Drug Resistant Tuberculosis: Evolution of an Ancient Threat

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More than 130 years past the breakthrough discovery by Robert Koch, while we observe yet another ‘World TB Day’ on 24 March, it is crucial to revise and reshape our existing policies to manage TB. It is the need of the hour to explore and implement policies and pursue cutting-edge translational research that can ensure novel, easily accessible and affordable drugs for TB.

Consumption, Phthisis, Pott's disease, Scrofula, White Plague – Tuberculosis (TB) since the ancient ages has been an epidemic with many names. Finding reference in some of the world’s oldest literatures, ranging from the Sultras in ‘Astharva Veda’ to Hippocratic writings and works of Galen, molecular evidence from ancient skeletal artifacts establish that TB has been afflicting human population from Indus to Greek since as early as 3000-5000 B.C.

*Mycobacterium tuberculosis* as seen under scanning electron micrograph (Source: https://sitetobacteriology.net/tuberculosis.html)

While humankind survived and evolved along the lines of Darwinian principles, growing to exercise control over the environment, it is interesting to note that the TB bacilli *Mycobacterium tuberculosis* (M.tb) has evolved parallelly. Today, despite the tremendous progress achieved by medical science, TB still remains a threat at large.

According to the World Health Organization's (WHO) World TB Report 2012, about 1.4 million people succumbed to TB in 2011 and 5.8 million new cases have emerged. It is estimated that at least one person in the world is newly infected with M.tb every second and there occurs 2 deaths every 3 minutes in India, making TB one of the formidable challenges of the 21st century.

Tuberculosis: A Short History

Tuberculosis is a highly contagious, airborne infection caused by *Mycobacterium tuberculosis* (M.tb). Previously known as the tubercle bacillus it belongs to a family of bacteria that are closely related to and have supposedly evolved from the microbes that constitute the “living” component of soil. Genetic studies suggest that this species of Mycobacteria probably emerged from the soil to find a different niche, first infecting and then infecting various mammals and birds.

It is postulated that M.tb evolved from a parent strain *Mycobacterium bovis*, an animal pathogen infecting primates and ruminants and the strain was first systematically introduced into human society when man domesticated cattle around 5000 B.C. The parental strain from
the cattle, needless to say, underwent a complex process of evolution and host adaptations within various organs of the human body to become the tubercle bacillus, in the process, causing TB.

While the disease manifested itself through various symptoms ranging from severe cough, fever, chills, night sweats, loss of appetite, severe weight loss, blood in sputum, etc., the underlying cause of the infection was unknown till 19th century. M.tb was first discovered by Robert Koch, a German physician in 1882. It is said that when Koch presented his findings on the infectious cause of TB on the evening of 24 March 1882, a day commemorated as ‘World TB Day’ today, silence engulfed the audience at the Berlin Physiological Society. It was a giant leap for healthcare and medicine when Koch announced:

“In the future the fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite, whose living conditions are for the most part known and can be investigated further.”

With the anonymity lifted, it was perceived that a means to combat TB, one of the leading killers of the century, was within reach.

**Hunt for Drugs and Problem of Resistance**

While the discovery of therapeutics for TB indeed marks a milestone in the history of modern medicine, it was not until 60 years after the historical announcement of Robert Koch that an effective cure for TB saw the light of the day. While the 1930s and 1940s saw the widespread use of antibiotics like Penicillin and Sulfa drugs, it soon became evident that M.tb was highly resistant to these drugs rendering them ineffective for the treatment of TB.

Later in 1943, Selman Waksman from Rutgers University identified and isolated the first anti tuberculosis agent Streptomycin, while screening soil microbes. It was reported as an effective anti-TB compound in 1944 after the first patient to be administered with it was declared cured of infection.

Following this, in 1948 the British Medical Research Council conducted the first published clinical drug trial using streptomycin. The trial revealed alarming results. Although streptomycin showed high degree of efficacy in alleviating the symptoms of TB, curing a large section of patients, it was observed that a substantial proportion underwent a relapse. Studies proved that while most bacilli in an M.tb population were susceptible to streptomycin, there occurred mutant strains, as found in the relapse patients which were resistant to streptomycin. Emerging fitter than the susceptible strains, and without competition for the host’s tissues these resistant strains soon evolved and established themselves as the dominant subspecies, necessitating the discovery of novel drugs.

Shortly afterwards, two new drugs, para-aminosalicylic acid and thiacetazone, were discovered and it was observed that simultaneous administration of these along with streptomycin significantly increased the cure rates declining the antibiotic resistance. In 1951, isonicotinic acid hydrazide commonly called isoniazid was proved to improve clinical outcomes followed by the development of more potent anti-TB drugs like pyrazinamide (1952), cycloserine (1952), ethionamide (1956), rifampicin (1957) and ethambutol (1962).

The discovery of these drugs, in particular rifampicin and isoniazid was expected to revolutionize TB therapy, and it indeed proved to be so; at least for a while. The high level of efficacy and ease of administration of these drugs proved pivotal in the treatment of TB, but soon after their introduction it was observed that the advent of every novel drug resulted in the selection of mutations conferring resistance rendering the emergence of stronger drug-resistant strains of M.tb. Laboratory data from clinical trials soon established the rapid onset of rifampicin and isoniazid resistance among patients who were subjected to single drug therapy.

It was also observed that resistance could, to a large extent, be suppressed when these medicines were used in combination with streptomycin or para-aminosalicylic acid. Extensive research and drug trials that followed these
Drug-resistant TB
A dangerous variant of the tuberculosis (TB) bacteria

- Resistant to the most powerful anti-TB drugs of the four first line (standard) drugs against TB.
- Resistant to three or more of six classes of second-line drugs (more expensive, less effective drugs used when first line fails).
- First described in 2006 after an outbreak in South African town of Tugela Ferry.
- More than 5,000 cases reported worldwide.

Multi-drug resistant TB (MDR-TB)
Strain that thwarts the two most powerful of first line drugs.

Drug resistance is caused by:
- Incorrect prescription
- Poor quality drugs
- Erratic supply of drugs
- Patient non-adherence

(Source WHO/NIH; © www.medindiat.net)

While extensive efforts and resources are channelled towards the discovery of drugs for various modern age life style diseases, the drug discovery pipeline for TB, the ancient disease affecting almost 1/3rd of the world population, is relatively dry.

...face side-effects varying from vomiting, dizziness and skin rashes to drug induced hepatitis. Both these factors often result in irregular or incomplete adherence to the drug regimen and discontinuation of courses often lead to the development of new drug resistant strains.

This process was further aided by the prolonged diagnosis of TB, often punctuated with inadequate and flawed administration of existing treatment. As a consequence, by the late 1980s and early 1990s outbreaks of a new type of infection – Multiple Drug Resistant Tuberculosis (MDR-TB) – was being reported in the US. MDR-TB is defined by microbial resistance to the two most commonly used first-line drugs in the four-drug regimen, isoniazid and rifampicin. While normal sputum-smear microscopy failed to detect drug resistance, by the early-to-mid-1990s, MDR-TB was being diagnosed in different parts of the world with the diagnostic capacity to trace it. While it was known that resistance was caused due to irregular intake of drugs, it was evident that with the aerial transmission of these resistant strains, MDR-TB was to soon become a global pandemic.

According to WHO Report 2012, the number of cases of MDR-TB notified in the 27 high MDR-TB burden countries has increased and reached almost 60000 worldwide in 2011, but this figure accounts only for 19% of the notified TB patients estimated to have MDR-TB. There were an estimated 310000 MDR-TB cases among notified TB patients with pulmonary TB in 2011. India is estimated to have the highest number of MDR-TB cases and 2.1% of new TB cases are MDR-TB in India. It is estimated that there were 21000 new MDR-TB cases among notified pulmonary TB cases in India in 2011.

MDR, XDR, XXDR & TDR – Evolving Threats

Over time, this intervention technique came to be the standard and globally accepted treatment regimen for TB due to its relative efficiency and cost-effectiveness. In 1993, WHO reformed and promoted this short-course chemotherapy under the name of DOTS (directly observed therapy, short-course) strategy. DOTS programme consists of TB diagnosis using sputum-smear microscopy, and a treatment approach based on the use of first-line anti-TB agents. The medications are administered under direct observation of medical staff and the cases and treatment outcomes are reported and recorded in a standardized manner.

While this intervention, to a large extent, proved to be useful in combating the threats posed by TB, there were also serious disadvantages to this method. The treatment regimen was too long ranging from 6-9 months and risk prone. It was also not uncommon for the patients to...

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A more severe ramification of this infection, called the Extensively Drug Resistant Tuberculosis (XDR-TB), was first reported in 2006. XDR-TB, is defined by microbial- resistance to at least four of the core anti-TB drugs. This involves resistance to the first-line drugs, isoniazid and rifampicin, as in the case of MDR-TB along with resistance to the second-line drugs under the category of fluoroquinolones (such as ofloxacin or moxifloxacin) and to at least one of three injectable second-line drugs (aminocin, capreomycin or kanamycin). While many countries across the world lack the required capacity to accurately diagnose XDR-TB, by 2012, 84 countries across the world confirmed the cases of XDR-TB.

While the management of drug sensitive TB in itself is a lengthy and risk prone process, the treatment of MDR and XDR cases with existing antibiotics can take up to two years or more, and is highly complex, expensive, and toxic. It is estimated that a third of all MDR-TB patients die owing to the heavy dose regimen and complications associated with treatment – 70% of XDR-TB patients die within a month of diagnosis.

Merely a year after the first reports of XDR-TB appeared, in 2007 another highly resistant form of TB was documented in Italy. Later in 2009, 15 patients from Iran were reported to be resistant to all the tested anti-TB drugs. These cases led the experts to postulate the terms Extremely Drug Resistant (XXDR-TB) and Totally Drug Resistant TB (TDR-TB). In 2011 medical practitioners from Hinduja Hospital, Mumbai reported the first case of TDR-TB in India. Studies described 4 patients who were resistant to all the first-line and second-line drugs. Subsequent media reports indicated 8 more cases. Though extremely rare and yet not clearly defined, TDR-TB is to be much feared as it is known to be the virtually untreatable form of TB.

The Road Ahead

With the existing TB regimen almost 60 years old and the pathogen having grown resistant to all the existing therapies, there is an urgent need to fuel research in the area of discovery of new and more potent drugs for TB. TB, commonly called the ‘poor man’s disease’, attracts little attention from pharma giants because of the lack of market incentives.

Hence, while extensive efforts and resources are channelled towards the discovery of drugs for various modern age lifestyle diseases, the drug discovery pipeline for TB, the ancient disease affecting almost 1/3rd of the world population, is relatively dry. Lack of profitable markets has discouraged the effort of manufacturing drugs for diseases like TB resulting them to be tagged as Tropical Neglected Diseases (TND) that predominantly afflict the poor population of the developing countries.

With the conventional research methodologies and patent systems failing to drive innovation, a novel, alternate healthcare model for drug discovery and development – the Open Source Drug Discovery Model (OSDD) has emerged as a solution (discussed in the issue under different sections).

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HUMOUR

DOWN TO EARTH GRAVITATION FORCE FALLACY

... not wasting but to gain weight, thus remain down to Earth.

Why are you wasting food of Mother Earth?

Contributed by Gauri Shankar Mukherjee
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