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The TB Bug and its resilience

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Abstract
Drug resistant pathogens today are emerging and spreading more rapidly than in previous decades. These organisms are widespread but also occur increasingly in the community, affecting developed and developing countries, and rapidly spreading through international travel the increase in microorganisms that have developed resistance to currently available antimicrobial agents has become a major cause for concern worldwide. Some of these strains are multi drug resistant/total drug resistant and the agents available to treat infections caused by them are few and dwindling. Over recent years there have been a number of responses by national, international and professional bodies to this situation, many aimed at curbing this unprecedented growth in resistance, but there is an increasing recognition that a major problem in the management of infections caused by such organisms is the paucity of new drugs, resistance to antimicrobials is complex and that multiple solutions are required. Treatment of infections caused by resistant microbes is increasingly hampered either by the prohibitive cost of existing 'new generation' agents or by a total lack of effective antimicrobial agents'. In this article, these issues are discusses in the context of treatment of tuberculosis.

Introduction
Tuberculosis (TB) is an obstreperous disease and common- and in many cases lethal-infectious disease. It usually attacks the lungs, but it can also affect other parts of the body, known as extra pulmonary TB (EPTB). It is spread through the air when people who have an active TB infection cough or sneeze. Symptoms of TB include a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Diagnosis relies on chest X-rays, a tuberculin skin test, and blood tests, as well as microscopic examination and microbiological culture of bodily fluids. TB is very challenging disease and fuelled by: (a) poor detection rate as it takes about 6 months or more to detect the resistant strains, (b) co-infection with HIV/AIDS (Kibret *et al* 2013) (c) enhanced transmission in overcrowded slums, hospitals and prisons,(Graddy *et al* 2011; Haider *et al* 2013) (d) high prevalence of malnutrition, extreme poverty and poor healthcare system, (Wilkinson et al 2012 ; Srivastava et al 2015) (e) increasing cases of diabetes (Pealing *et al* 2015) (f) absence of biomarkers to monitor the success of the treatment and complete eradication of the disease (Zhang 2009) and type of occupation (Patil et al 2014).

A person falls ill with TB about every three seconds—the vast majority of whom live in poor countries. According to the World Health Organization (WHO), 95 percent of all TB deaths occur in developing countries, resulting in about 10 million children who are orphaned due to TB deaths of one or both parents (WHO 2008). People in the developing world are more likely to contract TB because their immune systems are more likely to be compromised due to HIV/AIDS. Today, TB is the leading cause of death for people infected with HIV/AIDS

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(Kibret *et al* 2013). The above reasons presuppose the need of new drugs for the complete and successful treatment of DR-TB (WHO 2013).

This disease offers a glaring example of the health care inequities that exist in the world. Drugs to fight TB have been in existence for 50 years, yet the disease continues to kill almost 4,000 people every day- nearly all of them in developing countries (Narasimhan *et al* 2013). Treatment is difficult and requires long courses of multiple antibiotics - typically at least six months for drug-susceptible TB (Caminero *et al* 2008). Social contacts are also screened and treated if necessary. When people fail to complete the drug regimen for TB, the disease becomes resistant to treatment. It often develops into the more deadly MDR-TB (Madico *et al* 2016).

Discussion

TB is a global problem that we can't afford to keep ignoring. Several potent drugs have been available for the treatment of TB for over70 years (WHO 2015). However, poor management of TB continues to contribute to high mortality which is preventable. The disease has become prevalent in countries like Africa, India, China and Russia. In India nearly 500,000 people die every year due to this dreadful disease. In early times, in the absence of any cure, infected patients faced a slow and painful death, many patients died in infirmaries (WHO 2009, 2014, 2015).

There are about 10 million new TB cases every year worldwide. About 2 million people succumb to this life threatening disease. Some of the main factors which have contributed to this disease are the absence of basic sanitary facilities and the emigration of people from rural to urban crowded slums. About 2 billion people are carriers of M. *tuberculosis* (MTB) in the dormant form worldwide, only 1% of the population will develop an active form of the disease during their life time (WHO 2015). The development of the disease takes place whenever the immunity goes down due to various factors, e.g. old age, human deficiency virus (HIV)/acquired immunodeficient syndrome (AIDS), diabetes mellitus (DM) (Diedrich *et al* 2011; Seeley *et al* 2012). It is difficult to understand how the bacteria can survive for months and years without multiplying or showing any signs of the disease. However, the bacteria remains non-infectious during its dormant form which leads to an unlimited pool of infection(Pai 2014).The antiquated tuberculin test for latent TB is not authentic as it gives false positive results. Interferon Gamma Release Assay (IGRA) is an alternative test to detect for MTB infection instead of Mantoux test. IGRA testing should take place in the context of an overall risk assessment for latent TB infection which considers the individual's history of MTB exposure, clinical history, risk factors, chest radiography, and TST (if applicable). The test relies on the fact that T-lymphocytes release IFN-γ on exposure to specific antigens. Though the indications for the test are still disputed; it has been evaluated for the diagnosis of latent TB in HIV patients (who frequently have a negative Mantoux test) (Pai 2014; Asmar *et al* 2015a & b).

In 2015, TB killed 1.7 million people--almost twice as many people as malaria--and it is the leading cause of death among people living with HIV/AIDS (WHO 2015). This is all the more tragic because these deaths are preventable. For a long time the world thought that we had defeated TB, but just because TB doesn't make headlines doesnot mean it has gone away (Pai *et al* 2010). The fact is that TB is getting worse, as complacency and lack of adequate tools and funding fuel the disease and the spread of drug resistance (DR) (Bwanga *et al* 2009; Kant *et al* 2010). DR-TB is a wake-up call for researchers and doctors world over ; it is an

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airborne epidemic of increasingly untreatable disease. The quality of TB care remains suboptimal, especially in the private and informal sector, where most patients seek initial care. The average TB patient is diagnosed only after several months and seeing multiple providers, most of whom do not follow standard guidelines. Most patients who start treatment are not tested to see if their TB is drug resistant. Those who are found to have multi-drug resistant TB must endure years of therapy with serious adverse effects.

DR-TB develops when TB patients take low-quality drugs, do not finish their full course of treatment, or pass DR- TB from one person to another. Mismanagement of the anti-tubercular drugs may lead to the development of drug resistance (Farazi *et al* 2010; Tripathi *et al* 2012). The time duration for treatment is 6-9 months and symptoms usually disappear after 2-3 months of treatment(WHO 2008; Burki 2010). Hence the patient may discontinue the medication which in turnis the major cause for TB to develop resistant to medication (WHO 2010; Merza *et al* 2011). DR-TB occurs in many forms such as multi-drug resistant tuberculosis (MDR-TB), extensively drug resistant tuberculosis (XDR) and totally drug resistant tuberculosis (TDR-TB) (Borgdorff *et al* 2009; Gao *et al* 2010).
MDR-TB is resistant to the two most commonly used first-line TB drugs (Isoniazid and Rifampicin) and requires long, complex and expensive treatment. Several drugs like streptomycin, amikacin, kanamycin and oral fluoroquinolones can also be given as an alternate therapy. Apart from these, the duration of the treatment may extend up to 18-24 months instead of 6-9 months (Borgdorff *et al* 2009;Gao *et al* 2010). The faulty treatment regimen and unreliable diagnostic tests are also major factors which may lead to the development of resistance**.** XDR-TB is resistant to first- and second-line drugs, severely limiting treatment options(Migliori *et al* 2008; Agrawal *et al* 2009).It is mainly widespread in the countries like Africa, Asia and Soviet Union having majority of cases of HIV/AIDS (Diedrich *et al* 2011; Kibret *et al* 2013). XDR-TB has the highest mortality and morbidity rates if co-infected with HIV/AIDS. TDR-TB is the worst form of TB. It is a condition in which the patients become resistant to all the first and second line drugs ultimately leading to death (Kim *et al* 2008; Migliori *et al* 2008).

While progress is being made, much more is needed. Basic TB control is one of the most cost-effective interventions in global health. Appropriate treatment can save a life and stop the spread of disease for (Steingart *et al* 2014). It is essential that countries implement the WHO internationally recommended Stop TB strategy, which includes directly observed treatment short course programme (DOTS). But due to outdated tools and methods, DOTS alone is not enough. The remarkable fact is that global control of TB, a disease that kills someone every 20 seconds, depends upon a 125-year-old test, an 85-year-old vaccine and drugs that take six months to cure and haven't changed in four decades (Dobler 2016). To successfully treat TB and prevent resistance, we need to use current tools better and accelerate the development of new tools for the future. Simple improvements in TB control, such as expanding the use of under-utilized technologies, can have enormous impact. Fixed-dose combinations have existed for over 25 years, and could help ensure that more patients complete treatment; yet globally, only 15 percent of patients are using those (Satyanarayana *et al* 2011; Dobler 2016)). We also need new drugs, vaccines and diagnostics, as well as innovations in TB control and case management. Better diagnostics are already available, and new drugs and vaccines are coming(Steingart *et al* 2014; Madico *et al* 2016). But more commitment and resources are needed.

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Better prevention and control of TB is the surest way to stop drug resistance. In the last few years, new TB diagnostics have been introduced (Steingart *et al* 2014). The most significant shift in the TB-diagnostics landscape has been the worldwide rollout of Xpert MTB/ RIF. The Xpert MTB/RIF is a cartridge-based automated diagnostic test that can identify MTB DNA and resistance to rifampicin by polymerase chain reaction (PCR) (WHO 2013; UNITAID 2014; Pai 2015). The Xpert technology has significantly increased sensitivity for detection of TB compared to sputum-smear microscopy, and can also rapidly detect rifampicin resistance with high accuracy. Rifampicin resistance is highly indicative of MDR TB, although formal confirmation of Isoniazid resistance is required (UNITAID 2014; Pai 2015).

These include improved basic TB control, increased use of underutilized technologies such as fixed-dose combinations, and new technologies and health systems innovations. At the same time, we should expand access to M/XDR-TB treatment and diagnostics for those who already have DR-TB(WHO 2009; Kalo *et al* 2015). Some of the most innovative solutions can come from the private sector and through partnerships. An untapped market of two billion people carries the TB bacterium. Approximately one- third of the world's population harbors a latent TB infection which greatly complicates efforts aimed TB control (Pai *et al* 2010, 2014).The success of TB pathogen is attributed in significant measure to its ability to survive indefinitely in a dormant state within the host as a latent infection. Therefore priority research goal is to understand the properties of dormant bacteria in order to devise more effective strategies for TB control and to prevent reactivation and clinical control (Steingart *et al* 2014). Since TB requires a comprehensive approach, companies should also explore opportunities to work together and pool complementary technologies to ensure new tools are used most effectively. The major recommendations were as follows:

- Increased efforts are needed to reduce the spread of resistant strains both in the environment and in hospitals—these include improved hygiene and decreased use of some antimicrobials.
- Surveillance of resistance is a key factor and improved technology is needed to improve the potential for surveillance data to inform clinical practice.
- Rapid, sensitive and specific diagnostics are urgently needed.
- Identification and treatment of latent tuberculosis infection (LTBI) can substantially reduce the risk of developing active disease. However, there is no diagnostic gold standard for LTBI.
- Vaccine technology is available but is underused for the prevention of mycobacterial infections, particularly those caused by organisms resistant to antimicrobials.
- Incentives are required to encourage large pharmaceutical companies to partner small
- Biotechnology companies, which are more innovative and have the potential to deliver the new drugs, diagnostics and vaccines.
- In the longer term, basic research is necessary to identify highly predictive biomarkers.

Conflict of interest: None

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