Prevalence of Tuberculosis and associated factors in Sylhet, Bangladesh

By

Effat Ara

ID: 17326012

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

_____

Effat Ara

Student ID:17326012

Approval

The thesis/project titled "Prevalence of Tuberculosis and associated factors in Sylhet, Bangladesh" submitted by

1. Effat Ara (Student ID: 17326012)

of Summer, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Science in Microbiology in August 2020.

Examining Committee:

Supervisor: _____

(Member) Fahim Kabir Monjurul Haque, PhD

Assistant Professor

Department of Mathematics and Natura Sciences

BRAC University Program

Coordinator: _____

(Member) Mahbubul Hasan Siddiqee, PhD

Assistant Professor

Department of Mathematics and Natural Sciences

BRAC University

Department Head: _____

(Chair) A F M Yusuf Haider, PhD

Professor

Department of Mathematics and Natural Sciences

BRAC University

Ethics Statement

The ethical clearance was provided by the departmental review board of BRAC University, Dhaka, Bangladesh. Permission was taken from the respective authority of HEED Bangladesh before data collection. During data collection, the privacy of the respondents and the confidentiality of the data has been strictly maintained.

Abstract/ Executive Summary

In recent years, tuberculosis (TB) and multidrug-resistant TB (MDR TB) are increasing in several areas of this world. This study was conducted to provide a brief of recent findings and solutions for the underlying causes of the increased TB rate in Bangladesh's Sylhet division. This work has pointed out some major factors associated with tuberculosis in rural areas and the possible solutions that can serve as multipurpose documents, not only as evidence of scientific research but also to increase awareness among general people. Data were collected from three districts (Sylhet, Moulvibazar, and Habiganj) of the Sylhet division from January to March 2021 and thoroughly analyzed. A total of 25711 presumptive TB patients were tested, and among them, 4116 were confirmed to have TB aged between 0 to 65+ years. TB was more prevalent in males (59%) and people between 45 to 65 years. MDR TB was found in 0.48% of cases and, the number of patients with extra-pulmonary TB was 10.66%. Malnutrition, lack of female health workers, and lack of social awareness have been found as important associated factors contributing to the high incidence rate of TB in these areas. Further studies need to be done to generate more evidence-based data, which will help fight tuberculosis and save human lives.

Keywords: Tuberculosis, MDR-TB, RR-TB, XDR-TB, Extra-Pulmonary TB, Sylhet, Bangladesh, Treatment, Drug resistance, Incident, Mortality.

Dedication

I would Like to dedicate this Thesis to my beloved Parents & loving Friend Mahdi Hafiz Nabil.

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This research work would have not been possible without the help of many individuals. All of them are gratefully acknowledged.

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List of Acronyms

CXR	Chest X-ray
DS-TB	Drug sensitive
FLD	First line drugs
FNAC	Fine needle Aspirate and Cytology
HGT	Horizontal Gene transfer
LTBI	Late incident tuberculosis
MDR	Multi-drug resistance
NGO	Non-Government Organization
PPM	Public private mix
RR-TB	Rifampin resistant Tuberculosis
SLD	Second line drugs
TB	Tuberculosis
TST	Tuberculosis skin test
WHO	World Health Organization
XDR	Extensively drug resistant

Chapter 1

Introduction

Tuberculosis (TB) is an airborne contagious disease which was discovered by a renowned scientist Robert Koch in 1882. The causative agent of this infectious disease is a micro-organism of *Mycobacterium tuberculosis (M. tuberculosis)* complex. [1] Tuberculosis is becoming so deadly that it is now one of the ten leading diseases that cause deaths around the entire world. Approximately ten million people catch TB and nearly 1.4 million people lose their lives in 2019. Tuberculosis is a communicable disease because it can spread through human-to-human contact. When a TB-infected person discharges bacteria-contaminated fluid into the air through sneezing and coughing, the transmission occurs. [2] In terms of affecting body sites, there are mainly two types of Tb found, pulmonary TB and extra-pulmonary TB which indicates it is not only able to cause infection to the lungs but the other body organs as well. [1,3,4] According to the clinical point of view, TB patients can be differentiating by having latent TB or active TB infection. Between these two, LTBI is asymptomatic and remains non-transmissible where on the other hand, active TB infection can transmit from one person and can infect another. In case of active TB infections, an infected person may have high body temperature, loss of weight, fatigue, and less interest in consuming food. [1,3,4] However, TB can be treated and can also be prevented. With the proper treatment of TB, infected people can regain their previous healthy state. The treatment for TB is a lengthy process with 6 months medicine regimen. With this treatment method, nearly 60 million people have obviated deaths from the year 2000 to date. [2] For the treatment of Tuberculosis, there are several first-line antimicrobials are available such as isoniazid, rifampicin, pyrazinamide, ethambutol, etc. [1,3,4] Without the proper treatment the death rates can be much higher. [2,6] However, recently, success in the treatment of TB is becoming more difficult to achieve because of the appearance of drug resistance which adds extra threat to the disease. The

drug resistance not only adding threats but also making the disease harder to control and this is the scenario of the whole world. [7,8] In some case scenario resistance towards isoniazid and rifampicin has been found and the condition is named MDR TB. Not only that but also in some cases it has been noticed resistance towards drugs like fluoroquinolones which is termed as XDR-TB. [7,9] Tuberculosis is a significant reason for deaths in developing countries where people suffer from poverty and living a life below the margin. [1,2,5] Like, many other developing countries Bangladesh is also a developing country. Though in past years Bangladesh improves its condition in many ways, it is still one of the poor countries in the world with having a low GDP and lacks in many sectors, especially in education. [10,11] A life living below the line and lack of educational background influence people in many ways and eventually these things affect the treatment procedure because there are a lot of people living in the developing countries who have the fear about a lot of things for instance denial and separation from the other person and the society. As a result, they sometimes refuse to take medical attention which makes the entire condition even worse. [12,13,14,15,16] Moreover, gender discrimination adds some extra tension while seeking clinical advice especially the women who live in different rural areas in Bangladesh are having more disadvantages. [10,17] Furthermore, in the number of health workers, the number of females is very less comparatively male health supervisors.

This paper analyzed the present situation of Tuberculosis in the rural area of Bangladesh to highlight some of the major problems and suggest probable solutions to improve the scenario.

Chapter 2

2.1 Background

After analyzing the historical data, it is found that Tuberculosis has a long relationship with human lives. According to the early history, the existence of this deadly disease and the occurrence of infecting humans can be found from the beginning of the recorded history. Male has been found with a wound in the vertebrae and it was from the Neolithic period timing around 5000 BC [21, 22]. Tuberculosis was so vast that it has been found not only in the Neolithic age but also in mummies of Egypt during 3700 BC [21, 22]. According to modern research, Tuberculosis was present among the American eras even before the discovery of America by Columbus [21, 22]. From 1614 to 1672 a scientist named Franciscus Sylvius first came up with the designation tuberculosis when he was trying to explain some sort of lung nodules. Another scientist, Theophilus Bonetus listed incidents of around 3000 infectious materials in his book named 'Serpulchretum Sive Anatomica Practica' where nearly 150 cases were found with relatable symptoms of tuberculosis. Later, in 1700, Jean Jacques Manget, a French researcher mimeograph this book with some of his personal views and came up with the idea of Miliary Tuberculosis [21]. In after years, in 1772 it was found that tuberculosis is a contagious disease, and this invaluable information was discovered by Benjamin Martin who also assumed the transmission occurred by the air excreted from lungs. However, the fact was proved with evidence by a professor of an institution of Military Hygiene at Val-de-Grace [21]. The French physician observed some young soldiers and stated that tuberculosis is a communicable disease and infect people who lived in a congested place [21]. After the establishment of the theory and relative proofs, the scientist, later, introduce some fluids and pus from the infected person into rabbits [21]. Unfortunately, this huge experiment did not get much attention and was ignored by the world up until the incredible discovery by Robert Koch in 1882 who managed to stain the causative agent of tuberculosis and

surprised the whole world [19]. After the successful isolation, Robert Koch took his experiment to another level when he inserted tubercle bacilli into the skin of Guinea pig for primary infection to occur, but Koch observed that the infection was not healing. For further inquiry, the scientist again inoculated the pathogenic sample into the Guinea pig and this time he noticed the formation of red nodules which gradually cured. This experiment is known as the famous Koch phenomenon which generates the idea of immunity [19]. However, in 1890 his statement about the theory that tuberculosis can be healed by the infiltrations, lose its creditability. Tuberculosis was becoming so deadly in the eighteen and in the starting of the nineteen centuries that almost 30% of the death was recorded because of tuberculosis in Europe and American region [19]. From the evidence, it was also predicted that the transmission increases in number among the people who stayed in a crowded place and who lived a life without having the fundamental opportunities. This disease started spreading more into the people who used to live in the suburban areas of Europe and America and among them, most of the people were coming from a different place to get a job in the new industries. In the time of World War 1, among 3200 post-mortems 33% had active TB [19]. Finally, in 1943 two researchers from the USA named Albert Schatz and Selman Waksman found a soil organism, streptomyces griseus, that produces antibiotic which proved to be effective as the treatment of TB. In the next year, a Swedish scientist, Jorgen Lehmann manifested that an antibiotic named para-aminosalicylic acid, a similar medicine like aspirin can be used for effective treatment of tuberculosis with the alliance of streptomycin. Upon the invention of several medicines to cure TB, people became overconfident and somehow neglect the disease [19]. A prediction was made and according to that assumption by 1990 the disease would be hard to find in the UK and by the year 2010, it would only a matter of interest for researchers who wanted to analyze and study the medical history [19, 27]. However, taking TB lightly costed many lives of

people both in the UK and the USA and became a major health issue [19, 28, 29, 30, 31, 32]. Most of the infection occurred in people having HIV, using intravenous drugs, staying in prison, and old people. The main reasons for the incident were the irregular or stop using of anti-TB drug regimen, migrated people from a place with high TB load, and an over-crowded living style [19, 30]. There were some other factors responsible such as ineffective communication between health care workers and the patients, which eventually ended up causing the drug resistance of two main medicine isoniazid and rifampicin [19, 35] which was responsible for the 8 million new cases and 3 million deaths worldwide by 1990 [19, 36]. Nearly, one-third of the world's population was under threat of getting infected with M. Tuberculosis [19, 36]. Most people infected with the disease were from Africa and Asia and which made TB a killer disease, reasons of 6.7% of deaths in developing countries [19, 36] and 18.5% of deaths among adults aged between 15 and 59 years. Not only the adults this disease is so deadly it also infects children and according to a report of USA, the infection rate among children less than 15 years increased from 29% to 59% in the year 1990 [19, 25] and the report also showed that people from a minority group and people from urban areas had the high infection numbers. Not only in the USA but in Cape town the incident increased and reached 679 per 100000 people. In many countries, HIV added an extra threat to this situation, people having both the disease making the situation harder to control [19, 39]. Over time, people are becoming more susceptible to the disease and the drug resistance is making the scenario worse. According to World Health Organization (WHO), nearly 1 million people per year get infected by tuberculosis and it takes away approximately 4 thousand lives per day. In the year 2019, 87% of new cases have been reported. There are 30 countries identified by the World Health Organization having the high case numbers of Tuberculosis and about 87% of the cases of the whole world are from these countries and two-third of the global total is found in eight countries among them

countries like Pakistan, India, Bangladesh, China, Indonesia is leading [2]. In Bangladesh, the recent increase in tuberculosis incidents is alarming. A statistic in 2017 shows that around 13 thousand people died of tuberculosis that year in Bangladesh, which increases in 2020 with the death of 107 people and nearly 987 new cases get diagnosed per day [44] which is immensely concerning and because of the pandemic this issue is not getting as much attention as it should get. If the disease does not get the proper attention, it may cause an epidemic and take away many lives. ***fig 2.01*** indicates the number of deaths caused by the diseases that can be prevented with vaccines [45].

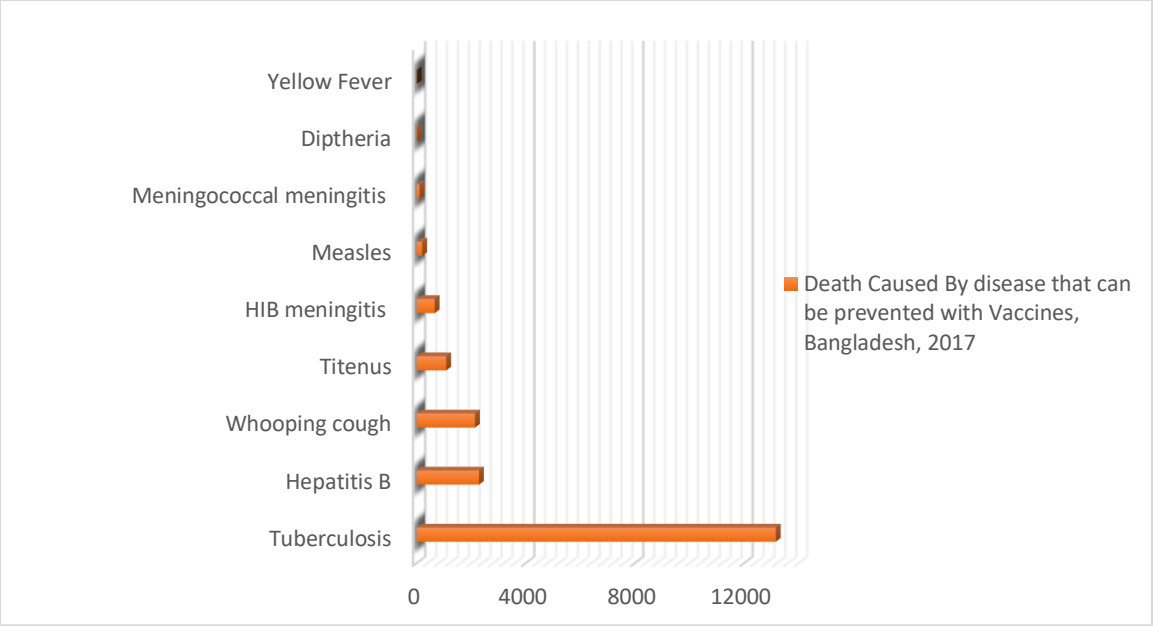

fig 2.01: Death caused by diseases that can be prevented with vaccines, Bangladesh 2017. **([Adopted from, Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017)]**

2.2 Overview of Tuberculosis

2.2.1 General Idea of Tuberculosis

Tuberculosis is an airborne disease, and the causative agent is Mycobacterium tuberculosis. This infectious organism mainly enters the body with the air inhaled into the lungs. TB spread into the body through the bloodstream, lymphatic system, or through the augmentation to other body parts in a direct way [46].

2.2.2 Tuberculosis Infection and Tuberculosis Disease

2.2.2.1 Tuberculosis Infection

The transmission of tuberculosis occurs through contaminated fluid excreted from the lungs. These fluids can stay into the air as air particles and upon inhalation a person can get infected. Among the infected people 90% does not develop the TB disease. The TB infected people do not have any significant sign symptoms and they cannot transmit TB to another human being. As because they do not have symptoms, they feel normal as a healthy individual [46].

2.2.2.2 Tuberculosis Disease

When a causative agent of TB increases their number and start multiplying into the lungs of a TB infected person, then that person gets the TB disease. Among all infected person only 10% of the infected person develops the disease. In this state, a person can spread the disease to another person and have noticeable sign symptoms of the disease [46].

2.2.3 Transmission of Tuberculosis

When droplets from a TB-infected patient get out into the air during coughing, sneezing and other activities like talking or singing, the air gets contaminated with a droplet that contains

Tuberculosis bacilli. This pathogen can stay in the air for many hours and when a healthy individual inhales the contaminated air, the bacilli get inside the lungs and started increasing their numbers. This way the transmission occurs from person to person. However, if a person does not get exposed regularly to the infecting agent, it may not affect infection. The person may overcome the infection. On the other hand, an individual living with the infected person or getting exposed to the organism regularly, that person may progress the tuberculosis disease [46] (***fig 2.02***).

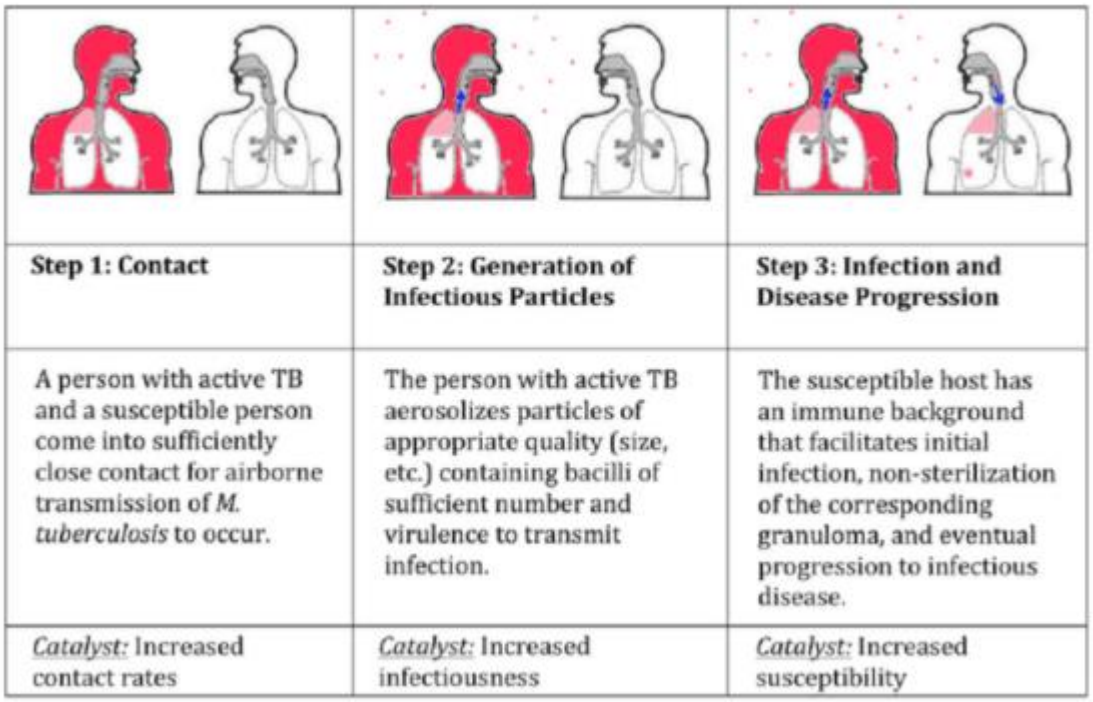

fig 2.02: Tuberculosis Transmission Cascade **(adapted from Dowdy, David & Azman, Andrew & Kendall, Emily & Mathema, Barun. (2014). Transforming the Fight Against Tuberculosis: Targeting Catalysts of Transmission. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 59. 10.1093/cid/ciu506.)**

2.2.4 Progression of Tuberculosis Disease

TB infection often gets destroyed by sunlight and well ventilation. That is why among infected people 90% do not get the disease and continue living as a healthy individual with no symptoms of being ill (Latent infection) [46]. However, 10% of the people progress the disease and among them half develop the disease within one to two years after being infected and the other half takes a very long time (active disease). These 10% people may have many medical conditions and may be deprived socially such as immune-compromised, malnourished, living a life below the margin and living in an over-crowded area, etc. [46] ***fig 2.03*** shows the progression of active and latent TB.

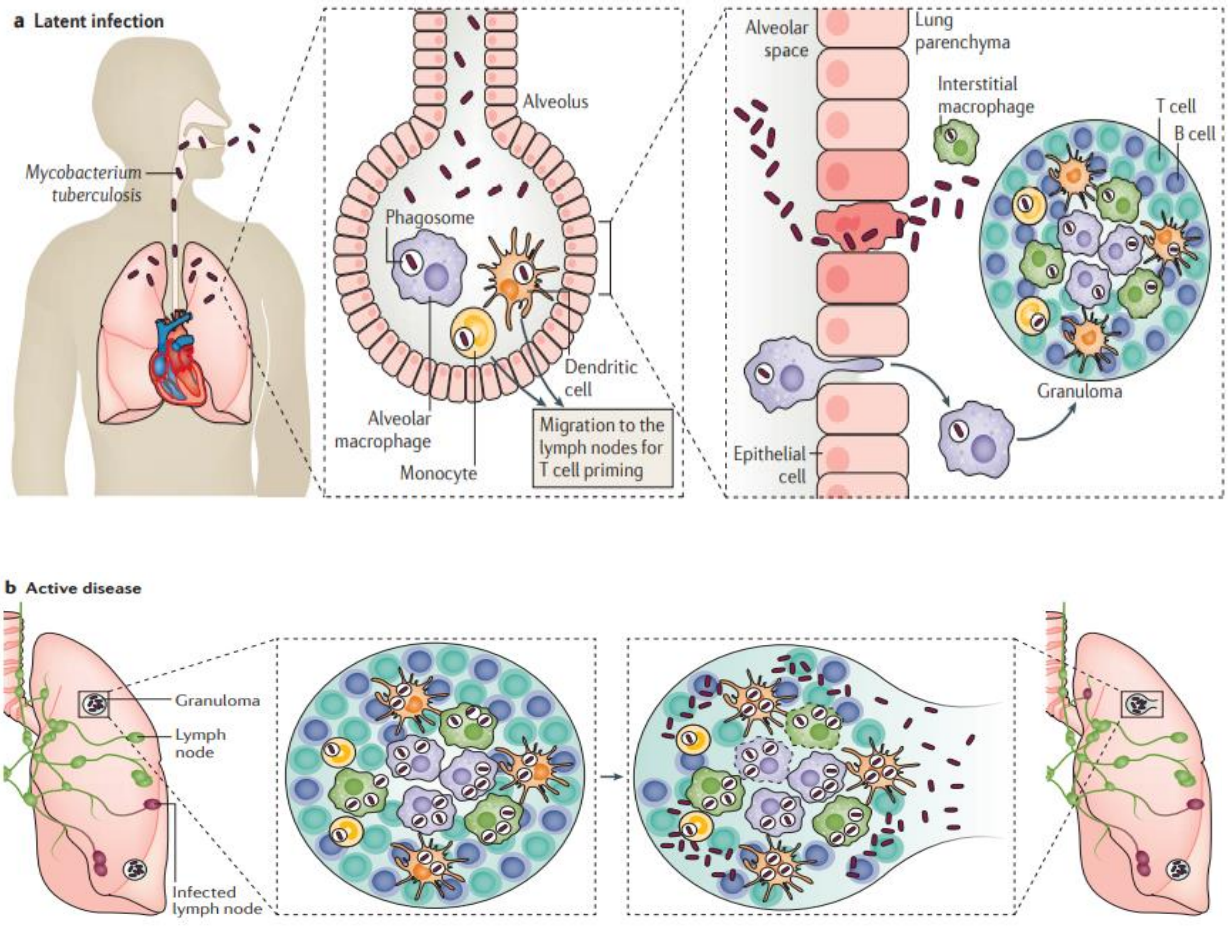

fig 2.03: Latent infection and active disease progression **(Adopted from Pai, M., Behr, M. A., Dowdy, D., Dheda, K., Divangahi, M., Boehme, C. C., … Raviglione, M. (2016). Tuberculosis. Nature Reviews Disease Primers, 2, 16076. doi:10.1038/nrdp.2016.76)**

2.3 Various types of TB

2.3.1 Pulmonary TB

When tuberculosis infects the lungs, parenchyma is known as pulmonary TB. Pulmonary TB is the most common form of tuberculosis found in the whole world. Now it is becoming the reason for the increased rate of mortality and morbidity rate in developing countries [46].

2.3.2 Extrapulmonary TB

The occurrence of TB in other organs instead of lungs is known as Extra-pulmonary tuberculosis. This kind of TB is more dangerous because it can attack any tissue or any body part. For example, hilar lymph nodes, larynx, pleura, cervical lymph nodes, meninges, CNS, skin, kidneys, intestines, etc. The risk of getting infected, increases upon immune-compromised condition [46, 48, 49].

2.3.2.1 Miliary TB

Miliary TB is a life-threatening type. It occurs when many bacilli accumulate into the bloodstream and infect different parts of the body. In this TB, the patient forms millet seed size granulomas in different body sites. Though the treatment is present, still it is becoming very dangerous because of not getting diagnose efficiently [46, 51].

2.3.2.2 Gastro-intestinal TB

This can happen if an individual consumes tuberculosis contaminated food. It can affect any part of the intestine, however; the ileum and cecum are the most common. The wounds in

the intestine can take the form of an ulcer. The symptoms involve are fever, abdominal cramps, weight loss, diarrhea, sweating at night, etc. [46].

2.3.2.3 Spinal TB

Lower thoracic vertebrae and upper lumbar spinal are generally get affected. In this case, the infection begins from the intervertebral disc and gradually infects the anterior and longitudinal ligaments. In the development of the next stage, kyphosis may occur due to the collapse of the vertebral parts [46].

2.3.2.4 Joint TB

Most of the time this type of TB affects those joints that carry most of the bodyweight for instance the joint of hips, knees. Consequence of this TB is very severe which may include the joint space narrowing, joint damage to destruction [46].

2.3.2.5 Genito-urinary TB

In this condition, most of the time patient remains asymptomatic and does not show any severe sign symptoms of the disease. However, this form of TB can also affect the body. It can be the cause of infections in different parts of the urinary tract. This is not so easy to diagnose and often get identified in serious condition such as presence of lesions in the kidney [46]. Genito-urinary tract TB is more commonly found in women rather than men. When women get infected, the fallopian tube may get serious damage and other issues may arise such as irregular menstruation cycle [46].

2.3.2.6 Hepatic TB

The infection in the liver is known as hepatic Tuberculosis. Most of the time it cannot be diagnosed easily [46].

2.3.2.7 Less Common Extra-pulmonary forms

There are some less common extra-pulmonary forms of TB.

2.3.2.8 CNS Tuberculosis

CNS tuberculosis involves tuberculous meningitis, intracranial tuberculomas, and spinal tuberculous arachnoiditis. It starts when tiny foci of tuberculosis progress on the brain, spinal cord, or meninges. Based on the foci formation position is responsible for different CNS infections [46].

2.4 Clinical symptoms and risk factors

To treat tuberculosis properly it is very important to identify the sign and symptoms early. The probability of getting correct medical help and overcoming the disease mostly depends on the timing of recognizing the symptoms. However, there is some difference in symptoms between the pulmonary TB and the extra-pulmonary TB. In general, a person should seek clinical advice on having a cough for three weeks continuously, as a susceptive of TB patient, now known as suggestive TB patient [46].

An individual with pulmonary TB may have the following sign, symptoms with the prolonged cough:

- Visible symptoms: weight loss, appetite loss, increased body temperature, sweating at night, etc.

- Respiratory tract symptoms: pain in the chest, cough with blood, difficulties to breath.

If the person does not have these additional symptoms yet sputum of the patient always needs to get through a microscopy test [46].

Sign and symptoms of extra-pulmonary TB depend on the location of the infection. Sign, symptoms for extra-pulmonary tuberculosis:

- Pain in the joints in case of joint tuberculosis
- Pain in the chest, fever, breathing difficulties if the person has pleural effusion.
- Swelling in the lymph nodes due to tuberculosis in lymphadenitis
- If the patient has CNS TB, then headache, fever, neck stiffness, a mental disturbance may be experienced.

Diagnosis of extra-pulmonary tuberculosis requires efficient medical personnel and, methods like X-ray, MT, CT scan, Biopsy, MRI, FNAC are used to identify and screen the disease [46].

2.5 Diagnosis of Tb

To treat tuberculosis, it is very important to diagnose the disease. There are several advanced methods available to screen and identify the disease such as examination of sputum, radiology or X-ray, biopsy, bronchoscopy, molecular test, culture test, Mantoux test, etc. [46]

2.5.1 Sputum Examination

The most effective way to detect pulmonary TB is the sputum smear test and this is also the most cost-effective method to identify. This examination is performed by the ZN method. Besides, this method of examination is most authentic when it comes to getting the maximum positive results. More than 65% of the pulmonary positive has been detected by the ZN

method [46]. However, recently LED fluorescent microscopy has been using by the recommendation of the WHO which will eventually succeed the ZN microscopy method as it generates 10% more accurate results [46]. Though this method has a great benefit, it has some drawbacks as well. To screen the disease through the ZN method or LED microscopy test, a minimum of 5000 bacilli needs to be present in the sample sputum. If the number of organisms is as low as 1000 then it is very difficult to detect them through this process and the possibility of getting a positive result is only 10%. [46]

2.5.2 Radiology

Radiology or X-ray is mainly done to the lungs of a suggestive TB patient. However, there are some problems with this type of test. Sometimes, other chest abnormalities may present in a patient, and which makes the thing difficult to detect the disease with accuracy. For different chest problems, this test may show similar kinds of images. That is why, after performing this process a smear test needs to be done to reinforce the test result and a well-trained physician is always needed to check the report to avoid any mistakes [46].

2.5.3 Mantoux Test

This test is also known as the Tuberculin skin test. By this test, the fact that a person gained immunity through previous exposure to *M. tuberculosis* can be identified. Some particles extracted from TB cultures, injected into the skin of a patient to observe any skin reaction. As *M. tuberculosis* produces some late hypersensitivity skin response. If a person has been infected by the causative agent of TB, upon injecting the PPD into the skin, the test will generate a positive result since bodies T cell get activated and tries to neutralize the PPD into the skin. However, this test has some huge drawbacks. For instance, if a person is exposed to another type of *mycobacterium* and if any individual has been vaccinated with BCG or has an

immune-compromised condition may also produce a positive result (false positive) even if the patient may not have the disease [46].

2.5.4 Biopsy

This is a special test performed by specialist medical staff to detect extra-pulmonary TB [46].

2.5.5 Molecular Test

The molecular test is introduced into the diagnosis methods because of the ability to generate quick and efficient results. It can give the result within a few hours or maximum in one day. By this test, the TB disease can be identified with a confirmation. Some popular molecular tests are NAAT, Xpert RIF/ MTB, etc. [46]

2.5.6 Culture Test

This is a very effective way to detect a very small number of tuberculosis bacilli. It can detect as small a quantity as 100 per ml in a clinical sample. The problem with this is, it is a very time-consuming procedure, and it takes approximately 6 weeks to give the proper result and so it is not very reliable as a regular method of screening tuberculosis [46].

2.5.7 ELISA

ELISA can also be used to detect tuberculosis. However, there is a huge variety of produced antibody and using this technic it is very difficult to identify active infection. So, it is not very reliable when it comes to the production of accurate results [46].

2.6 Treatment of Tuberculosis

2.6.1 General Information

It is globally known that TB is a curable disease, with proper treatment and consumption of drugs and following the clinical guideline will eradicate the disease. The entire treatment guideline has made mainly based on three exhortations; (1) treatment procedure should have included multiplex medicine (2) a patient should take the medicine regularly (3) the administration of the medicine should continue for a good amount of time and the focus of

the therapy should be providing danger-free and impactful treatment within a very less amount of time possible. There are different ranges of drugs available to treat and cure tuberculosis such as isoniazid, rifampin, pyrazinamide, ethambutol, ethionamide, etc. Not only that there a huge number of amalgamations of drug therapy which is considered to work against tuberculosis. Though there are multiple ways to treat the disease, it is always wise to start the treatment in the initial stage. The early-stage treatment plays a vital role to not only cure the person but also helps to save many other people who are at risk of infection. The monitoring of the patients should also consider as important as the treatment procedure because if the patient is not taking the medicine regularly and if that diseased person is not following the medical guideline, then the treatment method has no value. It is equally important to check the patient as the medicine needs to enter the body to fight the disease. The elimination of the disease depends on good communication between patients and clinical staff and the proper measurements to monitor the patients [46].

2.6.2 Brief information of the available drugs

2.6.2.1 Isoniazid

Isoniazid is the most classic medicine used to treat TB patients. It is one of the best-suited drugs for many reasons. Isoniazid is a very cost-effective medicine with a very low amount of side effects. Not only that, compared to the other medicine's isoniazid has fewer toxic properties and it can be easily absorbed by the body. This medicine has so well functioned that when it enters the body it almost acts like the other liquids found in the serum. It is also safe and can be provided to pregnant women. However, isoniazid has some negative properties as well (maybe not as much as other drugs). After a certain age,

consumption of the drug may cause hepatitis, many CNS diseases, and may be responsible for peripheral neuropathy [58].

2.6.2.2 Rifampin

Rifampin is another useful medicine. It gets absorbed by the gastrointestinal tract. Rifampin is a drug that binds with protein, but it can enter the other body tissues and cells equally well. Rifampin comes with a lot of drawbacks. First, its performance is very poor when it comes to infiltrating into the inflamed meninges. Then, it is unfavorable and is a reason for stomach upset, hepatitis, skin rash. In some intermittent conditions, thrombocytopenia and cholestatic jaundice can happen. Another very adverse disadvantage of consuming rifampin is, it can interfere with the function of other drugs and make their effect lesser. This bactericidal is also responsible for the discoloration of many fluids discharged from the body such as tears and urine [58].

2.6.2.3 Pyrazinamide

This medicine works best in an acid environment. Pyrazinamide kills and stops the growth of the micro-organism that causes tuberculosis. This kind of drug is very particular to identify the causative agent and work specifically against *Mycobacterium tuberculosis*. It does not directly block the action of the causative agent but indirectly inhibits the mechanism. It works well when combined with other drugs. Using pyrazinamide also has disadvantages. It can cause lesions on the liver. However, this problem can be overcome if pyrazinamide is combined with isoniazid and rifampin. Other than liver injury, skin eruptions and gastrointestinal abnormalities may also appear [58].

2.6.2.4 Ethambutol

In general, Ethambutol does not kill the bacteria instead it prevents the growth of the organism. It can kill the bacteria if it administers in a large quantity. The mechanism of

the drug is not clear yet. There is some adverse reaction to using ethambutol. Retrobulbar neuritis can be found in a patient with some symptoms like blurred vision, color-blindness, etc. The side effects mostly depend on the quantity of the drug. If the doge is high the possible side effects will be high and vice-versa. If ethambutol has been suggested to the diseased person, it is important to ask about any abnormalities in visuals. When administered to children's extra precautions should be maintained as children may not sometimes able to interpret their problems to a medical specialist [58].

2.6.2.5 Ethionamide

It is a by-product of isonicotinic acid which helps to prevent the growth of *M. tuberculosis*. The required amount is 15 to 20 mg per kg body weight. Some impacts of consuming the drug are nausea, vomiting, abdominal cramp, etc. In the most unfavorable condition, a person may experience hepatitis and the possibility is even higher than the consumption of pyrazinamide. Another issue, for instance, arthralgias, impotence, photosensitive dermatitis, hypothyroidism, and a distaste in the mouth. Patients who are prescribed ethionamide should monitor every month. If any effects are being noticed the consumption should immediately be stopped [58].

2.6.2.6 Streptomycin

This is not an oral drug therefore it needs penetration through injections. Streptomycin works best in alkaline conditions and can kill almost all *M. tuberculosis* strains. This medicine has very efficient penetration capability, but it only enters the cerebrospinal fluid in case of inflammation in the meninges. It always gets out of the body through the nephritic route. As a result, it may cause damage to the patient with pre-conditioned renal defects. Other than that, streptomycin can cause damage to the auditory nerve or vestibular system of the ear (known as ototoxicity) and harm the kidney because of having

nephrotoxicity properties. Therefore, patients with an age range of 65 years or above should not be prescribed this medicine or else should suggest a very lower dose [58].

2.6.2.7 Cycloserine

Cycloserine has also a bacteriostatic property like ethionamide. It is an oral drug and usually comes in 250 mg tablet. Administration of this medicine may have some serious problems especially to those patients who have any kind of psychiatric issues. In the case of mental unstableness, a person may experience different side effects. Therefore, it is very important to know the patient's previous medical conditions regarding mental illness. If a person with a psychiatric problem needs treatment for tuberculosis, cycloserine should not be prescribed [58].

2.6.2.8 Para-amino salicylic acid

This is also an effective drug with bacteriostatic properties. When taking the medicine, foods like orange juice should have taken with it as para-amino salicylic acid has a huge sodium load. It has few drawbacks such as gastrointestinal problems and sometimes hepatitis may occur [58].

2.6.2.9 Kanamycin

It also needs parenteral penetration. It has some ototoxicity and may cause a problem to the kidney. Therefore, a creatinine check is a must if this has been prescribed [58].

2.6.2.10 Thiacetazone

This drug mainly uses in most developing countries because of the cost-effectiveness. The properties of thiacetazone are very similar to isoniazid however, it is more toxic than isoniazid. The main issues are, jaundice, skin breakout, etc. and most commonly get to see in immune suppress patient having HIV infection. This is very effective among the people of East Africa than Asia [58].

2.6.3 Less used medicines

2.6.3.1 Amikacin

Amikacin can effectively fight against tuberculosis. It is a parenteral medicine and needs to inject five times a week. Though it is bactericidal, it has some serious side effects such as renal failure, loss of hearing, nausea, fatigue, etc. The level of magnesium, potassium, calcium needs to monitor as there is the possibility of chemical imbalance [58].

2.6.3.2 quinolones

Many fluoroquinolones have been invented which shows effectiveness in order to treat tuberculosis. However, these should be used carefully for pregnant women and children as there are some serious health risk factors [58].

2.6.3.3 Rifabutin

This can be a good alternative to rifampin as it is less toxic than rifampin. Though it also arises problems for example, stomach upset and in rare cases hypersensitivity [58].

2.5.3.4 Clofazimine

The drug was previously considered ineffective against tuberculosis. However, in a recent analysis, it is known to be impactful to fight drug-resistance TB. Eye discoloration, serious abdominal cramps, stomach upset, skin rash, etc. are some of the adverse effects of taking clofazimine [58].

2.6.4 Combination Drug therapy

There are a lot of studies done regarding combination drug therapy over the past 45 years. There is much important information about the combination drug therapy that came to light which may be helpful in the coming future to effectively fight tuberculosis. The first combination therapy was using streptomycin and PAS. In the study, it is noticed that treatment with the only streptomycin raises the resistance by 70%, and with the combination method, it decreases dramatically to 9%. Moreover, the treatment with the combination of drugs is very

less time-consuming [58]. Though it has some benefits, it needs further trials and experiments.

Table 2.1 listed all the drugs recommended by WHO.

Table 2.1: Drugs for tuberculosis treatment according to WHO recommendations.

Group Name	Agent
1. First line drugs	Isoniazid, rifampin, ethambutol, pyrazinamide
1. injectable drugs	Amikacin, capreomycin, kanamycin
1. fluroquinolones	Levofloxacin, moxifloxacin, gatifloxacin, ofloxacin
1. oral bacteriostatic second line drugs	Ethionamide, prothionamide, cycloserine/terizidone, paraaminosalicylic acid
1. Drugs with unclear efficacy	amoxicillin/clavulanate, clarithromycin, clofazimine, imipenem/meropenem, linezolid, thioacetone

2.6.5 Special considerations while using the medications.

2.6.5.1 Drug responsible for hepatitis

There are some drugs that induce hepatitis in patients getting treatment for tuberculosis. Among them isoniazid, rifampin has the most adverse effects. Patients with tuberculosis may also have the possibility to progress hepatitis during the treatment because of anti-tuberculosis drugs. If a person develops hepatitis because of consuming drugs, the use should be stopped up until the symptoms subside. After the disappearance of the symptoms, it is wise to wait two weeks before starting the treatment again if a liver test is not possible. After two weeks the patient can re-start the drug administration. Some

patients experience severe jaundice due to hepatitis and they are recommended not to take rifampin and pyrazinamide. In severe cases, a person can die of TB if not get proper treatment. In such a situation, a diseased person should be suggested to have streptomycin and ethambutol [46].

2.6.5.2 In case of active viral hepatitis

Consumption of any anti-TB drug should be forbidden if a person has acute viral hepatitis. However, sometimes some patients need treatment in the presence of active viral hepatitis. In those circumstances, the combination of streptomycin and ethambutol for three months is the preferable solution to avoid any kind of unwanted situation. Later, the patient can have isoniazid and rifampin for six months, or else if the person is not fully recovered from viral hepatitis, then streptomycin and ethambutol are advised to take continuously [46].

2.6.5.3 Pre-existing Liver disease

In case of chronic liver disease, a patient should advise not to take pyrazinamide. For the treatment, it is best to use combination therapy with isoniazid and rifampin and either streptomycin or ethambutol for eight months [46].

2.6.5.4 Renal Failure

In case of patients with renal failure should be extra cautious. Those medicines that get out of the body and do not use the kidney can refer to the patient having renal failure. For instance, drugs like isoniazid, rifampin, and pyrazinamide can be advised to use. In serious conditions, pyridoxine with isoniazid should prescribe. Though streptomycin and ethambutol are discharged by the kidney, they can be useful when given in a small amount. However, places where monitoring the patient is not possible should avoid prescribing these drugs [46].

2.6.5.5 Pregnancy and breast-feeding women

Almost all the available drugs for tuberculosis are safe to use during pregnancy. However, streptomycin has some adverse reactions and should not be used at the time of childbearing. On the other hand, the patient who has a newborn baby and needs to feed it should give some chemotherapy to prevent the transmission of the causative agent of tuberculosis. The baby should also receive treatment with isoniazid for six months and needs to get vaccinated after the end of the drug course. Moreover, while feeding the mother should wear a medical mask to avoid any possible contamination [46].

2.6.5.6 Consumptions of oral contraceptive pills

Some anti-tuberculosis drugs have the properties to interfere with estrogen, therefore, increase the risk of getting pregnant. In this case, rifampin should not be used [46].

2.6.5.7 Diabetics

A diabetic patient should continue the treatment with insulin [46].

2.7 Prevention of Tuberculosis

Vaccination plays the key role to prevent Tuberculosis and in TB prevention there is only one licensed vaccine available named BCG vaccine [1, 99, 100]. Globally more than 90% of newborn babies get injected with this vaccine [1, 99, 100]. This vaccine has been in use since 1921 and has many evidence to prevent the progress of active TB disease. However, there are also studies that found this vaccine works best in the children and can give protection for up to ten years. In adult, BCG vaccine has the efficiency of 0 to 80% based on different circumstances [1, 101, 102]. On the other hand, upon giving the vaccine to the children age below 5, shows better outcome. In those children (age <5 years old) it has been noticed that not only the TB disease, but the TB infection can be prevented [1, 103]. Nonetheless, TB disease has the tendency to develop in the

adolescence. As a result, the chances of BCG vaccine with the current regimen to fight TB epidemic and prevent TB disease is very less because in most of the countries this vaccine is administered one time when a child born but that is not sufficient to control TB disease [1, 100]. ***fig 2.04*** shows the world map and countries that have BCG vaccine policies.

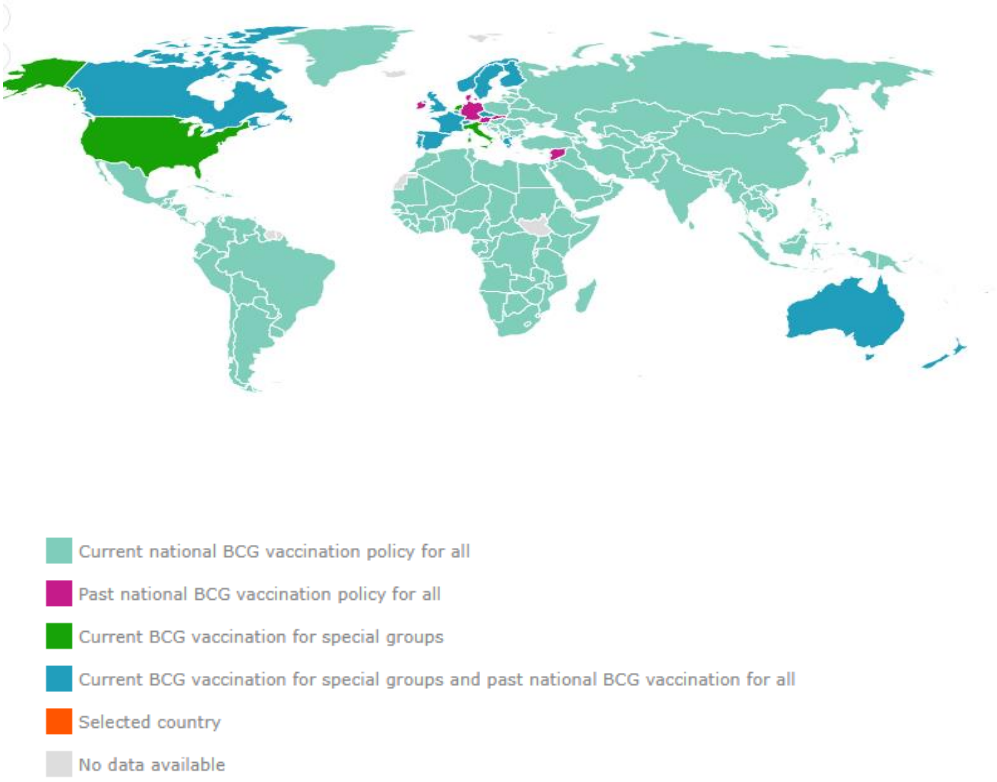

fig 2.04: Global BCG Vaccination policies and participation **(adapted from http://www.bcgatlas.org)**

2.8 Drug resistance

fig 2.05 illustrates how the *M. tuberculosis* gain resistant.

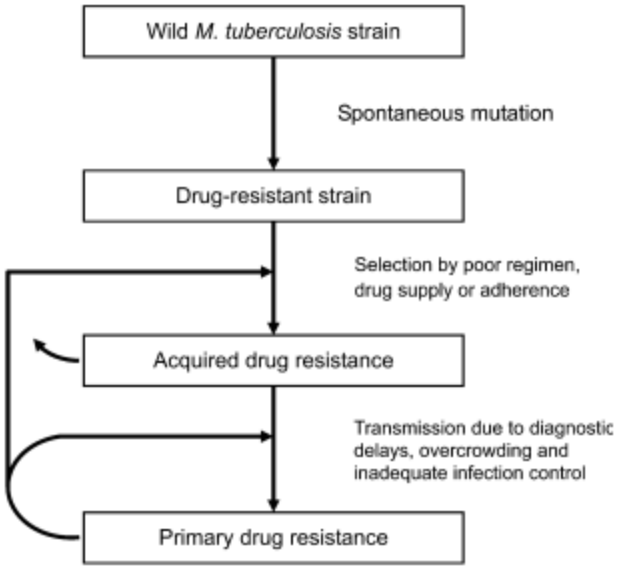

fig 2.05: The main concept of drug resistance. (**Adopted from Zhang, Y., & Yew, W. W. (2009). Mechanisms of drug resistance in Mycobacterium tuberculosis [State of the art series. Drug-resistant tuberculosis. Edited by CY. Chiang. Number 1 in the series]. *The International Journal of Tuberculosis and Lung Disease*, *13*(11), 1320-1330.**)

2.8.1 Mechanism of drug resistance

2.8.1.1 Resistance based on genetics.

2.8.1.1.1 Resistance due to mutation

Resistance through mutation occurs when a group of susceptible micro-organisms started developing mutation in their genes. As a result, even after the drug therapy it becomes very difficult to destroy the pathogen and hence, they survive. If the mutation can occur successfully the previous susceptible group also become resistant which makes the scenario even worse and hard to control. The resistant organism adapts many strategies to decrease the efficiency of the antibiotics. Some of the mechanisms are, i) alteration of the antimicrobial binding site, ii) efflux pump activation to get the drug particles out of the cell, iii) modifications of vital pathways etc. [93]

2.8.1.1.2 HGT

Horizontal Gene Transfer (HGT) is a very frequent way of bacteria to acquire resistance. Through this process bacteria can uptake genes from other organisms and activate different mechanism. HGT can occur in three ways, i) Transformation ii) Transduction and iii) conjugation. Besides, these three methods there is another named integrons which makes the uptake of foreign material easier for the pathogens. Among the three classical ways, transformation is very common when it comes to gain resistance. Through transformation micro-organism can uptake naked DNA from a relative organism but only few pathogens have this ability. On the other hand, in clinical settings, conjugation is very common way to acquire resistance. Through conjugation bacteria establish the cell-to-cell contact and by that they exchange genes. In clinical environment, there have been chances to become exposed to many pathogens and thus the antimicrobial resistance may arise as bacteria use MGEs to transfer genes from one to another [93, 104]. Lastly, integrons which are the easiest way to achieve resistance. It gives bacteria the ability to get open reading frames. This process is very simple, and bacteria can achieve resistance very quickly through this [93].

2.8.1.2 Acquired resistance.

2.8.1.2.1 Antibiotic Molecule Alteration

Most effective way to acquire resistance is the modification or destruction of antimicrobial compound. Through this alteration bacteria can neutralize the drug molecules and can escape from the harmful consequences. This alteration can take place mainly in two ways [93].

2.8.1.2.2 Chemical alteration

By using this method, pathogens can modify the target binding site by using different chemicals or enzyme groups. Those chemicals bind with the target site and alter the

binding site in a manner that the drug molecule cannot attach with them and hence become inactive. [93]

2.8.1.2.3 Destruction of the drug molecule

Some bacteria can produce enzymes that can destroy a key element of a drug. One of the major examples is production of β-lactamase enzyme that can successfully inactive a major component called β-lactam ring found in antibiotic like penicillin which is being used for the treatment of wide variety of infections [93].

2.8.1.2.4 Poor Antibiotic Penetration

Many micro-organisms have the capability to prevent antibiotic to enter the cell. To do that, bacteria decrease the permeability of their cell membrane as a result the drug molecules cannot pass through the membrane of the bacterial cell and cannot kill them [93].

2.8.1.2.5 Efflux Pump

Efflux pump in bacteria has many functions like transporting nutritional compound and molecules for signaling. However, these efflux pump might sometimes take the antibiotic particles out of the cell. As a result, the concentration of the therapeutic agents decreased dramatically and thus perform poorly. In many cases, through mutation some microbes may increase the production of these sort of efflux pump to get rid of the antibiotics and through this acquire resistance [93].

2.8.1.2.6 Target sites modification

Alteration of the target site of an antibiotic can be a crucial reason for gaining resistance. In this case, an organism modifies the structure of a target area and change the shape of it. Therefore, the antibiotic become dysfunctional and this way the bacteria prevent the interaction and become resistant towards the drug [93].

2.8.1.2.7 Resistance through Global cell adaption

During the lifetime of a bacteria, they need to go through different harsh environments and when inside a host must face many attacks from the host immune system. With time these pathogens learn how to cope up with the condition and survive. As a result, they evolve many strategies that helps them to survive and grow continuously. Through this evolution sometimes these pathogens develop the resistant mechanism and become resistant towards specific group of therapeutic agents [93].

2.8.1.2.8 Introduce Alternative proteins

Sometimes micro-organism develop some new protein which may not be recognized by the antibiotic particles. For instance, *Staphylococcus aureus* can produce an alternative protein for penicillin binding. This new protein has very low binding affinity as a result the antibiotic cannot bind efficiently and thus the bacteria keep on escaping the treatment and acquire resistance. In the ***fig 2.06*** all the resistance mechanism has been shown in one place for the better understanding [93].

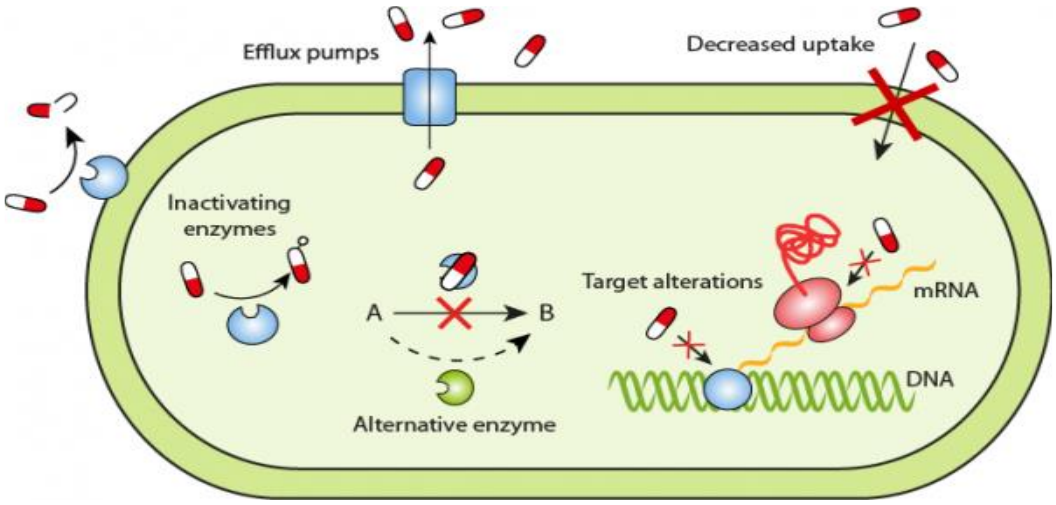

Fig 2.06: Antibiotic resistance mechanism (adapted from https://www.reactgroup.org/toolbox/understand/antibiotic-resistance/resistance-mechanisms-in-bacteria/ , courtesy of E. Wistrand- Yuen)

2.8.2 Causes of drug resistance

2.8.2.1 Consuming single antibiotics

Taking one single drug for a long period of time can make some of the micro-organism resistant to that antibiotic and even worst to many other drugs. These organisms may acquire more than one resistant mechanism to avoid getting neutralized by the therapeutic agents. In some research it is found that, some of the pathogens can take up these factors from other organism neighboring to them [87].

2.8.2.2 Resistance mechanism remains for a long time.

When an organism acquires the resistant mechanism, it usually does not go away very quickly. These resistance trait remains for a very long period and increase the survival rate of these pathogens into the host [87].

2.8.2.3 Use of antibiotics in food and agriculture.

With the growing population the need of more food has arisen and to produce and cultivate more products antibiotics are being using in many countries for the better survival of the animal and collectively high growth of agricultural products. As, antibiotics are being added there are chances, these antibiotics make some of the organisms found in different animals become resistant and later they get into the human body through consuming those micro-organisms from different foods. However, there are a controversy among the researcher about the theory and many countries has already banned using antibiotics in the human food [87].

2.8.2.4 Irregular consumption of drugs

Many patients do not take their medicines regularly and often when they start feeling better, they stop following the regimen in middle of the treatment. As a result, the micro-organism gets adapted with the medicine and generate defense mechanism against the therapeutic agent. When the patient re-starts the treatment, the medicine does not work on them [87].

2.9 Multi drug resistance

Among world's major health issues one of the most concerning and alarming thing is the antibiotic resistance and to be more specific multi drug resistance. When a group of bacteria or many other organisms become adapted and acquired capability to fight against a group of drugs, that organism becomes resistant, and it becomes a challenge to kill them. In case of MDR the situation is more complicated as in our world the number of antibiotics is limited, as a result, if these pathogens keep on acquiring adaptive methods it becomes a challenge to destroy them to protect humans from different diseases. The incident that creates more concern that the discovery of new antibiotics is not advancing with the rate the micro-organism inventing new ability to resist [92]. **Table 2.3** shows the general characteristics of MDR organisms.

Organism	Common Infections	Key Antibiotic Resistances	Drugs Considered for Treatment of MDR[a]
P. aeruginosa	Lung, wound	β-lactams, fluoroquinolones, aminoglycosides	Colistin
Acinetobacter spp.	Lung, wound, bone, blood	β-lactams, fluoroquinolones, aminoglycosides	Colistin, tigecycline
E. coli and *K. pneumoniae* bearing extended-spectrum β-lactamases	Urinary, biliary, gastrointestinal tracts, lung, blood	β-lactams, fluoroquinolones, aminoglycosides	Colistin (for *K. pneumoniae*), tigecycline
Vancomycin-resistant enterococci	Blood, heart, intra-abdominal	Vancomycin	Quinupristin-dalfopristin, linezolid, daptomycin
Methicillin-resistant *S. aureus*	Skin and soft tissue, respiratory tract, blood	β-lactams, fluoroquinolones, macrolides	Quinupristin-dalfopristin, daptomycin, linezolid, tigecycline, vancomycin
Multidrug-resistant *S. pneumoniae*	Ear, lung, blood, cerebrospinal fluid	β-lactams, macrolides, tetracyclines, co-trimoxazole	Fluoroquinolones, tigecycline
Extensively drug-resistant *M. tuberculosis*	Lung	Rifampin, isoniazid, and three of the following: aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, or para-aminosalicylic acid	3rd line agents, drug combinations

Table 2.2: General characteristics of MDR organisms. (Adapted from Molecular Mechanisms of Antibacterial Multidrug Resistance, Michael N. Alekshun, and Stuart B. Levy)

Now-a-days MDR is becoming so common in case of tuberculosis, and it is becoming one of the major threats to overcome the TB problem worldwide. MDR occurred when an individual develops resistant towards multiple drugs (mainly isoniazid and rifampin) at the same time. As new drugs are not easy to develop it become very difficult to treat these patients. Which not only increase the life threat but also increase the risk of transmission of the disease among healthy people.

Chapter 3

Methodology

3.1 Study Area

For the project Sylhet division has been fixed as a model area (***fig 3.01***). Sylhet division is an area of nearly 12.1 million people with four districts: Habiganj, Moulvibazar, Sunamganj and Sylhet. All the data for the thesis work has been collected from HEED Bangladesh –TB Control Programme-GFATM which is running under National TB Control Programme, currently is working in three districts of Sylhet: Habiganj, Moulvibazar and Sylhet district, respectively.

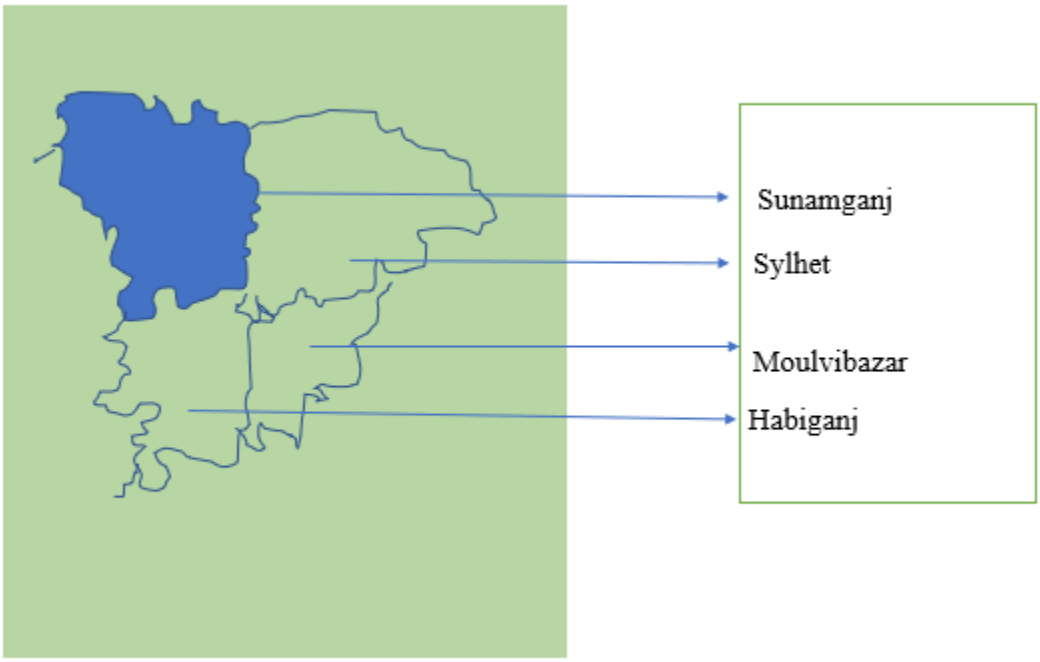

fig 3.01: Map of Sylhet Division

The geographic area covered by the project is almost 9-thousand-kilometer square. ***fig 3.02*** shows the total coverage of Sylhet Division separately and specifically.

fig 3.02: Geographic coverage (land area, km²) of Sylhet Division by HEED Bangladesh TB Programme.

3.2 Study Population

Though all types of people are included as the study population of the model area, the people of tea garden community, workers from tea garden, community members of punji (a tribal group), people of rubber garden, people of industrial areas and factories, slum dwellers, workers of stone Corey are the main concern.

3.3 Data Collection

A meeting was fixed with the health officer of the project for the permission to conduct the research and as well as the smooth running of the work. Before collecting the quantitative data, a hypothetical observation was made to identify the underlying causes of the problem. After that, a set of well-constructed questionary was made personally in a very organized manner based on the hypothetical theories, to get proper responses. All the questions covered four main aspects:

physical, economic, social, and psychological, respectively. Descriptive part of the findings was than presented through multiple tables and charts by using Microsoft office (MS word, MS Excel) and meta-chart. Besides, two health workers were interviewed for further information. After the collection of the data, all the information was under thorough study and after that the thesis paper was written.

3.4 Case identification

As, many of the patients are very unwilling to visit hospitals, the methods showed in ***fig 3.03, fig 3.04*** **and** ***fig 3.05*** were used for screening out the TB patients.

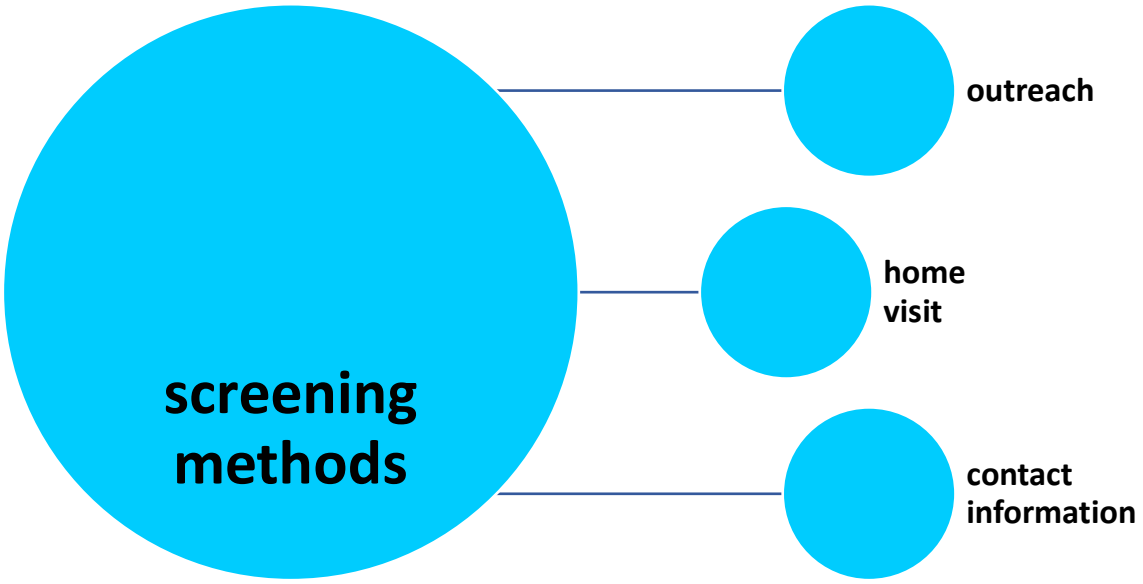

fig 3.03: Primary method of Screening out the patients by the health officer.

Frequent home visits have been done to screen out the patients. People has been asked multiple questions about symptoms related to tuberculosis. If the medical officers get to know any symptoms is resemblance with TB, sputum collection from that person is done for further inquiry.

Most of patients are being identified through home visits and very a smaller number of people pay visit to the hospital upon feeling unwell. ***fig 3.04*** and ***fig 3.05*** shows two primary screening methods for tuberculosis cases.

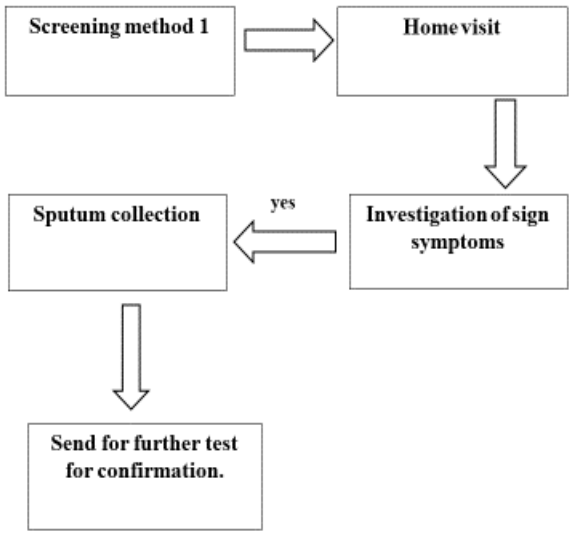

fig 3.04: Screen process through home visit.

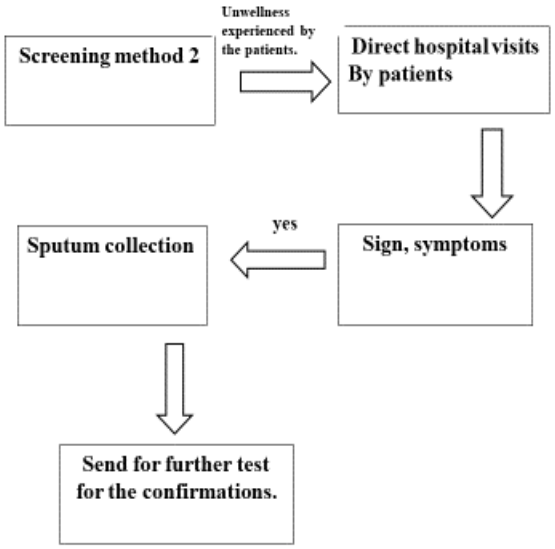

fig 3.05: Screening through direct hospital visits by the patients.

3.4.1 Sputum collection

During the home visits, the health workers identify the presumptive TB patients by different questionaries and collected the sputum. Sputum was also collected from the presumptive TB patients who directly visited the hospital. Most of the samples were collected from home visit as very few people directly went to the hospital upon feeling unwell (***fig 3.06***).

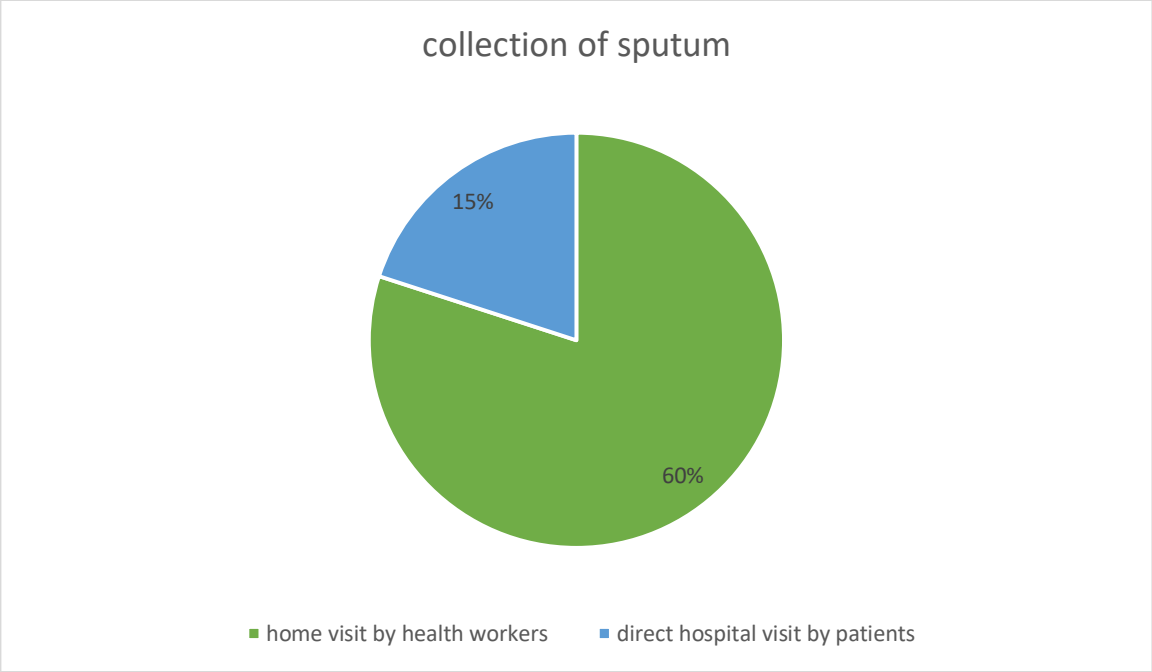

fig 3.06: The percentage of sputum collection through two main methods.

3.4.2 Procedure to identify confirmed TB cases

The main works starts after collecting the sputum from the suspected patients. All samples have been bringing into GeneXpert sites and after that the test begins to identify genuine patients and separate pseudo patients from them. GeneXpert is an automated system, that can identify not only the MTB cases but also the drug resistance, more specially rifampin resistance (***fig 3.07***). The sample found with RR-TB also considered to have resistance towards Isoniazid and in this way MDR-TB has been detected. Later, all the positive samples usually been sent to CDC Bangladesh for XDR confirmation and the report collected from there. Those who are not found with the disease after the test, they then get additional clinical attention as per their physical condition (***fig 3.07***).

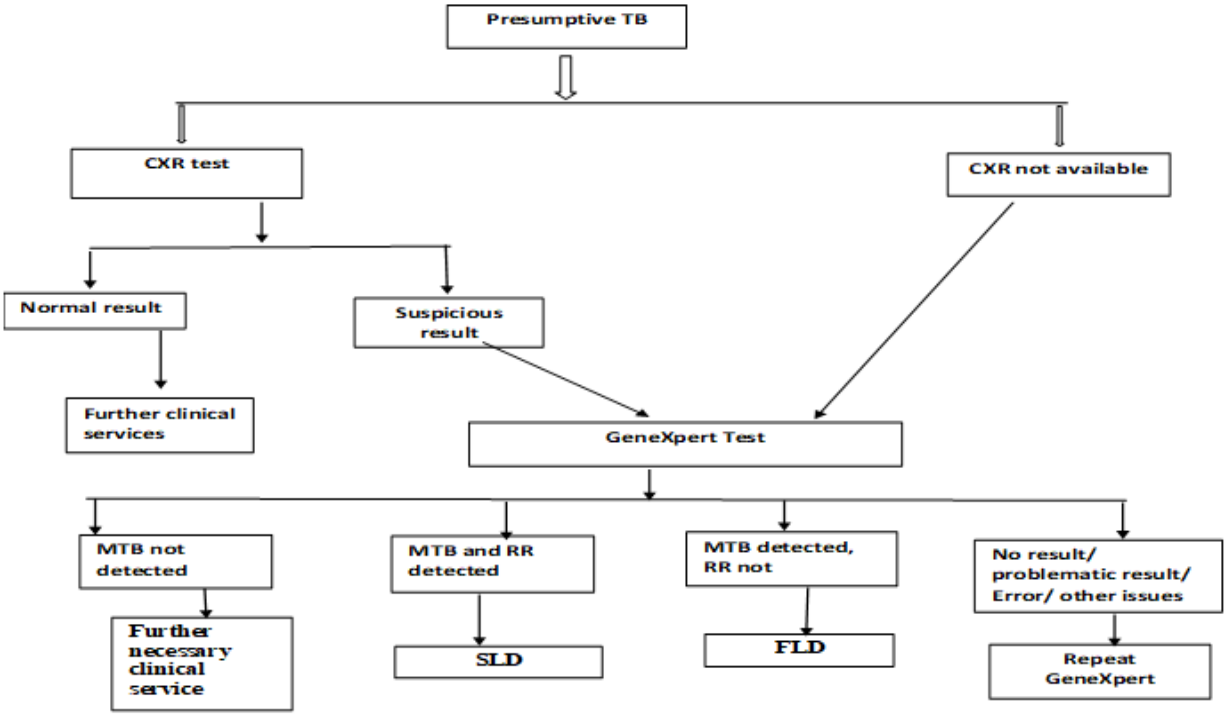

Fig 3.07: Process after sputum collection to identify confirm TB cases.

3.5 Available test facilities

After the collection of the sputum, the sample through for further tests to confirm the Tuberculosis in the patients with relatable sign, symptoms. For the confirmation, multiple tests perform by the health in charge using different advanced technology. **Table 3.1** shows all the facilities that are currently available for confirm the cases and identify the patients.

Table 3.1: available diagnosis facilities.

Method of Diagnosis
GeneXpert
LED microscope
Culture method
FNAC
Chest X-ray
TST

3.6 Limitations of methodology

It may be noticeable that the study is very geographically limited as it is not possible to cover a large area and population within a very short amount of time. The time limitation of the project was due to achieve the milestone of finishing the research in time and complete the present study. Also, because of covid crisis, it was a challenge and had to face many difficulties to collect the data.

3.7 Ethical consideration

Ethical consideration is being reserved and well prioritized. As a result, any personal data, such as names of the patients, prescriptions, pictures, or information that disclose the identity of any individual etc. were not collected or included to conduct the study.

Chapter 4

Research data incorporation and analysis

4.1 Overall world

4.1.1 TB incidence

Tuberculosis found in every corner of the world. In 2019, a huge number of new TB incidence started to take place. The study shows, 87% of new cases being found in the thirty high burden countries around the world. Among them, (***fig 4.01***) 44% of the new cases found in the WHO South-East Asia region, 25% of the new incidence being registered in the WHO Africa region and another 18% occurred in the WHO Western Pacific region. Among the 30 high TB burden countries, eight countries (India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, South Africa) is accountable for the two-third of the new Tuberculosis incidence. Reportedly, about 10.0 million people had Tuberculosis in 2019 with the highest number of male patients. ***fig 4.02*** shows the percentage of patients in 2019 based on sex. Though the TB incidence rate in the whole world is declining, it is not fast enough to achieve the first milestone of reduction of incidence to 20% by 2020. The falling rate was 9% between the year 2015 to 2019 worldwide and the rate was 2.3% in between year 2018 to 2019. ***fig 4.03*** shows the data of different region (European region, African, South-east Asia, European Mediterranean, and the western pacific) and their incidence rate reduction between the year 2015 to 2019. Even though in other region the incidence rate is dropping, the Americans region facing an increase due to the upward trend in Brazil. Already 78 countries are under study and according to the record these countries are about to reach the milestone by 2020. Among these countries seven high TB burden countries are also included that have already reached and achieved the milestone of case reduction by 2020. **Table 4.1 (right)** shows details about those seven high burden TB countries with their name [2].

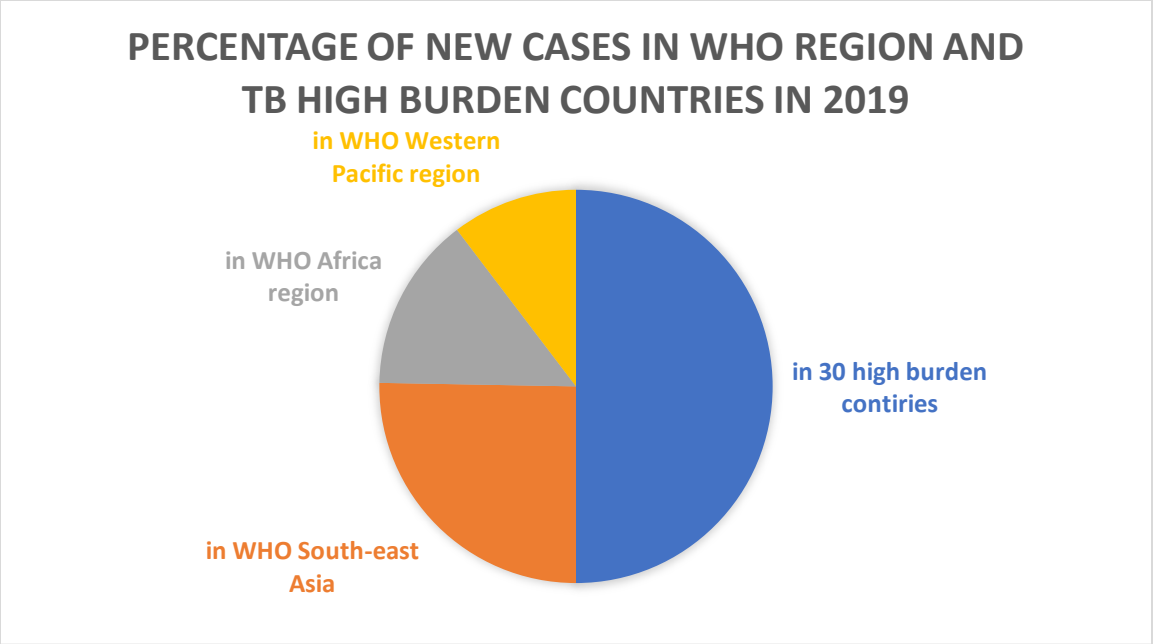

fig 4.01: Percentage of new cases in WHO region and in thirty high burden countries in 2019.

(Adopted from WHO annual TB report 2020)

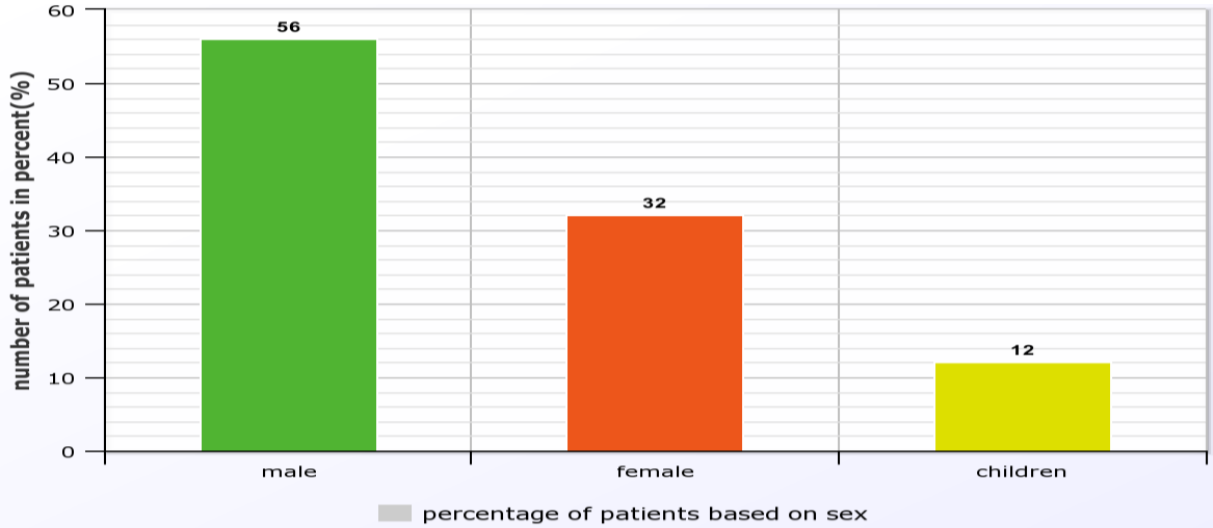

fig 4.02: Percentage of patients based on sex in 2019 worldwide **(Adopted from WHO annual TB report 2020) (Established with meta-chart).**

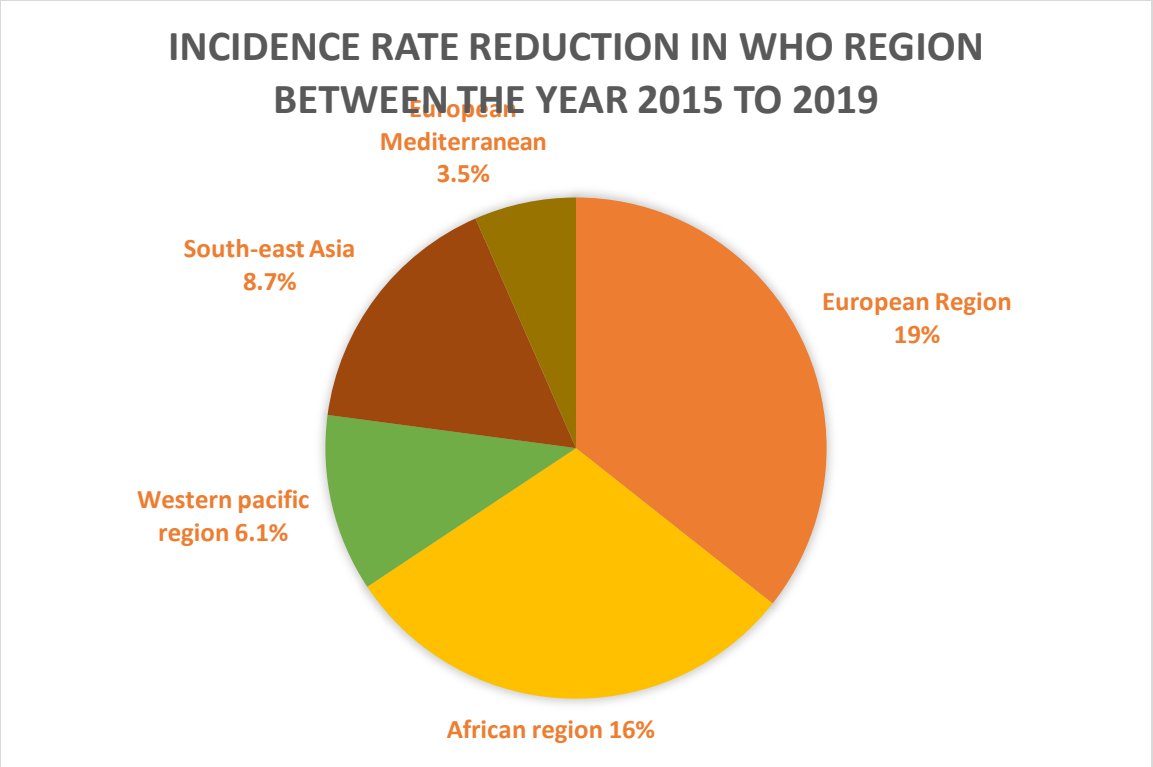

***fig 4.03*: Incidence rate reduction in WHO region without the Americans region between the year 2015 to 2019 according to WHO annual TB report, 2020. (Established by meta-chart).**

4.1.1.1 Drug resistant TB incidence

Drug resistant TB has become a worldwide problem especially MDR. In tuberculosis MDR refers to the resistant of two first line drugs isoniazid and rifampin, respectively. Other than these two drugs, TB patients can develop resistant towards fluroquinolones which can also create major obstacle in solving Tuberculosis problem. In 2019, around 1.4 million people has been found with isoniazid resistance among them 1.1 million people are susceptible towards rifampin [2] (*fig 4.04*).

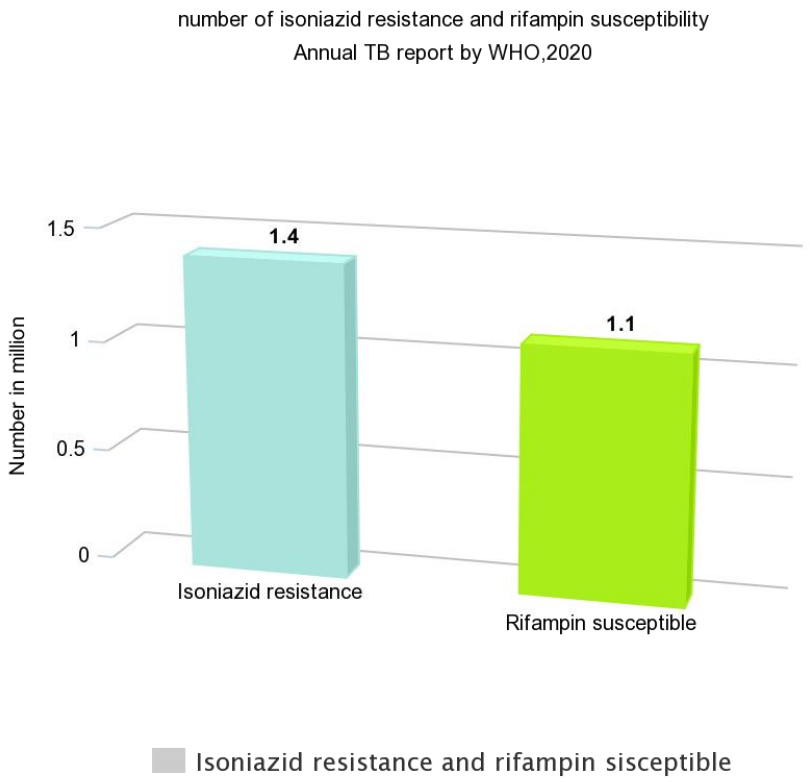

***fig 4.04: Estimated number of Isoniazid resistant and the rifampin susceptibility in 2019.* (WHO annual report 2020) (Established with meta-chart).**

1.4 million people that has develops isoniazid resistance, among them 13.1% people of new cases and 17.4% people of previously treated had the resistance [2] (***fig 4.05***).

fig 4.05: Estimated percentage of Isoniazid resistance in previously treated and new cases in 2019. **(WHO annual TB report, 2020) (Established with meta-chart)**

4.1.2 TB death rate

Tuberculosis is one of the top 10 leading causes of deaths worldwide. Approximately, 1.4 million deaths had been taking place in the year 2019 with 208 000 deaths with HIV positive cases. Though there has been a downfall noticed in the TB death rate, it is not enough to reach the milestone of the End TB strategies. To achieve the milestone, around 35% of death reduction needs to be completed between the year 2015 to year 2020. However, only 14% reduction had seen between the year 2015 to 2019, which not even the half of the milestone that needs to be achieved in order to end TB. ***fig 4.06*** represents, the difference between the milestone and the level of achievement in TB death reduction [2].

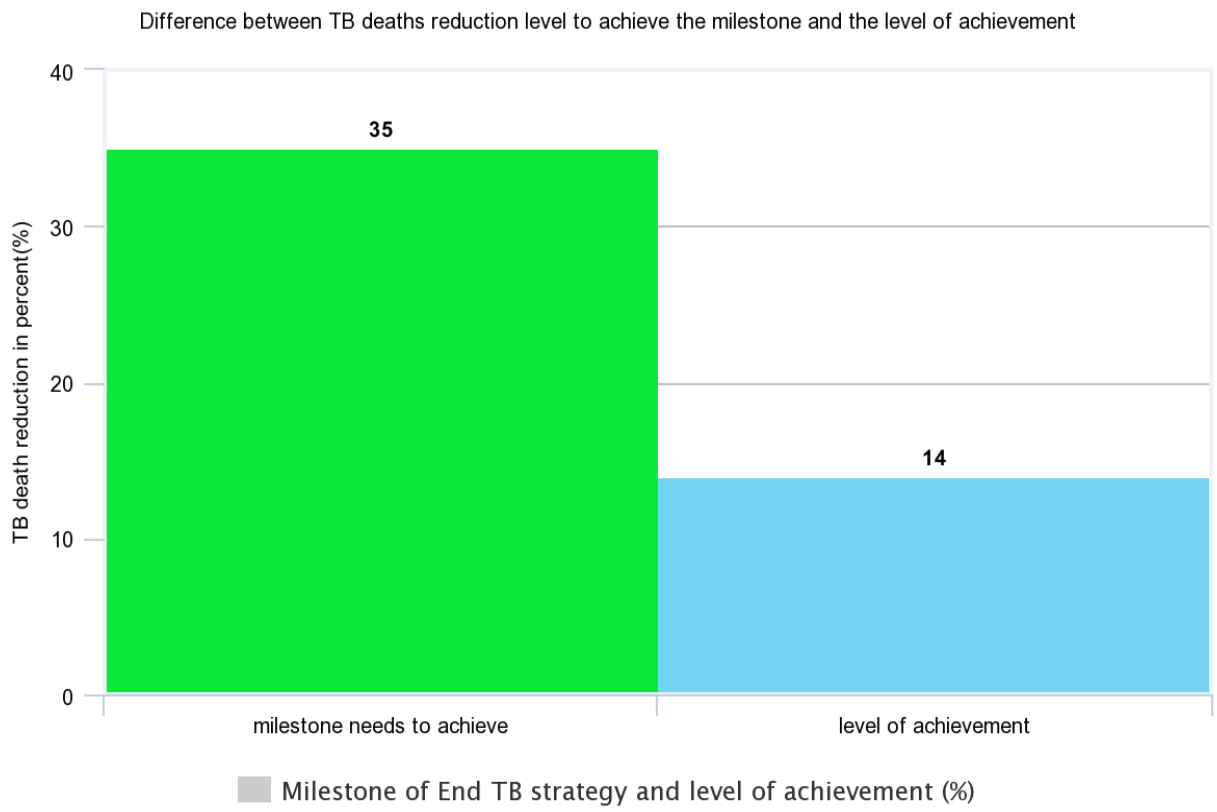

fig 4.06: Difference between TB deaths reduction level to achieve the milestone and the level of (between year 2015 to 2019) achievement. **(Adopted from WHO annual TB report, 2020) (Established with meta-chart).**

All the WHO included regions are on track to determine the reduction in death rate among TB patients. Between the year 2015 to 2019, WHO European region made the most progress to reduce the death rates and the reduction is about 31% (***fig 4.07***). African region also slowly making improvements with the 19% reduction of death (***fig 4.07***). Then, with the 17% of reduction, Western pacific is in the third position (***fig 4.07***). The Americas, European Mediterranean, and the south-east Asia in lacking behind compared to other three region, with the reduction of 6.1%, 11% and 10% respectively [2] (***fig 4.07***).

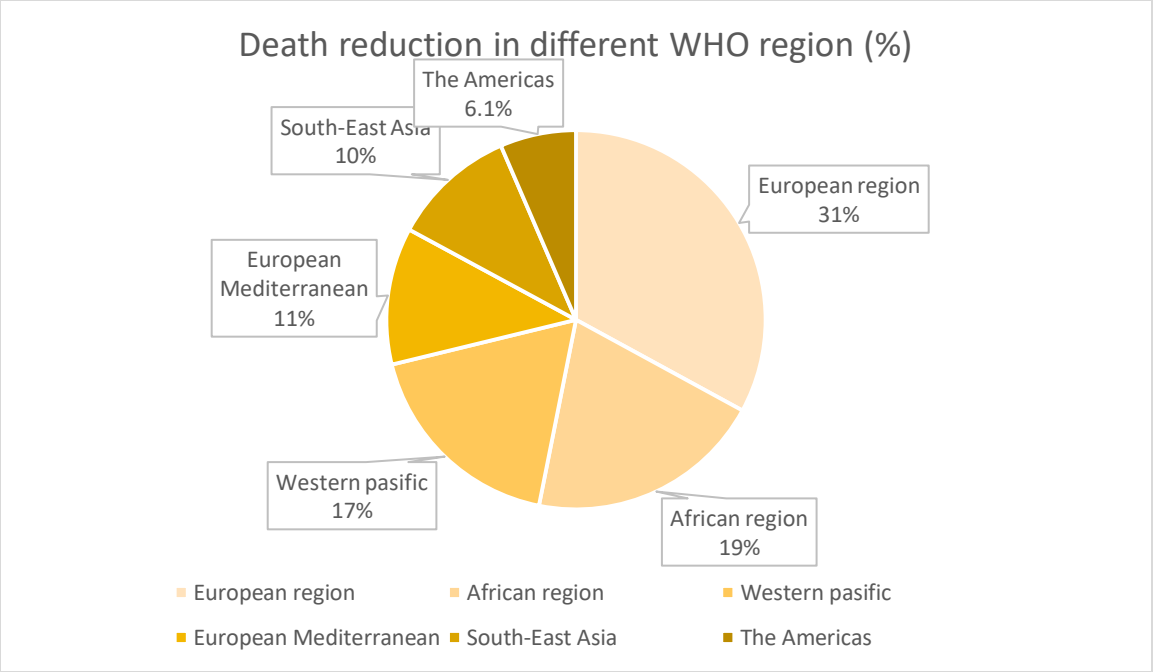

fig 4.07: Death reduction in percent in WHO region between the year 2015 to 2019. (Adopted from WHO annual TB report, 2020).

The End TB strategy set a milestone of achieving 35% of death reduction by 2020. A study suggests, 46 countries in total and among them seven TB high burden countries also have reached the milestone that needs to be fulfilled by 2020. **Table 4.1 (left)** shows the name of the seven TB high burden countries that have already reached the milestone of 2020 [2].

Table 4.1: Seven high TB burden countries that reached the milestone of 2020 in the declining of TB death reduction (left) and seven high TB burden countries that reached the milestone of 2020 in the reduction of TB incidence (right). (Adopted from WHO annual TB report, 2020).

Name of the countries reached the milestone of death reduction	Name of the countries reached the milestone of incidence reduction
Bangladesh	**Cambodia**
Kenya	**Ethiopia**
Mozambique	**Kenya**
Myanmar	**Namibia**
The Russian Federation	**The Russian Federation**
Sierra Leon	**South-east Asia**
The Republic of Tanzania	**The Republic of Tanzania**

4.1.3 TB treatment

4.1.3.1 General TB treatment

With the growing number of TB cases, the number of provided treatment has also increased over the years. More people have brought under the TB treatment to reduce the number of the patients. In 2015 according to the study, the number of people taking TB treatments were 6 million which increased slightly and reached to 7 million in the year 2018, keeping the record of increasing number, it continues in 2019 as well and the number of people provided with treatment was 7.1 million [2].

4.1.3.2 MDR/XDR TB treatment

Treatment of MDR/XDR TB has also increased with every passing year. More people reporting to have been provided treatment for MDR/XDR TB. **Table 4.2** shows the number of patients has been provided with MDR/XDR TB in recent years [2].

Table 4.2: Number of patients provided treatment for MDR/XDR TB. (Adopted from WHO annual TB report, 2020).

Year	Number of patients
2015	122 726
2018	156 205
2019	177 099

4.1.3.3 Preventive treatment

As per WHO recommendations, people with HIV, living with patients who has already pulmonary TB, patients with co-morbidities, children especially aged under 5, should get the TB preventive treatment. In recent years, the number of people receiving this sort of treatment has increase from 1 million in 2015 to 2.2 million in 2018 to 4.1 million in 2019 [2].

4.2 Current situation in Bangladesh

To understand the current situation, a specific health programee covering Sylhet, Moulvibazar, Habiganj district, has been selected as a model to portray and generate idea about the TB situation. From the targeted area, it has been found that, in Sylhet alone, about 8869 cases has been detected in the last six months (October 2020- March 2021) and in just one area and the number of people under treatment is nearly 9202. Among the new cases, 22 people found with MDR TB, and 4 cases detected with XDR TB in just three months from January 2021 to March 2021. Though there are so many future measures have been taken, there are still many underlying issues which is becoming major obstacles in the fight with Tuberculosis problem in the country.

4.3 Data analysis and Results

4.3.1 Number of total TB cases

The study has found (January 2021- March 2021) around 26 thousand presumptive TB patients among 7,658,777 people of Sylhet (Habiganj, Maoulvibazar, Sylhet district). Among them, nearly 9 thousand cases being found after performing GeneXpert test. Among 9 thousand cases, approximate 3 thousand people has been identified having new pulmonary bacteriologically confirmed cases. Table 4.3 listed the number of patients found in the first three months of 2021.

Table 4.3: TB diagnosis, number of TB cases (January-March 2021)

Cases	Number of people
Diagnosis through microscopy and gene expert (TB presumptive test)	25711
Gene X-pert	9231
New pulmonary bacteriologically confirmed cases	2804
New clinically diagnosed	693
New extra pulmonary	429
Relapse	185
Others	5
Total TB patients identified	4116

4.3.2 Percentage of TB patients based on age and male/female.

The number of patients (in percent) has been separated according to different age groups (*fig 4.08*). From the data analysis, it has been found that almost 4% of the patients (*fig 4.08*) has been found among the children (people aged 0-14 years old). Then, 9% of them are from the age group 15 to 24 years old (*fig 4.08*). The study shows, most of the cases found among the people in the age group from 45 to 64 years old (*fig 4.08*). Approximately 21% of the cases

found in both 45-54 and 55-64 age groups and a slight downfall has been noticed (around 18%) among the older people aged 65 or more than 65 years old (*fig 4.08*). *fig 4.09* shows the total percentage of male and female patients, and it has been found that maximum are male patients.

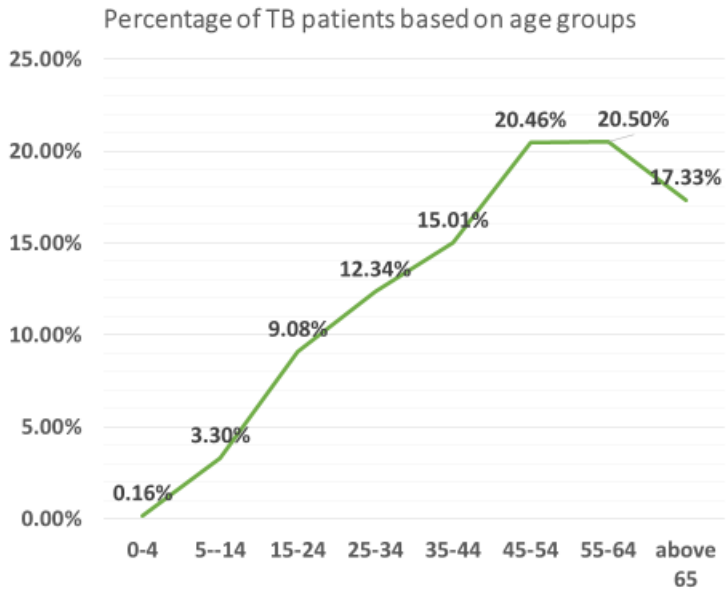

fig 4.08: Percentage of patients based on age groups.

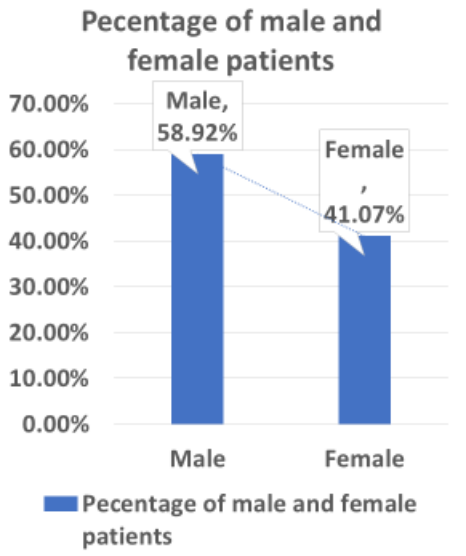

fig 4.09: Percentage of male and female patients

4.3.3 Study Population and confirm cases in three different districts of Sylhet.

4.3.3.1 Overall study population and cases

The research work has been carried out in three districts of Sylhet division, Habiganj District, Moulvibazar District and Sylhet district, respectively. The number of total populations under the study in these three districts is around 7,656,777. After studying the population around 4 thousand confirmed TB cases has been found. **Table 4.4** shows the disaggregated data of different districts and the cases found in each district. *fig 4.10* shows the percentage of confirm cases in three districts of Sylhet division.

DISTRICT	POPULATION	CONFIRMED CASES
Habiganj District	2 349 711	1 369
Moulvibazar District	1 979 605	1 303
Sylhet District	3 329 461	1 444
Total	7 656 777	4 116

Table 4.4: Population and confirmed cases in three different districts of Sylhet division.

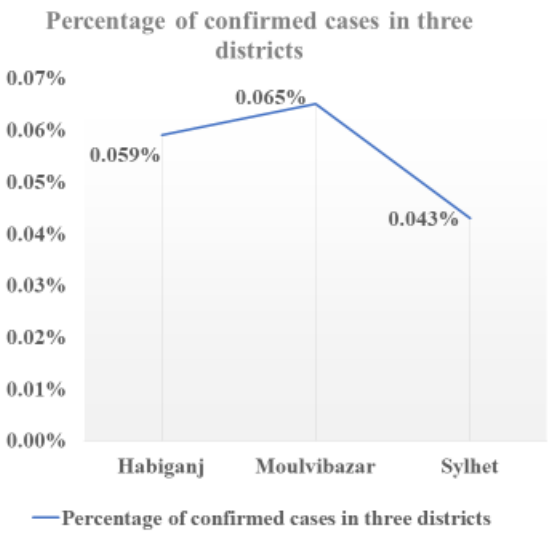

fig 4.10: Percentage of confirm cases in three districts.

The current work also found that the incident rate of first three months of 2021 is 0.053% and among three districts Sylhet district has the maximum number of cases detected compared to other two districts (Habiganj and Moulvibazar) and Moulvibazar has the least number of cases identified (**Table 4.4**).

4.3.3.2 Number of Patients based on age groups and two main categories (male/female) in three districts.

After the study it has been found that Sylhet district has more cases compared to other two districts. When the analysis was done beyond the surface level, and it has been found that age group between 55 to 64 and 45-54 has the maximum number of TB cases (**Table 4.5**). The study also reflects the male and female patients' number in every age group (**Table 4.5**). The number of male and female patients has been found through the work (**Table 4.6**). Upon investigation, it is found that about 59% patients are male (**Table 4.6**) and after the further

analysis, it is found that Habiganj is leading in terms of having most of the male patients (*fig 4.11*).

Table 4.5: Number of Cases in two main categories (male/M and female/F).

Districts	Age groups (years)															
	0-4		5-14		15-24		25-34		35-44		44-54		55-64		≥65	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Sylhet	6	0	15	27	53	86	101	86	103	95	159	122	167	111	226	87
Moulvibazar	1	0	20	19	70	56	80	91	91	103	128	134	184	88	180	58
Habiganj	0	0	26	29	47	62	70	80	124	97	182	117	204	89	188	54
Total	7	0	61	75	170	204	251	257	318	295	469	373	555	288	594	199

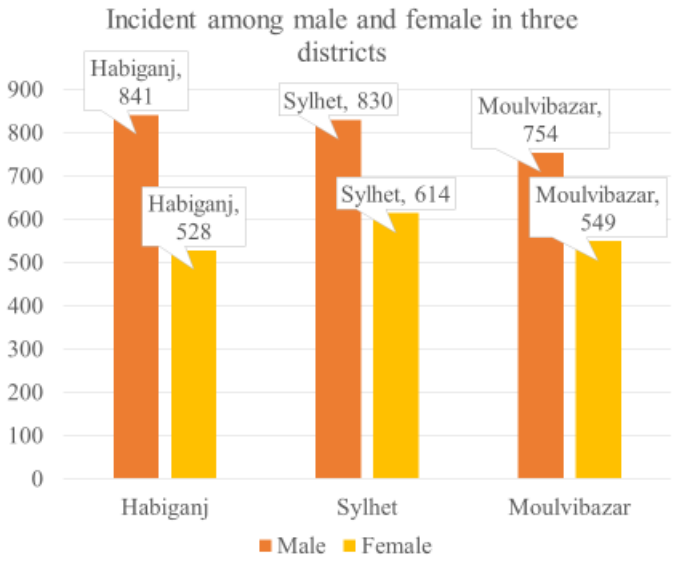

fig 4. 11: Difference of case number among male and female patients.

District	Number of male and female patients		
	Male	Female	Total
Sylhet	830 (57.47%)	614 (42.52%)	1444
Moulvibazar	754 (57.86%)	549 (42.13%)	1303
Habiganj	841 (61.43%)	528 (38.56%)	1369
Total	2425 (58.92%)	1691 (41.07%)	4116

Table 4.6: Number of total male female patients.

4.3.4 Number of Extra Pulmonary TB patients

The Number of extra pulmonary TB patients is also very noticeable. After the analysis of the data, it has been found that the percentage of the female patients of EP-TB is higher than the male patients (*fig 4.12*).

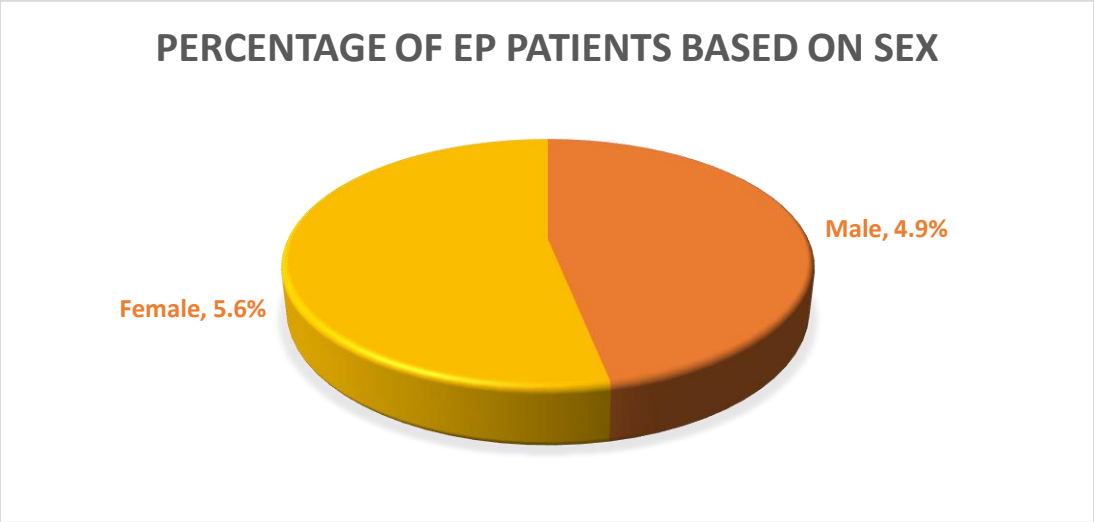

fig 4.12: Percentage of EP-TB patients based on sex.

According to the research work, among three districts of Sylhet division, Sylhet district has the greatest number of Extra Pulmonary cases (**Table 4.7**) other than the two-study area.

Table 4.7: Distribution of Extra Pulmonary TB based on sex in three districts.

District	EP patients based on sex		Percentage of EP patients		Total Number of EP patients	Total percentage (%)
	Male	Female	Male (%)	Female (%)		
Habiganj	57	66	4.2	4.8	123	8.9
Moulvibazar	85	108	6.5	8.2	193	14.81
Sylhet	57	56	3.9	3.9	113	7.82
Total	199	230	4.9	5.6	429	10.51

4.3.5 MDR/RR/XDR TB confirm cases.

4.3.5.1 Number of MDR/RR-TB cases.

In case of Tuberculosis, Multidrug resistance means, resistance towards two first line drugs isoniazid and rifampin in respect. Nonetheless, during the work it has been found that, those patients are tested positive for RR-TB by GeneXpert test, are also considered to have resistant towards another first line drug isoniazid. Therefore, in this study, RR-TB has counted as MDR-TB (**Table 4.8**). The study found 0.48% of people with MDR/RR-TB in the three districts of Sylhet division. Among them, Habiganj district has the highest number of cases (**Table 4.8**). After further study and analysis, it is found majority of the MDR/RR-TB patients are male and maximum number of male patients found in Habiganj district (**Table 4.8**).

Table 4.8: Number of MDR/RR-TB patients.

District	RR-TB/ MDR TB cases (in number)			RR-TB/ MDR TB cases (in percent)		
	Male	Female	Total	Male	Female	Total
Habiganj	5	3	8	0.36	0.21	0.57
Moulvibazar	4	2	6	0.30	0.15	0.45
Sylhet	3	3	6	0.20	0.20	0.40
Total	12	8	20	0.29	0.19	0.48

4.3.5.2 Number of XDR cases in three districts (male/female).

Table 4.9 shows the total cases of XDR-TB and the percentages in three districts of Sylhet division. The study also indicates that the XDR cases are almost equal (Table 4.9) in both male and female category. Moreover, majority of the cases have been found in Moulvibazar district (*fig 4.13*).

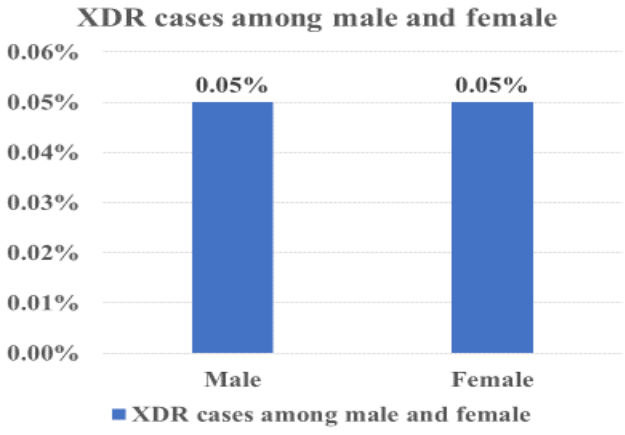

fig 4.13: Percentages of male and female XDR patients.

District	XDR TB cases (in number)		
	Male	Female	Total
Habiganj	1	0	1
Moulvibazar	1	1	2
Sylhet	0	1	1
Total	2	2	4

Table 4.9: Number of XDR-TB cases in male and female patients.

4.3.6 Mortality rate

According to the study, the mortality rate is 3.43% and Moulvibazar has showed the upward trend.

Mortality rate among the male patients is the highest than the female patients (**Table 4.10**).

Table 4.10: Mortality among TB patients.

District	Number of deaths		Total Number
	Male	Female	
Habiganj	33 (2.41%)	9 (0.65%)	42 (3.06%)
Moulvibazar	39 (2.99%)	12 (0.92%)	51 (3.91%)
Sylhet	38 (2.63%)	10 (0.69%)	48 (3.32%)
Total	110 (0.75%)	31(0.75%)	141 (3.43%)

4.3.7 Treatment of TB

Tuberculosis is a curable disease and if the patients get proper treatment, they can regain their previous healthy state. After the research, it has been known that around 9202 people are taking treatments among them 54 MDR-TB patients (***fig 4.14***).

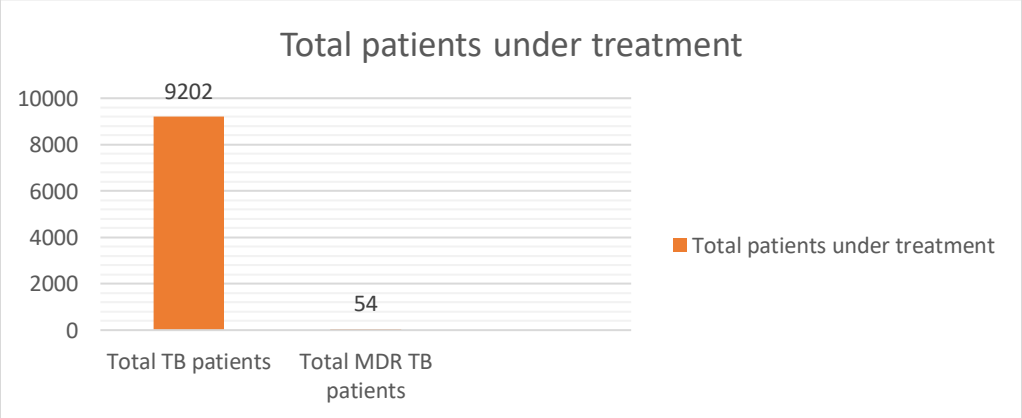

fig 4.14: Total patients under treatment.

4.3.7.1 Suggested medicine and duration

For the patients who newly infected with the TB (cat I) are suggested to have four drugs (Table 4.11) for 6 months (Table 4.12). On the other hand, six drugs (Table 4.11) are suggested to take for 6 months to 1 year for (cat II) the patient who relapse (Table 4.12). Longer regimen needs to be followed for MDR/pre-XDR TB patients about 18 months (Table 4.12).

Category of TB	Drugs
Cat I[1] DS TB	• Isoniazid (INH) • Rifampin (RIF) • Ethambutol (EMB) • Pyrazinamide (PZA)
Cat II[2] DS TB	• Isoniazid (INH) • Rifampin (RIF) • Ethambutol (EMB) • Pyrazinamide (PZA) • Levofloxacin

Table 4.11: SuggestedDrugs for the TB infected patients.

Category of TB	Duration
Cat I DS-TB	6 months
Cat II DS-TB	6 months – 1 year
MDR	9 months
Pre-XDR	18 months

Table 4.12: Duration of treatment for different TB categories

[1]catI represents new smear positive patients.

[2]cat II represents patients who have relapsed.

4.3.8 Monitoring

To reduce the TB incidence and to make sure of the continuity of treatment of the patients depends on the good monitoring system. This study has found that, in the model area, monitoring has been

taken very seriously and regular monitoring has been done in different time by different medical officer (***fig 4.15***).

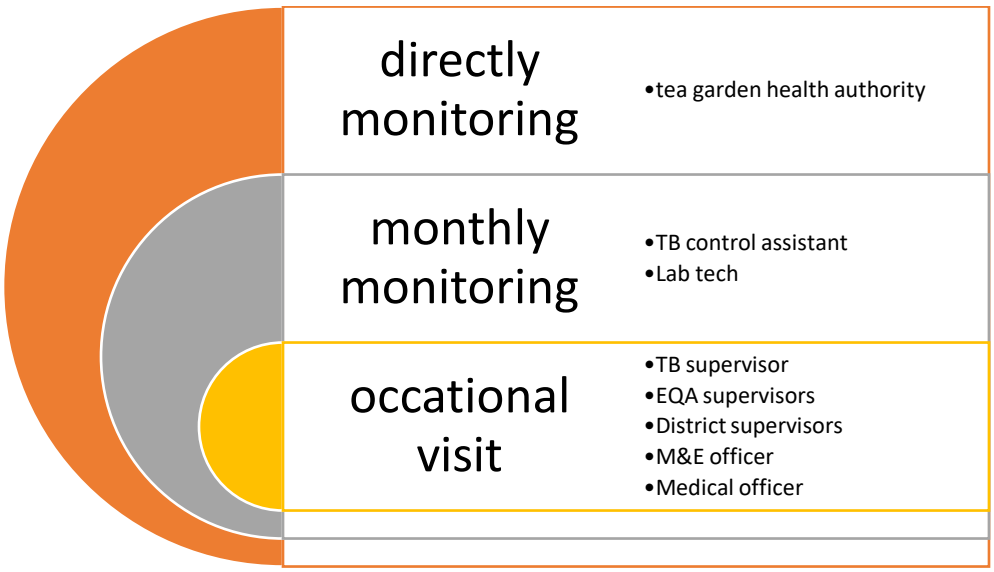

fig 4.15: Monitoring of the patients in different time by different medical personnel.

4.3.9 Health workers

Health workers play a vital role in every clinical situation. Lack of female health workers is one of the associated factors of increasing Tuberculosis as many female patients hesitate to open up with the medical officer of opposite sex. As a result, in most of the cases, the female patients remain undetected. The current work findings also justify this. It has been noticed that is a huge difference in the number of male and female medical stuff (***fig 4.16***).

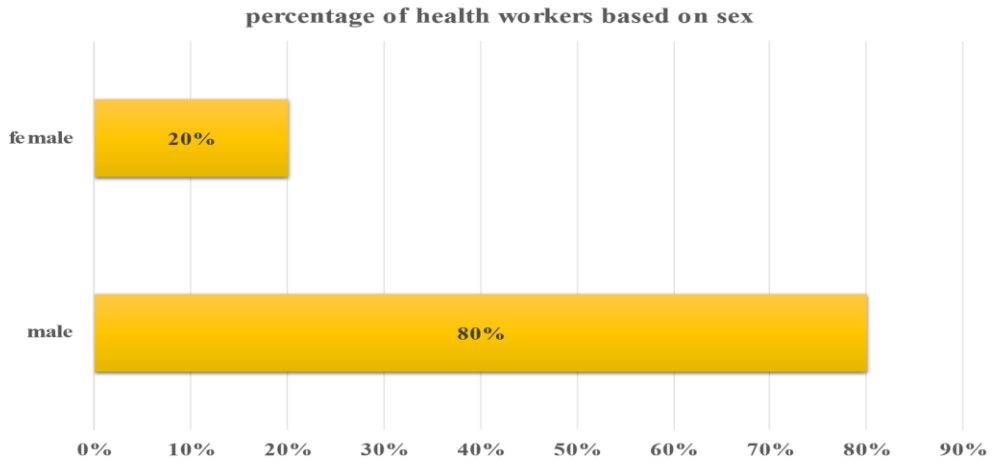

fig 4.16: percentage of health workers based on sex.

4.3.10 Challenges to minimize TB.

Though this research does not have the specific data on the socio-demo graphic data of the patients, 90% of the patients are day laborer, workers and their education level are also not satisfactory. As a result, they lack many knowledges, personal hygiene for instance. Because of lack of awareness, many social taboo and myths have become their daily life which causes difficulties for the health officers to identify them. Not only that, but there is also a scarcity of medical tools which sometimes act as a major drawback to screen out the patients (***fig 4.17***). Besides, as a because in the rural area many people has been leading a marginal lifestyle, they suffer from malnutrition which make the scenario even worse.

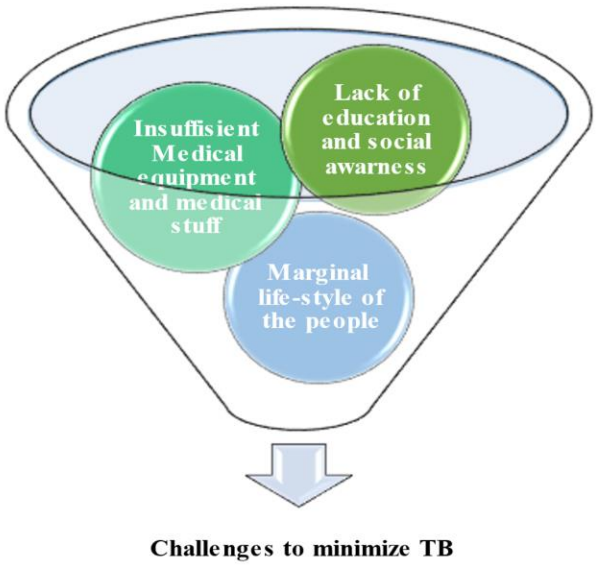

fig: 4.17: Major challenges to reduce TB cases.

4.3.11 Future plans

So many future projects and plans have been taken in hand by the government of the country to reach the milestone and End Tuberculosis for as early as possible (***fig 4.18***).

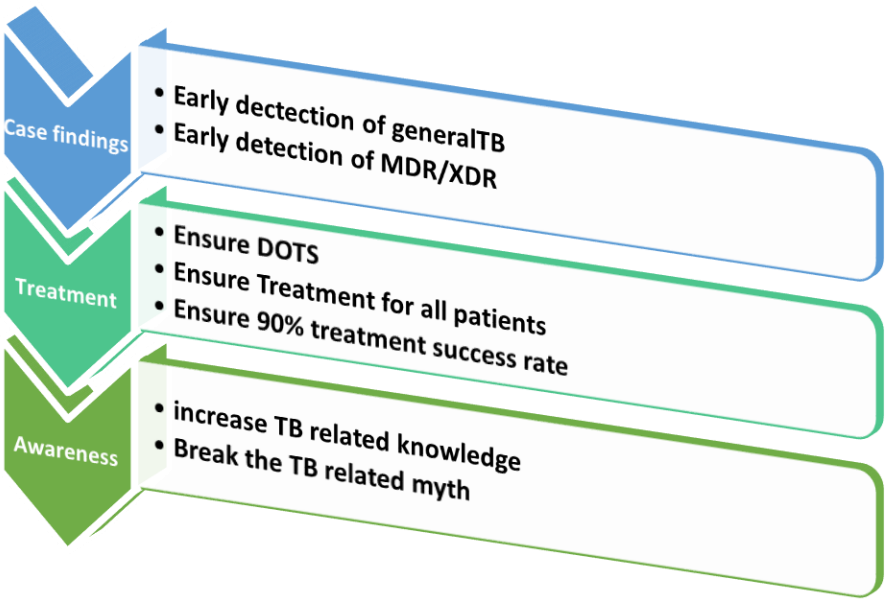

fig 4.18*: *Plan to minimize Tuberculosis.

4.4 Discussion

Though the study has done on a very small population and very limited area, it still provides valuable information about the Tuberculosis situation of three months of 2021 (January to March). The research found the model area has 4116 confirms cases (**Table 4.3**) with the incident rate of 0.53%. Among three district of Sylhet division, Sylhet district has the maximum incidence with 1444 number of patients. Tuberculosis is a disease found in almost every age group of people. However, adults, aged 55 to 64 has shown having the highest number (with 843 patients) of TB than other age groups (**Table 4.6**). With the research it is found that maximum are the male patients, about 59% (**fig 4.09**) which also justify an associated factor of TB, that is lack of female health workers (**fig 4.16**) that ultimately leads the smaller number of detections of female patients. It also indicates towards other factors such as smoking (main consumer is the male) and poor personal hygiene of the male patients. This work also found, Extra Pulmonary TB among the study

population. Total 429 people has been identified with Extra Pulmonary TB (**Table 4.7**); among them majority are the females (**fig 4.12**). Not only EP-TB, MDR/XDR TB has been also noticeable and almost 20 patients have MDR-TB (**Table 4.8**) and 4 people detected with XDR-TB (**Table 4.9**). The research also focuses and abled to find out mortality rate among the TB patients. In the study area, approximately 141 people lose their lives due to Tuberculosis (**Table 4.11**) and maximum death occurs in the male patients (**Table 4.10**) and the percentage is almost 6.27%. The paper also digs in deep to understand some of the associated factors that instigate TB or responsible for the increase of recent TB incidence (**fig 4.17**) and also the future plans to minimize tuberculosis and achieve the milestone (**fig 4.18**).

Chapter 5

Conclusion and Solutions

5.1 Challenges and opportunities

5.1.1 General challenges

5.1.1.1 Precautionary Apparatus

Vaccines are the main source to prevent the *M. tuberculosis* infection or disease. Currently, available BCG vaccine is able to decrease the death rate, however, cannot prevent the infection [1, 99, 100]. Therefore, people around the world still getting infected by the bacilli and successfully spreading the disease among other healthy individuals. In order to overcome this problem, vaccine is needed badly that will have the property of preventing infections. It requires a lengthy process of research and adequate knowledge about the organism. There are lacks information about *M. tuberculosis* in so many aspects such as the mucosal immune response of M. tuberculosis. To control or effectively prevent this data plays a huge role as the lung is the infection site. Without paying attention on acquiring these types of crucial data, developing a precautionary tool is next to impossible. However, there are some vaccines are in the process and it will take minimum 10 years for those vaccines to go through all the trails and therefore a preventive cannot be expected before 2027.

5.1.1.2 Development of new drugs

Currently available drugs in the pipeline have a lot of adverse side effects and treatment with these drugs are time consuming as well. On that account, it is very important to invent drugs that are less toxic and can work perfectly without taking a long time. Surprisingly, to develop some new drugs, one vital step is to gain a lot of knowledge about the mechanism of *M. tuberculosis*. Not only that, to run the medicine trials it is also crucial to find an appropriate animal model which resembles exactly the human body and

mimic the reactions. The previous experiments were used to perform on rats however these rodents are not sufficient to generate proper outcomes. As a result, it becomes extremely problematic for the scientists to develop new drugs due to appropriate animal models. Recent studies show that, combination treatment can be hugely beneficial to reduce the long regimen. Thus, the new drugs need to have the property so that they can be used in combination therapy when necessary. Moreover, the researcher needs to invent such drugs that does not generate drug resistance within the use of few weeks which is another tremendous obstacle of developing new drugs. The most difficult part of designing new medicament is the lengthy trial. The trial for phase 2 needs minimum of two years and pivotal trial requires approximately three years of time period.

5.1.1.3 Proper screening and monitoring

Many patients do not have well facilities especially in developing countries. Hence, majority of people does not get the opportunity to being screened the disease in time. It is very important to identify the disease and provide treatment immediately. Additional monitoring also required to get the full benefits. However, in many countries these opportunities are not available and which making even hard to control TB.

5.1.1.4 Drug Resistance

In recent time, drug resistance becomes a huge burden. To screen the drug resistance, different bioinformatic tools need to get involved in the program in order to have clear idea about the number of people developing resistance especially MDR and XDR-TB. Nevertheless, the implementation of bioinformatic apparatus is not an easy task to do because it requires more technologically advanced people to run these efficiently and needs a lot of resources to maintaining purpose.

5.1.1.5 Funding's

To cure and prevent the tuberculosis disease and infection, requires a multiple number of new drugs and new vaccines. Thus, need a lot of financial support to continue the development of new methods of treatment. Nonetheless, it is very disappointing that funds are not enough to support all the experiments. More than that, innovation of new therapies and medicaments are not all, sometimes previously existing cure method needs upgrades. Hence, need resources to carry the further work. For example, MTB/RIF GeneXpert assay is playing a vital role to identify the disease in early stage however it is not so effective and needs renovation. With the lack of adequate donation now it is generating new issues which further making TB harder to manage.

5.1.2 Challenges in perspective of Bangladesh

5.1.2.1 Population burden

The major issue in Bangladesh, is its population. Bangladesh has a huge population of nearly 1.55 million in 2012 with 1050 people living per kilometer [67,79,80]. The growth rate of the country is around 1.37% [67, 80]. With this large number of people living so closely to each other the chances of communicable disease far exceeded and these diseases are the leading cause of deaths among Bangladeshi people. Point to be noted, the country is in the top ten countries that has high TB cases [67, 81]. In Bangladesh, the number of new cases of TB is 225 per 100000 people with 45 deaths and total of 1.4% muti drug resistance cases [67, 82]. As, the country has a huge population it sometimes become very difficult to control the disease.

5.1.2.2 Lack of Nutrition

Bangladesh has the worst scenario in terms of proper diet distribution. About 50% of all children with age under five, suffers from malnutrition and the situation is even bad in urban areas [67, 105]. Since, this is an alarming problem, with it, comes many threats like

immune compromised condition and as results more possibilities to get infected to a certain disease.

5.1.2.3 Poor health management

A great number of people in Bangladesh does not have proper idea about personal hygiene. They live in poor condition with very unhealthy environment. Often consume unhealthy foods and lead a very imbalanced lifestyle. As a result, people here suffer from different disease and as they lack having accurate knowledge about healthy lifestyle and proper health management, it increases the challenge to manage tuberculosis and other diseases [67].

5.1.2.4 Lack of medical assistance

For 10000 people only 5.25% doctors are available in Bangladesh [83, 106] which make the scenario even worst when it comes to manage so many patients. In case of tuberculosis, a patient needs extensive care and monitoring. As, there is a smaller number of clinical staff working the health management is extremely poor. According to a survey by Bangladesh Health facility in 2017, 70% of rural health care system lacks the basic six equipment such as thermometers, stethoscopes, blood pressure gauge, weighing scales for infants and adults, and torchlights. Additionally, most of the health care center does not have enough medicament supplies [83, 107].

5.2 Possible Solutions

5.2.1 New drugs

After a long research of 40 years finally new hope has arrived [94]. New promising anti-tuberculosis compounds are waiting to help mankind to fight the disease. The drugs that are

available takes very long time to cure and has many adverse effects. As a result, there is no other alternatives other than developing new drugs which would be less time consuming and would also has very less side effects. Till date eleven new or remodeled medicines are under clinical observations. Among them, one in phase I, seven in phase II, another three are in phase III trials. The three medicine that are in phase three can have the potential to minimize the drug regimen to 4 months and the investigation for further information is still on going [94]. With the invention of the new therapeutic agent the possible problems with TB can be avoided with less destruction of human health and life. **Fig 5.01** shows the TB drug pipeline.

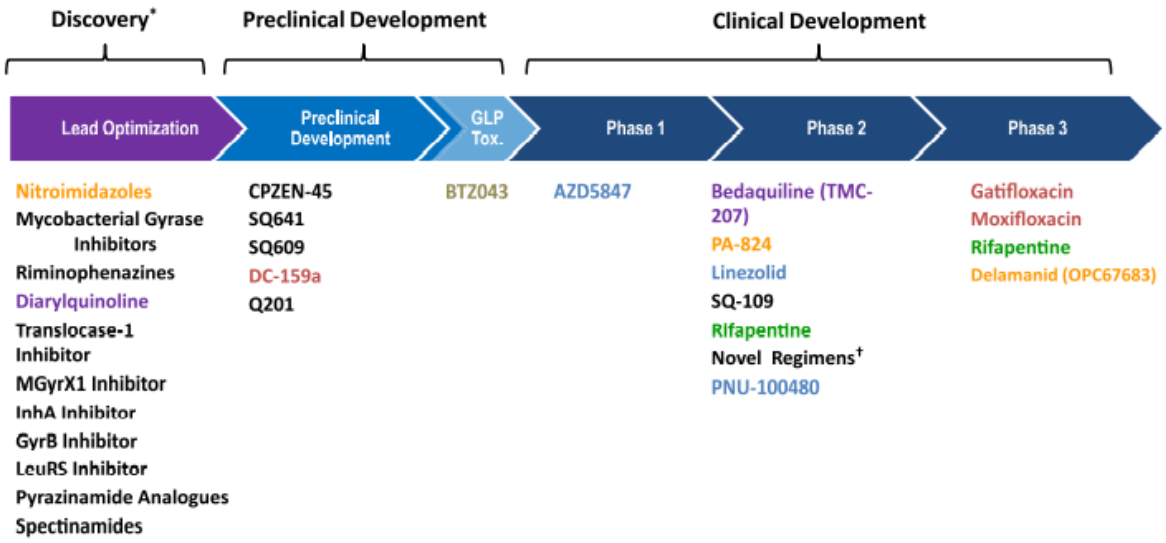

Fig 5.01: Global tuberculosis drug pipeline. Chemical classes are shown in various colors: fluoroquinolone (red), rifamycin (green), oxazolidinone (blue), nitroimidazole (yellow), diarylquinoline (purple), enzothiazinone (tan). *Ongoing projects without a lead compound series can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php. Combination regimens: first clinical trial (NC001) of a novel tuberculosis drug regimen testing the 3-drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated in November 2010. Abbreviation: GLP Tox, Good

Laboratory Practice Toxicology Study. (Source: Working Group on New Drugs, Stop TB Partnership.)

5.2.2 New vaccine

As the BCG vaccine which is in current use proved its efficacy to boost immunity to prevent TB disease, invention of new vaccine can be the revolutionary solution. BCG vaccine is proved to work best in the children and can give protection up to ten years. Nonetheless, most of the people develop the disease in their adolescence or in their adult age. As there are no such vaccine is available for the adults, the focus of producing new vaccine is to develop something that would work in the old people. A model statistic shows that even a vaccine with only 60% of effectiveness can give protection against active TB disease if only given to 20% of the adult population [1]. The modeling also suggests following this may prevent 30 million new cases to take place in the first 20 years of administration and 35 million cases can be adverted if the vaccine has given to 90% of newborn [1]. Though BCG is available and works perfectly in case of the newborn and young children, this vaccine cannot be administered to the children with HIV disease therefore it is essential to develop a new vaccine for the young people as well. It is not an easy task to generate a new vaccine overnight hence there are 13 new vaccine candidates are under clinical trials in various phases [1]. If even one these 13-vaccine work, it would be easier to fight against the deadly tuberculosis (**Table 5.1**).

Vaccine candidate	Development partners	Description	Current phase
Prevention of active TB disease in infants (BCG replacement)			
VPM 1002*	Serum Institute of India (India), Max Planck Institute (Germany), Vakzine Projekt Management GmbH (Germany) and TuBerculosis Vaccine Initiative (The Netherlands)	Recombinant BCG	Phase IIb
MTBVAC‡	Biofabri (Spain), TuBerculosis Vaccine Initiative and University of Zaragoza (Spain)	Live attenuated *Mycobacterium tuberculosis*	Phase I
Prevention of active TB disease in individuals with LTBI			
Vaccae	Anhui Zhifei Longcom (China)	Heat-inactivated, whole-cell *Mycobacterium vaccae*	Phase III
Adjunctive immunotherapy in individuals with LTBI			
RUTI	Archivel Farma (Spain)	Detoxified, fragmented *M. tuberculosis*	Phase II
Prevention of active TB disease recurrence in recently cured patients			
ID93+GLA-SE	Infectious Disease Research Institute (United States) and the Wellcome Trust (United Kingdom)	Adjuvanted recombinant protein expressing *M. tuberculosis* antigens Rv3619, Rv3620, Rv1813 and Rv2608	Phase IIb
Prevention of active TB disease in uninfected individuals and in those with LTBI			
H1or H56:IC31	Statens Serum Institut (Denmark), Valneva (France) and Aeras (United States)	Adjuvanted recombinant protein expressing *M. tuberculosis* antigens Ag85B, ESAT-6 [H1]; or Ag85B, ESAT-6, Rv2660c [H56]	Phase II
M72/ASO1E	GlaxoSmithKline (GSK) Vaccines (United Kingdom) and Aeras	Adjuvanted recombinant protein expressing *M. tuberculosis* antigens 32A and 39A	Phase IIb
DAR-901	Dartmouth College (United States)	Whole-cell, inactivated non-tuberculous mycobacterium	Phase II
H4:IC31	Sanofi Pasteur (France), Statens Serum Institut and Aeras	Adjuvanted recombinant protein expressing *M. tuberculosis* antigens Ag85B and TB10.4	Phase II
Ad5 Ag85A	McMaster University (Canada) and CanSino (China)	Viral vector (human adenovirus 5) expressing *M. tuberculosis* antigen Ag85A	Phase II
ChAdOx1-85A/ MVA85A	University of Oxford (United Kingdom)	Viral vectors (Chimp adenovirus/modified Vaccinia Virus Ankara) heterologous prime–boost expressing *M. tuberculosis* antigen Ag85A	Phase I
MVA85A/ MVA85A	University of Oxford	Viral vector (modified Vaccinia Virus Ankara) intradermal followed by aerosol; prime–boost vaccine	Phase I
TB/FLU-04L	Research Institute for Biological Safety Problems (Republic of Kazakhstan)	Viral vector (influenza A virus)	Phase I

Table 5.1: New TB vaccine candidates (adapted from Pai, M., Behr, M. A., Dowdy, D., Dheda, K., Divangahi, M., Boehme, C. C., … Raviglione, M. (2016). Tuberculosis. Nature Reviews Disease Primers, 2, 16076.)

5.2.3 Regular treatment

Taking anti-tuberculosis drug regularly is the key to get rid of the disease. Nevertheless, in most of the cases it has been noticed many of the TB patient stop taking their medicines after few weeks of the treatment as they start feeling well and fit. This however can lead to severe condition and may give rise of different critical problems as in drug resistance. When a TB diseased person stop taking medicine the pathogen may start regaining its strength. The causative agent of tuberculosis needs a lot of time get killed and that's why the treatment regimen is very lengthy. Every patient should take their medicines as long as the clinical experts suggest. Other than that, the person may get seriously ill and may transfer the disease to that person's family and to the people around. Not only that, but the previous drugs may

also not work on them and as a result they may need to take some different medicines which can have various adverse effects. Though tuberculosis treatment is a lengthy and time-consuming procedure, it can be prevented with taking proper and regular treatment as per the regimen. It not only helps the patient to regain their healthy state but also helps to control the spread in so many people.

5.3 Future plans and projects

5.3.1 Overall World

5.3.1.1 MDGs

There have been five MDG targets decided in order to control TB problem in different countries and different region all over the world. The targets are detection of 70% of new smear positive cases by 2005, by 2015 successfully treated 85% of the cases; to have halted and begun to reverse incidence; between 1995 to 2015 to have TB prevalence and mortality rate [68].

5.3.1.2 Improvement in case detection and treatment

It was the main objective to identify the patients in order to provide them the clinical assistance. In many countries it is still a major concern to screen out the infected person and prevent the active transmission among other healthy population. This the reason this target was being set and under this target nearly 182 countries taken the DOTS strategy. As the outcome of the program, by 2003 it was found 3.8 million TB new cases among them approximately 1.7 million new smear positive cases. The target expanded and the goal was to treat about 17.1 million diseases person under the DOTS program between the year 1995 and 2003 [68].

5.3.1.3 Resolve the financial crisis.

Financial crisis is being the most problematic issue among all the TB control measures. In many countries especially in developing countries, there is a lack of proper TB detection equipment's, as a result the detection procedure takes longer time than usual and sometimes becomes the cause of TB transmission. Not only that, in those countries most of the people lives a live below the marginal line as a result the Government must provide the infected person proper medications. These treatments itself is very costly and many people may refuse it to take as they live a life hand to mouth. Low budget makes the scenario even worse; people do not get proper treatment and the disease keep on the population infecting new people with every single day. Identifying this underlying cause, WHO grants many funds to support the developing country yet many countries as in Bangladesh are fighting to deal with the budget issues [68].

5.3.1.4 Involvement of NGOs

It is not a task for a single organization to avail large grants for so many countries around the world. Therefore, the active participation of NGOs should count as an additional help. As, these NGOs can contribute to many aspects not only financially but also increasing social awareness through different campaigns in the remote areas of any country [68].

5.3.1.5 PPM

This can be proved as another huge asset in controlling TB. This already brought fruitful outcomes in many Asian countries and yet to be implied in African region.

5.3.2 In Bangladesh

In 1993 DOTS showed 78% of cure rate and because of its huge success in 1996 a phase-based treatment plan was taken and had applied on 67 million people in rural settings. After this phase-

based treatment policy it was observed that 90% of cure rate had obtained. Now, a new strategy has been adapted named FAST program (find cases Actively, Separate safety and treat effectively) with the goal of identifying active TB disease and track the transmission of the disease among people. In a recent study it was found that most of the new transmission are taking place through the undetected cases but not from the pre-existing cases. The number of reported MDR-TB was increasing drastically enough to catch the attention of the experts and realize them the significance of screening out the undetected individuals. As a result, the clinical authority felt the urge to introduce something as early as possible to resolve this matter therefore the new novel project starts its journey. This strategy with the objective of identifying the unsuspected TB functions by testing the cough and the screening of drug resistance with rapid molecular tests so that through this the nosocomial spread of tuberculosis can be prevented in hospital settings. FAST was implemented into only three hospital sites (two in Dhaka and one in Chittagong) of Bangladesh: BERDEM (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders), NIDCH (National Institute of Diseases of the Chest and Hospital) and the Chest Disease Hospital in Chittagong based on high TB cases, availability of GeneXpert and relatively less strong administrative control [95].

Currently, so many future plans have been taken to minimize the number of new cases of tuberculosis by NTP. The main goal is to end TB epidemic aiming to achieve a target of 10 new cases/100,000/ year in 2035. In order to do that, there are multiple number of approaches under consideration. Among them: increase annual case detection of all forms of TB to more than 90% of all incidence rate by 2022 (from baseline of 57% in 2015) with childhood TB contribution of 8% by 2022, maintain a treatment success rate of at least 90% in all forms of detected non-MDR TB cases and ensure quality controlled treatment services at all implementation sites, increase

annual case detection to 112 cases by 2022 and improve management of MDR-TB cases, ensure that no affected families facing catastrophic costs due to TB by 2022, ensure that 100% of TB facilities receive regular supervision and monitoring with appropriate feedback resulting in remedial actions by 2022, ensure the long term availability 0f 100% of required funding for activities at all programme levels through effective planning and partner co-ordination and continue increase GoB contributions to the NTP budget and many more [95].

5.4 Conclusion

To conclude, the current situation of Bangladesh regarding Tuberculosis is not satisfactory. People here living below the marginal line and lacks proper knowledge about the disease. As a result, it is becoming more difficult to reduce the transmission of TB. Moreover, there are a huge scarcity of proper medical equipment's, medical stuff especially female health assistance (according to the HEED Bangladesh –TB Control Program 80% are the male workers and only 20% are the female clinical officers), insufficient nutritional support and so on. Not only that, but it is also a concern that about 15-30% patient relapse and infected with TB for the second time which becomes an add on while handing the new cases. Not to mention, amid covid-19, the situation taking a bad shape. Without solving these major issues, it would be very difficult to deal with the disease.

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