

Tuberculosis is a Fatal Disease among Some Developing Countries of the World

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Abstract Tuberculosis (TB) is an infectious fatal disease mainly among the developing countries. It is caused by a bacterium called *Mycobacterium tuberculosis* and spreads through the air and infects the lungs and other organs and parts of the persons who come in contact to the infected persons. It remains a major global health problem and about 2 billion people are thought to be infected with TB and about 1.3 million died each year from the disease. In the 95% of all cases, 99% of death occurs in developing countries, with the greatest burden in Sub-Saharan Africa and Southeast Asia. India alone accounts for an estimated one-quarter (26%) of all TB cases worldwide and only China and India combine accounting for 38%. To prevent TB, the WHO recommends that infants receive a BCG vaccine where TB is a common disease. At present each year globally about 100 million children receive BCG vaccine. Drug resistant TB is a rising global problem which is more difficult and expensive to treat and cure or sometimes it is impossible to treat successfully. It can occur when healthcare providers prescribe the wrong treatment, the wrong dose, or wrong length of time for taking the drugs or irregular and incomplete medicines are used by the patients.

Keywords: tuberculosis, pulmonary TB, WHO, drug resistant TB, BCG, developing countries

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1. Introduction

Tuberculosis (TB) is a contagious chronic bacterial infection. It is curable and preventable disease. It spreads through the air and infects the lungs and other organs and parts of the human body (about 15% patients) such as, the lymph nodes, the urinary tract and the abdomen, bones, brain, the kidneys, spine and even the skin. A person needs to inhale only a few of these germs to become infected. From the lungs, TB bacteria move through the blood to the different parts of the body. In people who develop active TB of the lungs called pulmonary TB [47]. Among people suffering from TB disease, 3 out of 4 have disease affecting the lungs. Between 2 to 8 weeks after being infected person's immune system responds to the TB germ by walling off infected cells. If not treated immediately, the bacteria have the potential to destroy the lungs and kill the person. It is usually treated with a schedule of drugs taken for 6 months to 2 years, depending on the type of infection. Most people undergo complete healing of their initial infection, and the bacteria eventually die off. TB infections in the world began to increase since 1980s, because of the appearance of HIV. The reason is HIV weakens a person's immune system, so it cannot fight the TB germs. TB and HIV have a strong fatal correlation; each drives the progress of the other. Worldwide, TB is one of the leading causes of death among people living with HIV. A person who has both

HIV infection and TB disease has an AIDS-defining condition. People with weakened immune systems, at a greater risk for developing TB disease are as follows [63]:

- people with HIV infection,
- people who are suffering from malnutrition,
- people who have diabetes,
- people who have chronic liver disease,
- people who are suffering from renal failure,
- patients who are at the end stage of kidney disease,
- patients who are suffering certain cancers (head and neck cancer) and are taking treatment of chemotherapy,
- some drugs users who to treat rheumatoid arthritis, Crohn's disease and psoriasis,
- infants and young children under-5,
- people who became infected with TB bacteria in the last 2 years,
- people who inject illegal drugs or drink alcohol,
- use of tobacco greatly increases the risk of getting TB and dying from it,
- people who are sick with other diseases that weaken the immune system,
- low body weight (10% below ideal),
- elderly people, and
- people who were not treated correctly for TB in the past.

TB is caused by a bacterium called *Mycobacterium tuberculosis* also called Acid-Alcohol Fast Bacilli (AAFB) because of its staining properties. This rod-shaped

bacterium, also called Koch's Bacillus, was discovered by Dr. Robert Koch in 1882. Characteristics of *M. tuberculosis* are as follows [60]:

1. It is a small, slow-growing bacterium that can live only in people. It is not found in other animals, insects, soil, or other non-living materials.
2. It is an aerobic bacterium, i.e., it needs oxygen to survive. For this reason, during active TB disease, *M. tuberculosis* complexes are always found in the upper air sacs of the lungs.

When *M. tuberculosis* bacteria enter the human body through breathes, causes TB infection. The immune system of human body cannot stop TB bacteria from growing and spreading after the initial infection. A positive TB skin test, blood test and old scars on a chest X-ray, may provide the evidence of the infection [8].

TB remains a major global health problem and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). About 2 billion people, one-third of the world's population, are thought to be infected with TB bacterium, *M. tuberculosis*. In addition, new infections are occurring at the rate of one per second. TB case rates vary by factors such as age, race and ethnicity, and country of origin. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease. The estimated number of TB deaths among HIV-positive people in 2011 was 336,000 and in 2012 was 320,000 [62].

The global TB mortality rate was 29 per 100,000 in 1990 and increased to peak at 32 per 100,000 in 2000 before decreasing to 27 per 100,000 in 2007. WHO has set the goal to reduce TB mortality below 15 per 100,000 by 2015 [53]. It is expected that the number of TB related deaths will rise from 3 million per year to 5 million by 2050. TB is not only a problem for the health of the individuals, but also a major obstacle to the economic and social development for the developing countries [59].

In 2008, TB mortality in the USA was 0.2 per 100,000 [5]. More than 95% of TB deaths occur in low- and middle-income countries of the world. In 2012, an estimated 530,000 children became ill with TB and 74,000 HIV-negative children died of TB. The TB death rate dropped 45% between 1990 and 2012. An estimated 22 million lives saved through use of directly observed treatment, short-course (DOTS) and the Stop TB Strategy recommended by WHO [64]. DOTS is a five-point package; i) Strong Government commitment to TB control activities, with adequate and sustained financing, ii) ensure early case detection, and diagnosis through quality-assured bacteriology, iii) provide standardized treatment with supervision and patient support, iv) ensure uninterrupted effective drug supply and management, and v) standardized system of patient records and reporting that allows supervision and assessment of the TB control programmes. This strategy was produced by Dr. Arata Kochi, who became the Director of the WHO TB Programme in 1989, with the assistance of a number of TB specialists [39]. The first targets set by the WHO for the DOTS strategy is the establishment of a system that will cure 85% of all sputum smear positive patients, and second is the achievement of 70% detection rate [20].

In Bangladesh TB control programme is implemented by the Government of Bangladesh (GoB), with various NGOs and several private and corporate sectors. About 40

public hospitals including medical college hospitals and military hospitals and some private hospitals have been involved to control TB in Bangladesh [55].

Blacks continue to have an inconsistent share of TB and the percentage of TB cases in blacks is higher globally. In the 95% of all cases, 99% of death occurs in developing countries, with the greatest burden in Sub-Saharan Africa (SSA) and Southeast Asia. So that prevention and control efforts should be targeted to these population.

In India alone, it is estimated that about 500,500 people died of TB in 2013 (not including those infected with HIV), making it the biggest killer among the three. India was far behind the rest of the world when it came to reducing prevalence of TB. The world prevalence of TB in those without HIV/AIDS in 2013 was 160.2 for every 100,000 people but in India, it was 275.3 [41].

2. Objective of the Study

The objective of the study is; to cure the patient and restore quality of life and productivity, to prevent death from active TB or its late effects, to prevent relapse of TB, to reduce transmission of TB to others, to the development and transmission of drug resistance TB. We want a TB free world so that it not only reduce sufferings of TB patients but also reduce economic burden of the nations. Our attempts are to advice about high-quality continuous care for all people with TB, prevention and control of TB and treatment of TB. We hope in our study will help the TB patients to take medicine properly to avoid multidrug-resistance TB. Our objective is to encourage researchers to invent drug resistant TB medicines, so that none will die from TB.

3. History of TB

Consumption, phthisis, scrofula, Pott's disease, and the White Plague are all terms used to refer to TB throughout history. Analysis of mycobacterial interspersed repetitive units has allowed dating of the bottleneck to approximately 40,000 years ago, which corresponds to the period subsequent to the expansion of *Homo sapiens* out of Africa. The term *phthisis* first appeared in Greek literature around 460 BC. Hippocrates identified the illness as the most common cause of illness in his time. He stated that it typically affected individuals between 18 and 35 and was nearly always fatal. Evidence of tubercular decay has been found in the spines of Egyptian mummies thousands of years old, and TB was common both in ancient Greece and Imperial Rome [67].

Various studies have enabled scientists to hypothesize that *M. tuberculosis* evolved from the closely related mycobacterium, *M. bovis*, possibly coincident with the domestication of cattle by humans approximately 15,000–20,000 years ago [9]. Studies have identified TB in mummies from Egypt dating back 5,400 years [7,10]. Skeletal remains show TB had spread throughout Europe and the Middle East during the Stone Age [37]. Notable advances in understanding the pathophysiology and clinical manifestations of TB occurred during the 17th, 18th, and early 19th centuries [4].

By linking the disease to its social context, scientists and political leaders advocated for social reform with mechanisms such as better nutrition, improved sanitation, and better housing to reduce the disease. Late in the 1800s, isolation and treatment of TB patients in Sanatoria [12] and the pasteurization of milk to eliminate the threat of *M. bovis* were highly visible attempts to control TB. In the 1940s, scientists discovered that the antibiotic, streptomycin, killed *M. tuberculosis*; however, the bacilli had a propensity to develop resistance to antibiotics when only streptomycin was used. By 1950, combined drug treatment was established and, a few years later, Isoniazid was introduced as a “miracle” cure for TB when combined with properly chosen drug combinations for sufficient duration [11].

Since that time, scientific advances, including the discovery of the tuberculosis mycobacterium and the development of new drugs and the Bacille Calmette-Guérin (BCG) vaccine, caused TB to lessen its grip on mankind during some periods of history. Albert Calmette, a French physician and bacteriologist, and his assistant and later colleague, Camille Guérin, invented BCG in 1919. The BCG vaccine was first used in humans in July 18, 1921 [14].

The vaccine was used increasingly in Europe during the 1920s, with early evidence for its efficacy coming from studies of student nurses in Norway. The first formal trials of BCG were organized among North American Indians in the 1930s [18]. By the late 1940s several studies had provided evidence for the utility of BCG in protection against tuberculosis [3]. Tuberculosis emerged as a major concern in the aftermath of World War II, and use of BCG was encouraged subsequently in many countries, stimulated in particular by UNICEF and by Scandinavian Red Cross Societies, and then by the WHO. Only two countries the USA, the Netherlands have never recommended to use universal BCG because of the low risk of infection with *M. tuberculosis* [13].

BCG vaccines are produced by 40 or more manufacturers around the world. The major commercial producers in terms of export volume are Pasteur-Merieux-Connaught, Evans-Medeva, and the Japan BCG Laboratory, which together accounted for 85% of 217 million (infant, 0.05 ml) doses provided through UNICEF in 1996 and 1997. An estimated 25–30% of the world’s BCG supply is purchased by UNICEF for distribution to developing countries [13].

BCG vaccination should not be given to persons who are immunosuppressed (e.g., persons who are HIV infected) or who are likely to become immunocompromised (e.g., persons who are candidates for organ transplant). BCG vaccination should not be given during pregnancy. BCG does not always protect people from getting TB. Effective drug treatments were first developed in the 1940s. BCG vaccine is an injection that has been prepared from a strain of the weakened live bovine tuberculosis bacilli. The most effective first-line anti-TB drug, Rifampicin, became available in the 1960s [59].

Tuberculosis was declared a global emergency by the WHO in 1993, and *M. tuberculosis* is now considered to be responsible for more adult deaths than any other pathogen [29].

At present various international organizations are working for the reduction of TB as follows [45]:

1. The Stop TB Partnership (Stop TB), launched in 1998 and hosted by the World Health Organization (WHO), is a global network of public and private organizations, including TB control programmes, technical agencies, service delivery organizations, research scientists, and donors. Stop TB raises awareness about the global TB burden and coordinates the activities of partners in key areas, including advocacy, technical support, and research and development (R&D).
2. The Global Drug Facility, run by the Stop TB Partnership, was established in 2001 to expand access to high-quality, affordable anti-TB drugs and diagnostics, and to carry out drug procurement for Green Light Committee (GLC) approved programmes.
3. In 2000, the Green Light Committee Initiative was established to expand access to second-line anti-TB drugs for the treatment of strains of TB that are resistant to standard first-line drugs, known as multidrug-resistant TB (MDR TB). The GLC is administered by WHO.
4. The Global Fund to Fight AIDS, TB and malaria is the world’s largest international source of financing for the global response to TB. It was created in 2002 as an innovative financing mechanism to raise and disburse funding to countries. As a global public-private partnership, the Global Fund uses a demand driven, performance-based model. Countries apply for grants to fund their response to TB, and continued financing is dependent on achievement of agreed upon targets. By the end of 2008, the Global Fund had approved \$3.1 billion in grants to TB programmes. In 2008, the Global Fund contributed 57% of all international (non-domestic) investments for TB.

4. Symptoms of TB

An individual may not notice any symptoms of illness until the disease is quite advanced. Early symptoms of active TB disease can include cough (coughing up blood) more than 2 weeks, unexplained weight loss, consistent low-grade fever, chills, haemoptysis, excessive night sweats, and loss of appetite [58]. Symptoms may be vague and go unnoticed by the affected person. The disease either goes into lessening or becomes chronic and more debilitating with cough, chest pain, bone pain if the bacteria have invaded the bones and bloody sputum (saliva). Signs and symptoms of TB of the lungs are; i) coughing that lasts three or more weeks, ii) coughing up blood or sputum (phlegm from deep inside the lungs), and iii) chest pain, or pain with breathing or coughing. When TB occurs outside the lungs, signs and symptoms vary according to the organs involved. For example, TB of the spine may produce back pain, and TB in kidneys might cause blood in urine, etc. [63].

When a person’s immune system is strong, it builds a wall around the germs so they cannot spread and hurt the body. These walls are called ‘tubercles’ that is why the disease is named tuberculosis. TB bacteria can remain in this latent state for months, years, and even decades without increasing in number and without signs and

symptoms, or radiographic or making the person sick. This is called latent TB infection (LTBI). People who have LTBI do not get sick, never show any symptoms of TB and do not spread the bacteria to others. Only about 10% of people infected with *M. tuberculosis* ever develop tuberculosis disease. Most people with LTBI will test positive on the tuberculin skin test (TST) or their chest X-ray will show signs of latent TB. Although most initial infections have no symptoms and people overcome them, they may develop fever, dry cough, and abnormalities that may be seen on a chest X-ray. This is called primary pulmonary TB and it frequently goes away by itself, but in 50%–60% of cases, the disease can return. It is important to get the appropriate treatment and get rid of the bacteria even in LTBI [6].

TB pleuritis may occur in 10% of people who have the lung disease from TB. The pleural disease occurs from the rupture of a diseased area into the space between the lung and the lining of the abdominal cavity. These patients have a nonproductive cough, chest pain and fever. The disease may go away and then come back at a later date. In a minority of people with weakened immune systems, TB bacteria may spread through their blood to various parts of the body. This is called miliary TB and produces fever, weakness, loss of appetite, and weight loss; cough and difficulty breathing are less common [58].

About 15% of people may develop tuberculosis in an organ other than their lungs. About 25% of these people usually had known TB with inadequate treatment. The most common sites are; lymph nodes, genitourinary tract, bone and joint sites, meninges, and the lining covering the outside of the gastrointestinal tract [59].

5. Infection of TB

When a person breathes in *M. tuberculosis* contaminated air, the inhaled TB bacteria reach the lungs, which causes an infection. TB is primarily an airborne disease. Only people with active TB can spread the disease to other. The bacteria are spread from person to person through tiny microscopic droplet nuclei (1–5 μm in diameter, invisible to the naked eye) when a TB sufferer coughs, spits, sneezes, speaks, shout, sings, or laughs and another person inhales the infected air. TB germs can float in the air for several hours, so it is possible to inhale them even when the sick person is left the room [8]. The active bacteria multiply and destroy the tissues of the infected person. A person with TB disease shows symptoms that vary, depending on where the TB bacteria are growing and in most cases, the bacteria attack the lungs. TB is not spread by shaking individual's hand, sharing food or drink, touching bed linens or toilet seats, kissing and sharing toothbrushes. To avoid TB an individual have to avoid long periods of time in enclosed rooms with someone who has TB, air out those rooms regularly and need a cover face with a mask [56].

To control TB infection we need the following three steps:

- prompt detection of infectious patients,
- airborne precautions, and
- treatment of people who have suspected or confirmed TB disease.

5.1 Infection Control Policy

Infection of TB control is a combination of measures aimed at minimizing the risk of TB transmission within people. For this we need the core interventions in TB control, HIV control and strengthening of health systems. For the successful implementation of TB infection control needs the followings [56].

- sound technical guidance,
- coordination between health authorities at national and sub-national level,
- adequate funding at all levels,
- coordinated efforts from ministries of health, finance, justice, labor, public works and environment,
- coordination between different national disease-specific programmes,
- contributions from technical partners and civil society, and
- major advocacy mobilization to remove obstacles that impede wide implementation of activities.

6. Classification of TB Cases

Cases of TB are classified according to the following rules [58]:

- anatomical site of disease,
- bacteriological results (including drug resistance),
- history of previous treatment, and
- HIV status of the patient.

A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (WRD), such as Xpert MTB/RIF. A clinically diagnosed TB case is one who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment [63].

Pulmonary TB (PTB) refers to a case of TB involving the lung parenchyma. Miliary TB is classified as pulmonary TB because there are lesions in the lungs. Extrapulmonary TB (EPTB) refers to a case of TB involving organs other than the lungs (i.e., without radiographic abnormalities in the lungs), e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB [27].

New TB patients are those who never have taken any treatment of TB. Previously treated patients are those who have received 1 month or more of anti-TB drugs in the past. Treatment after failure patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment. HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-antiretroviral therapy (ART) register or in the ART register once ART has been started [63].

7. Higher TB Risk Regions and Communities in the World

High incidence areas are defined as areas with reported or estimated incidence of ≥ 20 cases of TB per 100,000 populations. High prevalence areas are defined as areas with reported or estimated prevalence of ≥ 20 cases of TB per 100,000 populations. TB mostly affects young adults, in their most productive years [8].

Health care providers are in high risk of TB infection, as they always come into the contact of TB infected people. People who live or work in prisons, immigration centers are all at the risk of TB due to overcrowding and poor ventilation (adequately ventilated room has at least 12 air changes per hour). People who live in refugee camp or shelter are in the high risk of infection of TB due to poor nutrition and ill health, and living in crowded, unsanitary conditions. Army barracks of some countries are in congregate settings and are in the risk of TB infection [21].

7.1. Higher TB Risk Regions

More than 95% of cases and deaths due to TB are in developing countries. Higher rates of TB are in the following regions [66]:

- Sub-Saharan Africa (Ethiopia, Kenya, Nigeria, Mozambique, South Africa, Uganda, The Democratic Republic of Congo, The United Republic of Tanzania and Zimbabwe),
- India, Bangladesh, Pakistan, Myanmar, Afghanistan,
- China, Cambodia, Vietnam,
- Mexico,
- most countries in Latin America and the Caribbean,
- Eastern Europe,
- the islands of Southeast Asia and Micronesia (The Philippines, Indonesia), and
- parts of the former Soviet Union.

India alone accounts for an estimated one-quarter (26%) of all TB cases worldwide and only China and India combine accounting for 38% [60]. In BRICS (Brazil, the Russian Federation, India, China and South Africa) that have almost 50% of global TB cases. In 2012 the highest levels of MDR TB are found in Eastern Europe and central Asia, where in some countries more than 20% of new TB cases and more than 50% of those previously treated for TB have MDR TB [62]. Bangladesh is in rank 6th among the countries with a high TB burden and ranks 5th among 22 countries with global burden of TB [50]. Thailand is ranked 18th of the top 22 highest TB burdened countries [28]. High TB prevalence areas are more in the low- to middle-income countries, due to lack of effective control programmes [21].

7.2. TB Risk among Health Care Providers

Health care providers (doctors, nurses, pharmacists and laboratory technicians, health management and workers in health care centers) in the TB cure centers always come into the contact of TB infected people. When patients with TB visit for health care facilities, they are likely to transmit the disease to the health care providers (HCPs) and are in the higher risk of infection of TB. The infected HCPs also spread TB bacteria to the healthy people. The

patients with multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB) have relatively higher morbidity, which are difficult or sometimes impossible to treat successfully and visit the HCPs more frequently. HCPs often work in potentially incurable TB wards, where palliative and end-of-life care are being considered. The prevalence of latent TB infection (LTBI) in nurses has been found to be 1.3% to 35.6% times higher than other HCPs [15,17,68]. They must wear masks and frequent hand washing can reduce the risk of infecting TB.

Health care facilities in low- and medium-income countries had a median of 36 HCPs per 100 TB patients treated at the facility, which is much lower than facilities in high-income countries, which have a median of 6,450 HCPs per 100 TB patients [22]. Nosocomial transmission of TB in India is 5% per year to the HCP in comparison to the national average of 1.5% [27]. Nosocomial infection is an infection occurring in a patient in a hospital or other health-care centers in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections acquired by staff as a result of working at the facility [56].

The risk as compared with general population is highest among workers in TB in-patient facilities, laboratories (sputum collection areas and bronchoscopy rooms), general medicine wards, and emergency rooms. Workers in out-patient medical facilities have an intermediate risk, while workers in surgery, obstetrics, administration and operating theaters have the lowest risk [26].

7.3. TB Risk in Prisons

About 10 million people are detained worldwide (1.5 million in China and 0.89 million in Russia) in jails, prisons, detention centers and risk of TB remains a growing problem among them. The poor living conditions for prisoners are in India, Bangladesh, Sri Lanka, Afghanistan, Thailand, Brazil and SSA. The prisons of the developing countries keep two to five times more prisoners than they were meant to [19].

Prisoners are overwhelmingly male, are typically aged 15–45 years, and come mainly from poorly educated and socioeconomically deprived sectors of the population where TB infection and transmission are higher. Majority portion of them are involve with drug addiction and alcohol. A minor portion of them suffer from liver disease. As a result risk of TB infection remains a growing problem in jails, prisons, detention centers. TB incidence is 5 to 70 times greater in prisons than in general people, because of severe overcrowding, poor nutrition, poor ventilation and limited access to often insufficient health care [47,51].

The International Red Cross reports that the rate of TB infection in Kyrgyzstan prisons was 40 times that in the civilian population while in Peru, the TB infection rate in prison was 49 times that outside prison. Some countries in SSA TB infection rates per 100,000 in prisons are 3,797 in Botswana, 1,100 in Malawi and in Zambia 4,000 [38].

TB cases in prisons are not just about prisoners. TB in prisons threatens inmates and prison staffs, custodial staffs and health staffs, as they are entering and leaving every day. They are at particular risk of infection of TB. Visitors to prisons may also have regular close contact with the

prisoners. Sooner or later, prisoners are released and mix with people of different levels. Any health problem among the prisoner population will inevitably affect those people in close contact with them, and ultimately these problems will spill out into the innocent common people. Effective tuberculosis control in prisons is necessary to protect the wellbeing of both prisoners and the wider community. Prisons in SSA have no proper facilities to treat MDR TB and XDR TB. Some countries of SSA do not express the data of drug-resistant TB in prisons [32,51].

8. TB and HIV Co-infection

HIV infection is the major cause to the increase of TB across the world. About 9% of adults globally with newly diagnosed TB are HIV positive, but this rate is 31% in Africa. HIV co-infection with TB presents challenges to effective diagnosis of TB and diagnosis can also be more difficult in children [16].

High levels of HIV patients are seen in prisons which is a great problem on prison-seated TB epidemics. In several countries the numbers of TB patients become 4 times in the last 2 decade as a result of HIV. In some countries about 75% of TB patients are HIV-positive. TB is the single biggest killer of people infected with HIV [62].

The risk of progression from LTBI to TB disease is 7% to 10% each year for those with both LTBI and untreated HIV infection. People who are co-infected with HIV and TB are 21 to 34 times more likely to become sick with TB. This risk is reduced with ART for HIV. About half a million children (0–14 years) fell ill with TB, and 74,000 HIV-negative children died from the disease in 2012. In 2012 about 320,000 people died of HIV-associated TB. At least one-third of people living with HIV worldwide in 2012 are infected with TB bacteria, although not yet ill with active TB. In 2012 there were an estimated 1.1 million of HIV-positive new TB cases, 75% of whom were living in Africa. The TB epidemic in SSA is increased due to HIV epidemic, and up to 70% of adults with TB are co-infected with HIV [6].

9. Diagnosis for TB

There are two kinds of tests that are used to determine if a person has been infected with TB bacteria; (i) the tuberculin skin test (also called the Mantoux tuberculin skin test since 1910) and (ii) TB blood tests. The tuberculin skin test (TST) is the oldest test for TB and is especially useful in testing children. This test is easy, less expensive and less biological variability in serial testing, but operator dependence is difficult. It is often used for initial screening in developed counties, although it is under-utilized in Africa and Asia. To identify those who may have been exposed to *M. tuberculosis*, doctors typically inject a substance called tuberculin (0.1ml of 5 TU purified protein derivative (PPD) solution) under the skin (volar surface) of the forearm using a 27-gauge needle with a tuberculin syringe, which is called skin test. TST is both safe and reliable throughout the course of pregnancy [6]. If a red welt forms around the injection site within 72 hours, the person may have been infected. The

size of the bump (measure its size using a ruler) determines whether the test results are significant [31].

But TST does not necessarily mean one has active TB disease. The QuantiFeron-TB Gold test is a blood test that can detect infection and latent TB, and results are available in as little as 24 hours and measure how the immune system reacts to the bacteria that cause TB. This blood test is very useful because it is not subject to reader bias, and BCG immunization does not affect the results [30].

The most common method for diagnosing TB worldwide is sputum smear microscopy (first developed in the 1880s and basically unchanged today), in which bacteria are observed in sputum samples examined under a microscope. Sputum examination is indicated for persons with positive test results for TB infection and either an abnormal chest radiograph or the presence of respiratory symptoms [6,62]. Only an estimated 45% of infections are detected and the smear-negative diseases cannot be detected by sputum microscopy. It has the advantage of being simple, but is hampered by very low sensitivity. It is also very dependent on the skill of the technician, and a single technician can only process a relatively small number of slides per day [33]. A newly developed diagnostic test is the Interferon-Gamma Release Assay (IGRA) which is a T-cell based assay. This blood test is complicated and high expensive, but can be more specific than TST for diagnosing latent TB. IGRAs are also required a high level of experience to manage [35].

An IGRA measures how strong a person's immune system reacts to TB bacteria by testing the person's blood in a laboratory. IGRAs, unlike the TST, are not affected by prior BCG vaccination and are not expected to give a false-positive result in people who have received BCG. Two IGRAs that have been approved by the US Food and Drug Administration (FDA) are commercially available in the USA; i) QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and ii) T-SPOT®.TB test (T-Spot). The interpretation of IGRAs is based on the amount of INF- γ released, in QFT, or on the number of cells that release INF- γ , in T-SPOT®.TB. IGRAs are the preferred method of testing for groups of people who have poor rates of return for TST reading and interpretation and persons who have received BCG vaccination [6].

A positive TB skin test or TB blood test only tells that a person has been infected with TB bacteria. It does not tell whether the person has LTBI or already infected with TB. Other tests, such as a chest X-ray and a sample of sputum are needed to see whether the person has TB disease. A negative test means that the person's blood did not react to the test and that latent TB infection or TB disease is not likely. People who had a severe reaction to a previous TST should not receive another TST. In general, a person should have either a TST or an IGRA, but not both. Chest X-ray helps differentiate between LTBI and pulmonary TB disease in patients with positive tests for TB infection. Children under-5 should have both posterioranterior and lateral views; all others should have at least posterioranterior views [6].

People who may test positive on the tuberculin test are as follows:

- people with previous experience to *M. tuberculosis*,
- people who have not taken TB vaccine before, and

- one was vaccinated with the TB vaccine but it was not given in full dose or it may be in expire dated.

A positive TB skin test, and white spots on a chest X-ray in lungs where immune system has walled off TB bacteria, may provide the only evidence of the infection. Blood tests may be used to confirm or rule out latent or active TB.

The doctors also will take sputum and other samples to see if the TB bacteria will grow in the laboratory. If bacteria are growing, this positive culture confirms the diagnosis of TB. Because *M. tuberculosis* grows very slowly, it can take 4 weeks to confirm the diagnosis. An additional 2 to 3 weeks usually are needed to determine which antibiotics to use to treat the disease. TB is particularly difficult to diagnose in children. The gold standard for TB testing is chest radiography, which will reveal lesions, cavities, scar tissue, and calcium deposits [25]. Physical examination and medical history, which includes finding information about previous positive tests for TB infection, previous treatment for LTBI or TB disease, and a risk assessment for liver disease, are indicated for an individual with positive TB test results. Written documentation of a previously positive TST or IGRA result is required; a patient's verbal history is not sufficient [6].

10. Treatment for TB

TB bacteria become active if the immune system cannot stop them from growing. When TB bacteria are active, this is called TB disease. Applying appropriate antibiotic treatment, TB can be cured in most patients. Successful treatment of TB depends on close cooperation between patients and healthcare providers. For latent TB, patient may need to take just one TB drug but for TB disease,

doctor will prescribe several medicines of duration for 6 months or longer.

10.1. Treatment of LTBI Patients

There are two options for treatment with Isoniazid (INH): i) 9-month regimen, and ii) 6-month regimen. The 9-month regimen is preferred because it is more efficacious. The preferred regimen for children aged 2–11 years is 9 months of daily INH. The directly observed 12-dose once-weekly regimen of INH and Rifampentine (RPT) is recommended as an option equal to the standard INH 9-month daily regimen for treating LTBI [6].

The 12-dose regimen can be considered for healthy HIV-infected persons, 12 years of age and older, who are not on ART medications. It may also be considered for children aged 2–11 years if completion of 9 months of INH is unlikely and hazard of TB disease is great. The 12-dose regimen is not recommended for children younger than 2 years of age, people with HIV/AIDS who are taking ART, people presumed to be infected with INH or Rifampin-resistant *M. tuberculosis*, pregnant women, or women expecting to become pregnant while taking this regimen. A 4-month regimen of Rifampin (RIF) can be considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB. It should not be used to treat HIV-infected persons taking some combinations of ART [6].

10.2. Treatment of Active TB Patients

To make easy procurement, allocation and management of treatment to patients, the daily dosage may be standardized for three or four body weight bands, such as, 30–39 kg, 40–54 kg, 55–70 kg and over 70 kg [34]. Table 1 shows the essential anti-TB drugs and their recommended dosages based on the patient's weight.

Table 1. Recommended doses of first-line anti-tuberculosis drugs. Source: [52]

Drug	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin	15 (12–18)	–	15 (12–18)	1,000

Patients aged over 60 years may not be able to tolerate Streptomycin more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily [2].

Schedules for treating TB disease have an initial phase of 2 months, followed by a choice of several options for the *continuation phase* of either 4 or 7 months (total of 6 to 9 months for treatment) and sometimes longer (1 or 2 years) and can be cured in almost all cases by taking the medications as prescribed by the doctor for the full course of treatment. The exact drugs and length of treatment depend on age, overall health, possible drug resistance, the form of TB (latent or active) and the infection's location in the body. Recently a shorter term of treatment, 3 months instead of 9, with combined medication may be effective in keeping latent TB from becoming active TB.

With the shorter course of treatment, patients are more likely to take all their medication and the risk of side-effects is also lessened. For latent TB the patients need to take just one type of TB drug. But in active TB, particularly if it is a drug-resistant strain, will require several drugs at once. The most common medications (the first-line anti-TB agents) used to treat TB are Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA). In addition, doctor may recommend vitamin B6 (Pyridoxine) to prevent specific side-effects of INH [58].

Without treatment, a person with TB disease can progress from sickness to death. In studies of the natural history of the disease among sputum smear positive/HIV-negative cases of pulmonary TB, around 70% died within 10 years; among culture-positive (but smear negative) cases, 20% died within 10 years [42].

10.3. Patient Group Treatment

Patient group treatment is called standardized treatment which means that all patients in a defined group receive the same treatment regimen. Advantages of this type of treatment are as follows:

- the risk of development of drug resistance are reduced by avoiding prescription errors,
- costs are reduced,
- maintaining a regular drug supply when patients move from one area to another is made easier,
- outcome evaluation is convenient and results are comparable, and
- estimating drug needs, purchasing, distribution and monitoring are facilitated.

11. Side-effects of TB Medicines

Like all medicines, the medicines are taken to cure TB infection can have side-effects. However, most people can take their TB medicines without any problems. The side-effects of TB medicines are as follows [1]:

1. Dizzy or lightheaded when sitting, standing or lying down.
2. Less appetite or no appetite for food.
3. Stomach upset, nausea, or vomiting.
4. Flu-like symptoms with or without fever.
5. Severe tiredness.
6. Aches in joints
7. Fevers or chills.
8. Pain in lower chest or heartburn.
9. Severe diarrhea or light colored stools.
10. Shortness of breath.
11. Brown, tea-colored, or cola-colored urine.
12. Skin or whites of eyes appear yellow.
13. Skin rash or itching.
14. Bruises or red and purple spots on skin that cannot explain.
15. Nosebleeds or bleeding from gums or around teeth.
16. Pain or tingling in hands, arms and legs.

Numbness or a tingling or burning sensation of the hands or feet and occur more commonly in pregnant women and in people with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, renal failure. These patients should receive preventive treatment with Pyridoxine, 10 mg/day along with their anti-TB drugs. Other guidelines recommend 25 mg/day depending on the side-effects and other morbidities [23].

12. Prevention of TB

TB is an airborne disease and transmission essentially can be prevented through adequate ventilation and limited contact with patients. Many people who are infected latent TB, healthcare providers try to identify people infected with this disease as early as possible, before they advance from latent to active TB.

12.1. TB Prevention by BCG

At present each year about 100 million children receive BCG vaccine worldwide. To prevent TB, the WHO recommends that infants receive a BCG vaccine where TB is a common disease. BCG is fairly effective in protecting

small children from severe TB complications, but it does not protect adults very well against lung TB. BCG is used in many countries with a high prevalence of TB to prevent childhood tuberculous meningitis and miliary disease. BCG is not generally recommended for use in the USA and Netherlands because of the low risk of infection *M. tuberculosis*. BCG vaccination of health care workers should be considered on an individual basis in settings in which a high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both Isoniazid and Rifampin.

BCG vaccination should not be given to persons who are immunosuppressed (e.g., persons who are HIV infected) or who are likely to become immunocompromised (e.g., persons who are candidates for organ transplant). BCG vaccination should not be given during pregnancy.

Priming TB vaccines (pre-exposure TB vaccines) is intended for use in newborns or young infants at the time when the individual is not yet infected with TB. Booster TB vaccines (post-exposure TB vaccines) can be given together with other childhood vaccines during the first year of life and also, at almost any time point, to school children, adolescents, or adults, when the individual has either been vaccinated. Therapeutic TB vaccines are to be given to individuals with active TB disease, represent a special case of the above-mentioned post-exposure vaccines. These vaccines are used not as stand-alone agents, but rather as adjunct to antibiotic treatment, with the aim of shortening the duration of anti-TB chemotherapy [14].

A number of BCG vaccine strains are available, although the French Pasteur strain 1173 P2, the Danish strain 1331, the Glaxo strain 1077 and the Tokyo strain 172 account for about 90% of BCG vaccinations worldwide.

12.2. Environmental Controls to Prevent TB

Environmental controls of TB indicate the use of engineering technologies to help prevent the spread and reduce the concentration of infectious droplet nuclei in the air. The existing ventilation system in a medical hospital or a clinic may not have sufficient safeguards to prevent the spread of TB or some of the hospitals and clinics have no ventilation system at all. But TB clinics must need sufficient ventilation system and directional airflow to prevent the spread of TB. Ventilation is the movement of air in a building and replacement of inside air with air from the outside. In the TB clinics need two types of ventilations [8]: i) natural ventilation, which relies on open doors and windows to bring in air from the outside. Fans may also assist in this process and distribute the air and ii) mechanical ventilation, which usually refers to the use of mechanical air-moving equipment that circulates air in a building and may also involve heating and/or cooling.

When clean or fresh air enters in a room, by either natural or mechanical ventilation, it dilutes the concentration of airborne droplet nuclei in room air. Doors, windows and skylights of the clinic must keep open for the movements of air to inactivate droplet nuclei containing *M. tuberculosis*. Propeller fans can be an inexpensive way to increase the effectiveness of natural ventilation. Ceiling fans, desk fans, standing fans and window fans can be used to improve ventilation in a building (TB clinic, dormitory, prison, **refugee camp and**

army barrack). Fans help to mix air in a room to dilute any infectious particles by spreading them throughout the room and leaving outside. But this system may not be possible in extremely cold climates [46].

Central ventilation systems (forced-air systems) are mechanical systems that circulate air in a building. Some buildings have a mechanical system with 100% recirculation where air is supplied to a room to provide ventilation and/or heating or air conditioning. This air mixes with room air and then returned to the unit, where it is filtered and/or heated or cooled before being sent back to the room.

Filters are used to clean air by removing particles from air that is passed through them. The cleaned air is then distributed. By filtration many particles containing *M. tuberculosis* are removed and the risk of spreading TB by recirculation is reduced. Comparing the efficiency there are three different types of filters: i) high-efficiency particulate air (HEPA) filter which remove all particles in the size range of TB bacteria droplet nuclei, ii) pleated ASHRAE 25% efficient filter (MERV 7 or 8), which can remove approximately half of all particles in the size range of TB droplet nuclei, and iii) lint filter, which cannot remove particles in the size range of TB droplet nuclei.

Ultraviolet germicidal irradiation (UVGI) uses a type of radiation that has been shown to kill or inactivate *M. tuberculosis* in air. UVGI can have negative short-term health effects on the skin and eyes, a safety plan should be implemented when it is used. UVGI has two applications: induct UVGI and upper-air UVGI. Induct UVGI the installation of UV lamps in a return or exhaust air duct to kill any *M. tuberculosis*. In upper-air UVGI lamps are mounted high on walls or suspended from the ceiling and radiation is directed into the upper portion of the room, where the air is disinfected.

13. Drug Resistant (DR) TB

DR TB is a rising global problem which is more difficult and expensive to treat and cure. DR TB can occur when the drugs used to treat TB are misused or mismanaged. People who do not take all the required medicines, if healthcare providers prescribe the wrong treatment, the wrong dose, or wrong length of time for taking the drugs, the supply of drugs is not always available; the drugs are of poor quality can become sick again and spread TB to others. If some other persons have not taken all the prescribed medicines or skip times when they are supposed to take them, the TB bacteria evolve to outwit the TB antibiotics. Soon those medicines no longer work against the disease. In this situation it is called DR TB. It is divided into two types: primary resistance and secondary resistance. Primary resistance occurs when a person gets infected with TB that is already resistant and never treated for TB before. Secondary resistance occurs during treatment for TB, because the doctor prescribes inadequate treatment, patients with TB stop their treatment prematurely, or take their medicine at irregular intervals [8]. Rapid and reliable techniques for drug-susceptibility testing (DST) are needed urgently to save the life of the patient. DR TB threatens global TB control and is a major public health concern in several countries.

13.1. Multidrug-Resistant TB (MDR TB)

MDR TB is a man-made problem created by health care providers and patients, in situations where some Rifampicin (RIF) and Isoniazid (INH) (first-line drugs) treatment can be obtained and used erratically or incorrectly. Monoresistance TB is the resistance to one first-line anti-TB drug only. Polydrug resistance TB is resistance to more than one first-line anti-TB drug (other than both Isoniazid and Rifampicin). MDR TB is the resistant to at least two of the best Food and Drug Administration-approved anti-TB drugs, Isoniazid (INH) and Rifampicin (RIF). These antibiotics are considered first-line drugs and are the first medicines used to treat all persons with TB disease. For patients with MDR TB, second-line drug treatment is mandatory up to 2 years, requiring DST of these antibiotics as well. The extensive chemotherapy is required to treat MDR TB which is more costly and can produce severe adverse drug reactions in patients. It is very important to prevent the further development of MDR TB by the widespread application of DOTS and other measures such as health education, strengthened case-finding and respiratory isolation of infectious drug-resistant cases. At the global level, 15% of previously treated patients have MDR, which is 5 times higher than the global average of 3% in new patients [52]. The WHO estimates that 5% of all TB cases worldwide are MDR TB strain. There were an estimated 0.5 million cases of MDR TB in 2007 and about 511,000 new MDR TB cases were reported. Three countries of the world; China, India, and Russia are accounting for 56% of all global MDR TB cases. In 2007 only 3,681 people (1% of the estimated global total of MDR TB cases) were put on treatment in projects approved by the GLC. More than 110,000 patients die each year due to MDR TB [45, 53]. There are 27 countries (15 in the European Region) that account for 85% of all such cases; these countries have been termed the 27 high MDRTB burden countries [57]. In 2010, the WHO estimated that more than 650,000 people have MDR TB. The Global Plan to Stop TB outlines scale up of services within TB programmes to detect and treat 1.6 million MDR TB cases by 2015.

Treatment for drug-resistant TB often requires the use of special TB drugs, all of which can produce serious side-effects. People with MDR TB may have to take several antibiotics, at least three to which the bacteria still respond, every day for up to 2 years. Even with this treatment 4 to 6 out of 10 patients with MDR TB will die. According to the WHO, there is slow progress in tackling MDR TB, 3 out of 4 MDR TB cases still remain without a diagnosis, and around 16,000 MDR TB cases reported to the WHO in 2012 were not put on treatment [61].

The countries that ranked 1st to 5th in terms of total numbers of MDR TB cases in 2007 were India (131,000), China (112,000), the Russian Federation (43,000), South Africa (16,000) and Bangladesh (15,000) [57].

13.2. Extensively Drug-resistant TB (XDR TB)

XDR TB is a relatively rare type of TB that is resistant to MDR TB (Isoniazid and Rifampin (Rifadin, Rimactane)), plus any Fluoroquinolone and at least one of three injectable second-line drugs, such as, Amikacin, Kanamycin, or Capreomycin. XDR TB cases have been detected in at least 55 countries of the world. About

424,000 MDR TB cases are added each year and about 25,000 of these cases are expected to have XDR TB. It is estimated that about 9.6% of MDR TB cases had XDR TB [49,54]. In many developing countries, this type of TB is untreatable. XDR TB cases in South Africa were untreatable by any available drugs, and had a devastating mortality rate for example, 52 of 53 patients died [65]. WHO estimated that 40,000 cases of XDR TB occur each year [53]. By November 2009, 57 countries and territories had reported at least one case of XDR TB [57].

People may get XDR TB in the following two ways [54]:

1. Directly, if they spend time with an XDR TB patient and breathe in the XDR TB bacteria.
2. If they already have MDR TB or active TB, and do not properly follow their prescribed treatment regimen or TB medication is not reliably available to them.

XDR TB is resistant to first-line and second-line drugs, patients are left with limited treatment options that are much less effective. XDR TB is of special concern for people with HIV infection and has a higher risk of death once they develop TB. Although MDR and XDR TB are occurring globally, they are still rare. In 2011, almost 2 out of every 100 TB cases were resistant to at least two antibiotics [60].

Rifampicin-resistance TB (RR TB) is resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to Rifampicin, whether monoresistance, MDR, polydrug resistance or XDR [63].

14. Drug Susceptibility Testing

The demand for reliable drug susceptibility testing (DST) increased globally due to the expansion of anti-tuberculosis drug-resistance surveillance, and with the need for an appropriate treatment of MDR TB. In many countries, the wide use of the standard short-course regimen has led to an increasing incidence of MDR TB, defined as resistance to at least Isoniazid (INH) and Rifampicin (RIF) [24, 48].

It is a difficult procedure to standardize, and proficiency in performing the tests requires an understanding of many elements as follows [54]:

1. Origin of drug resistance and the criteria for resistance.
2. Potency and stability of drugs during laboratory manipulation.
3. Anti-mycobacterial activity of drugs when incorporated into different media.
4. Reading, interpretation, and reporting of results.

External quality assurance for DST of first-line drugs were begun internationally in 1993 through the Supranational Laboratory Network. In 2001, the guidance on DST for second-line drugs was published by WHO. Very few national TB programmes have capacity for DST for the first-line drugs and even fewer have the capacity to test for second-line drug resistance [49].

For many years conventional DST on solid egg-based Löwenstein-Jensen or agar-based 7H10 or 7H11 Middlebrook media was a standard technology and is still utilized in many countries worldwide. Measurement of recent laboratory capacity indicates that less than 5% of

MDR TB cases are currently detected [36]. The WHO Stop TB Department has three main objectives as follows:

- to develop an interim policy document,
- update existing technical guidelines, and
- develop plans for external quality assurance of second-line DST.

TB bacteria *M. tuberculosis complex* are tested by this method with the drugs included; Isoniazid, Rifampin, Ethambutol, Ciprofloxacin, Ofloxacin, Streptomycin, Kanamycin, Capreomycin, Amikacin, Rifabutin, Ethionamide and Para-aminosalicylic acid (PAS). Well performing DOTS programmes reduce the occurrence of DR TB to a minimal level and poor DOTS programmes performance generates DR TB cases.

15. Data and Statistics

TB is one of the world's deadliest diseases after HIV. One-third of the world's population is infected with TB and is a leading killer of people who are HIV infected. The majority of cases worldwide in 2012 were in Asia (55%), in the Southeast Asia (29%), African (27%) and Western Pacific regions (19%), in the Eastern Mediterranean Region (7%), the European Region (5%) and the Region of the Americas (3%). India and China alone accounted for 26% and 12% of total cases, respectively. In 2012, about 9 million people (about 3 million were women) around the world became sick with TB disease, among them 1.1 million (13%) were HIV-positive and about 75% of these cases were in the African Region. There were around 1.3 million TB-related deaths worldwide and about 410,000 TB deaths among women in 2012, including 160,000 among HIV-positive women. There were about 530,000 TB cases among children under 15 and 74,000 TB deaths were in 2012. Globally in 2012, an estimated 450,000 people developed MDR TB and there were an estimated 170,000 deaths from MDR TB [62].

A total of 9,945 TB cases (a rate of 3.2 cases per 100,000 persons) were reported in the USA in 2012. Both the number of TB cases reported and the case rate decreased; this represents a 5.4% and 6.1% decline, respectively, compared to 2011 [6].

The five countries that rank first to fifth in terms of total numbers of incident cases in 2008 are India (1.6–2.4 million), China (1.0–1.6 million), South Africa (0.38–0.57 million), Nigeria (0.37–0.55 million) and Indonesia (0.34–0.52 million). India and China alone account for an estimated 35% of TB cases worldwide. Of the 9.4 million incident cases in 2008, an estimated 1.2–1.6 million (13–16%) were HIV-positive. Of these HIV-positive cases, 78% were in the African Region and 13% were in the South-East Asia Region. The 22 high-burden countries are shown in Table 2 which account for 80% of all estimated cases worldwide [57].

Between 1995 and 2012, about 56 million people were successfully treated for TB in countries that had adopted WHO's global TB strategy, saving 22 million lives. In 2011, the treatment success rate continued to be high at 87% among all new TB cases. About 75% of the estimated 2.9 million missed cases, people who were either not diagnosed or diagnosed but not reported to national tuberculosis programmes (NTPs), were in 12 countries (in order of total numbers) India (31% of the

global total), South Africa, Bangladesh, Pakistan, Indonesia, China, Democratic Republic of the Congo, Mozambique, Nigeria, Ethiopia, the Philippines and

Myanmar. By the end June 2013, 1,402 testing machines and 3.2 million test cartridges had been procured by 88 of the 145 countries eligible for concessional prices [62].

Table 2. In 2008, 22 high TB burden countries of the world. Source: [57]

	Population	Prevalence		Mortality	
		Low	High	Low	High
Afghanistan	27,208,324	41,568	117,413	3,923	17,964
Bangladesh	160,000,128	418,373	982,401	31,463	152,003
Brazil	191,971,504	12,407	112,628	2,714	15,249
Cambodia	14,562,008	58,019	154,174	4,792	22,262
China	1,337,411,200	408,980	2,203,167	64,683	329,249
DR Congo	64,256,636	267,368	631,855	19,701	94,920
Ethiopia	80,713,432	281,164	688,741	20,831	99,280
India	1,181,411,968	1,044,202	3,739,672	119,082	553,196
Indonesia	227,345,088	229,832	828,415	26,826	124,570
Kenya	38,765,312	17,436	143,440	2,653	16,092
Mozambique	22,382,532	64,989	159,949	3,050	16,805
Myanmar	49,563,020	117,941	385,034	12,181	55,967
Nigeria	151,212,256	625,992	1,299,190	33,833	181,508
Pakistan	176,952,128	304,242	897,731	29,910	136,428
Philippines	90,348,440	217,088	597,488	19,943	91,576
Russian Federation	141,394,304	21,259	195,563	10,233	36,654
South Africa	49,667,628	142,051	514,650	8,257	39,064
Thailand	67,386,384	59,410	178,829	5,557	25,404
Uganda	31,656,864	66,744	165,870	3,217	17,516
UR Tanzania	42,483,924	36,198	77,478	2,601	9,395
Viet Nam	87,095,920	121,713	419,052	12,254	62,097
Zimbabwe	12,462,879	62,614	146,929	2,666	13,030

A total of 94,000 TB patients eligible for MDR TB treatment were detected in 2012: 84,000 people with confirmed MDR TB and 10,000 with Rifampicin resistance detected using Xpert MTB/RIF. Just over 77,000 people with MDR TB were started on second-line treatment in 2012, equivalent to 82% of the 94,000 newly detected cases that were eligible for treatment globally. At least one case of XDR TB had been reported by 92 countries by the end of 2012 [61].

Treatment success rates for TB remain lowest in the European Region, where in 2011 only 72% of new cases were successfully treated. Of the \$7–8 billion per year required in low and middle-income countries in 2014 and 2015, about two-thirds is needed for the detection and treatment of drug susceptible TB, 20% for treatment of MDR TB, 10% for rapid diagnostic tests and associated laboratory strengthening, and 5% for collaborative TB/HIV activities [62].

16. Progress in Declining TB

About 20 years after the WHO declaration of TB as a global public health emergency, major progress has been made towards 2015 global targets set within the context of the Millennium Development Goals (MDGs). The rate of new TB cases has been falling worldwide for about a decade but the rate of decline (2% per year) remains slow. Globally by 2012, the TB mortality rate had been reduced by 45% since 1990 and the target to reduce deaths by 50% by 2015 is within reach [62].

Between 2000 and 2013 deaths in Bangladesh from TB has fallen at a faster rate than the global average at 11.1% compared to 3.1% globally. Although active TB is declining but MDR TB and XDR TB are increasing globally. Because these diseases are not cured by first-line

drugs of TB and second-line medicines of these TB are expensive and have serious side-effects [40].

1 October 2011, The UN health agency reported that for the first time the number of people falling ill with TB each year is declining, but warned that current progress is at risk due to under-funding. The report shows that the TB death rate dropped 40% between 1990 and 2010, and all regions, except Africa. The number of new cases of TB has fallen and its prevalence was lower in 2010 than in 2005 in all the SSA. China's TB death rate fell by about 80%, falling from 216,000 in 1990 to 55,000 in 2010 [44].

New data published in the WHO shows that the number of people who fell ill with TB dropped to 8.8 million in 2010, after peaking at 9 million in 2005. The report also finds that TB deaths fell to 1.4 million in 2010, after reaching 1.8 million in 2003 [60]. Funding in the 22 high-burden countries is 80% of the world's TB cases early doubled from \$1.2 billion in 2002 to \$2.2 billion in 2009. In 2009, available investments for TB total become about \$3 billion [45].

The Global Alliance for TB Drug Development focuses on shortening the duration of TB therapy, treating MDR TB and ensuring compatibility with antiretroviral drugs to treat HIV. Several drugs in advanced stages of development may help shorten TB therapy from 6–8 months to 2–4 months [45].

17. Research and Development (R&D) in TB

Research is urgently needed for better vaccines, diagnostics, and treatment options to protect children from and cure them of TB. Funding for TB R&D overall is dangerously inadequate in 2012 and it is suffering a \$1.4

billion shortfall. In 2012, 85 donors reported investing \$627.4 million to support TB R&D, a 4.63% decrease from the \$657.8 million invested in 2011 and a 0.50% decrease compared with funding in 2010. The \$627.4 million spent on TB R&D in 2012 represents just 31.4% of the recommended \$2 billion annual investment. The keyword search yielded 14 donors in 2012, and 12 donors in both 2010 and 2011, this methodology likely resulted in an underestimate of pediatric TB R&D funding. In 2012, reported pediatric TB R&D funding amounted to \$10.3 million, with just 14 donors disclosing their funding. Pediatric TB R&D received just 2% of the \$627.4 million that 85 funders invested in overall TB R&D in 2012 [43].

The WHO has placed DR TB on the agenda of its 67th World Health Assembly, which will take place on 19–24 May, 2014. After 40 years with no new TB drugs, a new class of TB antibiotics has recently been approved for market entry. There are more products in the pipeline from large pharmaceutical companies for DR TB than for non-DR TB. There are two drugs that target the most DR TB: Linezolid from Pfizer and Bedaquiline from Johnson & Johnson. Investment in new TB vaccine development will be a cost-effective approach to saving lives. Experts estimate that it will cost more than \$24 billion for low- and middle-income countries to deal with this deadly disease through 2015 alone [64].

More than 50 companies are involved in development of new diagnostic tests. 10 new or repurposed TB drugs are in late phases of clinical development. In late 2012, Bedaquiline became the first novel TB drug approved in 40 years. In June 2013, WHO issued interim guidance for its use in treatment of MDR TB. There are 10 vaccines for TB prevention and two immunotherapeutic vaccines in the pipeline. In early 2013, results from a Phase IIb proof-of-concept study of one of the preventive vaccine candidates were published. While efficacy was not superior to the Bacille-Calmette-Guérin (BCG) vaccine alone, the study demonstrated that a trial of a novel TB vaccine is feasible in a high TB burden setting. Short, effective and well-tolerated treatments for latent TB infection, a point-of-care diagnostic test, and an effective post-exposure vaccine are needed to help end the global TB epidemic [62].

The Foundation for Innovative New Diagnostics (FIND) is working to develop rapid diagnostics to more efficiently and reliably detect TB and MDR TB. The Aeras Global TB Vaccine Foundation is supporting research into new TB vaccines, including working to make a modified BCG vaccine [45].

18. Recommendations

TB is a challenging disease to diagnose, treat, and control. In high MDR TB burden countries, increased capacity to diagnose MDR TB must be matched with supplies of quality drugs and scaled-up country capacity to deliver effective treatment and care. The top priority is needed to increase coverage of ART for HIV-positive TB patients towards the 100% target. Fund in TB treatment must be increased locally and globally.

In some developing countries BCG reaches often in late when bacteria already appear in the sputum and are being spread to previously uninfected contacts. The Government of these countries must be active to provide BCG vaccine

timely in these areas where TB prevalence is very high. The vaccines must be collected from the reputed companies and use before expire date.

Hospitals and clinics should reduce crowding, facilitate flow of patients and provide adequate ventilation to decrease TB transmission. Civil society and communities can create demand for TB infection control and help to implement it. The concentration of infectious respiratory aerosols i.e., droplet nuclei should be reduced in the air and control the direction of infectious air in the hospitals and TB care centers.

Hospitals and clinics take precautions to prevent the spread of TB by identifying patients with suspected TB and using ultraviolet light to sterilize the air, special filters, and special respirators and masks. In hospitals, people with TB are isolated in special rooms with controlled ventilation and airflow until they can no longer spread TB bacteria. Special care must be given in proper use of medicines to avoid MDR TB and XDR TB. HCPs must be conscious about the patients HIV-positive that are co-infected of HIV and TB, and treat the patients accordingly.

HCPs promptly identify people with TB symptoms, separate the infectious patients (from other patients) and keep them in special rooms with controlled ventilation and airflow, control the spread of pathogens (cough etiquette and respiratory hygiene) and minimize time spent in healthcare facilities. By having an infection control plan in place, healthcare settings can ensure the prompt detection and treatment of persons who have suspected or confirmed TB disease. Correct diagnosis of TB is needed to improve treatment, reduce transmission, and control development of drug resistance.

19. Concluding Remarks

In this study we have discussed the history, infection, diagnosis, treatment and prevention techniques of TB. As it is a curable and preventable disease, most people undergo complete healing of their initial infection, and the bacteria eventually die off if the patients find proper treatment. So that prevalence of TB and mortality rate can be reduced by the consciousness and proper treatment. Infection and mortality rate due to TB is very high (more than 95%) in the developing countries. TB infections in the world began to increasing since 1980s, because of the appearance of HIV. The TB death rate has dropped 45% between 1990 and 2012, and about 22 million lives are saved. DR TB is increasing globally due to misused or mismanaged of the required medicines. The patients with MDR TB and XDR TB have relatively higher morbidity, which are difficult or sometimes impossible to treat successfully. We have stressed on proper and regular continuous treatment to avoid MDR TB and XDR TB. To reduce or eradicate TB from the society fund in R&D in TB need to be increased. BCG is used in many countries with a high prevalence of TB to prevent childhood tuberculous meningitis and miliary disease. At present each year about 100 million children receive BCG vaccine worldwide. We hope in near future TB will be extinct from the world and human being will consider TB a mere painful disease of past.

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