Mycobacterium tuberculosis (Mtbb) has decimated populations through history, but has been treatable and curable since the 1940s. In spite of that, it is the number one killer of people with HIV, and worldwide is responsible for the deaths of nearly 1.5 million people each year.

People can become infected when they inhale Mtbb-contaminated air. When people are infected, but not sick from the bacteria, they have latent tuberculosis and may never become sick or transmit the organism. When their immune systems don’t stop the bacteria from growing and spreading, they become sick with tuberculosis (TB) and may become contagious. Although TB most commonly attacks the lungs, the TB bacteria can affect all parts of the body from the brain to the bones. While 90 percent of those infected with Mtbb will never get sick with active tuberculosis, more than 8 million people do develop the disease each year, and more than a million die from this disease that has been curable for more than 60 years. People with weakened immune systems, including those with HIV infection and diabetes, face greater risks of developing active TB disease and its consequences.

While HIV and urbanization have fueled tuberculosis globally, underfunded and poorly managed programs around the world have led to increasing numbers of people not completing treatment and developing strains of TB that do not respond to most, or all of the best available or first line drugs. These drug-resistant strains of disease are being spread widely, with the result that hundreds of thousands of people worldwide now have a disease that can only be treated by increasingly expensive and toxic drugs—if at all. About 60 percent of those sick with extensively drug resistant TB (XDR TB), which is resistant to at least three major classes of drugs, die. The death rate from XDR TB is higher still for those who are diagnosed late, have limited treatment access and/or are also infected with HIV.

Diagnostic tools have not kept pace with the disease. The most affected communities rely on the more than century-old method of having a patient cough and spit in a cup, and examining that sputum under a microscope. This method fails to detect tuberculosis disease more than half the time. It is particularly ineffective in detecting disease among children and people living with HIV. Microscopic analysis of cultures grown from sputum are more accurate but are often unavailable in poor countries, and take weeks to deliver results by which time patients may have transmitted the disease to those around them, and be lost to care, or die.

Failures to diagnose, prevent and treat tuberculosis have led to the emergence of virtually untreatable forms of the disease. It doesn't have to be this way. Research over the last 20 years has yielded advances that can, once again, stop the toll of tuberculosis.
TUBERCULOSIS TIMELINE

460 BC: Hippocrates recognizes the disease as “phthisis” (consumption).

1865: French surgeon Jean-Antoine Villemin proves TB is contagious.1

1882: Robert Koch identifies Mycobacterium tuberculosis (Mtbc).2

1890: Robert Koch's tuberculin fails as a vaccine against TB.3

1921: The first newborn is vaccinated with the BCG vaccine, developed by Albert Calmette and Camille Guerin4 against TB.

1927: BCG is shown effective in newborns.5

1943: Dr. Selman A. Waksman isolates streptomycin, an antibiotic that stops TB's progress.

1944: A patient treated with streptomycin is declared cured of TB.6

1948: One of the first published randomized controlled clinical research trials shows TB patients cured by streptomycin. When a number relapse, research indicates their disease has become resistant to the drug.7

1951: A new drug, isoniazid, shows improved outcomes.8

1952: It is recognized that the use of three drugs—streptomycin, paraaminosalicylic acid and isoniazid will deliver a cure.

1957: Rifampin brings greater improvements, but evidence of resistance to the drug soon follows.9

1950s–1970s: Worldwide disease and death rates drop and sanitariums in the United States close. The United Nations predicts the worldwide elimination of TB by 2025.10 Funding for scientific pursuit of new TB vaccines and treatments also drops.

Impact

- An estimated 8.7 million new cases of tuberculosis and an estimated 1.4 million deaths from TB1 occurred in 2011.

- One third of the world’s population has latent TB, which means they have been infected with TB but are not ill, or infectious to others, but could go on to develop TB disease.

- TB and poverty are intimately connected. Poverty results in crowding and under nutrition, each of which increases TB risk. Conversely, TB is a major cause of poverty, as people who are sick with TB become unable to work, lose employment and family income and may not be able to access and pay for treatment.

- The link between TB and diabetes could have even greater impact if obesity and diabetes become more widespread, as expected, in resource-poor regions grappling with already high rates of TB.2

- In parts of the world where TB has the greatest impact, TB diagnostics are primitive and not available, with resultant delays in diagnosis and treatment.

- Every year an estimated three million people with TB disease go undiagnosed and untreated according to international guidelines.

- TB treatment can be highly effective but is prolonged and challenging.

- TB resistance to the best available drugs is increasing worldwide, accompanied by high rates of mortality and transmission. Globally more than 3.7 percent of new cases and 20 percent of previously diagnosed cases of TB are resistant to multiple drugs.

- TB is one of the top killers of women worldwide.

- Women are at risk for TB during pregnancy or soon after delivery and of transmitting TB to infants.

- In 2010 alone, an estimated 10 million children lost a parent to TB.

- Approximately 10 percent of all TB occurs in children.

- TB frequently goes undiagnosed in children; it is estimated that at least half a million children become ill with TB each year, and as many as 70,000 children die of TB.

- Infants and young children are at greatest risk of severe forms of TB, including TB meningitis that can leave them blind, deaf, paralyzed or mentally disabled.

- Levels of TB in prisons have been reported to be as much as 100 times higher than that of the general population, accounting for up to 25 percent of some countries’ TB burden. While the world’s prisons hold 8 to 10 million prisoners on any given day, about 5 times that number pass through prisons each year, returning to outside communities and further spreading both drug susceptible and drug resistant TB widely.

- Other populations at significantly increased occupational risk for TB globally include miners and health care workers.
Responses

Most countries’ national TB programs have adopted the World Health Organization’s Stop TB strategy: Expanding and improving Directly Observed Treatment, addressing both HIV and TB, as well as multidrug-resistant TB among the poorest and most vulnerable populations, strengthening health systems based on access to primary care, engaging all care providers, building partnerships with those affected by TB, and enabling and promoting research.

In 2010, the World Health Organization approved a new diagnostic tool, Cepheid’s Xpert MTB/RIF for rapid diagnosis of TB, multidrug-resistant TB and TB in HIV-infected individuals. The machine, which incorporated modern DNA technology into TB diagnosis, produces results in about two hours. The United States Food and Drug Administration granted its approval to the diagnostic tool for use in the U.S., in 2013.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

Since 2003 the Global Fund has been the leading international donor for TB, accounting for 82 percent of funding for the international TB response in 2012. Global Fund recipients have detected and treated 9.3 million new TB cases.

The President’s Emergency Plan for AIDS Relief

PEPFAR supports country responses to TB-HIV co-infection, and in 2011, 230,000 patients in HIV care or treatment started TB treatment. Having developed in-country capacity to deliver AIDS medications, the PEPFAR platform is now being used to better deliver TB treatment and diagnostics as well. PEPFAR has deployed a significant number of Xpert machines to improve TB diagnosis at clinical sites in African countries with high rates of TB/HIV co-infection.

The United States Agency for International Development

USAID’S TB Program focuses on providing technical assistance to governments of the hardest hit countries across the globe, through programs that include TB CARE, and invests in research activities that improve country-level TB programs’ capacities to deliver earlier diagnoses and effective treatment. The agency also supports research for new TB medicines that can treat all strains of the disease more quickly and with fewer side effects.

The Centers for Disease Control and Prevention

The CDC hosts the TB Trials Consortium, a network of domestic and international clinical trials sites that evaluate new anti-TB drug candidates.

The National Institutes of Health

NIH is the largest funder of basic TB research in the world. In recent years, the extensive HIV clinical trials networks funded by the National Institute of Allergies and Infectious Diseases (NIAID) have expanded the reach of these networks to conduct TB clinical trials.
Progress

Worldwide the number of TB deaths has been declining and the death rate from TB has fallen by more than 40 percent since 1990.\(^4\) The number of TB cases has been falling since 2006\(^5\) and TB incidence has been falling since 2002.\(^6\)

At the end of 2012, the United States Food and Drug Administration gave its approval to bedaquiline, marketed as Sirturo, the first new TB drug in more than 40 years, opening the way for improved treatment for patients with multidrug resistant TB who have run out of other options. In June 2013, The World Health Organization issued a guidance that added bedaquiline to the list of WHO-approved TB treatment regimens.

While their availability to the millions of people who will need them remains years away, promising new drugs to treat TB infection and disease are in development.

After years of little action in TB research and development, numerous TB vaccine candidates are now being tested.

At the same time, given the magnitude of the worldwide TB problem, resources to implement a comprehensive global TB program remain insufficient.

Gaps

PREVENTION

TB vaccine: The only current vaccine, BCG, was developed in 1921 and while it offers some transient protection to infants, it does not offer lasting protection. It is not effective in preventing adult pulmonary TB, which accounts for most of the global disease burden worldwide and is responsible for transmission to others. Although BCG is the most widely administered vaccine in the world, the global burden of TB remains enormous. Research is ongoing to find a safe effective vaccine that can offer protection to adults, to people living with HIV, and against drug-resistant strains of the disease, but currently, there is no effective available TB vaccine.

Airborne infection control: Appropriate infection control strategies, including the use of masks by health care workers and patients with active disease, the segregation of coughing patients, and good ventilation, are often absent in developing world healthcare settings. This gap fuels the spread of TB, including resistant strains. Increasing evidence shows that the transmission of resistant TB organisms from one person to another, rather than incomplete treatment, is the most common cause for TB drug resistance. Increased attention to airborne infection control is needed.

Preventive treatment with isoniazid for people living with HIV: World Health Organization guidelines say that people with HIV can be protected from tuberculosis with regular, low-cost preventive medication—isoniazid—but this preventive measure continues to be inaccessible to most HIV patients in low resource, high disease burden settings.
SCREENING AND DIAGNOSIS
While experience has shown that the best way to prevent drug resistant TB is to diagnose and treat all cases promptly, accurate tools to rapidly diagnose the disease are often unavailable, or, when available, can take months to deliver results in resource poor settings. The resulting delays in treatment and inappropriate treatment can lead to drug resistance and ongoing transmission to others.

The Xpert leads to earlier diagnosis of TB, particularly among people living with HIV, and reveals some forms of drug resistant disease. More diagnostic tools are needed that deliver rapid results, can be administered by community health workers at rural clinics, can be low cost, and can diagnose TB and multidrug-resistant TB in children, adults and HIV-infected individuals. In addition, screening needs to be extended beyond health care facilities and into community and household settings in order to diagnose and treat TB earlier and interrupt transmission of TB to others. In areas with high prevalence of both diseases, integration of TB and HIV screening is essential.

TREATMENT
The treatment regimen for TB involves taking several antibiotic medicines for six months or more for “simple” TB that responds to first-line treatment, and two years or more for drug-resistant disease. This is best accomplished with the help of trained healthcare providers, adequate nutrition, reliable drug supplies and community support—all of which can be unavailable in resource poor settings. Logistical challenges on the ground and inadequacies of many TB treatment programs can result in individual patient treatment failure.

Effective community-based TB treatment programs that train and pay community healthcare workers to treat individuals in their homes, including patients with drug resistant TB, have shown promising results but need to be scaled up and adequately resourced.

Integration of TB and HIV treatment, among co-infected individuals improves the outcome of both diseases and is critically important. Providing antiretroviral treatment for TB patients known to be living with HIV must double to meet WHO’s recommendation that all TB patients living with HIV receive antiretroviral treatment. Weak and underfunded health systems, shortages of TB drugs and even fake and substandard medicines, all contribute to inadequate treatment of TB, treatment failure and drug resistance.

- Less than half of MDR-TB patients started on treatment worldwide in 2009 successfully completed treatment, with 15 percent dying, and 28 percent lost to follow up, with adverse drug reactions being among the causes. Of 200 extensively drug-resistant TB patients in 14 countries, just a third completed treatment successfully, while more than a quarter of the patients died. Only one in five of the drug-resistant cases among pulmonary TB patients reported in the world in 2011 was enrolled in treatment.

- New, less toxic drugs that can cure TB more quickly, and are effective against strains of TB that are resistant to current drugs, are urgently needed.

- Accurate means to test resistance to bedaquiline and other second-line drugs are still urgently needed.

The development of the GeneXpert led to quicker and more accurate diagnoses of TB. More diagnostic tools that can be used in clinics where patients receive care are urgently needed.
2006: WHO convenes a global task force on XDR-TB.  

2006: The nonprofit FIND and the diagnostics company Cepheid team collaborate to develop a novel TB test, leading to the development of the Xpert MTB/RIF to provide rapid and accurate diagnoses of TB disease and resistance to rifampin.  

2008: WHO convenes a meeting of international participants to develop recommendations for national TB programs to apply the Three I’s for people living with HIV: Isoniazid preventive treatment, Intensified case finding, and Infection control.  

2009: The development of Cepheid’s Xpert MTB/RIF is announced.  

2010: WHO recommends the use of the Xpert MTB/RIF after data showing its effectiveness are published in the New England Journal of Medicine.  

2012: A partnership between PEPFAR, USAID, UNITAID, and the Bill and Melinda Gates Foundation brings the price of Xpert MTB/RIF test cartridges down from 16.86 each, to $9.98 each, and by the end of the year, 77 countries around the world have adopted the test.  

2013: The World Health Organization issues a guidance to include bedaquiline in treatment for multidrug resistant tuberculosis for some patients. The FDA approves the Xpert MTB/ RIF test for marketing in the U.S.  

The Future

Although new TB research and development is gathering momentum after decades of neglect, TB, a curable disease, remains one of the world’s most important killers of young and productive adults and of children. Widespread implementation of TB prevention strategies, an accurate, rapid and cheap portable diagnostic test, effective new drug regimens to treat all types of TB, and a TB vaccine remain elusive and years away. Science, policy and funding have made strides in the last decade, but without continued and increased funding for research and strengthening of TB programs, progress will be unacceptably slow. We can accomplish a great deal with existing tools and with the full participation of communities to reduce the toll of one of the world’s oldest and deadliest infections. Science, in collaboration with government and affected communities, has proven that this is a disease that can be defeated. But TB has shown before that it can move stealthily, and more quickly than efforts to combat it that are not fully committed and sustained.
TUBERCULOSIS: An Ancient Disease, a 21st Century Global Crisis

1. World Health Organization, Global Tuberculosis Report 2012
3. World Health Organization, Tuberculosis in Prisons 2013
5. World Health Organization Global Tuberculosis Control 2011
6. World Health Organization 2011

TIMELINE ENDNOTES
1. Dallas Morning News, April 15, 2010, from Texas Department of State Health Services
9. Iseman, M.D. Tuberculosis therapy: past, present and future, European Respiratory Journal, 20, 36 suppl 87S-94s
10. NIAID, Age of Optimism, August, 2010
15. World Health Organization, 2006
17. World Health Organization February, 2013
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