

Executive Summary

- Tuberculosis (TB) is a severe and highly contagious bacterial disease that is frequently fatal if untreated
- TB annually causes 9M infections and 1.5M deaths, leading to 49M lost disability adjusted life years
- Co-infection with HIV/AIDS is common and increases both susceptibility and disease severity/mortality
- Sub-Saharan Africa and Southeast Asia are especially burdened, accounting for nearly 80% of TB cases
- Treatment and prevention options are limited and there is a pressing need for innovation in both areas

Tuberculosis is a severe, chronic, sometimes fatal bacterial infection

Tuberculosis (TB) is a chronic, highly contagious, sometimes fatal infection caused by the bacterial pathogen *Mycobacterium tuberculosis*. Tuberculosis is usually associated with lung disease, but can affect every organ system, and is found outside the lungs in roughly 20% of cases (Jindal 2011:549).

Tuberculosis is highly contagious and easily spreads through the air

The disease is spread through person-to-person contact, particularly through aerosols. When infected individuals cough, sneeze, or even speak, they release tiny droplets of lung fluid that contain live bacteria. This aerosol is highly contagious, as a single droplet is sufficient to cause infection (Nicas, Nazaroff, and Hubbard 2005). Those with prolonged or frequent contact with infected individuals are especially likely to contract the disease, with infection rates of over 20% (Ahmed and Hasnain 2011).

Tuberculosis causes severe symptoms that can persist for the patient's lifetime

TB infections are divided into two types: latent and active, which differ greatly in their development. Following inhalation of infectious aerosol, live bacteria travel into the lungs and collect in the alveoli, the smallest structures within the lungs. The bacteria are then surrounded and engulfed by immune cells, which encase and trap the bacteria inside a tough shell known as a granuloma. This entire process lasts from 2 to 8 weeks (CDC 2013).

In latent infections (~90% of cases), the granuloma is intact and prevents replication and dissemination of bacteria. These patients are asymptomatic, noninfectious, and do not have TB. In active infections (~10% of cases), the granuloma is unable to contain the bacteria, which begin rapidly growing and may spread to other organs. These patients have TB and are highly contagious. They develop chronic, bloody cough with persistent fever and rapid weight loss. Bacteria may also spread to other organs, causing severe, debilitating symptoms.

In both latent and active patients, without treatment, the bacteria persist in the body for the life for the patient, and there is always the chance that latent disease will progress to active disease. In addition, common co-morbidities include HIV/AIDS (see below), malnutrition, and diabetes.

HIV/AIDS is commonly associated with tuberculosis, enhancing infectivity and severity

By far the most significant co-morbidity associated with TB is HIV/AIDS, which impacts all areas of the disease: susceptibility, progression, treatment, and outcome. Taken together, HIV and TB are known as a syndemic, a convergence of two diseases that act synergistically. HIV infection is the strongest risk factor for developing active TB, and it greatly increases the risk of bacteria disseminating to other organs. Roughly 15% of new TB cases each year are co-infected with HIV, and roughly 30% of HIV patients have either latent or active TB. HIV co-infection doubles TB mortality, with 30% of TB deaths each year are in HIV patients (Kwan and Ernst 2011).

Tuberculosis infects millions per years, especially among vulnerable populations

There are roughly 9 million new cases of TB and 1.5 million deaths due to TB each year (WHO 2012). As of 2010, TB was responsible for the loss of more than 49 million disability adjusted life years, making it one of the 15 leading causes of death and disability worldwide (IHME 2010). The very young and the elderly are both more susceptible to TB infection and more likely to develop severe forms of the disease. In addition, TB is unequally distributed along geographic and socioeconomic axes, with 22 high-burden countries – nearly all located in Sub-Saharan Africa and Southeast Asia – accounting for 80% of all TB cases (WHO 2012). Contributing factors such

as malnutrition and overcrowding exacerbate both the spread and the progression of TB, leading to it being recognized as a “disease of poverty” (Grange and Zumla 1999). As a result, the TB burden falls unequally on vulnerable populations, particularly the homeless, incarcerated, and institutionalized.

Treatment is difficult, with substantial social barriers to success

The unique structure of the TB infection makes it difficult to target and treat, with cures usually requiring a six-month regimen of daily antibiotics. Compliance is a major barrier, with patients failing to complete adequate therapy in a large number of cases. Factors such as lack of follow-up care, lack of surveillance, difficulty accessing treatment locations, presence of side effects, and lack of family or community support structure all contribute to treatment failures (Castelnuovo 2010).

In addition, there is widespread drug resistance, in which the disease does not respond to the standard therapy. Roughly 4% of new and 20% of recurrent cases do not respond to the first-line treatments, and of those, roughly 9% do not respond to more than half of the second-line treatments (WHO 2012). Lack of compliance with therapy enhances the spread of drug resistance, creating a recurrent cycle. Left untreated, active TB kills 70% of patients within 10 years (Tiemersma et al. 2011).

Prevention options are limited in both availability and efficacy

TB prevention efforts rely primarily on surveillance and screening in order to identify and treat contagious individuals, requiring substantial public health personnel and tracking resources. A single vaccine – bacille Calmette–Guérin, abbreviated BCG – has been available for nearly a century, but it has limited efficacy. It is effective at preventing the severe disseminated form of the disease in children, but confers only weak resistance against the common lung infection, and its effectiveness wanes after 10 years (McShane 2011). Despite these shortcomings, the vaccine is widely used, with over 90% of all children vaccinated (Lawn and Zumla 2011).

Tuberculosis management requires a complex network of personnel and services

The World Health Organization declared TB a global emergency in 1993, and since then many private, public, and governmental initiatives have emerged to combat the disease. In particular, the Stop TB Partnership was launched in 2000, with a goal of reducing TB deaths by 50% relative to 1990 values by 2015 (Stop TB 2010). Similarly, the Millennium Development Goals established a target of halting and reversing TB incidence by 2015. Both of these goals are currently on track for success. Two decades of research and on-the-ground efforts have revealed a number of factors essential for TB control, including:

- Ample supplies of high quality first-line and second-line medications
- Point-of-care diagnostic tools for rapid screening and patient identification
- Rapid testing to identify drug resistance and alter treatment accordingly
- Social support services to combat common causes of therapy failure
- Personnel, including community health workers, to monitor therapy compliance
- Cross-testing for both HIV and TB in patients identified with either

There are large unmet needs to develop innovative solutions to manage the disease

There is a pressing need for innovative solutions to prevent, diagnose, and treat TB. These include traditional, laboratory R&D discoveries (vaccines, biomarkers, drugs) as well as more disruptive solutions that address the myriad social factors that influence the disease. While overall prevalence and incidence rates for TB have been falling steadily for several years, progress has lagged behind in addressing HIV/AIDS co-infection and slowing the spread of drug resistance. New solutions that enhance capacity to communicate screening results and survey treatment without relying on increasing available personnel would be especially impactful.

The estimated burden of cost for TB management is US\$ 8 billion for the 2013-2015 period, with an anticipated funding gap of US\$ 3 billion per year. International aid is particularly critical, accounting for more than 60% of funding in low-income, high-burden countries, mostly in Africa. In addition, US\$ 2 billion per year is expected to be required for continued research and development of novel technologies (WHO 2012).

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