Chapter 1
Introduction

"Wanted: Leaders for a TB-free world"- *focuses on building commitment to end TB, not only at the political level with Heads of State and Ministers of Health, but at all levels from Mayors, Governors, parliamentarians and community leaders, to people affected with TB, civil society advocates, health workers, doctors or nurses, NGOs and other partners. All can be leaders of efforts to end TB in their own work or terrain.*

The theme of World TB Day 2018

1. Introduction

Humans are a minuscule part of entire biomass on earth, but microorganisms spread throughout the biosphere. Most microorganisms participate in digestion of food, growth of plants, and recycling of nutrients in the environment. Human exploited the benefic nature of microorganisms in food and beverage preparation, nitrogen fixation and genetic engineering. In medicine, they are used as probiotics for good functioning of the gut and also for production of antibiotics. In another context, microorganisms are harmful to humans, as they cause diseases and even death. *Mycobacterium tuberculosis* (*Mtb*) is the most harmful among all disease-causing microorganisms. It infected 10.4 million people and claimed 1.8 million deaths in 2015 [1].

1.1. Tuberculosis: An Overview

Tuberculosis (TB) is most rampant disease of the world over the ages of human history [2]. It has been a curse of the human race. Morbidity and mortality of the disease is not matched with any other disease in the world. Among all the communicable diseases, it is the most miserable [3, 4]. Even now, it remains formidable by claiming millions of lives through development of resistance [5]. In 2014, 9.6 million new TB cases and 1.5 million deaths were reported. Out of 1.5 million deaths, 0.4 million were

immune compromised HIV-positive patients [6]. In 2015, the number of deaths had increased to 1.8 million (1.4 million HIV-negative and 0.4 million HIV-positive) and the number of new cases has risen to 10.4 million. 60% of the reported cases were from six countries, *i.e.* India, Indonesia, China, Nigeria, Pakistan and South Africa [1]. Lack of novel drugs in countering the resistance is a serious threat [7]. The transmission of pulmonary TB to Bacillus Calmette Guerin (BCG) vaccinated patients is also a pressing threat in the absence of any new TB vaccine [8, 9].

1.2. Geographical Distribution of TB

TB is predominant in tropical countries and is more concentrated in south-east Asia. Almost half and over quarter of the total cases are reported in south-east Asian and African countries, respectively. Western Pacific and Eastern Mediterranean countries account for 15 and 7 % of total cases, respectively. The rest 6 % of total cases are reported in American and European countries (**Figure 1-1**). WHO has categorized 30 nations as TB high burden countries on the basis of total numbers and severity of TB cases. They include Angola, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand, Zimbabwe, Bangladesh, Brazil, Cambodia, Congo, Central African Republic, DPR Korea, Lesotho, Liberia, Namibia, Pakistan, Philippines, Russian Federation, Sierra Leone, the United Republic of Tanzania, Vietnam and Zambia.

1.3. TB in India

India is in the list of high burden TB countries for several years and also accounted for a larger number of TB cases with over 25 % of the reported cases worldwide. In 2015 alone, WHO has estimated 2.8 million new TB cases, which was 2.9 million in 2014. India has strong commitment for TB free India and has formulated a national advocacy campaign called “The Call to Action for a TB-Free India” to create awareness, political

commitment, to increase public-private partnerships, and to mobilize national resources to eradicate TB by 2025.

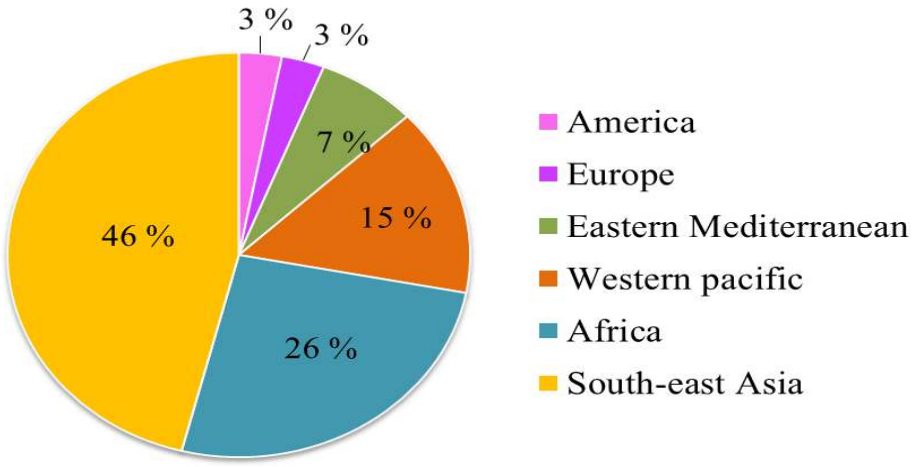

Figure 1-1: Geographical distribution of TB

1.4. Transmission of TB

TB is a contagious disease caused by *Mycobacterium tuberculosis* (*Mtb*) [10]. The TB infection gets transmitted through airborne particles released by pulmonary or laryngeal TB patients when they sneeze, cough, shout and sing. The transmission depends on proximity, frequency, and duration of exposure. It also depends on the susceptibility of transmitted individuals and quantity of *Mtb* release from transmitting individuals.

1.5. Pathogenesis of TB

When a person inhales the airborne particles released by the infected patient, it reaches the alveoli of lungs. There it gets multiplied and a small number of it spreads to different parts of the body through blood. The macrophages entrap the entered *Mtb* and form granuloma that keeps the bacilli under control as latent tuberculosis infection. When the immune system fails to control *Mtb*, it multiplies rapidly to form active TB disease. The active form is contagious as they may spread to other people, but the latent form is always non-contagious unless it is converted to the active form. TB usually

involves the lungs and is known as pulmonary tuberculosis. It can also occur outside the lungs, known as extra-pulmonary TB.

1.6. Latent Tuberculosis

One-third of the world's population harbors the latent form of *Mtb*, where one will have the TB infection but will not manifest with any sign or symptom, enduring a lifelong risk of reactivation. HIV infection, malnutrition, tobacco smoking, indoor air pollution, alcoholism, silicosis, insulin-dependent diabetes, malignancy, renal failure and immunosuppressive treatments are the major risk factors of reactivation. Co-infection with human immune deficiency virus (HIV) has increased the risk for reactivation of latent *Mtb* [11, 12]. Until now, the control of TB has been focused on detection and management of active disease and will continue to be an obligatory method. The treatment of latent infection will be crucial in total eradication of TB [13, 14]. Therefore, the latent infection needs to be detected by tuberculin skin test or by interferon-gamma release assays and should successively be treated to reduce the consequent risk of re-activation into active TB [15, 16].

1.7. Current TB Therapy

Directly observed treatment, short-course (DOTS) is the best therapy for TB globally, recommended by the World Health Organization (WHO) for its effective control. The treatment will be given in two phases, *i.e*. intensive phase and continuation phase (**Table 1-1**). The intensive phase lasts for two months with a daily dose of isoniazid, rifampicin, pyrazinamide, and ethambutol. It is followed by continuation phase for four months with isoniazid and rifampicin given a week thrice (**Table 1-2**). The standard treatment for latent TB is a daily dose of isoniazid for six to nine months. The dose, according to body weight for isoniazid, rifampicin, pyrazinamide, and ethambutol is 10, 15, 35 and 20 mg/kg/day, respectively (**Table 1-3**). The essential components of DOTS

program are commitment by the concerned government, case finding by sputum smear microscopy, standard treatment under direct observation for six months, adequate and regular supply of drugs, and systematic monitoring and recording of each patient. TB control is further hampered due to the increased incidence of MDR/XDR-TB and thus leading to life-threatening situations.

Intensive Phase	**Continuation Phase**	**Comments**
2 months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)	4 months of Isoniazid (H), Rifampicin (R)	
2 months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)	4 months of Isoniazid (H), Rifampicin (R), Ethambutol (E)	Followed, when new TB patients were noticed with high level of isoniazid resistance or when susceptibility testing against isoniazid was not done before the start of continuation phase

Table 1-1: Standard treatment regimen for new TB patients

Treatment Phases		**Comments**
Intensive Phase	**Continuation Phase**	
Daily	Daily	Optimal
Daily	3 times per week	Alternative for new patients receiving DOTs therapy
3 times per week	3 times per week	Alternative when the patients were receiving DOTs and not living with HIV or living in an HIV-prevalent setting

Table 1-2: Dosing frequency

Drug	**Dose**
Isoniazid (H)	10 mg/kg/day (10 to 15 mg/kg/day)
Rifampicin (R)	15 mg/kg/day (10 to 20 mg/kg/day)
Pyrazinamide (Z)	35 mg/kg/day (30 to 40 mg/kg/day)
Ethambutol (E)	20 mg/kg/day (15 to 25 mg/kg/day)

Table 1-3: Recommended dose according to body weight

1.8. WHO Classification of TB Drugs

According to WHO guidelines-2011, the drugs were classified on the basis of efficacy and toxicity. The group 1 forms the first line drugs and groups 2 to 5 forms the second line drugs. The group 2 consists of injectable anti-TB drugs. Group 3 includes all the Fluoroquinolones. Group 4 includes all oral bacteriostatic second-line anti-TB drugs. Group 5 includes anti-TB drugs with limited data on efficacy and long-term safety in the treatment of drug-resistant TB (**Table 1-4**).

Group 1 First-line oral anti-TB drugs	Isoniazid, Rifampicin, Ethambutol Pyrazinamide
Group 2 Injectable anti-TB drugs (injectable or parenteral agents)	Streptomycin, Kanamycin, Amikacin Capreomycin
Group 3 Fluoroquinolones	Levofloxacin, Moxifloxacin, Gatifloxacin Ofloxacin
Group 4 Oral bacteriostatic second-line anti-TB drugs	Ethionamide/ prothionamide, Cycloserine/ terizidone, *p*-Aminosalicyclic acid
Group 5 Anti-TB drugs with limited data on efficacy and long-term safety in the treatment of drug-resistant TB	Linezolid, Clofazimine, Amoxicillin/ clavulanate, Imipenem/ cilastatin, Meropenem, High-dose isoniazid, Thioacetazone, Clarithromycin

Table 1-4: 2011 Classification of TB drugs by WHO

Group A Fluoroquinolones	Levofloxacin, Moxifloxacin, Gatifloxacin	
Group B Second-line injectable agents	Amikacin, Capreomycin, Kanamycin (Streptomycin)	
Group C Other core second-line agents	Ethionamide/ prothionamide, Cycloserine/ terizidone, Linezolid, Clofazimine	
Group D Add-on agents (not core MDR-TB regimen components)	D1	Pyrazinamide, Ethambutol High-dose isoniazid
	D2	Bedaquiline, Delamanid
	D3	p-Aminosalicylic acid, Imipenem-cilastatin, Meropenem, Amoxicillin-clavulanate, Thioacetazone

Table 1-5: 2016 Classification of TB Drugs by WHO

WHO classified the drugs to treat MDR-TB as groups A-D. Group A includes the newer fluoroquinolones, in particular, moxifloxacin, levofloxacin, and gatifloxacin. Group B

consists of the second line injectables such as capreomycin, kanamycin, and amikacin. Group C contains ethionamide/ prothionamide, cycloserine/ terizidone, linezolid and clofazimine. Group D is subdivided into D1, D2, and D3. D1 includes high-dose isoniazid, pyrazinamide, and ethambutol. D2 consists bedaquiline and delamanid and D3 includes p-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate and thioacetazone (**Table 1-5**).

1.9. Treatment Failure

Several factors cause failure of TB treatment and they are categorized into three classes *viz*. patients related, doctors related and drugs related factors.

1.9.1. Patients Related Factors

TB is endemic in most of the developing and under developing countries. The following factors are more predominant in these countries and this would affect the outcome of the treatment of disease.

- Lack of information about TB
- Lack of money for treatment
- Actual or presumed side effects
- Lack of commitment to a long treatment course
- Malabsorption
- Social barriers

1.9.2. Doctors Related Factors

Failure of TB treatment could also occur when the doctors do not prescribe appropriate medications listed in WHO or national guidelines. It could be due to following reasons:

- Inappropriate guidelines
- Non-compliance with guidelines
- Absence of guidelines

1.9.3. Drugs Related Factors

The government should ensure easy availability of quality drugs at affordable prices. Poor management of drugs could lead to treatment failure. Treatment of TB should address the following factors:

- Poor quality of drugs
- Irregular supply of drugs
- Wrong delivery (dose/combination) of drugs
- Drugs unsuitable due to drug resistance

1.10. Drug Discovery and Development Pipeline

1.10.1. Clinical Development

Clinical trial is the final stage of drug development that explores the safety and effectiveness of drugs in human volunteers. The first line TB drugs were discovered about 60 years ago and are still being used without further advancement. Efforts are in pipeline to come up with new TB drugs. Recently, two new drugs *viz*. bedaquiline (diarylquinoline derivative) and delamanid (nitroimidazole derivative) were approved to treat MDR-TB but their phase 3 clinical trials are not completed yet. Pretomanid (nitroimidazole derivative) has slowly progressed to phase 3 clinical trial. Sutezolid (oxazolidinone derivative), delpazolid (oxazolidinone derivative) and SQ-109 (adamantyl derivative) have also reached phase 2 clinical trials. Q-203 (imidazopyridine derivative), OPC-167832 (carbostyril derivative), PBTZ169 (piperazine benzothiazinone derivative) stepped into phase 1 clinical study (**Figure 1-2**).

1.10.2. Preclinical Development

Preclinical development is a nonclinical study that is performed before the start of clinical trials. BTZ-043 (benzothiazinone derivative), TBA-7371 (nitroimidazole derivative), GSK-070 (oxaborole derivative) and TBAJ-587 (diarylquinoline derivative) are in preclinical toxicological study to enter the clinical stages of drug development.

CPZEN-45 (caprazene nucleoside), SATB082 (cyclopeptide derivative), 1810 (spectinamide derivative), TBI-166 (riminophenazine derivative), TBI-233 (oxazolidinone derivative), TB-47 (oxazole derivative) and SPR-720 (GyrB inhibitor) are in early stage of preclinical development (**Figure 1-2**).

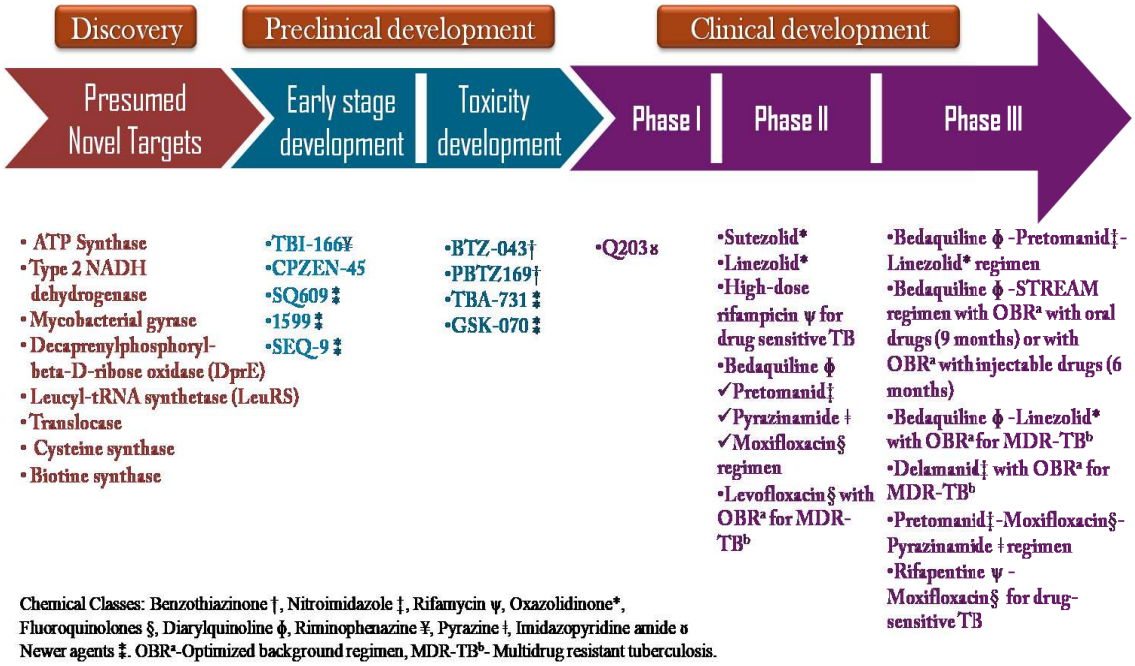

Figure 1-2: Drug discovery and development pipeline

1.10.3. Lead optimization

The lead optimization stage involves modification of chemical structures of lead compounds for improved target specificity and good ADME-Tox (absorption, distribution, metabolism, excretion and toxicity) properties. Several classes of drug molecules are in the lead optimization stage *viz*. diarylquinolines, diarythazoles, InhA inhibitors, DprE inhibitors (azaindoles), picolinate complexes, spectinamides, macrolides, oxazolidinones, pyrimidines, aryl sulfonamides, *etc*., (**Figure 1-2)**.

1.10.4. Hit to lead/ lead generation

Drug discovery starts with lead generation and it is the most crucial part in successful development of a drug. The hits (new chemical entities) obtained from high throughput screening (HTS) are optimized to obtain lead compounds. Different classes of chemical

compounds are screened through whole cell assays to obtain hits. ATP synthase, Type-2 NADH dehydrogenase, Mycobacterial gyrase, Decaprenylphosphoryl-d-ribose oxidase (DprE1), Leucyl-tRNA synthetase (LeuRS), Cysteine synthase, Biotin synthase and several other inhibitors have been developed as lead compounds (**Figure 1-2**).