The identification of Mycobacterium tuberculosis in 1882 brought the first scientific understanding of a disease that has taken a toll throughout recorded history, and with it, the first tools to combat it. Research over the next half century led to an anti-tuberculosis vaccine, treatments and cures, along with a steep decline in tuberculosis incidence across high-income countries. When research slowed during the latter half of the 20th century, however, the global HIV pandemic, increasing urbanization, and the spread of drug-resistant tuberculosis gave the disease a lead over science. In the 21st century, tuberculosis takes nearly 2 million lives every year, with drug-resistant strains identified in 144 countries, and extensively drug-resistant disease -- resistant to at least four of the core anti-tuberculosis drugs -- reported in 100 countries.1 Renewed momentum in tuberculosis research and development in the 21st century led to new tests offering chances to reach those whose disease has gone undiagnosed, new regimens offering prospects of faster cures, and new drugs offering hope to those whose disease is resistant to older medicines.

Still, tuberculosis continues to take a worldwide toll, because:

- The diagnostic tools still most widely used are inadequate to the needs of resource poor countries, miss up to half of all cases, and fail to detect resistance to medications;
- The duration of treatment required for cure, and the side effects of first-line medications are challenges to completing treatment. Incomplete treatment allows the development and transmission of drug-resistant strains of disease;
- Treatments for multidrug resistant and extensively drug resistant strains of tuberculosis are toxic, lengthy, and, for growing numbers of patients, ineffective;
- New medicines that offer the last hope for hundreds of thousands of patients with drug-resistant tuberculosis have reached fewer than 1,000 people;
- Children and people co-infected with HIV go undiagnosed, and then untreated for lack of appropriate and affordable technologies and medicines;
- Tuberculosis remains the leading killer of people infected with HIV;
- The only vaccine, developed nearly a century ago, has limited effectiveness, and only for young children, and is not recommended for infants with HIV.

Development of a new drug, vaccine or diagnostic technology can cost about a billion dollars, with clinical trials costing $50 million or more, but U.S. investments in tuberculosis research and development remain limited in an austere budget environment. The largest funder of tuberculosis research in the world, the U.S. National Institutes of Health, has $279 million to target the disease in fiscal year 2015.2 With the responsibility to fund advanced tuberculosis drug clinical trials, and with a budget of about $20 million, USAID also provides support for drug and diagnostic development. The CDC’s TB Trials Consortium has less than $8.5 million3 for 2015 to test drugs and treatment and prevention regimens, with USAID providing support for international trial sites. Current funding for the CDC’s TB Epidemiologic Studies Consortium, which focuses on finding ways to detect and treat tuberculosis infection before it progresses to disease, stands at $6.2 million. The work ahead of these agencies is only beginning. This briefing paper looks at the goals and challenges currently confronting tuberculosis research and development.
Diagnosis

The Goal:

A simple, accurate inexpensive point-of-care diagnostic tool that detects tuberculosis that is within or outside the lungs, detects drug resistance and can be used with limited training

The reality:

- In Tajikistan, a man whose two brothers are sick with drug resistant tuberculosis waits weeks for results from a sputum sample sent to Germany, to learn if he, too, has the disease;⁴
- In Indonesia, where tuberculosis kills about 300 people each day, a young woman with a persistent cough first seeks a diagnosis in the year 2000 and is treated with traditional medicine. It is not until 2005 that she learns she has tuberculosis and begins treatment. It is not until 2011 that she learns her tuberculosis is resistant to the most commonly used drugs;⁵
- In Zambia, autopsies on 125 patients who died in the capital city’s teaching hospital reveal that 78 were sick with tuberculosis. In almost half of those patients, the disease was extrapulmonary – disseminated outside their lungs.⁶

An estimated three million people sick with tuberculosis are left undiagnosed,⁷ and as a result, untreated and infectious each year . . .

A person can be sick with tuberculosis and infectious without having a sufficient amount of bacteria in the lungs for the disease to be detected in sputum. An estimated three million people sick with tuberculosis are left undiagnosed,⁷ and as a result, untreated and infectious each year, because they do not have access to adequate diagnostic tools.
The great majority of settings continue to rely on the more than century-old method of examining a sputum sample under a microscope, which misses 50 percent or more cases of active tuberculosis. Diagnosis from cultures of sputum samples is still considered the best method for determining tuberculosis drug resistance but can take four weeks or longer to return results in resource-poor settings. That method can miss cases of active tuberculosis in:

- Children who can’t cough up sufficient sputum for a sample;
- People with HIV, whose disease often is disseminated outside their lungs;
- Others with extrapulmonary tuberculosis, for whom a chest x-ray also will fail to detect disease.

In addition:

- During the wait, health care providers may start patients on empirical treatment (treatment based on their symptoms, and the tuberculosis prevalence in their settings) but many remain untreated. Drug resistance may also render treatment ineffective. When the results come back, not all of those waiting for them do. Some may have moved, some are by then too sick to come in and some have died. Many have unknowingly exposed family members and coworkers to the disease during the time they waited.
- Those who get their results are put on treatment immediately, but some of them don’t get better; the strain of tuberculosis they have is resistant to the first line of treatment.

**Breakthroughs:**

The development of Cepheid’s XpertMTB/RIF, a molecular diagnostic tool approved by the World Health Organization in 2010, made accurate diagnosis of disease, including in children, people with HIV, and others with extrapulmonary tuberculosis, possible in about two hours. Detecting resistance to the most common first drug to treat tuberculosis, it also made quicker, more effective treatment possible. Xpert’s immediate results improved rates of same-day treatment initiation based on diagnosis and decreased times before starting treatment compared to smear microscopy.

**Challenges:**

Xpert machines and the cartridges they use remain expensive as well as unavailable in many settings. In addition, a recent study discovered a mutation had rendered drug resistance undetectable among samples in Swaziland. As strains of drug resistance continue to multiply, capacities to detect them will be needed. While 145 countries are eligible for lower pricing of Xpert machines and the cartridges they use, communities without reliable electricity, health workers trained to use the machines, and technicians trained to maintain them remain without this modern tool.
The pipeline:

The development of Xpert has continued to inspire innovation, and the range of possible tools continues to grow. Innovations under investigation include technologies to detect tuberculosis reliably and rapidly, to determine and identify drug resistance, and to monitor treatment. It is likely that products on the horizon will be affordable, maintainable, and appropriate to environments where power supplies, human resource capacities, and budgets remain uncertain. But those products still await large-scale trials, and will need to be tested against realities on the ground.

Treatment

The goal:

Less toxic, inexpensive, oral short course treatment regimens for both drug-susceptible and drug-resistant tuberculosis.

Treatment for tuberculosis takes six months to complete, involves multiple medicines, brings debilitating side effects, interferes with work and family responsibilities, and must be taken with food, all of which can present insurmountable obstacles to many patients. Although full treatment succeeds in curing 95 percent of patients, many patients are unable to complete treatment. Patients who are not able to complete treatment can develop tuberculosis that is resistant to medications, and transmit drug-resistant tuberculosis to others. Options for treating drug-resistant tuberculosis remain limited, involving multiple medications, including ones that can only be administered by injection, are lengthy, and toxic.

Only 48 percent of people treated for multidrug-resistant tuberculosis are cured. The development of more tolerable and shorter course treatments is a major goal of tuberculosis research and development, and is essential to controlling the disease in resource-poor environments.

Tuberculosis treatment research and development, in turn, is challenged by the length of time required for late-stage human trials which must demonstrate that patients remain free of disease a full year after completing investigational treatment.
The reality:

- In Indonesia, a mother of three has learned her tuberculosis is drug-resistant. Now on a new drug regimen, doctors tell her she can expect to recover in 18 months, if she completes her treatment. Side effects from the treatment include depression and hallucinations, and are making her suicidal.12

- In South Africa, a physician has learned that the tuberculosis she was exposed to in her workplace is resistant to first-line treatment. The more toxic treatment she is given causes measurable hearing loss that threatens her ability to practice medicine.

- Linezolid, an antibiotic used to treat other bacterial infections, has appeared effective in treating highly resistant strains of tuberculosis. It has never been tested in a large clinical trial of people with tuberculosis. Its side effects include stomach pain, vision problems, anemia, and weakness as well as numbness in hands and feet. At a price of about $65 a pill, or $50,000 for a course of treatment, it remains out of reach for many of the patients who need it most.13

Breakthroughs

Bedaquiline became the first new drug to treat tuberculosis in nearly half a century to gain regulatory approval when the U.S. Food and Drug Administration in 2012 said the drug was acceptable for administration to patients with drug-resistant strains of disease.14 Delamanid, another novel drug, was approved by the European Medicines Agency for treatment of drug-resistant disease in 2014.15

Challenges

Since those approvals, bedaquiline, marketed as Sirturo, has been made available in combination with current medications to fewer than 1,000 of the hundreds of thousands of people to whom the drug represents a last resort. Delamanid has been given to fewer than 10 people outside of clinical trials.16 Approval, registration and distribution of both drugs have been slowed by limited capacities in the countries where they are needed most, and further trials are needed to establish the safety of both drugs. Questions remain about side effects of both drugs, which can cause irregular heart rhythms, and which are approved only for patients for whom other drugs are not safe or effective.
**The Pipeline:**

PaMZ is a combination of two drugs currently unapproved for tuberculosis, moxifloxacin and pretomanid, (formerly known as PA-824 ),and pyrazinamide. It is intended for patients with both drug-susceptible and multidrug-resistant tuberculosis. An oral regimen, it has been found to kill tuberculosis bacteria faster than the standard tuberculosis regimen, as well as faster than other experimental regimens in an early trial among patients. In a subsequent trial, it showed the potential to cure some forms of drug-resistant tuberculosis, as well as drug-sensitive tuberculosis in four months. The STAND trial (Shortening Treatments by Advancing Novel Drugs) is a later trial testing the regimen in 50 study sites across Africa, Asia, Eastern Europe and Latin America. This effort represents a new scientific approach to developing new treatments by testing drugs together and can reduce the time of developing a new tuberculosis regimen by up to 75 percent and provide new options for both drug susceptible and drug-resistant tuberculosis.

**Prevention**

**The goal:**

*A vaccine to prevent tuberculosis infection and improved technologies to keep tuberculosis infection from progressing to disease.*

When people who are sick with tuberculosis cough, sneeze, talk or spit, they send tuberculosis bacilli into the air. A person needs to inhale only a small amount of these organisms to be infected. One third of the world’s population is latently infected with tuberculosis, which can progress to disease. Left untreated, each person with active tuberculosis will infect on average between 10 and 15 people every year. An infected person whose immune system is weakened has a greater chance of getting sick. From 5 to 10 percent of people who are infected with tuberculosis who do not have an immune-compromising condition become sick and infectious over the course of their lifetimes. From 5 to 10 percent of people who are infected with tuberculosis and who also have HIV become sick and infectious each year. People with diabetes are three times more likely to develop active tuberculosis.

**Realities:**

- A young man in Haiti arrested for shoplifting is exposed to and becomes sick with drug-resistant tuberculosis in the crowded detention center where he awaits trial. Still awaiting trial, he dies of the disease. Many of his fellow inmates also are sick, but survive, and when the jail is damaged in an earthquake, all of the prisoners flee, taking the illnesses that have been incubated in detention with them.
- A Tennessee woman joins a church mission to work with tuberculosis patients in South Africa. Months after her return home she is diagnosed with drug-resistant tuberculosis.
- When a California elementary school teacher returns from overseas travel sick with tuberculosis, her students are screened, and one of her students is diagnosed with tuberculosis as well.
The Bacille Calmette-Guerin — BCG — vaccine, developed in the beginning of the last century and first used on infants in 1921, is still used routinely in many countries with a high prevalence of tuberculosis to prevent childhood tuberculous meningitis and disseminated disease. In the time since its development however, it has become clear that it does not offer lasting protection for children, poses health risks to infants infected with HIV, and it is largely ineffective for adults.

Preventive Treatment Research

Diagnosis and treatment of tuberculosis infection before it progresses to infectious disease is an important element in tuberculosis control.

In 1993, the same year the World Health Organization recognized tuberculosis as a global health emergency, the organization issued guidelines for the use of isoniazid, a tuberculosis treatment drug, to prevent progression from tuberculosis infection to active disease. Generally prescribed for a course of six months, isoniazid preventive therapy has been demonstrated to reduce the risk of developing tuberculosis disease by as much as 60 percent. Concerns about both toxicity and resistance have limited the use of isoniazid preventive therapy in most countries with high rates of tuberculosis. The protection it offers, however, has not been lasting in HIV and tuberculosis endemic settings. In addition, resource and program limitations, including lack of coordination between TB programs and HIV programs, continue to prevent full universal access to this intervention among those who need it most.

In 2011, CDC-funded research showed that isoniazid used with another medicine, rifapentine for three months was as effective as 9 months of isoniazid alone, and that rates of completing that shorter term preventive treatment were higher. Later that year, the CDC added the 3-month, 12-dose regimen to its recommendations as an alternative prevention measure for some healthy populations but it is not recommended for people with HIV taking antiretroviral treatment and children under 2 years old. The National Institutes of Health is currently conducting a clinical trial testing daily isoniazid and rifapentine for one month to prevent TB in HIV-infected patients.

In the largest study of its kind, The CDC Tuberculosis and Epidemiologic Studies Consortium is comparing the ability of tests to predict when tuberculosis infection will progress to disease.

Vaccine Research

MVA85A, the first human study of an engineered tuberculosis vaccine intended to boost the effectiveness of the BCG vaccine showed the candidate failed to offer significant protection. The results, however, also showed that the candidate was safe, simplifying and reducing failure risk of future trials that use the same immune stimulating formulation.
Breakthroughs

While the world still waits for a significant tuberculosis vaccine breakthrough, the MVA85A trial was the largest and longest tuberculosis vaccine candidate trial in a resource-poor environment, setting a path for future trials. In addition, researchers say samples collected in the course of the trial would be a source for further analysis that could provide valuable information on specific disease risk indicators.

Pipeline

Early trials of more than a dozen tuberculosis vaccine candidates now are underway. More extensive randomized clinical trials to bring successful vaccine candidates to approval and distribution will require extensive resources.

Children and People with HIV

The goal:
Clinical trial research and product development targeting the diagnostic and treatment needs of populations now left behind.

Realities:

- It is possible now for a person treated for HIV to live with a virus that remains incurable but die from tuberculosis, a disease considered curable more than half a century ago;
- Parents now can protect their children from acquiring the virus that leads to HIV, but have no means to protect their children from tuberculosis;
- Tuberculosis treatments remain untested on children, with consequences and outcomes yet to be determined.

The inadequacies of current tools to address the global realities of tuberculosis in the 21st century are amplified among the most vulnerable populations.

Clinical trial research to find appropriate tools for diagnosis, prevention and treatment among both populations has been limited. The newest medicines for drug-resistant tuberculosis have gone untested among these populations with the greatest need for quick and effective treatment. Among the results: tuberculosis, a curable disease, remains the leading cause of death for people living with HIV, while the number of children infected with, sick with, and dying of tuberculosis continues to go uncounted.
Use of Xpert MTB/RIF detects more cases of tuberculosis in children and of people living with HIV compared to sputum microscopy and sputum culture, making the obstacles that restrict access to the technology all the more urgent to address.

**HIV-TB Co-infection**

Immune suppression caused by HIV infection exponentially increases the risk that latent TB infection will progress to active disease; while a person without HIV faces a 5 to 10 percent chance of that progression in his or her lifetime, a person living with HIV faces a 10 percent chance each year that that progression will occur. Although HIV is a major acknowledged driver of the global TB pandemic, the numbers of people living with HIV who become sick with tuberculosis continues to grow, with each of the two diseases accelerating the impact of the other. Because tuberculosis is often disseminated outside the lungs in people living with HIV, it is often undetected by sputum microscopy, the most common diagnostic tool in places where both HIV and tuberculosis are endemic. Successful treatment for tuberculosis among people with HIV is challenged by advanced disease and interactions with antiretroviral medicines.

**Pediatric TB**

The BCG vaccine that children receive in tuberculosis endemic areas does not offer lasting protection, and is largely ineffective against pulmonary tuberculosis. In addition to programmatic obstacles between children and effective case detection, tuberculosis in children can go undetected because they have difficulty producing sputum for the most common microscopy and culture diagnostic methods. No treatment has been formulated in dosages or delivery systems specifically for children.

**Continued research is needed to:**

- Develop diagnostic tools that can quickly and accurately detect tuberculosis among children, who have difficulty producing sputum, and among adults and children whose disease is extrapulmonary, including people living with HIV;
- Develop tuberculosis drugs formulated for children with appropriate dosages, delivery and cost, tuberculosis treatments for people living with HIV, including children, that have been proven safe and effective in combination with antiretroviral medicines;
- Develop safe and durable prevention tools, including a vaccine with lasting efficacy to prevent all forms of pediatric tuberculosis, and nontoxic, short course preventive medicines in appropriate doses and formulations for children and people receiving antiretroviral treatment;
- Evaluate the safety and effectiveness of new regimens and novel drugs for people receiving antiretroviral treatment.
The Pipeline

- The urine LAM (Lipoarabinomannan) strip test has shown effectiveness in detecting tuberculosis among adults with advanced HIV, at the point of care in 30 minutes or less, without the need for equipment or reagents. No data exists on the effectiveness of this diagnostic tool in children.²⁷
- Recent findings from a seven-year study offered information that could lead to a “TB risk score” that in turn could lead to the discovery of a genetic “signature” that could lead to a cheap and effective test for childhood tuberculosis.²⁸
- A recent partnership between USAID and bedaquiline maker Janssen to expand access to the medicine will also lead to safety and efficacy trials of the treatment among people living with HIV.
- A grant from the global health financing organization UNITAID to the TB Alliance to develop pediatric tuberculosis treatments is aiming to bring three appropriately dosed and child-friendly versions of existing drugs to market by the end of 2015.

The Future of U.S. Investment

Funding for the National Institutes of Health has remained stagnant for the last half decade. Funding cuts that would reduce allocations for tuberculosis research and development at USAID have been proposed, and overridden, for each of the last three years. The budgets of the CDC TB Trials Consortium and the TB Epidemiologic Studies Consortium have declined in recent years.

In March 2015, the White House released its National Action Plan for Combating Antibiotic Resistant Bacteria²⁹ to guide responses to pathogens becoming resistant to currently available medicines. Designating multidrug-resistant tuberculosis as one of five “serious threats,” the plan calls for accelerated drug development through public-private partnerships between the National Institutes of Health and pharmaceutical companies, with goals that include at least two new drugs targeting bacteria listed as urgent or serious threats entering late stage clinical trials within three years. In addition, the Obama administration called for a plan specifically targeting tuberculosis to be submitted to the White House by September 15, 2015. The implementation of both plans will require significant additional funding. And as the search for new tools to prevent, diagnose, treat and cure tuberculosis progresses, the costs of late stage trials will demand greater investment in research and development.

With continued commitment, the payoffs can be greater still:

- Diagnostic tools that detect tuberculosis and drug resistance everywhere people live with the disease;
- Treatments that cure and contain tuberculosis everywhere the disease continues to take a toll;
- Tuberculosis infections that are cleared before they progress to disease;
- Children and people living with HIV who are no longer left behind;
- A vaccine that gives children and adults lasting protection against tuberculosis.
- An end to the threat that uncontrolled tuberculosis anywhere continues to pose everywhere.
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