Tuberculosis Disease Report

June 2009

Published by:
The FasterCures Philanthropy Advisory Service
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The FasterCures Philanthropy Advisory Service

FasterCures / The Center for Accelerating Medical Solutions

FasterCures / The Center for Accelerating Medical Solutions is a nonprofit “action tank” whose mission is to identify and implement global solutions to accelerate the process of discovery and clinical development of new therapies for the treatment of deadly and debilitating diseases. FasterCures, as a center of the Milken Institute, is nonpartisan, nonprofit, and independent of interest groups.

Barriers to progress in accelerating cures exist all along the research continuum—from basic research to development, from medical education to medical practice, from investment capital to human capital. FasterCures is working to clear the path to faster progress, not just by analyzing barriers, but by overcoming them through action. A force to catalyze systemic change, FasterCures:

- Evaluates current systems of disease prevention, research, development, and treatment;
- Identifies barriers to efficiency, effectiveness, and expediency in those systems;
- Creates achievable action plans to improve those systems; and
- Provides seasoned leadership and expertise in implementing those action plans in concert with organizations searching for new medical solutions.

To guide its efforts, FasterCures developed a Blueprint for Change focused on the transformation needed in three areas of medical research: research leadership and innovation; research tools and resources; and the medical research environment. The Philanthropy Advisory Service (PAS) aims to promote progress in all three areas through more informed philanthropic investment.

Helping Philanthropists Make Informed Investment Decisions

The lack of independent, reliable data about nonprofit disease research opportunities is a major barrier to encouraging significant support for such research and to improving the efficiency and productivity of philanthropy. With grants from the Bill & Melinda Gates Foundation and the Pioneer Portfolio of the Robert Wood Johnson Foundation, FasterCures has developed the PAS to address this problem.

The objectives of PAS include:

- Helping philanthropists align their goals and expectations with the capabilities and approaches of research organizations;
- Identifying gaps in funding for areas crucial to the success of specific disease research efforts; and
- Promoting among potential donors a "continuum of cure" perspective that can help develop cures for deadly and debilitating diseases.

PAS creates an information marketplace to support informed philanthropic investment. It improves the efficiency and productivity of both philanthropists and the nonprofit disease research
organizations that depend on their support, especially in areas where there are demonstrated funding gaps in research and development.

**Philanthropy Advisory Service Analyst Reports**

PAS provides two types of reports—disease and organization reports.

- **Disease Reports** discuss the burden, progression, and existing treatments for a given disease; highlight priority research areas; and provide an overview of relevant activities in the commercial and nonprofit research sectors. These reports provide a broader understanding of the disease, its toll on the greater society, and any potential products in the pipeline, as well as describe promising research areas. This information establishes the contextual knowledge for readers to consider as they evaluate nonprofit organizations in a specific disease area, particularly with regard to whether an organization is addressing key research areas and challenges.

PAS develops disease reports using desktop research. Each report is reviewed and validated by a Scientific Advisory Board, or SAB, composed of leading researchers and clinicians in that disease area.

- **Organization Reports** are developed describing the activities of nonprofit organizations involved in disease research. For diseases primarily affecting the developed world, organizations reviewed include those funding research, as well as those providing tools to support research efforts. For diseases primarily affecting the developing world, the organizations reviewed include product development partnerships as well as academic and private research organizations.

These reports provide detailed information on strategy, research portfolio, management, and financials. They also include an assessment of the organization’s practices according to a set of metrics that FasterCures believes contribute to the acceleration of biomedical research. Readers can use this information together with the context outlined in the disease report as an aid to making philanthropic investment decisions.

Organization Reports are developed based on information collected in the public domain, augmented by discussions with representatives of the organization, with input from the relevant PAS SAB.
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Summary

Disease Definition
Tuberculosis (TB) is the second leading infectious cause of death worldwide, killing an estimated 1.8 million people a year. TB is an infection caused primarily by *Mycobacterium tuberculosis* (*M.tb*), a slow growing bacterium that thrives in areas of the body rich in blood and oxygen (e.g., lungs). TB can be latent or active, and latent infections can become active. Most *M.tb* infections target the lungs, with common symptoms that include fever and a chronic cough resulting in blood-tinged sputum; however, the disease also may affect other important bodily systems such as the central nervous system and bone. TB also is the leading cause of death in people infected with HIV/AIDS, which increases the rate and frequency with which latent TB becomes active and ultimately transmissible.

Key Global TB Statistics
TB takes a toll on the health and economic condition of the global population as evidenced by the following statistics:

- Every four seconds, someone in the world falls ill from TB;
- Every 15 seconds, an *M.tb*-infected person dies of the disease;
- Nearly one percent of the world’s population is newly infected every year;
- One third of the world’s population is thought to be infected with the TB bacillus, although only 5 to 10 percent will ever become ill;
- TB-related productivity loss costs the global economy $12 billion per year.

Current Prevention and Treatment
The Bacillus Calmette-Guérin (BCG) vaccine developed in the early 1900s is considered effective against complications from TB disease in children. However, the efficacy of the BCG vaccine is incomplete, varies by location, and is universally low against adult pulmonary disease, the most transmissible form of TB with the largest public health consequences.

Current treatment protocols for active TB disease rely on a lengthy regimen under which trained health personnel watch the patient swallow every daily dose of a four-drug cocktail\(^1\) for two months, followed by another four months of treatment with a two-drug combination. Resistance to some of these drugs has become fairly widespread, with increasing incidence of multi-drug resistant TB (MDR-TB) and the recent emergence of extensively drug-resistant TB (XDR-TB). Although treatment protocols do exist for these strains, treatment is long and invasive and much less frequently successful than for drug-susceptible TB. Treatment also is possible for latent *M.tb* infection, particularly in high-risk individuals; however, it is difficult to convince patients who feel healthy to take drugs that may be poorly tolerated.

\(^1\) Consisting of isoniazid, rifampin, pyrazinamide, and ethambutol.
**Research Investment**

Funding for TB-related research has grown steadily in recent years, reaching about $410.4 million in 2007. Governments, led by the United States, contribute the majority of funding for TB research, followed by private foundations. The U.S. National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (Gates Foundation) combined account for nearly 60 percent of total spending. The development of new TB drugs currently is the largest area of research and development (R&D) investment, receiving 35.3 percent of all funds in 2007, followed by 32.3 percent for basic research, and 20 percent for preventive vaccines. Diagnostics research accounted for about 8.5 percent of spending. This funding falls far shy of the ten-year resource requirements projected by the Stop TB Partnership for R&D in these key areas.

**Key Research Areas**

Research efforts are underway to develop more effective tools and technologies for preventing, diagnosing, and treating TB. Efforts can be categorized according to the following:

- Developing more sensitive and specific diagnostic tools, while ensuring they remain appropriate for use in resource-poor settings
- Creating new drugs that would shorten and simplify the treatment process, effectively treat MDR-TB, and better address latent infections
- Developing more effective vaccines to prevent TB in adults and children
- Increasing the foundation of basic science that underpins research efforts aimed at developing new technologies and new health care interventions
- Creating medical evidence to maximize uptake and appropriate use of new drugs, vaccines and diagnostics, as well as optimizing use of existing tools to improve TB control.

**Challenges**

Many of these areas of research are hampered by critical challenges, including:

- Gaps in basic understanding of the disease, including limited information on how the bacterium resists immune response and the relationship between infection and disease;
- Lack of surrogate markers of effectiveness for new drugs and vaccines to shorten clinical trials, as well as limited disease-specific biomarkers to aid in development of diagnostics;
- Limited laboratory and clinical trial infrastructure in high-risk countries, particularly those with specific priority populations, to allow advanced-stage development of new drugs and vaccines; and
- Insufficient incentives for investment from the private sector, due to perceived market limitation, shifting the burden of funding to the public and nonprofit sectors.
**Key Nonprofit Research Organizations**

There are seven major nonprofit organizations that conduct and/or fund TB research, as outlined below.

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<th>Product Development Partnerships</th>
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<td>• Aeras Global TB Vaccine Foundation</td>
<td>• Infectious Disease Research Institute</td>
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<td>• Foundation for Innovative New Diagnostics</td>
<td>• Seattle Biomedical Research Institute</td>
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<td>• South African Tuberculosis Vaccine Initiative</td>
<td>Development Programme/World Bank/World Health</td>
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<td>• TuBerculosis Vaccine Initiative</td>
<td>Organization Special Program on Tropical Disease</td>
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<td>Research</td>
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**Key For-Profit Players**

The limited commercial market for TB-related products has offered little incentive for investment from for-profit industry. However, the growth of public-private partnerships aimed at developing new products for TB and other developing world disease has led to a resurgence of involvement from the pharmaceutical industry. Major industry players in TB product development consist of companies that have a significant, branded drug on the market, those that are involved in major research and development activities aimed at producing new drugs and vaccines, and those that are among the top 20 funders of TB research according to the Treatment Action Group. These major players, for whom interest in TB tends to be primarily philanthropic rather than commercial, include:

- AstraZeneca
- Eli Lilly
- GlaxoSmithKline (GSK)
- Lupin Limited
- Novartis
- Otsuka Pharmaceuticals
- Sanofi Aventis
- Sequella Inc.

TB also is attracting significant interest from biotechnology firms like Intercell and Crucell and device manufacturers like Cepheid.
Disease Burden

Overview
Despite the existence of effective treatment, tuberculosis (TB) continues to be the second leading single infectious cause of death worldwide, with the vast majority of deaths occurring in poor countries. TB is caused by infection with a slow-growing bacterium called *Mycobacterium tuberculosis* (*M.tb*). Until the development of streptomycin in the 1940s, TB had been a leading cause of death in developed and developing countries alike. Today anti-TB drugs like isoniazid and rifampin can successfully rid an infected person of the bacteria 95 percent of the time. Still, 1.8 million people die from TB disease every year, and millions more develop an illness that can threaten both personal and national economic health. Further, the emergence and spread of drug-resistant strains of *M.tb*, particularly those forms of the bacterium that do not respond to multiple first-line treatments, has placed an increased urgency on global TB research and control efforts.

Burden

Population Burden
TB causes more deaths worldwide each year than any other single infectious disease except HIV/AIDS. An estimated one-third of the world’s population is infected with the bacterium that causes TB, although many may never experience illness or are diagnosed.

Every four seconds, a new person becomes ill as a result of *M.tb* infection. According to the World Health Organization (WHO), in 2007, an estimated 9.3 million people around the world were diagnosed with TB—up from 9.2 million reported cases the year before—and 1.8 million died from the disease. The total worldwide TB prevalence in 2007 was estimated at about 13.7 million. People with HIV/AIDS are particularly vulnerable to *M.tb* infection, accounting for 14.8 percent of new cases and 25.7 percent of deaths in 2007, and TB has become the primary cause of death in persons with HIV/AIDS.

The growing epidemic of drug-resistant TB presents new challenges for global TB control efforts. More than 500,000 people each year develop multidrug-resistant (MDR) TB, which fails to respond
to at least two of the four available first-line treatment drugs (isoniazid and rifampin). Recent years also have seen the spread of strains of the bacterium that are considered extensively drug-resistant (XDR), meaning that in addition to being MDR—they also are resistant to second-line therapeutics, specifically fluoroquinolones plus one of the injectable drugs used to combat MDR-TB. MDR-TB and XDR-TB are expensive and difficult to treat and have high mortality rates. Further, totally drug-resistant strains of TB have begun to emerge, and there are concerns that they could become more widespread.

**Economic Burden**

TB disproportionately affects the poor, who are more susceptible to both infection and illness as a result of malnutrition, overcrowding, poor air quality, and sanitation issues. Once infected, the poor are the least likely to be diagnosed before they develop symptoms and transmit TB, and to receive adequate care for their illness. Further, the majority of TB illness and death occurs in productive adults, who normally would be contributing to their household and national economies but often are unable to work due to their illness. This loss of productivity is compounded by family members who have to take off work to care for the sick and by children who may have to drop out of school in order to help support the household. Additionally, the indirect costs associated with the lengthy treatment of TB infection can place a high burden on already struggling households. Economist Steven Russell estimated in a 2004 paper that, at the household level, the cost of treating TB can be as much as 8 to 20 percent of annual income, and the cost of lost productivity can be as much as 20 to 30 percent of annual income.

Beyond the household level, the economic burden posed by TB can have a profound impact on national economies and, by extension, the global economy. According to the WHO’s Global Public Goods for Health reader, the loss of productivity associated with illness and death caused by TB costs the global economy $12 billion per year. Economists Franque Grimard and Guy Harling estimate that, worldwide, TB causes an annual loss of $1.4 billion to $2.8 billion in economic growth.

**Risk Factors**

**Geographic Distribution**

TB’s reach is global, with infection, disease, and death occurring in all regions of the world. However, developing countries bear most of the disease burden—about 95 percent of all new cases and 98 percent of all deaths. Asia is hardest hit by the disease, in 2007 accounting for about 55 percent of all new diagnoses. Infection and death rates also are high in Africa—particularly in Southern Africa—where HIV co-infection is most prevalent (79 percent) and about one-third of all new diagnoses and two-fifths of all deaths occurred in 2007. Asia also is a center of the MDR-TB epidemic, with India and China alone accounting for nearly 250,000 of the 511,000 estimated cases in 2007. The transition economies of Eastern Europe also bear a significant amount of the burden of MDR-TB, in particular the Russian Federation (43,000 cases in 2007). Successful treatment regimens implemented by TB control programs in the established market economies of North America and Western Europe have caused a significant decline in incidence, prevalence, and deaths in these countries, leaving them only a negligible share of the disease burden.
Despite the rise in new cases of TB in 2006 and 2007, incidence rates have been declining worldwide since 2003.\(^2\) Incidence of TB remains highest in sub-Saharan Africa, which also is home to 13 of the 15 countries worldwide with the highest prevalence. Extremely high incidence rates in countries such as Swaziland (1,200/100,000) and South Africa (950/100,000) are reflective of a severe HIV crisis in southern Africa and the high levels of co-infection.

**Individual Risk Factors**

Because pulmonary TB produces airborne particles of the infectious agent, the disease is easily transmissible. Risk factors for acquiring *M. tb* infection or developing active TB fall into several categories: environmental, lifestyle, and genetics (Table 1). Given the infectiousness of TB and its transmission route, some risk factors may be obvious, but the magnitude of risk may not be as self-evident. Many of the risks for *M. tb* infection are most commonly associated with poverty, including overcrowding, which enhances exposure to infected individuals, and poor sanitation and air circulation, which can foster the spread of disease. Malnutrition and other factors that hamper immune response also play a role in the progression to active disease.

As discussed previously, being infected with HIV or living with AIDS also is an important risk factor for developing and dying from active disease. The immune-suppressed state of HIV/AIDS patients can dramatically increase the risk of reactivating a latent infection. In one study, researchers found

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| ● Sharing space with a TB patient  
● Poverty | ● Co-infection with HIV  
● Other forms of immunosuppression  
● Exposure to coat dust, silica, asbestos  
● Malnutrition or undernutrition  
● Smoke from domestic stoves and cigarettes | ● Family history |

\(^2\) WHO attributes this rise to population growth rather than a rise in incidence rates.
that the average relative risk\(^3\) of developing TB was 28 times greater among people also infected with HIV over the course of 25 months.

Similarly, medically induced forms of immunosuppression also put individuals at greater risk for developing active TB. This includes treatment with commonly prescribed treatments for conditions such as rheumatoid arthritis, irritable bowel syndrome, and psoriasis, among others.

Studies examining rates of TB among twins indicate that the disease can run in families and according to ancestral history. The extent to which family history of TB contributes to global disease burden, however, remains unclear due to the difficulty of separating environmental influences from genetic predisposition.

**Biology**

**Cause**

TB is caused by infection with *M. tb*, a slow growing bacterium that commonly infects the lungs but also can invade other parts of the body, including the central nervous system and the lymphatic system. The bacteria are spread by airborne droplets of fluid that are expelled when an actively infected person coughs, speaks, sneezes, spits, or laughs. These bacteria-filled droplets may be inhaled by another individual, eventually leading to infection if that person's immune system does not respond sufficiently.

**Progression**

Once inhaled, the bacterium that causes TB settles in the lungs for an incubation period that lasts approximately 4 to 12 weeks from exposure. During this period, inhaled infectious droplets lodge in the alveoli of the lungs, and the bacilli are taken up by the immune system (macrophages), thereby launching a cascade of events that results in either containment of the infection or progression to active disease.

In most patients, the natural immune response effectively walls off the bacteria in “tubercles,” rendering them inactive but not killing them. This is known as latent TB infection (LTBI), and the bacteria may lie dormant in the bloodstream for years. LTBI is not contagious and does not trigger any symptoms. In some cases, especially when the immune system is compromised, a latent infection may become active. Whether or not latent TB always persists throughout a person's lifespan remains undetermined, but the risk of reactivation is known to extend into old age.

When a person's immune system is incapable of suppressing replication, *M. tb* can grow anywhere in the body, leading to active TB. Although TB has high infection rates, many people who are exposed are able to contain the pathogen, and only approximately five percent of those infected develop active disease within five years of initial exposure.

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\(^3\) Relative risk is the ratio of the probability of developing disease among exposed to the probability of developing the disease among nonexposed. In this case, exposure is the presence of HIV infection.
**Symptoms**

The most common manifestation of active TB is pulmonary disease, for which common symptoms include a cough that produces blood-tinged sputum, fever, night sweats, and weight loss. However, in some cases the disease can spread to other parts of the body (e.g., the central nervous system), causing what is referred to as extrapulmonary, or disseminated, TB. Extrapulmonary, disseminated TB is more common among children and people who are immunosuppressed because of HIV or other factors.

Symptoms of active TB disease include:

- Persistent cough bringing up mucus from the lungs (sputum)
- Fatigue and weight loss
- Night sweats and fever
- Rapid heartbeat
- Swelling in the neck (when neck lymph nodes are infected).

Many of the symptoms of active TB resemble those produced by other diseases such as pneumonia and lung cancer, which can limit the likelihood that the patient will receive an accurate diagnosis during the first doctor visit.

**Interventions**

Current TB control efforts rely on three strategies:

- preventing initial infection;
- stopping progression from latent to active infection; and
- treating active disease.

**Prevention Mechanisms**

Global efforts to prevent the spread of TB rely heavily on the detection and treatment of active cases of disease. Overall attempts to address the conditions of poverty that amplify the spread of disease also are important. From an intervention standpoint, however, the only effective means of preventing TB disease is immunization with an effective vaccine, which has yet to be developed.

**Bacillus Calmette-Guérin (BCG) vaccine**: Although a number of vaccines are at various stages of development, the only current means of immunizing against TB is the BCG vaccine, a live-attenuated strain of *Mycobacterium bovis* that was developed in the early 1900s. BCG is inexpensive and considered to be highly effective against severe complications of the form of TB that is manifested in children, TB that affects the brain. However, the efficacy of the vaccine is incomplete, varies by location, and is universally low against adult pulmonary disease. Nevertheless, immunization of infants with BCG immediately after birth has been shown to be cost effective and is recommended by WHO as part of routine immunization schedules in areas of high TB incidence. BCG immunization is not recommended in areas of low incidence, such as the United States.
because the immune response it triggers causes a positive reading on diagnostics commonly used to track TB outbreaks.

BCG is among the most widely distributed vaccines in the world, with an estimated 100 million doses administered to children annually. Global coverage rates have increased significantly over the past 25 years, although coverage remains low in many parts of Africa.

**Diagnostics**

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<td>Clinical diagnosis</td>
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Due to emerging drug resistance and co-infection with HIV, early diagnosis of TB is essential for early disease control efforts. Several options are available for diagnosing TB, including microscopy, the tuberculin skin test, and several other laboratory tests. Clinical diagnosis based on symptoms also plays a critical role in many resource-limited countries.

**Tuberculin skin test:** The most common test for TB is the tuberculin skin test, the most frequent application of which is through the Mantoux test. To perform this test, a small amount of a fluid called PPD tuberculin is injected into the skin on a patient’s forearm. The injection site is checked 48 to 72 hours later for signs of swelling, development of a defined lump, and redness. The occurrence of these reactions indicates that the patient has been exposed to either the TB bacterium or has received the BCG vaccine at some point in their life. The size of the lump, together with a careful assessment of risk factors that may have led to contact with TB patients, provides information about the likelihood that the positive reactions are due to recent exposure to *M.tb*.

Although its use is common, many questions persist about the sensitivity of TB skin tests. The tests also often produce positive results in individuals who have been vaccinated with the BCG and exposure to other types of mycobacteria. Interferon gamma release assays (IGRAs) using blood are specific for *M.tb* and can differentiate between BCG vaccination and true *M.tb* infection in industrialized nations. This test currently is being evaluated for its utility in resource-limited countries with high rates of TB and co-infection with HIV, as well as in children where there is a critical need for accurate diagnosis of extrapulmonary TB.

Additionally, skin tests may produce false results in infected individuals who are immunosuppressed if their T-cell counts are too low. Diagnosticians may use a positive control test along with the tuberculin skin test in order to identify whether a negative result is occurring because of immunosuppression. To do this, the diagnostician administers a test for a type of infection that is widespread in the area alongside the tuberculin test. If the results of the control test are negative, it likely indicates that the patient’s immune system is not functioning properly.
Microscopy and culture: The standard laboratory diagnostic for TB is microscopy using a sputum smear from the patient. In patients with pulmonary TB, bacilli can be observed in samples of sputum extracted from the lungs through coughing. Typically, specific staining techniques are used to help identify TB bacteria. The sensitivity of microscopic techniques is further enhanced through the use of dyes to stain M.tb that are visualized with fluorescent instead of conventional light. Although low cost and simplicity make microscopy the preferred or sometimes the only form of testing for TB, sensitivity and specificity of M.tb diagnosis of this method remains quite low. Furthermore, microscopy is very labor intensive, requires trained staff, and is dependent on the availability of microscopes. Further, reliance on sputum smears severely limits the usefulness of microscopy in diagnosing TB in HIV-infected and otherwise immunosuppressed patients, who frequently do not present with pulmonary TB.

To improve the sensitivity and specificity of microscopic diagnosis, sputum may be added to a growth medium that encourages multiplication of the bacteria, increasing their number and making them easier to identify. Confirmation of bacterial growth on solid or in liquid culture medium is the gold standard for identifying live M.tb bacteria in human specimens. These culture-based methods are among the most sensitive available but remain out of reach in many TB endemic countries at the local level because of their price, long turnaround times, and requirements for a relatively sophisticated laboratory infrastructure. However, culture methods are frequently used in regional or country wide microbiological reference centers that serve hospital physicians for patient treatment, or serve to provide data for epidemiological studies.

Drug Sensitivity Testing (DST): Culture also may be used to determine if the strain of M.tb with which a patient is infected is drug resistant, which is particularly important to ensure that proper treatment is followed. To assess the sensitivity of the specific strain of M.tb with which an individual is infected, bacteria are added to control media and media that have been treated with various anti-TB drugs. Colonies of bacteria grow only on cultures treated with drugs to which the strain is resistant (Figure 5).

Molecular methods also may be used to assess strains of M.tb for sensitivity to treatment. These methods also rely on culture, after which genomic extracts are examined for mutations that are associated with drug resistance. However, this approach is expensive and requires better laboratory infrastructure than is commonly found in resource-limited settings.
Other tests: Several other laboratory tests also may be used for diagnosing TB, including nucleic acid-based amplification techniques such as polymerase chain reaction and the aforementioned blood-based IGRAs. However, these forms of diagnosis are limited primarily to use in developed countries due to cost and reliance on more sophisticated laboratory technologies.

Clinical diagnosis: Clinical examination of a TB patient is critical to determine the overall health of the individual and assess the stage of disease. Because pulmonary TB is the most common form, radiographs commonly are performed to confirm suspected TB. However, clinical diagnosis alone is not considered an effective method for confirming infection and determining the appropriate course of treatment for a patient thought to have TB.

TREATMENT

DOTS therapy: Under the DOTS treatment regimen, trained health personnel watch the patient swallow every daily dose of a four-drug cocktail consisting of isoniazid, rifampin, pyrazinamide, and ethambutol for two months, followed by another four months of treatment with isoniazid and rifampacin three times per week. Because the drugs used in DOTS all are over four decades old and can be produced generically, the strategy is quite inexpensive, with a six-month supply of drugs costing as little as $10 per patient.

DOTS therapy has been shown to be highly effective in some settings, demonstrating cure rates of more than 90 percent of patients treated, even in some developing countries. Further, by effectively curing infection and ensuring treatment compliance, DOTS can play an important role in preventing the spread of TB and reducing the risk of increased resistance to treatment in places where it is effective. Since it was developed and adopted in the early 1990s, DOTS has propagated considerable progress in global TB control.
Despite its successes, however, the limitations placed on program implementation by weak health systems and poor laboratory standards have kept DOTS from meeting its full potential. Case detection rates—which measure the first step in the DOTS programs and are essential to controlling the spread of infection—remain very low in many countries and globally (61 percent). Further, high treatment success rates are rare, and much lower rates can be found in many countries and regions. In 2006, the regional success rate for DOTS in new smear-positive patients in WHO’s Europe region was only 70 percent, while it was 75 percent in sub-Saharan Africa and the Americas. Cure rates may be even lower for patients who have relapsed after an earlier infection was cleared. In addition, DOTS programs focus on smear-positive cases of TB and frequently exclude patients who are least likely to respond to treatment, such as those with HIV co-infection and/or extrapulmonary TB.

In addition, the spread of drug-resistant (particularly MDR-and XDR) strains of *M. tb* threatens the success of treatment regimens that rely on the four first-line drugs.

**Treatment of MDR-and XDR-TB:** Patients infected with strains of *M. tb* that do not respond to the most effective drugs of the first- and second-line regimens for drug-sensitive and drug-resistant TB (i.e., MDR-TB and XDR-TB) are not treated effectively with the drugs provided through standard DOTS programs. Infection with drug-resistant strains of *M. tb* is much more challenging to clear. As a result, patients do not readily respond to treatment and are more likely to develop more advanced disease that often is fatal. Successful treatment is possible for MDR-and XDR-TB; however, the necessary clinical care, selection of the most appropriate regimen, and overall support of the patient requires resources frequently unavailable in TB-endemic countries.

Effective treatment of MDR-TB can take up to two years, including an intensive phase that involves at least four months of daily multi-drug cocktails, and sometimes requires surgery. Even with treatment, mortality rates from MDR-TB can be as high as 80 percent depending on factors such as how many drugs the strains are resistant to, side effects of the second-line drug regimens, treatment compliance, and the patient's HIV status. Treatment of XDR-TB is even more challenging and has even worse outcomes than treatment of MDR-TB.

**Treatment of LTBI:** Treatment of latent infection is offered to patients who have a positive tuberculin skin test, are at high risk for developing active TB, and, most importantly, have not demonstrated signs of active TB. Treatment regimens for LTBI range from four to nine months and may involve either isoniazid or rifampin. Nine months of treatment with isoniazid has been shown to be more than 90-percent effective at treating LTBI; however, this method is not widely disseminated outside of the United States. Rifampin is recommended for use only when a patient cannot tolerate isoniazid or has been exposed to an *M. tb* strain that is known to be isoniazid-resistant.

Although seemingly simple, daily preventive treatment has proved challenging from a public health perspective and LTBI is not widely treated. Compliance tends to be low, in part because otherwise healthy people are disinclined to take medications when they are asymptomatic. Given the high rates of HIV/*M. tb* co-infection, the public health community now has a reason to encourage wider adoption, particularly in sub-Saharan Africa. However, preventive treatment is considerably less effective in HIV co-infected patients, showing only 60-percent protection against progression to active TB for three years. After three years the protection level drops, and in population studies no
significant effect on mortality rates has been demonstrated. In addition, it is harder to identify potentially infected patients because the immune systems of HIV-positive individuals do not respond to tuberculin, rendering skin tests an ineffective tool.
Research

Overview
Recognition of the need for new drugs and vaccines has led to an influx of resources for TB research in the last several years. This increase in resources has allowed researchers to expand their efforts to better understand the disease and to develop new products to aid in global TB control efforts. Key areas of research include disease understanding, vaccines, diagnostics, treatment, and care delivery.

Global investment in TB research in 2007 was estimated to be around $410 million, with 60 percent coming from two funders: the U.S. National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (Gates Foundation). As of mid-2008, research was underway to test more than 20 new drugs (7 in clinical trials), at least 15 new vaccines (7 in clinical trials, and nearly 10 new diagnostics (2 in clinical trials).

Scientific Research
Table 2 summarizes the major areas of biomedical research in TB and areas where more investment is required to overcome challenges and accelerate research. The areas of current research and the challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for TB.

Table 2: Major Areas of Scientific Research and Challenges in TB

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<th>Current research focus</th>
<th>Challenges or areas requiring investment</th>
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<td>Disease Understanding</td>
<td>• Incomplete understanding of the natural history of human disease hinders all types of TB research</td>
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<td>• Incomplete understanding of the interpretability of data from various animal models</td>
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<td>• Lack of identified biomarkers limits efforts to improve diagnostics and contributes to a lengthy, expensive clinical trial process for other tools</td>
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<td>• Variation within and among strains of TB complicates research and limits the usefulness of animal models and other research tools</td>
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<td>Vaccines</td>
<td>• M.tb is very successful at evading the human immune system and the mechanisms for doing so are not well understood</td>
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<td>• Understanding the human immune response to M.tb</td>
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<td>• Developing improved vaccine candidates that rely on a variety of</td>
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| strategies, including both synthetic and live (weakened) mycobacteria and targeted antigens  
  • Devising post-exposure vaccines to clear latent and/or active infection  
  • Exploring alternate delivery approaches like nasal sprays | • Lack of immune correlates of protection makes the process of testing TB vaccines lengthy and expensive  
  • High levels of HIV co-infection raise safety concerns for testing and administering vaccines |

**Diagnostics**

- Improving the effectiveness of smear-based testing for TB  
- Making culture-based testing more efficient and accessible for low-resource settings  
- Developing diagnostic tools that could detect *M. tb* antigens or host-derived antibodies, particularly for use in rapid, point-of-care tests  
- Adapting highly sensitive molecular diagnostics for use in low-resource settings  
- Identifying better biomarkers for use in diagnostic tests and to advance clinical testing

- Reliance on sputum for testing excludes HIV co-infected patients  
- Dynamic range of infection types (LTBI, MDR, XDR, etc.) may require multiple diagnostic solutions  
- Limited laboratory capacity in endemic areas means new diagnostics either must be rapidly administered at the point-of-care or will require follow-up engagement with patients

**Treatment**

- Extending existing anti-infectives to anti-TB indications  
- Identifying and developing novel classes of anti-TB drugs  
- Improving treatment options for latent TB infection  
- Testing new regimens utilizing existing drugs that could shorten cure time  
- Understanding the relationship between drug exposure profiles and bacterial response (pharmacokinetics/pharmacodynamics)

- Rapid emergence of resistance requires specific strategies such as combination therapy and single-indication drugs must be explored  
- High co-infection rates require consideration of drug-drug interactions with common HIV drugs  
- Lack of early biomarkers for cure effectiveness lengthens trials  
- Existing regulatory frameworks impede testing drugs in combination  
- Incomplete understanding of the individual and population pharmacology of first- and second-line drugs, including their contribution to multi-drug regimens  
- Insufficient attention to development of pediatric formulations and regimens

**Care Delivery**

- Determining the best treatment regimen(s) for drug-resistant TB  
- Examining options for treating HIV co-infected patients  
- Considering the roles of the public and private sectors in delivering TB care

- Weakness of health and laboratory systems in many endemic countries limits patients’ access to treatment and other interventions  
- High HIV co-infection rates require more complicated treatment regimens and can introduce drug interaction issues  
- Need for development of community and patient centered approaches to treatment
Disease Understanding

Over a century after the discovery of M.tb, much remains unknown about basic questions such as how the bacterium interacts with its host and the role various host and pathogen genes play in establishing infection and TB disease. Unlocking the keys to major drivers of the continuing TB threat, particularly latency and drug resistance, is essential to the development of new tools to help control the disease. Further, understanding co-infections with epidemic diseases such as HIV/AIDS and diabetes requires additional research attention. In addition, it is not known with certainty whether variation among strains of M.tb alters host/pathogen interactions and to what extent any alterations, measured in animals, translate to human disease.

The following sections outline the major areas of ongoing research to improve understanding about these important factors.

Latency

Although the basic steps through which M.tb evades host immunity and establishes asymptomatic infection within animal hosts are known, many questions remain unanswered about the detailed molecular and immunological mechanisms underpinning this process. To increase knowledge in this area, researchers are working to identify the decision points within host-pathogen interaction that can lead either to long-term control within the body or to active infection. This includes efforts to understand the mechanisms that TB bacteria employ to avoid full elimination by the human immune system, resulting in the latent state. Another area of research looks at whether certain strains of M.tb, or even genetic variants within a given strain, are more or less likely to persist in a latent state rather than leading to progressive disease. The relationship between the location of M.tb bacteria within the human host and the likelihood that latency will occur also is being explored by researchers.

Additional research activities focus on characteristics (e.g. genetics, immunosuppression) within the human and animal hosts that may help determine whether after exposure to M.tb the host will clear the infection completely, banish it at least temporarily to latency, or develop active TB disease. Researchers also are working to understand the mechanisms and characteristics that result in progression from latency to active disease.

Additionally, work is being done to develop better in vitro and in vivo models for latent TB infection.

Progression to Active Disease

Bacterial replication precedes the development of active TB disease from latent, asymptomatic infection. However it is not known which bacterial versus host factors are important and critical to initiate this transition. Research into the key mechanisms and host/pathogen markers involved in progression to active disease will provide insight and access to biomarkers that should allow development of diagnostic tests that identify persons at highest risk of developing active disease.

Drug Resistance

Given the spread of MDR-TB and XDR-TB and their interference with global efforts to control the disease, significant attention is being paid to the basic science behind the development and also avoidance of drug resistance in TB. Some efforts are focused on identifying the genetic and
physiological traits of *M. tb* that lead to drug resistance and determining how those changes occur. This includes work to identify and catalogue specific genetic mutations that are tied to resistance to one or more existing TB drug(s), which may help in both diagnosis and the development of new treatments. Some findings also suggest that certain genetic mutations may make further mutations more likely, hastening the progression to MDR and XDR.

**Transmission Dynamics**

Researchers also are working to track the spread of individual strains of *M. tb* to better understand the factors that affect transmission of the bacteria, including whether drug-resistant strains are more communicable and virulent than other strains. Transmission patterns and the factors that affect them, such as poverty and the presence of migrant populations, also are of particular interest for efforts to control the spread of drug-resistant strains of *M. tb*.

**Risk Factors**

Understanding the individual risk factors that predispose individuals to developing active TB can help with disease control and management. The link between TB and HIV/AIDS, which suppresses the immune system and therefore vastly increases the risk of latent TB progressing to active disease, continues to be the focus of research efforts. In addition, the less understood connection that ties both type I and type II diabetes to increased incidence of active TB disease and extended cure times is garnering increased attention as researchers attempt to explain the causes of these increases. Looking beyond diabetes, significant research has tied other nutritional disorders, including malnourishment and obesity, to increased risk of contracting and dying from active TB disease, as well as spreading it to others. Diabetes and nutrition-related factors are becoming even more important as the obesity epidemic spreads in the developing world.

Additional research on a broad range of potential risk factors has shown that age, gender, smoking, and alcoholism all play a role in the progression of TB infection, with gender and age being the most important factors.

**Genomics**

The complete genome sequence for *M. tb* was published in 1998, providing an important tool for understanding the physiology of the pathogen and the role of bacterial components during infection and disease. Large, coordinated international efforts are underway to determine and analyze the molecular structures of key *M. tb* proteins to assist in rational drug design and allow characterization of important biological and enzymatic processes. Additionally, through mutation and functional elimination of key genes in *M. tb*, researchers are examining the role that various genes play in the establishment and maintenance of infection, evasion of the immune system, progression to active disease, and development of drug resistance, among others. Identification of key players that mediate these processes and availability of their molecular structures is an important tool for the identification of new targets for drugs and vaccines.

**Vaccines**

Despite the availability of the BCG vaccine to confer limited protection against complications from disseminated TB in children, the search continues for a more effective vaccine that prevents adult pulmonary disease. Most TB vaccine research focuses on a “prime-boost” approach that uses an
initial “prime” vaccine—currently BCG—to generate an initial immune response and a different “boost” vaccine to strengthen and extend that response. Additional, early-stage efforts are underway to develop therapeutic vaccines that could be given to individuals who already have TB to prevent disease progression or improve prospects for successful treatment.

Although progress has been made in TB vaccine development in recent years, significant obstacles continue to hinder efforts to develop a new, more potent TB vaccine. TB has evolved to be one of the world’s most successful pathogens, capable of evading the human immune system and mutating to resist chemical intervention. Further, there is no naturally acquired immunity to TB, meaning that individuals who have cleared a TB infection successfully do not develop any resistance to future infection. Efforts to develop a vaccine capable of stimulating an immune response that effectively prevents the bacteria from taking hold are hindered by a continued lack of understanding about the interaction between the pathogen and the human immune system. Incomplete comprehension of what constitutes natural protective immunity limits researchers’ ability to determine whether a new vaccine effectively elicits a comparable immune response. Improving knowledge in this area could help to target research efforts more effectively and to identify immune correlates of protection that could shorten the duration of clinical trials, which currently are lengthy and expensive.

An additional challenge with which vaccine researchers must contend is the question of how to evaluate vaccine candidates in HIV-infected individuals. Given their increased susceptibility to TB disease, patients with HIV are a priority group for prevention interventions. However, because these patients already have weak immune systems, there are significant safety concerns associated with testing the safety and efficacy of vaccine candidates in this population. Furthermore, persons with suppressed immune systems are more at risk for developing infections with live vaccine candidates. Approaches to create better vaccines using live mycobacteria must assure that these vaccines can no longer multiply in human hosts and therefore cannot establish infections in these patients.

Further limitations are imposed by the lack of an accurate animal model for earlier-stage testing of vaccine candidates. Although various animal models are employed by vaccine researchers, none of them accurately mimic the human immune response. As a result, preclinical testing in animals is a suboptimal predictor of whether a vaccine will work in humans.

The following sections outline the major areas of ongoing vaccine research.

*Understanding Protective Immunity*

Better understanding of how *M. tb* behaves inside the human host and how the human immune system responds to the bacterium is central to efforts to develop new and better vaccines.

Researchers are exploring the varying immune responses to *M. tb* infection and the factors that lead to them. The majority of individuals infected with *M. tb* have an immune reaction that is able to contain the bacterium in pockets of immune cells called granulomas but not to banish it completely. A small number of individuals are able to completely defeat the pathogen, while others, frequently those who are immunocompromised, immediately succumb to active disease. Understanding the various factors that determine the outcome of host-pathogen interactions is important for the design of tools to stimulate protective immunity. Key areas of exploration include the pathways for
presentation of mycobacterial antigens (including lipids), T-cell activation and recruitment at the site of infection, the role of nutrients in disease development and bacterial growth, and techniques that *M. tb* employs to evade the immune system.

In addition to its obvious role in advancing vaccine research, better understanding of the immunology of TB may be useful for determining new biomarkers for use in diagnostics and in assays used for clinical testing to determine the efficacy of candidate drugs and vaccines.

**Preventive Vaccines**

One approach to developing a new TB vaccine is to enhance the effectiveness of BCG by creating **genetically manipulated strains of BCG (rBCG)** that express more potent antigens. Scientists have tested three approaches to developing rBCG: (1) restoring genes that had previously been deleted when *M. bovis* was attenuated in culture to produce BCG; (2) creating strains that over express potent *M. tb* antigens; and (3) creating strains that express host immune molecules that could enhance how the host immune system responds to BCG. Research on an rBCG-based vaccine designed for HIV-positive individuals has found that it produces promising immune responses and is safe even in animals with severely compromised immune systems. Modified BCG vaccines currently are being explored both as possible boosters for an initial BCG vaccination and as primes in combination with other novel vaccines.

Researchers also are exploring other **attenuated mycobacterium vaccines**, which are created by weakening live bacteria to the point that they can no longer produce infection while leaving intact their ability to stimulate antibody response. One such candidate, based on a non-TB mycobacterium called *M. vaccae*, has been in development for a long time and has just undergone Phase 3 testing 2008 in HIV-infected persons. This candidate has shown promise as a booster to BCG in HIV-positive patients; however, these results need to be repeated since they were limited to a subset of HIV. Vaccine researchers also are exploring the idea that using an inactivated version of *M. tb* could confer better protection than non-TB mycobacteria because these do not express the full set of *M. tb* antigens. This approach has produced promising results that lay the foundation for additional studies and vaccine designs.

Vaccines that contain purified antigens from *M. tb* rather than using inactivated or live intact bacteria also are the subject of TB vaccine research. Newer research on these **subunit vaccines** is looking at using recombinant, or synthetic, subunits. A variety of antigens is under exploration for use in subunit TB vaccines, and all rely on boosting initial BCG vaccination. Some of the most promising approaches in this category rely on combinations of antigens fused together into one vaccine, and several candidates currently are being evaluated in clinical trials. Another area of subunit vaccine research that is being conducted, although without much success to date, is focused on using synthetic DNA to deliver the genetic code for production of immunogenic proteins by the host. Limitations in the availability of adjuvants to amplify the immune response to subunit vaccines present a challenge, and more research is needed to develop and test more effective adjuvant options.
Another strategy being tested is the use of live viral vectors \(^4\) engineered to encode genes for TB antigens that are produced when the virus multiplies and could stimulate an immune response. One such vaccine that uses a modified vaccinia virus (similar to the virus used for the smallpox vaccine) is now in Phase 2 clinical trials as a booster vaccine to BCG and continues to show promising results. Similarly, a candidate vaccine using an adenovirus as the carrier for the genetic material for a fusion of three \(M.tb\) proteins is being studied in Phase 2 clinical trials for eventual use as a booster vaccine for either BCG or rBCG.

Taken together, the availability, for the first time since the development of BCG, of vaccine candidates of sufficient quality and safety to be evaluated in human volunteers has demonstrated that product development in TB is feasible and that fundamental science has provided critical knowledge to be translated into new health care interventions. Furthermore, these clinical trials have paved the way for researchers to understand how best to develop protocols for TB vaccine testing in humans and have demonstrated that sufficient expertise and knowledge has been acquired to develop clinical trial sites that can indeed perform high-quality, licensure-type trials.

**Therapeutic Vaccines**

Researchers also are exploring the possibility of developing vaccines that could be administered after exposure to \(M.tb\) has occurred, either to enhance immune response against active disease or to clear LTBI. Based on studies conducted during the early 1900s, there continues to be concern about potential adverse events after vaccinating persons who already have been exposed to \(M.tb\). However, there is no clinical or solid animal model evidence to indicate that post-exposure vaccines are not feasible and, as a result, early stage safety studies are being conducted. Researchers continue to believe that a post-exposure strategy holds promise for clearing LTBI and possibly lowering bacterial load in patients with active TB who also receive drug therapy. Current research for a therapeutic vaccine is in its very early stages, currently focusing on identifying antigens that are expressed when \(M.tb\) has established active disease and is targeted actively by the immune system.

**Vaccine Delivery**

The first entrance of \(M.tb\) into the body is usually through the respiratory tract and the lungs, making mucosal surfaces the first barriers the pathogen encounters. Researchers are exploring whether stronger or more effective immune responses can be elicited if a vaccine is given either intranasally or orally. Several studies in mice have found that intranasal delivery of subunit vaccines could be the best way to stimulate a strong pulmonary immune response, and that it would be more effective at boosting a BCG vaccination than a vaccine that is injected. However, there are safety concerns associated with mucosal delivery of vaccines, particularly those that employ live viruses, and researchers are working to overcome these.

**Diagnostics**

Diagnostics are considered to be at the heart of the fight against TB, and significant efforts are underway to develop new products or approaches that are rapid, cheap, sensitive, robust, and easy

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\(^4\) The term vector refers to a living organism that does not cause disease (typically because it has been weakened) but can spread pathogens in the human body in order to stimulate an immune response.
to use. Many of the diagnostic tests that currently are under development are designed to identify drug-resistant strains of *M. tb* rapidly so that MDR-TB and XDR-TB patients can receive appropriate therapy at the time of initial diagnosis. Other diagnostics are being developed to supersede the tuberculin skin test by differentiating between exposure to *M. tb* and BCG vaccination. Given that TB can present with diffuse clinical symptoms also associated with other diseases, it is critical to identify, or rule out, *M. tb* infection and provide appropriate therapy.

Diagnostics under development span a wide range of approaches that include identification of immune markers that indicate *M. tb* infection or TB disease, measuring host antibodies that are specific to the TB pathogen, identifying genetic material from *M. tb* in human secretions or blood, and probing the immune system of the host to see whether it has encountered the pathogen. Most importantly, though, the diagnostic technology platforms that are being brought to bear on TB span all levels of sophistication, as the ultimate goal is to develop and roll out a point-of-care (POC) diagnostic test that can rapidly identify TB even in the most rural, resource-constrained areas of the world. There is no one approach to TB diagnosis that is appropriate for all settings and all care programs, and it has been accepted that multiple approaches must be developed in parallel.

In most TB-endemic areas, patients have severely limited access to even the most basic health services, let alone laboratories equipped with the technologies that currently are available to detect most known biological indicators of TB infection with any accuracy. TB diagnosis frequently relies on the assessment of the physician and on smear microscopy with rudimentary microscopes. Ideal diagnostics would cost very little and be able to deliver accurate results while the patient is still in the doctor’s office, while requiring only low levels of technology and skill to administer. Balancing the need for accuracy with the cost and technological infrastructure needed for current sophisticated tests presents a significant challenge for researchers looking to develop tools that will be useful in the ongoing fight against TB.

Further complications for researchers stem from the wide range of presentations of TB and the human specimens needed to use current diagnostics. For example, tests that rely on unprocessed sputum samples are considerably less accurate for patients with HIV co-infection, who tend to have much lower levels of bacteria in their respiratory secretions. Latent TB infection also cannot be detected in sputum since the patients do not display lung disease. Further, handling of sputum for diagnostic processing may expose workers to the pathogen and requires at a minimum basic biosafety considerations.

Beyond reliably identifying the presence of *M. tb* in human specimens, the increase of MDR-TB and XDR-TB also requires further characterization of the pathogen to rapidly assess whether drug-resistant genes are present. This added need greatly complicates diagnostic development, creating additional difficulty for efforts to develop tests that are applicable to resource-constrained settings.

The following sections outline the major areas of ongoing research on TB diagnostics.

**Sputum-smear Testing**

Several efforts are underway to improve on existing sputum smear microscopy practices, particularly by making the detection of stained bacteria more sensitive. The use of a fluorescent microscope can lead to at 10-percent increase in the sensitivity of sputum microscopy and can cut laboratory time required, although this technique may not be viable in low-resource settings.
because of the cost and requirements for reliable electrical power and functioning fluorescent light bulbs. Other research has shown that ultra-bright light-emitting diodes (LEDs), which are inexpensive, robust, long-lasting, and require only low levels of electrical power, generate equal results to fluorescent microscopy using a mercury vapor lamp.

Beyond improving the technology used to examine sputum samples, researchers also are looking at ways to increase the concentration of bacteria in sputum either as it is produced by the patient or prior to microscopic observation. Some studies have show that the use of nasal saline spray prior to producing a sputum samples significantly increases the number of bacteria present in both HIV and non-HIV patients. Other research focuses on techniques to treat and concentrate the sputum before examination through the microscope. These techniques include processing samples in a centrifuge, letting them sit for a period of time to allow particles to sediment, or processing them through filters.

**Culture-based Methods**

Researchers also are working to develop new diagnostics that improve on culture-based diagnostic methods and make them more feasible for use in poor countries or at the local level. Large-scale studies have focused on determining the feasibility and cost-effectiveness of introducing automated liquid culture systems, which produce results faster than solid culture, into resource limited countries. While more error-prone and susceptible to contamination through laboratory error, liquid culture tests have been shown to have 90 percent accuracy in detecting TB and also are suitable for identifying drug-resistant strains.

A variation of a cheap and readily available diagnostic approach combines small-scale liquid culture with microscopy. Sputum is inoculated directly into culture wells containing bacterial growth medium, and growth is checked daily with a microscope. Since M.tb grows in very characteristic elongated clumps at a slow rate, the bacterium is relatively easy to differentiate from other bacteria. This easy and quite accurate test is now being evaluated for detection of drug resistance by growing sputum samples in media with or without added antibiotics.

Another fast, cheap, and reliable approach that is being explored is the use of a dye that changes color to indicate growth of M.tb and has good sensitivity for detection of drug resistance.

A more sophisticated but highly specific approach to identifying M.tb in specimens is the use of engineered bacterial viruses that will only infect M.tb. These viruses (bacteriophages) carry a gene that emits bioluminescent light only when the phages multiply within mycobacteria, thus indicating the presence of the TB pathogen.

**Antigen and Antibody Detection**

Another approach under exploration is diagnostics that could detect the presence of M.tb antigens or antibodies in fluids other than sputum, including blood, spinal fluid, and urine. Such tests could be used to detect disseminated TB, which is more common among HIV co-infected patients and children. In addition, tools could be developed that require less reliance on laboratory facilities and shorter turnaround times, making them more feasible for use at the POC in low-resource settings. Another important application for these tests may be in diagnosing latent TB infection before it develops into active, transmissible disease.
Detection of host antibodies against mycobacterial antigens in blood is the focus of significant efforts, and several serological diagnostics already have found application in veterinary medicine, giving good proof of principle for the detection of TB. To differentiate between exposure to \( M.tb \) and exposure to other mycobacteria, blood tests have been developed that probe human immune cells and determine whether they have encountered the TB pathogen. These tests are specific for \( M.tb \) and are being tested for use in resource-limited countries, in persons with HIV co-infection, in small children, and in patients with other illnesses. These are available in the United States and in Western countries and are becoming standard of care in many settings. If developed successfully, these tests could replace the tuberculin skin test, which is less effective in countries where BCG vaccination and/or exposure to non-TB mycobacteria are common.

**Molecular Diagnostics**

The first set of new molecular diagnostics developed and tested for TB have been nucleic acid-based amplification tests (NAATs), which continue to present a platform that is constantly improved and adapted even to low-resource settings. NAATs can be used either to detect bacterial or host markers directly from sputum or to assess bacteria grown in culture media. The advantage of these tests is their high sensitivity and fast turnaround time. However, they also are technically demanding, require a constant supply of very high quality reagents, and can only be performed reliably by trained personnel. Several of these methods identify \( M.tb \) and the presence of drug resistance markers in one test.

The latest NAAT technology uses a fully automated system for sputum processing, nucleic acid amplification, and readout. This system dramatically shortens time to diagnosis, reduces exposure to pathogenic bacteria, and requires minimal operator training. However, this test platform is dependent on reliable electrical supply and access to many disposable reagents and is currently only suitable for more advanced laboratories.

**Biomarker Identification**

Significant research efforts are targeting discovery of effective and practical biomarkers that are needed to guide new products for prevention, diagnosis, and treatment of TB. Although effective biomarkers for use in diagnosing active TB infection exist, they tend not to be viable for POC testing in low-resource settings. As a result, researchers are working to identify biomarkers that can be used to detect \( M.tb \) infection with better sensitivity and specificity, even where high-technology laboratory tools are unavailable. Potential biomarkers could be antigens from the bacterium or markers generated by an infected person’s immune system. Research investigating the \( M.tb \) proteome for potential biomarker has concluded that about 100 of the 3,500 proteins that make up \( M.tb \) are worth investigating for potential diagnostic value.

Further, volatile organic compounds in the breath have been identified as potential biomarkers for TB, and devices are being developed to exploit breath testing. One promising test is portable, processes a sample in five seconds, costs only \$1 per test for reagents, and has demonstrated a specificity of almost 90 percent.

Biomarkers to indicate response to TB therapy or favorable immune responses after vaccination also are the focus of intense academic research. Early indicators of treatment or vaccine response
that can be validated to correlate with clinical cure or protective immunity would dramatically shorten the time needed for clinical trials.

**Treatment**

To improve the current treatment regimen and counter the development of drug resistance, the research community has identified several important objectives. Given the complication and duration of current treatment regimens, one of the most important goals in TB treatment research is to arrive at drug regimens that are well tolerated, use a minimum of pills, and can be completed in a short time. Ideal regimens also would be compatible with antiretroviral therapy (ART) so that the two therapies could be administered concurrently to patients who are co-infected with HIV/AIDS. Further, if a cadre of new antibiotics can be developed for TB that have mechanisms of action different from the currently used drugs, these interventions are expected to be effective against MDR/XDR and drug-sensitive TB alike.

Efforts to develop new TB drug regimens are slowed by the need to identify and test individual agents separately before they can be combined into new regimens or used to replace currently used drugs. This implies the need to develop a stronger understanding of the way that current TB drugs, as well as new chemicals in development, interact with one another to arrive at the most potent combination that offers the lowest chance for the pathogen to develop resistance. An additional complication stems from the fact that in many cases TB drugs will be administered alongside ART cocktails used on HIV patients, requiring additional understanding of the interaction of ART drugs and anti-TB drugs.

An additional challenge in the creation of combination therapies is that current regulatory frameworks are not comfortable with developing combination therapies starting at Phase 1 trials. Instead, regulators prefer advanced clinical testing for safety of individual agents before they are combined into new regimens, considerably extending the length of trials.

The main factor that drives the lengthy trial process is the lack of accurate biomarkers for use in estimating treatment effectiveness early in the trial. The currently accepted measure for drug efficacy is the absence of disease relapse up to two years after termination of treatment. This makes clinical testing long and expensive and underscores the need to identify early correlates of non-relapsing cure that can be measured after several months of treatment. Not only will these markers aid in the shortening of time for clinical trials, but they also will be an invaluable tool for clinicians to assure their patients received appropriate and effective therapy. Given the imperative to bring new anti-TB drugs to market, in June 2009, the U.S. Food and Drug Administration (FDA) took initial steps towards adopting an unvalidated surrogate trial endpoint that relies on sputum cultures that produce no bacterial growth. Although this is seen as progress, significant concerns remain about this step and the need for additional investment in research to identify and validate surrogate endpoints persists.

The following sections outline the major areas of ongoing R&D relating to new drugs for use in treating TB.
**Existing Drug Classes**

Several studies are ongoing to determine the efficacy of and gain approval for the use of existing antibiotics to shorten cure time and improve treatment of MDR-TB.

**Fluoroquinolones** are broad-spectrum antibiotics that are commonly prescribed for treatment of respiratory infections, intra-abdominal problems, and eye infections. Drugs in this class act at the level of DNA and make it impossible for bacteria to replicate. Two such drugs are in late-stage clinical development (Phase 3) and show evidence of shortening cure time, while a third has shown potential for the treatment of MDR-TB because of its ability to prevent the initiation of protein synthesis. Drawbacks to fluoroquinolones include a high-level of already existing resistance in some countries where they are widely prescribed for other conditions, as well as side effects that make them unsuitable to be used in treatment of children.

**Nitroimidazoles** are a class of antibiotics that poisons bacterial cell wall and protein synthesis and currently are marketed for treatment of both bacterial and protozoal disease. Existing drugs in this class have demonstrated effective killing of non-replicating *M. tb* when used in combination with rifampin. Additionally, two new nitroimidazoles are being tested against *M. tb* in Phase 2 trials and have shown very promising results.

Researchers also are exploring existing drugs that could be used as second-line treatments for MDR-TB. Linezolid is a relatively new antibiotic that acts by preventing the initiation of protein synthesis that currently is on the market for other bacterial infections. This compound also is the subject of intense clinical testing as a potential treatment for drug resistant TB.

**Novel Compounds**

In the short-term, drugs that already have been shown to be safe and effective against other bacterial infections offer the best hope for delivering new cures. However, antibiotics that are employed against multiple types of infection tend to develop resistance more rapidly, making them less useful in the long run. The development of completely novel compounds with unique mechanisms of action is therefore essential for long-term control of TB.

To date, only a few novel compounds have advanced beyond early-stage research, with only one in Phase 2 trials. Other classes of drugs with unique properties and modes of action are evaluated in animal studies and in early-stage human trials. Many of these new therapies target synthesis of the cell wall, transcription, or energy metabolism, while others are acting as protease inhibitors and RNA polymerase inhibitors. Screening efforts for new leads are employing both whole-cell and target-based approaches, and are tightly integrated with genomic, proteomic, structural biology, and bioinformatics approaches to continuously increase the number of potential drugs targets and innovative approaches to new TB drug development.

It is notable that efforts to shorten the duration of treatment required to clear *M.tb* infection completely are severely impeded by the bacterium’s ability to persist in a dormant state. While the lion’s share of bacteria are cleared in the first few days of treatment, a small share are able to achieve a non-replicating state that makes them unsusceptible to most standard antibiotics, which typically rely on mechanisms of action that target replication. Killing these “persisters” requires approaches that target the host-pathogen interactions that lead to dormancy in the first place.
Better understanding of these interactions is therefore crucial for the discovery of novel compounds to treat TB.

**LTBI Preventive Therapies**

Numerous studies are underway examining treatment regimens designed to clear latent TB infections and prevent development of active TB, particularly in areas with large numbers of HIV-infected patients. Researchers are evaluating whether isoniazid preventive therapy (IPT) contributes to the reduction of new cases of TB and whether different IPT regimens (i.e., continual vs. time-limited) provide more favorable results. Other studies are looking at options for shortening the duration of preventive therapy regimens, particularly those that combine isoniazid with other first-line TB drugs like ethambutol, pyrazinamide, and rifapentine.

**New Treatment Regimens**

Researchers are examining new treatment regimens that rely on existing first-line drugs, both to shorten cure time and to better treat HIV-infected patients. Approaches to shortening cure time include replacing rifampin with high-dose rifapentine during the first intensive phase of treatment, as well as shortening the second phase of treatment from four to two months in patients with less advanced forms of disease. Research to better understand the pharmacokinetics and pharmacodynamics of the existing drugs will help guide efforts to optimize and retool current treatment regimens, as it contributes to understanding the contribution of individual drugs to a regimen and evaluates whether efficacious drug levels actually are achieved in all patients.

**Care Delivery**

Despite the success of the DOTS strategy in many areas, researchers continue to explore the best ways to deliver TB care, particularly to vulnerable populations. Considerable research focuses on the problems associated with caring for patients with drug-resistant strains of *M. tb*, as well as those who are co-infected with HIV. Other research efforts in this category focus on engaging the private sector in delivery of TB care.

TB-endemic countries often lack adequate health system infrastructure, which reduces access to both clinics and laboratory facilities where diagnosis and disease treatment can be overseen by a qualified professional. For new vaccines, diagnostics, and treatments to be effective, capable technicians and equipment are needed to ensure their proper use. Further, weak health systems frequently lack the capacity to coordinate multi-intervention efforts, which are key to successfully controlling TB and managing co-infections. In particular, addressing the epidemic of TB-HIV co-infection requires a strong system capable of handling complicated treatment regimens and the potential for drug interactions or environmental factors than may endanger patient health.

The following sections outline the major areas of ongoing research on the delivery of TB care.

**Drug-resistant TB**

Determining the best treatment to combat drug resistant TB has been a question of great interest in the TB community since the emergence of the MDR and XDR strains. Research on treatment of drug-resistant TB often focuses on the **best combination and dosages of existing second-line drugs**. One such study conducted in South Korea found that treatment with at least four drugs that
were identified through DST and used in combination led to improved outcomes for patients. Further, the study found that surgery could improve the prognosis for patients with advanced disease. A Peruvian study on the treatment of MDR-TB and XDR-TB also found that a combination of five drugs was most effective, and that some cases required surgery. The study also found higher treatment success than others of its kind, while the number of patients completing treatment was the same (about 60 percent) for MDR-TB and XDR-TB. Work has been done to develop standardized treatment regimens, particularly for use in resource-poor settings; however, these strategies may not be effective against XDR-TB and can accelerate the spread of resistance.

Other research on the treatment of drug-resistant TB has looked at the issue of cost effectiveness. MDR-TB and XDR-TB both cost significantly more to treat than drug-sensitive TB due to longer treatment times, more expensive drugs, and the need to manage frequent side effects. Recent studies from Peru and the Philippines have concluded that treatment of MDR-TB is feasible and cost effective in low-income settings, although these studies do have limitations.

**HIV Co-infection**

Patients who are co-infected with *M.tb* and HIV have demonstrated a significantly increased risk of disease relapse after completion of therapy, as well as higher rates of acquired drug-resistance when compared to HIV-negative patients. As a result, researchers are exploring treatment delivery options that could limit the risk of resistance. Some research indicates that a longer course of treatment than the standard six months may be needed to avoid relapse and resistance in HIV co-infected patients. Studies on the impact of ART on the development of drug-resistant TB also suggest that treatment with ART in co-infected patients improved survival rates and may help reduce the development of resistant forms of TB. This research suggests that integrated TB and HIV treatment programs would both improve outcomes and limit resistance. Further efforts to test this in low-resource settings have found that doing so can be feasible and effective.

**Public-private Mix**

Issues relating to the quality, efficiency, and availability of public sector health care in low-resource countries and regions have led to a movement toward increasing the role of the private sector in the delivery of health care. Researchers have been working to assess the feasibility and effectiveness of engagement of the private sector in the delivery of TB treatment. A study conducted in Indonesia on public-private collaboration for TB control concluded that this collaboration is essential for addressing the population’s TB treatment needs effectively. Results from two studies in South Africa show that public-private collaboration can lower the cost and increase the effectiveness of TB treatment. Researchers in Kenya also found that the private sector can be engaged to treat both TB and TB-HIV effectively if given the proper tools and training. Another study on private sector attitudes toward cooperation with the public sector on TB treatment delivery found that in one district in India, the private sector was willing to engage but the public sector had not done enough to reach out.
Research Infrastructure

Table 3 summarizes major research tools available for TB. It also outlines major remaining gaps and challenges, as well as investment opportunities to address these challenges. These resources and challenges are explained in more depth in the sections that follow.

Table 3: Major Research Tools and Resources for TB and Challenges

<table>
<thead>
<tr>
<th>Existing tools and efforts</th>
<th>Challenges or areas requiring investment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biospecimens and databases</strong></td>
<td></td>
</tr>
<tr>
<td>• The National Institute of Allergy and Infectious Diseases (NIAID) contracts to provide free mycobacterial-derived research reagents and genomic/proteomic tools and technologies</td>
<td>• Lack of an easily accessible common stock of virulent strains of <em>M. tb</em> requiring major research</td>
</tr>
<tr>
<td>• UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases TB Specimen Bank</td>
<td>• Coordinated systems, biology approaches, and standardized protocols to populate databases</td>
</tr>
<tr>
<td>• Several major databases containing data and tools relating to the TB genome</td>
<td>• No repository for human clinical samples available to help validate new diagnostics and develop biomarkers</td>
</tr>
<tr>
<td></td>
<td>• Need for a shared database for drug development</td>
</tr>
<tr>
<td><strong>Research capacity</strong></td>
<td></td>
</tr>
<tr>
<td>• Significant capacity in select high-burden countries</td>
<td>• Limited laboratory capacity to handle biosafety requirements, even in developed countries</td>
</tr>
<tr>
<td>• Regional initiatives (Tuberculosis Vaccine Site Network, Central Africa Network on Tuberculosis, HIV/AIDS, and Malaria) to develop clinical trial sites, particularly in Africa</td>
<td>• Network funders drive agenda, leaving few opportunities outside of major initiatives</td>
</tr>
<tr>
<td>• Research capacity in endemic countries, though not necessarily TB focused</td>
<td>• Infrastructure not aligned with critical populations (e.g., HIV+, MDR/XDR,..)</td>
</tr>
<tr>
<td></td>
<td>• Lack of postdoctoral training opportunities for scientists in or from endemic countries</td>
</tr>
<tr>
<td></td>
<td>• Need for sustained investment in intellectual and physical infrastructure</td>
</tr>
<tr>
<td></td>
<td>• Current infrastructure disease-specific and not shared to facilitate co-infection research</td>
</tr>
<tr>
<td><strong>Animal models</strong></td>
<td></td>
</tr>
<tr>
<td>• Mouse models for single and combination drug testing</td>
<td>• Failure of existing animal models to reproduce human disease progression and immune response</td>
</tr>
<tr>
<td>• Guinea pig model for drug testing</td>
<td>• Lack of comparative animals models studies to appreciate the contribution of each model to TB research</td>
</tr>
<tr>
<td>• Vaccine testing in mice, guinea pigs, rabbits, cattle, and non-human primates (e.g., macaques)</td>
<td>• Lack of appreciation of matching human drug exposure profiles to animal models</td>
</tr>
<tr>
<td>• NIAID contract to provide free animal models for testing of vaccines, drugs, and mutant <em>M. tb</em> strains</td>
<td></td>
</tr>
<tr>
<td>• Special animal models to evaluate the biological activity of mutant <em>M. tb</em> strains</td>
<td></td>
</tr>
</tbody>
</table>
Existing tools and efforts | Challenges or areas requiring investment
--- | ---
**Data standards** | • Difficulties in comparing experiment results due to proliferation of multiple testing models, limited availability, and lack of standard procedures
• Lack of consensus around what data standards should be
• Need for coordinated and standardized protocols for testing of vaccine and drug candidates
- TB Trials Network efforts to standardize data elements for use in TB-related clinical trials worldwide
- WHO efforts to define TB case reporting standards for disease surveillance
**Collaboration** | • Dispersed research community needs more mechanisms to facilitate communication and collaboration
- Consortia designed to facilitate research cooperation around key questions or concerns (e.g., biomarkers)
- Various platforms for sharing results and collaborating on genomic research and target identification

Research infrastructure continues to strengthen worldwide, with several networks being created to perform clinical and laboratory work and enhance research knowledge. Support is provided from several governmental groups, nonprofit organizations, and university collaborations.

**Biospecimens and Databases**

Data and banks of research reagents provide important tools for standardization of research to produce comparable results. The TB community has developed a number of such resources in the past several years, providing access to biospecimens and genomic data. One significant remaining gap, however, is the lack of a common stock of virulent strains of *M.tb* that would be easily accessible to all researchers.

Through the NIAID, the U.S. government has established contracts designed to provide TB researchers with access to research materials and reagents for use in developing new products. Contracts are available to provide, free of charge, bacterial cells and sub-cellular fractions, native proteins, recombinant plasmids, lipids and carbohydrates, genomic DNA, antibodies, genomic arrays, transposon mutants, and tetramers. NIAID also supports large contracts for all aspects of “-omics” research and to support bioinformatics. To analyze the biological function of gene products in *M.tb*, animal models are offered under contract to test the behaviors of mutant *M.tb* strains in mice and rabbits. However, the process for qualifying for access may be daunting for scientists, particularly in endemic countries.

In addition to the NIAID-sponsored specimen repositories, the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases maintains a specimen bank that contains samples of sputum, serum, saliva, and urine from symptomatic TB and non-TB respiratory patients from around the world. The samples are intended for use in developing new diagnostic tools, and are associated with clinical, microbiological, and diagnostic information. Researchers who wish to use specimen from the bank can order lots of 20 or 200 samples, for which they pay only shipping and handling. The balance of samples between TB-positive and -negative and HIV-positive and -negative is determined by the size of the batch.
Efforts aimed at mapping the genome sequences for *M.tb* have expanded the knowledge base for researchers at the basic and translational levels of inquiry. Several electronic databases provide researchers access to these genome maps and the research and analysis they have supported. These databases include:

- TuberculList, hosted by the Ecole Polytechnique Fédérale de Lausanne, contains a complete dataset of DNA and protein sequences from the paradigm H37Rv strain of *M.tb*, linked to the relevant annotations and functional assignments;
- Stanford University’s TB Database (TBDB) contains annotated genome sequence data, microarray and reverse transcriptase PCR expression data, and access to a variety of analytical tools;
- The TB Drug Resistance Mutation Database (TBDReaMDB), supported by the Ellison Medical Foundation, contains data on the genetic mutations to *M.tb* that are associated with drug resistance, which are expected to be useful in diagnostic development and drug discovery efforts;
- The TB Structural Genomics Consortium’s WebTB site contains genome sequence data, protein structures, target analyses, and access to a variety of analytical tools; and
- The NIAID-supported Biodefense and Public Health Database (BioHealthBase) contains genome sequence, functional genomic and related data.

Despite the availability of a wide array of molecular tools and databases, insufficient attention has been paid by the research community to apply detailed molecular data to better understand the complexity of host/pathogen interaction and the true complexity of disease. Systems biology approaches to integrate these data and recreate complex bacterial systems or complex host interactions are lagging behind and constitute a great opportunity for additional investment.

**Research Capacity**

Serious deficits in research capacity in countries where TB is endemic have traditionally hindered efforts to develop better knowledge about the disease and to translate that knowledge into new tools. This capacity has been limited by a lack of investment in research infrastructure and human capital. Facilities that conduct TB research must have higher level capabilities in order to cope with the safety requirements posed by the bacteria’s virulence. To address the needs for expanded capacity, a variety of networks and partnerships are in place to develop capacity and conduct research on TB, particularly in Africa.

**Clinical Trial Networks**

Established in 2003, the European and Developing Countries Clinical Trial Partnership (EDCTP) is an organization that brings together 16 European and 46 sub-Saharan African countries to build clinical trial capacity. The partnership focuses its efforts on supporting development of new vaccines, drugs, and diagnostics for HIV/AIDS and malaria, along with TB. Projects supported by the EDCTP take a multi-center approach and combine clinical trials, capacity building and networking.

One initiative supported by EDCTP funding is the Tuberculosis Vaccine Site Network (TB VACSIN), a partnership that brings together organizations and expertise from developed and developing countries to develop additional TB vaccine trial sites in Africa. TB VACSIN includes trial sites in Kenya, Mozambique, South Africa, and Uganda. The consortium’s activities also are funded by the...
Aeras Global TB Vaccine Foundation, with additional support from the Netherlands-based KNCV Foundation and other European collaborators.

EDCTP funding also is being used to start up a new Central Africa Network on Tuberculosis, HIV/AIDS, and Malaria for the Conduct of Clinical Trials (CANTAM), which was announced in late February 2009. This network brings together researchers and institutions in Cameroon, Congo, Gabon, Germany, and Tanzania to build capacity in areas such as good clinical and laboratory practice, data management, quality control, and ethics. CANTAM is the first network funded under a grant program designed to develop “Networks of Excellence,” with additional networks planned for Eastern, Western, and Southern Africa.

Clinical trial sites in Asia are not as comprehensively organized as those in Africa, although capacity exists. The Asia Clinical Trials Portal (ASCTP) is an online network and information resource for sites that conduct malaria, HIV/AIDS, and tuberculosis clinical trials in Asia. The portal provides information on trial site capacity and ongoing trials, as well as news and other information that might be useful for trial sites. As of April 2009, 23 sites were listed as having ongoing TB trials focused on a variety of interventions. The ASCTP in not yet a comprehensive resource; however, its sponsors hope to expand the breadth and depth of information provided.

TB clinical trial networks also are active in Europe and the United States. The Tuberculosis Network European Trials group (TBNET) is a group of research-oriented scientists whose goal is to promote clinically oriented research on TB in Europe by sharing and developing ideas and research protocols among members of the network. In the United States, the Centers for Disease Control and Prevention (CDC) funds a Tuberculosis Trials Consortium that conducts clinical, laboratory, and epidemiologic research relating to TB infection and disease. These groups are focused primarily on research capacity and interest within their own countries and/or regions, and do not work to build capacity in endemic countries. The NIAID also funds the adult clinical trial groups for HIV research that also conduct limited clinical HIV/TB research for treatment, diagnosis, and management of patients.

Investments in developing clinical trial capacity, particularly in Africa, have paid off in terms of the availability of sites capable of engaging in clinical research on TB. However, there is concern that if there is no ongoing use of and support for this clinical capacity, it may degrade over time. Further, investment in capacity in other endemic regions has not matched that found in Africa, and in many places, particularly the transition economies of Eastern Europe, that capacity remains much less advanced. As a result, critical populations for TB control remain uncovered by clinical research due to a lack of capacity in the regions where they are located.

**Research Training**

In addition to investments in infrastructure, a variety of initiatives currently are seeking to bolster institutional and human capacity to conduct TB research in endemic countries. The U.S. National Institutes of Health (NIH) funds, among other more targeted international clinical training programs, an International Clinical, Operational, and Health Services Research Training Award for AIDS and TB (ICOHRTA AIDS/TB), which provides funding for institution-based research training in eight countries in Africa, Asia, and Latin America. Training topics include research methods and skills, along with a variety of support capacities to help institutions better manage their research programs. Additionally, WHO supports 14 collaborating centers for tuberculosis research in Asia.
(seven), Europe (four), Latin America (two), and the Middle East (one). These national research centers collaborate with WHO on its research efforts, including providing training for individual researchers and supporting other institutions within the country. Other groups provide fellowships and study exchanges meant to bolster human capital in research endemic-countries.

Despite these efforts, training opportunities still are not sufficient to attract researchers and develop their skills in TB. In resource-limited countries, career tracks for biomedical or basic research are non-existent and there are few centers of excellence where new investigators can build skills and experience and pursue post-doctoral training. There also are only very limited opportunities for scientists from endemic countries to pursue high-level academic study outside of their home countries. Those who do take advantage of outside education often see little incentive to return home, opting instead to work in the countries where they have trained. When they do return to their native countries, investigators trained in the United States or Europe usually do not have opportunities for academic careers or peer interactions. Therefore, infrastructure for research should be developed in conjunction with improvement of infrastructure for clinical care, since the limited healthcare funds available in resource-limited countries likely will not be allocated to academic research.

**Experimental Models**

Animal models are the key media through which potential treatment targets and methods are first identified and then studied. However, it should be noted that animals typically do not develop the exact same disease as humans. In some cases, animal models are based on a similar disease that animals contract, and in other cases, scientists artificially induce the disease to create animal models.

Since no single animal model reproduces all features of human TB, *M.tb* interventions typically are evaluated using models created by infecting animals with the bacteria. The most common model for testing drug efficacy is a mouse model created by infecting mice with aerosolized *M.tb*. Comparative data have shown that testing in this model may predict aspects of drug efficacy.

As was discussed in the section on current vaccine research, no single animal model adequately represents the human immune response to *M.tb* infection. As a result, vaccine testing relies on a mix of animal models to assess safety and efficacy during preclinical studies. These include mouse models, as well as guinea pig, rabbit, and non-human primate models. Guinea pig and rabbit models are used to measure protection against different manifestations of TB disease (disease progression and neurological manifestations, respectively). In later stages, a non-human primate model that relies on a certain type of macaque can provide important information on immune responses, particularly when evaluating vaccine candidates designed to improve on BCG.

While different animal models reproduce individual aspects of human disease, no one model adequately mimics all aspects of infection, latency, progression to active disease, immune responses, or pathology. Therefore, a more thorough understanding and appreciation of the unique contribution of each animal model needs to be gained through targeted comparative research. Additionally, new models are needed to assist researchers in their efforts to understand all aspects of TB more closely.
Data Standards
Despite an acknowledgement that data standardization would be beneficial to the field, the TB research community has not yet achieved consensus around any one set of standards. Efforts are underway to develop and adopt standards.

As part of the NIH Roadmap Initiative, the TB Trials Network has worked with the Duke Clinical Research Institute and the Clinical Data Interchange Standards Consortium to standardize data elements for use in TB-related clinical trials worldwide. This process has involved bringing stakeholders—including researchers, patients, funders, surveillance groups, and regulators—together to build consensus around a common vocabulary for use in TB clinical trials. The result is a set of common data elements and a domain analysis model that the group hopes will be adopted widely, thus facilitating research exchange and collaboration. In order to encourage adoption, the initiative is working with Health Level 7, an international voluntary organization that collaborates to develop data standards.

Further, there has been considerable effort by WHO to define TB case reporting standards for disease surveillance. In the United States, CDC has developed and maintained the Report of Verified Case of TB form for public health case reporting. Also, the Tuberculosis Clinical Trials Consortium has developed a body of data collection forms from conducted clinical trials. Furthermore, electronic TB case reporting has been defined under the Public Health Information Network and the National Electronic Disease Surveillance System.

Collaboration
Networks that bring together researchers and support their collaboration can play a key role in facilitating global TB research. Several networks have been created to focus on specific research questions or concerns. For example, the Grand Challenges in Global Health Initiative, launched in 2003 by the Gates Foundation, has resulted in the creation of consortia that seek to identify biomarkers with prognostic potential for use in testing new vaccines, to better understand and develop new drugs for latent TB, and to develop an immunotherapeutic vaccine. Other collaborations have formed around epidemiologic research, genomics, and HIV co-infection, among other topics.

As described in the earlier section on data and specimen banks, electronic collaboration tools such as databases and Web forums also promote collaboration and knowledge-sharing.

While it is clear that some networking resources do exist, opportunities and tools for networking and communication remain inadequate to bring together a research community that is quite dispersed and would benefit from greater global interaction.
Clinical Trials

As of April 2009, there were 175 ongoing clinical trials relating to TB (Figure 8). The portion of TB trials that are in Phases 1, 3, and 4 is comparable to clinical trials for all diseases. However, TB has a much larger percentage of trials for which phase data are listed as unknown. One reason for this may be that observational studies, which do not have phases, represent a significantly higher proportion of TB trials than all trials (Figure 10). Additionally, some internationally registered trials do not have phase data available. The share of Phase 2 and multi-phase trials were considerably lower for TB in relation to all diseases.

Government funding, from both the United States (including NIH) and other countries, was substantially higher for TB trials than for all clinical trials (Figure 9) that include funding by pharmaceutical companies. This likely reflects the fact that TB receives relatively little support from most private sources. In particular, the proportion of industry-sponsored trials is significantly lower for TB than for all diseases. The portion of trials listed as having unknown sponsors for TB is more than double the share for all trials, most likely due to difficulties classifying international organizations. Sponsorship from sources cataloged as other and network is comparable for TB with respect to all trials.

Figure 8: Clinical trials on TB, by phase.
Source: ClinicalTrials.gov; International Clinical Trials Registry Platform; FasterCures analysis.

Figure 9: Clinical trials on TB, by sponsor.
Source: ClinicalTrials.gov; International Clinical Trials Registry Platform; FasterCures analysis.
Significant differences were apparent between TB trials and all trials with respect to type, particularly in the area of observational studies (Figure 10). Approximately 30 percent of all observational TB studies were funded by NIH and nearly 60 percent were funded by sponsors categorized as “other.” Similarly, about 30 percent of NIH TB trials were observational. Consistent with all trials, drugs and biologics are the interventions most commonly probed by TB trials. More than two-thirds of the trials funded by organizations categorized as “other” evaluated drugs and biologics, likely attributable to the recent creation of a number of product development partnerships (PDPs)\(^5\) that are focused in those areas. Two-thirds of the trial types listed as “other”—which includes interventions that explore diagnostic tools, devices, and dietary supplements, among other things—were funded by other governments. The majority of procedure- and behavioral-focused studies were sponsored by NIH and organizations listed as “other.”

**Funding**

The Global Plan to Stop TB 2006-2015 maps out what is needed to achieve the United Nation’s Millennium Development Goals and TB Partnership goals by 2015. The plan set annual spending targets for TB efforts totaling $56.1 billion over 10 years. These numbers included more than $47 billion in funds for TB control efforts to expand the reach of DOTS programs, treat patients with resistant TB and HIV co-infection, and conduct other control activities. An additional $9 billion was projected for R&D relating to new drugs, vaccines, and diagnostics to improve the tool used for control.

Funding for TB-related research has grown steadily in recent years, reaching about $410.4 million in 2007. Governments, led by the United States, contribute the majority of funding for TB research, followed by private foundations. NIH and the Gates Foundation are by far the largest institutional investors in research relating to the disease, combining for nearly 60 percent of total spending. The remainder of the top 12 funders account for only about 20 percent. It is notable that funding from NIH has remained virtually flat over the past five years, while funding from the Gates Foundation has increased rapidly over this period. Funding from industry sources accounted for 16 percent ($66 million) of the total.

\(^5\) PDPs are standalone organizations that work to develop new products by leveraging resources from the public, private for-profit, and private not-for-profit sectors.
The development of new TB drugs is the largest area of R&D investment, receiving 35.3 percent ($145.1 million) of all funds in 2007. This was followed by 32.3 percent ($132.4 million) for basic research and 20 percent ($82.3 million) for preventive vaccines. Diagnostics research accounted for about 8.5 percent ($35 million) of spending.

These funding levels are far shy of what is needed to meet the ten-year resource requirements projected by various Stop TB working groups for R&D in these key areas, which total $9 billion (Table 4). This resource-constrained environment limits the number of leads that can be pursued actively and places pressure on researchers to minimize the number of products that reach potentially informative clinical trials. Instead, many projects get trapped in extensive animal modeling that is known to be a suboptimal approach to testing TB-related products.

### Table 4: Project R&D Resource Needs, 2006-2015

<table>
<thead>
<tr>
<th>Research Area</th>
<th>Projected Cost (USD millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Early stage/translational</td>
<td>$2,419</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>$2,373</td>
</tr>
<tr>
<td>Other</td>
<td>$8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$4,800</strong></td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td></td>
</tr>
<tr>
<td>Early stage/translational</td>
<td>$1,391$</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>$690</td>
</tr>
<tr>
<td>Other</td>
<td>$1,559</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$3,640</strong></td>
</tr>
<tr>
<td><strong>Diagnostics</strong></td>
<td></td>
</tr>
<tr>
<td>Early stage/translational</td>
<td>$206</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>$303</td>
</tr>
<tr>
<td>Other</td>
<td>$7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$516</strong></td>
</tr>
</tbody>
</table>

Source: Stop TB Partnership.

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6 Includes maintenance and improvement of existing BCG implementation programs.

7 Therapeutic vaccines accounted for less than one percent.
Market Analysis

Overview
A number of initiatives are underway to develop new tools to aid TB control efforts, including drugs, vaccines, and diagnostics. As a result of international PDPs, the TB R&D pipeline is currently much more robust than in the past and appears likely to produce new products in all three categories in the coming years. Financing the pipeline is of concern to industry developers who are working to replace skeletal private markets in the poor regions of the world where TB products are in highest demand.

Products

Vaccines
The BCG vaccine, introduced in 1921, is the only vaccine currently available for the prevention of TB infection. BCG is used predominantly in children and confers limited protection (up to 80 percent) against pulmonary TB for up to 15 years. As discussed previously, the level and duration of protection vary significantly geographically. Additional variation may result from the fact that multiple manufacturers produce the BCG vaccine using at least four different strains of the bacteria. BCG is considered cheap at between one and three U.S. dollars per dose, but its limited efficacy means that typically it is considered to be less cost effective than treating active TB infection.

Nevertheless, 160 countries worldwide include BCG in their routine childhood immunization policies, and WHO recommends BCG as a routine childhood immunization in highly TB endemic countries. WHO and UNICEF estimate that 83 percent of all infants born worldwide in 2005 received a dose of BCG vaccine, and regional coverage rates ranged from 77 percent in Africa to 96 percent in the Americas.

Several efforts to improve on BCG or develop completely new TB vaccines currently are underway. Cost-effectiveness analysis suggests that a new vaccine would require 75 percent efficacy against pulmonary TB and a price similar to that of BCG in order to be as cost effective as outpatient treatment. Estimates produced by BIO Ventures for Global Health suggest that the peak annual global market for a new TB vaccine could range from $450 million for a BCG-replacement vaccine that is at least 70-percent effective for a minimum of 10 years to almost $800 million for a vaccine designed to boost BCG’s effects that is 70-percent effective. A combination of the two that achieves at least 80-percent efficacy could be worth about $1 billion per year at peak coverage.

Drugs
There are a number of drugs used for TB treatment across the globe, many of which are commonly used to treat other forms of bacterial infections as well. A combination of four drugs (ethambutol, isoniazid, pyrazinamide, and rifampin), taken orally, is the most commonly-prescribed first-line treatment. However, in

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8 Other applications include both "on-label" indications that are approved by FDA and "off-label" indications that are not approved but are nonetheless commonly prescribed by doctors.
some cases other drugs may be prescribed either orally or by injection. Second-line drugs are prescribed when resistance is identified, typically because an attempt at first-line treatment does not yield results. In some cases multiple second-line drugs may be prescribed to overcome further resistance. Table 5 shows a sample of major TB drugs marketed around the world.

Table 5: Sample of TB Drugs Currently on the Market Worldwide9

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>Indication(s)</th>
<th>Brand/Generic Name(s)</th>
<th>Manufacturers</th>
<th>Other Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Second-line</td>
<td>Amikin; Amikozit; Likacin; Micin; Selemycin; many others worldwide</td>
<td>Pharmacia &amp; Upjohn (Adria Laboratories)</td>
<td>Yes (on- and off-label)</td>
</tr>
<tr>
<td>Capreomycin sulfate</td>
<td>Second-line</td>
<td>Capastat</td>
<td>Eli Lilly</td>
<td>No</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Pulmonary and extrapulmonary TB</td>
<td>Seromycin; many others worldwide</td>
<td>Eli Lilly</td>
<td>Yes (off-label)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>First-line, in combination</td>
<td>Myambutol; Mycobutol; many others worldwide</td>
<td>STI Pharma; Westward Pharmaceutical Corp.; Barr Laboratories Inc.</td>
<td>Yes (on- and off-label)</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Second-line</td>
<td>Trecator; Ethyl; Myobid</td>
<td>Wyeth Pharmaceuticals, Inc.</td>
<td>Yes (on-label)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>First-line, in combination; LTBI</td>
<td>Many worldwide</td>
<td>West-Ward; Barr Laboratories; Sandoz (Novartis); Akyna Pharmaceuticals; Teva Corporation; Southwood Pharmaceuticals</td>
<td>Yes (off-label)</td>
</tr>
<tr>
<td>Kanamycin sulfate</td>
<td>Second-line</td>
<td>Kantrex; many others worldwide</td>
<td>APP Pharmaceuticals</td>
<td>Yes (on-label)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>First-line, in combination; LTBI</td>
<td>P-Zide; P.T.B; Piraldina; many others worldwide</td>
<td>Clonmel Healthcare; Mikart</td>
<td>No</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>First-line, in combination</td>
<td>Mycobutin; Alfacid; Ansamycin; Ansatipin; Ansatipine; Rifabutin “Pharmacia”</td>
<td>Pharmacia &amp; Upjohn</td>
<td>Yes (on-label)</td>
</tr>
</tbody>
</table>

9 Drugs on this list were identified using treatment guidelines found in the Merck Manuals Online Medical Library, which can be found at http://www.merck.com/mmpe/index.html.
### Active Ingredient(s)  
### Indication(s)  
### Brand/Generic Name(s)  
### Manufacturers  
### Other Indication(s)

<table>
<thead>
<tr>
<th><strong>Active Ingredient(s)</strong></th>
<th><strong>Indication(s)</strong></th>
<th><strong>Brand/Generic Name(s)</strong></th>
<th><strong>Manufacturers</strong></th>
<th><strong>Other Indication(s)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin/ rifampicin</td>
<td>First-line, in combination; LTBI</td>
<td>Rifadin; Rifarad; Rimactane; Rimpacin; many others worldwide</td>
<td>Sanofi Aventis; Actavis/ Balkanpharma; Sandoz; Versapharm ; Lannett</td>
<td>Yes (off-label)</td>
</tr>
<tr>
<td>Rifampin+ isoniazid</td>
<td>First-line combination drug</td>
<td>Rifamate</td>
<td>Sanofi Aventis; West-Ward</td>
<td></td>
</tr>
<tr>
<td>Rifampin+ isoniazid+ pyrazinamide</td>
<td>First-line combination drug</td>
<td>Rifater</td>
<td>Sanofi Aventis</td>
<td></td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Pulmonary TB, in combination</td>
<td>Priftin®</td>
<td>Sanofi Aventis</td>
<td>No</td>
</tr>
<tr>
<td>Streptomycin sulfate</td>
<td>First-line</td>
<td>Ambistryn-S; Estrepto-Monaxin; Estreptomicina; Strepto; Strepto-Hefa; Streptocin; Streptomycinum</td>
<td>Pfizer; X-Gen Pharmaceuticals</td>
<td>Yes (on-label)</td>
</tr>
</tbody>
</table>

Companies that produce drugs and other products for use predominantly by poor people often are concerned about whether sales will be sufficient to recoup R&D costs. Uncertainty about demand and sales can serve as a strong deterrent for investment in R&D for products that serve these markets.

A 2007 study by the TB Alliance provided the first ever estimates of the global market for first- and second-line TB drugs (Figure 11). Low-end estimates based on DOTS notification and high-end estimates based on WHO projected incidence figures were calculated for 10 countries and extrapolated to the global level. The overlap in values between the estimates, $310-316 million,
A Tuberculosis Disease Report

**40**

represents the closest estimate of the global market for first-line TB drugs. Such scientific calculation of global estimates for second-line drugs are not possible; however based on data from the 10 high-burden countries, the researchers estimated the value of the second-line TB drug market in those countries\(^\text{10}\) to be approximately $54 million.

**Diagnostics**

Numerous TB diagnostic products are available in both developed and developing countries through both the public and private sectors. Developing countries purchase over 60 percent of all testing units consumed, although they only account for about 30 percent of global spending. In developing countries, the public sector provides the vast majority of diagnostic products and services. This includes nearly 70 percent of smear-microscopy services, more than 90 percent of culture services, about 60 percent of x-rays, and about 94 percent of all drug susceptibility testing.

As of 2006, estimates of the global market for TB diagnostics totaled about $1 billion, including $395 million for disposable materials and $638 million for labor. These estimates do not include costs associated with durable laboratory goods such as microscopes or other laboratory equipment. Estimates of market potential for new products vary based on the type of diagnostic being examined, with a test for latent TB and for POC use having the largest potential market.

**Financing Mechanisms**

The recent global interest in accelerating R&D activities to produce new tools in the fight against TB and other diseases that primarily affect developing countries has led to the emergence of new funding mechanisms designed to stimulate investment and induce participation. This section focuses on R&D oriented mechanisms that are designed to create direct incentives, particularly for industry contributions. There also are numerous market-focused financing mechanisms that could be used to ensure that new products will be purchased and distributed once they become available.

- **Advanced market commitments (AMCs):** An AMC is a market-based mechanism designed to accelerate the development, production, scale-up, and use of vaccines by establishing “pull” incentives for private industry investment. Credible sponsors (e.g., large foreign aid donors) would commit in advance to a minimum price paid per person immunized up to a certain number of individuals. In exchange, industry would commit to produce additional doses in the longer-term at a low price. If no product is developed, no payments are made. The AMC concept currently is being tested on the development of a vaccine against pneumococcal disease. Even if it succeeds, large questions remain about whether it could be applied for TB.

- **Priority Review Voucher (PRV):** A PRV entitles the holder to expedited review of a new drug application that does not meet the criteria typically required for priority review status, which can shorten approval time by four months to a year. The FDA) recently announced that it will offer PRVs to companies that develop new products targeting neglected tropical diseases, including TB. Under the program, PRVs will be transferable, allowing the rights to be sold if the recipient does not have another product for which it would like to secure

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\(^{10}\) Countries include high burden and high income: Brazil, China, France, India, Indonesia, Japan, Philippines, South Africa, the United Kingdom, and the United States.
priority review. Industry guidance on the PRV program was released in draft form in October 2008, with a public hearing held in December 2008.

**Pipeline**

**Drugs**
The majority of TB drugs on the market today were developed between 1948 and 1963, with the most recent major advance occurring more than 40 years ago. Of the 1,556 new chemical entities registered with the FDA between 1975 and 2004, only three were for TB. As recently as 2001, only two new TB drugs were under clinical development, and they were in the very early stages. However, the growth of the PDPs and the increased global focus on diseases of the poor—particularly HIV/AIDS, malaria, and TB—have led to a rapid expansion of activity and investment in anti-TB drug research. As of mid-2008, the TB treatment pipeline included more than 20 new drugs, including 7 in clinical trials, 3 in preclinical, and a number of others undergoing discovery work. Commercial players are involved in at least 21 of the ongoing research projects. Still, based on the probabilities of success for new drug candidates, the pipeline remains insufficient to meet the need for new anti-TB drugs.

**Vaccines**
The deficiencies of the BCG vaccine, particularly its variable efficacy and duration and lack of ability to prevent adult pulmonary disease, highlight the need for continued research to develop a new TB vaccine. As with drugs, the pipeline for new TB vaccine candidates has expanded dramatically in the past several years. As of mid-2008, at least seven vaccine candidates were in clinical trials and eight more were undergoing preclinical research. Commercial players were involved in at least four of these efforts.

**Diagnostics**
As seen previously, diagnostics is the R&D area that currently receives the least investment and attention from all players globally. As a result, the pipeline for new diagnostics is less robust than for drugs and vaccines. As of mid-2008, fewer than 10 diagnostic development projects were reported. Of these, two were undergoing Phase 3 trials and four were in preclinical studies. At least four of these projects include commercial partners.

Table 6 shows the array of TB products listed as being in development by or in collaboration with partners from the commercial sector. Products being developed without industry collaboration are not included in this list. Half of these products also involve at least one partner from the public or nonprofit sectors, demonstrating the influence that increased government and philanthropic interest in TB is having on commercial investment in TB research. Additionally, it is worth noting that this list may include products that are not being pursued actively at this time.
Table 6: TB R&D Projects in the Commercial Sector by Company/Sponsor and Stage

<table>
<thead>
<tr>
<th>Partners</th>
<th>Intervention</th>
<th>Product/Project Name</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>Drug</td>
<td>DNA synthesis/repair inhibitors</td>
<td>Discovery</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Drug</td>
<td>Screening, target identification</td>
<td>Discovery</td>
</tr>
<tr>
<td>Dafra Pharma</td>
<td>Drug</td>
<td>DF-152</td>
<td>Discovery</td>
</tr>
<tr>
<td>Eli Lilly/NIH</td>
<td>Drug</td>
<td>Screening program</td>
<td>Discovery</td>
</tr>
<tr>
<td>FASgen Inc.</td>
<td>Drug</td>
<td>FAS-20013 (synthase inhibitor)</td>
<td>Discovery</td>
</tr>
<tr>
<td>GSK/TB Alliance</td>
<td>Drug</td>
<td>Mycobacterial Gyrase Inhibitors</td>
<td>Discovery</td>
</tr>
<tr>
<td>GSK/TB Alliance</td>
<td>Drug</td>
<td>Pleuromutilins</td>
<td>Discovery</td>
</tr>
<tr>
<td>GSK/TB Alliance</td>
<td>Drug</td>
<td>InhA inhibitors</td>
<td>Discovery</td>
</tr>
<tr>
<td>GSK/TB Alliance</td>
<td>Drug</td>
<td>Malate synthase inhibitors</td>
<td>Discovery</td>
</tr>
<tr>
<td>GSK/TB Alliance/TAMU</td>
<td>Drug</td>
<td>Antimicrobial screening program</td>
<td>Discovery</td>
</tr>
<tr>
<td>Novartis/ Consortium 11 of the GCGH</td>
<td>Drug</td>
<td>Mini-portfolio</td>
<td>Discovery</td>
</tr>
<tr>
<td>Sanofi Aventis</td>
<td>Drug</td>
<td>Antimycobacterial screening program</td>
<td>Discovery</td>
</tr>
<tr>
<td>Sanofi Aventis</td>
<td>Drug</td>
<td>Target selection and screenings (3)</td>
<td>Discovery</td>
</tr>
<tr>
<td>Vertex</td>
<td>Drug</td>
<td>Kinase inhibitors</td>
<td>Discovery</td>
</tr>
<tr>
<td>Eli Lilly/NIH</td>
<td>Drug</td>
<td>CPZEN-45</td>
<td>X</td>
</tr>
<tr>
<td>EpiVax Inc.</td>
<td>Vaccine</td>
<td>TBVax (post-infection therapeutic)</td>
<td>X</td>
</tr>
<tr>
<td>ImmunoBiology</td>
<td>Vaccine</td>
<td>HspC™-TB vaccine</td>
<td>X</td>
</tr>
<tr>
<td>FIND/ Cepheid/ UNDMJ</td>
<td>Diagnostic</td>
<td>Automated nucleic acid amplification test</td>
<td>X</td>
</tr>
<tr>
<td>FIND/Eiken Chemical</td>
<td>Diagnostic</td>
<td>LAMP-based dx</td>
<td>X</td>
</tr>
<tr>
<td>Lupin</td>
<td>Drug</td>
<td>3 compounds</td>
<td>X</td>
</tr>
<tr>
<td>Otsuka</td>
<td>Drug</td>
<td>Nitroimidazole backup compound</td>
<td>X</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Drug</td>
<td>PNU-100480</td>
<td>X</td>
</tr>
<tr>
<td>Partners</td>
<td>Intervention</td>
<td>Product/Project Name</td>
<td>Stage</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Sequella Inc.</td>
<td>Drug</td>
<td>SQ-609 (dipiperadine)</td>
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<tr>
<td>Sequella Inc.</td>
<td>Drug</td>
<td>SQ-641 (capuromycin)</td>
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<tr>
<td>Aeras</td>
<td>Vaccine</td>
<td>AERAS r-BCG</td>
<td>X</td>
</tr>
<tr>
<td>Crucell/ Aeras/ SATVI</td>
<td>Vaccine</td>
<td>AERAS-402 (AdVac)</td>
<td>X</td>
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<tr>
<td>J&amp;J (Tibotec)</td>
<td>Drug</td>
<td>TMC-207 (diarylquinolone)</td>
<td>X</td>
</tr>
<tr>
<td>Lupin</td>
<td>Drug</td>
<td>Sudoterb/LL-3858 (Pyrrole)</td>
<td>X</td>
</tr>
<tr>
<td>Sanofi Aventis/SSI/ Aeras/ Intercell</td>
<td>Vaccine</td>
<td>Vaccine HyVac4 IC31 (AERAS-404)</td>
<td>X</td>
</tr>
<tr>
<td>Sequella Inc.</td>
<td>Drug</td>
<td>SQ-109 (diamine)</td>
<td>X</td>
</tr>
<tr>
<td>SSI/Intercell/TBVAC</td>
<td>Vaccine</td>
<td>Hybrid 1:85 billion-ESAT-6</td>
<td></td>
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<tr>
<td>GSK/Aeras</td>
<td>Vaccine</td>
<td>GSK-M72</td>
<td>X</td>
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<tr>
<td>Novartis/TB Alliance</td>
<td>Drug</td>
<td>PA-824 (nitroimidazole)</td>
<td>X</td>
</tr>
<tr>
<td>Otsuka</td>
<td>Drug</td>
<td>OPC-67683 (nitroimidazole)</td>
<td>X</td>
</tr>
<tr>
<td>Oxford University/ Emergent Biosolutions/Aeras</td>
<td>Vaccine</td>
<td>MVA-85A/AERAS-485</td>
<td>X</td>
</tr>
<tr>
<td>Bayer HealthCare/ TB Alliance/others</td>
<td>Drug</td>
<td>Moxifloxacin</td>
<td></td>
</tr>
<tr>
<td>FIND/Tauns Co. Ltd.</td>
<td>Diagnostic</td>
<td>Capilia TB test</td>
<td></td>
</tr>
<tr>
<td>Lupin/ TDR</td>
<td>Drug</td>
<td>Gatifloxacin</td>
<td>X</td>
</tr>
<tr>
<td>Sanofi Aventis</td>
<td>Drug</td>
<td>Improving existing treatments</td>
<td></td>
</tr>
<tr>
<td>Sequella Inc.</td>
<td>Diagnostic</td>
<td>MPT-64 TB Patch</td>
<td>X</td>
</tr>
<tr>
<td>SR Pharma</td>
<td>Vaccine</td>
<td>Mycobacterium vaccae (inactivated)</td>
<td></td>
</tr>
</tbody>
</table>

Commercial Players

Overview
This section provides a brief summary of selected companies that are active in TB R&D. Companies included in this survey include those involved in two or more research projects relating to new TB products, those with dedicated facilities for TB or neglected disease R&D, and/or those among the top 20 TB research investors according to the Treatment Action Group. It is important to note that most commercial players involved in TB R&D are not pursuing a profit objective, but rather view their investment from a philanthropic and/or public relations standpoint.

For each company, a brief discussion includes its investment in R&D broadly and in TB specifically, as well as any other ties that make the company an important player.

Key Companies

Major Pharmaceutical Companies

AstraZeneca is a U.K.-based pharmaceutical company with offices in over 100 countries and $29.6 billion in sales in 2007. In 2007, the company spent more than $5 billion on R&D activities. The R&D efforts focus on six therapy areas, including cancer, cardiovascular, gastrointestinal, infection, neuroscience, and respiratory and inflammation.

TB treatment research is the major focus of a state-of-the-art research facility in Bangalore, India, that opened in 2007. AstraZeneca spent $10 billion to build the facility, which employs over 100 scientists, and will spend $30 billion over five years to equip and run it. The company has promised to make TB medicines discovered in the Bangalore lab available for clinical development, as well as to supply them to poor countries at low prices.

Eli Lilly is a U.S.-based pharmaceutical company with nearly 40,000 employees and $18.6 billion in net sales in 2007. The company conducts research activities in over 50 countries and markets its products in 143 countries worldwide. Annual R&D expenditures are about $3.5 billion per year.

Two major second-line TB drugs—capreomycin and cycloserine—belong to Lilly, although it has transferred the technology, formula, and trademark for producing those compounds to generic drug makers in order to increase availability around the world. This transfer is part of the Lilly MDR-TB Partnership, launched in 2003, that is focused on improving treatment for MDR-TB through revised treatment protocols and efforts to make existing second-line treatments more accessible to patients in poor countries. Lilly has committed $120 million to fund the initiative since its launch.

In 2007, Lilly created the Lilly Not-for-Profit Partnership for TB Early Phase Drug Discovery, a collaboration with NIAID, Merck, the Infectious Disease Research Institute, the Seattle Biomedical Research Institute, and others. Lilly committed $15 million in start-up capital over five years and opened its library of 500,000 compounds for screening through the initiative.
GlaxoSmithKline (GSK) is a U.K.-based pharmaceutical company with offices in over 100 countries and $45.3 billion in sales in 2007. In 2007, the company spent $6.6 billion on R&D activities. Intensive R&D efforts resulted in the approval of the new chemical entities and one vaccine during 2007, while 10 additional new product opportunities were filed.

GSK has expressed a strong commitment to global health, demonstrated through its investment in both drug and vaccine research in the “big three” priority diseases of AIDS, TB, and malaria. GSK claims a global community investment of $563.2 million for 2007 (3.8 percent of total profit before tax) with a focus on HIV/AIDS, TB, and malaria. To carry out its global health research, GSK operates a dedicated drug discovery facility for neglected diseases in Tres Cantos, Spain, which is very active in malaria and TB. In addition, GSK works with PDPs by contributing R&D technology, manufacturing, and distribution expertise to the efforts of the TB Alliance and AERAS.

Lupin Limited is an India-based pharmaceutical company with $504.8 million in net sales for the year ending in March 2008. In 2008, the company spent $38.8 million on R&D activities. Lupin began as a generics manufacturer but has since expanded its ability to conduct R&D activities for new products. The company’s Novel Drug Discovery & Development program currently is working to develop drugs for TB, psoriasis, diabetes, migraine, and an anti-inflammatory product. Recently, Lupin also has begun to expand into biotechnology research. Lupin is the world’s largest manufacturer of TB drugs, producing more than 20 different formulations that include all of the core first-line drugs, as well as several combinations and second-line products.

Novartis is a Swiss chemical and pharmaceutical company with offices in over 140 countries and $38.1 billion in sales in 2007. In 2007, the company spent $6.4 billion on R&D activities. Novartis has divisions that produce drugs, vaccines, diagnostics (Chiron), consumer goods, and generic drugs (Sandoz).

To continue its advances in R&D for neglected diseases, in 2004 Novartis opened a dedicated facility in Singapore that applies state-of-the-art technology to discovery and development of new drugs and vaccines. The Novartis Institute for Tropical Diseases currently focuses its efforts on research relating to TB, malaria, and dengue fever. Like GSK, Novartis collaborates extensively with PDPs on its neglected diseases activities.

Otsuka Pharmaceuticals is a Japanese umbrella pharmaceutical group made up of more than 100 individual companies with offices in 18 countries worldwide. Although its core business is pharmaceuticals, Otsuka also produces consumer products such as nutritional supplements and cosmetics. The U.S.-based company Otsuka Pharmaceutical Development & Commercialization leads the group’s research on TB, which focused on development of a new class of TB drugs that have show promise in early testing. A TB research funding report produced by the Treatment Action Group, a nonprofit advocacy organization, indicates that in 2007 Otsuka was the fourth largest investor in TB research behind only NIH, the Gates Foundation, and the European Commission.

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11 All conversions from British Pounds using the December 31, 2007, exchange rate of $2 per £1.
12 All conversions from Indian Rupees using the March 31, 2008, exchange rate of R39.9 per $1.
**Sanofi Aventis** is a French pharmaceutical company that operates in over 100 countries and had sales of about $45.4 billion\(^\text{13}\) in 2007. The company invested $6.7 billion in R&D in 2007. The company produces both drugs and vaccines (Sanofi-Pasteur).

As the first manufacturer of rifampin, one of the core first-line TB drugs still in place, Sanofi has a long history in TB treatment. The company also markets two combination formulations that bring together multiple first-line agents, as well as an important treatment for pulmonary TB. Additionally, Sanofi continues to conduct R&D activities for TB, focusing on improving its existing treatments and identifying new targets and antimycobacterial compounds. Additionally, Sanofi-Pasteur is collaborating with AERAS and other partners on a TB vaccine project. Work on TB and other neglected diseases (malaria, epilepsy, leishmaniasis, sleeping sickness, and mental health) is coordinated by Sanofi’s Access to Medicines division.

**Other For-Profit Companies**

**Sequella Inc.** is a small, U.S.-based pharmaceutical company specializing in developing products relating to infectious diseases, starting with TB. In addition to TB, Sequella expects to develop products for candidiasis, Crohn’s disease, SARS, and bacterial pneumonia. Sequella currently has five products in its pipeline, all of which are being developed with indications for TB. These include a diagnostic patch that is undergoing Phase 3 trials, a treatment that is in Phase 1, and a compliance monitor and two more drugs that are in the earlier stages of research. Sequella funds its research through a combination of private capital and research grants, predominantly from NIH.

\(^{13}\) All conversions from Euros using the December 31, 2007, exchange rate of $1.47 per €1.
Nonprofit Players

Overview
In recent years, pharmaceutical companies, academic institutions, and research organizations have banded together to create nonprofit PDPs to drive product development in TB drugs, vaccines, and diagnostics. PDPs are now the major developers of TB products in all three categories. Independent research organizations, academic centers, and government agencies in both developed and developing countries, however, continue to play significant roles in TB treatment and prevention research.

Key Organizations

Product Development Partnerships (PDPs)
Aeras Global TB Vaccine Foundation
http://www.aeras.org

The Aeras Global TB Vaccine Foundation was created in 2003 with the aim to develop, test, characterize, license, manufacture and distribute at least one new TB vaccine regimen by 2015. Further, Aeras aims to ensure availability for all who need TB vaccines by reducing barriers to development and distribution. Utilizing more than 120 full time staff across two offices and a host of field sites, Aeras conducts its own research in addition to partnering with industry, academic, and government research organizations for vaccine candidate development and clinical research projects. Major Aeras funders include the Gates Foundation, CDC, the Dutch Ministry of Foreign Affairs, the Ministry of Foreign Affairs of Denmark, and the Research Council of Norway.

Foundation for Innovative Diagnostics
www.finddiagnostics.org

The Foundation for Innovative Diagnostics (FIND) is a Geneva-based organization that was launched at the 2003 World Health Assembly to develop more accurate and cost-effective diagnostic technologies for developing world diseases. FIND’s work on malaria includes efforts to improve the accuracy of rapid diagnostics tests for use in the field, to develop a new generation of malaria tests, and developing new assays. Other FIND programs look at diagnostics for TB and sleeping sickness, as well as laboratory preparedness. The organization receives funding from the Gates Foundation, the Dutch Government, the European Union, the U.S. Agency for International Development, Google, and Fondation André & Cyprien (Switzerland).
Global Alliance for TB Drug Development

http://www.tbballiance.org

Founded in 2000, the Global Alliance for TB Drug Development strives to “ensure the widespread availability of affordable, faster and better tuberculosis drug regimens that will advance global health and prosperity.” The Alliance relies on collaboration with the public, private, academic, and philanthropic sectors to drive development for products that will serve neglected markets. With this model it is able to combine the R&D of its team and the skills and resources of its partners to create a streamlined path toward drug development.

South African Tuberculosis Vaccine Initiative

http://www.satvi.uct.ac.za

The South African Tuberculosis Vaccine Initiative (SATVI) was founded in 2003 to develop capacity and conduct clinical trials on new TB vaccines. Based at the University of Cape Town, SATVI conducts clinical, epidemiological, and immunological research, and has conducted field trials and epidemiological cohort studies, as well as initiated Phase 1 and 2 trials to support vaccine development efforts. The organization receives funding for its efforts from AERAS, NIH, the Wellcome Trust, the Dana Foundation, the EDCTP, the European TB vaccine consortium, the Gates Foundation, and Immunopedia.

TuBerculosis Vaccine Initiative

www.tbvi.eu

The TuBerculosis Vaccine Initiative (TBVI) was established in late 2008 by the European Commission as a spin-off of the European Union-funded TB-VAC project, which it now implements. The foundation, which is registered in the Netherlands, seeks to “foster development of new vaccines against tuberculosis through projects in which research institutes collaborate with pharmaceutical companies, including [small and medium enterprises].”

Research Organizations

Infectious Disease Research Institute

www.idri.org

Founded in 1993, the Infectious Disease Research Institute (IDRI) calls itself a “nonprofit biotech.” IDRI works closely with the Malaria Vaccine Initiative and other partners on development of malaria vaccine candidates. The Institute’s work on these projects capitalizes on its adjuvant and formulation capabilities. In addition to malaria, IDRI also works on projects relating to leishmaniasis, TB, leprosy, Chagas disease, Chlamydia, and Buruli Ulcer. Major funders of IDRI’s work include American Leprosy Missions, the Gates Foundation, GlaxoSmithKline, the TB Alliance, Eli Lilly and Company, MJ Murdock Charitable Trust, NIH, and WHO.
Seattle Biomedical Research Institute

www.sbri.org

Since 1976, the Seattle Biomedical Research Institute (SBRI) has conducted research in support of new drugs, vaccines, and diagnostic technologies for developing world diseases. SBRI’s malaria program, which is one of the largest U.S.-based malaria efforts, has over 70 scientists focused on three key areas: vaccine discovery for pregnancy malaria, severe malaria in children, and liver-stage malaria. Other projects within SBRI work on issues relating to African sleeping sickness, candidiasis, Chagas disease, HIV/AIDS, *H. influenzae*, leishmaniasis, listeriosis, toxoplasmosis, and TB. SBRI has numerous funding sources, including several U.S. government agencies, the Gates Foundation, and others.

UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

www.who.int/tdr

The Special Programme for Research and Training in Tropical Diseases (TDR) was established in 1975 to “coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged.” TDR’s work on malaria includes efforts to identify drug leads for development by other partners, develop new and improved vector control methods, and produce evidence that can support sound policymaking on the use of antimalarial drugs. TDR, has four main sponsors (UNICEF, UNDP, the World Bank, and WHO), and receives funding from 22 governments and 12 other groups.

**Academic Centers**

Academic centers and individual researchers are important contributors to global research and development efforts in the TB field. Numerous dedicated centers have been established by universities in the United States, Europe, and Australia, as well as those in endemic countries. Although not a focus of the Philanthropy Advisory Service, these centers, along with other academic researchers, are an important source of expertise and research capacity.

**Government Research Agencies**

Substantial amounts of TB research continue to be conducted by government research centers in the developed and developing worlds. Groups like the Medical Research Council in South Africa, the Kenya Medical Research Institute, and the Indian Council of Medical Research are important partners in many of the clinical research efforts underway in endemic countries. Meanwhile, research being done at the U.S. NIH, the Swiss Tropical Institute, and other government research groups in developed, non-endemic countries provide important expertise and contribute to ongoing R&D efforts globally. Although also not a focus of the Philanthropy Advisory Service, these entities provide another important source of expertise and research capacity.
<table>
<thead>
<tr>
<th>Acronyms</th>
<th>Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC</td>
<td>Advanced Market Commitment</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<tr>
<td>ASCTP</td>
<td>Asia Clinical Trials Portal</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly Observed Treatment, Short Course</td>
</tr>
<tr>
<td>DST</td>
<td>Drug Sensitivity Testing</td>
</tr>
<tr>
<td>EDCTP</td>
<td>European and Developing Countries Clinical Trials Partnership</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon Gamma Release Assay</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
</tr>
<tr>
<td>IPT</td>
<td>Isoniazid Preventive Therapy</td>
</tr>
<tr>
<td>LED</td>
<td>Light-emitting Diode</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent TB Infection</td>
</tr>
<tr>
<td>M.tb</td>
<td>Mycobacterium Tuberculosis</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi-drug Resistant</td>
</tr>
<tr>
<td>NAAT</td>
<td>Nucleic Acid-based Amplification Test</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>PDP</td>
<td>Product Development Partnership</td>
</tr>
<tr>
<td>POC</td>
<td>Point of Care</td>
</tr>
<tr>
<td>PRV</td>
<td>Priority Review Voucher</td>
</tr>
<tr>
<td>rBCG</td>
<td>recombinant BCG</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>research and development</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBDB</td>
<td>Tuberculosis Database</td>
</tr>
<tr>
<td>TBDReaMDB</td>
<td>TB Drug Resistance Mutation Database</td>
</tr>
<tr>
<td>TBNET</td>
<td>Tuberculosis Network European Trials Group</td>
</tr>
<tr>
<td>TBVACSIN</td>
<td>Tuberculosis Vaccine Site Network</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>TDR</td>
<td>UNICEF/UNDP/World Bank/WHO Special Programme for Training and Research on Tropical Diseases</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations Development Programme</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR</td>
<td>Extensively Drug Resistant</td>
</tr>
</tbody>
</table>
Glossary

**Incidence**: Incidence is a mathematical quantity that describes the occurrence of a disease Y in a population. Incidence is the measure of new cases of disease in a time period.

**Macrophages**: Macrophages remove necrotic (dead) debris from the lungs.

**MDR-TB**: Multidrug-resistant TB is defined as bacteria resistant to isoniazid and rifampin (two of the most effective first-line TB drugs).

**Mycobacterium**: Mycobacterium is a genus of Actinobacteria and is the bacteria that cause TB and leprosy.

**Prevalence**: Prevalence is a mathematical quantity that describes the presence of a disease Y in a population. It is the proportion of persons in the population with the disease. It is important to note that prevalence is a good measure of the amount of a chronic, low mortality disease in a population, but is not a good measure of the amount of short duration or high fatality disease. This is because for diseases with a high fatality rate, in a cross-sectional analysis, it is unlikely a study will adequately capture and count those with the disease.

**Relative Risk** indicates the strength of the association between the risk factor and the disease outcome and is calculated by dividing the risk in the group exposed to a risk factor by the risk in the unexposed group. A RR value statistically significantly larger than 1 indicates the exposure is associated with increased risk of disease, a RR value not statistically significantly different from 1 indicates there is no association between the exposure and the risk of disease, and a RR value statistically significantly less than 1 indicates the exposure is associated with decreased risk of disease; that is, the exposure is protective.

**XDR-TB**: Extensively drug-resistant TB is MDR-TB that is resistant to three or more first-line drugs, as well as at least one of the six classes of second-line drugs.
References


