TUBERCULOSIS

STRATEGY OVERVIEW

OUR MISSION

Guided by the belief that all lives have equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program supports this mission by harnessing advances in science and technology to save lives in poor countries.

We focus on problems that have a major impact on people in the developing world, but get too little attention and funding. Where proven tools exist, we support sustainable ways to improve their delivery. Where they don't, we invest in research and development of new interventions, such as vaccines, drugs, and diagnostics.

Our financial resources, while significant, represent a very small fraction of the overall funding needed to improve global health on a large scale. We therefore advocate for the policies and resources needed to provide people with greater access to health solutions. Strong partnerships are also essential to our success in making a difference and saving lives.

THE OPPORTUNITY

Since 1993, when the World Health Organization (WHO) declared tuberculosis (TB) a global emergency, there has been tremendous progress in the fight against the disease. Directly observed therapy short-course (DOTS), the recognized case management approach for TB, has been implemented in the 184 countries that account for 99 percent of all estimated TB cases. The global burden of TB is falling slowly, and at least three regions in the world are on track to achieve global targets for halving the number of cases and deaths by 2015.[1]

Despite this progress, TB remains an urgent global health issue. Although TB is curable and preventable, one in three people in the world is currently infected with the TB bacterium, and the active form of the disease kills 1.8 million people annually. Co-infection with TB and HIV (TB/HIV) and a surge in multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are threatening to disrupt recent global successes in TB control. MDR-TB has now emerged in nearly every country in the world, with an estimated half million cases in 2007.[1] Africa and Eastern Europe will not achieve globally set targets for TB control, due mainly to the spread of TB/HIV and MDR-TB.

In the history of the fight against TB, there have been periods of urgency, and there have been periods of innovation. But only rarely have urgency and innovation come together. When our TB program began, there was an acute need to stimulate research and development (R & D) of modern TB tools to fight the evolving epidemic. For decades, much of the industrialized world thought TB was defeated, and investment in TB R & D essentially dried up. The drugs, vaccine, and diagnostics used to fight TB were antiquated, slow, and ineffective, and they were being implemented in the context of weak health systems.

Today that is changing. The rise of TB/HIV and MDR-TB co-infection has given a new sense of urgency to global TB control efforts, and after a decade of focused investment in TB innovation by us and others, a promising pipeline of new tools is in development. These new drugs, diagnostics, and eventually a vaccine could vastly improve the way the world responds to the disease.

The convergence of innovation and urgency presents a unique opportunity to make a significant impact on the global TB epidemic. Further research, more resources, an expanded pipeline of new tools, and improvement in their delivery through health systems remain urgently needed to address the rapidly changing nature of the TB epidemic.

OUR STRATEGY

Our aim is to support the development and delivery of innovative tools and approaches to improve prevention, diagnosis, and treatment of TB. Our TB strategy focuses on intensive R & D of new diagnostics, faster-acting treatment regimens, and more effective TB vaccines, as well as their rapid deployment. We also invest in improvements that enhance the effectiveness of currently available TB tools and approaches. Underlying this focus are our investments in advocacy to expand funding and political commitment for the development and deployment of TB innovations.

Our strategy exists within the context of our support for the Stop TB Strategy, put forth by WHO and the Stop TB Partnership, which was designed to achieve a world free of TB by dramatically reducing the disease's global burden by 2015.[2] The Stop TB Strategy set forth the following targets for TB control:

- diagnose at least 70 percent of people with active disease by 2005, and cure at least 85 percent of those;
- reduce the prevalence of and deaths due to TB by 50 percent relative to 1990, by 2015; and
- eliminate TB as a public health problem by 2050.[2]

We rely on our partners to continue delivering high-quality TB care, expand and enhance DOTS, and strengthen health systems so the integration of innovative TB tools and approaches can be accelerated.

INTERVENTION AREAS

Develop new vaccines

The current TB vaccine, Bacillus Calmette-Guérin (BCG), was developed in 1921. It is the world's most widely used vaccine, provides some protection against severe forms of pediatric TB, and is estimated to save approximately 40,000 children each year. However, the vaccine has little to no efficacy in preventing pulmonary TB, the most common and most infectious form of TB among adolescents and adults.

A safe, more effective TB vaccine is needed, especially for populations with high rates of HIV. It has been projected that even a partially effective new TB vaccine could decrease TB incidence 39 to 52 percent by 2050.[3] We believe investing in a new TB vaccine would provide the best long-term hope for eliminating TB.

In the near term, we are directing the majority of our funding for TB vaccine development to the nonprofit product development partnership (PDP) **Aeras Global TB Vaccine Foundation (Aeras).** Aeras' mission is to develop and license improved TB vaccines for use in high-burden countries. Aeras currently has a pipeline of six TB vaccine candidates, including a modern replacement for the BCG vaccine and booster vaccines. Four of these vaccines are currently undergoing Phase I and Phase II clinical trials in Africa, Asia, Europe, and the United States. Aeras initiated the first Phase IIb clinical trial of a new TB vaccine candidate in infants in July 2009. This proof-of-concept trial will enroll nearly 3,000 infants.

Develop more effective drugs

The drugs currently used to treat TB were discovered more than 40 years ago and do not meet the demands of today's TB epidemic. TB requires treatment with multiple drugs, and existing regimens require at least six months of monitored use to cure. They are burdensome for patients and care providers alike, which can lead to poor adherence among patients. Those who do not or cannot complete their treatment may develop drug-resistant TB strains that take up to two years to treat with second-line drugs, often with severe side effects. The current treatment is also not compatible with some common antiretroviral therapies (ART) used to treat HIV/AIDS, requiring a change in the regimen to avoid drug-drug interactions.

There is an urgent need for novel TB drug regimens that cure more rapidly, and for drugs that can be safely taken concurrently with ART. Our strategy supports the discovery and development of more effective and faster-acting TB drugs and regimens that can be used by all infected people, including those with drug-resistant TB or HIV. The majority of our investments in this area are directed to the PDP **Global Alliance for TB Drug Development (TB Alliance).** The TB Alliance is developing new therapies and currently has two drug candidates in Phase II clinical trials and one candidate in Phase III. We are also funding the **TB Drug Accelerator** program, which provides grants to organizations working to advance knowledge of TB persistence biology by identifying new ways to target the pathogen, develop new tools for drug discovery, and discover new leads. This comprehensive discovery effort will lay the groundwork for the development of new TB drugs for ultra-short treatment regimens. To date, more than 20 grants have been made under the TB Drug Accelerator program.

There are many challenges to TB drug development, in part because there are no validated biomarkers or surrogates to determine efficacy, and therefore long clinical studies are needed. Additionally, conventional drug development requires that new TB compounds be evaluated separately in clinical trials, substituting them individually into the existing four-drug regimen. This means new drugs can only be tested in new combinations after they have been individually approved. Under this approach, obtaining regulatory approval for a completely new TB regimen can take more than 20 years.

To address this challenge, we are working with a wide range of pharmaceutical companies, the Critical Path Institute, regulatory agencies, and the TB Alliance to determine new pathways for combination-drug development. In doing so, we hope to greatly accelerate the availability of new treatments.

Develop better diagnostics

Rapid and accurate TB diagnosis is critical to TB patient care and arresting disease transmission. However, sputum smear microscopy, the standard diagnostic used in the developing world, is more than 100 years old. It fails to detect more than half of all active cases, is labor-intensive for both the patient and the health provider, and cannot detect infection among the majority of those co-infected with TB/HIV.

In industrialized countries, where the TB burden is relatively low, TB diagnosis relies on high-tech molecular techniques and rapid culture systems. These tests have not been implemented in high-burden developing countries due to their level of sophistication and cost.

It has been estimated that improved TB diagnostics could help save at least 400,000 lives every year.[4] Our strategy prioritizes the development of rapid, accurate, and affordable diagnostic tests for case detection and diagnosis of MDR-TB, and latent infection that can be used at resource-poor health facilities, including central reference laboratories, hospital and clinic laboratories, and ultimately at the point of care.

Our largest grant in this area is to the **Foundation for Innovative New Diagnostics (FIND),** a PDP that is currently advancing the development of more than 10 new TB diagnostic tests for use in poor countries. To date, WHO has endorsed three of these diagnostics, which are changing TB practices in many settings. To support this effort, we are also investing in the discovery of novel biomarkers of TB infection and treatment response that will improve detection and clinical management.

Introduce innovation in TB control

The uptake of existing and emerging tools, such as fixed-dose combination (FDC) drugs, X-ray, isoniazid preventive therapy (IPT), culture, molecular diagnosis, and even DOTS, has been slow in many countries. Concerted efforts are needed to promote the rapid and equitable uptake of these innovations.

Our TB strategy is designed to address a wide range of potential constraints to the equitable uptake and use of improved TB technologies. We make strategic investments based on rigorous analysis to identify the most important bottlenecks and opportunities. One area of focus is the prevention of TB among populations with a high burden of HIV using IPT. Although IPT has long been shown to be clinically effective, TB and HIV programs have not deployed this innovation to scale. We support the **Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE),** which is leading three large-scale, community-randomized clinical trials of improved case finding and IPT in three countries severely affected by TB/HIV: Zambia, South Africa, and Brazil.

Introducing Innovations to Improve TB Control in China

At the April 2009 ministerial meeting on M/XDR-TB in Beijing, opened by Margaret Chan and Chinese Vice-Premier Li Keqiang, Bill Gates joined Chinese Minister of Health Chen Zhu to announce an innovative partnership to fight the TB epidemic in China. The partnership, led by the Ministry of Health of the People's Republic of China and supported by a grant from the foundation of $33 million (U.S.) over five years, aims to demonstrate and scale up effective innovations to prevent, control, and manage TB, thereby accelerating progress to control the country's large TB and M/XDR-TB epidemics.

In the first half of the five-year partnership, China will pilot the following innovative tools and delivery approaches in a population of 20 million:

- new diagnostic tests that can dramatically improve detection of TB
- drug-resistance tests that can identify MDR-TB in a matter of hours, as opposed to the six or more weeks standard tests currently require
- new strategies in the community to help TB patients take their medicines regularly, such as cell phone text messaging and medication monitors with built-in reminder alarms
- a new model of collaboration between hospitals and the public health system to provide high-quality and affordable diagnosis and treatment of MDR-TB
- new incentives and approaches for health-care workers to provide effective follow-up of TB patients during treatment
- new approaches to ensure high-quality FDC drugs and second-line TB drugs are produced and used in the national TB control program

During the second half of this partnership, with substantial contribution of governmental funds, the most effective innovations will be combined in a comprehensive program and scaled up in 20 cities with a combined population of 100 million.

Grand Challenges in Global Health

Through our Grand Challenges in Global Health initiative (www.grandchallenges.org), we are working to stimulate innovation in TB control and other health issues facing the developing world. These projects include efforts to study the biomarkers of protective immunity against TB in the context of HIV/AIDS in Africa, and efforts to develop drugs and vaccines against latent TB.

We also award small grants of $100,000 (U.S.) each to support early-stage research projects through our Grand Challenges Explorations initiative.

A second area of focus is large, emerging economies with a high TB burden, such as China, India, and Brazil, where we believe there may be special opportunities to facilitate innovation that will be supported by local industrial and technological infrastructure and sustained by government commitment. To date, our most substantial grant has been to the **Ministry of Health of the People's Republic of China,** which has embarked on a program to prevent and control MDR-TB by testing and scaling up a range of innovations (see box on the previous page).

Advocate for funding and commitment

In the past decade, TB, especially MDR-TB, has become a more visible global health issue, and new, highly effective advocates for TB have emerged. However, the shortage of funding to fight TB remains a significant challenge, and the Global Plan to Stop TB 2006–2015 (Global Plan) currently faces a funding gap of $31 billion (U.S.).[5] There is no funding available to build the extensive clinical-trials infrastructure needed to carry out large-scale, long-term Phase II/III efficacy and Phase IV post-marketing studies of new TB drugs and vaccines.

Increased resources and political will are needed to support innovation and continue to make progress toward the Global Plan's goals. Our strategy supports advocacy for increased financing and awareness of TB control innovations, R & D for new tools, TB/HIV co-infection, and MDR-TB prevention. To support this effort, we are currently making investments to:

- mobilize resources and commitment for TB R & D from the public and private sectors, and hold developed countries accountable for their financial commitments
- maximize commitments to TB control by donor countries and multilateral organizations, including the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), and UNITAID
- catalyze the uptake of innovative TB tools in high-burden countries, led by emerging economies

PROGRESS

We have made global investments in TB R & D and advocacy for the last decade. Though our investments to introduce innovations into TB control programs are too recent to have yielded substantial results, our investments in advocacy for and development of vaccines, drugs, and diagnostics are leading to several products that have the promise to significantly impact the TB epidemic. One recent study suggests the introduction of these combined tools could reduce TB incidence 71 percent by 2050.[6]

Vaccines

Aeras is making progress toward the goal of bringing a new TB vaccine to licensure by 2016. For the first time in more than 80 years, new TB vaccines have entered preliminary efficacy trials in infants, and trials are also under way to test safety in people living with HIV and those previously exposed to TB. Aeras has two TB vaccine candidates in pre-clinical testing and four undergoing clinical trials in North America, Europe, and Africa.

- The leading priming vaccine candidate for the planned prime boost regimen, AERAS-rBCG, is expected to enter Phase I in early 2010. The other five candidates are boost vaccines.
- Two candidates—MVA85A/AERAS-485 and AERAS-402/Crucell Ad35—are currently in Phase IIb proof-of-concept clinical trials.
- Among the others, GSKM72 is in Phase II; HyVac4/AERAS-404 is in Phase I; and AERAS-405 is planned to enter Phase I in early 2010.

Aeras is building lab infrastructure and staff capacity in countries with high burdens of TB, forging new partnerships around the globe to create the trial sites that form the front lines of TB new-tools research. Aeras has also inaugurated a state-of-the-art TB-vaccine manufacturing facility that spans the entire process of vaccine production and is capable of producing 200 million doses of a new TB vaccine—enough to meet worldwide need.

Drugs

In partnership with the largest pharmaceutical companies in the world, including GlaxoSmithKline, Bayer, Novartis, Tibotec, and sanofi-aventis, the **TB Alliance** has assembled the largest portfolio of potential new TB drugs in history. There are currently more than 20 projects in its pipeline, including three compounds in clinical development as ongoing trials:

- A Phase III trial called REMoxTB is designed to evaluate whether either of two moxifloxacin-containing regimens can reduce the current standard of treatment for drug-sensitive active disease from a six- to eight-month period down to four months. This global study is helping to build urgently needed clinical trial infrastructure and capacity to test future TB drugs.
- A Phase II trial of TMC-207 is evaluating the first-ever TB drug under parallel development for both drug-resistant and drug-sensitive disease. Interim data in MDR-TB patients found that 48 percent of patients receiving TMC-207 in combination with standard treatment converted to negative sputum culture after eight weeks, compared with 9 percent of those who received a placebo and the standard treatment.
- A Phase II trial of PA-824 is an evaluation of a nitroimidazole in-licensed from Chiron that shows tremendous promise for treating both drug-sensitive and drug-resistant disease.

Diagnostics

FIND has developed a number of new and better diagnostics, which has resulted in an evolution in TB practice and global policy:

- WHO has endorsed three FIND-supported diagnostics: MIGT liquid culture and drug susceptibility testing, Capilia *Mycobacterium tuberculosis* speciation test, and the Hain GenoType® MTBDRplus Assay. The global TB community has hailed the Hain line probe assay test, in particular, as a breakthrough in the field. It allows the determination of isoniazid and rifampicin drug resistance in a matter of one to two days, instead of several weeks, and thus greatly accelerates detection of MDR-TB cases. All three WHO-endorsed diagnostics are now being scaled up in more than 27 countries by FIND, and WHO's Global Laboratory Initiative and Global Drug Facility with support from UNITAID.
- FIND has supported the Zeiss light-emitting diode fluorescence microscope, which is designed for increased sensitivity, higher throughput, and ease of maintenance when compared with standard-light microscopy. FIND submitted the Zeiss test to WHO's Strategic and Technical Advisory Group for Tuberculosis for approval in September 2009.
- FIND is also in the demonstration phase for the GeneXpert System from Cepheid. This fully automated, closed, molecular detection test has very high sensitivity in both smear-positive and smear-negative patients, and can also detect rifampicin-resistant cases. Its simplicity and high speed (90 minutes) will enable this technology to be used in district laboratories and microscopy centers. WHO is expected to endorse the GeneXpert System in 2010.
- By 2011, FIND expects to submit another fully manual, easy-to-operate, visual reading molecular platform—the Eiken LAMP—which will also work for malaria, sleeping sickness, and early infant diagnosis for HIV. This technology is well suited to lower-level microscopy centers in developing countries.

Advocacy

In recent years, TB has gained increased awareness on the global stage, with donor countries and multilateral organizations prioritizing funding for and addressing TB. Recent successes include:

- the re-authorization of the President's Emergency Plan for AIDS Relief (PEPFAR) with $4 billion (U.S.) for TB[7]
- increased access to MDR-TB diagnostics and treatment, first-line drugs, and pediatric treatment through funding from UNITAID
- the detection and treatment of 5.4 million TB cases through funds mobilized by the Global Fund.[8]

Recently, a number of high-burden emerging economies have made new commitments to pilot innovative approaches to TB control:

- In March 2009, at the Stop TB Partners' Forum in Rio de Janeiro, the Brazilian Ministry of Health committed to removing the country from the list of high-TB-burden countries, introducing FDCs, and testing new TB diagnostic tools.
- In April 2009, at the ministerial meeting on M/XDR-TB in Beijing, the Ministry of Health of the People's Republic of China and the foundation launched a partnership to pilot a number of TB innovations, including new diagnostics and FDCs.
- At the Pacific Health Summit in June 2009, Indian manufacturers and government officials, along with international pharmaceutical companies, demonstrated new momentum and enthusiasm for contributing to the development and delivery of new tools for fighting TB.

CHALLENGES

National TB control programs currently face challenging decisions regarding whether and how to introduce multiple new and expected diagnostic technologies. Once they become available, the uptake of new drugs may be constrained by their cost, the extent to which they disrupt current regimens, the variability of current regimens, requirements for national manufacture, and the capacity of most national TB programs to deliver them. We will work toward developing a more grounded understanding of the many operational factors that influence the uptake of TB innovation by providers and patients.

TB-effort awareness and commitment have increased, yet the global community, including both the public and private sectors, is still not sufficiently galvanized to fight TB. TB is a disease of poverty, and to date there has been relatively little market incentive for the private sector to become involved in TB R & D. At the same time, governments have become accustomed to decades-old tools even though they are highly ineffective. We will hold ourselves and the public and private sectors accountable for the failure to adequately support research, and work hard to spur market incentives in support of expanded funding.

WHAT WE'RE LEARNING

Efforts to apply innovation and conquer TB have also been constrained by a lack of scientific understanding of the disease. A lack of biomarkers that correlate with TB disease status and a poor understanding of host immunity to TB impede the development of even more effective vaccines, drugs, and diagnostic tests beyond those in the current pipeline.[6] To address this, we are investing more in basic research to better understand the disease and its mechanisms.

In the clinical stage, nearly all the TB trials we've supported have been challenged by logistical constraints, limited capacity, and cumbersome regulatory processes. The CREATE initiative has faced significant delays due to the enormous complexities of implementing community-randomized trials. We are thus now questioning whether there is an alternative to these trials that could achieve the same goals.

THE WAY FORWARD

Strong partnerships and commitments are needed to develop and deliver new tools that diagnose, prevent, and treat TB, and dramatically reduce the global burden by 2015. TB remains an urgent health threat, but innovation and collaborative efforts will help turn back the epidemic. We look forward to working with government, donor, private-sector, research, nongovernmental, and community partners to achieve the goals set out by the Stop TB Partnership.

TO LEARN MORE

About the Global Health initiative:
www.gatesfoundation.org/global-health

About Tuberculosis:
www.gatesfoundation.org/tuberculosis

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