast majority of TB patients live in low-income countries, apparently distant from the interests of many of the key agents in international health, such as pharmaceutical companies and health financiers. The establishment of the Stop TB Partnership has helped to galvanize interest worldwide in promoting TB control. The Partnership's Global Plan to Stop TB 2006-2015, sets out the key activities aimed towards achieving the TB control targets for 2015, in implementing the currently available interventions and in developing the new tools for TB control. Ensuring the Global Plan's full implementation will save 14 million lives by 2015.<sup>1</sup>

Under the Global Plan, the implementation of the ten-year strategic plans by each of the Partnership's Working Groups on new tools - one each for diagnostics, drugs, and vaccines - will represent considerable progress in R&D. However, there remains the need for more resources for R&D (as for other areas of TB research), and for more a more coherent approach to filling the gaps and overcoming the barriers that are often common to the three Working Groups. The purpose of this document is to inform the work of the Partnership's Working Groups on new diagnostics, drugs and vaccines, to help fill gaps and overcome barriers in R&D and thereby speed up progress in the development of these crucial new tools.

## List of abbreviations

**AIDS**, Acquired Immune Deficiency Syndrome  
**APC**, Advance Purchase Commitment  
**BCG**, Bacille Calmette Guerin  
**CDC**, Center for Disease Control (US)  
**DOTS**, the "brand name" of WHO's strategy for TB control (derived from "directly observed therapy, short-course") and now a key element of the Stop TB Strategy  
**GFATM**, Global Fund for AIDS, Tuberculosis and Malaria  
**FDA**, Federal Drug and Agricultural (US)  
**EMEA**, European Medicinal Association  
**EDCTP** European and Developing Countries Clinical Trials Partnership  
**HIV**, Human Immunodeficiency Virus  
**IFFIm**, International Finance Facility for Immunization  
**MDR-TB**, Multi-Drug Resistant Tuberculosis  
**NIAID**, National Institute of Allergy and Infectious Disease  
**NIH**, National Institute of Health (US)  
**R&D**, Research and Development  
**TB**, Tuberculosis (the disease caused by *Mycobacterium tuberculosis*)  
**TBRU**, Tuberculosis Research Unit  
**TBTC**, Tuberculosis Trials Consortium  
**TDR**, Tropical Disease Research  
**TM**, Technology Managers  
**WHO**, World Health Organization  
**US**, United States  
**XDR-TB**, Extensively Drug Resistant Tuberculosis

## Useful Websites for Reference

[www.aeras.org/](http://www.aeras.org/)  
[www.accessmed-msf.org/](http://www.accessmed-msf.org/)  
[www.biomarkers-for-tb.net/](http://www.biomarkers-for-tb.net/)  
[www.cartha.org/](http://www.cartha.org/)  
[www.cdc.gov/tb/](http://www.cdc.gov/tb/)  
[www.doctorswithoutborders.org](http://www.doctorswithoutborders.org)  
[www.essentialmedicine.org/](http://www.essentialmedicine.org/)  
[www.finddiagnostics.org/](http://www.finddiagnostics.org/)  
[www.health.nih.gov/result.asp/691/15](http://www.health.nih.gov/result.asp/691/15)  
[www.lillymdr-tb.com/](http://www.lillymdr-tb.com/)  
[www.msf.org/](http://www.msf.org/)  
[www.stoptb.org \(/researchmovement, /retooling\)](http://www.stoptb.org)  
[www.tballiance.org](http://www.tballiance.org)  
[www.tbtrialsnetwork.org/tbtc](http://www.tbtrialsnetwork.org/tbtc)  
[www.who.int/tb/en/](http://www.who.int/tb/en/)  
[www.who.int/tdr/](http://www.who.int/tdr/)

## **1. Introduction**

In view of the scale of the global TB epidemic and limitations in the currently available tools for TB control (diagnostics, drugs and vaccines) there is an urgent need to increase the scale, scope and speed of research to develop new tools. The purpose of this discussion paper is to identify R&D needs for new TB tools and propose next steps for discussion and consideration by TB research stakeholders. The idea for the paper arose following the January 2007 meeting for new TB drugs hosted by MSF in New York "No Time to Wait" addressing gaps and proposing solutions for speeding R&D for new TB drugs.<sup>2</sup> The focus of the meeting on new drugs is expanded in this paper by including vaccines and diagnostics, while recognizing barriers and potential solutions for all three. The barriers and possible ways to overcome them were identified through review of key documents and interviews with a range of research stakeholders engaged in promoting neglected disease research.

## **2. Background**

### **2.1 Brief history of the global TB epidemic**

Throughout the turbulent relationship between *M tuberculosis* and its host, often one side or another gains the upper hand. Although evidence of TB exists in early civilizations, it became a significant burden of disease with increasing urbanisation and therefore with increased population density favouring transmission. The Middle Ages saw TB flourish in the crowded cities of Europe becoming an epidemic known as the "white plague".<sup>3</sup> In 1819, the TB epidemic had reached high levels in Europe, killing 800-1000 of every 100,000 people a year with similar rates in the US. From the mid 19<sup>th</sup> century onwards, TB began to decline in the developed world due to increased wealth and higher living standards. The development of effective anti-TB drug treatment in the 1940s and 1950s led to the further decline of TB to low levels in developed countries. This disease decline led to a decline in interest in global TB control by developed countries, accompanied by decreased public funding for TB control and for developing new TB control technologies. Many patients require TB drugs, diagnostics and vaccines, however, the market itself is not valuable because many cannot afford the treatment, resulting in a low profit margin. This makes TB less appealing for investment by industry.

### **2.2 Current scale of the global TB problem**

One third of the world's population is infected with *M tuberculosis* (i.e. they have a latent infection). 10% of people with latent infection will develop active TB.<sup>4</sup> The global TB burden in 2006 amounted to 9.2 million cases and 1.7 million deaths.<sup>5</sup> TB is a leading cause of death in the developing world. It kills more women than pregnancy-related causes and is a leading killer of people with HIV.<sup>6</sup> TB is prominent in developing countries (due to many factors, including poverty, weak health systems, political instability, and HIV) and in marginalized populations, immigrants, and the elderly in developed countries.<sup>7</sup>

In the developing world 75% of TB deaths occur between the ages of 15-54, costing developing countries an estimated US\$12 billion dollars a year or a loss of productivity between 4-7% of GDP.<sup>8</sup> In common with other diseases of poverty, TB is a result of, and perpetuates, poverty and "has a negative impact on families, education, productivity and the entire social fabric of society."<sup>7</sup>

In 1993, WHO declared TB a global emergency. Progress in implementation of the DOTS strategy resulted in attainment of a global case detection rate of 60% and treatment success rate of 84% by 2005. As the global TB incidence rate appears to have peaked in 2005, the prospects are encouraging for global achievement of the Partnership's targets for 2015 through implementation of the activities laid out in *The Global Plan to STOP TB 2006-2015*. However, the increasing problems of TB/HIV and drug-resistant TB make achievement of the Stop TB Partnership goals unlikely in sub-Saharan Africa and Eastern Europe respectively without new tools.<sup>9</sup>

## **2.3 Tools for TB control**

### **2.3.1 Brief history of development of tools**

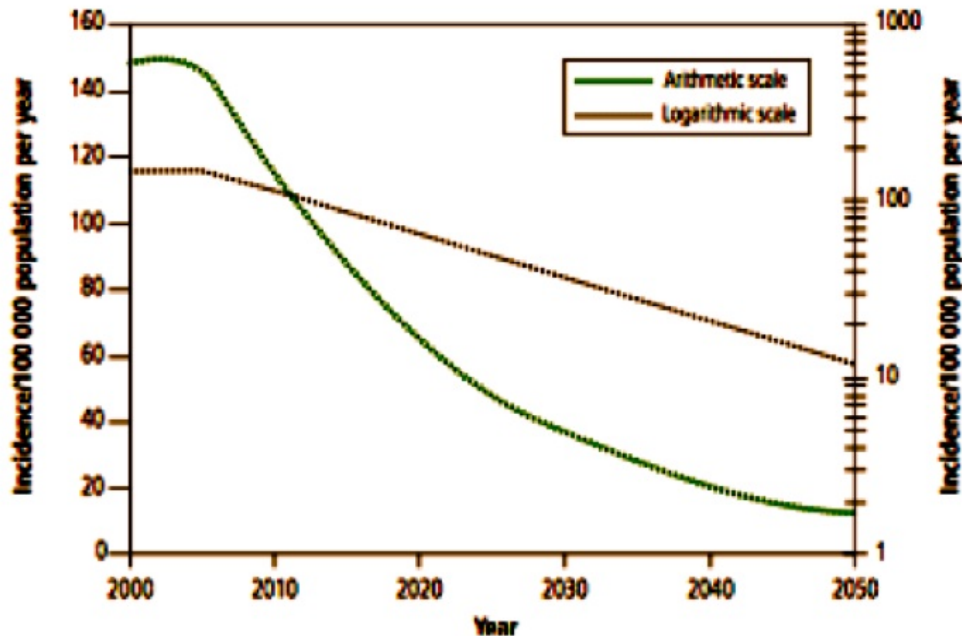
Although physicians as early on as Hippocrates suggested potential causes and treatments of the disease, the first effective tool to control TB was not developed until the late 1880s in the form of sputum-microscopy. This diagnostic tool is still widely used today. Robert Koch used microscopy to discover *Mycobacterium tuberculosis* as the causative agent of TB.<sup>3</sup> In 1895, X-rays discovered by Röntgen allowed for further diagnosis and evaluation of disease progress. In 1922 the Bacille Calmette Guerin (BCG) vaccine was tested and discovered useful in infants and children at risk for TB infection. The drugs used today were developed throughout the 1940s and 60s with the last class of drugs to be widely used, the rifamycins, approved by the US FDA in 1971.

### **2.3.2 Need for new tools**

More effective diagnostics, new drugs, and new vaccines are needed to make a greater impact on the global TB burden, especially where HIV and drug-resistance complicate TB control. The *Global Plan to Stop TB* lays out the planned activities towards achieving the Partnership's targets for 2015 as a step on the way to TB elimination by 2050. Projections show that continued implementation of the planned interventions under the Stop TB Partnership's *Global Plan to Stop TB* at the level of scale-up to be reached in 2015 will not result in the Partnership's goal of TB elimination (less than 1 TB case per million population per year) by 2050 (figure 1). At the average rate of decline in tuberculosis incidence of 5-6% per year expected globally between 2010 and 2015 under the Global Plan to Stop TB, the incidence rate in 2050 will still be about 100 times larger than the elimination target of 1 per million. A revolutionary new technology for tuberculosis control will be needed for any realistic process of achieving this goal.<sup>9</sup> Overcoming problems in TB control to reach the TB elimination goal will require

innovative technology to develop new tools, which are likely to have a synergistic effect when combined in acting against latent infection and active disease.<sup>10</sup>

Figure 1 “Projected tuberculosis incidence 2000-2050 plotted on a linear scale and a logarithmic scale



Source: Maher, Dermot et al. “Planning to improve global health: the next decade of tuberculosis control.” *Bulletin of the World Health Organization*. May 2007, 341-347.

### 2.3.3 Recent progress in promoting new tool development

The 1990s saw a resurgence of interest in developing technologies to address "new diseases and old diseases with new faces."<sup>11</sup> Stakeholders in TB R&D have started to move towards developing this revolutionary new technology, beginning with a limited pipeline and limited funds. Over the last decade there has been significant progress in boosting TB R&D. The Bill and Melinda Gates Foundation funds three new public-private partnerships for TB R&D: Aeras for vaccines, TB Alliance for drugs and FIND for diagnostics. The Stop TB Partnership has established working groups for each of the new tool categories. The Partnership continues to prepare for the introduction of new tools at country level through the retooling task force.<sup>1</sup> Significant advances have been made, but more investment is necessary to support R&D initiatives and better coordination among initiatives is needed to fill existing gaps in new tool development.

### 2.3.4 The relation of R&D to the continuum of TB research

The continuum of TB research embraces basic and discovery research, R&D for new tools to control TB (diagnostics, drugs and vaccines), and applied (implementation) research in the field to maximize the benefit of the use of TB control tools (*figure 2*). An understanding of how R&D for new tools fits on the continuum is important, since

"upstream" research feeds the R&D pipeline, and "downstream" research is necessary to make the best use of tools for TB control.

The definitions provided are defined for the purpose of this paper, as their use is not uniform across the research field. Basic research on the characteristics of *M. tuberculosis* and on host-pathogen interaction is necessary in drug, diagnostic and vaccine development. Operational/implementation research is crucial to optimize the effectiveness, efficiency, availability and cost-effectiveness of field use of TB control tools, but is currently under-funded.<sup>12</sup>

Figure 2. Context of R&D within the Research Continuum



There are two transitions along the continuum: 1) translational research (linking basic research and R&D), and 2) market approval and manufacture (linking R&D and operational/implementation research). Translational research results in leads being taken up by new tool developers. The link between R&D and operational/implementation research involves market approval and manufacture, includes development of adequate clinical trial capacity. Preparing countries for new tool implementation is known as "retooling". Retooling refers to the process of adoption, introduction and implementation of the new and improved TB technologies and strategies, with the goal to maximize their wide spread use and minimize delays to roll-out. The retooling task force is working closely with the Stop TB working groups and WHO to guarantee proper dissemination of the information on the TB products currently in the pipeline and provide tools and guidance to countries to help them for planning ahead and ensuring timely implementation.<sup>13</sup>

The dialogues in these two transitions should be bi-directional. Those involved in operational/implementation research need to inform developers of the ideal new tool characteristics, especially for application in resource poor settings. New tool developers need to raise questions for basic science to answer. There may be disconnects between each of the stages in the continuum, in part because of the lack of a forum for dialogue and shared distribution of funding resources.

The continuum of TB research is part of a larger context of health research (*figure 3*) and reflects the wider political and funding problems of health research for diseases mainly affecting people in developing countries. The majority of health research funding is on behalf of a small percentage of the world's population, a discrepancy known as the 10/90 gap. This is true for TB as 90% of cases occur in the developing world.<sup>14 15</sup>

## **2.4 The Stop TB Partnership and the Research Movement**

*"The immediate responses of the public health community must not focus solely on strengthening control programmes. It is also urgent to mobilize all necessary resources for the rapid delivery of new drugs and diagnostic tools." <sup>2</sup>Doctors Without Borders/Medecins Sans Frontieres*

The Stop TB Partnership was established in 2000 "to eliminate TB as a public health problem and ultimately to realize a world free of TB." The Partnership is a network of over 600 stakeholders who share the same goal of TB elimination.<sup>16</sup> Of the Partnership's seven Working Groups, three address R&D of new tools for TB control (one each for new diagnostics, drugs and vaccines).

### **STOP TB Partnership Working Groups**

Advocacy, Communication and Social Mobilization Working Group  
DOTS Expansion Working Group  
Working Group on MDR-TB  
TB/HIV Working Group  
Working Group on New TB Diagnostics  
Working Group on New TB Drugs  
Working Group on New TB Vaccines

One of the six elements of the Partnership's Stop TB Strategy is to enable and promote research. Within the Stop TB Partnership, the newly proposed Research Movement aims to promote this research element by helping to generate increased support among research stakeholders and increased funding for TB research across the continuum. In the middle of its approval stage, the goal of the Research Movement "is to stimulate, support and expand research to ensure the elimination of TB as a global public health problem by 2050."<sup>17</sup> The objectives of the Research Movement are "to provide leadership and advocacy to mobilize increased resources to support a coherent and comprehensive global TB research agenda," and "to provide a forum for funders and implementers of TB research to coordinate plans and actions with the result of ensuring that research needs are addressed, opportunities prioritized and gaps filled.

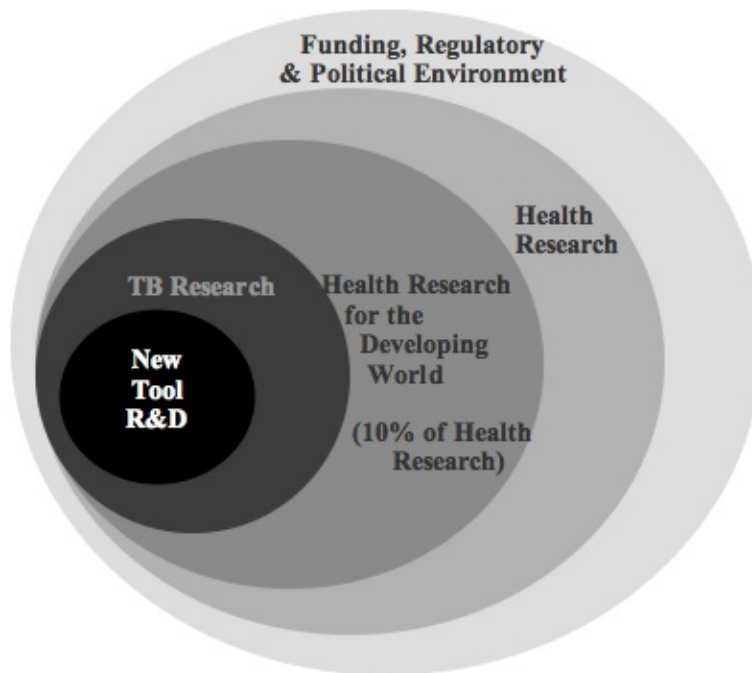
In providing a forum for dialogue between research stakeholders in the two transitions described above, the Research Movement can facilitate the interaction necessary between the R&D Working Groups and those involved in basic and operational/implementation research to increase the scope, scale and speed of TB research. A full explanation of the research movement's expectations is outlined in the STAG recommendations.<sup>18</sup>

## **3. R&D problem statement**

Filling gaps and overcoming barriers to TB R&D begins with the identification of those gaps and barriers. The problem of epidemic TB is often confounded by poverty, and the

response is handicapped by weak health systems, inadequate laboratory networks, and the limitations of the current tools for TB control. Improving the currently available tools lies within the domains of TB R&D and of the overall health research framework. The research framework for health has funding, regulatory and intellectual property issues that are particularly pressing in health research relevant to diseases of poverty. This section addresses firstly the limitations of the specific tools currently available for TB control, and secondly, generic R&D problems.

*Figure 3. The Context of New Tool R&D*



### **3.1 Limitations of current tools in TB control**

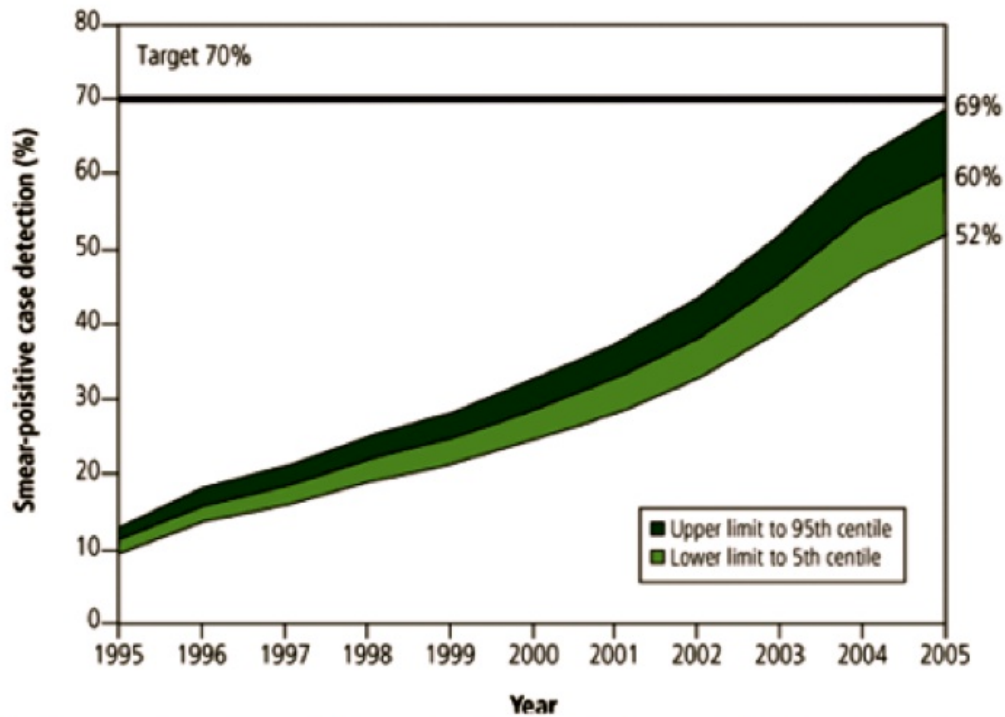
Considerable improvements in the current tools are needed to control TB. HIV-related TB and drug-resistant TB have uncovered the limitations of current drugs, diagnostics and vaccines. Although huge strides have been made with implementation of the DOTS strategy, the currently available tools are unwieldy. Arising at least in part from the limitations of current diagnostics and drugs, the difficulties in fully and effectively implementing the DOTS strategy are exacerbated by HIV and result in the generation of anti-TB drug-resistance. New tools should be developed that are effective in people of all ages with TB, whether drug-resistant or not, and whether coinfecting with HIV or not.

#### **3.1.1 Diagnostics**

TB control needs new TB diagnostics. Sputum-smear microscopy, developed in 1882, is widely available but unwieldy. It involves a patient coughing up a sputum sample and a

laboratory technician examining it under a microscope for approximately 15 minutes after processing it with various reagents. A recommended two sputum-smear samples must be taken per patient to diagnosis a pulmonary case, involving multiple trips to the health clinic.<sup>19</sup> The skill and time required of laboratories is often not optimal, especially in low resource settings. Sputum-smear microscopy, unfortunately, has low sensitivity, as 5,000 to 10,000 bacilli per millilitre need to be present in a specimen to allow detection. Thus, in countries with high TB incidence, sputum smear microscopy has only 40%-60% sensitivity for detection of all TB cases, and this figure is lower in TB patients with HIV coinfection and in children. A significant proportion of patients with pulmonary TB have negative sputum smears. One in three patients have extrapulmonary TB and must be diagnosed by other means, mainly biopsy, pathological examination or culture. Sputum-smear microscopy cannot distinguish between drug-sensitive and drug-resistant TB and is also often insufficient to diagnose or rule out childhood tuberculosis.”

Figure 4. “New smear-positive case detection in DOTS programmes globally 1995-2005”



<sup>a</sup> Shading represents uncertainty around the annual point estimates towards upper (dark) and lower (light) 95% confidence limits.

Source: Dye, Christopher. Mehran Hosseini and Catherine Watt. “Did we reach the 2005 targets for tuberculosis control?” Bulletin of the World Health Organization. May 2007, 364-369

Against the 2005 global target of 70% for detection of smear-positive cases in DOTS programmes, the global achievement was 61% (up from 10% in 1995). This represents huge progress.<sup>20</sup> However, this means that 40% of smear-positive patients remained undetected within DOTS programmes. A smear-positive patient is infectious and if patients with smear-positive pulmonary TB are undetected with the current diagnostic

tools then patients remain untreated and are capable of spreading TB to others. On average a patient with smear-positive pulmonary TB infects 10-15 people per year.<sup>21</sup>

An estimated three million TB patients annually are not treated because they are smear-negative.<sup>22</sup> The length of time for diagnosis sometimes surpasses the survival time for HIV patients, an example being the outbreak in South Africa in 2006 where 52 of the 53 patients with XDR-TB and HIV coinfection die.<sup>23</sup> Additionally, in view of the expanding MDR-XDR-TB epidemic, rapid DST diagnostic tests must be developed.

### 3.1.2 Drugs

TB chemotherapy is lengthy (usually 6-8 months but up to 2 years for drug-resistant patients), complex and can have toxic side effects. There is a lack of options in treating latent *Mycobacterium tuberculosis* infection. The problems of drug-resistance and HIV show up the limitations of existing drugs:

- (i) *Mycobacterium tuberculosis* evolved over time, and, like all antibiotics, can develop resistance to antimicrobial drugs in certain conditions. Anti-TB drug resistance is an outcome of poor TB treatment or the interruption of drug therapy (due to failing health systems, lack of access to treatment, or health system or patient non-compliance). Anti-TB drug resistance can occur to one drug but more severe cases are categorized as multi-drug resistant tuberculosis (MDR-TB) and extremely drug resistant tuberculosis (XDR-TB). MDR-TB is resistance to at least the two principle first-line drugs, rifampicin and isoniazid. XDR-TB is MDR-TB with additional resistance to at least one fluoroquinolone and one of three injectable drugs.<sup>22</sup> Drug-resistant cases are on the rise (489,139 estimated cases in 2006), with few effective drugs for treatment, especially because drugs can be prohibitively expensive in poor areas. In Azerbaijan and Republic of Moldova, more than 19% of TB cases are MDR-TB.<sup>24</sup>
- (ii) Treatment of TB patients with HIV coinfection is difficult due to interactions between ARVs and anti-TB drugs and an increased risk of side-effects.

There is thus an urgent need for new drugs at affordable prices to enable shorter regimens to help improving adherence to treatment, treat drug-resistant TB and establish the best regimens for the combination of anti-TB chemotherapy and anti-retroviral therapy.

### 3.1.3 Vaccines

The BCG vaccine administered to children shortly after birth is effective against severe and disseminated forms of TB in children (i.e. miliary and meningeal TB). The efficacy of BCG is, however, limited in protecting against pulmonary TB especially in adults, varying from 77% in the UK to 0% in Chingleput, India.<sup>25</sup> The BCG vaccine is not recommended for use in TB/HIV infected children according to the WHO.<sup>26</sup> During the past ten years, there has been an increasing effort to identify novel vaccines for TB that have shown equal or greater efficacy than BCG in animal models. A series of new

candidates are presently entering Phase I and II trials. By 2010, it is expected that 9 candidates will enter phase II trials, and that at least 2 vaccines will be in "proof of concept" trials.

### 3.2 Generic R&D problems

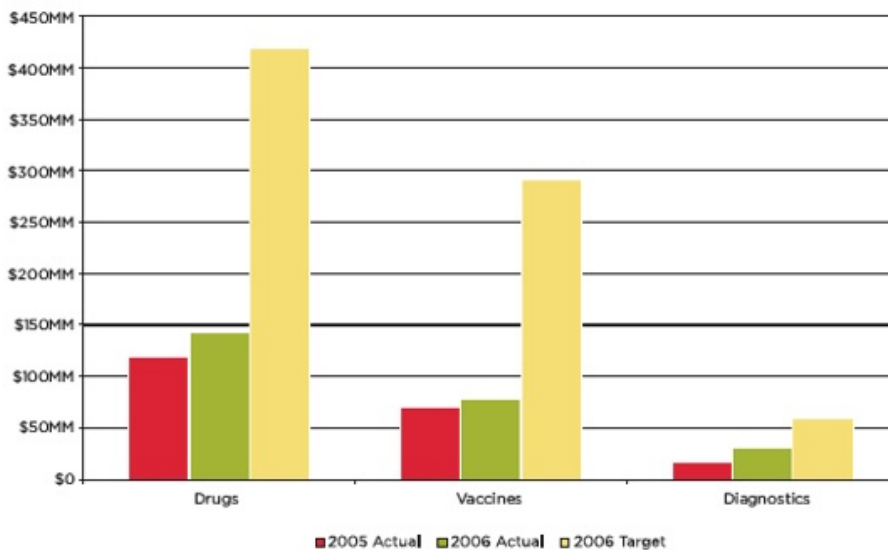
*"To make any real difference, we need to see a dramatic increase in funding and political will."* <sup>2</sup> - Dr. Von Schoen-Angerer

#### 3.2.1 Insufficient funding for R&D

TB receives very little funding from governments and private donors when compared with other diseases. For example, TB research receives less R&D funding, from the US National Institute of Health than smallpox and anthrax.<sup>8</sup> Global funding for new TB tools is currently only US\$413 million a year, a funding gap of over \$6 billion over the next ten years according to estimates in *The Global Plan to Stop TB*.<sup>1</sup>

The in depth funding analysis compiled in *Tuberculosis Research and Development: A Critical Analysis of Funding Trends, 2005–2006*, lays the landscape of funding for TB, how it compares to other diseases and the top research investors. It reveals how little TB receives when compared to HIV and Malaria.

*Figure 5 – Global Plan Investment Target*



*Source:* Feuer, Cindra. “Tuberculosis Research and Development: A Critical Analysis Funding Trends, 2005–2006.” Treatment Action Group. *November 2007* <sup>12</sup>

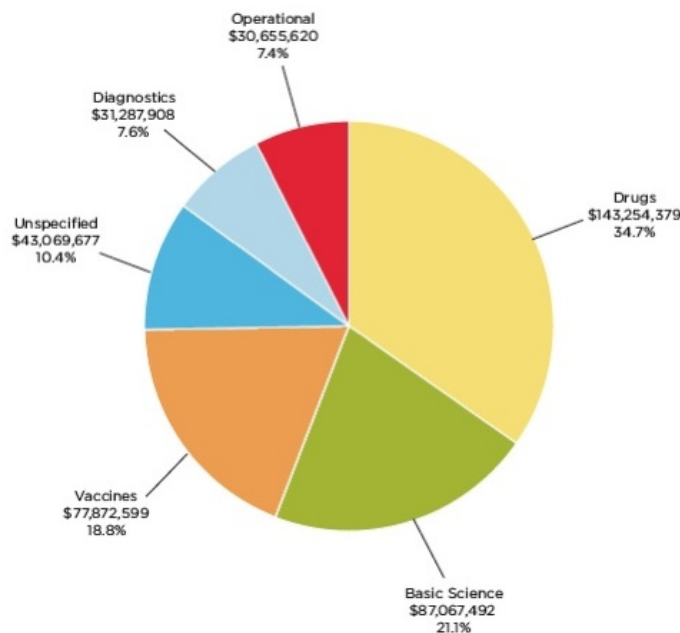
The report concludes funding for TB research was far beneath what was required according to the Global Plan to Stop TB, 2006-2015 by five-fold (refer to *figure 5*).<sup>8</sup>

There was only a slight increase in funding from 2005-2006, from US\$393 million to US\$413 million. According to the report:

*The main impression is one of stagnation in TB R&D funding from 2005 to 2006. Despite the release of the Global Plan 2006–2015 at the World Economic Forum in January 2006 with much fanfare, and despite the emerging worldwide threat of extensively drug-resistant TB (XDR-TB), which was identified in 2006 and is now present in over forty countries, governments have not responded with the requisite urgency or ambition to step up their investments in TB R&D.*<sup>12</sup>

There was a decrease in public funding by 5.8%, including a decrease in funds from NIH and the UK Medical Research Council and a raise in funding from private organizations such as the Gates Foundation. Bilaterals did not tend to fund R&D directly, while foundations did.<sup>27</sup> By category, according to the TAG report, “investment in research on diagnostics, drugs, and vaccines increased, while basic science and operational research funding declined.” As noted later in the discussion paper, funding for basic research and operational research are crucial to improve R&D for diagnostics, drugs and vaccines.

Figure 6: 2006 TB Research: Investment by Category



Source: Feuer, Cindra. “Tuberculosis Research and Development: A Critical Analysis.” Treatment Action Group. November 2007

### 3.2.2 The research environment

The pharmaceutical industry over the last 50 years developed rapid and highly successful drugs to cure or alleviate many diseases and conditions. Once more oriented towards public health than they are today, pharmaceutical companies prior to 1980 were smaller and allocated more funding to R&D.<sup>28</sup> In the 1970s, leadership in pharmaceutical companies changed, taking away the identity of contributors to public health and replacing it with a market-driven business identity. “Shareholders, investment bankers,

and analysts, who know little about drug discovery, place intense pressures on CEOs and their boards for quick returns.”<sup>28</sup> The average drug costs US\$802 million for development, according to independent analysis. In the 1980s only 3 in 10 drugs recovered their development costs, leaving pharmaceutical companies dependent on risky blockbuster drugs. Within the health R&D market there is intense competition between companies and additional pressure with the addition of generic competition, which now accounts for 47% of the drug market in the US. With increased regulations and requirements in clinical trials, the time that a drug is on the market and under patent protection is severely reduced. In the mid-1990s the average length of time a marketed drug was protected by a patent was 11-12 years because the previous 8-9 years were spent in approval pre-market stages. R&D relevant to problems in the developing world is risky with a low-profit margin, and therefore an unappealing investment for business. R&D for TB is no exception.

The consequences have been apparent of the high risks and costs (involving high levels of investment) of R&D for problems relevant to developing countries. Only 1% of all chemical entities in the market from 1975-1997 were for diseases in developing countries, and only four were originally targeted for human products. A new drug would not have a profitable market, and reasons to develop are mainly humanitarian or of security interest for developed countries. Tuberculosis drugs provide a small incentive for research because only 5% of the people who have TB can afford the medication.<sup>29</sup>

Inadequate political will to increase funding and awareness is hindering new tool development significantly, not only for TB but also for developing country health issues. Already, countries like the UK are seeing a 10% rise in TB cases because of immigration. The involvement of politicians will be necessary in increasing funds for new tool R&D and creating incentives for organizations and companies to engage in R&D in a way that favors both innovation and access. Political will is necessary to stop TB and review of legal frameworks to provide industry with greater incentives for participation in TB R&D.

### **3.2.3 Insufficient basic research**

Basic research is crucial for new tool development and gaps in basic research create problems downstream for all three new tool working groups (see *figure 2.*) Basic research aims primarily to further understanding of the disease. "Some of these unanswered fundamental questions include how *Mycobacterium tuberculosis* hides from the immune system, the relationship between infection and disease, and the bacterial load in different body sites."<sup>30</sup> Basic research is necessary to identify biomarkers to shorten clinical trials and antigens to improve diagnostics options. The completion of the mapping of the *Mycobacterium tuberculosis* genome is a great step in basic research. With the help of the Gates Foundation, Stanford, MIT and Harvard published the TB genome for open access.<sup>31</sup>

The ease of conducting clinical trials for TB could be greatly improved by the identification and validation of biomarkers of response to treatment. Determining

“surrogate markers of relapse would provide evidence on the efficacy and the sterilizing activity of a drug/regimen” and reduce the time of follow up.<sup>32</sup> Additionally, the identification of biomarkers to determine earlier indication of shorter drug treatment and marker of sterilizing activity to shorten phase III trials could greatly reduce time and costs in trials. TB Alliance is currently working with BG medicine to identify biomarkers for TB that may help to improve and shorten clinical trials.<sup>33</sup> However, they cannot remain the only funders. Also, vaccine trials are also slowed down by the absence of biomarkers for protective immunity. The Gates Foundation is funding a consortium lead by the Max-Planck in Berlin that is attempting to identify biomarkers of immunity to TB in individuals with HIV coinfection.

Researchers consider TB new tool development high risk because there is insufficient basic research to identify which drugs, diagnostics and vaccines in development is most likely to succeed. Although industry may take on basic research for diseases that affect people in wealthy countries, they are unlikely to engage in basic research for TB because it is unrealistic they would make the return in their investment due to the low profit margin. TB research is high-risk, with low potential pay-offs from a business perspective.

Traditionally basic research is conducted within universities. Universities play a key role of early drug discovery, but the “transfer of compounds from industry libraries to academia has also been complicated by legal and intellectual property issues.”<sup>30</sup> As most technology is transferred before it is fully developed universities often lack the facilities to discover or develop leads further. The technology transfers from university to industry are often slow and wrought with red tape from both university and industry. However, with the transition refined, the relationship may become more appealing, with university research reducing the costs and risk to new tool developers. It is necessary to look at the barriers to the universities playing a larger role in R&D for the diseases of the poor, and the barriers to their success, while weighing the benefits of simply fostering more industry-university partnerships.

Although the public-private partnerships (such as FIND, TB Alliance and Aeras) have helped to catalyse advances in development of new TB diagnostics, drugs and vaccines, the tool development pipelines need to be more robust with more compounds to stock the pipeline, to have a chance of success.<sup>33</sup> There is a less than 5% chance that the approximate 40 compounds in the TB pipeline currently in various stages of development will reach the market by 2010.<sup>34</sup> The Bill & Melinda Gates Foundation is funding a US\$40 million program, the TB Drug Accelerator, which will support early stage drug discovery over the next two years. Eli Lilly is now involved with compounds research in order to help feed the drug pipeline, working closely with TB Alliance.

### **3.2.4 An inadequate clinical trial platform**

There are very few clinical trial platforms presently available for TB and funding is scarce. TB Alliance recently evaluated clinical trial platforms for drugs, with only a handful available to start in the near future. The US only spends US\$20 million annually for clinical trials for TB drug compared to around US\$300 million for HIV drugs.<sup>12</sup> The

largest barriers to building a clinical trial platform for TB is a lack of funding and lack of health research capacity in the developing world.

There has been little funding to build the infrastructure of the large-scale trials that need to be completed as drugs enter clinical phase II and III trials. TB trials will require a large number of participants because of multiple drug regimens and to show statistical significance of the effect of these regimens. Trials must be carried out where the majority of TB patients live, i.e. the developing world, however, developing countries have insufficient research infrastructure to perform extensive clinical trials TB drugs and vaccines require. Currently, the TBTC (Tuberculosis Trials Consortium) and the TBRU (Tuberculosis Research Unit) supported by the CDC (Center for Disease Control) and NIAID (National Institute of Allergy and Infectious Disease) and the EDCTP (funded by the European Union) are supporting clinical trial development.<sup>35</sup>

### **3.3 Specific R&D barriers**

This section addresses the specific problems and barriers to development for new tools in each of the three areas (diagnostics, drugs and vaccines).

#### **3.3.1 Diagnostics**

Despite the pressing need for new diagnostics, only 7.6% of the current R&D funding for TB research is available for new diagnostics research, amounting to US\$31 million a year in 2006.<sup>12</sup> Inadequate diagnostic tools hinder not only TB control but also the development of new vaccines and drugs, since better diagnostics would help facilitate vaccine and drug trials. New diagnostics with better specificity could reduce diagnostic time and increase access treatment in general and particularly benefit children and TB patients with HIV coinfection.

The regulatory framework for diagnostics is fragmented, as different countries require different standards. Some countries have strict regulations, forbidding the transfer of human specimens for testing across borders and some countries have no regulation at all which involves a lengthy process to gain access to patients. This situation leads to bureaucratic red tape when attempting clinical trials abroad and obtaining human samples for clinical testing in developed countries when some laws severely limit or prohibit the movement of human blood and sputum samples.

Transferring blood and sputum samples across borders happens very slowly, deterring potential industry partners. In addition, the safety level required of TB research laboratories is not common at non-profit or even industry facilities. It is not feasible to move industry to the high-burden countries to test the sputum samples, but satellite labs could do more initial testing. FIND (Foundation for Innovative New Diagnostics) is involved in opening a laboratory in Kampala, Uganda with biosafety levels appropriate for TB research.<sup>36</sup>

### 3.3.2 Drugs:

*"The increasing challenge to providing patients with quality care is outpacing R&D: TB is becoming an ever increasing global threat in the face of insufficient R&D for drugs."*  
37

Drug research for TB has a funding gap of US\$4.2 billion for the next ten years according to *The Global Plan to Stop TB, 2006-2015*.<sup>1</sup> In 2006, TB drug research received only \$143 million.<sup>12</sup> The lack of focus and funding in basic research limits the development of drug compounds and creates barriers in clinical trial development. With a number of drugs entering clinical trials, funding for these projects is increasingly inadequate. The lack of basic and translational research to stock the drug pipeline is a continuous problem. Identifying disease characteristics and biomarkers for trials are additional needs that originate within basic research. The current biomarker of sterilizing activity, sputum conversion, is inadequate as a biomarker for drug trials. More biomarkers for TB are needed or the trials will be lengthy and therefore more expensive.<sup>38</sup>

Some collaborative groups are presently conducting multicentre trials in developing countries including development of clinical trial capacity to meeting GCP standards. However, these initiatives are scarce. Inadequate clinical trial capacity is a huge barrier upcoming in the development of new tools for TB.<sup>39</sup> For TB drugs, the clinical trial process can take a minimum of 6 years.<sup>34</sup> The "No Time to Wait Symposium" concluded that, "Funding bodies should support the creation of a TB clinical trial platform and the massive expansion of clinical trial capacity, particularly in developing countries."<sup>2</sup> The TB Alliance completed a study of 51 potential trial sites and found only a few available for immediate use while other could be ready in two years.<sup>39</sup>

Although some groups are running clinical trials in the developing world, few groups are working on building the clinical trial platform in the developing world. The EDCTP (European and Developing Countries Clinical Trials Partnership) and the TBTC (TB Clinical Trials Consortium) are acting on a recognized gap in clinical trial platforms in the developing world. The recognition and plan for action to build clinical trials in Africa for malaria, tuberculosis and HIV needs to happen quicker. The *Independent External Review Report of the EDCTP*, released on 12 July 2007 was a great advising step and the recommendations should be taken into account and improvements in EDCTP governance should be followed.<sup>40</sup> Member States should not be reluctant to put money forward, especially as the funds were previously promised. The main explanation for poor progress is the lack of direct funding from states.

According to recommendations in *Building Clinical Trials Capacity for Tuberculosis Drugs in High-Burden Countries*, components necessary to build up TB drug trials include:

- (i) A funding commitment of US\$300 - \$500 million a year.
- (ii) A direct investment made to clinical trial infrastructure than investment on a product-by-product basis.

- (iii) The creation of an existing consortia involved in running TB clinical trials in order to coordinate and create an agenda.<sup>40</sup>

The US FDA (Food and Drug Administration) and the EMEA (European Agency for the Evaluation of Medicinal Products) are important regulatory authorities involved in the approval of TB drugs.<sup>36</sup> No new drugs for TB have been created in over 30 years and regulatory authorities do not currently have the evaluation tools ready for the swift approval of a new TB drug. However, the FDA is playing an active role in developing TB trial guidelines.

### **3.3.3 Vaccines**

Vaccines are key to infectious disease eradication, and yet are the most difficult tool to develop. In 2006, vaccines research received US\$77 million under TB R&D.<sup>12</sup> *The Global Plan to Stop TB, 2006-2015* stated that US\$291 million was needed for vaccine research in 2006.

TB vaccine development is the slowest of the three tool categories because of TB disease characteristics, unknowns in basic research and the high-risk development characteristics of a vaccine. These three problems are intertwined, as more funding and industry involvement are needed to fill gaps that are making TB vaccine R&D risky.

Vaccines, and specifically TB vaccines are high-risk R&D endeavors. There are few incentives for industry involvement. In the recent history of vaccine development, R&D companies realized they were often forced to lower their prices after development, resulting in inability to make a profit or recoup R&D costs. This severely reduced incentives to invest in something that has a developing world link. Despite TB vaccine development is high risk and contains few incentives there is industry interest and involvement.

Before a vaccine is developed, governments want vaccine producers to invest in R&D and establish large-scale production facilities. But once a vaccine has been developed, governments want the vaccine to be sold at the lowest possible price, to allow limited budgets to purchase the vaccine for as many individuals as possible.<sup>41</sup> The lack of biomarkers of protective immunity is a barrier to vaccine development. The Gates Foundation also provides funding in this area of research.

The vaccine development community saw the exit of many players because of the unpredictability of markets post-development. One industry development said in reference to AIDS vaccine development, "Our worst nightmare would be to discover a vaccine for AIDS. We would be forced to give it away."<sup>25</sup> This fine balance between innovation and access is more crucial for vaccines than the other tools. Ways to entice industry involvement do not exist, as evident in the lack of participation. Basic research, is one way to lower risk and increase private sector involvement and expertise.

## **4. Filling gaps, overcoming barriers**

The suggestions in this section are aimed at filling the gaps and overcoming the barriers to improved R&D for new tools. Firstly, there are generic suggestions on funding and the research environment relevant to development of diagnostics, drugs and vaccines, and secondly there are suggestions relevant to each particular new tool.

### **4.1 Generic**

#### **4.1.1 Funding**

*Additional funds should be earmarked for TB research.* There is a need to increase total funding for TB research across the research continuum and to increase the proportion of funding for overall TB control dedicated to TB research (only 3% of TB funds are currently earmarked for TB research).<sup>28</sup>

*Advocate for increased government funding for addressing health needs of developing countries, including TB.* Previously, as in the era of Robert Koch, governments played a large role in TB research funding. Progress in TB research in the late 19<sup>th</sup> and early 20<sup>th</sup> century was mainly due to state funding. According to the Commission on Intellectual Property Rights, Innovation and Public Health Report;

[Governments] should seek to define explicit strategies for R&D and devote a growing proportion of their total health R&D funding to the health needs of developing countries, with an emphasis on upstream and translational research.<sup>42</sup>

*The importance of international commitments such as the Millennium Development Goals and poverty alleviation should be included when advocating for funds because both factors determined TB funding decisions.*<sup>28</sup> Additionally, impact of R&D on TB control was a further incentive to donate. Apart from more funding advocacy "push" and "pull" funding mechanisms can be used to increase industry involvement and investment.<sup>43</sup>

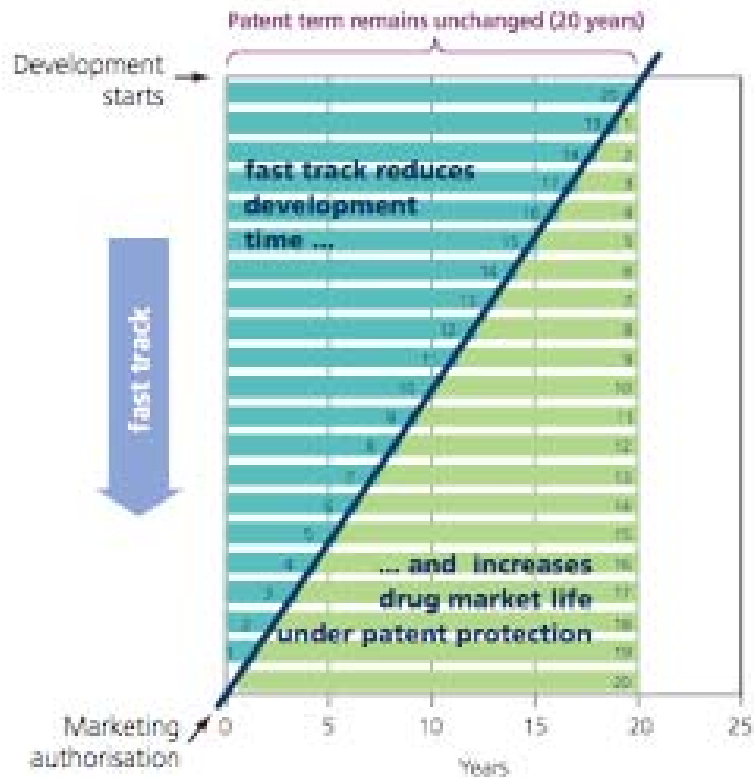
*Use the comprehensive market analysis for diagnostics and drugs to attract companies.* A market analysis for vaccines should be created similar to *Pathway to Patients* and *Diagnostics for Tuberculosis Global Demand and Market Potential*. Both encompassing market analysis should be made accessible to new tool developers. With TB infecting 1/3 of the world with a latent infection, and 9.2 million people contracting the disease every year, there are a large number of people needing or potentially needing treatment, diagnosis or vaccination.

*In addition to using a market analysis, investigate the following possibilities as mechanisms to draw interest to TB market.* The following arrangements could be an incentive for R&D participation, multi-tiered pricing and product bundling.

*Multi-tiered pricing or differential pricing* allows for the optimization of supply and demand. Poor countries pay a lower price (usually at cost or a little more), while wealthier countries pay a cost that covers R&D costs and allows for some profit.<sup>44</sup> There can be multiple-tiers, categorizing each country by need and ability to pay, if agreed upon before development. This reduces uncertainty felt by potential industry partners or developers, who worry not to recover R&D costs if they produce a tool for markets, because they will be required to turn it over to generic production.

*Auction a fast track option (FTO) to a commercial drug company to raise funds for research.* The pharmaceutical R&D policy project at London School Economics proposed auctioning a fast track option to a commercial drug company. In a FTO, a drug is expedited through the approval process. The drug is available up to two years earlier and remains under the patent longer, allowing for a significant increase in profit. Auctioning this fast track option alone could raise \$0.5 to \$0.75 billion per FTO auctioned, to be used for research. If done specifically for TB for 7 years, the funding gap would be eliminated with no other increase in funding from other sources.<sup>45</sup>

Figure 7 - *The Fast Track Mechanism*



Source: Moran, Mary Dr. Anne. Laura Ropars, Dr. Javier Guzman, Dr. Jose Diaz and Christopher Garrison. *The New Landscape of Neglected Disease Drug Development*. September 2005

*Granting patent-extensions, to give innovators monopoly protection past twenty years in exchange for a new TB tool can be an incentive for research.*<sup>45</sup> As most new tools for TB would not be profitable, or would be only be accessible to patients at a lower cost, exchanging a patent extension on a profitable drug for the creation of a TB would provide a pull mechanism for industry development. This “wild card” would act as a prize, with costs distributed through patients buying the non-generic drug widespread. Ideally, the “wild card” could be used on not crucial or life-saving drugs. However, this incentive and auctioning of the fast track option needs high-level negotiation and agreement from industry and regulators.

#### **4.1.2 Changes in the research environment**

*"It is necessary to rethink the traditional roles played by academia and pharmaceutical industry in drug discovery and development and push academia into fields that are traditionally ground for industry when it comes to drugs for diseases that do not ensure appealing market perspectives."*<sup>33</sup> Carl Nathan

*NGOs and International Organizations concerned with TB should improve collaboration with HIV researchers and advocates e.g. by holding joint meetings.* Tuberculosis is the leading killer of HIV infected people, and the collision of these two problems of TB and HIV is evident. HIV issues receive more funding and publicity than TB. In order to promote TB new tool development for the benefit of both groups increased collaboration between TB and HIV must occur. HIV advocates should push to have new drug trials include TB/HIV patients and vice-versa.

*TB Stakeholders should engage with the IGWG (Intergovernmental Working group on Public Health, Innovation and Intellectual Property) in order to support the cause of TB within intellectual property framework.* The IGWG established in 2006 at the World Health Assembly is tasked with producing a "global strategy and plan of action" to "secure an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area."<sup>46</sup> This group can be a crucial player in determining next steps for TB and other developing world disease research. Some suggestions for engagement are as follows:

With the IGWG, TB stakeholders should investigate financial incentives that cut costs for the recipients of new tools without reducing the incentive to invent.<sup>47</sup>

The Research Movement within the STOP TB Partnership should comply with the WHO STAG (Strategic and Technical Advisory Group) recommendation to investigate innovative financing mechanisms with IGWG.<sup>48</sup>

*The New Drugs Working Group should guide, monitor and evaluate the success of trials and quickly navigate, with the help of the intellectual property advisers from IGWG the regulatory barriers to making the drug readily accessible.*

*Investigate the use of patent pools to collaborate and avoid intellectual property litigation.* Patents are put into a pool so a research coalition can develop the entities further, allowing different companies to optimize their strengths and save money. Patent pools reduce transactions costs and spread the risk through multiple players. Cons of patent pools include hidden invalid patents and reduced competition. Since many of the current players in TB research are in research for the public good and not to make money the cons are less worrisome. Indeed, patent pools may be a good mechanism to speed R&D and streamline collaboration efforts by minimizing litigation over patent rights.<sup>49</sup> In July 2008, UNITAID gave the go ahead to create a patent pool for AIDS medicines and created a task force to design and prepare the management, licensing and procedures of the patent pool with help from WIPO.<sup>50</sup>

*An award should be created for high risk and basic research.* High-risk and basic research are important and often unrecognized parts of R&D that lack monetary incentives. Recognition for industry participants is good for advertising and company image. Universities also appreciate the good publicity associated with awards. The award could be granted from numerous players including leading NGOs, donors or governments but ideally from a prestigious or well-known player in TB control.

*Support more basic and operational research to increase research in areas other than new tools development.* Supporting and funding basic and operational research is an important and crucial step in improving the number of compounds entering the pipeline of development and the effectiveness of the new tools produced, however they are not obvious needs to potential donors or political advocates outside the research and TB community. Filling gaps can be achieved by providing grants for upstream and downstream research to universities and industry through public funding.<sup>46</sup>

*Within basic research, determine biomarkers and surrogate endpoints for clinical trials of new TB tools.* A biomarker is a biological measurement and a surrogate endpoint defines an outcome based on a measurement.<sup>51</sup> Biomarkers are necessary in discovering the persistence of *Mycobacterium tuberculosis* in their human hosts.

*Support PPMs (Public-Private Models).* There are some pharmaceutical companies engaged in R&D with public institutions. For example, Pfizer is sharing 12,000 compounds with scientists in UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR), providing research space and additional scientists. Thirteen other companies are doing the same.<sup>52</sup> Their model is effective and costs very little for developers. Eli Lilly announced in June 2007 that they will conduct a special early-phase drug discovery programme to help feed the drug pipeline of the TB Alliance. Not only are they providing research space and 15 million dollars, they opened their 500,000 medicinal compounds to other TB researchers.<sup>53</sup> Public-private models are effective, and need to be expanded and used in other ways.

*Incentives for pharmaceutical companies to open up drug compound library to TB researchers.* If non-profit researchers investigated the "druggability" of compounds in industry databases, pharmaceutical companies would also benefit. Drug lead failure,

could benefit another more profitable drug market. From the pharmaceutical perspective this can be perceived as a win-win arrangement, providing compounds for the public good and gaining more information about their compounds to be used for profit.<sup>54</sup> From a pharmaceutical perspective it would be best to allow the compounds to be used only for TB and other neglected disease drug research, in order to keep the donation non-profit and not competitive to their other interests. Intellectual property agreements should be made before engagement to avoid problems in compound ownership and development.

*An increased dialogue between basic researchers and new tool developers should be encouraged for the successful transfer of compounds from research to development and the identification of basic research gaps.* This dialogue occurs in the translation and discovery phase in *figure 2* and could be further facilitated by the STOP TB Partnership working groups with the help of the Stop TB Research Movement. TDR plays a role in the movement of compounds discovered in basic research to the new tool companies for TB. TDR created an effective bridge from compound research to the drug development community through their online compound database. The database allows researchers to submit compounds to library and researchers interested in developing drugs and vaccines apply for the compounds, paying only shipping and handling costs. Although there are some problems, such as the inability to amass large enough quantities of compounds for effective research and a slow turn around in procurement, both are being addressed. Additionally, the "druggability" of targets are ranked and kept in a database being developed by the network.<sup>54</sup> However, TDR facilitates only one part of basic research and more money is needed to fund the transition of basic research to compounds development. Currently, there are few grants to facilitate projects that "fall between basic and applied research" and more need to be provided.<sup>34</sup>

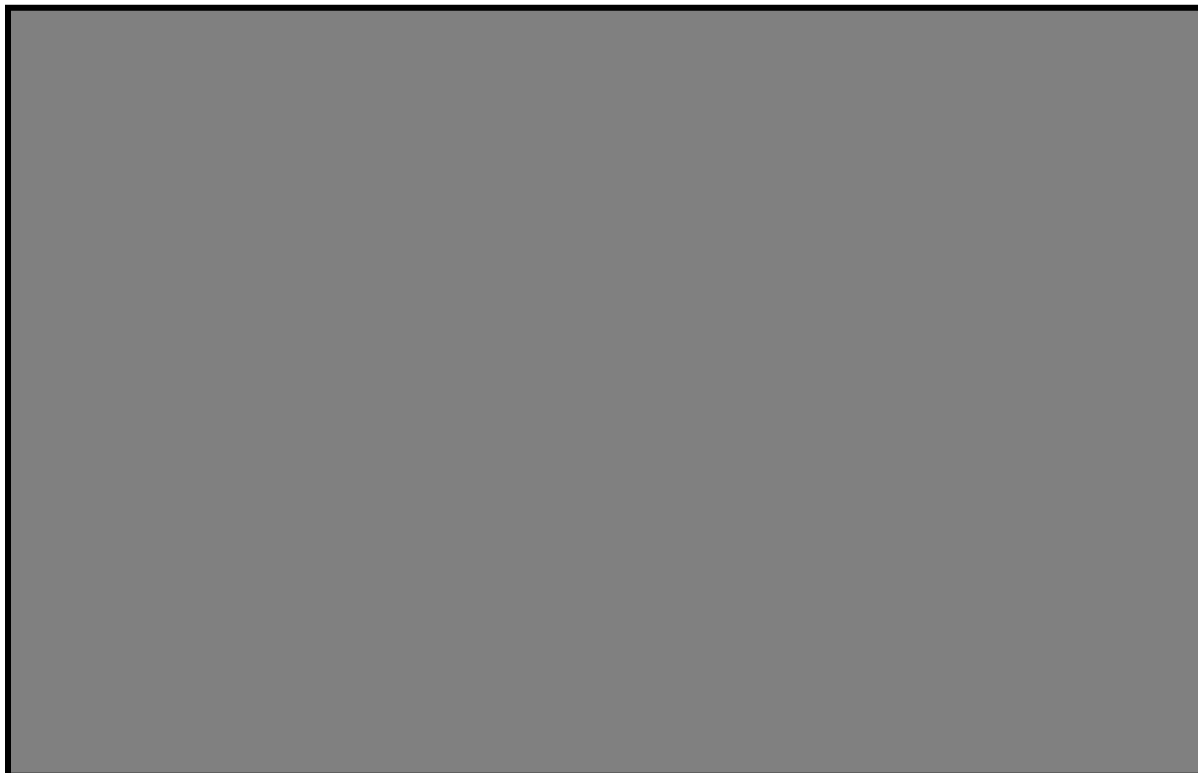
*Increase strength and dialogue of transition through subgroups such as the laboratory strengthening group and the retooling task force.* In the market approval stage, the retooling task force and the laboratory strengthening subgroup facilitate dialogue between the new tool developers and implementers.

*More partnerships and developers are needed to build health research infrastructure in the developing world, especially for clinical trials.* This involves increased funding and the involvement of developed countries. More organizations need to follow the lead of the TBTC and the EDCTP, but with more available and extensive scale funding (note that the EDCTP is limited to Africa).

*Engage universities and public research institutions for the benefit of basic research and the development of public-private mixes.* Universities have previously been a part of large drug breakthroughs. For AIDS, universities contributed Zerit, Epivir, Ziagen, Emtriva and Fuzeon.<sup>55</sup> Engaging universities as key partners in basic and translational research is easier than engaging pharmaceutical industries, and more cost-effective. In the US, the Bayl-Dole Act encouraged universities to engage with industry in public-private partnerships. Organizations such as GlaxoSmithKline have sponsored basic research in universities with success.

*“Over the last ten years, GSK’s Action TB initiative, which concluded in 2003, brought together academic research groups in the UK, South Africa, the Gambia and the USA to work with GSK to identify and validate targets for therapeutic intervention in tuberculosis. Action TB researchers identified and validated novel TB drug targets which have been brought into GSK and screening efforts are now in progress to identify leads for drug discoveries.”<sup>56</sup>*

Partnerships like the Action TB initiative should be encouraged between universities and industries.



*Initiatives such as CARTHA should be encouraged. An additional survey would be useful investigating incentives and problems from the perspective of researchers, industry and NGOs who wish to collaborate with universities. The initial focus could be on American universities, as they seem to harbor more intellectual property issues. Dentico noted that, "Forging agreements with North American universities is often lengthy...the US and Canada taking up to eight months, while Europe only four."<sup>59</sup> However, a global perspective would be ideal.*

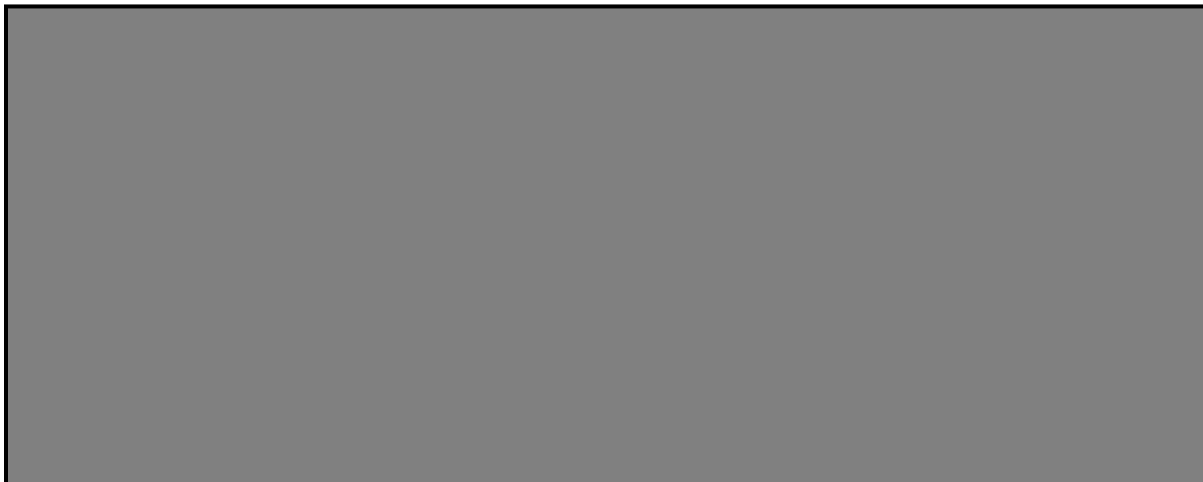
*From this study, guidelines for university researchers, industry, NGOs and technology transfer officers should be created to help them maneuver the complicated world of intellectual property and partnerships for the benefit of global health and specifically, for neglected disease. The document should cover ways to include humanitarian clauses in licenses (as in the agreement between Yale and Bristol-Myers Squibb over d4T), Equitable Access Licenses (EAL),*

provisions in the "Nine Points to Consider in Licensing University Technology" and case studies."<sup>60 61</sup>

*Specifically for TB, a list of industry, NGO, and funding agency partners willing to collaborate on genres of basic and compound research should be published, distributed, or made available online to technology managers. In addition, a list of "experts" or technology managers more familiar or experienced with Global Health technology management issues surfaced as a needed resource to help technology managers promote the Global Health agenda.<sup>56</sup>*

*A seminar to qualify technology transfer officers in transfers for global health should be made available and a ranking of universities who provide their technology transfer officers with the qualification should be published. As technology managers are working in the interest of the universities, the universities must be held accountable and adequately supported for the work they can provide to advance global health research translation and technology transfer partnerships.*

*Universities should push to use their resources to conduct more neglected disease research and foster industry partnerships in research for the best use of funding and expertise.*



## **4.2 Specific suggestions**

These specific suggestions address the specificities of development of new diagnostics, drugs and vaccines. They have different needs in basic research, and have their own set of intellectual property regulations and levels of risk.

### **4.2.1 Diagnostics**

*Government funding to support TB basic research should be increased. Improved basic research and the discovery of biomarkers are needed to create new diagnostics and test*

their validity in field conditions will facilitate TB control, R&D and surveillance. The spread of TB through travel and immigration highlights the need for increased government funding of basic research for diagnostics.

*Increased investment in implementation research is needed.* How to use the new tools, “including better data on the impact of early case detection on TB transmission, would further the cause of diagnostic R&D.”<sup>33</sup>

*High-burden countries should meet with diagnostic R&D stakeholders, to streamline regulatory barriers to research.* Regulations surrounding the cross-border movement of human samples for testing need to be streamlined. As research is for the benefit of the TB patients, from which the samples are taken, an agreement specifically for TB research that determines procedures could reduce red tape and time. Reducing regulatory problems through agreements that reduce time and effort of new tool developers could possibly increase the number of industry players.

#### **4.2.2 Drugs**

*“Without the stimulation of basic research, there won’t be sufficient priming at the start of the development pipeline to feed intense research and development for TB. We need to do more.”*<sup>63</sup> Dermot Maher

*An increase in basic research is needed (figure 2).* In order to keep the pipeline stocked with new chemical entities for possible drug development, basic research capacity must be strengthened. Ways to increase the scope of basic research are addressed above.

*Increasing basic research to find biomarkers is required to speed clinical trials.* In clinical drug trials, a biomarker that assesses the sterilizing activity of a drug is necessary to reduce the length of time a patient in trials needs to be followed. Sputum-smear microscopy is used to determine a patient’s reaction to drug treatment by noting the change in bacillary numbers, however sputum conversion is not an adequate biomarker for drug trials. Determining the sterilizing activity of a drug will determine the rate of relapse and the chance of cure.<sup>35</sup>

*An increase in discovery research relevant to new drugs is needed (figure 2).* GSK, Novartis, Astra Zeneca and Sanofi Aventis have set-up R&D facilities for TB drug discovery, but not on an open-access basis. The Eli Lilly partnership has an open access policy and is a good start to compound development and availability. More organizations need to create similar accessibility to compound libraries. Governments should, “create incentives for pharmaceutical and biotech companies to run in-house phenotypic screens for anti-TB drugs with all available existing compound libraries.”<sup>31</sup> This should be done in addition to supplying the laboratory equipment required.

*Ways to speed up and build clinical trial capacity are required to facilitate TB drug R&D.* In particular, trials for DR-TB drugs must be prioritized because of the explosive spread of drug resistance and the potential of these trials to show efficacy rapidly.”<sup>2</sup>

*FDA and EMEA members should create guidelines and procedures for TB combination drug trials.* The lack of experience in FDA and EMEA regulation authorities may be a problem when approving new TB drugs in clinical trial because they have not been done in 40 years.<sup>34</sup>

*Investigate the inclusion of MDR-TB and HIV infected individuals in clinical trials for new TB drugs.* The newly formed MDR-TB Clinical Trials Research Task Force within the Stop TB working group on MDR-TB is going to form a draft paper to create an agenda. According to *Randomized Trials to Optimize Treatment of Multi-Drug Resistant Tuberculosis*, the way forward in MDR-TB trials would need to include;

- (i) Increased funding for TB trials in light of Global Plan Estimates of a US\$334 million gap for MDR- and XDR- TB R&D.
- (ii) Additional work on the drug pipeline to focus on current leads that have not worked as alternative 1<sup>st</sup>-line treatments for drug-susceptible TB and can instead be focused towards MDR-TB.
- (iii) An integration of efforts is needed along the research continuum in order to create a parallel design for drug-resistant and susceptible TB for trials and research.
- (iv) Understanding that MDR-TB clinical trials, although difficult, is a beneficial endeavour for TB control, patients and TB research.<sup>64</sup>

Tibotec and Otsuka are two pharmaceutical companies that have announced plans to investigate a new drug in MDR-TB patients. Currently, there is little focus in current clinical trials for TB on HIV coinfecting patients and also from HIV drug trials on TB/HIV patients. Including these patients in trials may expedite the effect of a new drug on TB control.<sup>65</sup>

*Better diagnostics could ease clinical trials.* The improvement of the current diagnostics tools would not only improve TB control but also facilitate the development of new tools. Phase III Clinical Trials for new drugs/regimens offer opportunity to test and validate new diagnostic tools, thus avoiding duplications of studies and demands on TB patients.

### **4.2.3 Vaccines**

Vaccines are a crucial part to disease elimination and also the hardest to develop. For developers, the process is high-risk and lengthy. For diseases like TB, with few market incentives, there is a fine balance between promoting access and encouraging innovation.

*NIAD suggests the need for collaboration among current vaccine stakeholders* by combining “the expertise of NIH in basic science, CDC in epidemiology, FDA in regulatory affairs and interactions with industry, USAID in international health...in addition to close links with WHO and the International Union Against Tuberculosis and Lung Disease for their global experience in TB control.”<sup>66</sup> Groups such as these could also play a role defining endpoints and safety procedures.

*An analysis of the potential market for vaccines, similar to those in diagnostics and drugs should be created.* Although it remains to be seen what impact these analysis have on industry involvement, it may be helpful in recruiting drug companies to facilitate research and trials. An estimate on the number of people vaccinated and which governments would agree to include this as standard vaccination regimens could be conducted. The analysis can be modeled after the comprehensive *Pathway to Patients and Diagnostics for tuberculosis Global Demand and Market Potential*.<sup>67 68</sup>

Advance purchase commitments (APCs) (known also as advance market commitments) should be investigated as an incentive to new vaccine developers. A debated issue within the research community, APCs are thought to only be potentially relevant for vaccines over the other new tools. In a paper by Nathan and Goldberg, advance purchase commitments are strongly discouraged as an option for drugs but believed to be a good option for vaccines.

*Vaccine availability would be advanced enormously by Model 1 ('pull' by government-funded advance-purchase contracts), government's financial support of a warm' industrial base for vaccine production and the transfer of product liability from manufacturers to government.*<sup>69</sup>

With an advance purchase commitment (APC), countries that cannot afford the vaccine, could pay (for example) 1 dollar a person, or a donor can on their behalf. The donor sponsors the vaccine to a per person development price (15-20/dose) to cover the remaining development costs. After this initial batch, the developers would be required to either turn over the patent for cheaper production or offer the drug or vaccine at a more affordable price.<sup>37</sup> An APC can also be used in broad terms. For example, a group could sign a contract saying they agree to purchase a certain amount if it fits a certain criteria. This not only provides an incentive for competition but also tailors the tools exactly towards what will be most useful for all. There are many pros and cons to APCs. They provide competition, which can reduce sharing among researchers.<sup>25 70</sup>

APCs avoid unpredictability felt by R&D institutions caused by government and international organization's price control industry and could enter production agreements that ensure no money would be lost. These agreements also ensure access to products after development, and avoid complicated intellectual property fights. Advance purchase commitments, product-bundling and multi-tiered pricing are all mechanisms to eliminate disincentives to industry development of TB vaccines.

Advance purchase commitments are a debated issue within the vaccine community. The pros and cons of this issue are strongly debated within the articles "Making Practical Markets for Vaccines" and "Making Markets for Vaccines"<sup>25 70</sup> As the success of APCs depend on the nature of the agreement, here are some possibilities to make APCs a success for vaccine development.

(i) Possible government sponsors include the US, because there is no technical obstacle to prevent the agreement. It would, however, require strong political support. The UK through their Department for International Development (DFID)

can commit to APCs. Do to the current rise in TB cases within the UK, they would be a good target group for proponents of APCs.

(ii) Another problem for APCs that arises with World Bank and other International Organization commitment is the length of time the APC would be granted in advance, as TB vaccine development is a lengthy process.

(iii) Private foundations lack regulatory obstacles that would prevent them from engaging in advance market commitments and are ideal players for APCs because “they have a substantial asset base and no ability to legislate away from their obligations, greater continuity of leadership and strategic focus and less vulnerable to lobbying from special interest groups.”<sup>23</sup>

Overall, main problems include the length of time in advance the market commitment would be made (10+ years) and the decreased incentive to collaborate and how to keep collaboration up to investigate combination vaccines.

TB vaccine stakeholders should investigate the IFFIm (International Finance Facility for Immunization) as a player to help stimulate investment in new TB vaccine R&D. They could potentially provide an APC for the TB vaccine community. Since a TB vaccine is unlikely to be available before the next ten years, an additional APC from donors would be ideal.<sup>25</sup>

## 5. Conclusions

*“Whatever the technological developments, they need to find field application urgently, not just to accelerate toward the MDGs, but to provide any hope that TB can be eliminated by 2050”<sup>71</sup> Mario Raviglione*

The impact of developing and applying new tools on the global TB epidemic would be substantial. The Stop TB Partnership's goal to eliminate TB as a public health problem by 2050 can only happen with the introduction of new TB tools. Each new tool (diagnostics, drugs and vaccines) has its own impact. If a diagnostic that was, “rapid and widely available diagnostic for TB with  $\geq 85\%$  sensitivity for smear-positive and smear negative cases, and 97% specificity, could save ~400,000 lives annually.”<sup>72</sup> Even pre- or post-exposure vaccines with (50%-90%) efficacy are likely to reduce the number of TB cases by one third, resulting in 700,000 saved lives a year and substantially reduced emergence of drug-resistant TB.<sup>73</sup> For drugs, a model that “examined effects on tuberculosis incidence and mortality in Southeast Asia, revealing[ed] that an effective two-month course of treatment introduced by 2012 could reduce new cases by as many as 11 million and avert up to five million deaths by 2030.”<sup>74</sup> In addition, new tools are likely to have a synergistic effect when combined in acting against latent infection and active disease.

The pace of technological innovation to control TB has been too slow in the past. The severity of the global TB epidemic demands a faster pace, with a much greater effort to increase “the scope, scale and speed of TB research.”<sup>17</sup> There is an urgent need for effective new tools to be developed and made rapidly available as early as possible in the twenty-first century to finally lay the centuries-old problem of TB to rest.

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