Tuberculosis

OUR MISSION

Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program is dedicated to this mission by helping to ensure that life-saving advances reach those who need them most.

We focus on problems that have a major impact on the poor 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 small fraction of the overall funding needed to improve global health on a large scale. We therefore advocate for policies and financial resources to promote greater access to health solutions. Strong partnerships are also essential to our success in making a difference and saving lives.

THE OPPORTUNITY

Significant progress has been made in rolling out treatment for tuberculosis (TB). Between 1990 and 2009, the mortality rate related to TB fell by 35 percent. Due to implementation of directly observed therapy short-course (DOTS), the recommended treatment approach for TB, and coordinated global efforts, 46 million people have been successfully treated and up to seven million lives saved from 1995 through 2010.1

Despite this progress in treating TB, there are nearly nine million new cases of TB each year, and TB remains one of the main causes of death worldwide. 1 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 making TB treatment and control more complicated. The TB epidemic in countries with a high prevalence of HIV has accelerated. In 2010, 350,000 people died of HIV-related TB.2 MDR-TB has now emerged in nearly every country in the world, with an estimated half million cases in 2008.3 Current tools for preventing, diagnosing, and treating TB are inadequate to reign in the epidemic.

After a decade of focused investment in TB innovation, a promising pipeline of new tools is in development. New drugs, diagnostics, and eventually a vaccine could vastly improve the way the world responds to TB, but more research and development is needed to ensure that these tools are fast acting, accessible, affordable and simple to use.

OUR STRATEGY

Our goal is to accelerate a reduction in global TB incidence.

To realize this goal, our strategy prioritizes the research and development of more effective vaccines, rapid, point of care diagnostics, and faster-acting treatment regimens. We are also focused on how these tools can be deployed successfully in countries with the highest incidence of TB. Underlying this focus is our effort to lower the cost of new TB tools that are developed and advocate for expanded financing to ensure that effective interventions reach all who need them. Our strategy relies on partnerships with both the public and private sectors to foster the development of products that will be affordable and accessible for use in the developing world.

INTERVENTION AREAS

Discover & develop improved vaccines

Projections show that even a partially effective new TB vaccine could decrease TB incidence by 39 to 52 percent by 2050.4 We believe investing in a new TB vaccine would provide the best long-term solution for eliminating TB. The current TB vaccine available, Bacillus Calmette Guérin (BCG), formulated over a century ago, is far from ideal. Although the vaccine provides some protection against severe forms of TB in newborns and children, it is unable to prevent infection and protect against pulmonary TB in adults, which accounts for most of the TB burden worldwide.

We are directing the majority of our funding for TB vaccine development to **Aeras**, a nonprofit product development partnership (PDP). The focus of our work with Aeras is to develop and license improved TB vaccines for use in high-burden countries. Aeras currently has a pipeline of six TB vaccine candidates in clinical trials, including a modern replacement for the BCG vaccine and booster vaccines. Three candidates are now undergoing Phase IIb efficacy trials, which will demonstrate how well the vaccines work in a small population.

Though several candidate TB vaccines have entered the pipeline, there remain a number of barriers to the discovery and development of TB vaccines. The mechanisms of vaccine-induced protection against disease are poorly understood. There are no known biomarkers that can predict the efficacy of vaccine candidates. Moreover, there is no evidence that the animal models commonly used in vaccine testing provide a reliable indication of vaccine efficacy in humans. Thus, new TB vaccines cannot currently be developed without conducting lengthy and costly Phase IIb/III trials.

To address these challenges, we are creating the **TB Vaccine Accelerator** program, which is working toward identifying correlates of protection through systems biology approaches, developing a safe and predictive human challenge model, and identifying vaccine concepts and designs that represent stark alternatives to those currently in the pipeline. In the coming years, we will support a number of grants under the TB Vaccine Accelerator program to improve our understanding of TB and move towards more rational vaccine development approaches. In the meantime we will continue to support the empiric approach with new TB vaccine candidates, based on a diversity of antigens.

If we are successful, our investments in vaccine discovery and development will lead to a TB vaccine candidate entering a Phase III trial by 2016.

Discover, develop & launch more effective drug regimens

Globally, the most widely used TB drug regimen is a combination of four drugs that takes six months to complete and has significant side effects. All too often, these drawbacks cause some patients to default on their treatment—globally, it is estimated that between 20-30 percent of all patients who start treatment interrupt it before completion.1 Consequently, many patients relapse, transmit TB to others, or develop drug-resistant TB strains that take up to two years to treat with more expensive second-line drugs, often with severe side effects. With the occurrence of MDR-TB, accelerating the development of shorter, simpler, and more effective drug regimens is no longer just an option, but a major public health imperative.

Our strategy supports the discovery and development of shorter, safer, tolerable TB regimens that can be used by all infected people, including those with drug-resistant TB and HIV coinfection. We also anticipate that in the future, the choice of therapy will be guided by rapid drug-resistance testing. The majority of our investments in drugs are directed to the PDP **Global Alliance for TB Drug Development (TB Alliance).** In partnership with pharmaceutical companies, 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, with three drug candidates in Phase II clinical trials and one candidate in Phase III.

RECENT SUCCESSES

- **VACCINES:** For the first time in decades, a new TB vaccine candidate is in a Phase IIb proof-of-concept study in infants. We expect results from this Phase IIb study in 2012.
- **DRUGS:** The pace of new drug and drug regimen development has accelerated over the last decade. At the turn of the century, no new drugs were in clinical development. Now there are ten compounds in different stages of clinical development for TB.
- **DIAGNOSTICS:** Five new TB diagnostics have been developed and have received WHO endorsement. These new diagnostics have significantly improved performance compared with traditional light microscopy. They offer the potential to increase the accuracy, and shorten the duration of the diagnostic process.
- **DELIVERY & ADVOCACY:** China is adopting use of fixed-dose combination TB drugs and has classified MDR-TB as a "highly reimbursable disease" under its health insurance schemes, which will significantly increase the amount of funding for TB in China.

We are also funding the **TB Drug Accelerator** program, which provides grants to organizations working to identify new ways to target more effectively those bacteria that persist in the face of current chemotherapy, develop new tools for drug discovery, and discover new drug leads. This comprehensive effort is laying the groundwork for the development of new TB drugs for treatment regimens that work in weeks rather than months. The TB Drug Accelerator has already produced

new tools that enable better lead molecule finding, which include whole cell screens, genetic tools, mechanism of action identification, primary screening tools, and computational screens.

Given TB's ability to rapidly develop resistance to a single drug, the treatment of TB will always require a combination of multiple effective drugs. Conventional drug development requires that new TB drugs be evaluated separately in clinical trials, substituting them individually into the existing 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 would take more than 20 years.

The world cannot wait a quarter century for the development of appropriate treatments for TB. To accelerate the development of new drug regimens, we support the **Critical Path to TB Drug Regimens (CPTR)** initiative to improve the pathway for combination TB drug regimen development. Under CPTR, drug companies and other product developers are collaborating to identify and test promising combinations of individual TB drug candidates as early as possible. At the same time, CPTR partners are working with regulators to develop new tools to quickly evaluate and register these combination therapies.

If we are successful, our investments will result in one combination TB drug regimen in a Phase III trial by 2016.

Discover & develop new TB diagnostics

Rapid and accurate TB diagnosis is critical to TB case detection, starting appropriate therapy, and ultimately interrupting disease transmission. The standard diagnostic used in the developing world, sputum smear microscopy, is 125 years old, detects only half of all cases, and is labor-intensive for both patients and health providers. Culture-based drug susceptibility testing (DST) is the most sensitive method available, but it is technically challenging and can take weeks to months to return results. Rapid DST methods that use line probe assays are expensive and require investments in infrastructure. New cartridge-based amplification of nucleic acid technologies, such as GeneXpert, are a significant improvement in terms of speed and performance. However, they are currently too expensive and require too much supportive infrastructure to reach the majority of those in greatest need.

A diagnostic tool that is simpler, cheaper, and more applicable to a wider percentage of the patient population is urgently needed. Our strategy prioritizes the development of rapid, accurate, and affordable diagnostic tests for case detection and diagnosis of TB that can be used 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 a number of TB diagnostic tests for use in less developed countries. 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 of TB.

By 2016, we hope our investments will have helped to identify one new TB biomarker and develop two new molecular TB diagnostics that are endorsed by the World Health Organization (WHO).

Catalyze uptake of innovation in TB control

As new TB tools are developed, concerted efforts are needed to promote their rapid and equitable uptake. However, questions remain about the best way to finance new tools, use them optimally, and eventually scale-up their use in ways that have the greatest impact on TB incidence.

Our TB strategy prioritizes research on the most cost-effective ways to use new tools in health systems. Our efforts are focused on India, China, and South Africa, as they collectively have approximately 40 percent of the world's TB burden, including a high percentage of drug-sensitive TB, MDR-TB, and HIV-associated TB. Additionally, these countries have the potential to supply the global market with low-cost TB vaccines, drugs, and diagnostics.3

Our focus is on conducting pilot implementation studies of innovative tools and delivery approaches in focus countries and then using these findings to increase the uptake of the most effective TB innovations globally. The work of this initiative is largely completed at the country level where we focus on projects that support the adoption and uptake of innovations. For example, one of our projects focuses on identifying the most cost-effective ways to deploy the GeneXpert diagnostic in China, India, and South Africa. Other projects are focused on optimizing treatment adherence, referral networks, and private sector engagement in TB care.

By 2016, we hope that our strategy will have led to at least eight new TB tools and service delivery models adopted by national TB control programs in India, China, and South Africa.

Increase global access, cost reductions & efficiency

Accelerating the decline in global TB incidence will require that new products and practices achieve high coverage rates in high-burden countries. This will entail addressing a number of finance and policy challenges. Most newly developed TB tools are more expensive and effective than tools currently on the market. Though the increasing number of new technologies is a positive development for TB control, policy makers often lack the evidence and guidance on how to choose which tools are most effective for their countries and how to implement these cost-effectively.

Our strategy supports global finance mechanisms to reduce the cost of innovative technologies and accelerate their uptake. This includes our efforts to attract a sufficient number of manufacturers to ensure a stable and affordable price of fixed-dose combinations and second-line drugs. We also are focused on collaborating with critical global health partners like the Global Fund to Fight AIDS, Tuberculosis and Malaria, WHO, and UNITAID to maximize the effectiveness of their resources and thus obtain cost efficiencies, drive demand, and clarify the pathway for adopting new TB technologies.

By 2016, we hope that our efforts will have led to a reduction in the cost of second-line drugs and manufacturers selling pediatric and adult fixed-dose combinations at stable and affordable prices globally.

Advocate for funding & commitment

Completing trials for the promising pipeline of new tools, and delivering new, effective tools requires increased financial resources. There is particularly a need for funding to carry out large-scale, long-term Phase II/III trials of new TB drugs and vaccines. Our strategy prioritizes advocacy for greater political commitment and funding

for TB, particularly for late-phase research and development. We believe that strengthened partnerships with donor governments and multilateral institutions, the pharmaceutical and biotechnology industries, and governments of high-burden emerging economies, such as India, China, and South Africa, is critical. Such partnerships encourage greater investment in research and development and greater and more effective investments in the delivery of existing and new tools.

By 2016, we hope that due to our efforts, sufficient funding will be made available for one vaccine and one drug Phase III trial.

THE WAY FORWARD

There is an urgent need to accelerate the development and scale-up of new vaccines, point of care diagnostics, and effective shorter course TB drug regimens. As the pipeline of new tools advances, we will need to learn the most effective ways to deploy them in real world health systems. We will be managing our investments closely with an eye on results and making amendments to our strategy when appropriate. We look toward working with our government, academic, foundation, donor, private sector, and community partners to reduce the number of TB cases worldwide.

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