A Survey on Side Effects of Anti-Tuberculosis Drugs in Dhaka, Bangladesh

Submitted By

Jebunnessa Jeba

ID: 2012-1-70-032

Department of Pharmacy

East West University

A Survey on Side Effects of Anti-Tuberculosis Drugs in Dhaka, Bangladesh

A Dissertation Submitted To the Department of Pharmacy, East West University, in Partial Fulfillment of the Requirements for the Degree of Bachelor of Pharmacy

Submitted By

Jebunnessa Jeba

ID: 2012-1-70-032

Department of Pharmacy

East West University

DECLARATION BY THE CANDIDATE

I, Jebbunnessa Jeba, hereby declare that this dissertation, entitled **"A Survey on Side Effects of Anti-Tuberculosis Drugs in Dhaka, Bangladesh"** submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Honors) is a genuine & authentic research work carried out by me. The contents of the dissertation, in full or in parts, have not been submitted to any other institute or University for the award of any degree or diploma of fellowship.

_____

Jebbunnessa Jeba
ID: 2012-1-70-032
Department of Pharmacy
East West University
Aftabnagar, Dhaka

CERTIFICATION BY THE SUPERVISOR

This is to certify that the dissertation, entitled **"A Survey on Side Effects of Anti-Tuberculosis Drugs in Dhaka, Bangladesh"** is a bona fide research work done by Jebbunnessa Jeba (ID: 2012-1-70-032), in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

_____

Tilka Fannana
Senior Lecturer & Supervisor
Department of Pharmacy
East West University
Aftabnagar, Dhaka

ENDORSMENT BY THE CHAIRPERSON

This is to certify that the dissertation, entitled **"A Survey on Side Effects of Anti-Tuberculosis Drugs in Dhaka, Bangladesh"** is a bona fide research work done by Jebbunnessa Jeba (ID: 2012-1-70-032), in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

_____

Dr. Shamsun Nahar Khan
Associate Professor & Chairperson
Department of Pharmacy
East West University
Aftabnagar, Dhaka.

ACKNOWLEDGEMENT

All praise is for the Almighty for all the bounties granted to me and only with his guidance and help this achievement has become possible.

It is my pleasure and proud privilege to express my heartiest regards and gratitude to my respect teacher and supervisor **Tilka Fannana**, Senior Lecturer, Department of Pharmacy, East West University, for her expert supervisor, constructive criticism, valuable advice, optimistic counseling, constant support & continuous backup and encouragement throughout every phase of the project as well as to prepare this dissertation.

I would also like to put forward my most sincere regards and profound gratitude to Ph. **Dr. Shamsun Nahar Khan**, Professor & Chairperson, Department of Pharmacy, East West University, for giving me the opportunity to conduct such an interesting project and for facilitating a smooth conduction of my study.

I owe special thanks to my fellow research group members for her immense support and contribution in my research work.

Last but not the least, I would like to thanks my family and friends for their care and encouragement during my research work.

Dedication

This Research Work Is Dedicated to My Beloved Parents and Honorable Faculties for Their Immense Support.

CONTENTS

List of contents

List of Tables

List of Figures

List of Abbreviation

TB	Tuberculosis
MDR-TB	Multi-Drug Resistant Tuberculosis
XDR-TB	Extensively Drug Resistant Tuberculosis
DOTS	Directly Observed Treatment Strategy
WHO	World Health Organization
MTb	Mycobacterium Tuberculosis
MDG	Millennium Development Goals
EU	European Union
EEA	European Economic Area
NTP	National Tuberculosis Control Programme
HNPSP	Health, Nutrition & Population Sector Programme
FDC	Fixed Dose Combination
ATT	Anti-Tuberculous Treatment
PAS	Para-aminosalisylic acid
ADR	Adverse Drug Reaction
ADARs	Adverse Reaction to Anti-Tuberculosis Drugs
NIDCH	National Institute of Diseases of the Chest and Hospital
DM	Diabetes Mellitus

ABSTRACT

Tuberculosis is a major cause of morbidity and mortality worldwide, resulting in the greatest number of deaths due to any one single infectious agent. Drug resistance threatens global tuberculosis control efforts. The aim of the study was to assess adverse reactions of TB drugs in patients treated for TB and MDR-TB at NIDCH. This study included 100 TB patients among them 61 patients were MDR-TB patients. The MDR-TB patients were resistant to at least Rifampicin and Isoniazid. All patients' files were analyzed and the following data were discussed: complete clinical examination, drug susceptibility testing and initial laboratory investigations and adverse reactions were determined by clinical criteria or laboratory data.

In our study 53% were male and 47% were female. The most observed side effects suffered by the patients were gastrointestinal disorder (93%), ototoxicity (18%), psychiatric (46%), neurological (61%), dermatologic (42%), endocrine (19%), electrolytic imbalance (26%), arthralgias (43%) and some other major side effects (95%). The other major side effects include weight loss, anemia, body weakness, vitamin deficiency, asthma etc. Overall MDR-TB patients suffered more gastrointestinal, psychiatric, neurologic, dermatologic, arthralgias and other major side effects than the TB patients. The most important predictors of side effects suffered by the patients are large and complex drug regimen, number of previous TB treatment and presence of co-morbidities.

Key Words: *Tuberculosis, Drug Resistance, MDR-TB, NIDCH, Rifampicin, Isoniazid.*

1.1: Overview

Tuberculosis (TB) remains a major problem in health systems. In 2013, 6.1 million TB cases were reported to WHO and of these 5.7 million were people newly diagnosed and another 0.4 million were already on treatment. More than 100,000 tuberculosis (TB) patients are receiving directly observed treatment strategy (DOTS) around the world every year. Single drug therapy can lead to the development of a bacterial population resistant to that drug. Inadequate treatment can lead to treatment failure, relapse, and drug resistance. Responsibility for successful treatment is assigned to the health care providers. First line antituberculosis drugs recommended by WHO are a combination of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin.

It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions. The adverse drug reactions may be mild to severe. Studies have shown that multidrug regimens can cause undesirable adverse drug reactions such as arthralgia, neurological disorders, gastrointestinal disorders, hepatotoxicity, and allergic reactions. The principal adverse reactions include irritating reactions, allergic reactions and toxic reactions. Gastrointestinal intolerance occurs due to the irritating effect of the drugs. Allergic reactions can be mild (urticaria, rash, itching or cholestatic jaundice) or severe (anaphylactic shock, bleeding disorders or interstitial nephritis) (Maciel, *et al*., 2010).

Adverse drug reactions increase patient discomfort and cause substantial additional costs because of excess outpatient visits, laboratory tests, and even in serious instances hospitalization. In addition, adverse drug reactions are regarded as one of the major causes of non adherence to anti-TB treatment. At the same time, alternative drugs may cause severe complications with few effects. Adverse drug reactions may lead to prolonging of treatment, drug resistance, and treatment failure. Adverse drug reactions may also increase morbidity and mortality of disease.

The frequency, severity, and the nature of anti-TB therapy induced adverse drug reactions have been always a concern. The overall incidence of adverse drug reactions caused by anti-TB therapy ranges from 5.1% to 83.5%. In this study, I got an overview of adverse drug reactions of anti-tuberculosis drugs suffered by patients. These patients were admitted in NIDCH, Mohakhali, Dhaka (Farazi, *et al*., 2015).

1.2: Tuberculosis (TB)

Tuberculosis is the second major cause of death due to an infectious disease in adults worldwide with 9 million new cases and close to 1.8 million deaths annually. It is the major cause of death in HIV-infected individuals. Increase in the number of HIV-positive individuals has led to a significant increase in the number of TB patients over the last decade in both developing and developed countries. Tuberculosis (TB) is a bacterial infection spread through inhaling tiny droplets from the coughs or sneezes of an infected person. TB is caused by *Mycobacterium Tuberculosis* (MTb). *Mycobacterium Tuberculosis* is an airborne pathogen which transmitted among humans through air. It infects mainly macrophages in the lungs. It can also affect any part of the body; include the glands, bones and nervous system. Tuberculosis is often underrecognized.

Tuberculosis has recently reemerged as a major health concern. Each year, approximately 2 million persons worldwide die of tuberculosis and 9 million become infected. In the United States, approximately 14000 cases of tuberculosis were reported in 2006, a 3.2% decline from the previous year; however, 20 states and the District of Columbia had higher rates. The prevalence of tuberculosis is continuing to increase because of the increased number of patients infected with human immunodeficiency virus, bacterial resistance to medications, increased international travel and immigration from countries with high prevalence, and the growing numbers of the homeless and drug abusers.

With 2 billion persons, a third of the world population, estimated to be infected with mycobacteria, all nurses need to understand the pathophysiology, clinical features, and procedures for diagnosis of tuberculosis. The vulnerability of hospitalized patients to

tuberculosis is often underrecognized because the infection is habitually considered a disease of the community. Most hospitalized patients are in a suboptimal immune state, particularly in intensive care units, making exposure to tuberculosis even more serious than in the community. By understanding the causative organism, pathophysiology, transmission, and diagnostics of tuberculosis and the clinical manifestations in patients, critical care nurses will be better prepared to recognize infection, prevent transmission, and treat this increasingly common disease (Knechel, 2015).

1.3: Current Status of Tuberculosis in Developing Countries

TB is present in all regions of the world and the *Global Tuberculosis Report 2014* includes data compiled from 200 countries and territories. According to WHO in 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease. TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment. However, given that most deaths from TB are preventable, the death toll from the disease is still unacceptably high and efforts to combat it must be accelerated if 2015 global targets, set within the context of the Millennium Development Goals (MDGs) are yet to be met (WHO, 2014).

1.3.1: India

India accounts for 25% of the global burden of TB and 29% of global TB mortality. TB causes an estimated 320 000 annual deaths in India: 17.6% of communicable disease deaths and 3.5% of all-cause mortality. According to the TB India Report 2014 by WHO, 40% of the country's population carries the *Mycobacterium tuberculosis* (the TB bacteria) in the passive form. About 3.3 million people are suffering from one or the other type of TB and annually 276,000 lives are lost due to tuberculosis.

As many as 9.4 million cases of TB are detected worldwide every year. India accounts for more than one-fifth of the same at about 1.98 million. It appears that a major change

has come about in detection and treatment of tuberculosis cases between 1990 and 2014. It is believed that the incidence of tuberculosis has reduced from 216 per 100,000 per year in 1990 to 176 per 100,000 per year in the year 2014 in India, the tuberculosis mortality per 100,000 populations having been reduced from 38 in year 1990 to 22 in 2014. In absolute numbers, mortality due to TB has scaled down from 330,000 to 270,000 annually (WHO, 2015).

1.3.2: China

1 million new cases of tuberculosis have been estimated in China every year, more than any other country except India. In recent years, the Government has made great progress in TB control and prevention, resulting in a significant decline in the burden of TB. According to the report of WHO report- the estimated overall prevalence rate per 100,000 populations fell from 215 in 1990, to 108 in 2010. The rate of decline was 2.2% per year between 1990 and 2000, and 4.7% per year between 2000 and 2010. TB mortality has declined rapidly, at an average rate of 8.6% per year between 1990 and 2010 and TB incidence rate was estimated to have declined by 3.4% per year since 1990 (WHO, 2015).

1.4: Current Status of Tuberculosis in Europe

Tuberculosis (TB) is still a public health concern in most of the countries within the WHO European Region. Countries outside of the European Union (EU) and European Economic Area (EEA) still suffer from high rates of TB and multidrug resistant (MDR) TB. In 2012, an estimated 353 000 new (incident) TB cases (range 330 000–376 000) occurred in the WHO European Region, equivalent to an average of 39.4 cases (36.9–41.9) per 100 000 population. This represents about 4% of the total burden of incident TB cases in the world (WHO, 2013).

1.5: Current Status of Tuberculosis in United States

Since the 1992 TB resurgence peak in the United States, the number of TB cases reported annually has decreased. A total of 9,582 TB cases (a rate of 3.0 cases per 100,000 persons) were reported in the United States in 2013. Both the number of TB cases reported and the case rate decreased; this represents a 3.6% and 4.3% decline, respectively, compared to 2012. In 2013, a total of 65% of reported TB cases in the United States occurred among foreign-born persons.

The case rate among foreign-born persons (15.6 cases per 100,000 persons) in 2013 was 13 times higher than among U.S.-born persons (1.2 cases per 100,000). There were 536 deaths from TB in 2011, the most recent year for which these data are available. The number of TB deaths reported annually has decreased by 69% since 1992. Since 1993, when the TB surveillance system was expanded to include drug-susceptibility results, reported multidrug-resistant (MDR) TB cases have decreased in the United States.

Among all culture-positive TB cases in the United States with initial drug-susceptibility testing results, the percentage of MDR TB cases increased slightly from 1.2% (86 cases) in 2012 to 1.4% (95 cases) in 2013. Since 1997, among U.S.-born culture-positive cases with initial drug-susceptibility testing results available, the percentage of cases that are MDR TB has remained below 1.0%. Of the total number of reported MDR TB cases, the proportion occurring among foreign-born persons increased from 30.8% (149 of 484) in 1993 to 89.5% (85 of 95) in 2013(WHO, 2013).

1.6: Tuberculosis in Bangladesh

Tuberculosis is a major public health problem in Bangladesh. Over 300,000 people develop the disease and 70,000 people die every year. The incidence of tuberculosis (per 100,000 people) in Bangladesh was last reported at 225.00 in 2010, according to a World Bank report released in 2011. The incidence of tuberculosis (per 100,000 people) in Bangladesh was 225.00 in 2009, according to a World Bank report published in 2010.

The incidence of tuberculosis (per 100,000 people) in Bangladesh was reported at 225.00 in 2008, according to the World Bank. Incidence of tuberculosis is the estimated number of new pulmonary, smear positive and extra pulmonary tuberculosis. In 1993 World Health Organization (WHO) declared TB as a global emergency and recommended a standard strategy for control of the disease that is known as the Directly Observed Treatment Short Course (DOTS) Strategy.

Bangladesh adopted this strategy in 1993 and had expanded at all upazillas in collaboration with the partner NGOs by June 1998. At present the NTP of Bangladesh, together with its partners, is expanding the DOTS strategy in order to achieve the target of at least 70% case detection and 85% cure rates under Health, Nutrition and Population Sector Programme (HNPSP). The overall goals of TB control are to reduce morbidity and mortality and thus decrease transmission of infection and to prevent development of drug resistance (WHO, 2015).

1.7: Pathophysiology of Tuberculosis

1.7.1: Mycobacterium Tuberculosis

Tuberculosis is an infection caused by the rod-shaped, non–spore-forming, aerobic bacterium *Mycobacterium tuberculosis*. Mycobacteria typically measure 0.5 μm by 3 μm, are classified as acid-fast bacilli, and have a unique cell wall structure crucial to their survival. The well-developed cell wall contains a considerable amount of a fatty acid, mycolic acid, covalently attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan, providing an extraordinary lipid barrier.

This barrier is responsible for many of the medically challenging physiological characteristics of tuberculosis, including resistance to antibiotics and host defense mechanisms. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate. The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cell membrane, another contributor to the permeability barrier of mycobacteria. Another important component of the cell wall is

lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macrophages. The cell wall is the key to the survival of mycobacteria and a more complete understanding of the biosynthetic pathways and gene functions and the development of antibiotics to prevent formation of the cell wall are areas of great interest (Knechel, 2015).

1.7.2: Transmission of Mycobacterium Tuberculosis

Mycobacterium tuberculosis is spread by small airborne droplets, called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis. These minuscule droplets can remain airborne for minutes to hours after expectoration. The number of bacilli in the droplets, the virulence of the bacilli, exposure of the bacilli to UV light, degree of ventilation, and occasions for aerosolization all influence transmission. Introduction of *M tuberculosis* into the lungs leads to infection of the respiratory system; however, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary tuberculosis (Knechel, 2015).

1.7.3: Effects of Mycobacterium Tuberculosis in the Body

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. This system provides the body with an initial physical defense that prevents infection in most persons exposed to tuberculosis.

Bacteria in droplets that bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages, the most abundant immune effector cells present in alveolar spaces. 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. 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.

The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor. The complement system also plays a role in the phagocytosis of the bacteria. 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.* The subsequent phagocytosis by macrophages initiates a 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.

The outcome is essentially determined by the quality of the host defenses and the balance that occurs between host defenses and the invading mycobacteria. After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours. 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. 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. 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.

For persons with intact cell-mediated immunity, the next defensive step is formation of granulomas around the *M tuberculosis* organisms. These nodular-type lesions form from an accumulation of activated T lymphocytes and macrophages, which creates a micro-environment that limits replication and the spread of the mycobacteria. This environment destroys macrophages and produces early solid necrosis at the center of the lesion; however, the bacilli are able to adapt to survive. In fact, *M tuberculosis* organisms can change their phenotypic expression, such as protein regulation, to enhance survival.

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. 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. Lesions in persons with less effective immune systems progress to primary progressive tuberculosis (Knechel, 2015).

1.8: Risk Factors of Tuberculosis

Tuberculosis is caused by an airborne pathogen which transmitted among humans through air. Anyone can get tuberculosis, but certain factors can increase the risk of the disease. These factors include:

1.8.1: Weakened Immune System

A healthy immune system often successfully fights TB bacteria, but our body can't mount an effective defense if our resistance is low. A number of diseases and medications can weaken our immune system, including:

1. HIV/AIDS
2. Diabetes
3. End-stage kidney disease
4. Certain cancers
5. Cancer treatment, such as chemotherapy
6. Drugs to prevent rejection of transplanted organs
7. Some drugs used to treat rheumatoid arthritis, Crohn's disease and psoriasis
8. Malnutrition
9. Very young or advanced age

1.8.2: Traveling or Living in Certain Areas

The risk of contracting tuberculosis is higher for people who live in or travel to countries that have high rates of tuberculosis and drug-resistant tuberculosis, such as:

1. Sub-Saharan Africa
2. India
3. China
4. Russia
5. Pakistan

1.8.3: Poverty and Substance Abuse

Lack of medical care: If one receives a low or fixed income, lives in a remote area, has recently immigrated to the United States, or is homeless, he/she may lack access to the medical care needed to diagnose and treat TB.

Substance abuse: IV drug use or alcohol abuse weakens our immune system and makes us more vulnerable to tuberculosis.

Tobacco use: Using tobacco greatly increases the risk of getting TB and dying of it.

1.8.4: Place of Work or Living

Health care work: Regular contact with people who are ill increases our chances of exposure to TB bacteria. Wearing a mask and frequent hand-washing greatly reduce our risk.

Living or working in a residential care facility: People who live or work in prisons, immigration centers or nursing homes are all at a higher risk of tuberculosis. That's because the risk of the disease is higher anywhere there is overcrowding and poor ventilation.

Living in a refugee camp or shelter: Weakened by poor nutrition and ill health and living in crowded, unsanitary conditions, refugees are at especially high risk of tuberculosis infection (Mayoclinic.org, 2015).

1.9: Types of Tuberculosis

Tuberculosis may be divided into two types- Pulmonary and Extra pulmonary Tuberculosis.

Pulmonary TB includes-

1. Primary Tuberculosis Pneumonia (uncommon type of TB presents as pneumonia): It is very infectious. In Primary Tuberculosis Pneumonia, patients have a high fever and productive cough. It occurs most often in extremely young children and the elderly.

2. Tuberculosis Pleurisy (develops soon after initial infection.): It develops soon after initial infection. Once the bacteria invade the edge of the lung, the amount of fluid increases dramatically, and compress the lung, causing shortness of breath and sharp chest pain.

3. Cavitary TB (involves the upper lobes of the lung): Cavity TB involves the upper lobes of the lung. The bacteria cause progressive lung destruction by forming cavity.

4. Miliary TB (causes very small nodules throughout the lungs): Miliary describes the appearance on chest X-ray of very nodules throughout the lung. It can occur shortly after infection.

5. Laryngeal TB (infect the larynx or the vocal chord area): Laryngeal TB infects the larynx, or the vocal chord area. It is extremely infectious.

Extra pulmonary TB includes:

1. Lymph Node Disease (develop a fistula from the lymph node to the skin.):
2. Tuberculosis Peritonitis (*Mycobacterium tuberculosis* affects outer lining of the intestine & causes increased fluid)
3. Tuberculosis Pericarditis (The membrane surrounded the heart is affected)
4. Osteal Tuberculosis (Infection of any bone)
5. Renal Tuberculosis (causes asymptomatic pyuria)
6. Adrenal Tuberculosis (may lead to adrenal insufficiency)
7. Tuberculosis Meningitis *(Mycobacterium tuberculosis* affects the meninges, the spinal cord and brain) (NTP, 2013).

1.10: Symptoms of Tuberculosis

Although our body can fight against the bacteria that cause tuberculosis. Our immune system usually can prevent us from becoming sick. For this reason, doctors make a distinction between:

Latent TB: In this condition, we have a TB infection, but the bacteria remain in our body in an inactive state and cause no symptoms. Latent TB, also called inactive TB or TB infection, isn't contagious. It can turn into active TB, so treatment is important for the person with latent TB and to help control the spread of TB in general. An estimated 2 billion people have latent TB.

Active TB: This condition makes us sick and can spread to others. It can occur in the first few weeks after infection with the TB bacteria, or it might occur years later.

Sing and Symptoms of Active TB Include:

- Coughing that lasts three or more weeks
- Coughing up blood
- Chest pain, or pain with breathing or coughing

- Unintentional weight loss
- Fatigue
- Fever
- Night sweats
- Chills
- Loss of appetite
- Sweating at night (Centers for Disease Control and Prevention, 2013)

Tuberculosis can also affect other parts of our body, including our kidneys, spine or brain. When TB occurs outside your lungs, signs and symptoms vary according to the organs involved. For example, tuberculosis of the spine may give you back pain, and tuberculosis in your kidneys might cause blood in your urine.

People with latent TB infection do not feel sick, do not have any symptoms, and cannot spread TB bacteria to others (Mayoclinic.org, 2015).

1.11: Diagnosis of TB

If a person is in close contact with someone who has TB or a person who has cough that lasts more than three weeks or a person who may experience the above mention symptoms, tests may be carried out to see if he/she is infected by Tuberculosis or not. Tests are include- Chest X-ray to see the condition of lungs, Blood test to determine the presence of pathogens and how immune system works against pathogens. Mantoux test (a skin test) also conducts. Sputum culture (for MDR-TB) conducts to determine drug susceptibility whether anti-tuberculosis drugs (Rifampicin and Isoniazid) become resistant or not.

1.11.1: Diagnosis of Pulmonary TB

A diagnosis of pulmonary TB (TB that affects the lungs) can be difficult and several tests are usually needed. This will include a chest X-ray to look for changes in the appearance of our lungs that are suggestive of TB. Samples of phlegm will also often be taken and

checked for the presence of TB bacteria. These tests are important in helping to decide on the most effective treatment for us.

1.11.1.1: Skin Test

During the physical exam, doctor will check one's lymph nodes for swelling and use a stethoscope to listen carefully to the sounds lungs make while he/she breathe. The most commonly used diagnostic tool for tuberculosis is a simple skin test, though blood tests are becoming more commonplace. A small amount of a substance called PPD tuberculin is injected just below the skin of inside forearm. Within 48 to 72 hours, a health care professional will check his/her arm for swelling at the injection site. A hard, raised red bump means they're likely to have TB infection. The size of the bump determines whether the test results are significant.

1.11.1.2: Blood Tests

Blood tests may be used to confirm or rule out latent or active tuberculosis. These tests use sophisticated technology to measure our immune system's reaction to TB bacteria. Quanti FERON-TB Gold in-Tube test and T-Spot TB test are two examples of TB blood tests. These tests require only one office visit. A blood test may be useful if we're at high risk of TB infection, but have a negative response to the skin test, or if we've recently received the BCG vaccine.

1.11.1.3: Chest X-ray

If one's has had a positive skin test, his/her doctor is likely to order a chest X-ray or a CT scan. This may show white spots in his/her lungs where their immune system has walled off TB bacteria, or it may reveal changes in their lungs caused by active tuberculosis. CT scans provide more-detailed images than do X-rays.

1.11.1.4: Sputum Tests

If one's chest X-ray shows signs of tuberculosis, his/her doctor may take samples of his/her sputum the mucus that comes up when they cough. The samples are tested for TB bacteria. Sputum samples can also be used to test for drug-resistant strains of TB. This helps doctor choose the medications that are most likely to work. These tests can take four to eight weeks to be completed (Mayoclinic.org, 2015).

1.11.2: Diagnosis of Extrapulmonary TB

If we have suspected extrapulmonary TB (TB that occurs outside the lungs), several tests can be used to confirm a diagnosis.

These may include:

- a computerized tomography (CT) scan, magnetic resonance imaging (MRI) scan, or ultrasound scan of the affected part of the body
- urine and blood tests
- a biopsy – a small sample of tissue or fluid is taken from the affected area and tested for TB bacteria

One may also have a lumbar puncture. This involves taking a small sample of cerebrospinal fluid (CSF) from the base of his/her spine. CSF is fluid that surrounds the brain. It can be checked to see whether TB has infected your central nervous system (brain and spinal cord).

1.11.3: Diagnosis of Latent TB

In some circumstances, we may need to be tested to check for latent TB (when we have been infected with TB bacteria but do not have any symptoms). For example, one may need to be screened if they have been in close contact with someone known to have an active TB infection (an infection that causes symptoms), or if one have recently spent time in a country where TB levels are high.

1.11.3.1: Mantoux Test

The Mantoux test is a widely used test for latent TB. It involves injecting a substance called PPD tuberculin into the skin of your forearm. It's also called the tuberculin skin test (TST).If one's have a latent TB infection, his/her skin will be sensitive to PPD tuberculin and a hard red bump will develop at the site of the injection, usually within 48 to 72 hours of having the test. If one's have a very strong skin reaction, the may need a chest X-ray to confirm whether they have an active TB infection.

If one's do not have a latent infection, their skin will not react to the Mantoux test. However, as TB can take a long time to develop, they may need to be screened again at a later stage. If one does have had the BCG vaccination, they may have a mild skin reaction to the Mantoux test (Nhs.uk, 2015).

1.12: Drugs Used in the Treatment of TB

1.12.1: Treatment of Pulmonary TB

Isolate patients with possible tuberculosis (TB) infection in a private room with negative pressure (air exhausted to outside or through a high-efficiency particulate air filter). Medical staff must wear high-efficiency disposable masks sufficient to filter the tubercle bacillus. World Health Organization (WHO) recommends that patients should have six months of TB drug treatment. For the two months "intensive" TB drug treatment they should receive: Isoniazid, Rifampicin, Pyrazinamide, streptomycin and Ethambutol (first line drug). Treatment consists of three drugs that are effective against organisms.

Sputum should be negative after 2 or 3 months, if not treatment followed by four months "continuation" phase with Isoniazid and Rifampicin. For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued.

After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampicin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is documented, discontinue isoniazid and continue treatment with rifampicin, pyrazinamide, and ethambutol for the entire 6 months. Therapy must be extended if the patient has cavitary disease and remains culture-positive after 2 months of treatment.

Directly observed therapy (DOT) is recommended for all patients. With DOT, patients on the above regimens can be switched to 2- to 3-times per week dosing after an initial 2 weeks of daily dosing. Patients on twice-weekly dosing must not miss any doses.

1.12.1.1: Monitoring

Patients diagnosed with active TB should undergo sputum analysis for *Mycobacterium tuberculosis* weekly until sputum conversion is documented. Monitoring for toxicity includes baseline and periodic liver enzymes, complete blood cell (CBC) count, and serum creatinine to avoid drug abuse and drug toxicity. (Emedicine.medscape.com, 2015)

Table 1: Standardized treatment regimen for each diagnostic category (Adults)

TB diagnostic Category	**Type of Patient**	**Treatment regimen**	
		Intensive phase (Daily)	**Continuation phase (Daily)**
Cat. I	-New smear-positive --bacteriologically positive PTB patients -New smear-negative -PTB -New Extra-	2(HRZE) Here, H=Isoniazid R=Rifampicin Z=Pyrazinamide E=Ethambutol	4 (HR) Here, H=isoniazid R=Rifampicin

	pulmonary TB -New concomitant/ associated HIV/AIDS		
Cat. II	-Sputum smear-positive PTB with history of treatment of one month or more -Relapse -Treatment failure after Cat. I Treatment after loss to follow up -Others	1(HRZE) 2(HRZE)/S Here, H=Isoniazid R=Rifampicin Z=Pyrazinamide E=Ethambutol S=Streptomycin	5 (HRE) Here, H=Isoniazid R=Rifampicin E=Ethambutol

Dosages of FDC Tablets:

FDC tablets are composed as follows:

4FDC: isoniazid 75 mg + rifampicin 150 mg + pyrazinamide 400 mg + ethambutol 275 mg

2FDC: isoniazid 75 mg + rifampicin 150 mg

3FDC: isoniazid 75 mg + rifampicin 150 mg + Ethambutol 275 mg (NTP, 2013).

1.12.2: Treatment of Extrapulmonary TB

Extrapulmonary TB (TB that occurs outside the lungs) can be treated using the same combination of antibiotics as those used to treat pulmonary TB. However, we may need to take them for 12 months. If one's has TB in areas such as brain, he/she may also be prescribed a corticosteroid such as prednisolone for several weeks to take at the same time as your antibiotics. This will help reduce any swelling in the affected areas. As with

pulmonary TB, it's important to take medicines exactly as prescribed and to finish the whole course (Nhs.uk, 2015).

1.13: Multidrug-Resistant Tuberculosis (MDR-TB)

Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* isolate that does not respond to isoniazid and rifampicin, the two most effective first line antituberculous treatment (ATT) drugs. Anti-tuberculosis drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients. MDR-TB usually fails to respond to the conventional first-line antituberculous treatment but is curable with second-line drugs. However, those drugs are limited in number and less effective. MDR-TB is identified from the sputum-culture strain of the patient (ATS, 2015).

1.14: Current Status of MDR-TB Globally

Reporting on MDR-TB globally presents drug resistance data from 114 countries and updated information from 35 of them. Despite the growing understanding of the magnitude and trends in drug-resistant TB, major gaps remain in geographical areas covered. Since 1994, only 59% of all countries globally have been able to collect high quality representative data on drug resistance. There is an urgent need to obtain information, particularly from Africa and those high MDR-TB burden countries where data have never been reported: Bangladesh, Belarus, Kyrgyzstan, Pakistan and Nigeria. Moreover, countries need to expand the scope of their surveys to cover entire populations, repeat surveys are needed to better understand trends in drug resistance and countries need to move towards adopting systematic continuous surveillance.

Six countries are featured throughout the report in special focus sections. Bangladesh (one of the very few developing countries in which continuous surveillance among previously treated TB cases is being carried out in selected areas); China (first nationwide drug resistance survey conducted); Ethiopia (one of the first countries to introduce rapid

molecular laboratory tests); Nepal and Romania (successful treatments of MDR-TB through Green Light Committee Initiative programmes); South Africa (policy changes for improving the management and care of M/XDR-TB).

In China it is estimated there are 63,000 new multidrug-resistant tuberculosis (MDR-TB) cases among the 1 million notified new cases of TB every year. China contributes approximately one third of the world's MDR- TB. In India, various studies have found MDR TB levels of about 3% in new cases and around 12-17% in retreatment cases (WHO, 2015).

1.14.1: MDR-TB in Africa

In Africa, there is a low percentage of MDR-TB reported among new TB cases compared with that in regions such as Eastern Europe and Central Asia, due in part to the limited laboratory capacity to conduct drug resistance surveys. Latest estimates of WHO put the number of MDR-TB cases emerging in 2008 in Africa at 69 000. Previous reports found high levels of mortality among people living with HIV and infected with MDR-TB and XDR-TB. In KwaZulu Natal in South Africa, an outbreak of XDR-TB killed 52 out of 53 people within three weeks, most of whom were HIV positive (WHO, 2015).

1.14.2: MDR-TB in Bangladesh

Globally, an estimated 450,000 people developed MDR-TB and at least 170,000 deaths were caused by the disease in 2012. Bangladesh ranks 10th among 27 high MDR TB burden countries. The emergence of MDR-TB has become a major threat for TB control in Bangladesh. A general TB patient gets cured completely if he/she takes drugs takes for six month regularly. If the patient does not take drugs regularly, or does not complete full course or if the drugs are below quality, then TB germs become drug-resistance. This is called MDR-TB and it generally not cured with existing drugs. The patients have to take new drugs for about 22 to 24 months.

According to World Health Organization (WHO) estimate, there are 10,000 MDR-TB patients in Bangladesh. Ironically, many of these MDR-TB patients stay out of the treatment facilities for various reasons. Most of them cannot afford to stay in the hospital for long 2 years. These people pose a great risk of contracting the MDR-TB germ to other people raising the burden further. A WHO report said MDR-TB puts the global TB control programme in trouble. It appeared as a public health problem in a number of countries in the world. Twenty nine percent of old patients turned into MDR-TB patients in Bangladesh (WHO, 2015).

1.15: Diagnosis of MDR-TB

Drug resistant TB can be detected by using sputum culture tests which test the sensitivity of bacteria towards the drugs or detect resistance patterns of the drugs (mainly Rifampicin and Isoniazid). These tests can be molecular in type (Xpert MTB/RIF) or else culture-based. Using standardized DST procedures with conventional methods, eight to 12 weeks are required to identify drug-resistant microorganisms on solid media (ie, Lowenstein sensitivity of bacteria towards the drugs or detect resistance patterns of the drugs (mainly -Jensen medium). In general, such methods assess inhibition of *M tuberculosis* growth in the presence of antibiotics to distinguish between susceptible and resistant strains.

The proportion method allows precise determination of the proportion of resistant mutants to a certain drug; the resistance ratio method compares the resistance of an unknown strain with that of a standard laboratory strain. While relatively inexpensive and undemanding of sophisticated equipment, results usually take weeks and this is challenging; inappropriate choice of treatment regimen may result in death within weeks of initiation, such as in the case of XDR-TB (especially in HIV-infected patients). In addition, delayed identification of drug resistance results in inadequate treatment, which may generate additional drug resistance and continued transmission in the community (Myoclinic.org, 2015).

1.16: Drug Used in the Treatment of MDR- TB

MDR-TB is the major challenge of health system. It is quite difficult to treat. The treatment of MDR-TB relies upon a backbone of an injectable agent and a fluroquinolone. The choice of injectable agent and fluroquinolone for patient treatment is based on drug-sensitivity results from the sputum-borne strain of the patient. Drug from the first line agents are administered if the strain is sensitive to any of these and combined with second line drugs with the goal of having five active drugs based on drug sensitivity results. Second line agents-

- Injectable Agents (aminoglycosides other than streptomycin)
- Fluoroquinolones
- Oral Bacteriostatic agents -Para-aminosalisylic acid (PAS), Cycloserin, Terizidone, Ethionamide, Prothionamide, Ofloxacilin, Levofloxacilin.

Drugs are chosen with a stepwise selection process through five groups on the basis of efficacy, safety, and cost. Among the first group (the oral first-line drugs) high-dose (500 mg) isoniazid, pyrazinamide, and ethambutol are thought of as an adjunct for the treatment of MDR and XDR tuberculosis. The second group is the fluoroquinolones, of which the first choice is high-dose (250 mg) levofloxacin. The third groups are the injectable drugs, which should be used in the following order: capreomycin, kanamycin, and then amikacin and high dose are 4ml.

The fourth groups are called the second-line drugs and should be used in the following order: thioamides, cycloserine, and then aminosalicylic acid at high dose (250 mg). The fifth group includes drugs that are not very effective or for which there are sparse clinical data. Drugs in group five should be used in the following order: clofazimine, amoxicillin with clavulanate, linezolid, carbapenems, thioacetazone, and then clarithromycin at high dose (250 mg). MDR-TB patients take the combination of these groups of drugs as Cat IV. Example of a standard dose regimen (Cat IV) taken by the MDR-TB patients-

Cat IV: Pyrazinamide (500mg) + Kanamycin (4ml) + Ofloxacilin/Levofloxacilin (250mg) + Cycloserin (250mg) + Ethionamide (250mg)

MDR-TB treatment is divided into a 6-9 months intensive phase that includes the injectable agent and followed by a continuation phase of up to 18 months for a total of 24-30 months of treatment (Caminero, J.A., 2015).

1.16.1: Administration of Drugs

All doses should be used in combination with at least three other anti-TB drugs to which the patient's MDR TB isolate has been shown to be susceptible through laboratory testing. Each dose should only be given by directly observed therapy (DOT) and with case management strategies to ensure treatment adherence. Each dose should be taken with food to maximize drug absorption.

Missed Doses: If a dose is missed during the first 2 weeks of treatment, patients should not be given the missed dose but should continue the usual dosing schedule. From Week 3 onwards, if a dose is missed, patients should be given the missed dose as soon as possible, and then resume the 3 times a week regimen (Caminero, J.A., 2015).

1.17: Side Effects of Anti-Tuberculosis Drugs

A side effect or adverse drug reaction (ADR) is usually regarded as an undesirable secondary effect which occurs in addition to the desired therapeutic effects of a drug or medication. Side effects (ADRs) may vary for each individual depending on the person's disease state, age, weight, gender, ethnicity and general health. Second line agents used in the MDR-TB treatment are often less effective and cause more ADRs and toxicities. It seems that completion of the full course of therapy without significant ADRs is achieved only by a minority of patients. These ADRs may be mild or life-threatening.

Occurrence of severe ADRs is common particularly in hospitalized patients with pulmonary MDR-tuberculosis. ADRs decrease treatment effectiveness through negative impact on patients' adherence, which is an extremely important determinant of treatment outcome. Morbidity and mortality can increase when patients experience severe ADRs to anti-TB medications, which may lead to discontinuation of the drug. Meanwhile,

administration of an alternative agent may increase toxicity and may eventually increase the risk of treatment failure and relapses (Vender, M. *et al*, 2013).

1.17.1: Rifampicin

Rifampin is an antibiotic. Rifampin prevents bacteria from spreading in your body. Rifampin is used to treat or prevent tuberculosis (TB). Rifampin may also be used to eliminate bacteria from your nose and throat that may cause meningitis or other infections, even if we do not have an infection. Rifampin prevents us from spreading bacteria to other people, but the medication will not treat an infection caused by the bacteria. It may causes the following side effects-

Serious side effect such as:

- Fever, chills, body aches, flu symptoms
- Joint pain or swelling; easy bruising or bleeding, weakness;
- Urinating less than usual or not at all;
- Nausea, stomach pain, loss of appetite, itching, dark urine, clay-colored stools,

Less serious side effects may include:

- Tired feeling; or
- Red or orange colored urine, stools, tears, sweat, or saliva (RxList, 2015).

1.17.2: Isoniazid

Isoniazid is an antibiotic that fights bacteria. Isoniazid is used to treat and to prevent tuberculosis (TB). Other TB medicines should be used in combination with isoniazid. When treating active TB, isoniazid must be used with other TB medicines. Tuberculosis can become resistant to treatment if isoniazid is used alone. It may cause the following side effects- nausea, upper stomach pain, loss of appetite, and feeling weak or tired. It may increase the risk of liver damage while patients are taking isoniazid.

We should not use isoniazid if we are allergic to it, or if we have:

- Active liver disease;
- A history of severe allergic reaction to isoniazid;
- A history of hepatitis or other liver problems caused by taking isoniazid; or
- A history of severe isoniazid side effects such as fever, chills, or joint pain and Swelling (Everydayhealth.com, 2015).

1.17.3: Ethambutol

Ethambutol is an antibiotic that prevents growth of the tuberculosis bacteria in the body. Ethambutol is used to treat tuberculosis (TB), and is usually given together with at least one other tuberculosis medicine. Ethambutol can cause serious vision problems or irreversible vision loss. It may also cause the following side effects-

- Blurred vision or trouble focusing;
- Loss of vision in one eye that lasts an hour or longer;
- Increased sensitivity of your eyes to light;
- Loss of color vision (Everydayhealth.com, 2015).

1.17.4: Pyrazinamide

Pyrazinamide is used with other medications to treat tuberculosis (TB). It is an antibiotic and works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It will not work for viral infections (such as common cold, flu). Unnecessary use or misuse of any antibiotic can lead to its decreased effectiveness. It may report the following side effects-

More common:

- Pain in large and small joints

Rare:

- Pain and swelling of joints, especially big toe, ankle, and knee
- Loss of appetite

- Tense, hot skin over affected joints
- Unusual tiredness or weakness
- Yellow eyes or skin (Drugs.com, 2015).

1.17.5: Streptomycin

Streptomycin is used to treat active tuberculosis (TB) infection if it is taken with other drugs for TB. Streptomycin belongs to a class of drugs known as aminoglycoside antibiotics. It works by killing the organisms that cause the infection. It may causes the following side effects-

- Nausea, vomiting, stomach upset, or loss of appetite may occur.
- Pain/irritation/redness may occur at the injection site.
- If any of these effects persist or worsen, we should consult with doctor immediately (RxList, 2015).

1.17.6: Pyrazinamide

Pyrazinamide, the pyrazine analogue of nicotinamide, is an anti-tuberculous agent. Each pyrazinamide tablet contains 500mg of pyrazinamide for oral administration. During taking pyrazinamide one may experience some serious or minor side effects. Such as-

- An allergic reaction (difficulty breathing; closing of your throat
- Swelling of your lips, tongue, or face; or hives), fever, unusual weakness
- Fatigue, nausea, vomiting, or loss of appetite
- Yellow skin or eyes, dark urine, difficult or painful urination
- Painful or swollen joints, worsening gout, and rash in skin (RxList, 2015).

1.17.7: Kanamycin

Kanamycin is an aminoglycoside antibiotic. It kills sensitive bacteria by stopping the production of essential proteins needed by the bacteria to survive. Kanamycin mainly

used in drug-resistant tuberculosis treatment. Kanamycin may causes some side effects, but many people experience no, or minor, side effects. Side effects include-

- Diarrhea, nausea, pain, redness, or swelling at the injection site and vomiting are the common side effects.
- Kanamycin also causes severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue)
- Decreased urination; dizziness; hearing loss; increased or difficult urination
- Lightheadedness; muscle weakness; numbness or tingling; ringing or roaring in the ears; vaginal irritation or discharge etc (Drugs.com, 2015).

1.17.8: Ofloxacilin

Ofloxacilin is a second generation fluoroquinolone antibiotic. It used in drug-resistant tuberculosis treatment. It kills sensitive bacteria by stopping the production of essential proteins needed by the bacteria to survive. It may cause some sever or minor side effects. Minor side effects include-

- Diarrhea; dizziness; headache; loss of appetite; nausea;

Severe side effects are-

- Sensitivity to sunlight; trouble sleeping; vomiting etc.
- Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest
- Swelling of the mouth, face, lips, or tongue; unusual hoarseness)
- Agitation; anxiety; bloody stools; confusion; convulsions; dark urine
- Decreased urination; depression; diarrhea (severe or continuing)
- Difficulty swallowing; excessive urination, thirst, or hunger; fainting; fast or irregular heartbeat; fatigue; fever, chills, or unusual cough
- Hallucinations; joint pain or swelling; light-headedness; loss of consciousness; mental or mood changes
- Muscle pain or weakness; nervousness; nightmares; pale stools; red, swollen,

blistered, or peeling skin

- Restlessness; seizures; shortness of breath; shock (pale skin); sleeplessness; severe or persistent stomach pain or cramps (Drugs.com, 2015).

1.17.9: Levofloxacin

Levofloxacin is used for treating infections caused by certain bacteria. It is also used to prevent or treat anthrax or plague in certain patients. Levofloxacin is a third generation quinolone antibiotic. It works by killing sensitive bacteria. It may causes the following side effects-

- Constipation; diarrhea; dizziness; gas; headache; nausea
- Trouble sleeping, severe allergic reactions (rash; hives; itching; difficulty breathing or swallowing; tightness in the chest or throat; swelling of the mouth, face, lips)
- Bloody or tarry stools; chest pain; decreased or painful urination; fainting
- Fast or irregular heartbeat; fever, chills, persistent sore throat, or unusual cough; hallucinations
- Inability to move or bear weight on a joint or tendon area
- Moderate or severe sunburn; mood or mental changes (new or worsening anxiety, nervousness, agitation, confusion, depression, paranoia, restlessness, sleeplessness)
- Muscle pain or weakness etc (Drugs.com, 2015).

1.17.10: Ethionamide

Ethionamide is used for treating tuberculosis (TB) infections in combination with other medicines. Ethionamide is an antibacterial agent. It works by inhibiting or stopping the growth of TB cells, which results in cell death. It may causes the following side effects-

- Diarrhea; dizziness; drowsiness; headache; increased salivation
- Loss of appetite; metallic taste; mouth sores; nausea
- Restlessness; stomach pain; vomiting; weight loss
- Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest)

- swelling of the mouth, face, lips, or tongue
- Change in sense of smell; depression; easy bruising or bleeding
- Low blood sugar (increased heartbeat, headache, chills, sweating, tremor, increased hunger, changes in vision, nervousness, weakness, dizziness, drowsiness, fainting)
- Tingling of hands or feet; vision changes (loss of vision)
- Yellowing of the skin or eyes (Drugs.com, 2015).

1.17.11: Cycloserine

Cycloserine is used for treating tuberculosis (TB) in the lungs and other places in the body (including the kidneys) when treatment with other medicines has not been effective. Cycloserine should be used in combination with other medicines. It may also be used to treat certain urinary tract infections. Cycloserine is an antibiotic. It works by blocking the growth of the bacterial cell wall. It may causes certain side effects, such as-

- Severe allergic reactions (rash; hives; difficulty breathing
- Tightness in the chest; swelling of the mouth, face, lips, or tongue)
- Aggression; bizarre behavior; coma; confusion
- Depression; disorientation; dizziness; drowsiness
- Exaggerated reflexes; excessive irritability; feeling of a whirling motion
- Headache; memory loss; mental or mood changes; mood swings
- Numbness or tingling of the skin; paralysis; seizures
- Slurred speech or other speech problems
- Swelling of the hands or feet; tremors
- Thoughts of suicide; unusual tiredness or weakness (Drugs.com, 2015).

1.17.12:Prothionamide

Prothionamide is a thioamide, and is considered to be interchangeable with ethionamide. It causes certain side effects, such as-

- Nausea, vomiting, diarrhea, anorexia,

- Excessive salivation, metallic taste, stomatitis, and abdominal pain
- Acute hepatitis (rare), Dizziness, encephalopathy, peripheral neuropathy
- Optic Neuritis (rare), Psychotic disturbances, depression
- Gynaecomastia, hypoglycemia, hypothyroidism (TB Drug Monographs, 2015).

1.17.13: Para-aminosalisylic Acid

Para aminosalisylic acid is used in combination with other drugs to treat tuberculosis. Aminosalicylic acid is known as an antituberculosis antibiotic. It works by stopping or slowing the growth of bacteria. It causes certain side effects, such as-

- Upset stomach
- Nausea, vomiting
- Diarrhea may occur (Webmd.com, 2015).

1.17.14: Terizidone

Terizidone is similar to cycloserine. It acts by inhibiting cell wall synthesis by competitively inhibiting two enzymes, L-alanine racemase and D-alanine ligase, thereby impairing peptidoglycan formation necessary for bacterial cell wall. It may cause some effects, such as-

- Dizziness, slurred speech, headache and convulsions
- Others include tremors, insomnia, confusion, depression.
- The most dangerous side effect is suicidal tendency.
- Nausea, vomiting, skin allergies and rashes are also reported (Drugs.com, 2015).

2. Literature Review

2.1: Adverse Reactions among Patients Being Treated for MDR-TB in Tomsk, Russia

Shin, S.S. *et al* conducted a retrospective case series of 244 MDR-TB patients enrolled in Tomsk between 10 September 2000 and 10 September 2002. Adverse reactions were determined by laboratory data and/or clinical criteria. A multiple logistic regression model was performed to determine whether the occurrence of adverse reactions was associated with poor treatment outcome. In this cohort, 76.0% were cured, 6.6% failed, 4.9% died and 11.5% defaulted. Adverse events were observed in 73.3% of patients, occurring in 74.8% of patients who were adherent (taking at least 80% of prescribed doses) and 59.1% of non-adherent individuals (P 0.11).

The impact of adverse events on outcome was modified by non-adherence; among adherent patients, the occurrence of any adverse reaction was associated with treatment cure (adjusted odds ratio 3.24, 95% confidence interval 1.56–6.70). Conclusion of this experiment is that adverse reactions occurred frequently in MDR-TB patients in Tomsk, Russia, but did not negatively impact treatment outcome. The occurrence of adverse reactions among adherent patients was associated with treatment cure (Shin, S.S. *et al*., 2015).

2.2: Adverse Events Associated with Second-Line Drugs in the Management of MDR-TB in Estonia, Latvia, Peru and Philippine

Nathanson, *et al* conducted an experiment to determine the adverse events associated with second-line drugs have been mentioned as obstacles in the management of multidrug-resistant tuberculosis (MDR-TB). Data on adverse events were collected from five DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast).

The results show that among 818 patients enrolled on MDR-TB treatment only 2% of patients stopped treatment, but 30% required removal of the suspected drug(s) from the regimen due to adverse events. The study shows that adverse events are manageable in the treatment of MDR-TB in resource-limited settings provided that standard management strategies are applied (Nathanson, *et al*., 2004).

2.3: Adverse Effects of Multidrug-Resistant Tuberculosis Treatment with a Standardized Regimen: a Report from Iran

Baghaei, *et al* conducted a study to evaluate adverse drug reactions of treatment of MDR-TB. This study was conducted at the national referral center of tuberculosis in Tehran, Iran, to evaluate adverse drug reactions of treatment of MDR-TB. From 2006 to 2009, all patients admitted into Masih Daneshvari Hospital in Tehran, Iran, for MDR-TB were considered for this study.

The standard treatment for MDR-TB consisted of amikacin, prothionamide, ofloxacin, and cycloserine. Ethambutol and pyrazinamide were added to treatment if mycobacterium was sensitive to them. All adverse effects observed in patients were recorded in this registry. Eighty patients were considered in the study; of this cohort, 44 were male and 36 were female. The mean age of patients was 40.64 ± 17.53 years (range, 14-81 years). All patients received standardized therapy for MDR-TB.

The major adverse effects included neurologic side effects (depression, convulsions, consciousness, psychosis, suicide; 7.5%), hepatitis (5%), rash (1.3%), renal toxicity (3.8%), and auditory toxicity (14.5%). Those with neurologic side effects had less favorable outcome (P value = 0.038) and risk of death was increased among them (odds ratio, 13.8; 95% confidence interval, 2.2-86.77).

Other adverse effects did not show statistical significance in this analysis. A major adverse effect such as neurologic side effects (depression, convulsions, consciousness,

and psychosis) can result in an increased chance of death among patients with MDR-TB **(**Baghaei, P. *et al*., 2015).

2.4: Serious Treatment Related Adverse Drug Reactions amongst Anti-Retroviral Naïve MDR-TB Patients

Walt Martha, *et al* conducted a survey amongst Anti-Retroviral naïve MDR-TB patient to evaluate adverse side effects. They evaluated the impact of severe adverse drug reactions among a prospective cohort of MDR-TB patients in South Africa (2000–2004). The HIV-infected study participants were anti-retroviral naïve. Of 2,079 patients enrolled, 1,390 (66.8%) were included in this analysis based on known HIV test results (39.1% HIV-infected).

At least one severe ADR was reported in 83 (6.9%) patients with ototoxicity being the most frequent ADR experienced (38.9%). They found that being HIV-infected but antiretroviral naïve did not increase occurrence of sever adverse drug reactions in patients on second-line anti-tuberculosis drugs. Early screening and proactive management of adverse drug reactions in this patient population is essential, especially given the rollout of decentralized care and the potential for overlapping toxicity of concomitant MDR-TB and HIV treatment (Van der Walt, M. *et al*., 2015).

2.5: Analysis of 63 Patients of MDR TB on DOTS Plus Regimen: An LG Hospital, TB Unit, Ahmadabad Experience

Vishakha, *et al* conducted an analysis to analyze demographic, clinical, radiological and bacteriological profile, drug sensitivity pattern, adverse drug reactions and treatment outcome in Multi Drug Resistant TB (MDR TB i.e. in vitro resistance to isoniazid and rifampicin) patients treated with DOTS plus regimen. From August 2007 to June 2012, 63 MDR TB patients were analyzed retrospectively.

Sputum smear and culture examination for tubercle bacilli were performed every month in intensive phase started at the end of third month and then every third month in

continuation phase until end of treatment. Regular chest radiography was done at commencement of therapy, at the end of intensive phase and at the end of treatment. Analysis was made for following variables: age, gender, extent of lung lesion, correlation of sputum smear and culture conversion with clinical and radiological improvement, drug sensitivity pattern, risk factors for adverse outcome and adverse drug reactions.

Nine patients (39.13%) were cured, three patients (13.04%) failed, six patients (26.08%) defaulted and five patients (21.73%) died of total 23 patients whose outcomes are available after 30 months of enrolment. Out of remaining 40 patients four patients defaulted, eight patients died and 28 were still on therapy. Mean time for sputum smear and culture conversion were 4.2±2.1 and 4.29±2.4 months, respectively. Extensive lung lesion, cavitations, poor adherence to treatment, high initial bacterial load and BMI less than 18 are variables associated with poor outcome. Thirty six (57.14%) patients experienced adverse drug reactions and 21 of them required drug modifications (Vishakha, *et al*., 2015).

2.6: Side Effects Associated with the Treatment of Multidrug-Resistant Tuberculosis

Törün, *et al* conducted a survey to report the frequency of treatment side effects in cases of multidrug-resistant (MDR-TB) tuberculosis. A retrospective review of the medical records of 263 patients who received individualized treatment for MDR-TB between April 1992 and June 2004.One or more side effects developed in 182 cases (69.2%). These effects led the clinicians to withdraw one or more drugs from the treatment regimen in 146 cases (55.5%)

Side effects observed most frequently included: ototoxicity (41.8%), psychiatric disorders (21.3%), gastrointestinal disturbance (14.0%), arthralgia (11.4%), epileptic seizures (9.9%), hepatitis (4.5%), and dermatological effects (4.5%). At the time of analysis, treatment was successful in 204 (77.6%) cases. Fifty-nine patients (22.4%) had poor outcomes. Timely and aggressive management of drug side effects means that high side

effect rates in MDR-TB treatment need not compromise success rates (Törün, T. *et al*., 2015).

2.7: Adverse Drug Reactions in Multidrug-Resistant Tuberculosis

Palmero, D. *et al* conducted a survey to analyze adverse drug reactions in multi-drug resistant tuberculosis. Multidrug-resistant tuberculosis (MDRTB) poses difficulties in diagnosis and treatment, including increased frequency of adverse reactions to anti-tuberculosis drugs (ADRAs), which compromise the effectiveness of treatment. This is specially complicated in the treatment of patients co-infected with HIV which includes the antiretroviral therapy plus the treatment of eventual co morbidities.

A total of 121 MDRTB patients, 87 HIV-negative and 34 HIV positive, assisted in the Hospital F. J. Muñiz, Buenos Aires, during the period 2003-2007 were retrospectively studied. The incidence of ADRAs among the two groups of patients was compared. All the patients with adherence to treatment (no more than one abandon, recovered) were included in the study. Antituberculosis drugs used were: ethambutol, pyrazinamide, ofloxacin, moxifloxacin, cycloserine, ethionamide, PAS, streptomycin, kanamycin, amikacin and linezolid.

The emergence of ADRAs and the proportion of severe reactions attributed to antituberculosis drugs were similar in both groups: 44.8% in HIV negative and 44.1% in HIV positive, but it was observed an additional 23.5% of adverse reactions to antiretroviral therapy in the second group. There were differences in the type of reactions and time of occurrence between the two groups.

One HIV positive patient died of epidermolysis. The proportion of adverse reactions in HIV/AIDS patients increased 50% when those attributed to antiretroviral treatment were included. We conclude that the studied population showed a frequency of ADRAs higher than it would be expected in the treatment of susceptible TB, but there was no difference in its frequency among HIV-negative and positive patients (Palmero, D. *et al*., 2015).

3.1: Type of Study

The study was a clinical survey based study.

3.2: Aims and Objective of the Study

The objective of the present study was to conduct a survey among the TB and MDR-TB patients of NIDCH and to study the side effects of TB and MDR-TB medications in such patients.

3.3: Study Area

The study was done in National Institute of Chest Disease and Hospital (NIDCH), Mohakhali, Dhaka-1212, Bangladesh.

3.4: Study Population

From July-September 2015, the survey was performed on 100 TB patients (MDR-TB inclusive), who were admitted into the hospital.

3.5: Inclusion Criteria

In this survey, all ages of patients were included having TB/MDR-TB (with or without DM).

3.6: Exclusion Criteria

In this survey, surgery patients and pregnant women were excluded.

3.7: Study Tool

To facilitate the study of Side effects of TB and MDR-TB medications in patients in Bangladesh, a questionnaire was established in June 2015. Through this questionnaire, demographic information of patients was collected along with some question regarding

awareness of TB and some question about side effects suffered by TB and MDR-TB patients. We have collected information on patient's general information, their living status, their TB history, TB treatment, TB treatment outcome, DM status and the side effects **etc.** suffered by the TB & MDR-TB patients.

3.8: Questionnaire Development

The questionnaire was developed based on some common factors that lead to incidence of TB/MDR-TB along with side effects of TB and MDR-TB medications in such patients, in Dhaka, Bangladesh.

The questionnaire was prepared to obtain maximum clinical history of the patients along with demographic information and lifestyle factors that would help us link this information to the side effects suffered by patients. The questionnaire was developed from the perspective of Bangladesh so that maximum accurate statistical data can be collected from the survey.

3.9: Data Analysis

After data collection, all the filled in questionnaires were checked and crosschecked in order to correct inconsistency in information and coding. Data were analyzed using Microsoft Office Excel (Version 2007).

3.10: Ethics

This study was done without conflicting any the ethical issues. Ethical consideration was checked by the research supervisor with the research policy of the East West University.

4.1: Demographic Data

Table 4.1: Basic Demographic Information

Characteristic	Percentage (%)
Gender	
Male	53
Female	47
Age	
≤ 20 years	18
21-30 years	22
31-40 years	31
41-50 years	17
51-60 years	11
≥60 years	1
Education level	
Illiterate	31
Primary	17
Secondary	15
College	24
Graduate	12
Post Graduate	1
Occupation	
Govt. Employee	8
Private Employee	9
Private Business	21
Housewife	27
Student	18
Garments worker	10
Farmer	7

Characteristic	Percentage (%)
Income per month(BDT)	
No income	33
≤ 5000	12
5000-10,000	36
10,000-25,000	16
≥25,000	3
Weight (kg)	
≤ 30	1
31-40	25
41-50	51
51-60	14
61-70	9

4.2: No. of People Living in the Household

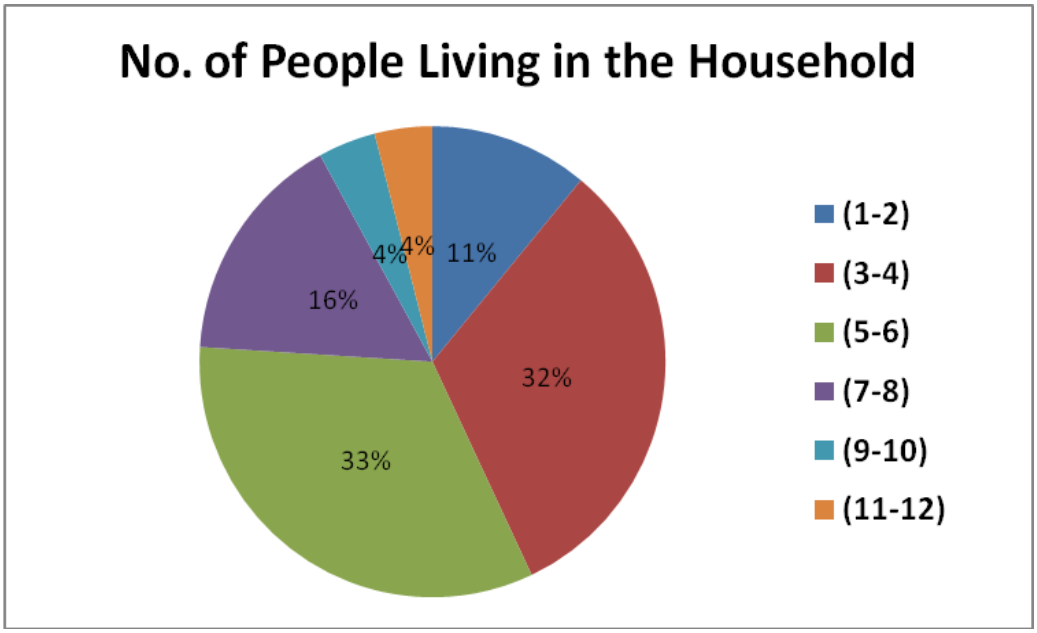

Fig 4.1: No. of People Living in the Household

The above figure shows that the major percentage of patients (33%) lived in a household with (5-6) people whereas the least percentage of patients (4%) lived in a household with (9-10) and (11-12) people.

4.3: No. of People Living in the Same Room

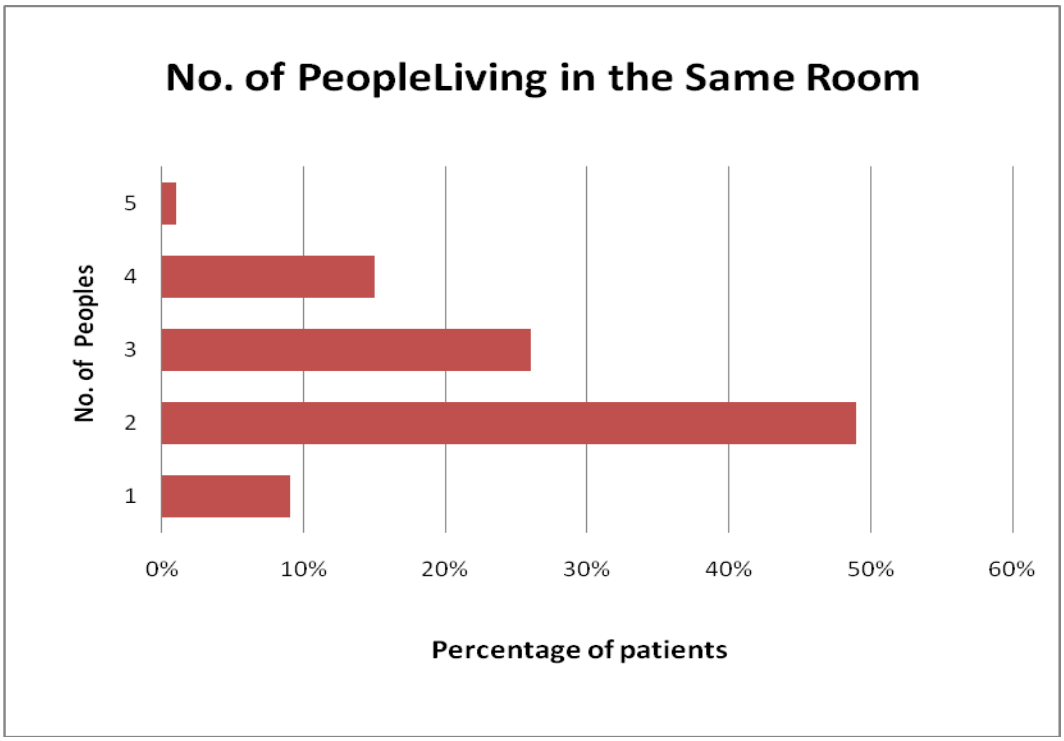

Fig 4.2: No. of People Living in the Same Room

We found that the major percentage (51%) of patients had 2 people living in the same room whereas the least percentage (6%) of patients had 5 people living in the same room.

4.4: Diagnosed with TB for the 1st time

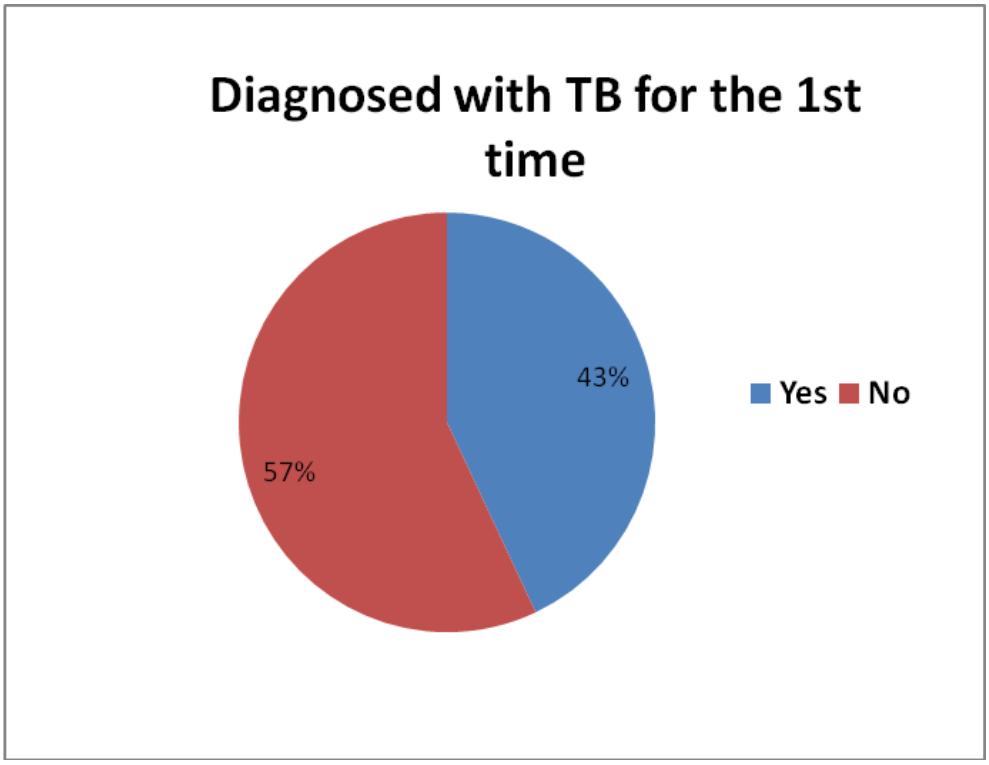

Fig 4.3: Diagnosed with TB for the 1st time

According to our study, we found that among 100 TB patients 43% patients are diagnosed with TB for the 1st time.

4.5: No. of Times Diagnosed with TB

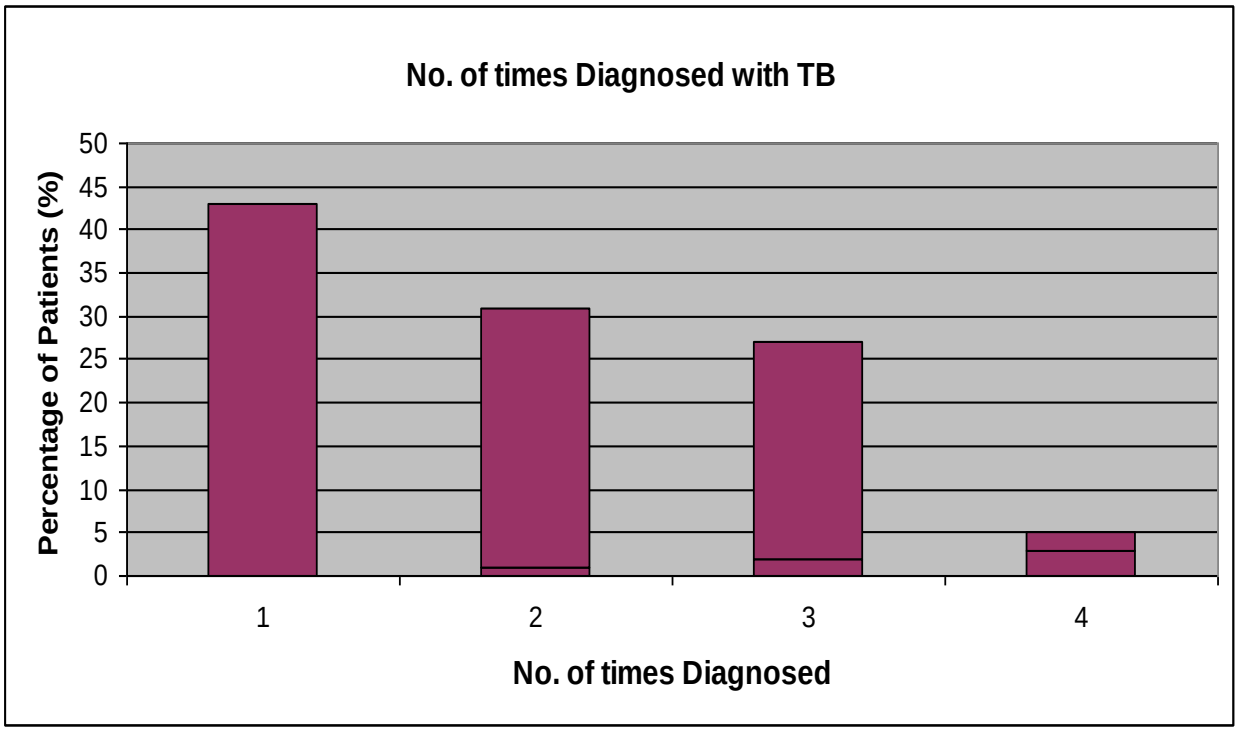

Fig 4.4: No. of Times Diagnosed with TB

Among 100 TB patients, we found that majority of patients (43%) were diagnosed once before their current diagnosis and the least percentage of patients (5%) were diagnosed 4 times before their current diagnosis.

4.6: Presence of TB Patients in Family

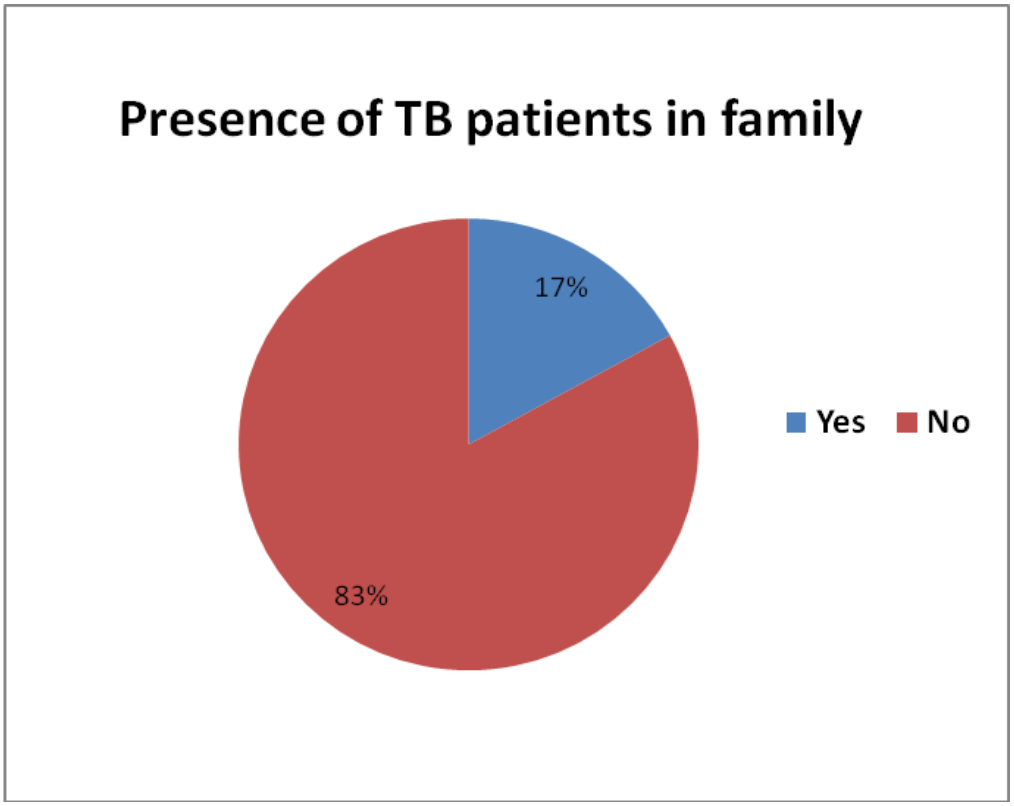

Fig 4.5: Presence of TB patients in Family

In our study, we found that majority of patients (83%) do not have TB patients present currently in their family.

4.7: Smoking Status

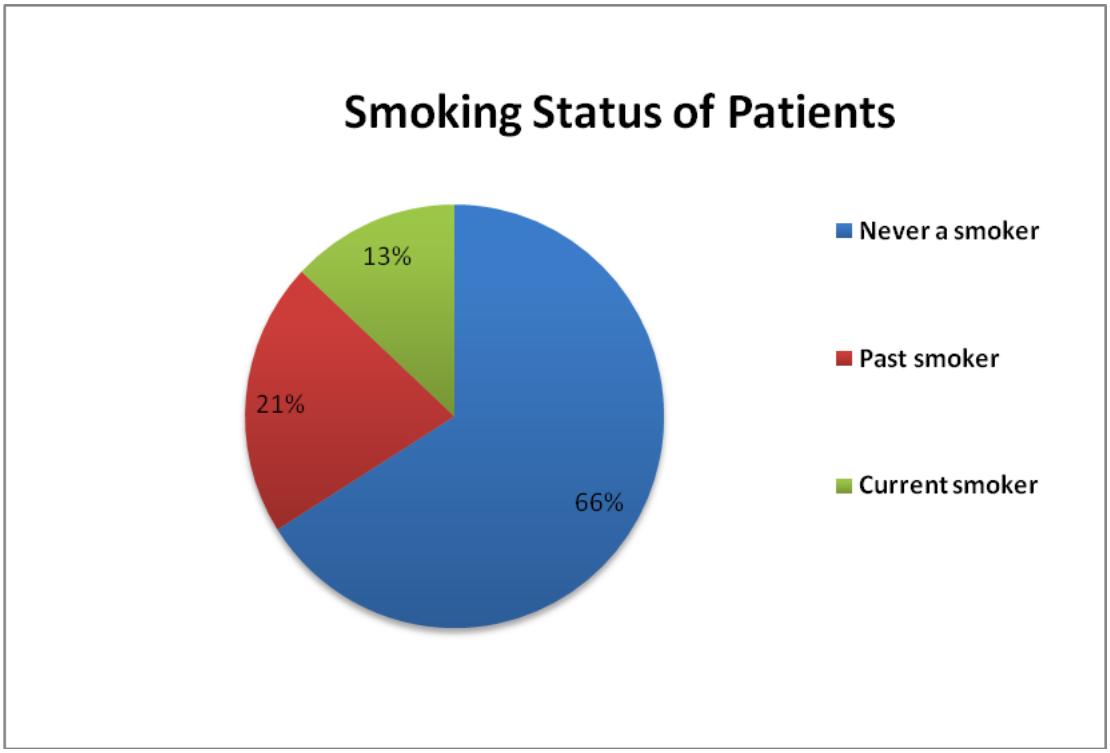

Fig 4.6: Smoking Status

In our study, we found that majority of patients (66%) never smoked 21% patients were past smokers and 13% patients are current smokers.

4.8: Drinking Status

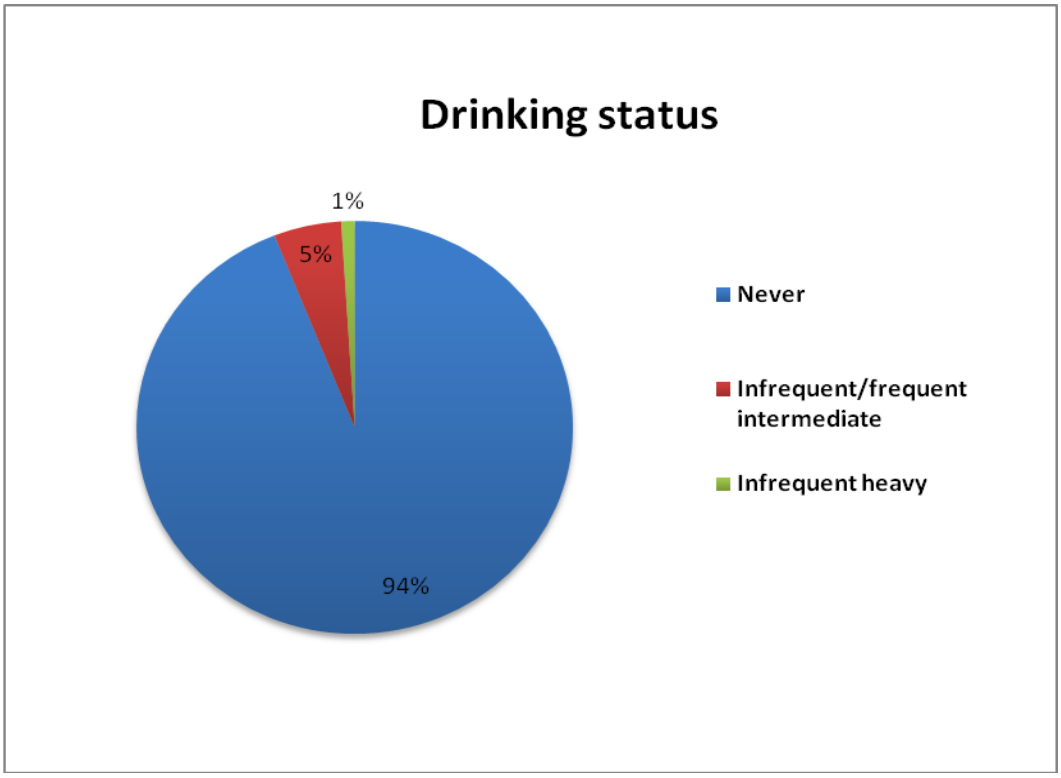

Fig 4.7: Drinking Status

We found that, among 100 TB patients, 94% patients never drank alcohol, 5% patients drank alcohol infrequently/ frequent intermediately and 1% of patients never drank alcohol.

4.9: Habituation of Other Toxic Substances

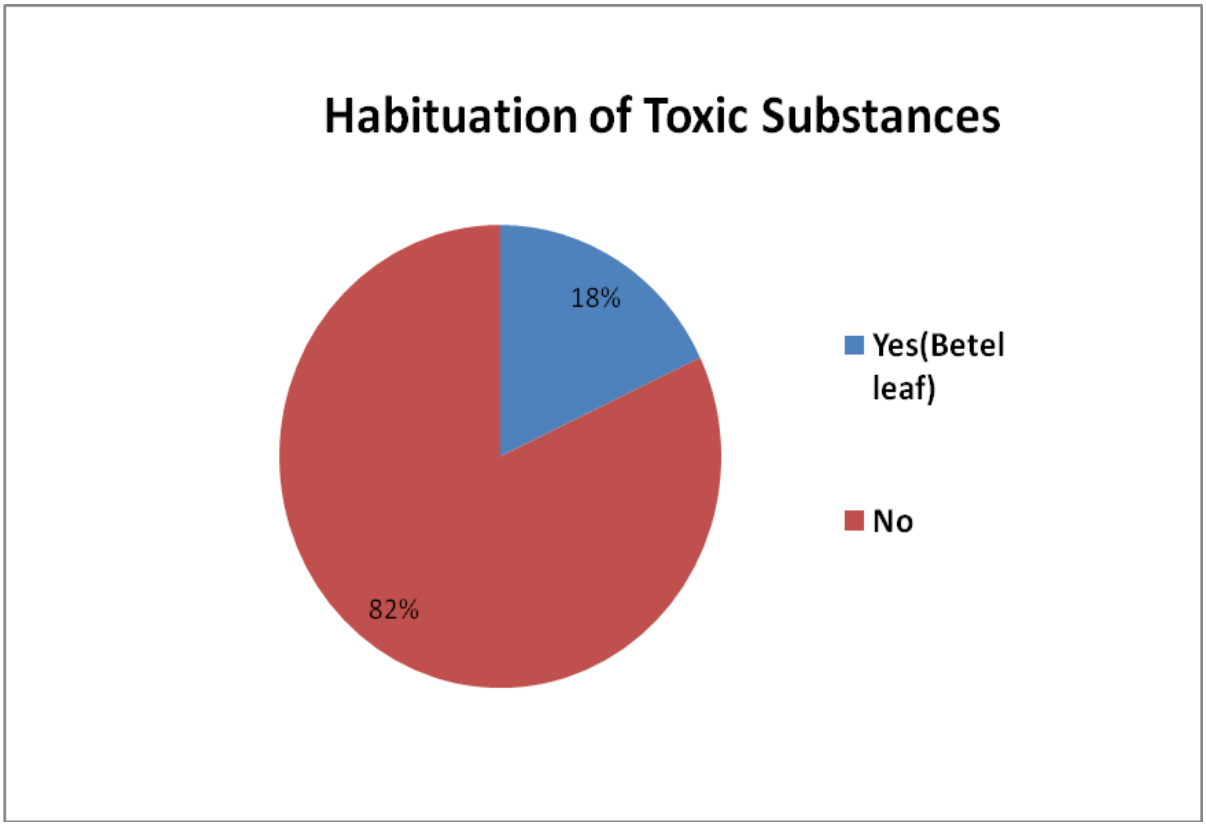

Fig 4.8: Habituation of Other Toxic Substances

In our study, we found that among 100 TB patients 18% patients had habituation of Betel leaf and 82% patients were not habituated of any toxic substance.

4.10: Prevalence of DM in TB Patients

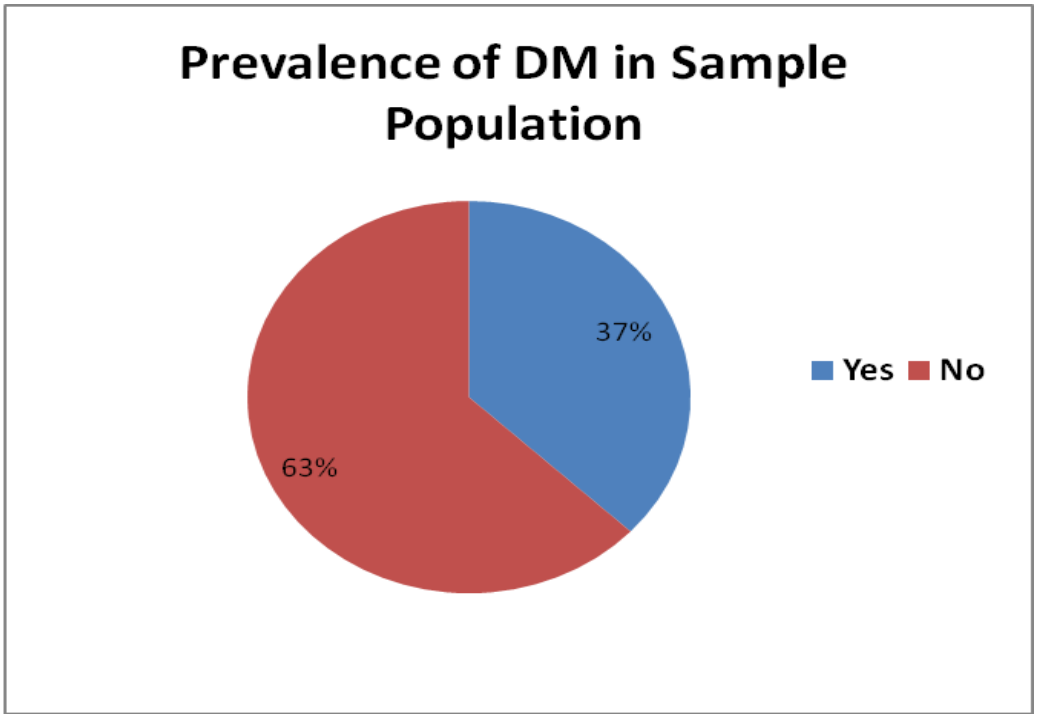

Fig.9: Prevalence of DM in TB patients

We found that, among 100 patients (both TB and MDR-TB), 37% patients had diabetes mellitus.

4.11: Symptoms Observed by the TB Patients

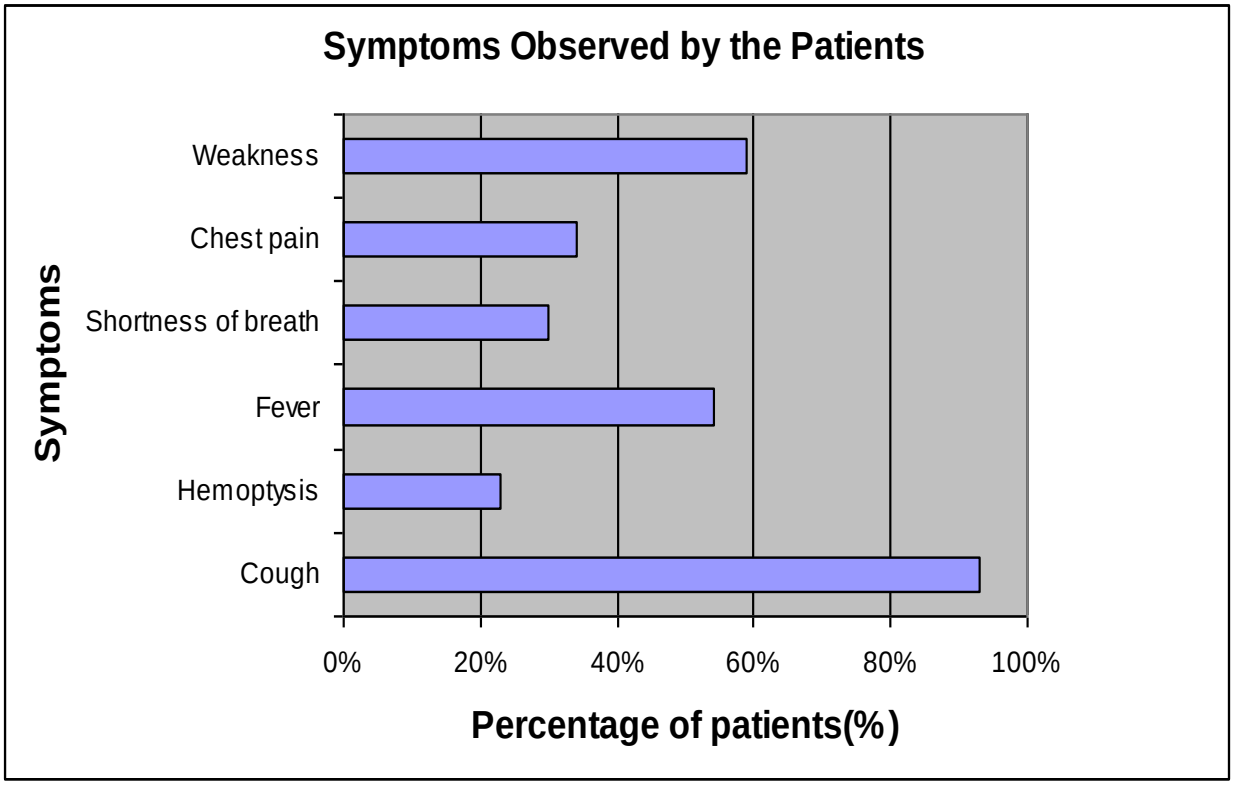

Fig 4.10: Symptoms Observed by the TB Patients

In our study, we have seen that majority of patients suffered cough (93%), followed by weakness (59%), fever (54%), chest pain (34%), shortness of breath (30%).The least number of patients suffered from hemoptysis (23%).

4.12: Time Elapsed between Onset and Treatment

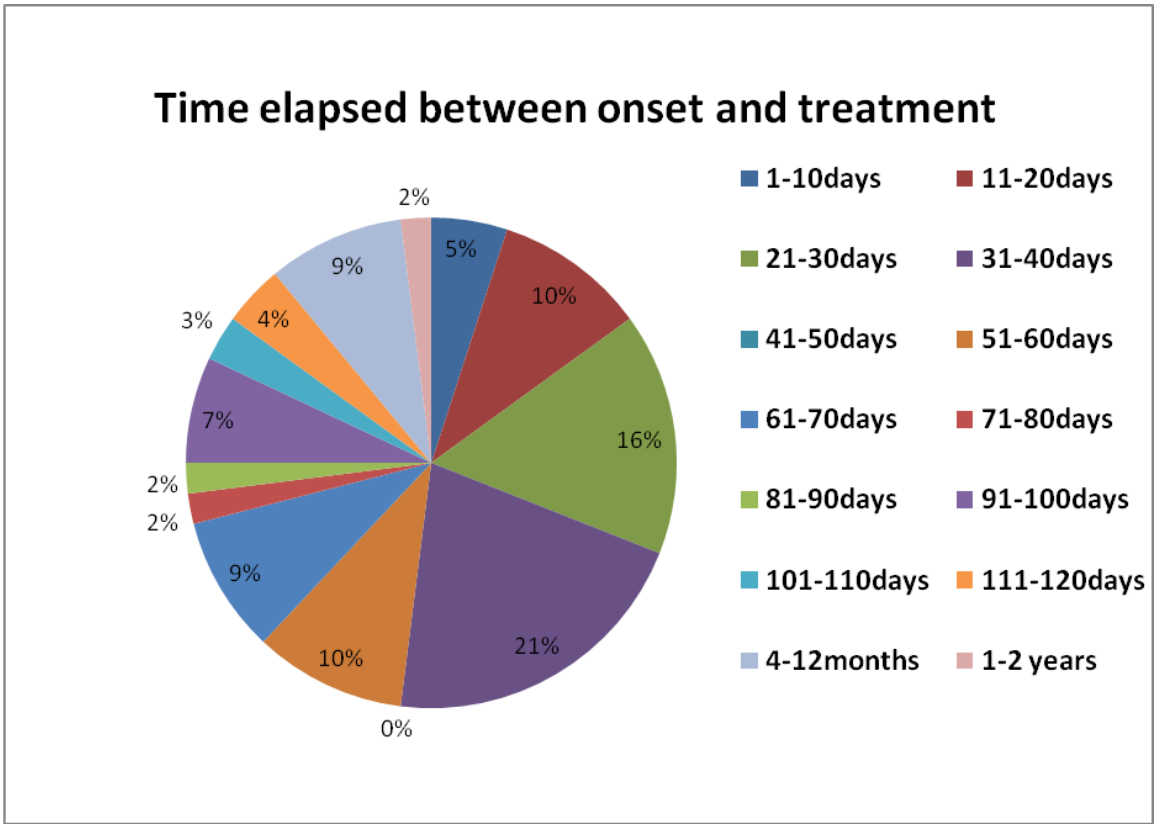

Fig 4.11: Time Elapsed between Onset and Treatment

In our study, we found that majority of patients (21%) received treatment (31-40) days after onset. The least number of patients (2%) received treatment after (11-20) days, (71-80 days) or (81-90) days.

4.13: Diagnosis Techniques of TB

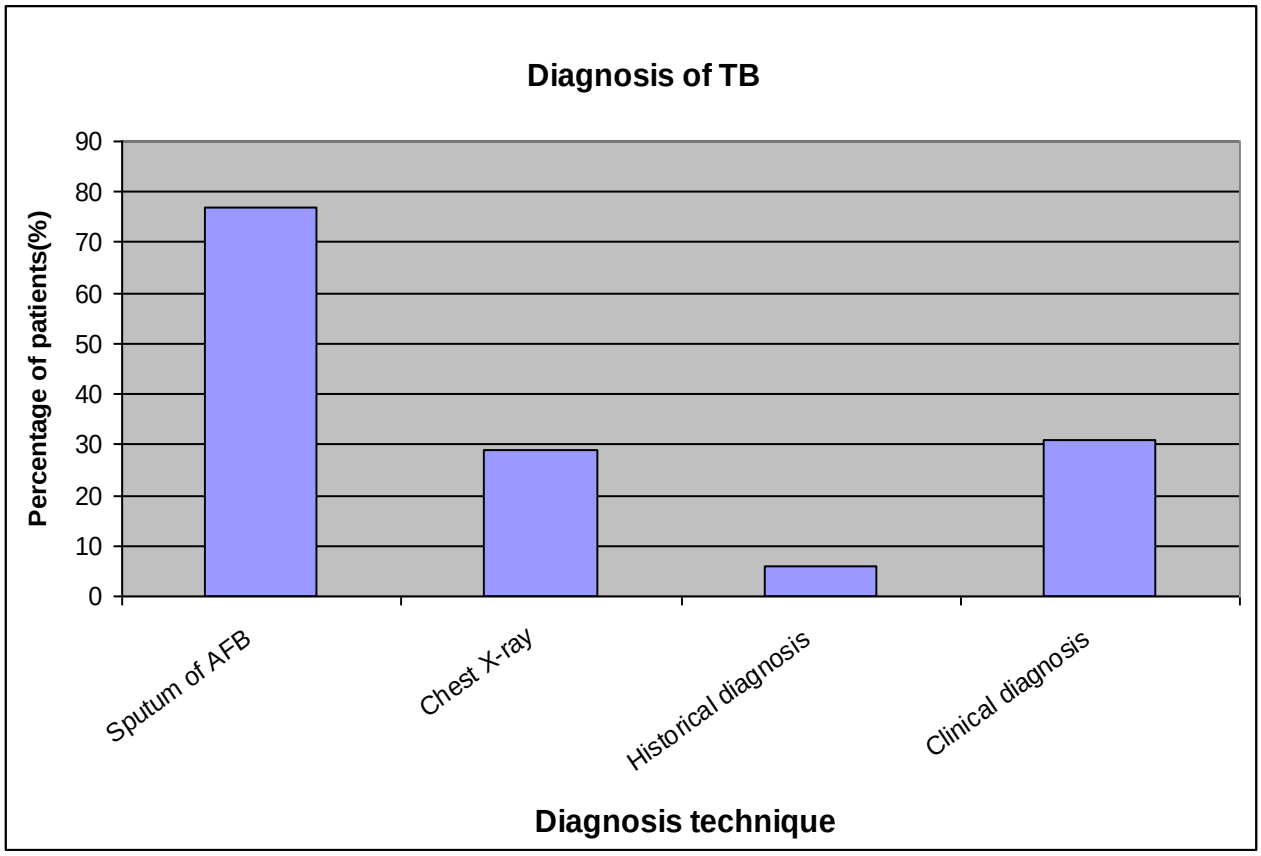

Fig 4.12: Diagnosis Techniques of TB

We found that, among 100 TB patients, 77% patients were diagnosed by sputum of AFB, 29% patients were diagnosed by Chest X-ray, 31% patients were diagnosed by clinical diagnosis and 6% of patients were diagnosed by historical diagnosis.

4.14: Type of TB

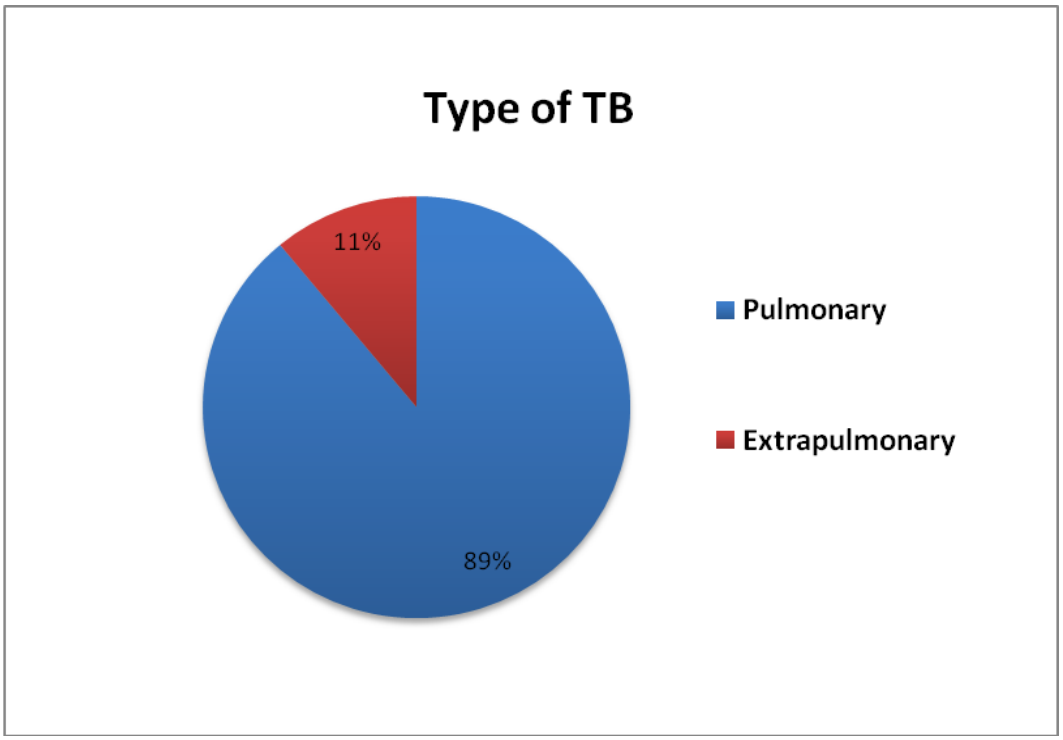

Fig.13: Type of TB

In our study, we found that 89% had pulmonary TB whereas 11% of patients had extrapulmonary TB.

4.15: Medications Taken by TB Patients

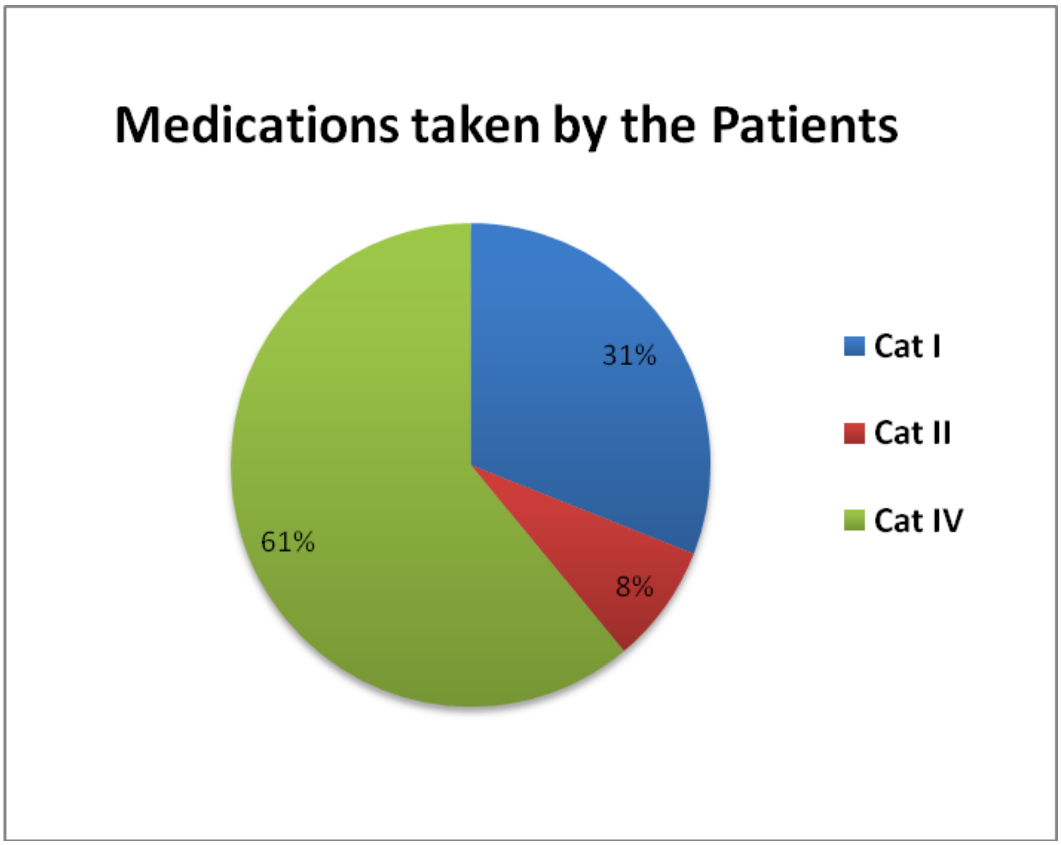

Fig 4.14: Medications Taken by TB Patients

In our study, we found that 61% of patients took Cat IV medications for MDR-TB, 32% of patients took Cat I and 8% of patients took Cat II medications for TB.

4.16: Completion of Primary Treatment

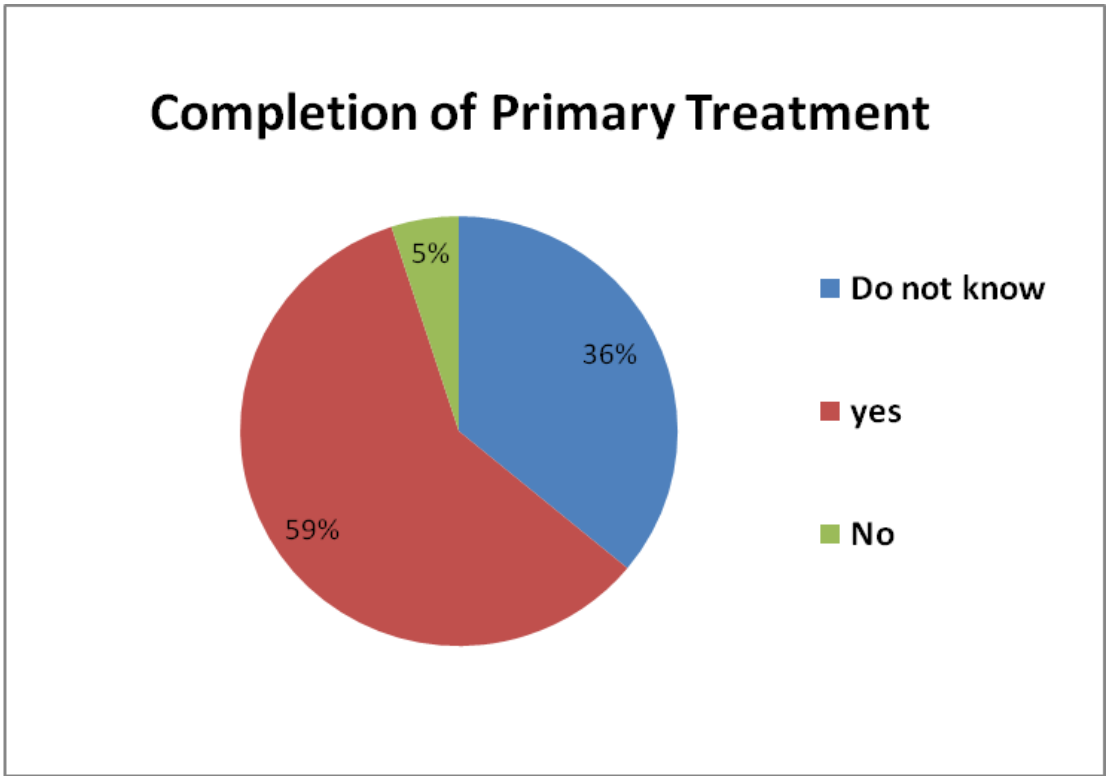

Fig 4.15: Completion of Primary Treatment

In our study, we found that among 100 TB patients, 59% patients completed their primary treatment and 5% of patients said that they did not complete their primary treatment and 36% of patients did not know about their primary treatment.

4.17: Prevalence of MDR-TB in the Sample Population

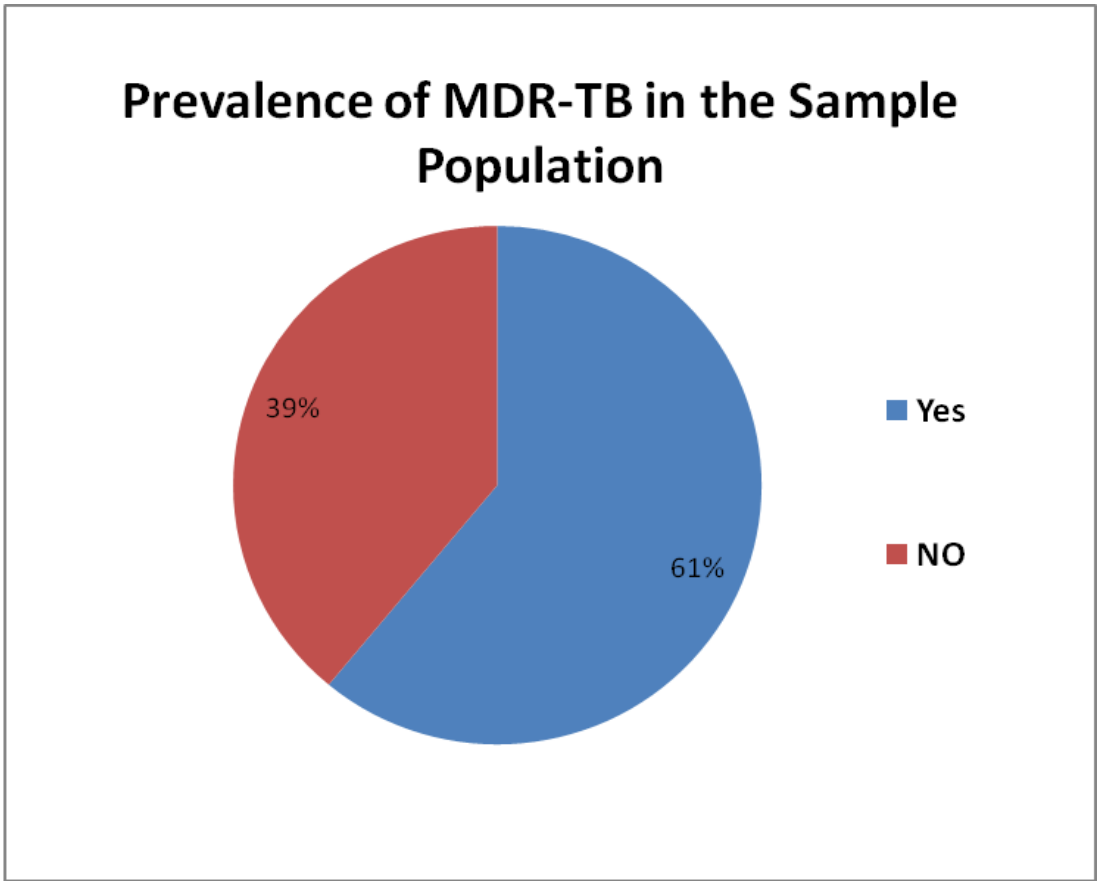

Fig 4.16: Prevalence of MDR-TB in the Sample Population

According to our study, we found that among 100 patients majority of patients (61%) were MDR-TB patients.

4.18: History of TB Treatment

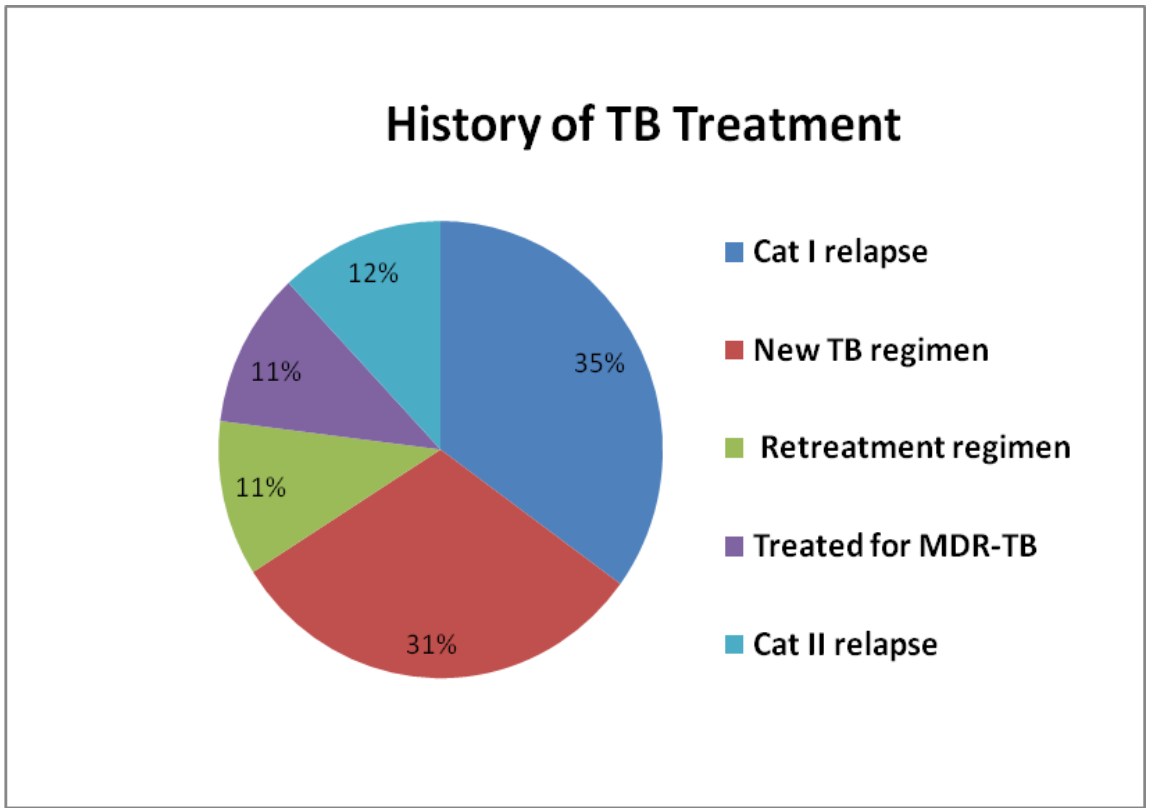

Fig 4.17: History of TB Treatment

In our study, we found that 35% patients are treated for TB due to Cat I relapse, 12% patients are treated due to Cat II relapse and 29% patients are treated for new TB regimen.

4.19: Awareness Regarding Causes of TB

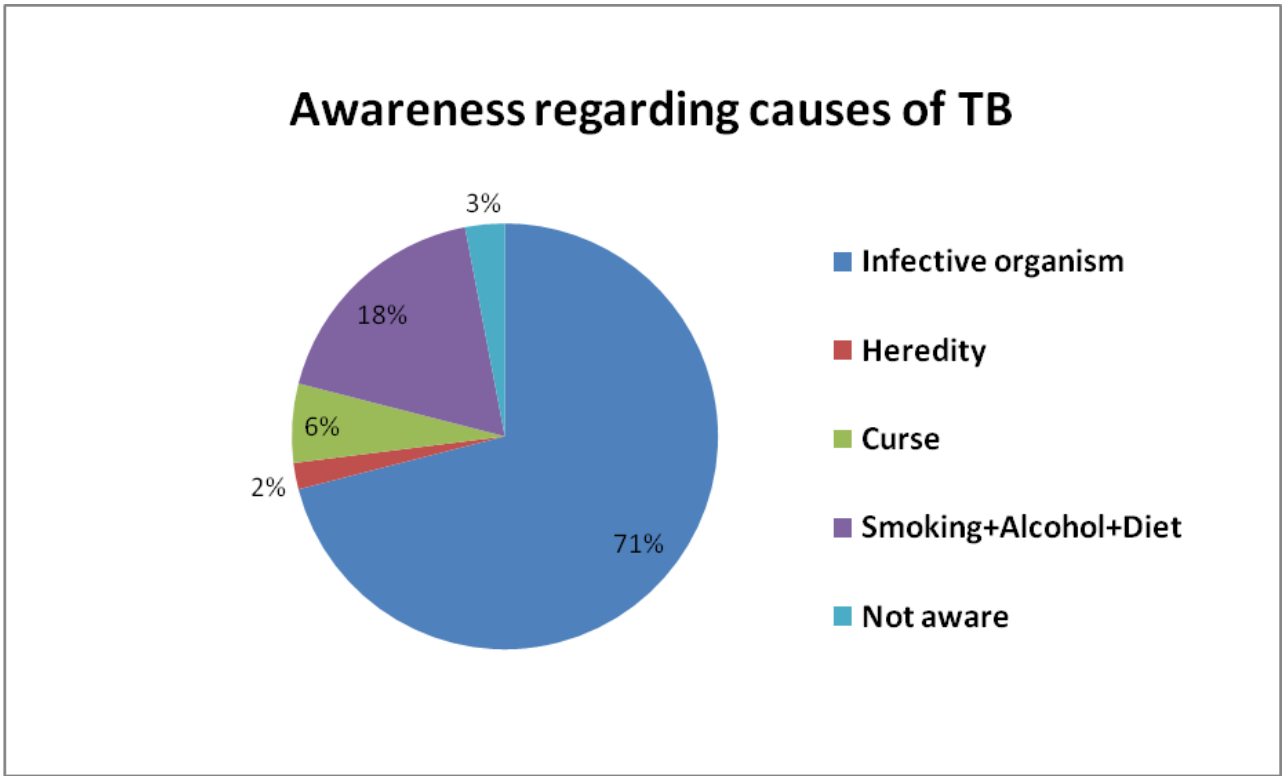

Fig 4.18: Awareness Regarding Causes of TB

Majority of patients (71%) knew that TB was caused by infective organism and least number of patients (2%) knew that TB was caused by heredity.

4.20: Awareness of Mode of Spread of TB

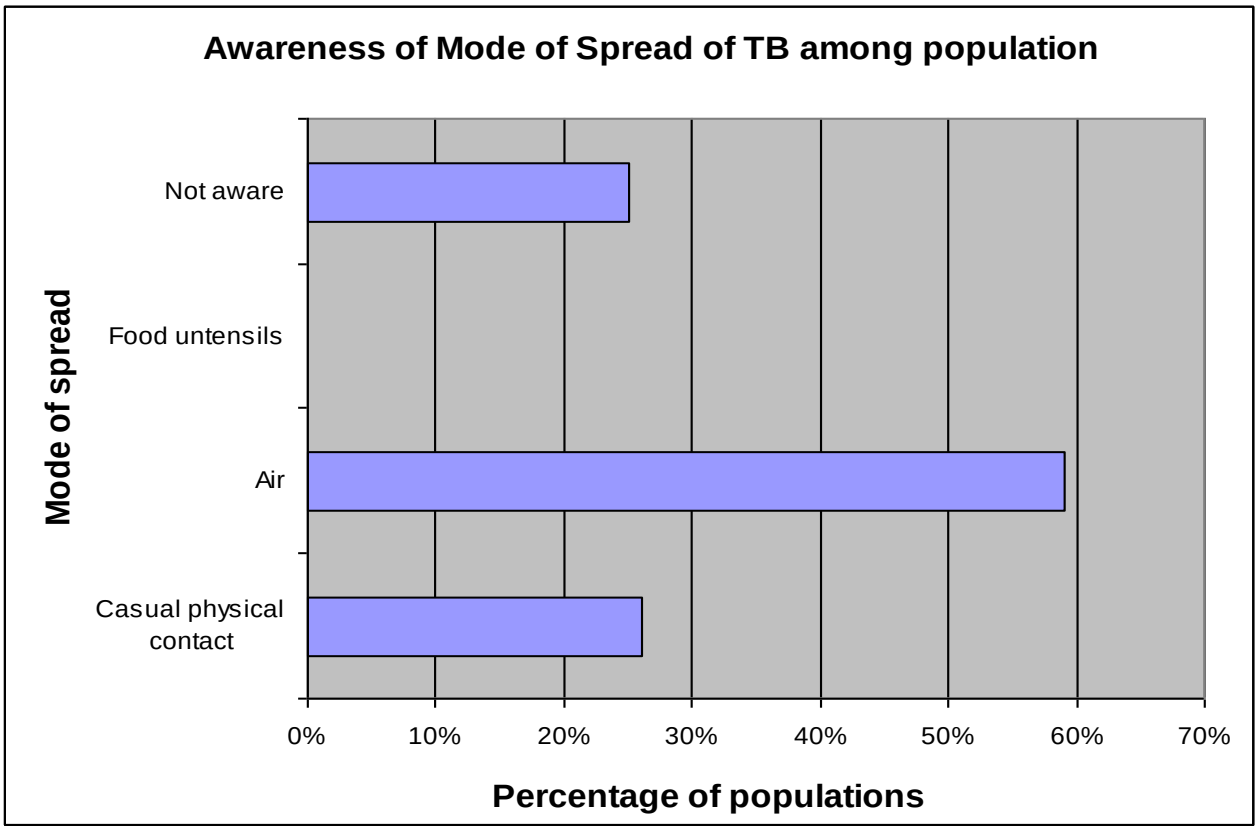

Fig 4.19: Awareness of Mode of Spread of TB

Majority of patients (59%) thought that Air is the mode of spread of TB whereas 26% of patients thought that Casual physical contact and 26% patients did not know about the mode of spread of TB.

4.21: Awareness Regarding Diagnosis of TB

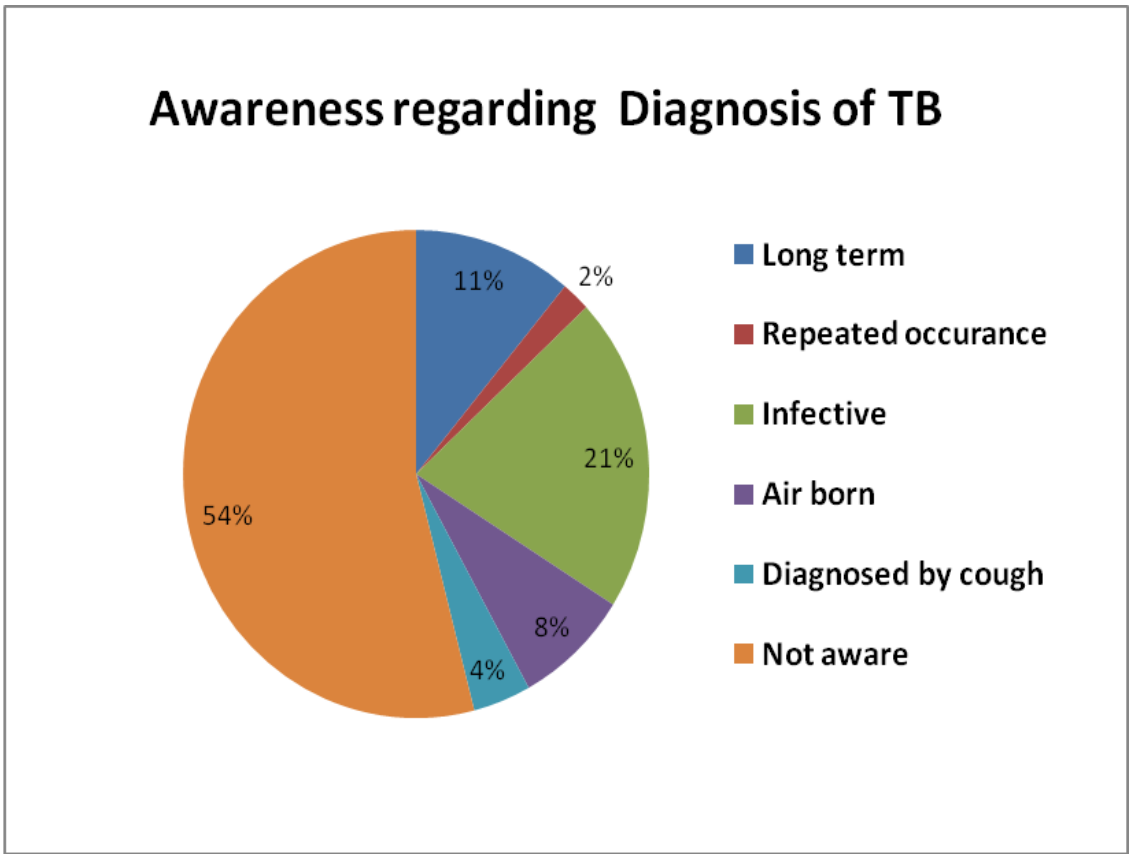

Fig 4.20: Awareness Regarding Diagnosis of TB

We found that, Majority of patients (54%) did not know about diagnosis of TB whereas 21% of patients thought TB is Infective, 11% of patients thought TB is a long term disease and 8% of patients thought TB is an air born disease.

4.22: Awareness Regarding Treatment of TB

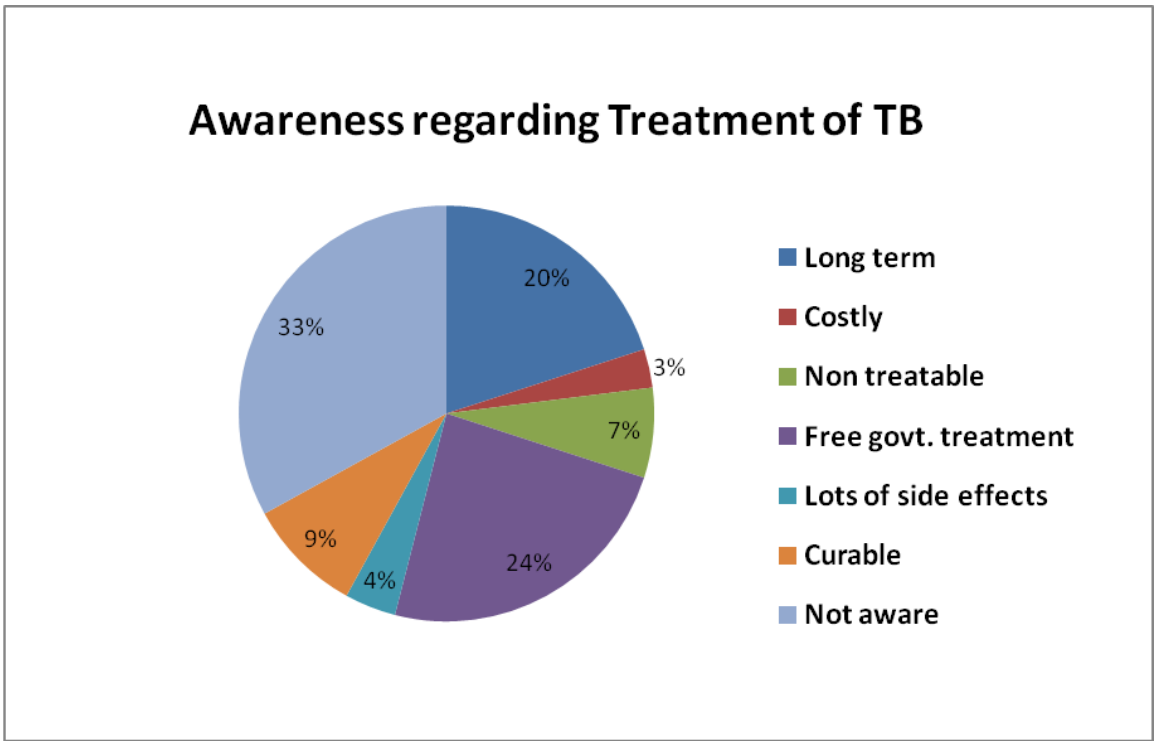

Fig 4.21: Awareness Regarding Treatment of TB

Majority of patients (33%) were not aware of treatment of TB, 24% of patients knew that TB treatment is free and the least number of patients (3%) thought that the treatment was costly.

4.23: Awareness Regarding Prevention of TB

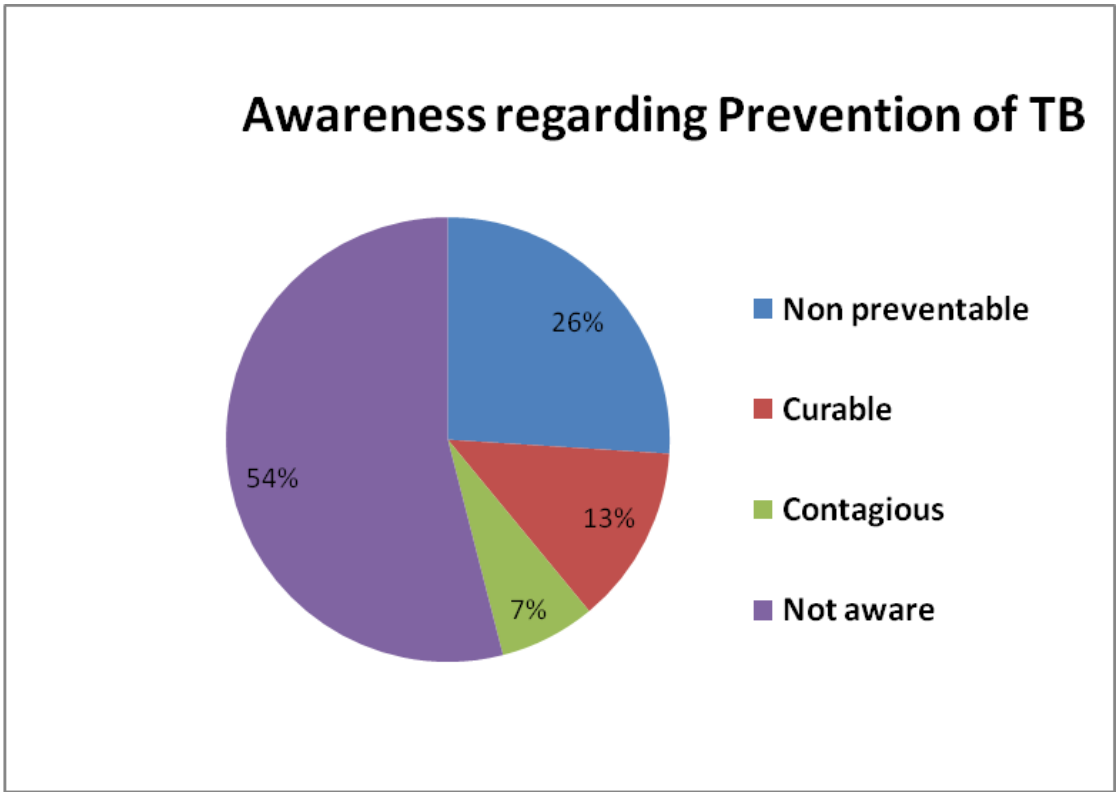

Fig 4.22: Awareness Regarding Prevention of TB

Majority of patients (54%) were not aware of Prevention of TB, 26% of patients knew that TB treatment is not preventable and the least number of patients (7%) thought that TB is contagious.

4.24: Sources of Information

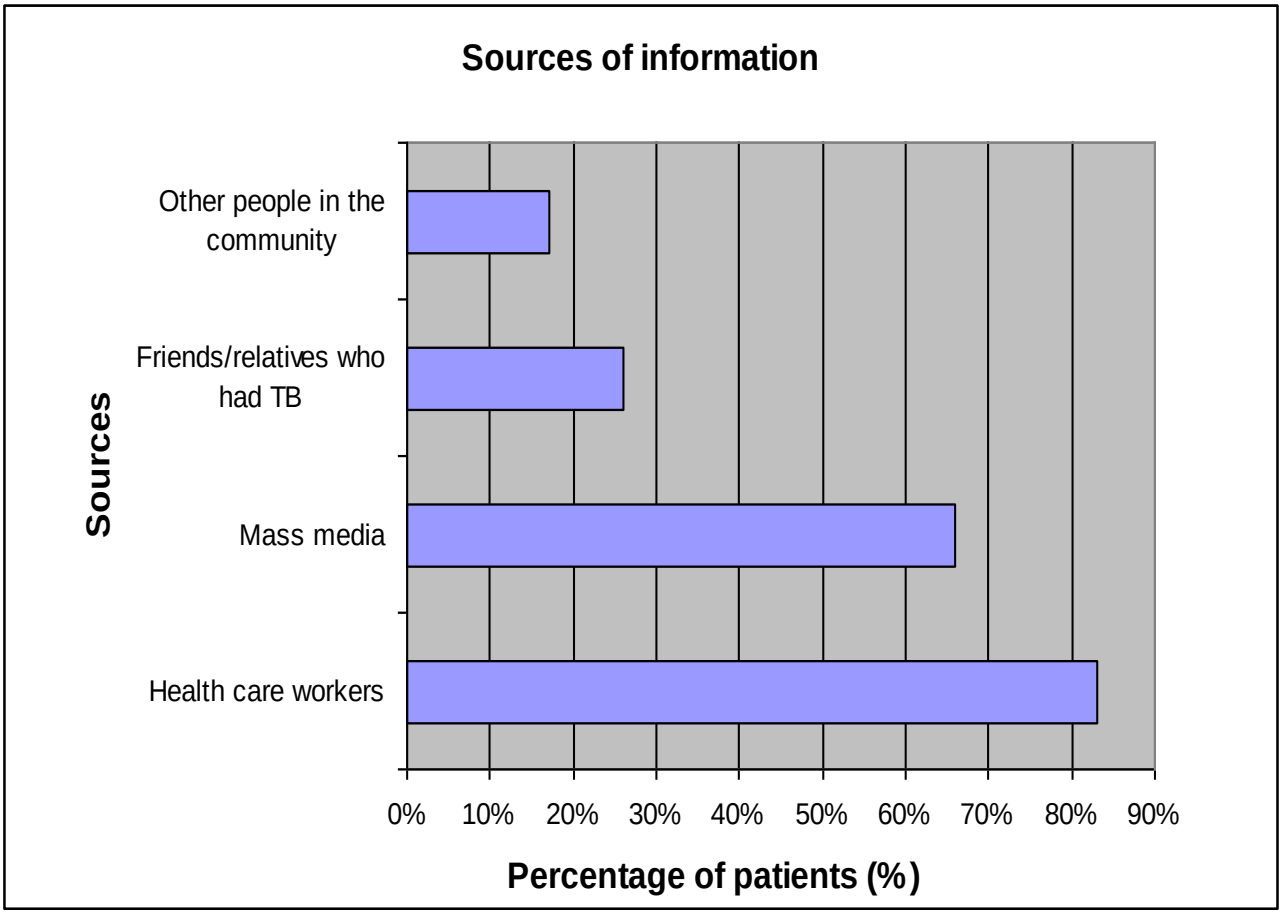

Fig 4.23: Sources of Information

Majority of patients (83%) knew about TB from Health care workers whereas 68% patients knew from mass media and 26% patients knew from friends/relatives who had TB.

4.25: Prevalence of Side Effects in TB Patients

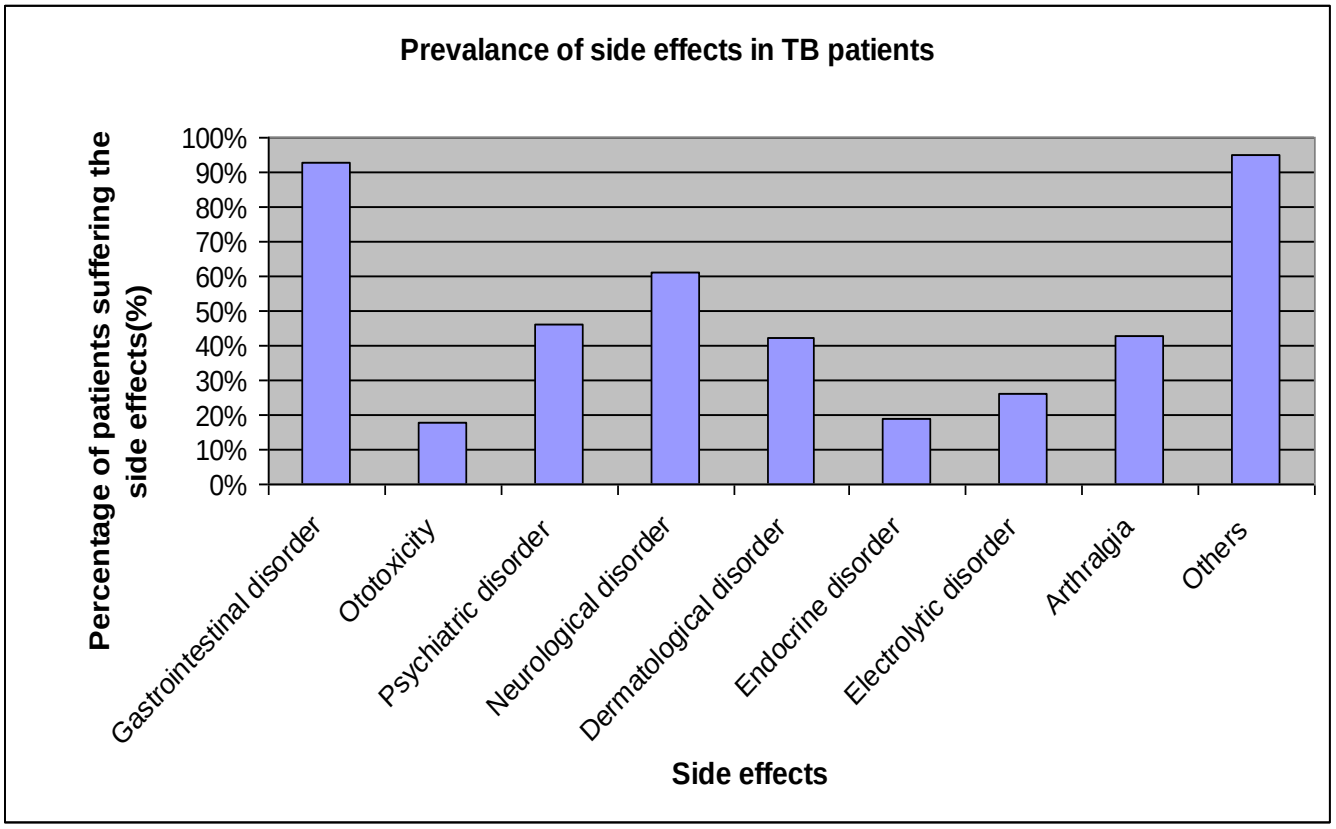

Fig 4.24: Prevalence of Side Effects in TB Patients

In our study, we found that among 100 TB and MDR-TB patients majority of them suffered from gastrointestinal disorder (93%), followed by neurological disorder (61%) and psychiatric disorder (46%). Other side effects (95%) suffered were weight loss, body weakness, vitamin deficiency, anemia etc.

4.26: Prevalence of Gastrointestinal Disorder in Patients

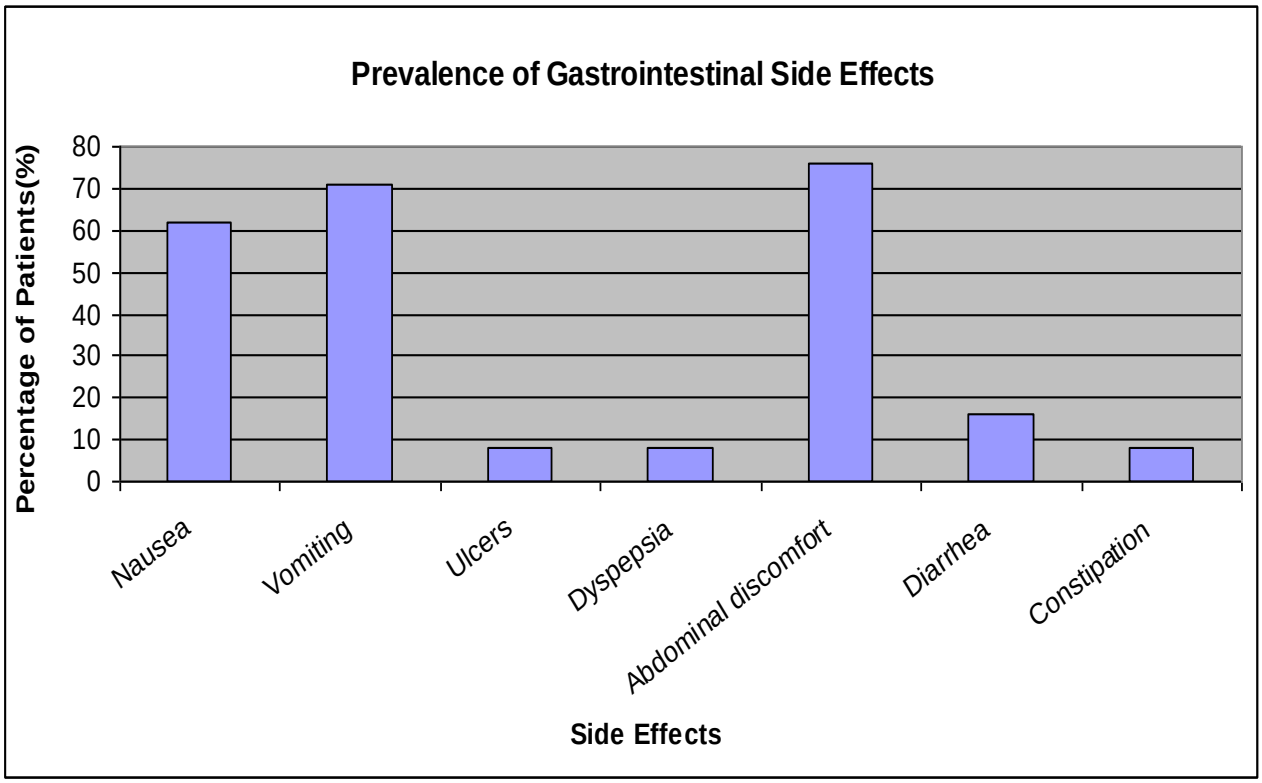

Fig 4.25: Prevalence of Gastrointestinal Disorder in Patients

Amongst the gastrointestinal disorders, majority of patients (76%) suffered from abdominal discomfort followed by 71% of patients who suffered from vomiting followed by 67% of patients who suffered from nausea. The least number of patients (8%) suffered from ulcer, dyspepsia or constipation.

4.27: Prevalence of Ototoxicity in Patients

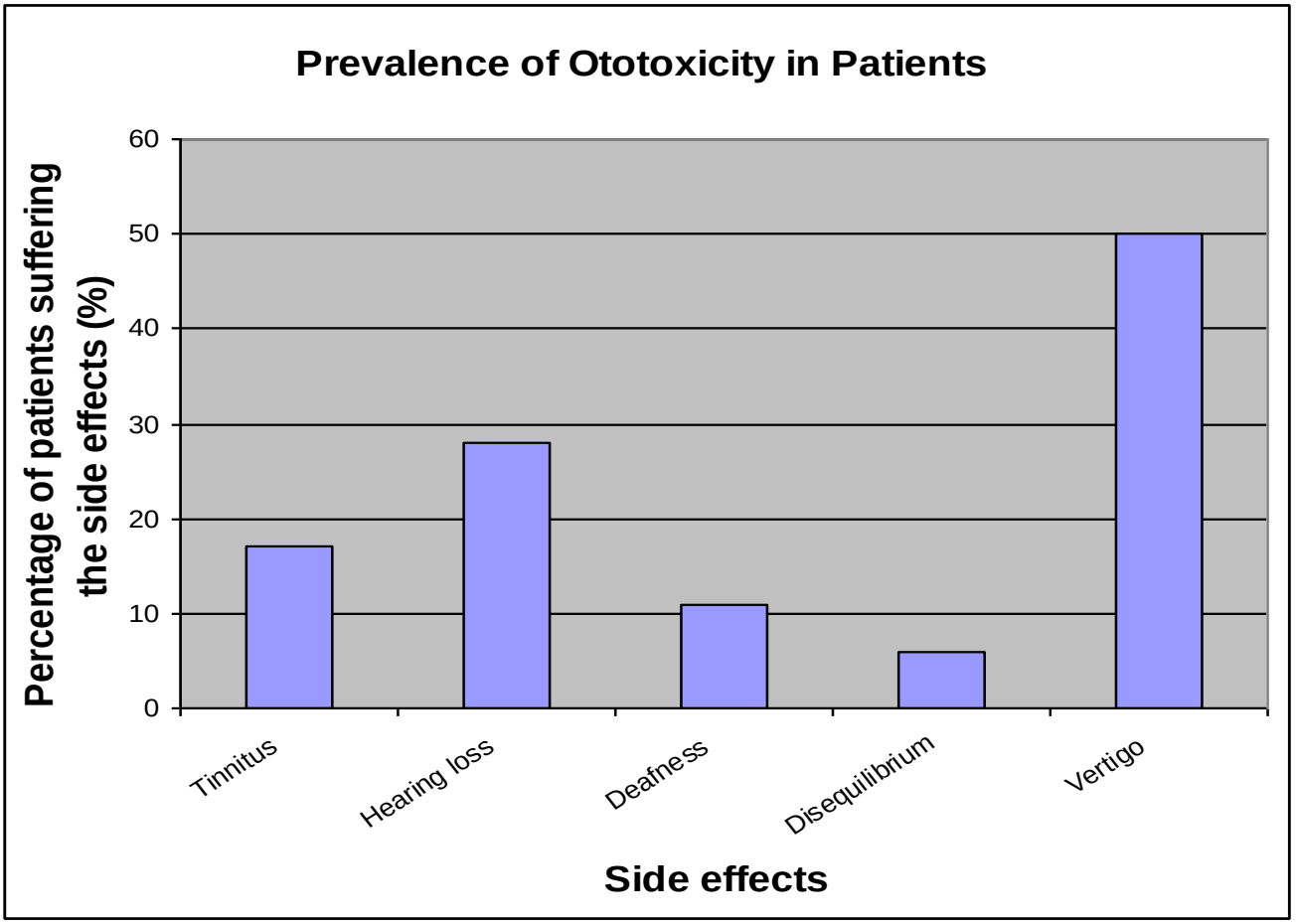

Fig 4.26: Prevalence of Ototoxicity in Patients

Amongst the ototoxicity, majority of patients (50%) suffered from vertigo followed by 28% of patients who suffered from hearing loss followed by 17% of patients who suffered from tinnitus. The least number of patients (6%) suffered from disequilibrium.

4.28: Prevalence of Psychiatric Disorder in Patients

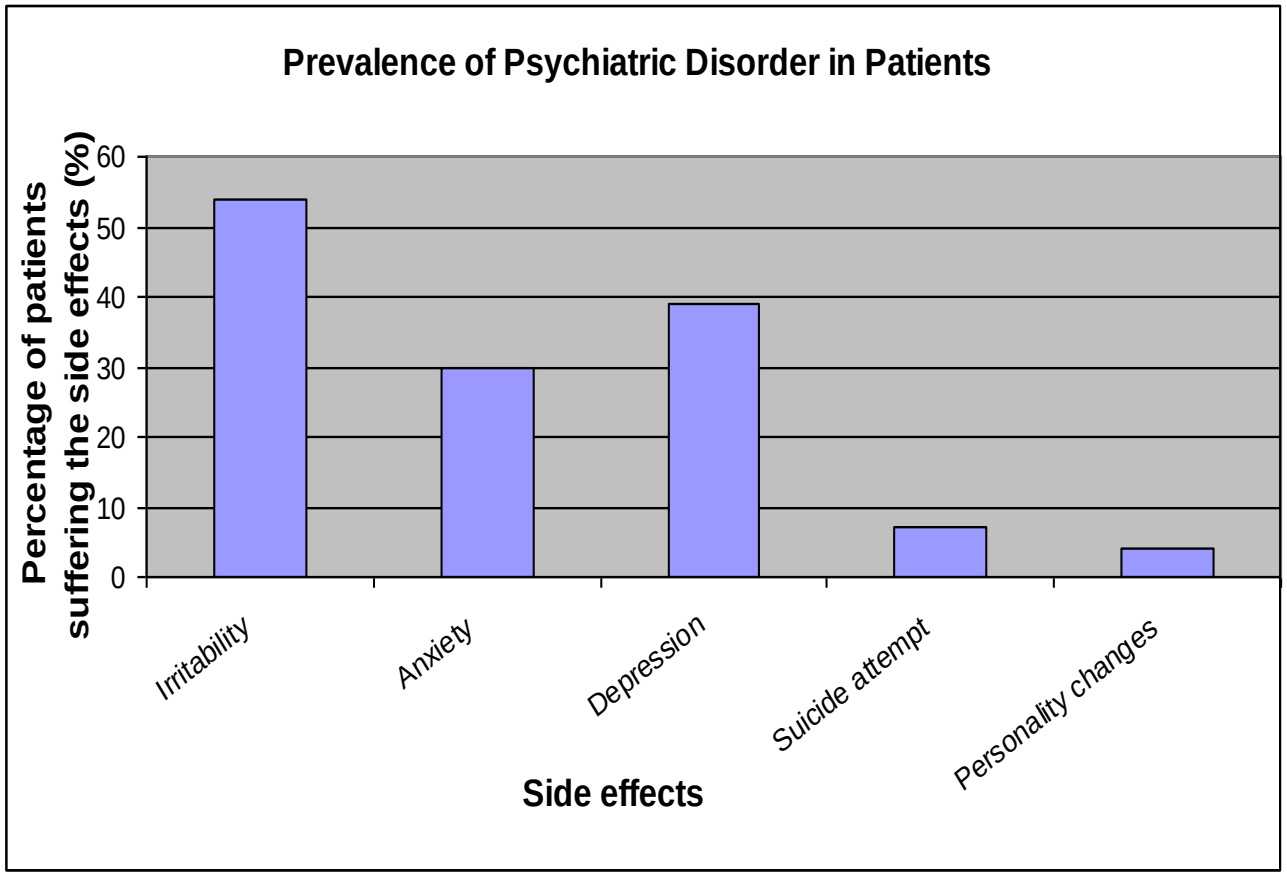

Fig 4.27: Prevalence of Psychiatric Disorder in Patients

Amongst the psychiatric disorder, majority of patients (54%) suffered from irritability followed by 39% of patients who suffered from depression and the least number of patients (4%) suffered from personality changes.

4.29: Prevalence of Dermatological Disorders in Patients

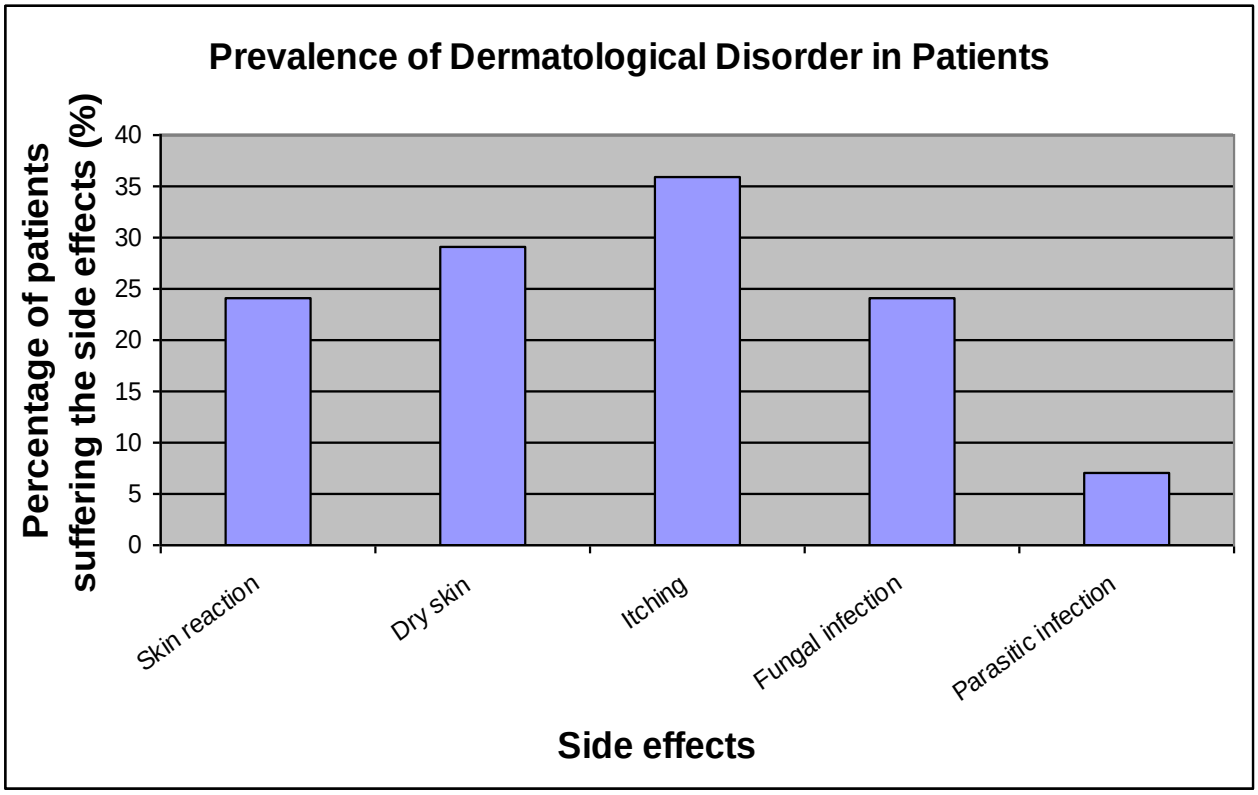

Fig 4.28: Prevalence of Dermatological Disorders in Patients

Amongst the dermatological disorder, majority of patients (36%) suffered from itching, followed by 29% of patients who suffered from dry skin followed by 24% of patients who suffered from skin reaction or fungal infection and the least number of patients (7%) suffered from parasitic infection.

4.30: Prevalence of Endocrine Disorders in Patients

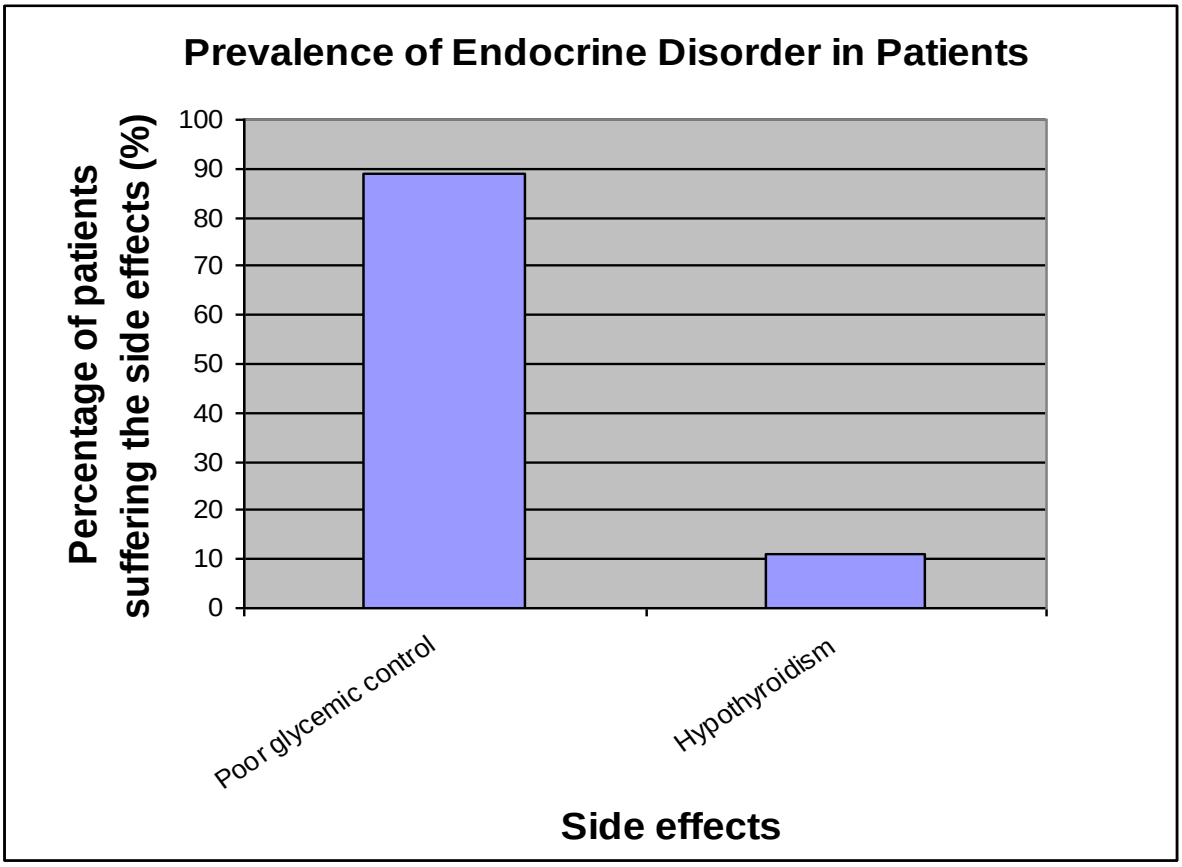

Fig 4.29: Prevalence of Endocrine Disorders in Patients

We found that, amongst the endocrine disorder, majority of patients (89%) suffered from poor glycemic control and the least number of patients (11%) suffered from hypothyroidism.

4.31: Prevalence of Arthralgias in Patients

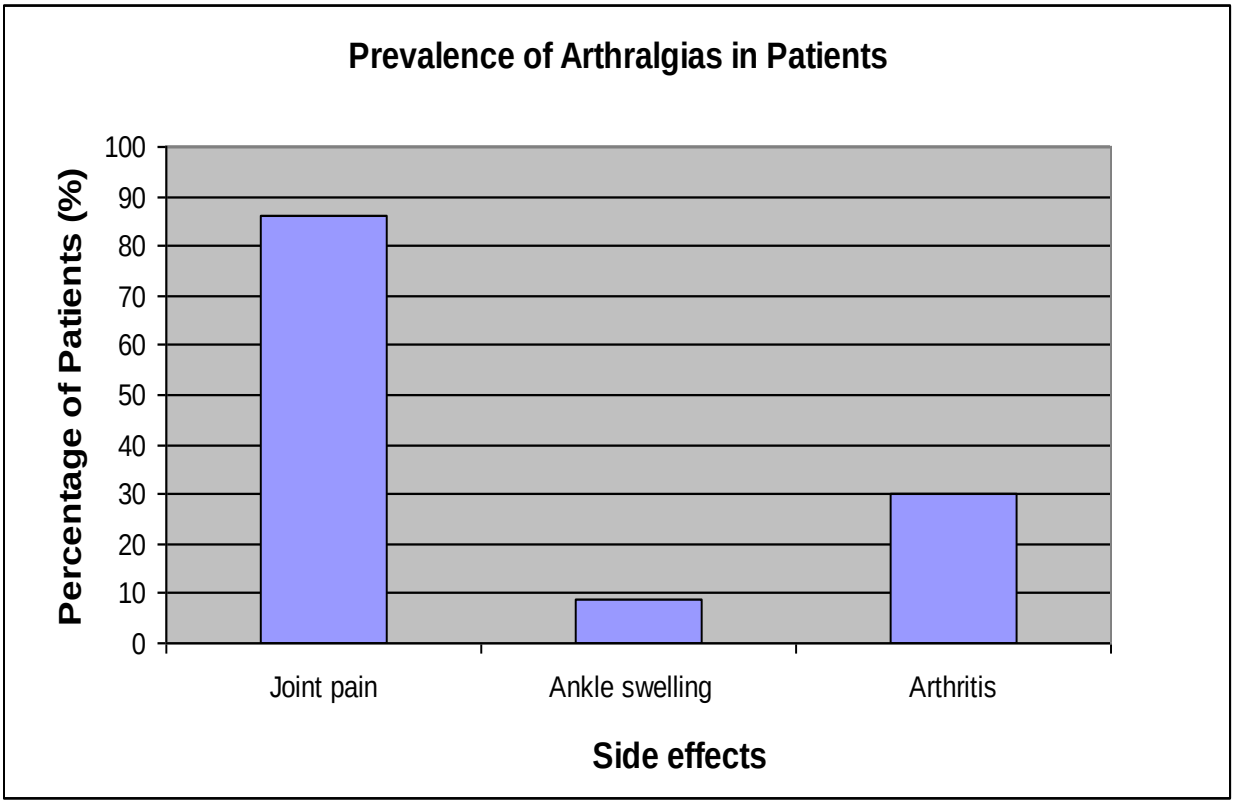

Fig 4.30: Prevalence of Arthralgias in Patients

According to this graph, we found that amongst the arthralgias, majority of patients (86%) suffered from joint pain and the least number of patients (9%) suffered from ankle swelling.

4.32: Prevalence of Neurological Disorder in Patients

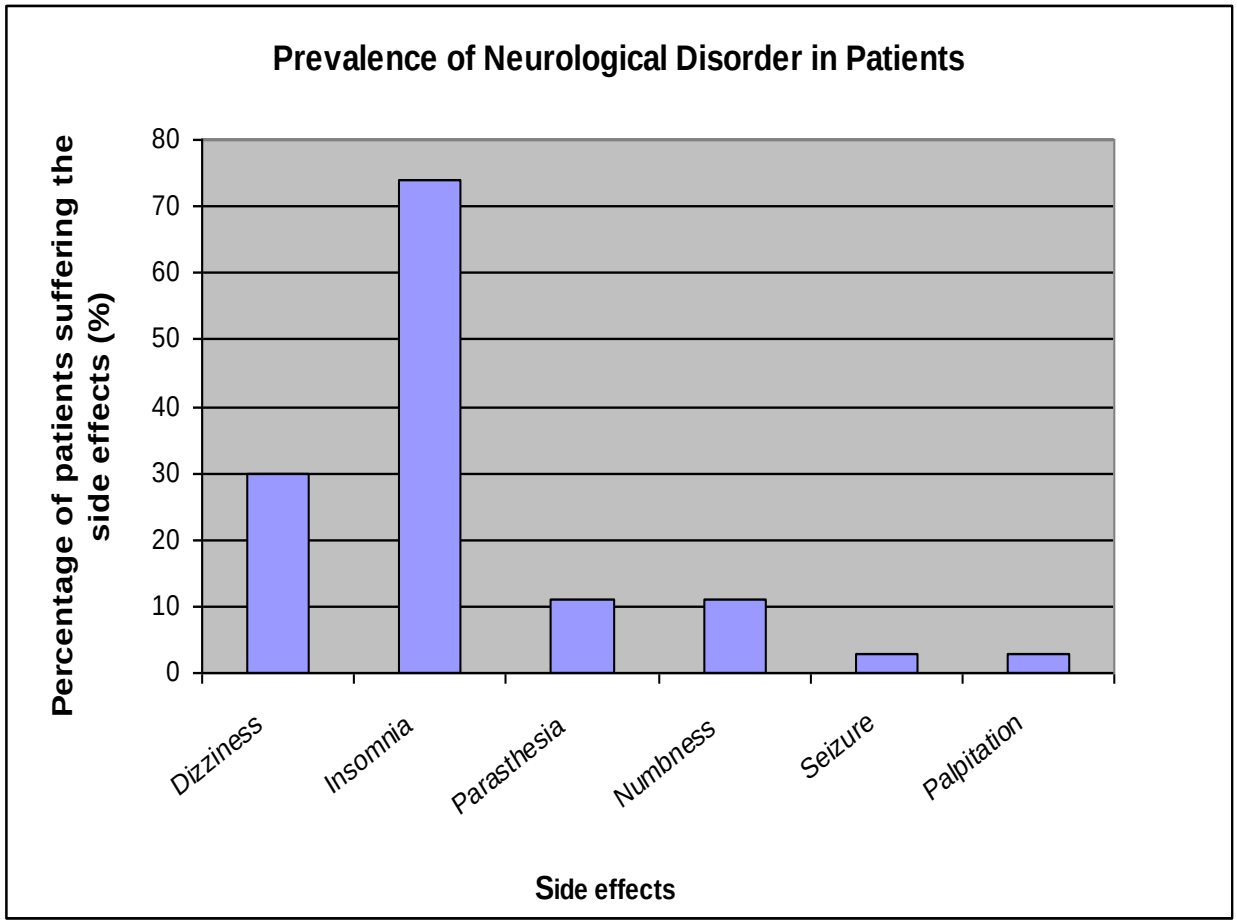

Fig 4.31: Prevalence of Neurological Disorder in Patients

Amongst the neurological disorder, majority of patients (74%) suffered from insomnia, followed by 30% of patients who suffered from dizziness and the least number of patients (3%) suffered from seizures or palpitation.

4.33: Prevalence of Electrolytic Imbalance in Patients

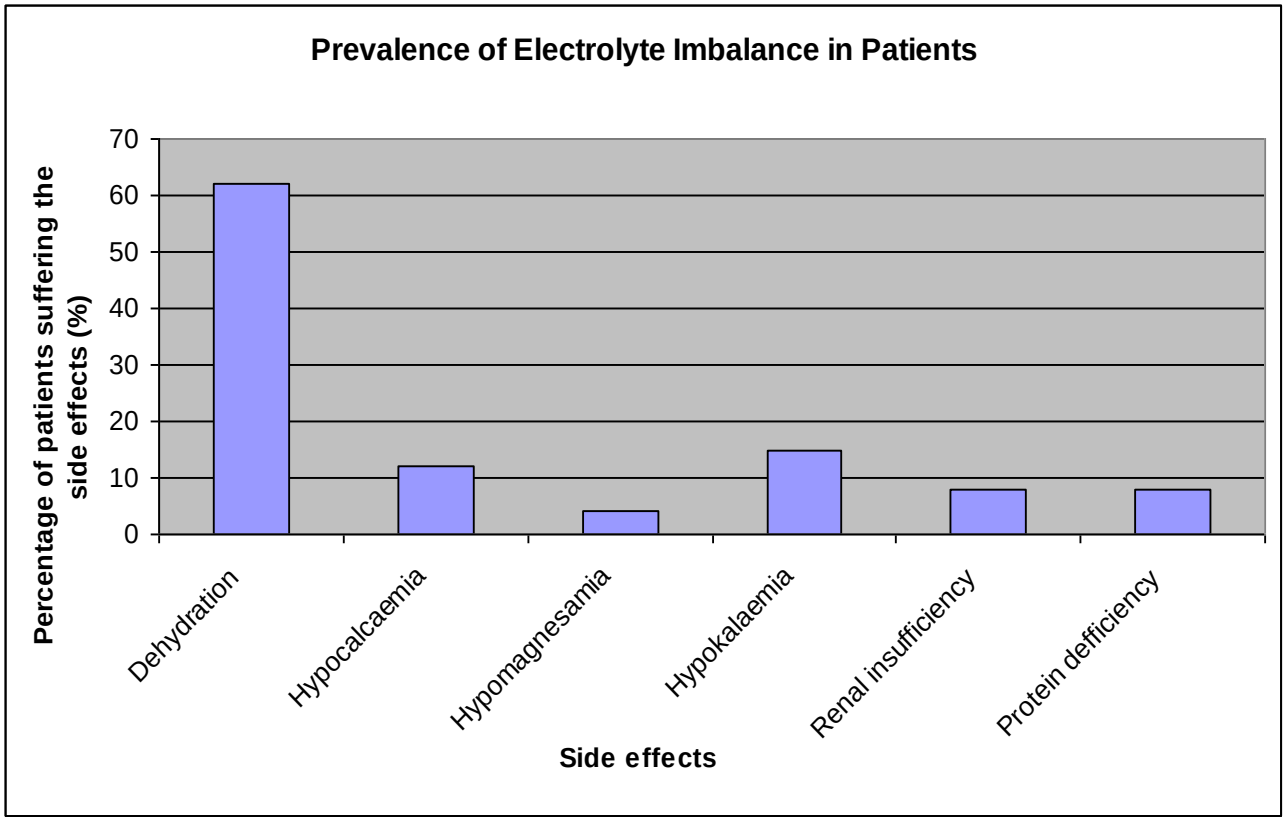

Fig 4.32: Prevalence of Electrolytic Imbalance in Patients

Amongst the electrolytic imbalance, majority of patients (62%) suffered from dehydration, followed by 15% of patients who suffered from hypokalaemia and the least number of patients (4%) suffered from hypomagnesaemia.

4.34: Prevalence of Other Major Side Effects in Patients

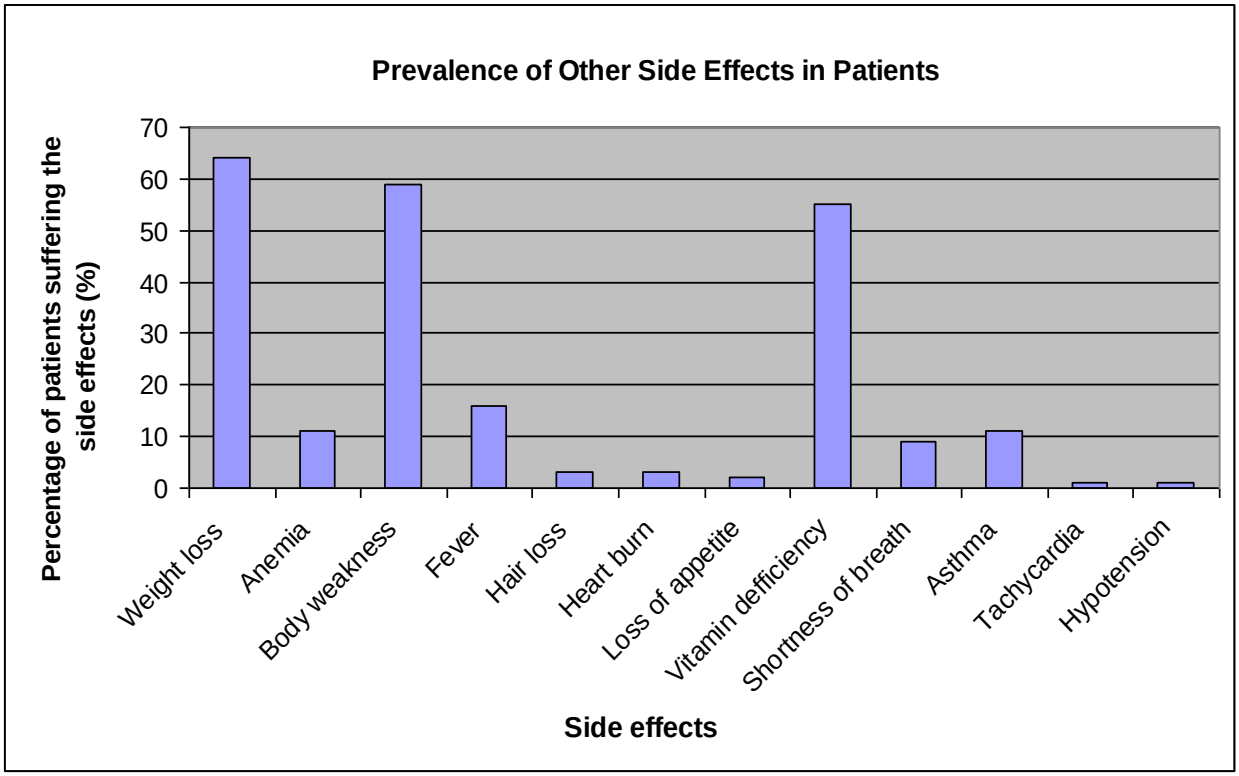

Fig 4.33: Prevalence of Other Major Side Effects in Patients

Amongst the other major side effects, majority of patients (64%) suffered from weight loss, followed by 59% of patients who suffered from body weakness followed by 55% of patients who suffered from vitamin deficiency and the least number of patients (1%) suffered from tachycardia or hypotension.

4.35: Comparison of Side Effects Suffered by the TB and MDR-TB Patients

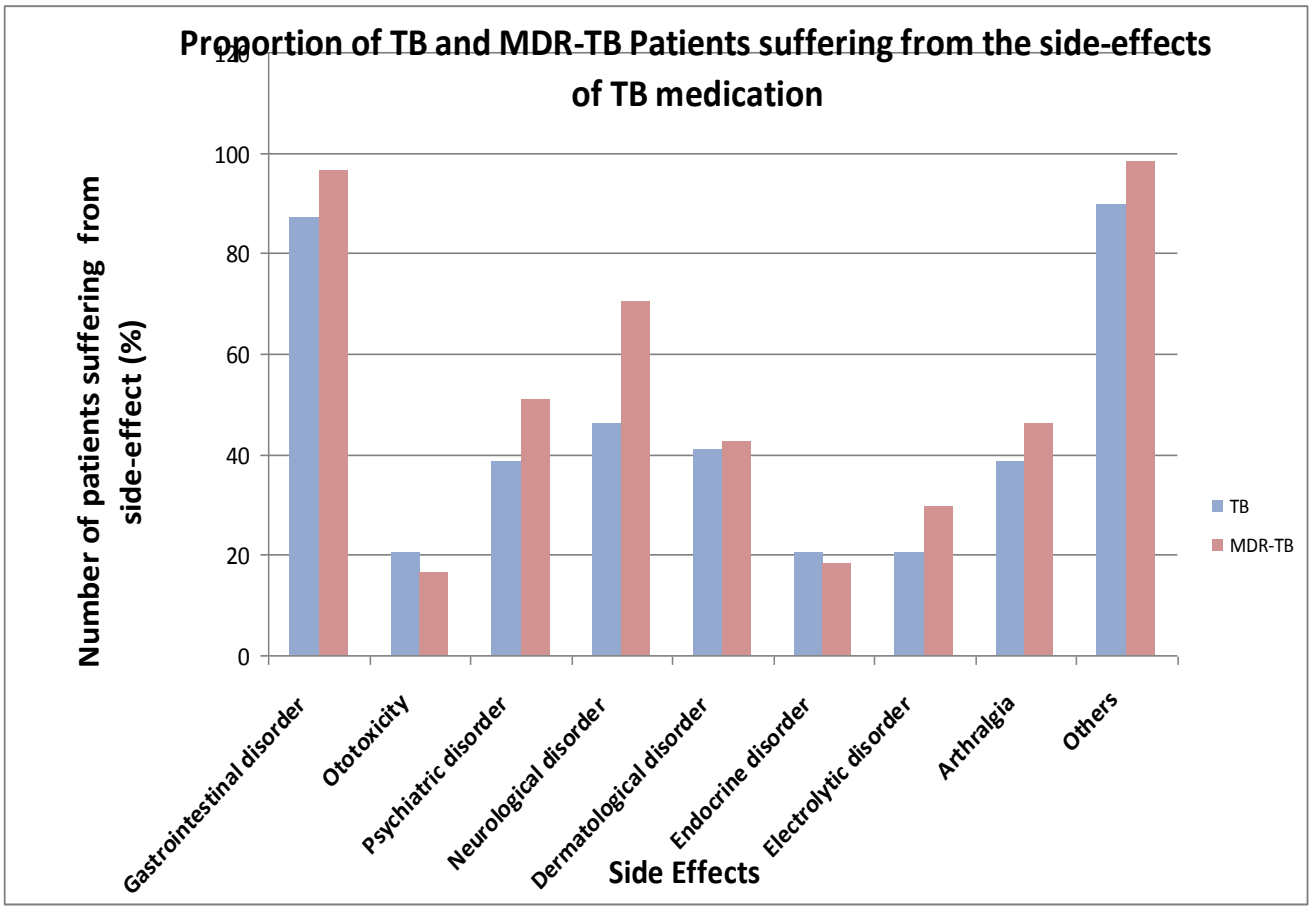

Fig 4.34: Comparison of Side Effects Suffered by the TB and MDR-TB Patients

According to this graph, we found that majority of MDR-TB patients (97%) and TB patients (87%) suffered from gastrointestinal disorders and the least number of MDR-TB patients (16%) and TB patients (21%) suffered from ototoxicity.

5: Discussion

In our study, 100 samples were analyzed among them 61% were MDR-TB patients and 39% were TB patients. This is the study to report the adverse side effects of TB medications in Bangladesh, even though the nation has been treating patients using these medications. Previously published studies on MDR-TB focused either on the prevalence of MDR-TB or MDR-TB treatment out-comes, without evaluating the occurrence of adverse side effects in great detail. We show a considerable burden of adverse side effects in the MDR-TB and TB population.

Our study has three important findings. Firstly, we reported a wide range of adverse side effects among the participants, which confirmed existing knowledge on the toxicity of TB medications reported in several studies. We reported that majority of patients suffered from gastrointestinal disorder followed by neurological disorder followed by dermatological disorder and psychiatric disorder. Majority of patients also suffered from some other major side effects including weight loss, body weakness, anemia etc. This finding echoes the overriding importance of managing adverse effects concurrently with TB & MDR-TB treatment, which the WHO has stressed.

Secondly, we have identified the frequently experienced adverse effects in the patients (gastrointestinal, ototoxic, psychiatric and neurological). We found that amongst the gastrointestinal disorder majority of patients suffered from nausea (62%), vomiting (66%), abdominal discomfort (71%) and least number of patients suffered from constipation (7%). Amongst the Ototoxicity majority of patients suffered from hearing loss (5%), vertigo (9%) and least number of patients suffered from deafness (2%).We reported that, amongst the dermatological disorder majority of patients suffered from skin reaction (10%), itching (15%), dry skin (12%) and least number of patients suffered from parasitic infection (3%)

Amongst the Psychiatric disorder, majority of patients (54%) suffered from Irritability followed by 39% of patients who suffered from depression and the least number of

patients (4%) suffered from Personality changes. Amongst the Endocrine disorder, majority of patients (89%) suffered from Poor glycemic control and the least number of patients (11%) suffered from Hypothyroidism. Amongst the Neurological disorder, majority of patients (74%) suffered from Insomnia, followed by 30% of patients who suffered from Dizziness and the least number of patients (3%) suffered from Seizures or Palpitation.

Amongst the Electrolytic Imbalance, majority of patients (62%) suffered from Dehydration, followed by 15% of patients who suffered from Hypokalaemia and the least number of patients (4%) suffered from Hypomagnesaemia. Amongst the Other major side effects, majority of patients (64%) suffered from Weight loss, followed by 59% of patients who suffered from Body weakness followed by 55% of patients who suffered from Vitamin deficiency and the least number of patients (1%) suffered from Tachycardia or Hypotension. So, health workers should be alert for these adverse effects.

Thirdly, we found the proportion of side effects suffered by the TB & MDR-TB patients. We reported that MDR-TB patients suffered more side effects than the TB patients. In our study, we reported that 97% MDR-TB patients suffered from gastrointestinal disorder whereas 87% TB patients suffered from gastrointestinal disorder on the other hand 21% TB patients suffered from ototoxicity whereas 16% MDR-TB patients suffered from ototoxicity. We also reported that 51% MDR-TB patients suffered from psychiatric disorder whereas 38% TB patients suffered from psychiatric disorder on the other hand 21% TB patients suffered from Endocrine disorder whereas 18% MDR-TB patients suffered from Endocrine disorder.

According to our study, we found that MDR-TB patients suffered more side effects such as Gastrointestinal (97%), Psychiatric (51%), Neurological (70%), Dermatological (43%), Electrolytic (30%), Arthralgias (46%) and other major side effects (98%) than the TB patients whereas TB patients suffered more Ototoxicity (21%) and Endocrine disorder (21%) than the MDR-TB patients.

From previously published study, we knew that Rifampicin causes fever, joint pains, weakness, nausea and itching; Isoniazid causes renal insufficiency, fever and joint pain with ankle swelling; Ethambutol causes deafness and blurred vision; Pyrazinamide causes loss of appetite, weakness, hearing loss and joint pain; Streptomycin causes nausea, vomiting and abdominal discomfort; Kanamycin causes dizziness, numbness, itching, diarrhea and hearing loss; Ofloxacilin/ Levofloxacilin causes diarrhea, constipation, abdominal discomfort, dizziness and nausea; Ethionamide causes low blood sugar, weight loss, dizziness; Cycloserin causes dry skin, itching, seizures and thought of Suicide.

In our study, we have seen that the standard treatment for TB consists of Rifampicin, Isoniazid, Ethambutol, Pyrazinamid and Streptomycin and the standard treatment for MDR-TB consisted of Kanamycin, Amikacin, Prothionamide, Ofloxacin, Levofloxacilin, Ethionamide and Cycloserine. Ethambutol and Pyrazinamide were added to the treatment for MDR-TB if mycobacterium was sensitive to them. MDR-TB treatment consists of the combination of 5 drug on the other hand TB treatment consist of the combination of 3 drugs (Rifampicin+Isoniazid+ Ethambutol/Pyrazinamid). So, MDR-TB patients might suffer more side effects than the TB patients might be due to the large and complex drug regimen or might be due to the fact that the number of MDR-TB patients included was low. The result of our study is quite relevant with the study of Torun, *et al*.

Törün, et al conducted a survey to report the frequency of treatment side effects in cases of multidrug-resistant (MDR-TB) tuberculosis (263 patients) and determine the side effects observed most frequently included: ototoxicity (41.8%), psychiatric disorders (21.3%), and gastrointestinal disturbance (14.0%), and arthralgia (11.4%), epileptic seizures (9.9%), hepatitis (4.5%), and dermatological effects (4.5%). At the time of analysis, treatment was successful in 204 (77.6%) cases. Fifty-nine patients (22.4%) had poor outcomes. Timely and aggressive management of drug side effects means that high side effect rates in MDR-TB treatment need not compromise success rates (Törün, T., 2015).

The adverse effects recorded on the patients' side effects monitoring form were based on patients-reported symptoms. Hence, there was a possibility of subjectivity and of selective under-reporting of adverse events by patients or the selective recording of adverse events by clinicians, which may have biased the results away from the true prevalence. Some symptoms of reported adverse events may have overlapped with symptoms of the co-morbidities.

6. Conclusion

Tuberculosis is a major cause of morbidity and mortality as it associated with lots of side effects. Regular follow up of treatment should be done to detect early side effects of medicines. Health care workers should monitor the patients carefully to detect the adverse effects that are suffered by them. Physician should optimize dose regimen to reduce the prevalence of adverse effects. Health education about TB and TB medications should be done to make people aware about it. TB patients with associated diseases, especially diabetes suffered more side effects, so these associated diseases should be well controlled. MDR-TB might result from non-adherence of TB treatment, so adherence of patients to treatment even at home is more important than admission at hospital because resistance is more liable to occur at hospital. There is an urgent need to develop new anti-tuberculosis drugs to shorten the duration of treatment, to reduce the side effects and to make development of resistance less likely to emerge.

Questionnaire

Name:	**Date:**

Sex: □ Male □ Female

Marital status: □ Single □ Married □ divorced

Age: □ <20 □ 21-30 □ 31-40 □ 41-50 □ 51-60 □ >60

Religion: □ Islam □ Hinduism □ Buddhism □ Christianity

Educational status:

□ Illiterate □ Primary □ Secondary □ College □ Graduate

□ Post-graduate

Occupation:

□ Govt. employee □ Private employee □ Private business □ Housewife

□ Student □ Garments worker □ Farmer

Income per month:

□ <5000 □5000-10,000 □10,000-25,000 □ >25,000

Weight: □30-40kg □40-50kg □ 50-60kg □ 60-70kg □ 0-10kg

Living with family: □ Yes □ No

Place of residence: □ Urban □ Rural □ Semi urban

How many people are living in the household?

□ 1-2 □3-4 □5-6 □7-8 □9-10 □11-12

How many people are living in the same room?

□ 1 □2 □3 □4 □5

Are you being diagnosed with TB for the first time? □Yes □No

If no, how many times were you diagnosed with TB? □1 □2 □3

Presence of TB patients in family currently: □Yes □No

Have your family members ever been diagnosed with TB? □Yes □No

If yes, who? □Mother □Father □Wife/Husband □Brother

□Sister □Son/Daughter □ Other relatives

Plasma glucose (After 2hour): □50-100mg/dl □101-150mg/dl □151-200mg/dl □201-250mg/dl □251-300mg/dl □301-350mg/dl □351-400mg/dl

Creatinine: □0-0.5mg/dl □0.6-1mg/dl □1.1-1.5mg/dl □1.6-2.0mg/dl □2.1-2.5mg/dl □2.6-3.0mg/dl □3.1-3.5mg/dl

HbA1c: □0-5g/dl □6-10g/dl □11-15g/dl □16-20g/dl

Are you HIV-positive? □Yes □No

What is your smoking status? □Never a smoker □Past smoker □Current smoker

Do you drink alcohol? □Never □Infrequent/Frequent intermediate □Infrequent heavy □Frequent heavy

Do you have any kind of habituation of other toxic substances? □Yes (Betel leaf) □No

What symptoms do you suffer from?

□Cough □Haemoptysis □Fever □Shortness of breath □Chest pain □weakness

From which duration? □1-10days □11-20days □21-30days □31-40days □41-50days □51-60days □61-70days □71-80days □81-90days □91-100days □101-110days □111-120days □4-12months □1-2years

Time elapsed between onset of symptoms and duration:

□1-10days □11-20days □21-30days □31-40days □41-50days □51-60days □61-70days □71-80days □81-90days □91-100days □101-110days □111-120days □4-12months □1-2years

How was your TB diagnosed?

□Sputum for AFB □Chest X-ray □Historical Diagnosis (biopsy) □Clinical Diagnosis

What type of TB it is? □Pulmonary □Extra pulmonary □I don't know

Are you a MDR-TB patient? □Yes □No

In case of MDR-TB, have you completed your primary treatment? □Yes □No □I don't know

If MDR-TB patient, are you aware of the drugs you are resistance to?

□Yes □No

If yes, please mention : □Rifampicin □Isoniazid

What medications are you taking for TB? □Cat I □Cat II □Cat IV

What is/are the history of prior TB treatment?

□Cat I relapse □New TB regimen □Retreatment regimen □Treated for MDR-TB □Cat II relapse

What is the cause of TB? □Infective organism □Heredity □Curse □Smoking+alcohol+diet □Others □Not aware

What is the mode of spread of TB? □Casual physical contact □Air □Food utensils □Others □Not aware

What do you know regarding diagnosis of TB?

□Long term □Repeated occurrence □Infective □Air born □Diagnosed by cough □Don't know

What do you know regarding treatment of TB?

□Long term □Costly □Non treatable □Free govt. treatment □Lots of side effects □Curable □Don't know

What do you know regarding prevention of TB?

□Non preventable □Curable □Contagious □Don't know

What sources of information do you have regarding TB?

□Health care workers □Mass media □Friends/Relatives who had TB □Other people in the community

Are you diabetic? □Yes □No □Don't know

If yes, what is the duration? □<5years □6-9years □>10years

What type of DM you have? □Type 1 □Type 2 □Don't know

If you have diabetes, what kind of medication are you on?

□Insulin □Metformin □Glicazide □Sitagliptin

Do you have a family history of diabetes? □Yes □No

Do you know what the symptoms of Hyperglycemia are? □Yes □No

Do you suffer from any of the symptoms of Hyperglycemia?

□Increased thirst □Frequent urination □Others □Fatigue □Weight loss □Blood sugar more than 180mg/dl □Headaches □Difficulty in concentrating □Blurred vision

If diabetic, how frequently do you meet the doctor? □Very often □Rarely □Twice in a year □Yearly □Whenever needed

If diabetic, how would you categorize your care for diabetes?

□Frequent care □Some care □None

For non diabetic patient, if you suspect diabetes, what will be your mode of action?

□Consult doctor □Take medicine

Do you know that diabetes can increase chances of TB incidence?

□Yes □No

Do you have any other concurrent disease? □Yes □No

Put thick mark on the following side effects that you have suffered with:

Gastrointestinal Disorder:

□Nausea □Vomiting □Ulcers □Dyspepsia □Abdominal discomfort □Gastrointestinal bleeding □Diarrhea □Constipation

Ototoxicity:

□Tinnitus □Hearing loss □Deafness □Disequilibrium □Vertigo

Psychiatric Disorder:

□Irritability □Anxiety □Depression □Suicidal Ideation □Personality changes □Psychosis

Neurological Disorder:

□Dizziness □Insomnia □Parasthesia □Numbness □Seizures □Palpitation

Dermatological disorder:

□Skin reaction □Photosensitivity □Dry skin □Itching □Fungal infection □Skin reaction □Parasitic infection

Endocrine Disorder:

□Poor glycemic control □Hypothyroidism

Electrolyte Abnormalities:

□Dehydration □Hypocalcaemia □Hypomagnesaemia □Hypokalaemia

□Renal insufficiency □Protein deficiency

Arthralgia:

□Joint pain □Ankle swelling and pains □Arthritis

Others:

□Weight loss □ anemia □ Body weakness □ Fever □ Hair loss

□ Heart failure □ Hypertension □ Heart burn □ Loss of appetite

□Vitamin deficiency □ Urinary tract infection □ Shortness of breath

□Asthma □ Tachycardia □ Hypotension

7. Reference:

American Lung Association, (2015). Available at: http://American Lung Association. [Accessed 15 Aug 2015].

Baghaei, P., Tabarsi, P., Dorriz, D., Marjani, M., Shamaei, M., Pooramiri, M.V., Mansouri, D., Farnia, P., Masjedi, M. & Velayati, A., (2015). Adverse Effects of Multidrug-Resistant Tuberculosis Treatment with a Standardized Regimen: A Report From Iran. *National Center for Biotechnology Information*. 23(5). p.456-488.

Centers for Disease Control and Prevention, (2015). *TB Disease Symptoms*. Available at: *Ncbi.nlm.nih.gov.* [Accessed 2 Nov 2015].

Caminero, A., (2015). Best Drug Treatment for Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis. *National Center for Biotechnology Information*. 18(2). p. 29-34.

Centers for Disease Control and Prevention. (2014). Atlanta, *GA: U.S. Department of Health and Human Services, CDC.* Available at: http://www.cdc.gov/tb/statistics/reports/2013/default.htm. [Accessed 2 Nov 2015].

Drugs. com, (2015). *Kanamycin: Indications, Side Effects, Warnings.* Available at: http://www.drugs.com/cdi/kanamycin.html. [Accessed 1 Sep 2015].

Drugs. com, (2015). *Ofloxacin Tablets: Indications, Side Effects, Warnings*. Available at: http://www.drugs.com/cdi/ofloxacin.html. [Accessed 1 Sep 2015].

Drugs. com, (2015). *Levofloxacin Tablets: Indications, Side Effects, Warnings*. Available at: http://www.drugs.com/cdi/levofloxacin.html. [Accessed 1 Sep 2015].

Drugs. com, (2015). *Ethionamide: Indications, Side Effects, Warnings.* Available at: http://www.drugs.com/cdi/ethionamide.html. [Accessed 1 Sep 2015].

Drugs. com, (2015). *Cycloserine: Indications, Side Effects, Warnings*. Available at: http://www.drugs.com/cdi/cycloserine.html. [Accessed 1 Sep 2015].

Medscape. com, (2015). *Tuberculosis Treatment & Management: Approach Considerations, Treatment during Pregnancy, Treatment in Children*. Available at: http://emedicine.medscape.com/article/230802-treatment. [Accessed 3 Nov 2015].

Farazi, G. & Aliasghar, P., (2014). Adverse Reactions to Antituberculosis Drugs in IranianTuberculosis Patients. *Tuberculosis Research and Treatment*. 65(6). p.1-6.

Flora, M., Amin, M., Karim, M., Afroz, S., Islam, S., Alam, A. & Hossain, M., (2013). Risk Factors of Multi-Drug-Resistant Tuberculosis in Bangladeshi Population: A Case Control Study. *Bangladesh Medical Research Council Bulletin*. 84(4). p.39.

Knechel, N. A., (2009). Tuberculosis: Pathophysiology, Clinical Features & Diagnosis. *Critical Care Nurse*. 29(2). p.34-43.

Maciel, k. & Leonor N., (2010) Efeitos Adversos Causados Pelo Novo Esquema De Tratamento Da Tuberculose Preconizado Pelo Ministério Da Saúde Do Brasil. *Jornal Brasileiro de Pneumologia*. 36(2). p. 37-39.

Mayoclinic.org, (2015). Tuberculosis Tests and Diagnosis. Available at: http://www.mayoclinic.org/basics/tests-diagnosis of tuberculosis/con-20033091. [Accessed 17 Aug 2015].

Mayoclinic.org, (2015). Tuberculosis Risk Factors. Available at: http://www.mayoclinic.org/risk factors of tuberculosis/con-20033093. [Accessed 17 Aug 2015].

Mayoclinic.org, (2015). Tuberculosis Symptoms. Available at: http://www.mayoclinic.org/symptoms of tuberculosis/con-20033097. [Accessed 17 Aug 2015].

Microbewiki, (2015). Tuberculosis in Children in Developed Countries. Available at: http://www.microbewiki.kenyon.edu/tuberculosis in developed countries.html. [Accessed 4 Nov 2015].

Nathanson, E., Gupta, R., Huamani, P., Leimane, V., Pasechnikov, A. & Tupasi, E., (2015). Adverse Events in the Treatment of Multidrug-Resistant Tuberculosis: Results From the DOTS-Plus Initiative. *The International Journal of Tuberculosis and Lung Disease.* 8(11). p.1 382-1392.

National Tuberculosis Control Programme (NTP), Bangladesh, (2013). *National Guidelines and Operational Manual for Tuberculosis Control*. Available at: http://www.ntp.gov.bd/index.php?option=com_content&view=article&id=46&Itemid=28 .[Accessed 17 Aug 2015].

National Health Service, (2015). *Tuberculosis (TB) – Treatment and Diagnosis NHS Choices.* [Available at: http:// nhs.uk/treatment and diagnosis of tuberculosis.com]. [Accessed 3 Nov 2015].

Palmero, D., Golubchikova, V., Tonkel, P. & Yanova, G., (2015). Adverse Drug Reactions Multi-Drug Resistant Tuberculosis. *National Center for Biotechnology*. 4(2). p.687-767.

Purohit, M., Mustafa, T., Wiker, H. & Sviland, L. (2011). Rapid Diagnosis of Tuberculosis in Aspirate, Effusions & Cerebrospinal Fluid by Immunocytochemical Detection of Mycobacterium Tuberculosis Complex Specific Antigen MPT64. *Diagnostic Cytopathology*. 40(9). p.782-791.

RxList, (2015). Pyrazinamide (Pyrazinamide) Drug Information: Description, User Reviews, Drug Side Effects, Interactions - Prescribing Information. Available at: http://www.rxlist.com/pyrazinamide-drug.htm. [Accessed 1 Sep 2015].

Shin, S.S., Pasechnikov, A., Gelmanova, I., Peremitin, G., Strelis, A. & Mishustin, S., (2015). Adverse Reactions among Patients being Treated for MDR-TB in Tomsk, Russia. Available at: *Ncbi.nlm.nih.gov*. [Accessed 2 Nov 2015].

Tuberculosis Control India, (2013). Available at: http://tbcindia.nic.in. [Accessed 1 Sep 2015].

TB Drug Monographs, (2015). *Prothionamide*. Available at: http://www.tbdrugmonographs.co.uk/prothionamide.html [Accessed 1 Sep. 2015].

World Health Organisation, (2015). The Use of Short Regimens for Treatment of Multidrug-Resistant Tuberculosis. Available at: http://www.world health organization.com. [Accessed 17 Aug 2015].

Törün, T., (2015). Side Effects Associated with the Treatment of Multidrug-Resistant Tuberculosis. *National Center for Biotechnology Information*. Available at: *Ncbi.nlm.nih.gov*. [Accessed 1 Nov 2015].

The American Thoracic Society, (2015). Incidence Of Serious Side Effects from First-Line Anti-Tuberculosis Drugs among Patients Treated for Active Tuberculosis. *American Journal of Respiratory and Critical Care Medicine*. p. 314-317. Available at: http://www.atsjournals.org/journal/ajrccm. [Accessed 1 Nov 2015].

Vander, M., Langendam, M., Tiemersma, E., Marieke, J. & Sandgren, A., (2013). Serious Treatment Related Adverse Drug Reactions amongst Anti-Retroviral Naïve MDR-TB Patients. *National Center for Biotechnology Information.* 34(4). p. 122-222.

Vishakha, K. & Tripathi S., (2015). Analysis of 63 patients of MDR-TB on DOTS plus regimin. *National Center for Biotechnology Information*. Availabe at: ncbi.nlm.nih.gov. [Accessed 1 Nov 2015].

Webmd.com, (2015). *Aminosalicylic Acid Oral:Uses, Side Effects, Interactions, Pictures, Warnings & Dosing*. Available at:http://www.webmd.com/drugs/2/drug-11409/aminosalicylic-acid-oral/details#side-effects. [Accessed 1 Sep 2015].

World Health Organisation (2014). *WHO | Global tuberculosis report 2014*. Available at: http://www.who.int/tb/publications/global_report/en/. [Accessed 29 Aug 2015].

Who.int. (2015). *WHO | Drug-Resistant Tuberculosis Now At Record Levels.* Available at: http://www.who.int/tb/en/. [Accessed 3 Nov 2015].

WHO (2013). Bangladesh: National Tuberculosis Control Programme. *National Guidelines and Operational Manual for Programmatic Management of Drug Resistant TB (PMDT)*. Avaialbe at. http://www.who.int/mediacentre/factsheets/fs104/en/. [Accessed 3 Nov 2015].

Whitcher, J., Srinivasan, M. & Upadhyay, N., (2001).Tuberculosis Treatment with a Standardized Regimen.*World Health Organ*. 79(3). P. 214-221.