A Study on Hematological Indices of Tuberculosis Patients Attending in a Tertiary Care Hospital in Dhaka City

Submitted by
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Bachelor of Pharmacy

Under the Guidance of
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Declaration by the Research Candidate

I, Rabita Israt, hereby declare that the dissertation entitled "**A Study on Hematological Indices of Tuberculosis Patients Attending in a Tertiary Care Hospital in Dhaka City",** submitted by me to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the award of the degree of Bachelor of Pharmacy (B. PHARM) is a complete record of original research work carried out by me during the period 2011-2012 under the supervision and guidance of **Dr. Sufia Islam,** Associate Professor, Department of Pharmacy, East West University and it has not formed the basis for the award of any other Degree/ Diploma/ Fellowship or other similar title to any candidate of any University.

Place: Dhaka

Date:

Signature of the candidate

Rabita Israt

2008-3-70-047

Thesis Certificate

This is to certify that the thesis entitled "**A Study on Hematological Indices of Tuberculosis Patients Attending in a Tertiary Care Hospital in Dhaka City**", submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the award of the degree of Bachelor of Pharmacy (B. PHARM) is a complete record of original research work carried out by Rabita Israt (ID. 2008-3-70-047) during the period 2011-2012 of her research in the Department of Pharmacy at East West University, under my supervision and guidance and the thesis has not formed the basis for the award of any other Degree/ Diploma/ Fellowship or other similar title to any candidate of any University.

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Dedicated

to

My Loving Parents

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List of Abbreviations

AFB	Acid Fast Bacillus
AIDS	Acquired Immunodeficiency Syndrome
CBC	Complete Blood Count
DOTS	Directly Observed Treatment Short Course
E	Ethambutol
ESR	Erythrocyte Sedimentation Rate
FDC	Fixed-Dose Combinations
H	Isoniazid
HIV	Human Immunodeficiency Virus
MDR	Multidrug-Resistant
Mtb	*Mycobacterium tuberculosis*
PTB	Pulmonary Tuberculosis
R	Rifampicin
S	Streptomycin
SS+	Sputum Smear Positive
SS-	Sputum Smear Negative
TB	Tuberculosis
TB Drugs	Tuberculosis Drugs
USAID	United States Agency for International Development
WHO	World Health Organization
Z	Pyrazinamide

Abstract

Background: Among all the infectious diseases, tuberculosis (TB) remains the deadliest. In 2008, the World Health Organization (WHO) ranked Bangladesh 6th among the world's 22 high-burden TB countries.

Objective: The objective of this study was to observe the hematological status of tuberculosis patients and to observe the change in patients' medical condition (AFB smear test) followed by diagnosis after one month.

Methodology: The prospective study was carried out among admitted patients in National Institute of Diseases of the Chest and Hospital (NIDCH) of Dhaka city. A total of 22 new TB cases were selected by simple random sampling technique. Patients who have been diagnosed with tuberculosis by AFB microscopy or radiological test were considered for this study. After taking informed consent from patients, a semi-structured questionnaire was administered for data collection.

Results: The study showed that 60% poor TB patients admitted at NIDCH were from the rural areas whereas 87.5% urban patients were found to be from middle class family and no poor class urban patients. The association was found to be significant (P= 0.012). The gender distribution of patients illustrated that men (90.9%) are more likely to affected by TB. 95.5% patients were found to have higher ESR value. 81.8% patients were diagnosed to have anemia. The Mean (± SD) ESR was 58.18 (± 25.73) and White Blood Count was 10081.81 (± 2747.05) respectively. Among the patients, 7 were observed again after one month among which 4 patients became sputum smear negative (SS-) from sputum smear positive (SS+) in the initial diagnosis.

Discussion: The complete blood count with ESR was conducted as the first test on a patient suspected to have a disease or infection. In the light of these preliminary findings, higher ESR rate may be useful to detect tuberculosis. Around one-third of tuberculosis cases went undetected, resulting in a larger number of undiagnosed and untreated cases that might spread the disease further. In addition to that extension of Directly Observed Treatment Short Course (DOTS) along with development of rapid diagnostic methods may reduce relapse rate of tuberculosis and improve the current scenario.

Key words: AFB microscopy, CBC, drug resistance, ESR, *Mycobacterium tuberculosis*, tuberculosis.

1.1 Tuberculosis

Tuberculosis (TB) continues to be an important health and socio-economic issue, especially in developing countries. Among all infectious diseases that afflict humans, tuberculosis remains the deadliest. The disease process itself produces no clear, typical clinical symptoms which make the infection more difficult to detect enabling it to freely disseminate and affect those in contact with a diseased individual. The development of TB is affected by social and economic factors more than any other disease. Epidemiological studies of these factors are fundamental, as they may influence TB frequency and distribution and interaction between people, as well as the course of treatment and its final outcome (Ilic *et al*., 2012; Stop, 2006).With the discovery in the late 1940s and early 1950s of antimicrobial drugs specific for tuberculosis, it became possible for the first time to discuss realistically the elimination of this communicable disease. Thoughts of eradication were exhilarating. A more realistic goal would be the elimination of tuberculosis as a public health problem and that is still the goal.

Tuberculosis is an infectious disease mainly caused by *Mycobacterium tuberculosis*, which is an aerobic pathogenic bacterium that establishes its infection usually in the lungs. The infection is spread like a cold, mainly through airborne droplets breathed into the air by a person infected with TB. The bacteria causes formation of small tissue masses called tubercles. In the lungs these tubercles produce breathing impairment, coughing and release of sputum. TB may recur after long periods of latency if not treated adequately. Many variations of TB exist and are distinguished by the area of the body affected, degree of severity and affected population. Progression of TB infection is fundamentally regulated by hosts' immune system integrity (Davidson & Haslett, 2002). Most people who are exposed to TB never develop symptoms, because the bacteria can live in an inactive form in the body. But if the immune system weakens, such as in people with HIV or elderly adults, TB bacteria can become active. In their active state, TB bacteria cause death of tissue in the organs they infect. Active TB disease can be fatal if left untreated.This disease today is considered curable and preventable.Despite the first anti tuberculosis drugs being discovered more than 60 years ago, tuberculosis today still kills an estimated 1.7 million people each year (World Health Organization, 2011). Progress in the scaling up of tuberculosis diagnostic, treatment, and control efforts worldwide over the past decade has been associated with improvements in tuberculosis control in many parts of the world. On the other hand, this progress has been substantially undermined by the HIV-1 epidemic, the growing challenge of drug resistance, and other increasingly important epidemiological factors that continue to stimulate the

tuberculosis epidemic. Unfortunately the majority of these cases are likely to occur in the world's poorest nations, who struggle to cover the costs associated with management and control programmes (Ducati, Ruffino-Netto, Basso, & Santos, 2006).

1.2 History of TB

Tuberculosis is a disease of antiquity (Gagneux, 2012). TB, also known as the white plague (McMillen, 2008; Stewart, 1936), became the principal cause of death worldwide. This disease still represents a global threat, as it stands as the leading cause of death due to an infectious agent among adults worldwide. In 2008, evidence for tuberculosis infection has been discovered in human remains from the Neolithic era dating from 9,000 years ago, in a settlement in the eastern Mediterranean (Hershkovitz *et al.,* 2008). This finding was confirmed by morphological and molecular methods; to date it is the oldest evidence of tuberculosis infection in humans. Some authors call tuberculosis the first disease known to mankind. Signs of the disease have also been found in Egyptian mummies dated between 3000 and 2400 BCE. The slow progress of the disease allowed for a "good death" as sufferers could arrange their affairs. The disease began to represent spiritual purity and temporal wealth, leading many young, upper-class women to purposefully pale their skin to achieve the consumptive appearance. It was seen as a "romantic disease." Suffering from tuberculosis was thought to bestow upon the sufferer delicate sensitivity. The first reference to tuberculosis in Asian civilization is found in the Vedas (Ducati *et al.*, 2006).

Though removed from the cultural movement, the scientific understanding advanced considerably. By the end of the 19th century, several major breakthroughs gave hope that a cause and cure might be found. One of the most important physicians dedicated to the study of physiology was René Laennec, who died from the disease at the age of 45, after contracting tuberculosis while studying contagious patients and infected bodies. Laennec invented the stethoscope which he used to corroborate his auscultatory findings and prove the correspondence between the pulmonary lesions found on the lungs of autopsied tuberculosis patients and the respiratory symptoms seen in living patients. His most important work was his discoveries on the utility of pulmonary auscultation in diagnosing tuberculosis which represents the beginning of the modern scientific understanding of tuberculosis. He identified for the first time the TB manifestation unit (Ducati *et al.*, 2006).

In 1869, Jean Antoine Villemin demonstrated that the disease was indeed contagious, conducting an experiment in which tuberculous matter from human cadavers was injected into laboratory rabbits, which then became infected. One of the greatest works on TB was performed in 1882 by Robert Koch, an esteemed scientist of his time. Koch isolated and cultured *M. tuberculosis* from crushed tubercles. His experimental work identified the bacterium as the TB etiological agent (Bloom & Murray, 1992). On 24 March 1882, Robert Koch revealed the disease was caused by an infectious agent. In 1895, Wilhelm Roentgen discovered the X-ray, which allowed physicians to diagnose and track the progression of the disease, and although an effective medical treatment did not come for another fifty years, the incidence and mortality of tuberculosis began to decline (Ducati *et al.*, 2006).

After the establishment in the 1880s that the disease was contagious, TB was made a notifiable disease in Britain; there were campaigns to stop spitting in public places. A significant decline in the incidence of TB cases in the US began to decrease around 1900. It was thought that this was due to a natural decline in the epidemic. However, some was credited to the quarantining the ill in the sanatoriums as well as public health education campaigns that were pushed. The advancement of scientific understanding of tuberculosis, and the contagious nature created the need for institutions to house sufferers. The promotion of Christmas Seals began in Denmark during 1904 as a way to raise money for tuberculosis programs. It expanded to the United States and Canada in 1907–1908 to help the National Tuberculosis Association (later called the American Lung Association). In the United States, concern about the spread of tuberculosis played a role in the movement to prohibit public spitting except into spittoons (Hershkovitz *et al.*, 2008).

In the 1940s, the development of a successful TB vaccine took the back burner to advancing effective drugs for TB. Streptomycin, Isoniazid, Rifampin, and Ethambutol were developed in the 1940s and 50s. Many patients began therapy, sometimes with a combination of the effective drugs. The discovery of these drugs brought the sanatorium use to a halt. False confidence arose quickly as many people believed that the development of these drugs would eradicate the illness. The UN even predicted that TB would be gone by 2025. Sadly, and obviously, this will not be so (NIAID, 2008).

With the discovery of what the bacterium causing this disease, the bacille Calmette-Guérin, vaccine, and the use of new drugs, TB still runs rampant throughout the world and is one of the leading causes of death in the category of infectious diseases. In 2009, 9.4 million new

TB cases are estimated to have emerged. The global TB incidence rate is falling per capita, but the decline rate is quite slow (<1% each year) (World Health Organization, 2009). Also in recent years, drug-resistant strains of TB have started emerging along with co-infections of HIV and TB. In 2010, 15% of new TB patients were also infected with HIV. This brings into the picture a whole new challenge to the fight with Mycobacterium tuberculosis (World Health Organization, 2009).

1.3 Epidemiology

1.3.1 Current Global Tuberculosis Burden

According to the WHO, TB kills more people than malaria and AIDS together. Annually, TB is responsible for the death of 100,000 children worldwide, and 161,800 new cases occur only in Brazil. From now until 2020, it is estimated that 1 billion more people will be infected, 200 million will develop the disease, and 70 million will die in case surveillance and control strategies continue as they are (Pasqualoto & Ferreira, 2001).

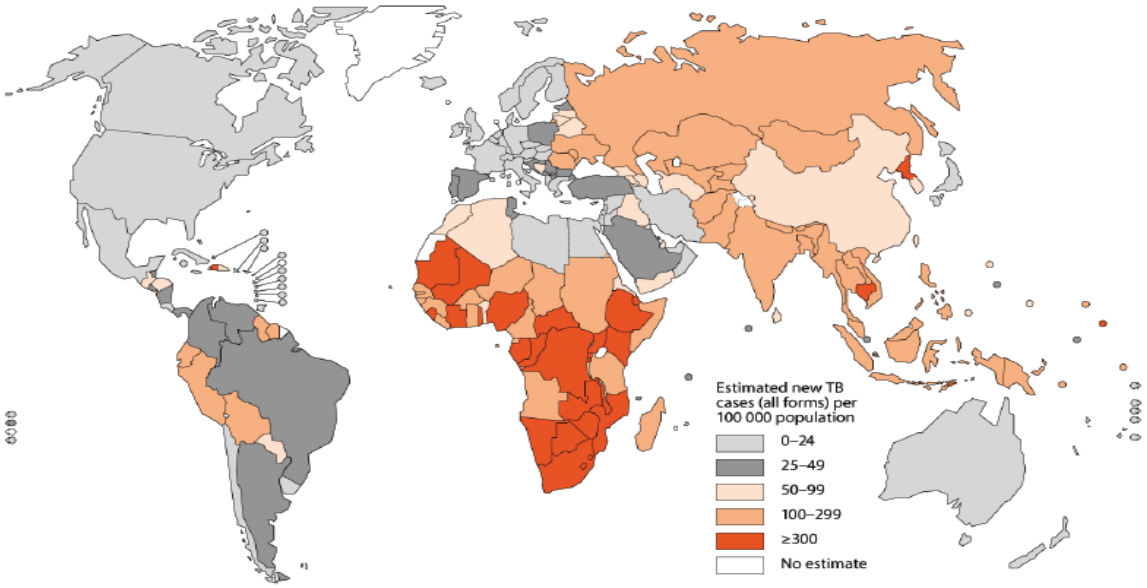


Figure 1.1: Global Tuberculosis Burden (World Health Organization, 2009)

The boundaries and names shown and the designations used in this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement (World Health Organization, 2009).

The World Health Organization (WHO) estimates that there were 9.2 million new cases of tuberculosis (TB) in 2006, including 4.1 million new smear-positive cases, corresponding to incidence rates of 139/100,000 and 61/100,000, respectively (World Health Organization, 2009). In the same year, there were an estimated 14.4 million prevalent TB cases (all forms, 219/100,000), and 1.7 million deaths (25/100,000) from TB, of which 95% occurred in developing countries. Asia accounted for 55% of the global cases, and Africa for 31.1% Among the 15 countries with the highest estimated TB incidence rates, 12 were in Africa, where the TB incidence rate was 363/100,000 (World Health Organization, 2009). This is mainly the result of high HIV prevalence and lack of health system capacity to cope with the dual epidemic. Among all estimated new TB cases in 2006, around 700,000 (7.6%) were estimated to be HIV infected. In 2006, there were an estimated half a million cases of multidrug resistant (MDR)-TB, of which 85% are concentrated in 27 WHO MDR-TB priority countries, including 15 countries in eastern Europe, where rates per capita were highest (World Health Organization, 2009). Although the total number of incident cases of TB is increasing in absolute terms as a result of population growth, the number of cases per capita is falling. The rate of decline is slow, at less than 1% per year. Globally, rates peaked at 142 cases per 100000 population in 2004. In 2007, there were an estimated 139 incident cases per 100000 population. Incidence rates are falling in five of the six WHO regions (the exception is the European Region, where rates are approximately stable) (World Health Organization, 2009).

There were an estimated 13.7 million prevalent cases of TB in 2007 (206 per 100000 population), a decrease from 13.9 million cases (210 per 100000 population) in 2006. There were an estimated 0.5 million cases of multi drug resistant TB (MDR-TB) in 2007 (World Health Organization, 2009).

1.4 Clinical Manifestation

As the cellular processes occur, tuberculosis may develop differently in each patient, according to the status of the patient's immune system, stages include:

- Latency
- Primary disease
- Primary progressive disease
- Extra pulmonary disease

Each stage has different clinical manifestations as shown in Table 1.1.

Table 1.1: Clinical Manifestation of Tuberculosis

Early infection	Early primary progressive (active)	Late primary progressive (active)	Latent
Immune system fights infection Infection generally proceeds without signs or symptoms Patients may have fever, paratracheal lymphadenopathy or dyspnea Infection may be only subclinical and may not advance to active disease	Immune system does not control initial infection Inflammation of tissue ensues Nonproductive cough develops Diagnosis can be difficult: findings on chest radiographs may be normal and sputum smears may be negative for mycobacteria	Cough becomes productive More signs or symptoms as disease progresses Patient experience progressive without weight loss, rales, anemia Findings on chest radiographs are normal Diagnosis is via cultures of sputum	Mycobacteria persist in the body No signs or symptoms occur Patients do not feel seek Patients are susceptible to reactivation of disease Granulomatous lesions calcify and become fibrotic, become apparent on chest radiographs Infection can reappear when immunosuppression occurs

(Centers for Disease Control and Prevention, 2012)

1.4.1 Latent Tuberculosis

Mycobacterium tuberculosis organisms can be enclosed, but are difficult to completely eliminate. TB spreads through droplet infection. TB bacilli stay suspended in the air as droplets. Healthy people become infected with TB through inhalation of the droplets containing TB bacilli. Around 90% of the infected people do not progress to TB disease because of their immunity. Persons with latent tuberculosis have no signs or symptoms of the disease, do not feel sick, and are not infectious. However, viable bacilli can persist in the necrotic material for years or even a lifetime, and if the immune system later becomes compromised, as it does in many critically ill patients, the disease can be reactivated. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease (Davidson & Haslett, 2002).

Many people who have latent TB infection never develop TB disease. Some people develop TB disease soon after becoming infected like within weeks before their immune system can fight the TB bacteria. Other people may get sick years later when their immune system becomes weak for another reason. For people whose immune systems are weak, especially those with HIV infection, the risk of developing TB disease is much higher than for people with normal immune systems (Centers for Disease Control and Prevention, 2012).

Table 1.2: TB Infection vs. TB Disease

TB Infection	TB Disease
Tubercle bacilli in the body	Tubercle bacilli in the body
Tuberculin skin test reaction usually positive	Tuberculin skin test reaction usually positive
Chest X-ray usually normal	Chest X-ray usually abnormal
Sputum smears and culture negative	Sputum smears and cultures positive
No symptoms	Symptoms such as cough, fever, weight loss
Not infectious	Often infectious before treatment
Not a case of TB	A case of TB

(Mori et al., 2004)

Although co-infection with human immunodeficiency virus is the most notable cause for progression to active disease, other factors, such as uncontrolled diabetes mellitus, sepsis, renal failure, malnutrition, smoking, chemotherapy, organ transplantation, and long-term corticosteroid usage that can trigger reactivation of a remote infection are more common in the critical care setting. Additionally, persons 65 years or older have a disproportionately higher rate of disease than any does other age group, often because of diminishing immunity and reactivation of disease (Centers for Disease Control and Prevention, 2012).

Tuberculosis Disease

Tuberculosis disease means tuberculosis infection plus presence of signs and symptoms of TB. Around 10% of the people infected with TB bacilli may progress to TB disease in their lifetime. TB bacilli multiply in their lungs or other organs and produce the symptoms and signs. Around 5% of the infected people develop TB disease within months or years and the remaining in their old age that is known as reactivation of the disease (Kaufmann, 2001).

There are three potential outcomes of infection of the human host in *Mycobacterium tuberculosis*:

i. The frequency of abortive infection resulting in spontaneous healing is unknown, but is assumed to be minute.

ii. In the immuno-compromised host, disease can develop directly after infection.

iii. In most cases, mycobacteria are initially contained and disease develops later as a result of reactivation.

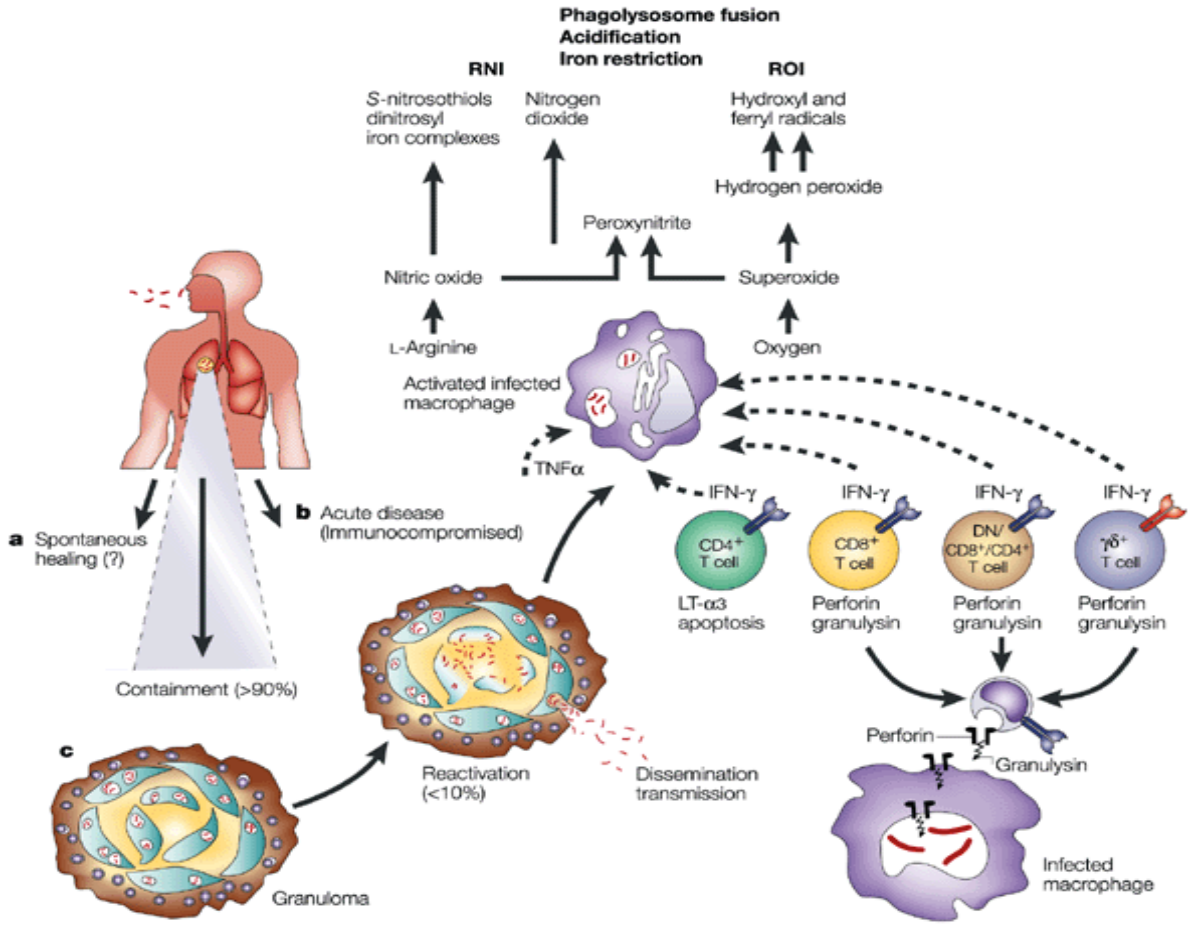


Figure 1.2: Main features of tuberculosis: from infection to host defense (Kaufmann, 2001).

The granuloma is the site of infection, persistence, pathology and protection. Effector T cells (including conventional $CD4^+$ and $CD8^+$ T cells, and unconventional T cells, such as γδ T cells) and macrophages participate in the control of tuberculosis. Interferon-γ (IFN-γ) and tumour-necrosis factor-α (TNF-α), produced by T cells, are important macrophage activators. Macrophage activation permits phagosomal maturation and the production of antimicrobial molecules such as reactive nitrogen intermediates (RNI) and reactive oxygen intermediates (ROI) (Kaufmann, 2001).

1.4.2 Primary Disease

Primary pulmonary tuberculosis is often asymptomatic, so that the results of diagnostic tests are the only evidence of the disease. Although primary disease essentially exists sub clinically, some self-limiting findings might be noticed in an assessment. The bacilli spread from the lungs through the lymphatic system. If the primary lesion enlarges, pleural effusion is a distinguishing finding. This effusion develops because the bacilli infiltrate the pleural space from an adjacent area. The effusion may remain small and resolve spontaneously, or it may become large enough to induce symptoms such as fever, pleuritic chest pain, and dyspnea. Dyspnea is due to poor gas exchange in the areas of affected lung tissue. Dullness to percussion and a lack of breath sounds is physical findings indicative of a pleural effusion because excess fluid has entered the pleural space (Davidson & Haslett, 2002).

1.4.3 Primary Progression of Tuberculosis

Active tuberculosis develops in only 5% to 10% of persons exposed to *M. tuberculosis.* When a patient progresses to active tuberculosis, early signs and symptoms are often nonspecific. Manifestations often include progressive fatigue, malaise, weight loss, and a low-grade fever accompanied by chills and night sweats. Weight loss, a classic feature of tuberculosis is due to the lack of appetite and the altered metabolism associated with the inflammatory and immune responses. Wasting involves the loss of both fat and lean tissue; the decreased muscle mass contributes to the fatigue. Finger clubbing, a late sign of poor oxygenation, may occur; however, it does not indicate the extent of disease. A cough eventually develops in most patients.

Table 1.3: Manifestations of Infection

Time from infection	Manifestations
3-8 weeks	Primary complex, positive tuberculin skin test
3-6 months	Meningeal, miliary and pleural disease
Up to 3 years	Gastrointestinal, bone and joint, and lymph node disease
Around 8 years	Renal tract disease
From 3 years onwards	Post-primary disease due to reactivation or reinfection

(Davidson & Haslett, 2002)

Although the cough may initially be nonproductive, it advances to a productive cough of purulent sputum. The sputum may also be streaked with blood. Hemoptysis can be due to destruction of a patent vessel located in the wall of the cavity, the rupture of a dilated vessel in a cavity, or the formation of anaspergilloma in an old cavity. The inflamed parenchyma may cause pleuritic chest pain. Extensive disease may lead to dyspnea or orthopnea because the increased interstitial volume leads to a decrease in lung diffusion capacity. Although many patients with active disease have few physical findings, rales may be detected over involved areas during inspiration, particularly after a cough. Hematologic studies might reveal anemia, which is the cause of the weakness and fatigue. Leukocytosis may also occur because of the large increase in the number of leukocytes, or white blood cells, in response to the infection.

1.5 Type of TB

1.5.1 Primary Tuberculosis

Primary tuberculosis refers to the infection process which eventually eliminates the pathogen or results in a stalemate between the *Mycobacteria* and the immune system. With most TB infections, the immune system is able to contain, although not eliminate, the *Mycobacteria* within the tubercle, preventing the spread of bacteria and progression of the disease. *M. tuberculosis* (Mtb) can remain in this impasse of dormant infection for many years (Davidson & Haslett, 2002).

1.5.2 Secondary or Reactivated Tuberculosis

The infection can become reactivated if the *Mycobacteria* are able to rupture the tubercle and spread through the lungs. This reactivation typically happens to those with a weakened or suppressed immune system.

1.5.3 Disseminated Tuberculosis

The spread of the disease within the body may result if infected macrophages moving through the blood and lymph transport the bacteria to other sites. Once infected, symptoms of disseminated TB correspond to the locations infected. The antiquated term "consumption" arose from the myriad of symptoms associated with disseminated tuberculosis, when those infected seemed to slowly waste away (Davidson & Haslett, 2002).

1.5.4 Osseous Tuberculosis

This form of TB can cripple the child for life. It presents itself in the spine, hips, knees and other bones. The joints swell and the person finds it difficult to walk and bend.

1.5.5 Laryngeal Tuberculosis

Laryngeal TB occurs when the bacterium attacks the throat's vocal chords. This highly uncommon pulmonary TB is frequently confused with other throat diseases like chronic laryngitis and laryngeal carcinoma.

1.5.6 Cavitary Tuberculosis

Cavitary TB infects a lung's upper lobes and slowly destroys them. Symptoms include a cough with sputum and possibly blood, night sweats, fever and weight loss. This type of TB is very contagious and can spread to other parts of the lung.

1.5.7 Miliary Tuberculosis

Similar to primary TB pneumonia, those with a weakened immune system are at greater risk for contracting this pulmonary form of the disease. In addition to a high fever, weight loss and night sweats, miliary TB is diagnosed when small granules appear in the lungs as seen on an x-ray (Davidson & Haslett, 2002).

1.5.8 Tuberculosis Pleurisy

Those who catch TB pleurisy will quickly show symptoms as the disease enters and ruptures the pleural space in the chest or the space between the lungs and the chest wall. Patients usually experience chest pain and difficulty breathing, and fluid is often present in the lungs. According to the pulmonarychannel.com website, close to two-thirds of patients with TB pleurisy develop other forms of pulmonary TB within five years (Davidson & Haslett, 2002).

1.5.9 Adrenal Tuberculosis

Adrenal TB is an extrapulmonary form of TB that affects the adrenal gland and the production of adrenal hormone. Patients with this form of TB often feel weak or faint due to insufficient adrenal gland production(Davidson & Haslett, 2002).

1.5.10 Lymph Node Tuberculosis

When the TB bacterium impacts the lymph nodes and causes them to become enlarged, lymph node disease is diagnosed. This extrapulmonary TB can even cause the lymph nodes to become so large they rupture through the skin if not diagnosed in time (Davidson & Haslett, 2002).

1.5.11 Cryptic tuberculosis

Cryptic tuberculosis is seen patients over sixty years of age. Patients undergo unexplained weight loss, general debility etc. Another feature is Negative tuberculin skin test. For diagnosis Normal chest X-ray is done. Confirmation by biopsy of liver or bone marrow is also performed (Davidson & Haslett, 2002).

1.6 Causative Agent

Mycobacterium tuberculosis is the principal etiological agent for tuberculosis in humans. Of all bacteria, *Mycobacterium tuberculosis* is one of the most effective human pathogens, with one-third of the world's population being infected (Kaufmann, 2001).Most of the infected population neither develops disease nor becomes infectious, despite persistence of the pathogen. Tuberculosis is caused by *Mycobacterium* tuberculosis complex, mainly by *M. tuberculosis, M. bovis, M. caprae* and *M. africanum.* Other mycobacteria, (known as non-TB, atypical or environmental) can also more rarely cause pulmonary or extrapulmonary pathology (Orcau, CaylÄ, & MartÃnez, 2011).

Mycobacterium is immobile, aerobic, acid-fast with a size of 0.8-4 microns. It is a weak Gram-positive, slender, rod-shaped bacterium that has no flagellum, does not form spores nor produces toxins and has no capsule. The organism is sensitive to solar and ultraviolet light, heat, and disinfectants, but resistant to drying. It has lipid-rich cell walls that stain poorly with the Gram stain, but once stained, the walls cannot be easily decolorized by treatment with acidified organic solvents. Hence, they are termed "acid-fast." The most widely encountered mycobacterial infection is tuberculosis, the leading cause worldwide of death from infection. Members of the genus Mycobacterium also cause leprosy, as well as, several tuberculosis-like human infections. Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction (Orcau *et al*., 2011).

1.6.1 Mycobacterial Cellular Envelope

Mycobacteria produce an extremely uncommon cell wall structure; the peptidoglycan contains *N*-glycolylmuramic acid instead of the usual *N*-acetylmuramic acid, found amongst most other bacteria.

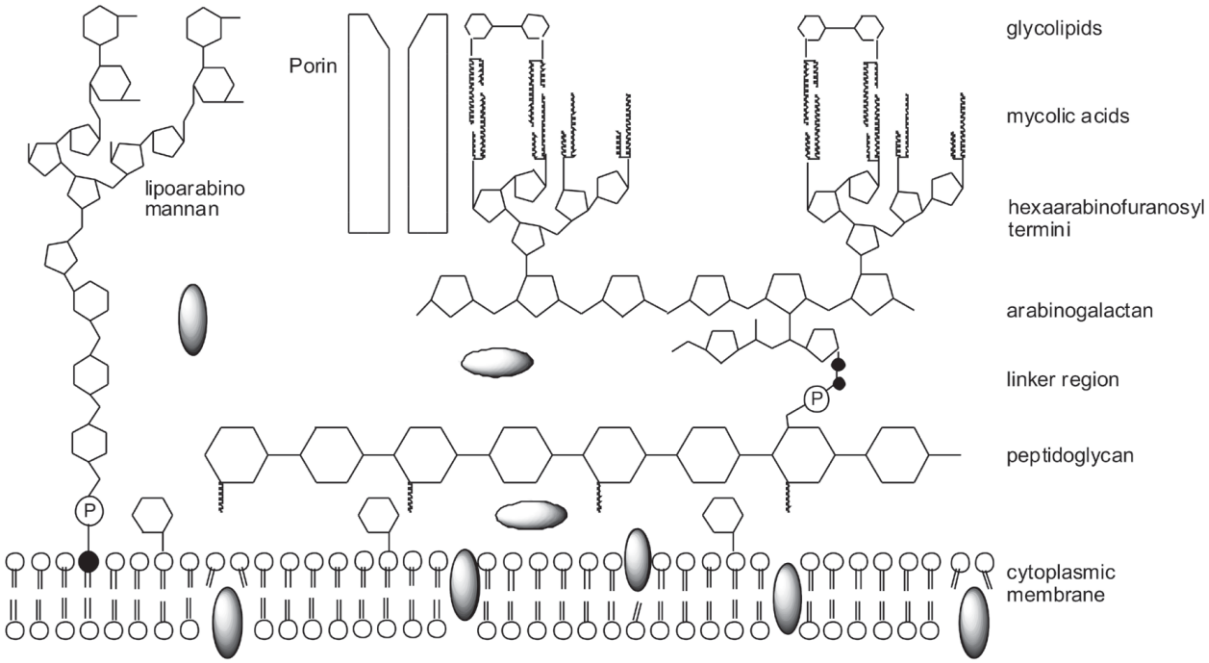


Figure 1.3: Schematic representation of the mycobacterial cell wall (Ducati *et al.*, 2006).

Since *M. tuberculosis* has a cell wall with a relatively high permeability, the inactivation of the second factor in synergism may allow an effective chemotherapy. *M. tuberculosis* cell wall has become a target of the more recent researches towards the elucidation of the mechanism of action of many old drugs and the search of targets for the design of new ones. New data on genes specifically involved in its synthesis may represent potential drug targets (Ducati *et al.*, 2006).

1.6.2 *M. tuberculosis* Genome

M. tuberculosis sequence determination establishes a new phase in the battle against one of the more successful predators of the human race. Although *M. tuberculosis* genome is smaller than *Escherichia coli*, it is very versatile, coding for most of the typical bacterial anabolic and catabolic pathways and amino acid synthesis/degradation (Ducati *et al.*, 2006).

1.7 Pathophysiology

Once inhaled, the infectious droplets settle throughout the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist. The mucus produced catches foreign substances, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal (Freiden, Sterling, Munsiff, Watt, & Dye, 2003). This system provides the body with an initial physical defense

that prevents infection in most persons exposed to tuberculosis (Jensen, Centers for Disease, Prevention, National Center for Hiv, & Prevention, 2005).

Bacteria in droplets that by pass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages (Freiden *et al.,* 2003),the most abundant immune effector cells present in alveolar spaces (Korf *et al.,* 2006). These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection (van Crevel, Ottenhoff, & van der Meer, 2002). Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens. Several mechanisms and macrophage receptors are involved in uptake of the mycobacteria (Nicod, 2007). The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor (Nicod, 2007). The complement system also plays a role in the phagocytosis of the bacteria (Li, Petrofsky, & Bermudez, 2002).

The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. Opsonization by C3 is rapid, even in the air spaces of a host with no previous exposure to M tuberculosis (Ferguson, Weis, Martin, & Schlesinger, 2004). The subsequent phagocytosis by macrophages initiate cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease, called primary progressive tuberculosis (Freiden *et al.,* 2003). The outcome is essentially determined by the quality of the host defenses and the balance that occurs between host defenses and the invading mycobacteria (Guyot-Revol, Innes, Hackforth, Hinks, & Lalvani, 2006; van Crevel *et al.,* 2002). After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours (Freiden *et al.,* 2003). Regardless of whether the infection becomes controlled or progresses, initial development involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria (Nicod, 2007; van Crevel *et al.,* 2002). Released cytokines attract T lymphocytes to the site, the cells that constitute cell-mediated immunity.

Macrophages then present mycobacterial antigens on their surface to the T cells (van Crevel *et al*., 2002). This initial immune process continues for 2 to 12 weeks; the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test (Freiden *et al.,* 2003). For persons with intact

cell mediated immunity, the next defensive step is formation of granulomas around the *M. tuberculosis* organisms (Guyot-Revol *et al.*, 2006). These nodular-type lesions form from an accumulation of activated T lymphocytes and macrophages, which creates a microenvironment that limits replication and the spread of the mycobacteria (Freiden *et al.*, 2003).

This environment destroys macro phages and produces early solid necrosis at the center of the lesion; however, the bacilli are able to adapt to survive (Dheda *et al.*, 2005). In fact, *M tuberculosis* organisms can change their phenotypic expression, such as protein regulation, to enhance survival (Li *et al.*, 2002). By 2 or 3 weeks, the necrotic environment resembles soft cheese, often referred to caseous necrosis, and is characterized by low oxygen levels, low pH, and limited nutrients.

For less immune competent persons, granuloma formation is initiated yet ultimately is unsuccessful in containing the bacilli. The necrotic tissue undergoes liquefaction, and the fibrous wall loses structural integrity. The semi-liquid necrotic material can then drain into a bronchus or nearby blood vessel, leaving an air-filled cavity at the original site. In patients infected with *M. tuberculosis,* droplets can be coughed up from the bronchus and infect other persons. If discharge into a vessel occurs, occurrence of extrapulmonary tuberculosis is likely. Bacilli can also drain into the lymphatic system and collect in the tracheobronchial lymph nodes of the affected lung, where the organisms can form new caseous granulomas (Dheda*et al.*, 2005).

Macrophases and T lymphocytes act together to try to contain the infection by forming granulomas (Raqib *et al.*, 2004**).**In weaker immune systems, the wall loses integrity and the bacilli are able to escape and spread to other alveoli or other organs. Pathophysiology of tuberculosis: inhalation of bacilli (A), containment in a granuloma (B), and breakdown of the granuloma in less immunocompetent individuals (C) (Centers for Disease Control and Prevention, 2012).

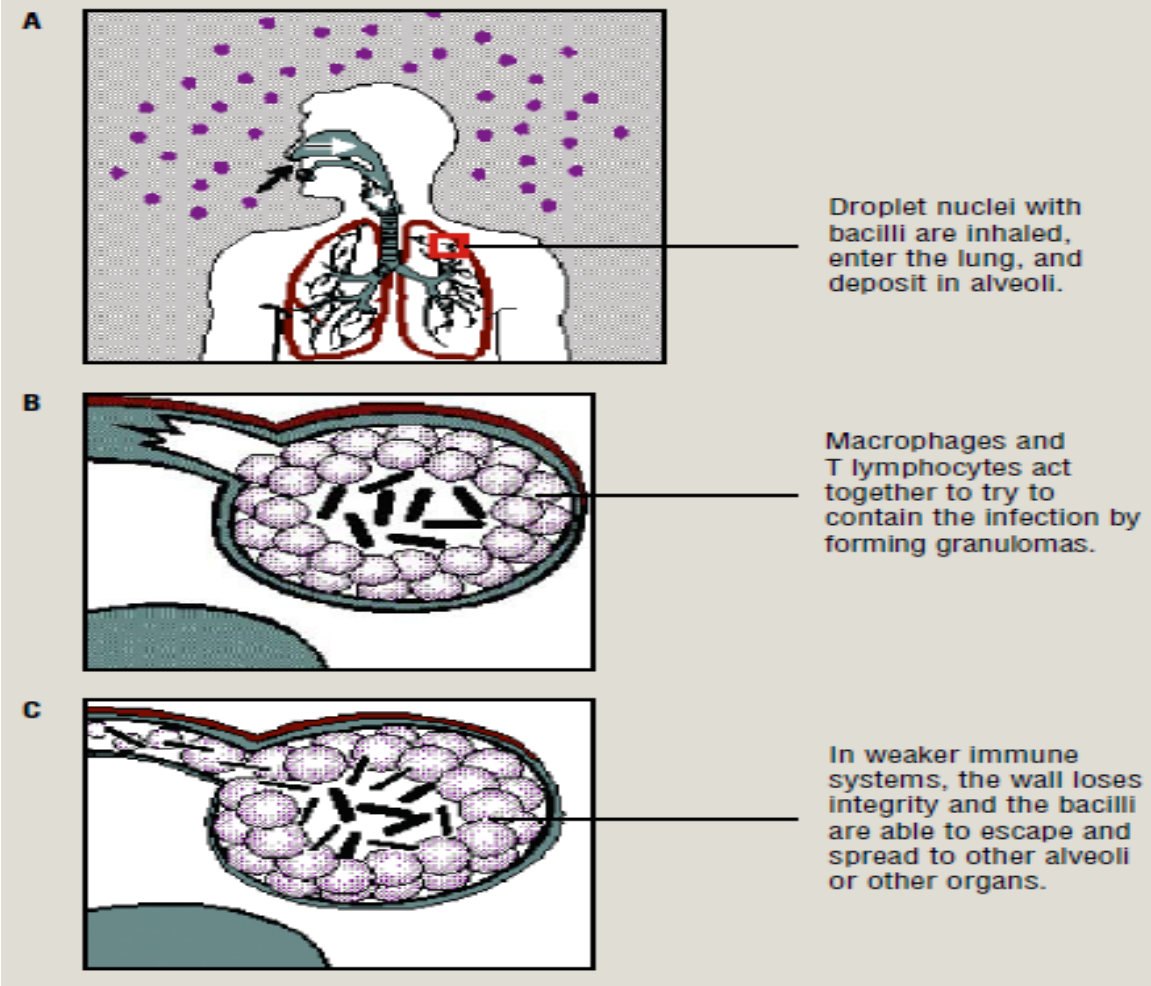


Figure 1.4: Pathophysiology of tuberculosis (Dheda *et al.*, 2005)

This condition restricts further growth and establishes latency. Lesions in persons with an adequate immune system generally undergo fibrosis and calcification, successfully controlling the infection so that the bacilli are contained in the dormant, healed lesions.18 Lesions in persons with less effective immune systems progress to primary progressive tuberculosis (Dheda *et al.*, 2005; Li *et al.*, 2002).

1.7.1 Post-primary Pulmonary Tuberculosis

Pulmonary TB is the most frequent form of post-primary disease. The onset is typically insidious and develops slowly over several weeks. Systemic symptoms include fever, night sweats, malaise, loss of appetite and weight, and are accompanied by progressive pulmonary symptoms. The earliest radiographical change is typically an ill-defined opacity situated in one of the upper lobes. Disease often involves two or more areas of lung and may be bilateral. As disease progresses, consolidation, collapse and cavitation develop to varying degrees. The presence of a miliary pattern or cavitation indicates active disease although

there is a wide differential. In extensive disease, collapse may be marked and result in significant displacement of the trachea and mediastinum. Occasionally, a caseous lymph node may drain into an adjoining bronchus, resulting in tuberculosis pneumonia (Rekha *et al.* 2011).

1.7.2 Extra-pulmonary Tuberculosis

Although the pulmonary system is the most common location for tuberculosis, extra pulmonary disease occurs in more than 20% of immune competent patients, and the risk for extra-pulmonary disease increases with immunosuppression. The most serious location is the central nervous system, where infection may result in meningitis or space occupying tuberculomas. If not treated, tubercular meningitis is fatal in most cases, making rapid detection of the mycobacteria essential. Headaches and change in mental status after possible exposure to tuberculosis or in high risk groups should prompt consideration of this disease as a differential diagnosis. Another fatal form of extra-pulmonary tuberculosis is infection of the bloodstream by mycobacterium; this form of the disease is called disseminated or miliary tuberculosis. The bacilli can then spread throughout the body, leading to multi organ involvement. Miliary tuberculosis progresses rapidly and can be difficult to diagnose because of its systemic and nonspecific signs and symptoms, such as fever, weight loss, and weakness. Lymphatic tuberculosis is the most common extra-pulmonary tuberculosis and cervical adenopathy occurs most often. Other possible locations include bones, joints, pleura, and genitourinary system (Davidson & Haslett, 2002).

1.8 Diagnosis:

1.8.1 Tools for diagnosis of TB

Because active TB disease can be difficult to diagnose, especially in children and those who have weakened immune systems, additional tests beyond medical examinations are required. To determine if a patient has active TB disease, the following tests may be used:

Sputum Smear Examination (AFB Microscopy)

The most cost-effective tool for screening pulmonary TB suspects is microscopy examination of their sputum by the Ziehl-Neelsen method. Over 65% of pulmonary TB patients are smear-positive and will be detected by this method. In the remaining pulmonary TB patients, the number of bacilli in their sputum is too low to be detected through this method. Sputum examination is the most reliable procedure for diagnosis of TB.

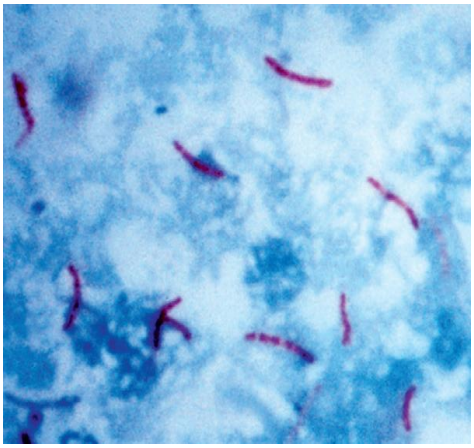


Figure 1.5: High-power micrograph of acid-fast bacilli in the sputum of a patient with tuberculosis, shown by Ziehl-Neelsen staining (×1000) (WHO Country Office for Bangladesh, 2009).

Microscopy should be performed on three sputum specimens, as follows (WHO Country Office for Bangladesh, 2009):

- ❒ "On-the-spot" specimen: the first specimen is collected on the spot when a patient is identified as a pulmonary TB suspect (Spot-I specimen),
- ❒ Early morning specimen: the patient is given a sputum container to collect the second specimen, at home on the following morning (Early Morning Specimen),
- ❒ A second "on-the-spot" specimen: the third specimen is collected when the patient returns to the health facility with the early morning specimen (Spot-II specimen).

Radiological (X-ray) Examination of the Lungs

Chest X-Ray findings do not specifically indicate pulmonary tuberculosis because there are other chest diseases which may show the same changes on X-ray. Chest X-ray findings suggestive of pulmonary tuberculosis in patients with smear-negative microscopy should always be supported by clinical findings. A qualified physician should decide on the diagnosis of TB.

Tuberculin Skin Test (Mantaux Test)

This test is only used for supporting TB diagnosis in young children. In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB disease in adults. A positive tuberculin skin test does not by itself differentiate *M. tuberculosis* infection from TB disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. With increasing age an increasing percentage of the population will

have been infected with *M. tuberculosis* (almost 100% at the age of 40-50 years) and 90% of them will not have developed TB disease. Hence, diagnosis of TB based on Mantoux test will lead to over-diagnosis of many patients. Conversely, the tuberculin skin test result may be negative, even when the patient has TB.

Table 1.4: Diagnostic Test for identifying Tuberculosis

Variable	Sputum smear	Sputum culture	Polymerase chain reaction	Tuberculin skin test	QuantiFERON-TB test	Chest radiography
Purpose of test or study	Detect acid-fast bacilli	Identify *Mycobacterium tuberculosis*	Identify *Mycobacterium tuberculois*	Detect exposure to mycobacteria	Measure immune reactivity to *M. tuberculosis*	Visualize lobar infiltrates with cavitation
Time required for result	<24 hours	3-6 weeks with solid media, 4-14 days with high pressure liquid chromatography	Hours	48-72 hours	12-24 hours	Minutes

(Centers for Disease Control and Prevention, 2012).

Culture of TB Bacilli

Culture is more sensitive than smear microscopy, detecting a higher proportion of patients among suspects. If resources permit and adequate, quality-assured laboratory facilities are available, culture should be included in the algorithm for evaluating patients with negative sputum smears. However, it takes about six weeks to provide a definite result, and is not accessible to most patients. Therefore, it is unsuitable as routine procedure. The probability of finding acid-fast bacilli in sputum smears by microscopy is directly related to the concentrations of bacilli in the sputum. Sputum microscopy is likely to be positive when there are at least 10 000 organisms per ml of sputum. At concentrations below 1000 organisms per ml of the sputum, the chance of observing acid-fast bacilli in a smear is less than 10%. In contrast, a properly performed culture can detect organism even concentrations below 100 organisms per ml (WHO Country Office for Bangladesh, 2009).

FNAC and Biopsy

FNAC stands for fine needle aspiration cytology. It is a diagnostic procedure sometimes used to investigate superficial lumps or masses. These are special tests performed to confirm extra pulmonary TB to be referred to concerned specialists. Fine needle aspiration biopsies are very

safe, minor surgical procedures. Often, a major surgical biopsy can be avoided by performing a needle aspiration biopsy instead. In 1981, the first fine needle aspiration biopsy in the United States of America was done at Maimonides Medical Center, eliminating the need for surgery and hospitalization. Today, this procedure is widely used in the diagnosis of cancer (WHO Country Office for Bangladesh, 2009).

Blood Tests

Recently developed blood Tests (e.g., The T-SPOT, TB Test)are testing for both active disease and latent TB infections (College of Physicians & Surgeons of Saskatchewan, 2012). A blood sample is needed to run this test which is performed in the laboratory. The results are available to the doctor the next day. The T-SPOT, TB test holds several major advantages over the tuberculin skin test in that it does not require a second visit, it is not affected by BCG vaccination and it is very reliable--even in patients with weakened immune systems (College of Physicians & Surgeons of Saskatchewan, 2012; Peters *et al.*, 2008).

1.8.2 Hematological Indices

Apart from the diagnostic tests specific for diagnosis of tuberculosis, some common routine tests are done such as:

- CBC with ESR
- Biochemical analysis(blood glucose, blood urea, Serum creatinine etc.)

Complete Blood Count (CBC)

A complete blood count is a diagnostic test that uses a blood sample to estimate the values of various components found in human blood and is conducted as a routine test in almost every medical condition. The complete blood count is usually the first test conducted on a patient when the patient has symptoms of a disease or infection and also when the patient is admitted to hospital. The complete blood count test is conducted on a sample of blood, usually drawn from a vein in the upper forearm of the patient. The blood is responsible for transporting nutrition, oxygen, hormones and many other substances around the body. The heart creates pressure which allows the blood to move continuously around the body. The blood is measured for its components because it carries so many different components that are diagnostically relevant. The most important components when it comes to a complete blood count are the red blood cells, the white blood cells, the platelet count and the hemoglobin

levels. Many common conditions are diagnosed using these parameters (College of Physicians & Surgeons of Saskatchewan, 2012; Peters *et al.*, 2008).

Erythrocyte Sedimentation Rate

ESR stands for erythrocyte sedimentation rate and is also known as sedimentation rate or Westergren ESR. It is the rate at which red blood cells sediment in a period of 1 hour. It is a common hematology test, and is a non-specific measure of inflammation. The ESR is a commonly ordered test for the assessment of inflammation and is not meant to be used to screen an asymptomatic person for disease. It is a test that indirectly measures how much inflammation is in the body. It is a test that is conducted to check the speed at which the red blood cells precipitate over a period of time. The results are measured as millimeters per hour. Typically, the complete blood count with ESR is conducted as the first test on a patient suspected to have a disease or infection. The results of the ESR test are useful to plan further testing and to commence treatment depending on the condition that is suspected (College of Physicians & Surgeons of Saskatchewan, 2012; Peters *et al.*, 2008).

Once a diagnosis has been made, this test may be used to monitor whether the illness is becoming more active or flaring up. It is a screening test, which means it cannot be used to diagnose a specific disorder. However, it is useful for detecting and monitoring:

- ❒ Autoimmune disorders
- ❒ Certain forms of arthritis
- ❒ Inflammatory diseases that cause vague symptoms
- ❒ Tissue death
- ❒ Tuberculosis

An increased ESR rate may be due to some infections, including:

- ❒ Body-wide (systemic) infection
- ❒ Tuberculosis
- ❒ Bone infections
- ❒ Infection of the heart or heart valves
- ❒ Rheumatic fever
- ❒ Severe skin infections, such as erysipelas

An increased ESR rate may be due to:

- ❒ Anemia
- ❒ Cancers such as lymphoma or multiple myeloma

- ❒ Kidney disease
- ❒ Pregnancy
- ❒ Thyroid disease

The immune system helps protect the body against harmful substances. In autoimmune disorder is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. ESR is often higher than normal in people with an autoimmune disorder (College of Physicians & Surgeons of Saskatchewan, 2012).

Very high ESR levels occur with less common autoimmune disorders, including:

- ❒ Allergic vasculitis
- ❒ Giant cell arteritis
- ❒ Hyperfibrinogenemia (increased fibrinogen levels in the blood)
- ❒ Macroglobulinemia - primary
- ❒ Necrotizing vasculitis
- ❒ Polymyalgia rheumatica

Lower-than-normal levels occur with:

- ❒ Congestive heart failure
- ❒ Hyperviscosity
- ❒ Hypofibrinogenemia (decreased fibrinogen levels)
- ❒ Low plasma protein (due to liver or kidney disease)
- ❒ Polycythemia
- ❒ Sickle cell anemia(College of Physicians & Surgeons of Saskatchewan, 2012).

Erythrocyte Sedimentation Rate and Tuberculosis

The determination of the Erythrocytic Sedimentation Rate provided it is done under very accurate technique and in constant conditions, helps us assess the progress and prognosis of a case of tuberculosis (Ganguli, Dutt, & Ghosh, 1954). Day (1940) introduced the determination of "Sedimentin Index" which he claimed to be better than the erythrocytic sedimentation rate. He recorded the fall of erythrocytes in the Westergren Sedimentation tube every 10 minutes, and plotted the readings on a time-distance curve as described by Cutler. Day showed that this curve is comprised of three periods:

i. The period of acceleration during which the erythrocytes are agglutinated into clumps
ii. The period of maximum fall

iii. The period of slowing due to packing of the clumps.

From the second period the maximum fall in millimeters per 100 minute scan be calculated. The logarithm of this maximal fall per 100 minutes is called by Day (1940) as the sedimentin index of the blood. Day (1939) has shown by increasing dilution of blood plasma that the logarithm of the maximal velocity is indirectly proportional to the amount of sedimentin present in the blood. Sedimentin is a generic term for fibrinogen, serum globulin and any other substances present in the plasma which causes sedimentation of the red blood cells, and the sedimentin index expresses in arbitrary units a quantitative measurement of the amount of sedimentin present in the blood. Day regards the sedimentin Index as a more sensitive test to assess the prognosis and activity of the underlying pathological process than the first hour Westergren Sedimentation Rate. Further it is not affected by any fluctuations in the count of the red blood cells.

A study was conducted with an aim to analyze the relationship between hematological and biochemical parameters and tuberculosis process activity time according to clinical complaint duration. It was found that, in relation to ESR and platelet count, values were higher in those with less clinical disease duration, as at the beginning of the tuberculosis process there is strong pro-inflammatory cytokine activity (IFN-γ & TNF-α) which stimulates expression of acute-phase proteins and thrombocytosis. With disease evolution, anti-inflammatory cytokine (IL-10) expression increases, which promote cooling down of inflammatory activity. Also, α_2 and γ-globulin values are much higher than normal in patients with less disease duration, although not statistically significant. The study showed some degree of relationship between higher ESR values and platelet counts in tuberculosis patients who presented less clinical duration, though Prospective studies are necessary to confirm this relationship (Oliva, *et al*., 2008). In another study it was shown that Erythrocyte Sedimentation Rate May Be an Indicator for Screening of Tuberculosis Patients for Underlying HIV Infection (Sarkar,*et al*., 2011).

1.9 Novel Detection Methods

1.9.1 Detection of LAM

A recent innovative approach that has been explored is the urinary detection of lipoarabinomannan (LAM). LAM is a 17.5-kD glycolipid component of the outer cell wall of mycobacteria. LAM is heat stable, cleared by the kidney, and detectable in urine. As a bacterial product, it has theoretical potential to discriminate active TB from latent infection, the former having higher quantities of bacteria. The sensitivity of urinary LAM in adults

varies widely (44%– 67%). Higher estimates have been reported in HIV-coinfected patients with advanced immunosuppression, presumably because of higher bacterial burden and increased frequency of disseminated disease. At present, there are limited data for urinary LAM in children (Shingadia & Novelli, 2003).

1.9.2 Detection of ALS

It has been revealed that that Bacille Calmette-Gue´rin (BCG) vaccine-specific IgG Antibodies in Lymphocyte Supernatant (ALS) can be used as a rapid diagnostic method for the identification of patients with active pulmonary TB in adults and in pediatric patients using BCG vaccine as an antigen (Raqib *et al.*, 2011). A study was conducted to validate the ALS method in the diagnosis of pulmonary TB among well-characterized patients with symptomatic respiratory diseases and healthy controls and to evaluate TB specific antigens other than BCG in the assay, and to explore methods to provide results more rapidly. Multiple TB antigens were used singly and in combination for evaluation in the ALS assay. Adult patients with suspected pulmonary TB who attended the National Institute of Diseases of the Chest and Hospital (NIDCH) in Dhaka, Bangladesh, were prospectively studied. This study was part of the WHO/TDR Tuberculosis Specimen Bank activity in which blood, sputum and urine specimens were collected from well-characterized TB patients. The sensitivity and specificity of the ALS assay was calculated using non-TB patients as controls. The findings of the prospective study show that simultaneous detection of antigens improves the diagnostic potential of the ALS assay; the modified method increases sensitivity and can provide results in 48 hours and enable detection of some cases of pulmonary TB that are not detectable by standard methods (Raqib *et al.*, 2011).

1.10 Case definitions

Case definition is necessary for:

- ❒ Correct choice of standard regimen
- ❒ Correct patient registration and reporting
- ❒ Cohort analysis
- ❒ Determining trends in the proportions of the different types of patients

Diagnosis of TB should be followed by specification of the type of TB or case definition. Case definition takes the following into account (World Health Organization, 2008):

- ❒ The anatomical site of disease (pulmonary or extra-pulmonary)
- ❒ The bacteriological results (smear-positive or smear-negative)
- ❒ The history of previous treatment (new or retreatment)

Anatomical site of the disease

The categories by anatomical site are pulmonary and extra-pulmonary TB (WHO Country Office for Bangladesh, 2009).

Bacteriological Status

Defining the smear status in pulmonary cases is important to:

- ❒ Identify smear-positive cases. These patients are the most infectious cases and usually have higher mortality;
- ❒ Record, report and evaluate programme performance (smear-positive cases are the cases for which bacteriological monitoring of treatment progress is most practicable.

Pulmonary TB is divided into smear-positive and smear-negative pulmonary cases. Smear-positive cases represent 65-70% of all pulmonary cases and more than 50% of all TB cases (WHO Country Office for Bangladesh, 2009).

Previous Treatment History

The treatment history is very important for proper categorization of the patient subsequently choosing the correct regimen.

- ❒ New – A patient who has never received anti- TB drugs or a patient who received anti- TB drugs for less than one month.
- ❒ Relapse – A patient previously treated for TB who has been declared "cured" (page 12) or "treatment completed" and is diagnosed with bacteriologically positive (smear or culture) tuberculosis(WHO Country Office for Bangladesh, 2009).

1.11 Factors increasing the risk of TB

1.11.1 Patient Related

- ❒ Age (children > young adults < elderly)
- ❒ First-generation immigrants from high-prevalence countries
- ❒ Close contacts of patients with smear-positive pulmonary tuberculosis
- ❒ Overcrowding: prisons, collective dormitories
- ❒ Chest radiographic evidence of self-healed tuberculosis
- ❒ Primary infection < 1 year previously

1.11.2 Associated diseases

- ❒ Immunosuppression-HIV, infliximab, high-dose corticosteroids, cytotoxic agents
- ❒ Malignancy (especially lymphoma and leukaemia)
- ❒ Type 1 diabetes mellitus
- ❒ Chronic renal failure
- ❒ Silicosis
- ❒ Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)
- ❒ Deficiency of vitamin D

1.12 Treatment of Tuberculosis

Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly; thus, are difficult to culture and may have to be treated for 6 months to 2 years. Resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol.

Aims of treatment

The aims of treating TB are:

- ❒ To cure the patient of TB
- ❒ To prevent death from active TB or its late effects
- ❒ To prevent relapse of TB
- ❒ To decrease transmission of TB to others
- ❒ To prevent the development of acquired drug resistance

It is currently estimated that about one-third of the world's population is infected with *M. tuberculosis*, with 30 million people having active disease. Worldwide, 9 million new cases occur, and approximately 2 million people die of the disease each year.

The basic principles of good TB treatment are:

i. Right combination of drugs to kill different bacterial populations
ii. Drugs are given for the right duration (several months) to kill the bacilli
iii. Drugs are given in the right dosage to achieve therapeutic but not toxic effect

Effective chemotherapy consists of two phases (WHO Country Office for Bangladesh, 2009):

i. The initial or intensive phase administered daily for two months in new cases and three months in re-treatment cases. The aim of this phase is to rapidly reduce and eliminate the multiplying bacilli without allowing the development of acquired resistance to the prescribed drugs. During the intensive phase, the tubercle bacilli are killed rapidly. The infectious patients quickly become non-infectious (within approximately two weeks).

ii. The continuation phase is essential to eliminate the remaining bacterial population. Drugs administered daily for the rest of the treatment duration according to category.

1.12.1 Commonly used Drugs

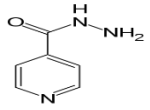
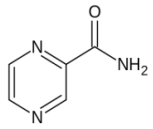
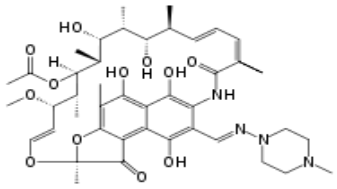
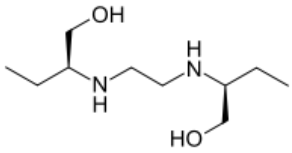
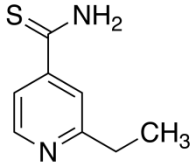
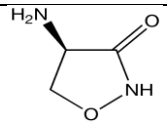
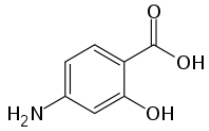
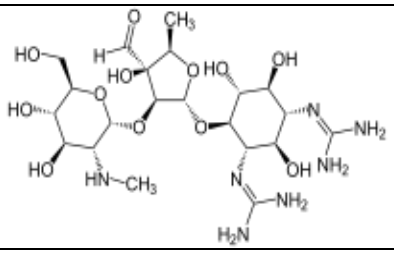
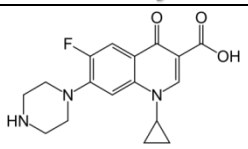
There are five key anti-tuberculosis drugs:

- ❒ Isoniazid
- ❒ Rifampicin
- ❒ Pyrazinamide
- ❒ Streptomycin
- ❒ Ethambutol

Second line drugs:

- ❒ Aminoglycosides: Amikacin, Kanamycin
- ❒ Polypeptides: Caprcomycin
- ❒ Quinolones: Ciprofioxacin, Ofioxacin
- ❒ Thioamides: Ethionamide&Prothionamide
- ❒ Paraminosalicyclic acid (PAS): Cycloserine

Table 1.5: TB Drug Name, Structure and Mechanism of Action

Drug	Structure	Mechanism of action
Isoniazid		Inhibit long chain fatty acid biosynthesis (FAS II) by inactivating InhA.
Pyrazinamide		1. Hydrolyze bacterial pyrazinamidase and retard bacterial growth. 2. Act as antimetabolite of Nicotinamide and interfere with NAD synthesis.
Rifampicin		Bind to the β-subunit of bacterial DNA Dependent RNA Polymerase (DDRP) and inhibit RNA synthesis.
Ethambutul		Inhibit arabinosyltransferase and retard micolic acid maturation in cell wall biosynthesis.
Ethionamide		Inactivates InhAenoylreductase in long chain fatty acid biosynthesis (FAS II).
Cycloserine		Inhibit alanine ligase and alanine recimase; inhibit cell wall synthesis.
Para-aminosalicylic acid		Inhibit folic acid biosynthesis.
Streptomycin		Binds with 16s RNA and inhibit protein synthesis.
Ciprofloxacin		DNA replication inhibition (topoisomerase inhibition).

(Harvey, 2008)

1.12.2 Strategies for Addressing Drug Resistance

Strains of *M. tuberculosis* that are resistant to a particular agent emerge during treatment with a single drug. For example, resistance rapidly develops in patients given only streptomycin. Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of resistant strains. Isoniazid, rifampin, ethambutol, and pyrazinamide are the principal or so-called "first-line" drugs because of their efficacy and acceptable degree of toxicity. Today, however, because of poor patient compliance and other factors, the number of multidrug-resistant organisms has risen. Some bacteria have been identified that are resistant to as many as seven anti-tubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs, preferably with both being bactericidal. The combination of drugs should prevent the emergence of resistant strains. The multidrug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms. For example, the initial short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months and then isoniazid and rifampin for the next 4 months. Before susceptibility data are available, more drugs may be added to the first-line agents for patients who have previously had tuberculosis or those in whom multidrug-resistant tuberculosis is suspected. The added drugs normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (injectable agents), a fluoroquinolone, and perhaps a second-line antituberculosis agent such as cycloserine, ethionamide, or p-aminosalicylic acid. Once susceptibility data are available, the drug regimen can be individually tailored to the patient. Patient compliance is often low when multidrug schedule last for 6 months or longer. One successful strategy for achieving better treatment completion rates is "directly observed therapy," also known as DOT, in which patients take their medication while being supervised and observed. DOT has been shown to decrease drug resistance as well as relapse and mortality rates and to improve cure rates. Most local and state health departments offer DOT services (Harvey, 2008).

1.12.3 The Role of Treatment in the Control of Tuberculosis

Treatment and cure of infectious cases of tuberculosis will interrupt transmission of TB infection in the community. Therefore, successful completion of treatment is the most effective way of prevention of TB (WHO Country Office for Bangladesh, 2009).

Fixed-dose combinations (FDCs)

Tablets of fixed-dose drug combinations have several advantages over individual drugs:

a) Prescription errors are likely to occur less frequently because dosage recommendations are more straightforward and adjustment of dosage according to patient weight is easier.
b) The number of tablets to ingest is smaller and may thus encourage patients' adherence. A new smear-positive patient of 38-54 kg body weight has to take three tablets of 4-FDC daily during the intensive phase of treatment. In case of loose drugs this would be nine tablets.
c) Drug resistance is less likely to occur; patients swallow all drugs and cannot skip any particular drug (WHO Country Office for Bangladesh, 2009).

Table 1.6: Standardized treatment regimen for each diagnostic category (Adults) (WHO Country Office for Bangladesh, 2009)

TB diagnostic category	Patient Category	Treatment regimen	
		Intensive phase (Daily)	Continuation Phase (Daily)
I	❒ New smear (+) positive PTB patients ❒ New smear (-) negative PTB patients ❒ Extra-pulmonary TB patients ❒ Concomitant/associated HIV/AIDS	2(HRZE)	4(HR)
II	❒ Sputum smear (+) positive PTB with history of treatment of more than one month ❒ Relapse ❒ Treatment failure after Cat. I ❒ Treatment after default ❒ Others	2(HRZE)S/ 1(HRZE)	5(HR)E

(WHO Country Office for Bangladesh, 2009)

1.12.4 Start of Treatment

Treatment should be started as soon as possible after the diagnosis is made. Treatment should only be started after a confirmed diagnosis has been made. The responsible medical officer/graduate physician should categorize the patient. A paramedical staff may fill in the

treatment card and register the patient in the TB register and maintain other documents related to diagnosis of the patients. The first dose of drugs should be given at the respective health facility, where after the patient is referred to the DOT provider. At the time of start of treatment all drugs for the whole course of treatment (intensive and continuation phase) of the respective patient should be ensured. In case of transfer or death of a patient, the remaining drugs should be returned and added to the general stock. The medical officer or TB manager/supervisor should weekly review and cross check the TB register with the laboratory register to ensure that all patients diagnosed in the laboratory are registered and enrolled for treatment (WHO Country Office for Bangladesh, 2009).

Patients who are smear-positive according to the laboratory register but did not begin treatment should be traced within two weeks after the laboratory result is available. Adherence to treatment Patient compliance is a key factor to treatment success. A proportion of patients stop treatment before completion, for various reasons so strict adherence to treatment should be ensured to cure the patients and prevent the development of drug-resistant TB. Directly observed treatment (DOT) is a very important component in the internationally recommended policy package for TB control (DOTS strategy). DOT means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures that the patient takes the right anti-TB drugs, in the right doses, at the right intervals and for the right period. All patients, irrespective the treatment category, should receive all doses of the anti-TB drugs under DOT. Ambulatory versus hospital treatment Over 95% of the patients can be treated as ambulatory TB cases (WHO Country Office for Bangladesh, 2009). Hospitalization itself has little or no effect on the outcome of the treatment except in severe forms of tuberculosis. Hospitalization may be necessary if the patient cannot receive ambulatory treatment under direct observation. In-patient treatment may also be necessary (often only for a short period) for severely ill patients, e.g. tuberculosis with complications viz. severe hemoptysis (bloodstained sputum), spontaneous pneumothorax (air in the inter-pleural space resulting in collapse of the lung) or for those with other associated serious diseases (WHO Country Office for Bangladesh, 2009).

1.12.5. New smear positive patients

One sputum specimen should be examined at the end of month 2, 5 and 6 after the start of treatment. The sputum at six months can also be collected during the last two weeks of treatment. Patients whose sputum is positive at month 2 should continue the intensive phase for one more month. After one month of extended intensive phase, one specimen of sputum

should be examined and the patients be put on the continuation phase, regardless of the smear result. In case of extension of the intensive phase based on positive smear results, the duration of the continuation phase will remain the same; hence the total treatment period will be extended by one month. If the sputum is positive at month 5 or 6 the outcome will be registered as treatment failure. The patient must be re-registered as "treatment after failure" and be treated with a course of Category II regimen (WHO Country Office for Bangladesh, 2009).

1.12.6 Retreatment of smear-positive patients

One specimen of sputum of patients treated with Category II regimen should be examined at the end of month 3, 5 and 8. The sputum at eighth month can also be collected during the last two weeks of treatment. Patients whose smear is positive at month 3 should continue the intensive phase for one more month. After one month of extended intensive phase, one specimen of sputum should be examined and the patients be put on the continuation phase, regardless of the smear result at month 4. In case of extension of the intensive phase based on positive smear 24 results, the duration of the continuation phase will remain the same; hence, the total treatment period will be extended by one month. If the smear is still positive at month 5, patient should continue Category II treatment and meanwhile necessary steps should be taken for sputum culture and DST. If the patient remains smear positive after completion of the entire course of the treatment, the patient is no longer eligible for a new re-treatment regimen. In this case, the outcome will be recorded as "treatment failure" and the patient be considered as a "chronic case" and referred to a specialized hospital for further interventions (WHO Country Office for Bangladesh, 2009).

1.12.7 Smear negative and extra-pulmonary patients

One specimen of sputum should be examined of smear-negative pulmonary TB at the end of month 2 to ensure that they remain negative. In case the smear is positive (a second smear should confirm the result), the patient should be put on Category II treatment and be re-registered as failure. If the sputum is negative the patients should continue the treatment and progress of the patient should be assessed clinically. In case of extra-pulmonary TB, no smear examination is necessary and the patients should be assessed clinically. Follow-up of patients after completion of treatment is not needed (WHO Country Office for Bangladesh, 2009).

Management of side effects or adverse reactions related to the use of anti-tuberculosis drugs
Most TB patients complete their treatment without any significant adverse effects of drugs.

However, a few patients do experience adverse effects. Patients sometime discontinue the treatment due to major or even minor adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary. Health workers/ DOT providers can monitor side effects of drugs by teaching patients how to recognize symptoms of common side effects and to report if they develop such symptoms, and by asking about symptoms when the patients report to collect drugs.

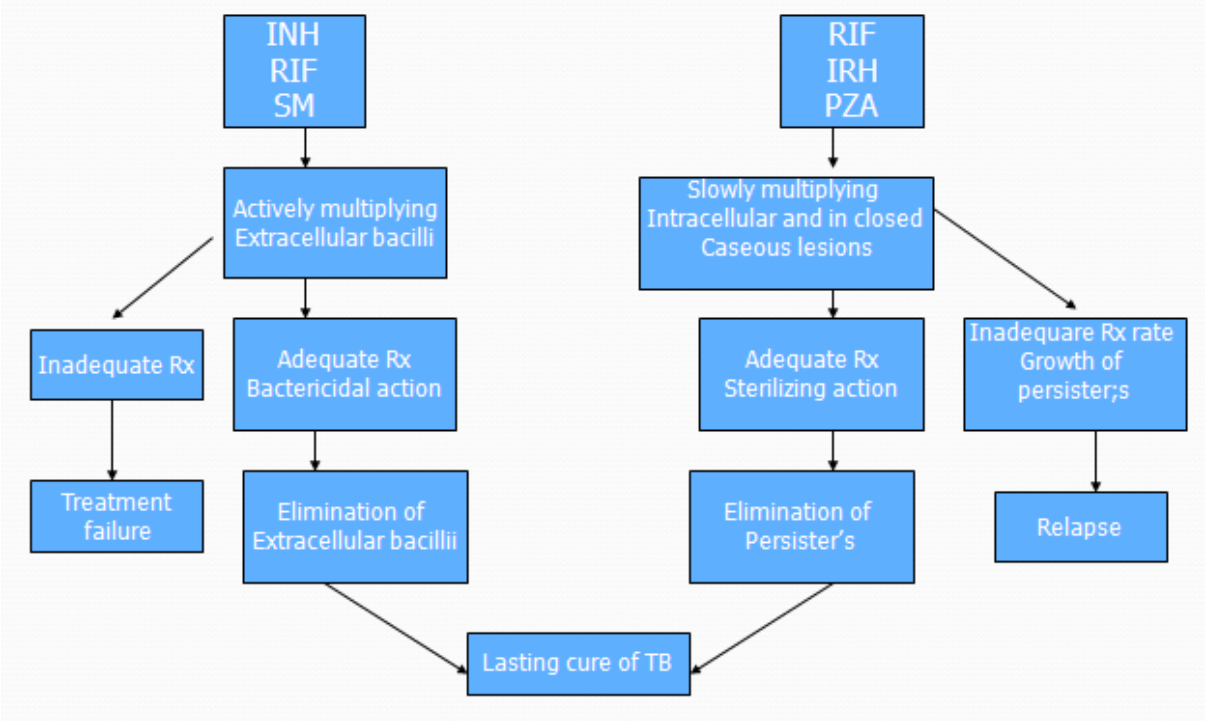


Figure1.6: Principles of Modern Chemotherapy of Tuberculosis (WHO Country Office for Bangladesh, 2009)

1.13 Tuberculosis Control

The latest data suggest (i) that the incidence rate has been falling since 2004, (ii) that prevalence and death rates will be halved in at least three of six WHO regions by 2015 compared with a baseline of 1990, but that these targets will not be achieved for the world as a whole, (iii) that the case detection rate reached 63% in 2007 and (iv) that the treatment success rate reached 85% in 2006 (World Health Organization, 2009).

1.14 Methods of Prevention

Two landmark documents in global TB control – the Stop TB Strategy and the Global Plan to Stop TB – were launched in 2006. The Stop TB Strategy, developed by WHO, sets out the

interventions that need to be implemented to achieve the MDG. The Stop TB Strategy is WHOs recommended approach to reducing the burden of TB in line with global targets (World Health Organization, 2009).

1.14.1 The Six Major Components of the Strategy

- ❒ Pursue high-quality DOTS expansion and enhancement;
- ❒ Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations;
- ❒ Contribute to health system strengthening based on primary health care;
- ❒ Engage all care providers;
- ❒ Empower people with TB, and
- ❒ Communities through partnership; and enable and promote research.

The Stop TB Partnerships Global Plan to Stop TB, 2006–2015 sets out the scale at which the interventions included in the Stop TB Strategy need to be implemented to achieve the 2015 targets.

The combination of preventive latent therapy and a 2-month drug treatment regimen reduces incidence by 94%. Novel technologies in the pipeline would achieve substantial reductions in TB incidence, but not the Stop TB Partnership target for elimination. Elimination will require new delivery strategies, such as mass vaccination campaigns, and new products targeted at latently infected people (Abu-Raddad *et al.*, 2009). Tuberculosis (TB) control in the world today must face the challenge posed by the global spread of Mycobacterium tuberculosis strains that are resistant to standard anti-TB drugs (Falzon *et al.*, 2011).

It is estimated that, 3% of incident new TB cases in the world have multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampicin, the two most effective anti-TB drugs. Around 440,000 MDR-TB cases (95% CI 390,000– 510,000) are estimated to emerge annually among new and retreated TB patients. The frequency of MDR-TB varies according to region and is much higher among previously treated patients. Amongst the vast majority of MDR-TB patients, very little is known about their access to quality care. Treatment of MDR-TB is complex and uses toxic drugs that must be administered for a longer duration than for drug-susceptible TB patients, with a lower likelihood of treatment success (Orenstein *et al.*, 2009).

In 2009, in recognition of the threat posed by drug-resistant TB to global public health security, the World Health Assembly urged Member States to achieve universal access to diagnosis and treatment of patients with this form of disease. The WHO was mandated to provide technical support to countries for the development and implementation of national

frameworks of care for drug-resistant TB patients. The production of guidelines for the programmatic management of drug-resistant TB is part of this role. WHO has previously developed guidelines on this subject, which were based on an assessment of available evidence and best practice by a large group of TB specialists.

1.15 Vaccination Development

The search for a vaccine against tuberculosis began 110 years ago with great expectations. Only 8 years after discovering the tubercle bacillus in 1882, Robert Koch devised a subunit vaccine for the treatment of tuberculosis, a disease that constituted the worst threat to mankind at the time. This therapeutic vaccine completely failed. The second attempt was initiated 10 years later by the French scientists Calmette and Guérin. After more than 200 passages, they obtained an attenuated strain of *M. bovis*, the etiological agent of cattle tuberculosis, which can, though rarely, cause tuberculosis in humans. This attenuated vaccine, now termed BCG (from Bacille Calmette–Guérin) proved more successful. After more than 3 billion administrations, it is still in use today. However, it did not match the expectations it evoked. Although BCG prevents disseminated tuberculosis in newborns, it fails to protect against the most common form of the disease, pulmonary tuberculosis in adults. The Bacille Calmette-Guérin (BCG) vaccine is recommended as soon as possible after birth. The vaccine is known to prevent the more severe types of TB such as TB meningitis and miliary TB. However, the efficacy of the vaccine in general ranges from 0% to 80%. The reasons for this variability are: different types of BCG used in different countries, differences in the strains of *M tuberculosis* prevailing in different regions, different levels of exposure, etc. Revaccination offers no added protection, and is therefore not recommended (WHO Country Office for Bangladesh, 2009).

Satisfactory control of tuberculosis can only be achieved using a highly efficacious vaccine. Tuberculosis is particularly challenging for the immune system. The intracellular location of the pathogen shields it from antibodies, and a variety of T-cell subpopulations must be activated to challenge the bacterium's resistance to antibacterial defense mechanisms. The combined information from recent studies of natural infection with *M. tuberculosis* and vaccination with BCG, combined with information from the *M. tuberculosis* genome, transcriptome and proteome, offer good prospects for the development of an efficacious new vaccine (Kaufmann, 2001).

1.16 TB-HIV Co-Infection

Tuberculosis (TB) is the major opportunistic infection of acquired immunodeficiency syndrome (AIDS) in developing countries. One in four tuberculosis (TB) deaths in the world are HIV-related, twice as many as previously thought, according to a new report by the World Health Organization. Approximately 1/3rdof HIV-infected persons are co-infected with TB (Mahmood, 2010).Africa represents the continent with the highest incidence and the most HIV co-infection (Orcau *et al.*, 2011). TB/HIV co infection denotes two diseases in one body. There is a positive co-relation between TB incidence and HIV prevalence. Generally, the lifetime risk of developing active TB is around 10 percent while for TB/HIV co infection the risk is around 60 percent. HIV is the most powerful known risk factors for reactivation of latent tuberculosis to active disease, HIV infected people are most susceptible to be TB when they are exposed to Mycobacterium Tuberculosis, HIV increase the rate of recurrent TB, TB-HIV cases poses an increased risk of TB transmission to the general community, whether or not HIV infected. The estimated TB/HIV co-infection is 0.1% according to the study done on a sample of 1000 patients in Dhaka. Although the data show, by now, a low HIV prevalence in TB patients while the TB prevalence in PLHIV is high, the country situation with its 50% of population infected by TB called for a rationale for collaboration between TB and HIV activities. Considering the facts, functional collaboration has been established between NTP and NASP for implementing the collaborative TB/HIV programmes (WHO Country Office for Bangladesh, 2009). According with the WHO guidelines and the Bangladesh country profile, Bangladesh is classified in category 2 in TB/HIV collaboration model for two reasons: the national country adult HIV prevalence is below 1% and there is area with adult prevalence rate higher than 1%. According to these criteria TB/HIV activities need to be established as TB/HIV Co-infection burden in different administrative and geographic setting (World Health Organization, 2011). In national context to identify the trend of TB/HIV co-infection burden and to design the activities National Survey for TB in HIV patient to be done 2-3 yearly. Considering all facts a country specific National Guideline on TB/HIV Programme Collaboration has been developed (WHO Country Office for Bangladesh, 2009).

1.17 Molecular Epidemiology of Tuberculosis

A combination of molecular biology and conventional epidemiology, molecular epidemiology has been used to provide novel information about the spread of tubercle bacilli in mini-epidemics and outbreaks, analyse the transmission dynamics of tuberculosis (TB) and

determine the risk factors for TB transmission in a community. It is also being used to track the geographic distribution and spread of clones of Mycobacterium tuberculosis of public health importance (Banu *et al*., 2012).

The most frequently used genotyping methods for M. tuberculosis are restriction fragment-length polymorphism (RFLP), which targets the insertion sequence (IS) 6110 transposable element, and spoligotyping. RFLP analysis using IS6110 as a probe has long been considered the gold standard (Van Embden *et al*., 1993).

A most recent study of Bangladesh suggest that TB in rural Bangladesh is caused primarily by reactivation of latent infections (Banu *et al.*, 2012).

Asia (the South-East Asia and Western Pacific regions) accounts for 55% of global cases and the African Region for 31%; the other three regions (the Americas, European and Eastern Mediterranean regions) account for small fractions of global cases. The magnitude of the TB burden within countries can also be expressed as the number of incident cases/100000 population. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, a phenomenon linked to high rates of HIV confection (Banu *et al.*, 2012).

1.18 Bangladesh Situation

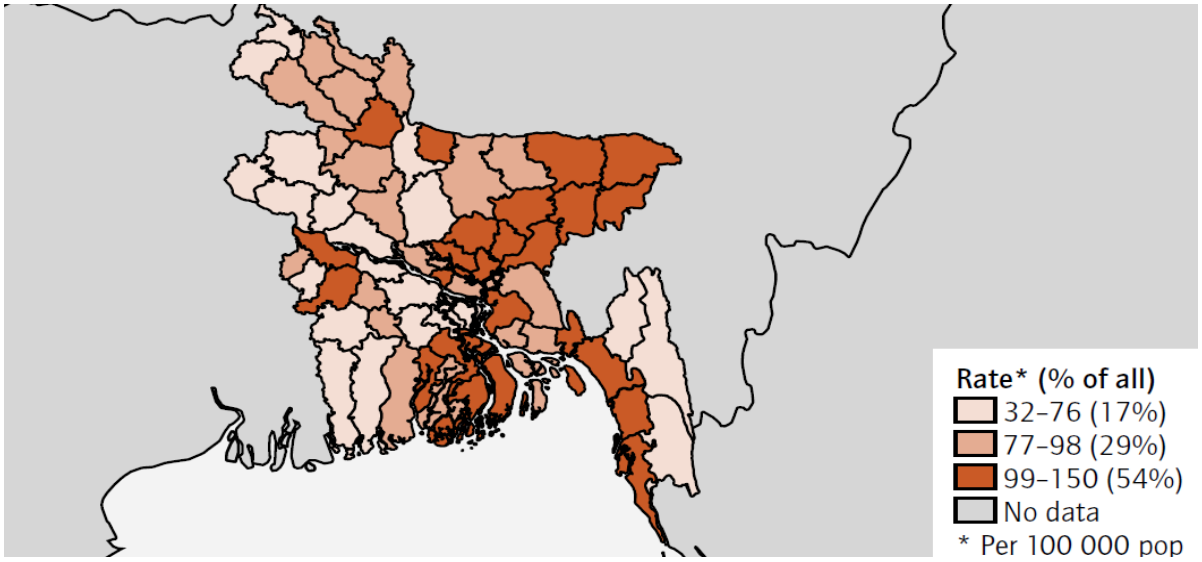


Figure 1.7: TB notification rate (new and relapse), 2007 (World Health Organization, 2009)

Bangladesh increased the case detection rate of new smear-positive cases to 66% in 2007 and has maintained a treatment success rate exceeding 90% since 2004. The provision of EQA has expanded to almost all peripheral-level laboratories. Support from the GDF has secured an uninterrupted supply of drugs. Community-based DOTS through village doctors (Damien

Foundation) and community health volunteers (BRAC) ensures supervised drug intake. Programmatic guidelines for MDR-TB and TB/HIV were developed in 2008. The Damien Foundation expanded its MDR-TB treatment project and supported the development of a regional reference laboratory, and the NTP will soon begin enrolling patients in an MDR-TB treatment programme (World Health Organization, 2009). Major challenges include limited capacity for diagnosis of smear negative and extra pulmonary TB, and MDR-TB. Weak coordination among health-care providers is a major challenge for TB control in large urban areas. The latest WHO estimates (2005) of the TB incidence, prevalence and mortality are summarized in Table 1.7 WHO estimates on TB in Bangladesh (2005).

Table 1.7: WHO estimates (2005) of the TB incidence, prevalence and mortality

	Number of cases	Percentage of rate per 100000 population (95% CI)	
Incidence of all TB cases	321936	227	(165-294)
Incidence of new smear positive TB cases	144658	102	(73-135)
Prevalence of all TB cases	575797	406	(286-524)
TB mortality	66656	47	(33-64)
Adult TB cases that are HIV-positive	n.a.	0.1%	(0-0.1)
MDR among new cases of TB	5800	1.8%	(0.3-9.7)

Source: WHO Report 2007 – Global Tuberculosis Control; National Tuberculosis Control Programme, Bangladesh, Report of the Fourth Joint Review, 17–28 October 2007 (World Health Organization, 2008)

Table 1.8: Case Notification 2010

New cases	n	(%)	Retreatment cases	n	(%)
Smear-positive	105772	70	Relapse	2989	38
Smear-negative	21625	14	Treatment after failure	961	12
Smear unknown	0	0	Treatment after default	594	8
Extra-pulmonary	23506	16	Other	3251	42
Other	0	0			
Total new	150903		Total retreatment	7795	
Total < 15 years	4235				
Total new and relapse			153892	(97 % of total)	
Total cases notified			158698		

(World Health Organization, 2011)

Significance of the Study

Tuberculosis (TB) is a major public health problem in Bangladesh. In 2008, the World Health Organization (WHO) ranked Bangladesh 6th among the world's 22 high-burden TB countries (USAID, 2009). About one-third of the world's population is believed to be latently infected with *M. tuberculosis*. Emerging mycobacterial drug resistance is further complicating the situation. Studies have shown that ESR may be an indicator for screening tuberculosis patients (Oliva, *et* al., 2008; Sarker, *et al.*, 2011). Prospective studies like this are necessary to confirm this relationship. In DOTS programs, AFB-microscopy is the only recommended technique for diagnosis of tuberculosis as well as follow-up of patients during treatment (WHO Country Office for Bangladesh, 2009). To the best of our knowledge there was no such study conducted on Bangladesh to observe the hematological status of tuberculosis patients and the change in patients medical condition (AFB smear test) followed by diagnosis records. In a public health context, these methods are recommended because they return the highest yield for the lowest expenditure of resources, and consider clearly defined, justifiable objectives.

Objective of the Study

The objectives of this study were to-

- ❒ Observe the hematological status of tuberculosis patients admitted in National Institute of Diseases of the Chest and Hospital (NIDCH).
- ❒ Observe the change in patients' medical condition (AFB smear test) followed by diagnosis records after one month.

2.1 Method

This study was done on tuberculosis patients admitted in NIDCH who have been diagnosed with tuberculosis by AFB Microscopy test or radiological test. Along with a semi-structured questionnaire, a verbal informed consent was taken from each of the study patient admitted in that hospital. After having consent, socio-demographic information and bio-chemical (diagnostic data from medical records) information was collected. All the wards of the hospital were visited for this purpose. Patients were selected based on their willingness to have a follow up sputum smear test after one month period. In addition to AFB Microscopy test results, patient's hematological data was be collected from medical reports. Along with AFB microscopy results, CBC with ESR test report was also collected. Each of the patients was debriefed appropriately. Support from the hospital stuff was taken. Proper protection was taken e.g., both patients and researcher wore masks.

After one month, patients were given calls for the purpose of follow up. They were also asked about their adherence to treatment. The diagnostic questions were applied again to collect acid-fast bacillus (AFB) smear test information to observe their disease status.

2.2 Study place

The study was conducted at National Institute of Diseases of the Chest and Hospital (NIDCH). NIDCH is a state supported research institute and hospital in Bangladesh. It was established in 1955 as TB Hospital. In 1962 it was upgraded as National Chest Diseases Institute. It is a tertiary level hospital specially designed to treat difficult TB cases like smear negative cases, MDR-TB cases, chronic and relapse cases and also extra pulmonary TB cases.

2.3 Research approach

After having approval of the research proposal from the respected research supervisor, permission was obtained from Hospital Director, National Institute of Diseases of the Chest and Hospital.

2.4 Inclusion criteria

- Male and female patients diagnosed with TB
- Patients within the age of 18-60 years

- Patients who were admitted in NIDCH i.e., indoor patients

2.5 Exclusion criteria

- Outdoor patients
- Patients below the age of 18 years i.e., children
- MDR TB patients

2.6 Study type

It is a prospective study.

2.7 Study Period

The study period was 1 year. The study started with data collection from tuberculosis patients at NIDCH. After month long data collection, the patients were subjected to a second AFB smear microscopy test.

2.8 Sample size

The sample size for this study was 22. Among the 22 patients, 7 patients were diagnosed in a follow up AFB smear test after one month.

2.9 Sampling technique

It was a Simple Random Sampling. A semi structured questionnaire was used for the purpose of data collection.

2.10 Study Population

The target population for this study was tuberculosis patients admitted in NIDCH who have been diagnosed with tuberculosis by AFB Microscopy test or radiological test.

2.11 Data analysis

After collection of data, all data was checked. Data was analyzed with the help of Microsoft excel and SPSS to compute frequency distribution, mean, mode, median and also standard deviation (SD) based on different parameters in the questionnaire. Data sets were presented in both in tabular form and graphically using pie chart, histogram etc.

Table 3.1: Distribution of tuberculosis patients according to their age:

Age Groups (Years**)**	**n (%)**
<30	11 (50.0)
31-40	3 (13.6)
41-50	3 (13.6)
>50	5 (22.7)
(Mean ±SD)	36 ± 15

The above table (Table 3.1) depicts the distribution of patient's age. Column percentage is shown here. It shows that the age group <30 years (50 %) is mostly affected with TB. The mean value of age was found to be 36 ± 15 indicating TB hits the most economically productive age group hardest. Thus the epidemic has a devastating economic as well as social impact.

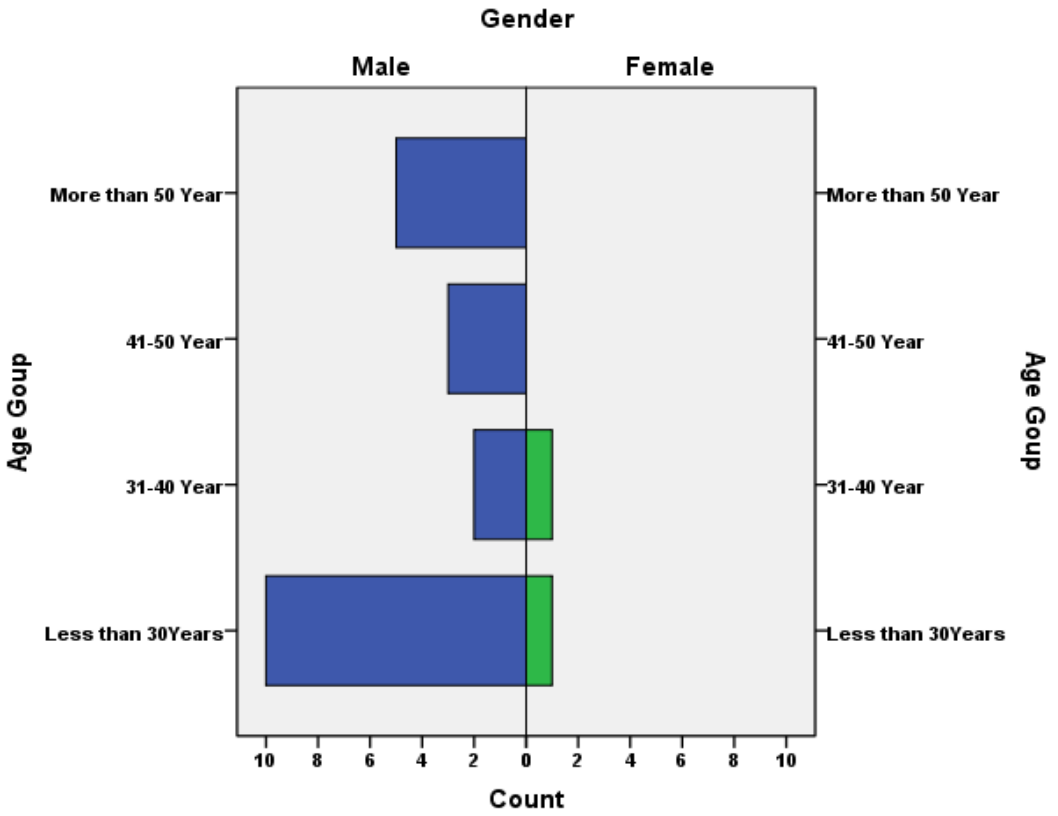


Figure 3.1: Distribution of patients' age according to gender

From the population pyramid (Figure 3.1) it is illustrated the distribution of age in accordance with gender where male were disproportionately distributed in all age groups except female (2 in number) found to be younger and the contribution compared to male were less in number which indicates the beneficiary effect in a sample of urban hospital.

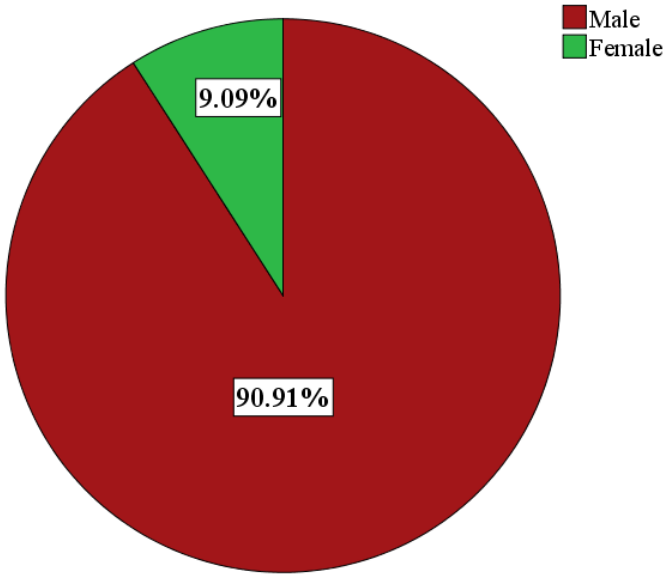


Figure 3.2: Gender distribution in tuberculosis patients

Figure 3.2is a pie chart showing 90.9% (20) patients were male and 9.1% (2) patients were female which indicates menare more commonly affected by TB than women. This result may be due to small sample size which is not consistent with national representative sample.

Table 3.2: Distribution of patients' educational status

Educational status	n (%)
Illiterate	5 (22.7)
< Class 5	7 (31.8)
Class 5- SSC	6 (27.3)
HSC	4 (18.2)

From the Table 3.2 it was observed that 22.7% (5) patients were illiterate whereas most patients (31.8%) dropped out of schools before completing primary education.

Table 3.3: Distribution of tuberculosis patients according to area of residence and social status

Area of Residence	n (%)	Social status	n (%)
Rural	5 (22.7)	Poor	4 (18.2)
Semi-urban	9 (40.9)	Lower Middle	7 (31.8)
Urban	8 (36.4)	Middle	11 (50.0)

In table 3.3 it is also observed that 50 % of the patient belongs to middle class whereas 31% belongs to lower middle class and 18.2% patients were poor. There is abundant evidence that poverty increases vulnerability to TB. The malnutrition, overcrowding, poor air circulation, and unhygienic sanitation facilities commonly experienced by the poor all increase the probability of TB infection.

Table 3.4: Relationship between Patients area of residence and social status

Area of Residence	Poor	Lower Middle	Middle	P value
Rural	3 (60.0%)	2 (40.0%)	0 (0.0%)	.012*
Semi-urban	1 (11.1%)	4 (44.4%)	4 (44.4%)	
Urban	0 (0.0%)	1 (12.5%)	7 (87.5%)	

Pearson's chi-squared test ($\chi 2$)
**Significant at the 0.05 level*

From the cross tabulation ($\chi 2$), major poor TB patients admitted from the rural areas (60%) whereas most of the urban patients (87.5%) were found to be from middle class family and no poor class urban patients (0%) were admitted during that period. The association was found to be significant *($p = 0.012$).*

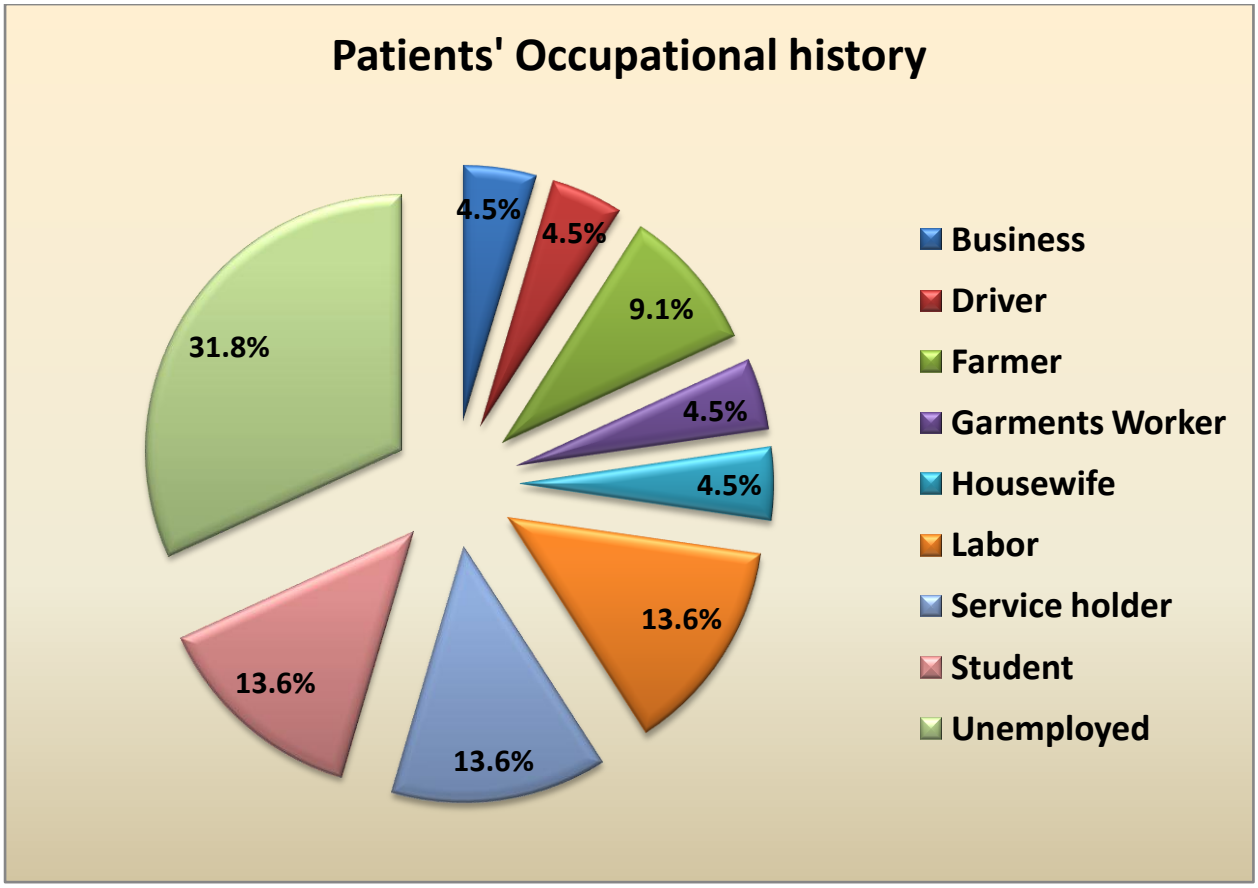


Figure 3.3: Distribution of tuberculosis patients according to occupational history.

Figure 3.3 shows distribution of tuberculosis patients according to occupation. Majority of the patients (31.8%) in Figure 3.6 were unemployed. Tuberculosis decreases individual's capacity to work.

Table 3.5: Distribution of patient's weight

	Weight in KG
Mean ± SD	38.86 ± 4.873
Median	38.50
Mode	40
Minimum	30
Maximum	50

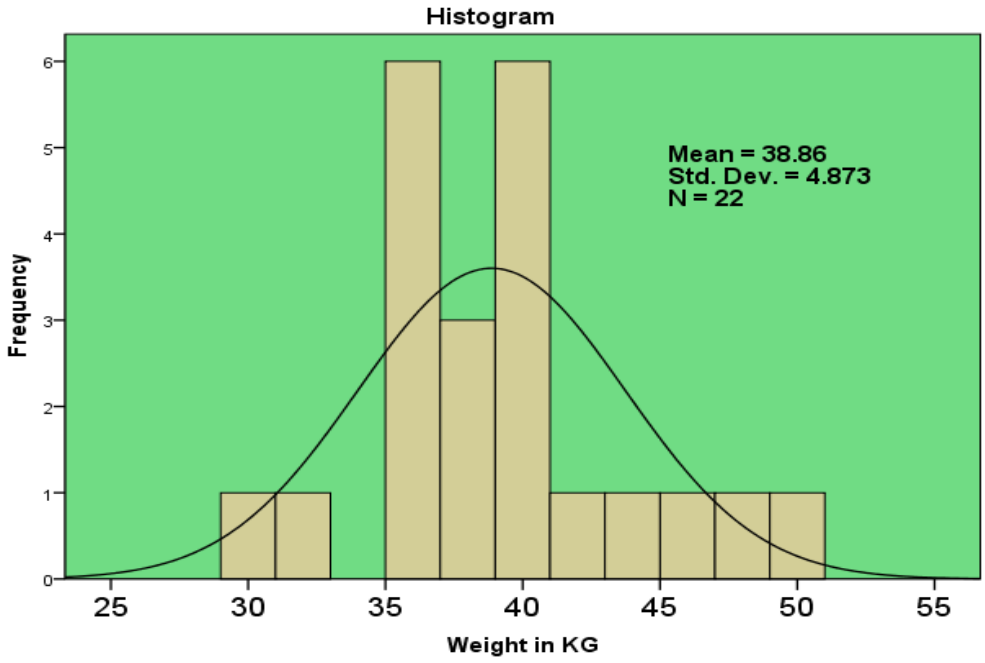


Figure 3.4: Distribution of patient's weight

Figure 3.4 shows that weight of 22 tuberculosis patients was normally distributed. The range lies between 30 KG and 50 KG respectively. The Mean ± SD of the weight of patients is found to be 38.86 ± 4.873 (Table 3.5). The median value for the data set is 38.5. The mode value is 40 meaning the most of the patients' body weight was 40 KG indicating malnutrition is a risk factor for TB. Adhering to the six-month TB treatment regimen is a challenge for patients who are malnourished.

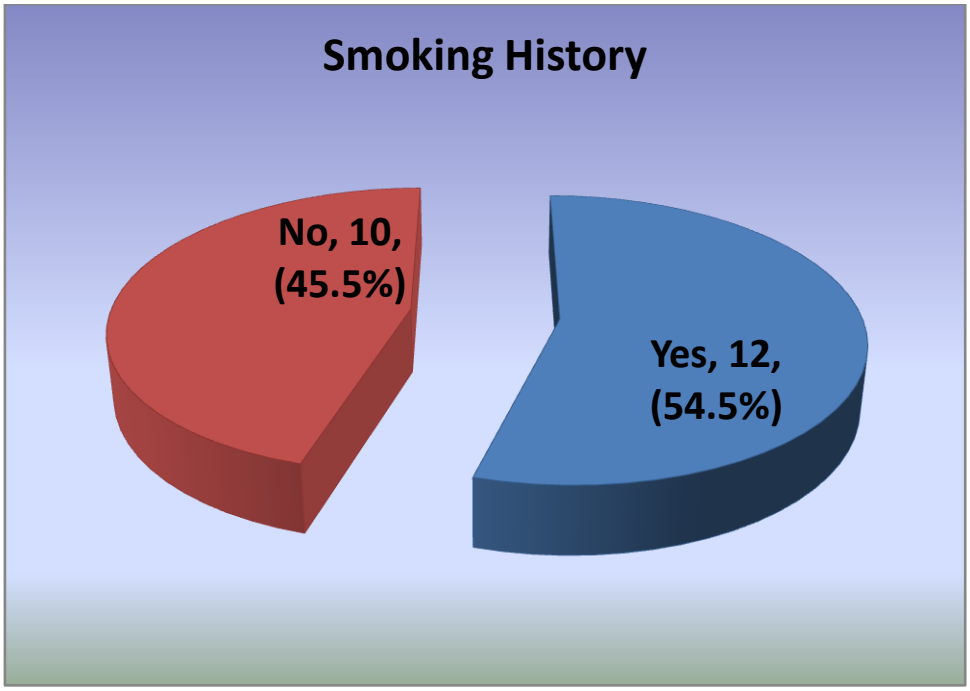


Figure 3.5: Distribution of tuberculosis patients according to smoking history

Figure 3.5 shows distribution of tuberculosis patients according to smoking history. 54.5% patients were former smokers. Smoking is a risk factor for tuberculosis. This result shows smokers are more likely to be affected by tuberculosis than non-smokers.

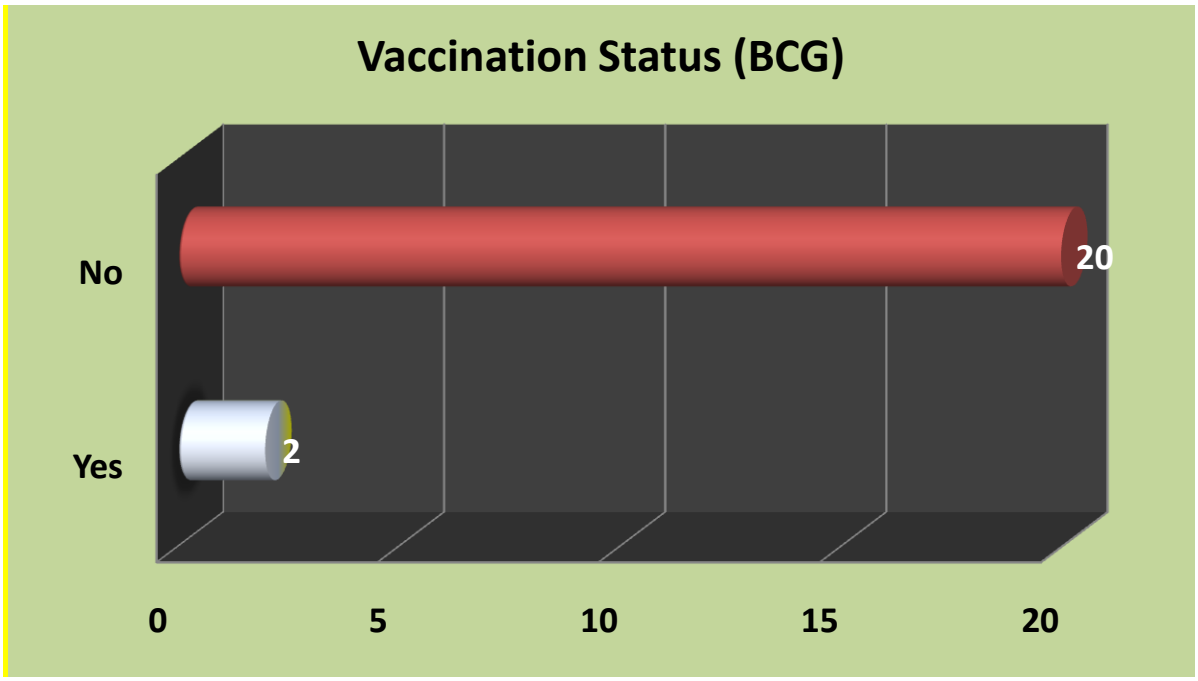


Figure 3.6: Vaccination status among tuberculosis patients

Among the tuberculosis patients (Figure 3.6) 9.1% patients were vaccinated whereas 90.9% were not.

Table 3.6: Patients' Hematological Report

Hematological Report

	Hb (Gm/dl)	TWBC (/cmm)	PC (/cmm)	HCT (PCV) (%)	ESR (mm1st hr)
Mean	11.03[a]	10081.81[a]	376318.18[a]	35.72[a]	58.18[a]
Median	10.65[a]	10750.0	356500	34.70	62.50
Mode	10.40[a]	8900.00[a]	346000	39.60	40.00[a]
SD	2.47[a]	2747.05[a]	1.34[a]	6.27[a]	25.73[a]
Range	9.5	10200	506000	21.40	85
Minimum	6	3900	193000	25.50	10
Maximum	15.50	14100	699000	46.90	95

a. Multiple modes exist. The smallest value is shown

Table 3.6 representing distribution of Hematological report of haemoglobin (iron-containing oxygen-transport metalloprotein in the red blood cells of all vertebrates) (Mean ± SD; 11.03 ± 2.47), Total White Blood Count, (Mean ± SD; 10081.81 ± 2747.05), Platelet count (Mean ± SD; 376318.18 ± 1.34), Hematocrit (HCT) or Packed Cell Volume (PCV) (fraction of whole blood volume that consists of red blood cells) (Mean ± SD; 35.72 ± 6.27) and Erythrocyte sedimentation rate (ESR; the rate at which red blood cells sediment in a period of 1 hour) (Mean ± SD; 58.18 ± 25.73). Other values are presented in the table.

Table 3.7: Distribution of tuberculosis patients according to normal & abnormal hematological indices:

			n (%)
Anemia	Yes	-	18 (81.8)
	No	-	4 (18.2)
TWBC (/cmm)	Normal	4000-11000	11 (50.0)
	Low	<4000	1 (4.5)
	High	>11000	10 (45.5)
PC (/cmm)	Normal	150000-450000	16 (72.7)
	High	>450000	6 (27.3)
HCT (PCV) (%)	Normal Range	M=42-52, F=37-47	4 (18.2)
	Low	M=<42, F=<37	18 (81.8)
ESR (mm1st hr)	Normal	M=0-15, F=0-20	1 (4.5)
	High	M=>15, F=>20	21 (95.5)
Neutrophil (%)	Normal	60-75%	9 (40.9)
	Low	<60%	5 (22.7)
	High	>75%	8 (36.4)
Lymphocytes (%)	Normal	20-30%	8 (36.4)
	Low	<20%	8 (36.4)
	High	>30%	6 (27.3)
Monocytes (%)	Normal	2-8%	18 (81.8)
	Low	<2%	1 (4.5)
	High	>8%	3 (13.6)
Eosinophil (%)	Normal	1-6%	20 (90.9)
	High	>6%	2 (9.1)
Basophil (%)	Normal	0-1%	20 (90.9)
	High	>1%	2 (9.1)

Among the tuberculosis patients in Table 3.7, 81.8% had anemia. A number of 11 (50%) patients had normal TWBC count whereas 10 (45.5%) patients had higher TWBC value. 21.7% patients had higher PC count where most of the patients (72.7%) had PC count within normal range of 150000-450000/cmm(College of Physicians & Surgeons of Saskatchewan, 2012).

Majority of the patients (81.8%) had lower HCT (PCV) value. Among the tuberculosis patients 4.5% had normal ESR with the normal range M=0-15, F=0-20 mm after 1sthr (College of Physicians & Surgeons of Saskatchewan, 2012).On the other hand, 95.5% patients had higher ESR value which is diagnostically useful to detect tuberculosis since higher ESR rate may be due to this infectious disease.

40.9% patients had normal neutrophil (60-75%) count. 22.7% patients had a low neutrophil count (<60%) while 36.4% patients had a higher neutrophil count (>75%). Among the TB patients 27.3% had a higher lymphocyte count (>30%). Among the tuberculosis patients 81.8% had normal count of monocytes (2-8%). 90.0% patients had a normal eosinophil count (1-6%). A total of 20 patients (90.9%) had their basophil count within normal range.

Table 3.8: AFB Microscopy Examination of follow up patients (n=7)

AFB Microscopy Examination		Baseline (Initial Diagnosis)		After one month	
		Count	(%)	Count	(%)
AFB Specimen 1	Negative	1	14.3	7	100
	Scanty (1-9)	0	0	0	0
	1+	3	42.9	0	0
	2+	3	42.9	0	0
	3+	0	0	0	0
AFB Specimen 2	Negative	0	0	4	57.1
	Scanty (1-9)	2	28.6	1	14.3
	1+	2	28.6	1	14.3
	2+	2	28.6	1	14.3
	3+	1	14.3	0	0.0
AFB Specimen 3	Negative	0	0	4	57.1
	Scanty (1-9)	2	28.6	1	14.3
	1+	1	14.3	1	14.3
	2+	2	28.6	1	14.3
	3+	2	28.6	0	0

The table 3.8 above shows a combination of the two main quantification scales for the AFB microscopic examination and here AFB smear distribution according to specimen is presented. In the initial diagnosis of all three specimens, only one patient was negative that is no AFB was found in 100 fields. After one month 16 negative specimens were found and for specimen 1, it was 100%. In both initial and follow up diagnosis of AFB specimens, no specimen was found to be scanty that is 1-9 AFB per 100 fields whereas specimen 2 and 3 had two and one scanty each in scanty each in the initial and one month after diagnosis respectively. For a 1+ result, minimum 1 AFB per 10 fields or 10/100 needs to be present in ordinary microscopy. A total of 6 specimens were found to be 1+ in the initial diagnosis of the specimens. In the diagnosis after one month, 2 specimens were found to be 1+. 7 specimens were found to be 2+ that is 1-9 AFB per field, in the initial diagnosis of the specimens and it came down to 2 in the diagnosis after one month. A total of 3 specimens were found to be 3+ (more than 100 AFB in one field) in the initial diagnosis of and no specimen was found to be 3+ in the diagnosis after one month.

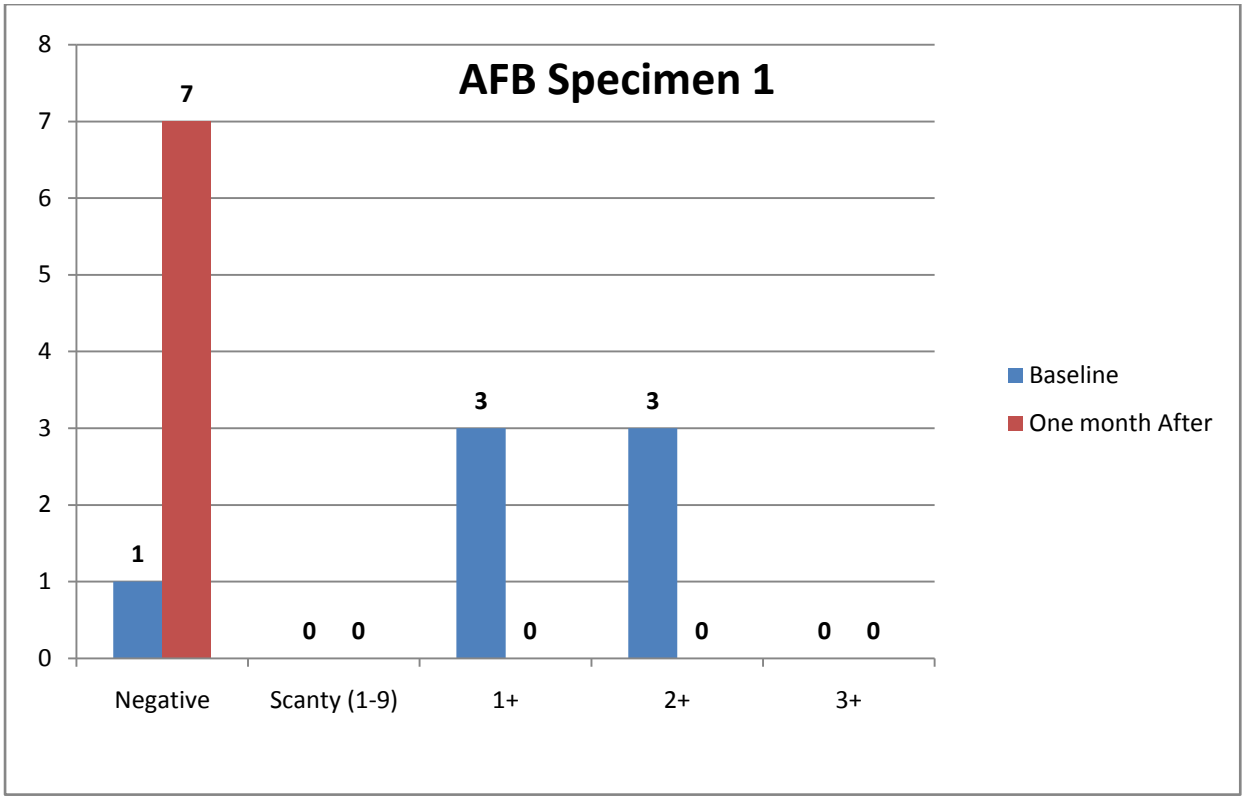


Figure 3.7: Distribution of the patients' sputum smear specimen 1 (spot sample)

Figure 3.7 shows distribution of the patients' sputum specimen according to AFB smear results of spot-I sample. In the baseline, 1 specimen was found to be negative and after one month 7 specimens were found negative i.e., no AFB was found in 100 fields. No specimen was found to scanty. 3 specimens were found to be 1+ in the initial diagnosis and no specimen was found to be 1+ in the diagnosis after one month. 3 specimens were found to 2+ that is 1-9 AFB per field, in the baseline and no specimen was found to be 2+ in the follow up. No specimen was found to be 3+ (more than 100 AFB in one field) in the AFB specimen 1.

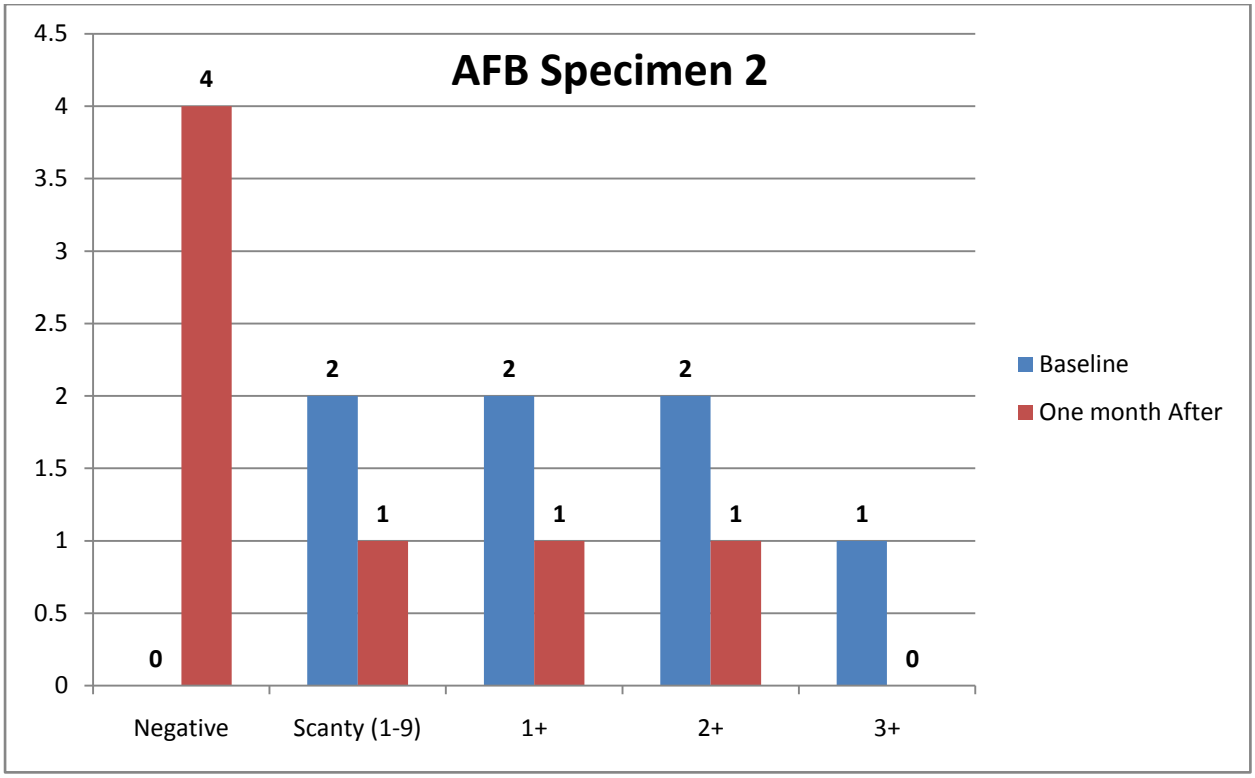


Figure 3.8: Distribution of the patients' sputum smear specimen 2 (early morning specimen).

Figure 3.8 shows distribution of the patients' sputum smear specimen according to AFB smear results of specimen 2 (early morning specimen). In the baseline, no specimen was found to be negative and after one month 4 specimens were found negative i.e., no AFB was found in 100 fields. 2 specimens were found to scanty in the initial diagnosis and 1 was found scanty in the follow up. 2 specimens were found to be 1+ in the initial diagnosis and 1 specimen was found to be 1+ in the diagnosis after one month. 2 specimens were found to 2+ that is 1-9 AFB per field, in the baseline and 1was found to be 2+ in the follow up. 1 specimen was found to be 3+ in the initial diagnosis and no specimen was found to be 3+ (more than 100 AFB in one field) in the follow of diagnosis of AFB specimen 2.

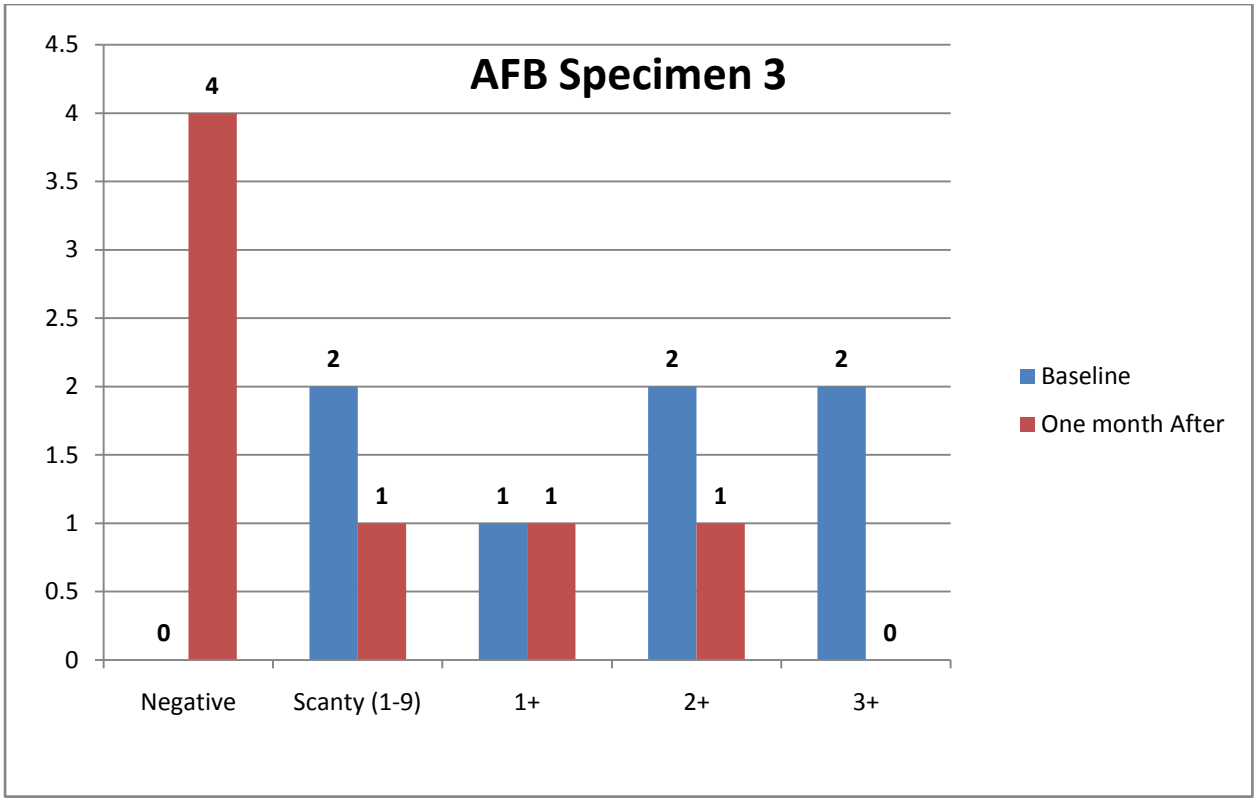


***Figure 3.9*:** Distribution of the patients' sputum smear specimen 3 (spot-II specimen)

Figure 3.9 shows distribution of the patients' sputum smear specimen according to AFB smear results of AFB specimen 3 (spot-II specimen). In the baseline, no specimen was found to be negative and after one month 4 specimens were found negative i.e., no AFB was found in 100 fields. 2 specimens were found to scanty in the initial diagnosis and 1 was found scanty in the follow up. 1 specimen were found to be 1+ in the initial diagnosis and 1 specimen was found to be 1+ in the diagnosis after one month. 2 specimens were found to 2+ that is 1-9 AFB per field, in the baseline and 1was found to be 2+ in the follow up. 2 specimen was found to be 3+ in the initial diagnosis and no specimen was found to be 3+ (more than 100 AFB in one field) in the follow of diagnosis of AFB specimen 2.

Table 3.9: AFB microscopy test analysis of tuberculosis patients (n= 22)

	Specimen 1	Specimen 2	Specimen 3
Negative	8	6	7
Scanty (1-9)	3	2	3
1+	0	3	1
2+	3	1	3
3+	1	3	1

Table 3.9 shows AFB microscopy test analysis of all patients. The combination of the two main quantification scales for the AFB microscopic examination of patients is shown here. In all 3 specimens, highest number was found to be negative i.e., no AFB was found in 100 fields examined. Out of 22 patients, both specimen 1 and 3 had 3 patients having scanty (1-9) result in their AFB microscopy test whereas specimen 2, 2 patients had a result of scanty (1-9). In specimen 1 (spot specimen), no patient belong to 1+ whereas 3 patients were 1+ in specimen 2 and for specimen 3, 1 patient was found to be 1+. Both specimen 1 and 3 had 3 patients having 2+ results in their AFB microscopy test whereas specimen 2 had 1 patient in this category. Specimen 1 and specimen 3 (spot I and spot II specimen) had 1 one patients each having 3+ count in AFB microscopy result. 3 patients had 3+ counts in their specimen 2 (early morning specimen).

Discussion

Tuberculosis (TB) is a major public health problem in Bangladesh. Recent analysis of global burden of TB revealed that Bangladesh ranks 6th on the list of 22 highest burden TB countries in the world (USAID, 2009). This prospective study was conducted with 22 tuberculosis patients admitted at NIDCH.

TB remains to be one of the leading causes of morbidity and mortality in the developing countries including Bangladesh. This study revealed a mean value of age of 36±15 indicating TB hits the most economically productive age group hardest. Thus the epidemic has a devastating economic as well as social impact.

Zaman *et al.* (2010) found that men are more commonly affected by TB than women. Thus the case notification rates in most countries are higher in males than females which are not inconsistent in this study. This study revealed the gender distribution where male patients dominated (90.9%) in number.

The nation-wide TB prevalence survey was implemented during 2007-2009 and included 52, 098 people aged 15 years or older and 33 new smear-positive cases were detected. The survey results revealed that the overall adjusted prevalence of smear positive TB was 79.4 per 100,000 population aged 15 years and above. It was higher among males, among rural population and people with low socio-economic conditions which are also unfailing in this study (USAID, 2009). The study showed that major (60%) poor TB patients admitted at NIDCH were from the rural areas whereas most of the urban patients (87.5%) were found to be from middle class family and no poor class urban patients (0%) were admitted during that period. The association was found to be significant (*P= 0.012*).

The complete blood count with ESR is conducted as the first test on a patient suspected to have a disease or infection. In this study, 95.5% patients had higher ESR value which indicates likelihood to detect tuberculosis since higher ESR rate may be due to this infectious disease. Thus ESR could be used as a diagnostic marker for the diagnosis of tuberculosis by correlating the higher ESR value to this infectious disease.

Around one-third of the cases of tuberculosis go undetected, resulting in a larger number of undiagnosed and untreated cases that spread the disease further (Public Health Watch, 2006). In this study, among 22 new cases TB 19 were smear positive (SS+). Among 22 tuberculosis patients, 7 patients took the follow up test and of which 4 patients became sputum smear

negative (SS-) from sputum smear positive (SS+) in the initial diagnosis. A total of 42 specimens were diagnosed among which 21 was diagnosed in the initial phase from 7 follow up patients and 21 were diagnosed after one month from the same patients.

The study revealed that 50% of the patient belongs to middle class whereas 31% belongs to lower middle class and 18.2% patients were poor. In a study conducted by public health watch in 2006, it was shown that poverty increases vulnerability to TB. The malnutrition, overcrowding, poor air circulation, and unhygienic sanitation facilities commonly experienced by the poor all increase the probability of TB infection.

Microscopic examination is a critical step in determining the reliable smear result in sputum microscopy that has direct implication on treatment and its monitoring. Direct sputum smear microscopy still remains gold standard and the most cost effective tool for diagnosing patients with infectious tuberculosis and monitoring the progress of treatment (Wangchuk. S. & Tshering, 2008). Standardization of sputum microscopy for the detection of infectious TB cases across the peripheral diagnostic centers and to validate the reported acid-fast bacilli (AFB) microscopy results from these centers should be done.

TB and HIV are frequently referred to as co- or dual-epidemics due to their high rate of co-infection (UNAIDS, 2006). HIV weakens the immune system, increasing the likelihood that an individual will become infected and develop active TB, and since the 1980s has been largely responsible for the resurgence of the TB epidemic. Additionally, TB is harder to diagnose and progresses more rapidly in someone with HIV (UNAIDS, 2006). As a result, TB is a leading cause of death among people with HIV, especially in developing countries (WHO, 2010). With 3.2 million new TB cases, South-East Asia is the second most affected region in the world, as measured by incidence and prevalence rates. Despite these high numbers, case detection rates (65%) and treatment success rates (88%) were both higher than the global rates. South-East Asia is home to 5 HBCs, four of which (Bangladesh, India, Indonesia, and Myanmar) have met global treatment targets.

The implementation of directly observation therapy short course (DOTS) has been a breakthrough in the control of tuberculosis. The DOTS was started in Bangladesh in 1993 under the National Tuberculosis Control Programme (NTP) of the Government of Bangladesh and gradually it covered the whole country (WHO Country Office for Bangladesh, 2009).

This study lacked adequate research funding which slowed the process and made it difficult to conduct the study with utmost efficiency. With adequate research funding, this preliminary study is intended to be extended up to additional six months to see further changes in disease condition of the patients and to bring out robust data which would be helpful in the detection, treatment and prevention of tuberculosis.

Future challenges for tuberculosis in Bangladesh includes: 1) Scarcity of epidemiological data; 2) Involvement of private sectors; 3) Strategies to increase case detection; 4) Continuation of MDR surveillance; 5) Diagnosis and management of childhood TB/extra pulmonary; 6) Development of rapid diagnostic methods; 7) Extension of DOTS to work place and hard reach areas.

Conclusion

One-third of the world's population, or two billion people, carry the TB bacteria, more than 9 million of whom become sick each year with active TB which can be spread to others. TB disproportionately affects people in resource-poor settings, particularly those in Bangladesh. More than 90% of new TB cases and deaths occur in developing countries, posing significant challenges to the livelihoods of individuals and developing economies as TB primarily affects people during their most productive years. DOTS aims to decrease TB-related morbidity, prevent TB deaths, and decrease TB transmission. These efforts have shown some promising signs. Though TB case detection and treatment rates have increased, still, many challenges remain. Poor health systems, limited laboratory capacity for case detection, treatment barriers and complications such as unreliable drug supply, patients not completing treatment, or prescribing errors; TB and HIV co-infection, and the emergence of drug-resistant TB pose serious threats to TB control. Moreover, around one-third of the cases of tuberculosis go undetected, resulting in a larger number of undiagnosed and untreated cases that spread the disease further. Present study showed ESR could be used as a diagnostic marker for the diagnosis of tuberculosis by correlating the higher ESR value to this infectious disease. With judicious case detection and implementing appropriate measures, TB incidence, prevalence and morbidity can be minimized to a greater extent.

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জ্ঞাতলিখিত সম্মতিপত্র

গবেষক ঃ রাবিতা ইসরাত

গবেষণার উদ্দেশ্যঃ

TB একটি নিরাময় অযোগ্য ফুসফুসের রোগ যা প্রকাশ পায় দীর্ঘমেয়াদী শ্লেষ্মাযুক্ত কাশি এবং শ্বাসকষ্ট বৃদ্ধির মাধ্যমে। এটি উন্নয়নশীল দেশসমূহে প্রাপ্তবয়স্কদের অসুস্থতা এবং মৃত্যুর অন্যতম প্রধানকারণ। সাধারণত: ধূমপান, পরিবেশজনিত তামাকের ধোঁয়া, আভ্যন্তরীন বায়ুদূষণ এবং পেশাগত কারণে ধোঁয়া বা ধোঁয়ার কণা/কণিকার সংস্পর্শে আসা হচ্ছে TB হওয়ার কারণ।

আপনার এলাকায় একটি গবেষণা করতে যাচ্ছি যেখানে মানুষের TB পরীক্ষা করা হবে। এই গবেষণার মাধ্যমে আপনি জানতে পারবেন যে, আপনার TBর কার্যকারিতা স্বাভাবিক নাকি ।

অংশগ্রহণকারীর নিকট থেকে প্রত্যাশা ঃ

আপনি যদি এই গবেষণায় অংশগ্রহণের জন্য সম্মতি দেন, তাহলে আমরা আপনাকে আপনার স্বাস্থ্য সম্পর্কে কিছু প্রশ্ন জিজ্ঞেস করবো।

ঝুঁকি এবং সুবিধা ঃ

এই গবেষণায় অংশগ্রহণের ফলে মূলত: কোন ঝুঁকি নেই। এটি আপনার স্বেচ্ছায় অংশগ্রহণ।

গোপনীয়তা, নামহীনতা এবং নিশ্চয়তা ঃ

আমরা আপনাকে আশ্বস্ত করছি যে, আপনার নিকট থেকে সংগৃহীত তথ্য এবং আপনার স্বাস্থ্যগত অবস্থা সম্পর্কে কাউকে জানতে দেয়া হবেনা। এই গবেষণায় কোন কাগজপত্রে আপনার নাম থাকবে না। আপনার নাম অথবা ব্যক্তিগত তথ্য (যা দ্বারা আপনাকে খুঁজে বের করা যাবে) কোথাও প্রকাশ করা হবে না বা কাউকে দেয়া হবে না।

ভবিষ্যতে ব্যবহার যোগ্য তথ্য ঃ

এই গবেষণায় সংগৃহীত তথ্য ভবিষ্যতে গবেষণার কাজে ব্যবহার করা হতে পারে। কিন্তু আবারো নিশ্চয়তা দিচ্ছি যে, আপনাকে চেনা যায়এমন কোন তথ্য কাউকে দেয়া হবেনা।

অংশগ্রহণ না করার এবং প্রত্যাহার করার অধিকার ঃ

এই গবেষণায় আপনার অংশগ্রহণ স্বেচ্ছায়। তার মানে হচ্ছে, আপনি এই গবেষণায় আপনার অংশগ্রহণ বর্জন বা পরিহার করতে পারেন। যে কোন সময় আপনি চাইলে আপনার অংশগ্রহণ প্রত্যাহার করতে পারেন, যদিও আপনি পূর্বে বলেছিলেন যে এই গবেষণায় অংশগ্রহণ করবেন। যে কোন ধরনের অস্বস্তিকর প্রশ্নের উত্তর আপনি এড়িয়ে যেতে পারেন। এই গবেষণা সম্পর্কিত আপনার যেকোন প্রকারের প্রশ্নের উত্তর আমরা খুশী মনে দিব।

আপনার কি কোন প্রশ্ন আছে? হ্যাঁ / না

আপনি কি এই গবেষণায় অংশগ্রহণের জন্য রাজী আছেন? হ্যাঁ / না

এখন আমরা আপনাকে এই গবেষণায় অংশগ্রহণের জন্য আমন্ত্রণ জানাচ্ছি। আপনি যদি রাজী থাকেন, তাহলে অনুগ্রহপূর্বক অংশগ্রহণের সম্মতির নির্দেশনা স্বরূপ নীচে নির্ধারিত স্থানে আপনার নাম অথবা স্বাক্ষর দিন।

_____ _____

অংশগ্রহণকারীর স্বাক্ষর অথবা নাম তারিখ

_____ _____

প্রধান গবেষকের স্বাক্ষর তারিখ

Case Report Form (CRF) for Patients

<u>Study Name:</u> A Study on Hematological Indices of Tuberculosis Patients Attending in a Tertiary Care Hospital in Dhaka City

By- Rabita Israt

Duration of Interview: ……

Patient Identification

Patient Registration No.: ……

Patient's Name: ……

Age: ……

Sex: ☐ Male ☐ Female

Weight (in KG): ……

Patient's Contact No. (For follow up purpose):

Socio-demographic History

1. Educational status:
    - Illiterate
    - Below class 5
    - Class 5-10
    - SSC
    - HSC
    - Graduate or higher

2. Place of residence-
    - Rural (Specify _____)
    - Urban (Specify _____)
    - Semi-Urban (Specify _____)
    - Slum (Specify _____)

3. Impression about social status:
    - Rich
    - Upper middle
    - Middle
    - Lower middle
    - Poor

Patients' Awareness about the Disease

1. Do you know it is contagious?
   a. Yes b. No
2. Has anyone in your family ever been infected with tuberculosis?
   a. Yes b. No
3. Are you aware of the proper management of the tuberculosis treatment?
   a. Yes b. No
4. Did you take vaccine (BCG)?
   a. Yes b. No

Patient's Occupation History

1. What is your occupation? ……

2. Is there working hazards; i.e. explosive industry, pollutants, dusts, chemicals?
   ☐ Yes ☐ No
3. Do you have any working disabilities? ☐ Yes ☐ No

If yes, then details _____

Patient's Smoking History (Current Smokers)

i. Do you currently smoke? Yes No

Smoking (Past history)

i. Did you smoke? Yes No

ii. How long ago did you stop smoking? _____

Risk factors

- Malnutrition (Y/N)
- Advanced age (Y/N)
- Smoking (Y/N)
- Unhygienic environment (Y/N)
- Diabetes (Y/N)
- Chronic kidney disease (Y/N)

Diagnosis History

Type of TB:

- Pulmonary
- Extra Pulmonary

AFB Microscopy Examination:

Date of Collection	Specimen	Result				
		Negative	Scanty (1-9)	1+	2+	3+
	1					
	2					
	3					

Date of Collection	Specimen	Result				
		Negative	Scanty (1-9)	1+	2+	3+
	1					
	2					
	3					

Hematological Report:

CBC with ESR:

Hb (Gm/dl)	Total count of WBC (/cmm)	HCT (PCV) (%)	Platelet count (PC) (/cmm)	ESR (mm 1st hr)

Differential count of WBC:

Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophil (%)	Basophil (%)	Immature Cells (%)

NATIONAL TUBERCULOSIS CONTROL PROGRAMME (NTP)

Directorate General of Health Services, Bangladesh

Request Form for AFB Microscopy Examination

(The completed form with results should be sent promptly by the Laboratory to the referring facility)

Name of Referring Facility[1]/Providers: _____ **Date:** _____

Name of Patient: _____ **Age:** _____ **Sex:** ☐ M ☐ F

Occupation _____ **Name of Father / Husband** _____

Full Address of Patient: _____

_____ **Telephone no. (if any):** _____

OPD Reg. No. (if any); (For suspects only): _____

Reason for examination: ☐ Diagnosis ☐ Follow-up If follow-up, **No. of month of Treatment:** _____

Disease Classification: ☐ **Pulmonary** ☐ **Extra-pulmonary (EP)** If EP, Site: _____

Nature of Specimen: ☐ Sputum ☐ Urine ☐ Pus ☐ Other, specify: _____

Specimen identification no: _____ **Patient TB Registration No:** _____
(For follow-up patients)

Signature of person requesting examination: _____

Name & designation of person requesting examination: ----------

1. Including all public and private health facility/providers

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RESULTS (To be completed in the Laboratory)

Lab Registration No: _____

Visual appearance of the specimen (if it is sputum): ☐ Muco-purulent ☐ Blood-stained ☐ Saliva

Microscopy results

Date of Collection*	Specimen	Result				
		Negative	Scanty (1-9)	1+	2+	3+
	1					
	2					
	3					

Sputum collected by:

Signature: _____

Name: _____

Examined by:

Signature of Medical Tech (Lab) _____

Name: _____

Date: _____

Name of Lab/Organization: _____

* To be completed by the person collecting the sputum