A Descriptive Study on Use of Fixed Dose Combination (FDC) Tablets and Role of DOT in TB Treatment

A Dissertation submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Masters of Pharmacy (M Pharm)

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation, entitled **"A Descriptive Study on Use of Fixed Dose Combination (FDC) Tablets and Role of DOT in TB Treatment"** is an authentic and genuine research work carried out by me during the term 2017 under the guidance of Nigar Sultana Tithi, Senior Lecturer, Department of Pharmacy, East West University, Dhaka and that no part of the thesis has been submitted for any other degree.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that, the thesis on **"A Descriptive Study on Use of Fixed Dose Combination (FDC) Tablets and Role of DOT in TB Treatment"** submitted to Department of Pharmacy, East West University, Aftabnagar, Dhaka, in partial fulfillment of the requirements for the degree of Masters of Pharmacy (M. Pharm), was carried out by Nusrat Jahan (ID: 2013-1-79-021) under my guidance and supervision. I further certify that all the sources of information in this connection are duly acknowledged.

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ENDORSEMENT BY HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled **"A Descriptive Study on Use of Fixed Dose Combination (FDC) Tablets and Role of DOT in TB Treatment"** is a genuine research work carried out by Nusrat Jahan (ID: 2013-1-79-021) under the supervision of Nigar Sultana Tithi, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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Acknowledgement

At first, I would like to express my gratitude to Almighty Allah for giving me the strength and opportunity to complete my dissertation within the schedule time successfully.

I feel proud to express my deepest sense of gratitude and admiration to my mentor, guide and supervisor **Nigar Sultana Tithi,** Senior Lecturer**,** Department of Pharmacy, East West University, Dhaka, Bangladesh, for her careful guidance, day to day supervision, dexterous management, adept analysis, keen interest, optimistic counseling, unremitting backup, constructive criticism and valuable time without which I would not have been able to complete this work.

I am very much pleased and thankful to **Dr. Chowdhury Faiz Hossain**, Professor and Chairperson of the Department of Pharmacy, East West University, for giving me all the necessary support and facilities to complete this research work.

I would like to take this opportunity to thank **Dr. Shamsun Nahar Khan,** Associate Professor and Former Chairperson of the Department of Pharmacy, East West University, for giving me all the support throughout my work.

I would also like to take the opportunity to express my gratitude to senior officials and staffs of Upazilla Health Complex, Kanaighat and HEED Bangladesh for extending their helping hands whenever needed and has always been an inspiration and assistance during the period of constructing the research report.

I would also like to show my gratitude to all the patients who have participated in this research and has given me their precious time for this study despite their busy schedule.

I would like to convey deepest love and obedience to my parents, husband, friends and to all my well-wishers for their support, inspiration and guiding me all through my life until today, which keeps me strong and firm that helps me further to reach my desired goal.

DEDICATED TO

My beloved parents, my loving husband and Honorable research faculty who inspired and supported me all throughout my work.

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List of Abbreviation

Abbreviation	Elaboration
AFB	Acid-fast baccili
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
DOT	Directly observed treatment
DOTS	Directly Observed Treatment, Short-course(the internationally recommended control strategy for tuberculosis)
DRA	Drug Regulatory Authority
EDM	Essential Drugs and Medicines Policy Department (WHO)
FDC	Fixed-dose combination
GTB	Global TB Programme
H	Isoniazid
IUATLD	International Union Against Tuberculosis and Lung Disease
MDR-TB	Multidrug-resistant tuberculosis
MOH	Ministry of Health
NGO	Non-governmental organization
NTP	National tuberculosis programme
PTB	Pulmonary tuberculosis
QA	Quality assurance
R	Rifampicin
RIF or R	Rifampicin
S	Streptomycin
TB	Tuberculosis
TB/HIV	TB and HIV co-infection
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

Abstract

Tuberculosis (TB) is a major public health problem worldwide and Bangladesh is one of the high burden countries with high incidence and prevalence rates. Fixed dose combinations (FDC) is recommended for any type of TB cases in order for the patient to completely get cure from the disease. The role of Directly Observed Treatment (DOT) is an important factor to ensure the proper dosage and time of treatment. In order to determine the use of FDC tablets for TB treatment and the role of DOT for effective tuberculosis control program, a descriptive study was carried out in Kanaighat Upazilla of Sylhet, Bangladesh. After taking written consent, a total of 50 TB patients, registered in Kanaighat health complex, were interviewed using a standard questionnaire. Detail information regarding the patients` course of treatment were recorded from their treatment cards preserved in the health complex. In-depth data analysis were done using the software SPSS, version 19. In our study, most of the patients (34%) infected with tuberculosis were in between 50-65 years. Majority of the cases were smear positive (54%), whereas 36% cases were smear negative. All patients in our study were treated with Category 1 and DOT followed. The results have shown that the sputum conversion rate was higher among those who had taken the drugs following DOT (75%). About 86% of all the patients enrolled in our study had followed their treatment regimen under DOT. About 90.5% of the patients with smear positive cases were declared as cured after completion of their treatment course. The use of FDC has benefited the patients when the dosage regimen of these tablets were prescribed according to weight and consumed under supervision of a DOT provider. The result of this study has shown that a very good outcome was obtained when patients get treated with anti-TB drugs as FDC and the need for DOT to improve the outcome of the patient.

Key words: Tuberculosis, Bangladesh, Kanaighat health complex, Fixed Dose Combination (FDC), Directly observed treatment (DOT).

CHAPTER – 1

Introduction

1.1 Over view

Tuberculosis (TB) continues to be a major cause of morbidity and mortality worldwide, with 9 million new cases of TB diagnosed and 1.5 million TB-related deaths recorded globally in 2013. Approximately 95% of the estimated numbers of TB cases occur in low-income countries, with 82% of these cases being concentrated in 22 countries. (World Health Organization, 2017a). Furthermore, the global burden of drug-resistant TB is growing. In 2010, an estimated 650,000 cases of drug-resistant TB were reported worldwide (World Health Organization, 2012).

Alongside the rising prevalence of drug-resistant TB, there has been an increase in the spread of cases due to direct contact with drug-resistant TB patients. Consequently, drug-resistant TB has become an epidemic itself, especially in high-burden settings. (Keshavjee & Farmer, 2010; World Health Organization, 2015). Multidrug resistance is a further threat to TB control. Development of drug- or multi-drug-resistant (MDR) TB is caused by inadequacies in treatment, such as in the number of drugs in the regimen to which the bacilli are susceptible, the dose or dosing frequency, the drug quality, or the treatment adherence. (World Health Organization, 2012; Wright *et al.*, 2009; Malangu & Mngomezulu, 2015)

WHO declaration of tuberculosis as a global public health emergency in 1993 ended a period of prolonged global neglect. Together, the subsequent launch of the directly observed treatment, short course (DOTS) strategy; inclusion of tuberculosis-related indicators in the Millennium Development Goals; development and implementation of the Stop TB Strategy that underpins the Global Plan to Stop TB 2006–2015; and adoption of resolution WHA62.15 on the prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis by the Sixty-second World Health Assembly have all helped to accelerate the global expansion of tuberculosis care and control (WHO Global strategy, 2014)

Tuberculosis (TB) is a major public health problem in Bangladesh since long. Estimates suggest that daily about 880 new TB cases and 176 TB deaths occur in the country.

Nearly one-third of the global population, i.e. two billion people, is infected with *Mycobacterium tuberculosis* and thus at risk of developing the disease. More than nine million people develop active TB every year and about two million die.

More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years). In 1993 the World Health Organization (WHO) declared TB as a global emergency and recommended

a standard strategy for control of the disease known as “DOTS” or Directly Observed Treatment, Short course (National TB Control Programme, 2008).

In Bangladesh, under the Mycobacterial Disease Control (MBDC) Directorate of the Directorate-General of Health Services (DGHS), the National Tuberculosis Control Programme (NTP) adopted the DOTS strategy during the Fourth Population and Health Plan (1992-98) under the project “Further Development of TB and Leprosy Control Services”. The NTP started its field implementation in November 1993 in four thanas (upazilas) and progressively expanded to cover all upazilas by June 1998. NGO partners were involved from the inception of DOTS in the country. In July 1998, the NTP was integrated into the Communicable Disease Control component of the Essential Services Package under the Health and Population Sector Program (HPSP). In 2003, HPSP was renamed “Health, Nutrition and Population Sector Program” (HNPSP) and tuberculosis control is recognized as one of the priorities in HNPSP.

From 2002, NTP expanded its collaboration with other public and private health care providers. The DOTS strategy was rolled out to all metropolitan cities in collaboration with different NGOs. Administrative DOTS coverage is considered universal in the country.

The Government of Bangladesh, together with its many and diverse partners from the public and private sectors, is committed to further strengthen the TB control programme. It has adopted the Stop TB strategy in 2006, which includes and builds on the DOTS strategy. This is done with a view of sustaining the achievements of the past years and reaching the TB control targets linked to the Millennium Development Goals (MDGs) (National TB Control Programme, 2008).

1.2 Facts about global TB

- 49 million lives saved between 2000 -2015 (TB deaths fell by 22% in the same period)
- TB was one of the top ten causes of death worldwide (TB was responsible for more deaths than HIV and malaria)
- MDR-TB crisis with gaps in detection and treatment (Only 1 in 5 needing MDR-TB treatment were enrolled on it)
- Funding short fall for TB implementation (Gap of over US$1 billion per year for TB research) (World Health Organization, 2017b)

1.3 Tuberculosis

Tuberculosis is an infectious disease, caused by the bacillus called *Mycobacterium tuberculosis*. The bacilli usually enter the body by inhalation through the lungs and spread to other parts of the body via the blood stream, the lymphatic system, or through direct extension to other organs.

People infected with TB bacteria have a lifetime risk of falling ill with TB of 10%. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill. When a person develops active TB (disease), the symptoms (cough, fever, night sweats, weight loss etc.) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People ill with TB can infect up to 10-15 other people through close contact over the course of a year. Without proper treatment up to two thirds of people ill with TB will die (World Health Organization, 2017c).

1.4 Difference between latent TB infection and TB disease

People with latent TB infection have TB germs in their bodies, but they are not sick because the germs are not active. These people do not have symptoms of TB disease, and they cannot spread the germs to others. However, they may develop TB disease in the future. They are often prescribed treatment to prevent them from developing TB disease.

People with TB disease are sick from TB germs that are active, meaning that they are multiplying and destroying tissue in their body. They usually have symptoms of TB disease. People with TB disease of the lungs or throat are capable of spreading germs to others. They are prescribed drugs that can treat TB disease (CDC, 2017a).

Preventing Latent TB Infection from Progressing to TB Disease:

Many people who have latent TB infection never develop TB disease. But some people who have latent TB infection are more likely to develop TB disease than others. Those at high risk for developing TB disease include:

- People with HIV infection
- People who became infected with TB bacteria in the last 2 years
- Babies and young children
- People who inject illegal drugs
- People who are sick with other diseases that weaken the immune system
- Elderly people
- People who were not treated correctly for TB in the past (CDC, 2017a).

1.5 Spread of tuberculosis bacilli

Patients with pulmonary tuberculosis who cough up TB bacilli through coughing, sneezing and spitting are the main source of TB infection. Presence of TB bacilli in the sputum can be identified on microscopic examination of sputum specimens. Such patients whose sputum contains TB bacilli are known as smear- positive cases.

If the bacilli cannot be identified on microscopy examination of sputum specimens of pulmonary cases, the patients are known as smear-negative cases. In contrast to smear-positive cases, smear-negative cases are less infectious and the disease is usually less severe. Extra-pulmonary cases are almost never infectious, unless they have pulmonary tuberculosis as well.

An infectious tuberculosis patient expels TB bacilli into the air through tiny droplets during coughing and sneezing. These droplets dry quickly, become droplet nuclei carrying

the bacilli, and may remain suspended in the air for several hours. Infection occurs if the inhaled bacilli in these droplet nuclei enter and settle in the lungs of a healthy person and begin to multiply.

The degree of exposure is extensive for those who are in close and prolonged contact with an infectious case (i.e. persons who are living in the same household with infectious TB cases).The bacilli are rapidly destroyed by exposure to sunlight and their concentration in the air is reduced by good ventilation.

1.6 Development of tuberculosis

If the body immune mechanism is not seriously compromised, approximately 90% of the infected cases will not develop tuberculosis disease; in this case the bacilli usually remain dormant within the body. The remaining 10% of infected individuals will subsequently develop disease, half of them shortly after infection, the other half later in their life. (National TB Control Programme, 2008).

People with weakened immune systems (those with HIV/AIDS, those receiving chemotherapy, or children under 5 years old, for example) are at a greater risk for developing TB disease. When they breathe in TB bacteria, the bacteria settle in their lungs and start growing because their immune systems cannot fight the bacteria. In these people, TB disease may develop within days or weeks after the infection.

In other people who are healthy at the time of the initial limited infection, TB disease may develop months or years after the initial infection, at a time when the immune system becomes weak for other reasons and they are no longer able to fight the germs (Mycobacteria).

When a person gets active TB disease, it means TB bacteria are multiplying and attacking the lung(s) or other parts of the body, such as the lymph nodes, bones, kidney, brain, spine, and even the skin. From the lungs, TB bacteria move through the blood or lymphatic system to different parts of the body. Symptoms of active disease include cough, loss of weight and appetite, fever, chills and night sweats as well as symptoms related to the function of a specific organ or system that is affected; for example, coughing up blood or sputum in TB of the lungs, or bone pain if the bacteria have invaded the bones (American Lung Association, 2017)

1.7 Diagnosis of Tuberculosis

1.7.1 Signs and symptoms of TB

The highest priority for TB control is identification and successful treatment of patients who are suffering from smear-positive pulmonary TB. Pulmonary TB should be suspected in a person who presents with persistent cough for three weeks or more, with or without production of sputum despite the administration of a non-specific antibiotic.

Often a patient with pulmonary TB has one or more of the following symptoms in addition to cough:

- Respiratory symptoms: shortness of breath, chest pain, coughing up of blood
- General symptoms: loss of weight, loss of appetite, fever, night sweats

Sputum microscopy should always be requested for a patient, who has cough for three weeks or longer, even in the absence of any other symptom.

Signs and symptoms of extra-pulmonary TB depend on the site involved. Most common examples are:

- TB lymph adenitis: swelling of lymph nodes
- Pleural effusion: fever, chest pain, shortness of breath
- TB arthritis: pain and swelling of joints
- TB of the spine: radiological findings with or without loss of function
- Meningitis: headache, fever, stiffness of neck and subsequent mental confusion

1.7.2 Organization of case finding by medical staff and non-medical persons

By medical staff

Selection of people symptomatic for TB referred by different health providers and volunteers and arranging for examination of their sputum is the responsibility of medical doctors of governmental health facilities and NGO facilities involved in the NTP.

By non-medical persons

Community participation plays an important role in identification of TB suspects and motivating them to have their sputum examined or to visit a health facility for diagnosis. Non-medical community members include the following persons:

- Village doctors
- Cured patients and patients under treatment

- Shasthya shebikas or volunteers
- Other important persons in the community such as religious and village leaders, political leaders, members of union councils, school teachers and persons who have close communication with women in the community (National TB Control Programme, 2008).

1.7.3 Tools for diagnosis of TB

Sputum smear examination

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

Radiological (X-ray) examination of the lungs

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

Tuberculin skin test (Mantaux Test)

This test is only used for supporting TB diagnosis in young children. (see details in children tuberculosis section)

In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB disease in adults. A positive tuberculin skin test does not by itself differentiate *M. tuberculosis* infection from TB disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. With increasing age an increasing percentage of the population will have been infected with *M. tuberculosis* (almost 100% at the age of 40-50 years) and 90% of them will not have developed TB disease. Hence, diagnosis of TB based on Mantoux test will lead to over-diagnosis of many patients.

Culture of TB bacilli

Culture is more sensitive than smear microscopy, detecting a higher proportion of patients among suspects. If resources permit and adequate, quality-assured laboratory facilities are available, culture should be included in the algorithm for evaluating patients with negative sputum smears. However, it takes about six weeks to provide a definite result, and is not accessible to most patients. Therefore, it is unsuitable as routine procedure. The probability of finding acid-fast bacilli in sputum smears by microscopy is directly related to the concentrations of bacilli in the sputum. Sputum microscopy is likely to be positive when there are at least 10 000 organisms per ml of sputum.

FNAC and Biopsy

These are special tests performed to confirm extra pulmonary TB to be referred to concerned specialists.

Xpert for MTB/RIF

This is a rapid diagnostic tool for confirmation of diagnosis Mycobacterium tuberculosis and whether the bacterium is Rifampicin sensitive or not. In adults thought to have TB, with or without HIV infection, Xpert® MTB/RIF is sensitive and specific. Compared with smear microscopy, Xpert® MTB/RIF substantially increases TB detection among culture-confirmed cases. Xpert® MTB/RIF has higher sensitivity for TB detection in smear-positive than smear-negative patients. Nonetheless, this test may be valuable as an add-on test following smear microscopy in patients previously found to be smear-negative. For rifampicin resistance detection, Xpert® MTB/RIF provides accurate results and can allow rapid initiation of MDR-TB treatment, pending results from conventional culture and DST. The tests are expensive, so current research evaluating the use of Xpert® MTB/RIF in TB programmes in high TB burden settings will help evaluate how this investment may help start treatment promptly and improve outcomes (Steingart, *et al*, 2014).

The diagnostic accuracy of Xpert for RMP resistance is high, although the predictive value for MDR-TB was lower than anticipated. Xpert allows for faster initiation of second-line treatment than culture-based drug susceptibility testing under programmatic conditions (Metcalfe, 2016).

1.7.4 Examination of sputum specimens

Microscopy should be performed on two sputum specimens, as follows:

- "On-the-spot" specimen: the first specimen is collected on the spot when a patient is identified as a pulmonary TB suspect (Spot-specimen),
- Early morning specimen: the patient is given a sputum container to collect the second specimen, at home on the following morning (Early Morning Specimen), (National TB Control Programme, 2013).

The responsible medical officer or paramedic/laboratory technologist should provide clear instruction to the patient on how to collect the sputum: in the open air and as far as possible away from other people. If the patient attends a center where microscopy facilities are available, he/she should either be instructed to bring the specimens to the responsible medical officer or paramedic or directly to the laboratory. If the patient attends a center without microscopy facility, the responsible staff should ensure that the two sputum specimens are brought within five days after collection to the microscopy center (National TB Control Programme, 2008).

1.7.5 Diagnosis of extra-pulmonary TB in adults

Extra-pulmonary TB can occur at any age and can involve any organ. Many patients with EPTB may also suffer from pulmonary TB.

Definitive diagnosis of extra pulmonary TB is often difficult. Diagnosis may be presumptive, provided other conditions mimicking tuberculosis can be excluded. Patients usually present with constitutional features (fever, night sweats, weight loss) and local features related to the site of disease. The degree of certainty of diagnosis may depend on the availability of diagnostic tools, e.g. X-ray, ultrasound, FNAC, biopsy, etc.

Tools for diagnosing EPTB cases:

1. Smear and/or culture for AFB of bodily fluids: pleural fluid, pericardial fluid, ascetic fluid (laparoscopic), cerebrospinal fluid (by lumbar puncture), urine, aspirate (FNAC) from any solid organ e.g. lymph node, spine, epididymis
2. Histopathological examination (biopsy) – finding of caseating granuloma in the biopsy material obtained from body tissues such as lymph node, peritoneum (laparoscopic), synovium, spine, bone, liver, spleen, genital tract, etc.
3. X-ray of involved structure, e.g. lung, spine, bone, joint, adrenal gland
4. Biochemical test, e.g. exudate (low sugar and high protein)
5. Cytological examination of effusions, ascites, CSF fluid, etc.
6. Tuberculin test.

Different types of EPTB

1. Tuberculosis lymphadenopathy
2. Miliary (disseminated) TB
3. Tuberculous serous effusions (pleural, pericardial, ascites)
4. Gastro-intestinal TB
5. Spinal TB (Pott's disease)
6. Joint TB
7. Genito-urinary TB
8. Hepatic/Splenic TB

Less common extra-pulmonary forms

Tuberculosis may cause chorioretinitis, uveitis, panopthalmitis, phlyctenular conjunctivitis. In the nasopharynx, tuberculosis may simulate Wegner‟s granulomatosis. Cutaneous manifestations of tuberculosis include primary infection due to direct inoculation, abscess and chronic ulcers, scrofuloderma, lupus vulgaris, miliary lesions, and erythema nodosum. Adrenal tuberculosis is a manifestation of advanced disease presenting as sign of adrenal insufficiency (National TB Control Programme, 2013).

1.8 Case Definition

Case definition takes the following into account:

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

Case definition is necessary for:

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

1.8.1 Anatomical site of the disease

The categories by anatomical site are pulmonary and extra-pulmonary TB.

Pulmonary TB

Pulmonary TB refers to disease affecting the lung parenchyma.

Extra-pulmonary TB

Extra-pulmonary TB refers to tuberculosis of organs other than the lungs only. TB may affect any organ or tissue. Examples are: mediastinal and/or hilar lymph nodes, larynx, cervical lymph nodes, pleurae, meninges, central nervous system, spine, bones and joints, kidneys, pericardium, intestines, peritoneum and skin.

In miliary TB, there is acute haematogenous spread. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs.

Patients diagnosed with both pulmonary and extra-pulmonary TB should be classified as pulmonary TB (National TB Control Programme, 2013).

Extra-pulmonary TB (EPTB) manifests with protean symptoms, and establishing a diagnosis is more difficult than pulmonary TB (PTB). The risk factors for EPTB compared with PTB. Awareness of these factors is essential for physicians to have a high index of suspicion for accurate and timely diagnosis (Lin, *et al*, 2009).

1.8.2 Bacteriological status

Pulmonary TB is divided into two categories according to their bacteriological status:

1. **A Bacteriologically confirmed TB case:** This is one from whom a biological specimen is positive by smear microscopy, culture or WRD (WHO approved Rapid Diagnostic tool such as Xpert MTB/RIF)

2. **A clinically diagnosed TB case:** this is one who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician, or other graduate medical practitioners who has decided to give the patient a full course of TB treatment. These includes the cases diagnosed based on X- ray abnormalities or suggestive histology and extra pulmonary cases without Laboratory confirmation.

1.8.3 Previous treatment history

The treatment history is very important for proper categorization of the patient subsequently choosing the correct regimen (National TB Control Programme, 2013).

Table 1.1: Case definition by site and bacteriological status in adults (National TB Control Programme, 2013).

Case classification	Definition
Pulmonary smear-positive TB (PTB+)	• A patient with at least one sputum specimen positive for AFB, including and scanty smear
Pulmonary smear negative TB (PTB-) but positive on Xpert (MTB+/RIF)	(If Xpert is available) • A patient with symptoms suggestive of TB with two sputum specimens negative for AFB and • Found positive on Xpert MTB+/RIF-(MTB detected Rifampicin susceptible)
Pulmonary smear-negative (PTB-)	(If X Ray is available) • A patient with symptoms suggestive of TB with two sputum specimens negative for AFB; and • Xpert MTB/RIF (if available) is Negative and • Chest X Ray abnormalities consistent with active TB and • Diagnosis made by a qualified physician
Extra-pulmonary TB (EPTB)	• A patient with TB of organs other than the lungs as confirmed by a qualified physician, eg pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

Table 1.2: Case definition by previous treatment history (National TB Control Programme, 2013).

Case classification	Definition
New	• A patient who has never received anti-TB drugs; or • A patient who received anti-TB drugs for less than one
Relapse	• A patient previously treated for TB who has been declared "cured" or "treatment completed" at the end of their most recent course of treatment, and are now diagnosed with recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
Treatment after failure	• Treatment after failure patients are those who have previously been treated for TB and whose treatment failed at the end of the most recent course of treatment.
Treatment after loss to follow- up /default	• Treatment after loss to follow- up patients have previously been treated for TB and were declared loss to follow up at the end of their most recent course of treatment. (They were previously known as default patients).
Transfer in	A patient already registered for treatment in a DOTS centre and who is subsequently transferred to another registration
Chronic	• A patient who remained smear-positive after completing a directly observed re-treatment regimen
Other (s)	• Other previously treated patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is un known or undocumented.

1.9 Treatment of Tuberculosis

1.9.1 The role of treatment in the control of tuberculosis

Treatment and cure of infectious cases of tuberculosis will interrupt transmission of TB infection in the community. Therefore, successful completion of treatment is the most effective way of prevention of TB.

1.9.2 Aims of treatment

1. To cure TB patients
2. To prevent death from active TB or its late effect
3. To prevent relapse of TB
4. To decrease transmission of TB to others
5. To prevent the development of acquired drug resistance

1.9.3 Basic principles of TB treatment

1. Appropriate combination of drugs to kill different bacterial populations.
2. Drugs are given for the required duration (several months) to kill the bacilli.
3. Drugs are given in the correct doses to achieve the therapeutic effect (National TB Control Programme, 2013).

1.9.4 Treatment phases

Effective chemotherapy consists of two phases:

- The initial or intensive phase administered daily for two months in new cases and three months in re-treatment cases. The aim of this phase is to rapidly reduce and eliminate the multiplying bacilli without allowing the development of acquired resistance to the prescribed drugs. During the intensive phase, the tubercle bacilli are killed rapidly. The infectious patients quickly become non-infectious (within approximately two weeks).
- The continuation phase is essential to eliminate the remaining bacterial population. Drugs administered daily for the rest of the treatment duration according to category (National TB Control Programme, 2013).

Table 1.3 Standardized treatment regimen for each diagnostic category (Adults)

(National TB Control Programme, 2013).

	Patient Category	Treatment regimen	
		Intensive phase (DAILY)	**Continuation phase (DAILY)**
I	• New smear-positive bacteriologically positive PTB patients • New smear-negative PTB • New Extra-pulmonary TB • New Concomitant/ associated HIV/AIDS	2 (HRZE) *(HRZE= Isoniazid+ Rifampicin+ Pyrazinamide+ Ethambutol)	4 (HR) *(HR= Isoniazid+ Rifampicin)
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	2 (HRZE)S / 1 (HRZE)	(HR)E

1.9.5 Dosages of FDC tablets

FDC tablets are composed as follows:

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

The dosages of FDC tablets for adults are as follows:

Table 1.4: Category I (National TB Control Programme, 2013).

Pre-treatment weight (kg)	**Intensive Phase**	**Continuation Phase**
	Daily (first 2 months)	Daily (Next 4 months)
	Number of 4FDC tablets	Number of 2 FDC tablets
30 – 37	2	2
38 – 54	3	3
55 – 70	4	4
> 70	5	5

Table 1.5: Category II (National TB Control Programme, 2013).

Pre-treatment weight (kg)	**Intensive Phase**		**Continuation Phase**	
	Daily (first 3 months)	Daily (first 2 months)	Daily (next 5 months)	
	Number of 4-FDC tablets	Injection Streptomyc in	Number of 2-FDC tablets	Ethambutol 400mg (Number of tablets)
30 – 37	2	500mg	2	2
38 – 54	3	750mg	3	3
55 – 70	4	1gm*	4	3
> 70	5	1gm*	5	4

* The dose of streptomycin should not exceed 750 mg daily after the age of 50 year.

1.10 Start of Treatment

Treatment should be started as soon as possible after the diagnosis is made. Treatment should only be started after a confirmed diagnosis has been made.

The responsible medical officer/graduate physician should categorize the patient. A paramedical staff may fill in the treatment card and register the patient in the TB register and maintain other documents related to diagnosis of the patients.

The first dose of drugs should be given at the respective health facility, where after the patient is referred to the DOT provider .At the time of start of treatment all drugs for the whole course of treatment (intensive and continuation phase) of the respective patient should be ensured. In case of transfer or death of a patient, the remaining drugs should be returned and added to the general stock.

The medical officer or TB manager/supervisor should weekly review and cross check the TB register with the laboratory register to ensure that all patients diagnosed in the laboratory are registered and enrolled for treatment.

Patients who are smear-positive according to the laboratory register but did not begin treatment should be traced within two weeks after the laboratory result is available.

Patient compliance is a key factor to treatment success. A proportion of patients stop treatment before completion, for various reasons so strict adherence to treatment should be ensured to cure the patients and prevent the development of drug-resistant TB. (National TB Control Programme, 2013).

1.11 Directly observed treatment (DOT)

Directly observed treatment is a very important component in the internationally recommended policy package for TB control (DOTS strategy).

DOT means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures that the patient takes the right anti-TB drugs, in the right doses, at the right intervals and for the right period. All patients, irrespective the treatment category, should receive all doses of the anti- TB drugs under DOT (National TB Control Programme, 2013).

In one such study, it was shown that the community based DOTS (CBD) strategy was more cost-effective than the FBD strategy in the study context, the estimates of cost-effectiveness were sensitive to relatively small changes in underlying costs and treatment outcomes. Even using these relatively patient-friendly approaches to DOTS, social costs can represent a significant financial burden for TB patients (Mirzoev, *et al*, 2008).

1.11.1 DOT providers

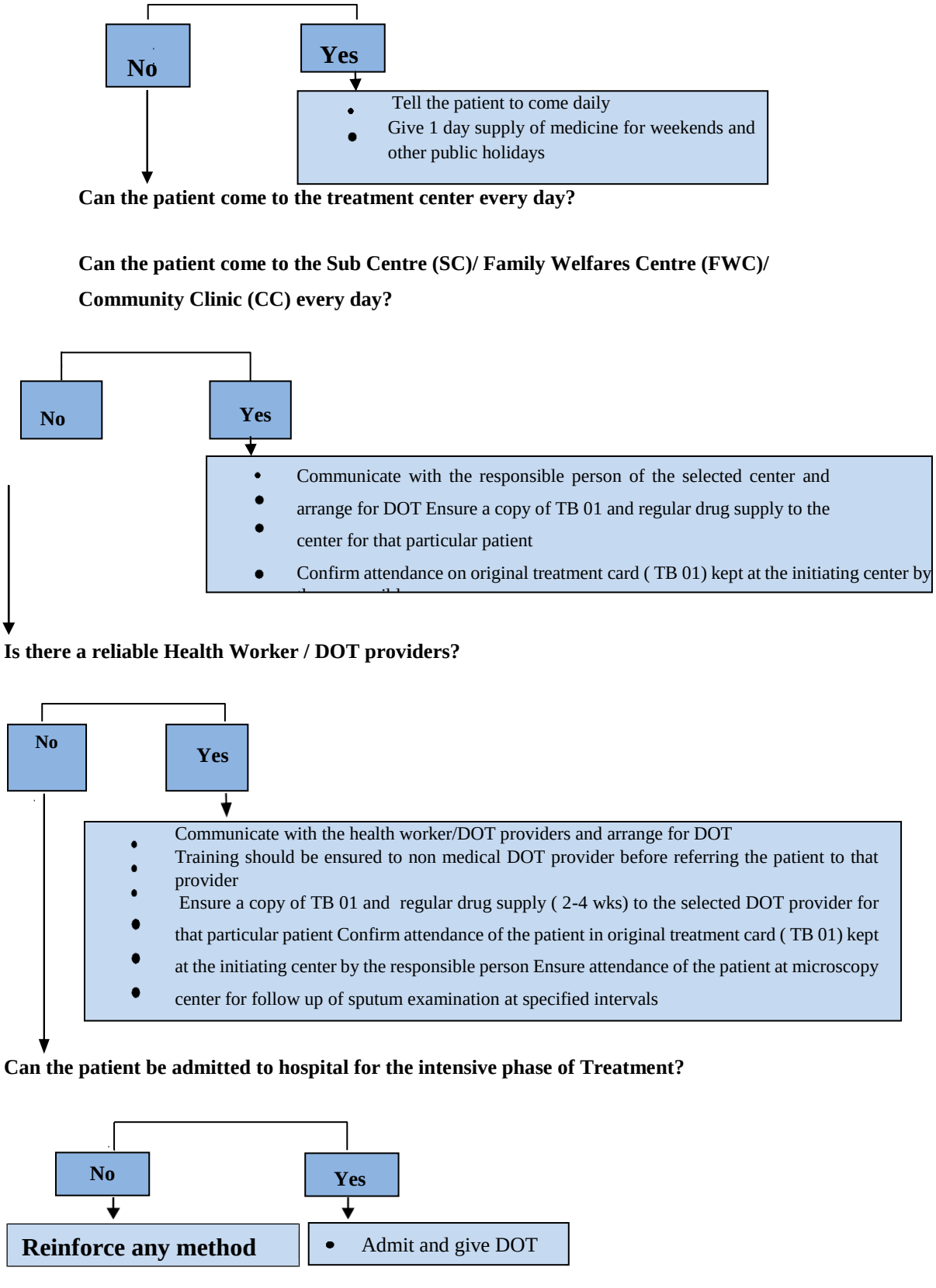
To ensure adherence to treatment, DOT should be provided as conveniently as possible to the patient. This often means as close to the patient‟s home or workplace as possible. Patients may wish to attend any of the NTP recognized DOT centres according to patients convenience.

The DOT provider may be a facility- or community-based health worker or a trained and supervised community member. These DOT providers include health assistants (HAs), assistant health inspectors (AHIs), community health workers (CHWs), shasthya shebikas, village doctors, community leaders, cured patients, etc. All non-medical personnel who deliver DOT should be supervised at least monthly.

Medical officers and paramedics in consultation with patients should identify the DOT provider, the name and address of whom should be recorded on the patient‟s treatment card. The medical officer or paramedic has to ensure that the DOT provider receives the filled-in copy of Treatment Card (TB 01) and Identity Card (TB 02) and drugs at the specific intervals (National TB Control Programme, 2013).

1.11.2 Methods of DOT

The following flow chart shows the decision tree for DOT. (National TB Control Programme, 2013).



1.12 Follow-up of treatment

In order to evaluate the result of treatment, sputum smear examinations should be performed at defined intervals.

1.12.1 New smear/Xpert MTB/RIF positive patients

One sputum specimen should be examined at the end of month 2/3, 5 and 6 after the start of treatment. The sputum at six months can also be collected during the last two weeks of treatment.

1 The patient should NOT be continued with the intensive phase of treatment but be started on the continuation phase of the treatment.

2 In these patients, the sputum sample should be sent to Xpert MTB/RIF lab to check whether patient is RIF resistant or not.

3 Follow up of all RIF sensitive cases should be done by smear microscopy.

4 Further management of this patient will depend on the outcome of the Xpert MTB/RIF result.

1.12.2 Retreatment smear/ Xpert MTB/RIF positive patients

One specimen of sputum of patients treated with Category II regimen should be examined at the end of month 3/4, 5 and 8. The sputum at eighth month can also be collected during the last two weeks of treatment.

In case the sputum smear is positive at the end of the third month:

a. The patient should NOT be continued with the intensive phase of treatment, but be started on the continuation phase of the treatment.

b. In these patients, a sputum sample should be sent to Xpert MTB/RIF lab to check whether the patient is RIF resistance or not.

If the smear is positive at month 5 or 8, the outcome should be recorded as treatment failure and the patient should be referred for examination for DR-TB.

1.12.3 Smear negative and extra-pulmonary patients

At the end of second month of treatment, one sputum specimen should be examined of all smear negative pulmonary TB patients to ensure that they remain negative.

In case the smear is positive (a second smear should confirm the result), the patient should be confirmed as 'treatment failure' and referred for MTB/Xpert result. This patient must be registered as treatment after failure of CAT 1 and CAT II course should be started.

In case of extra pulmonary TB, no smear examination is necessary and the patient should be assessed clinically.If the patient does not improve clinically, patient should be assessed for DR EPTB.((National TB Control Programme, 2013).

1.13 Management of side effects or adverse reactions related to the use of anti-tuberculosis drugs

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects. Patients sometime discontinue the treatment due to major or even minor adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly.

Table 1.6 Symptom-based approach to side effects of anti-TB drugs and their management (National TB Control Programme, 2013).

Side-effect	Drug(s) probably	Management
Minor		**Continue anti-TB drugs, check drug doses**
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with after meals
Joint pain	Pyrazinamide	Give non steroidal anti-inflammatory drug (NSAID)
Burning sensation in the feet	Isoniazid	Give pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance; the patient should be informed at the beginning of the treatment that it happens commonly
Itching with minor skin rash	All drugs	Exclude skin diseases Give antihistamines
Major		**Stop responsible drug(s)**
Itching with skin rash	All drugs	Stop anti-TB drugs. Identify the offending drug **(need expert opinion)**
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin and never use again
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin and never use again
Jaundice (other causes excluded), hepatitis	Most anti-TB drugs (especially isoniazid, pyrazinamide and rifampicin)	Stop all anti-TB drugs until jaundice resolves **(need expert opinion)**
Vomiting and Confusion (suspect drug induced acute liver failure if jaundice present)	Most anti-TB drugs	Stop all anti-TB drugs until jaundice resolves Urgent Liver function test and prothrombin time test **(need expert opinion)**
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol and never use again
Shock syndrome, purpura, acute renal failure, acute hemolytic anemia	Rifampicin	Stop rifampicin and never use again

1.14 Treatment outcomes

At the end of the treatment course, one treatment outcome will be recorded for each TB patients. Table 6 shows the possible, mutually exlcusive treatment outcomes (National TB Control Programme, 2013).

Table 1.7: Treatment outcome description (National TB Control Programme, 2013).

Treatment Outcomes	Description
Cured	• A pulmonary TB patient with bacteriologically confirmed TB at the beginning of the treatment who was smear or culture- negative in the last month of treatment and on at least one previous follow-up occasion.
Treatment Completed	• A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous follow-up occasion were negative, either because tests were not done or because results are unavailable. • EP TB cases are also recorded as treatment completed as no sputum test is done after completion of full course treatment.
Treatment failure	• A TB patient whose sputum smear or culture is positive at month 5 or later during treatment or • A new or retreatment smear positive patient who was diagnosed with DR-TB during the course of treatment or • A patient who was initially smear negative and was found smear- positive at the end of the second month of treatment.
Died	• A TB patient who dies for any reason before starting or during the
Loss to follow-up/Defaulted	• A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Transfer out	• A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known (this should occur only in a minority of cases) to the reporting unit.
Not evaluated	• A patient whose treatment outcome is not known, other than transfer
Treatment success	• The sum of cured and treatment completed

1.15 Infection control in health care settings

Tuberculosis (TB) transmission has been documented in health care settings where health care workers and patients come in contact with people who have TB disease.People who work or receive care in health care settings are at higher risk for becoming infected with TB; therefore, it is necessary to have a TB infection control plan as part of a general infection control program designed to ensure the following:

1. Prompt detection of infectious patients,
2. Airborne precautions, and
3. Treatment of people who have suspected or confirmed TB disease.

In all health care settings, particularly those in which people are at high risk for exposure to TB, policies and procedures for TB control should be developed, reviewed periodically, and evaluated for effectiveness to determine the actions necessary to minimize the risk for transmission of TB.

The TB infection control program should be based on a three-level hierarchy of control measures and include:

1. Administrative measures
2. Environmental controls
3. Use of respiratory protective equipment (CDC, 2017b)

CHAPTER - 2

Literature Review

2.1 Fixed-dose combination chemotherapy (Rifater/Rifinah) for active pulmonary tuberculosis in Taiwan: a two-year follow-up

The main objective of this study was to assess the efficacy and safety of a fixed-dose combination (FDC) of Rifater (RFT)/Rifinah (RFN) in the treatment of newly diagnosed smear-positive pulmonary tuberculosis.Patients were randomly assigned to two 6-month short-course chemotherapy regimens. One group of patients were treated with FDCs and another were given the four component drugs (INH, RMP, EMB and PZA) as separate formulations.The 105 patients enrolled in the study were divided into two treatment groups. Fifty-one patients who had completed treatment without interruption, 26 in the FDC group and 25 in the separate regimen, were eligible for analysis at the end of 2 years. Among the patients with a drug susceptibility test result available, four in the FDC group had bacilli resistant to pyrazinamide. In the separate regimen group, two patients had bacilli resistant to ethambutol and six had bacilli resistant to pyrazinamide. The two regimens were of similar effectiveness with regard to sputum conversion, compliance and radiological improvement. No patient with FDC treatment developed gastointestinal symptoms, visual disturbance or peripheral neuropathy ($P < 0.05$). However, FDC treatment resulted in drug-induced fever in one patient. One patient (3.8%) in the FDC group relapsed 5 months after completing treatment.This study suggests that the two regimens had similar effectiveness in the treatment of smear-positive pulmonary tuberculosis. However, the fewer adverse drug events among those patients treated with the FDC regimen suggests that it has a better safety profile (Su & Perng, 2002).

2.2 Tuberculosis control in Bangladesh: success of the DOTS strategy

Routine programme data on all new sputum smear-positive patients registered in the TB project since its inception until 1996 were analysed. Case finding results are presented until 1996, as are results of sputum smear conversion after 2 months of treatment in new smear-positive patients for the same cohort of patients. Final treatment outcome results were analysed for new smear-positive patients registered up to 1995.

In this study, a total of 41,525 patients were registered in the project during the 3-year period. Two-thirds of these were new smear-positive cases and 27% were new smear-negative patients. Sputum smear conversion in 26,151 new smear-positive patients at 2

months was 85%; 5% remained smear-positive, 3% had died and the rest had no sputum examination. Final treatment outcome results in 10,142 new smear-positive patients registered during 1993-1995 showed that 75% were cured, 4% completed treatment but did not have a sputum smear result, 2% remained smear-positive, 6% died, 10% defaulted and 3% were transferred out.

The DOTS strategy can be successfully implemented in phases in large countries with a high tuberculosis burden. This success is due to decentralizing sputum smear microscopy and treatment delivery services to peripheral health facilities, utilizing the existing primary health care network. High cure rates can be maintained despite rapid expansion of coverage, with proper implementation of the strategy and regular monitoring of reports on case finding, sputum smear conversion and treatment outcome. Case detection needs to be further increased by informing and involving the community in TB control efforts through social mobilization (Kumaresan, *et al*, 1998).

2.3 Implementation of the DOTS strategy for tuberculosis control in rural Kiboga District, Uganda, offering patients the option of treatment supervision in the community, 1998-1999

This study was done in Kiboga district, a rural district in central Uganda. As part of routine tuberculosis control programme operations, to measure the effectiveness and acceptability of community-based tuberculosis (TB) care using the directly observed treatment, short-course (DOTS) strategy for TB control. The implementation of the DOTS strategy with active participation of local communities in providing the option of treatment supervision in the community is known in Uganda as community-based DOTS (CB-DOTS).

Effectiveness was measured by comparing TB case-finding and treatment outcomes before and after the introduction of CB-DOTS in 1998. Acceptability was measured by administering a knowledge, attitudes and beliefs questionnaire to community members, health care workers and TB patients before and after the intervention:

In this study, a total of 540 TB patients were registered in the control period (1995-1997) before the introduction of CB-DOTS, and 450 were registered in the intervention period (1998-1999) after the implementation of CB-DOTS. Following the implementation of

CB-DOTS, treatment success among new smear-positive pulmonary TB cases increased from 56% to 74% (RR 1.3, 95%CI 1.2-1.5, P < 0.001) and treatment interruption decreased from 23% to 1% (RR 16.5, 95%CI 6.1-44.7, P < 0.001). There was no significant difference in the proportion of deaths before and after the implementation of CB-DOTS (15% vs. 14% for new smear-positive pulmonary, and 38% vs. 29% for new smear-negative and extra-pulmonary TB cases). The acceptability of CB-DOTS was very high among those interviewed, mainly because CB-DOTS improved access to TB care, decreased costs and enabled patients to stay with their families.

The study also focused in enabling patients to choose TB treatment supervision in the community, CB-DOTS provided a highly effective and acceptable additional option to conventional TB care. Efforts are underway to address the high case fatality rates in both study groups before and after the introduction of CB-DOTS. CB-DOTS is an example of shared responsibility between health services and communities in tackling a major public health priority (Adatu, *et al*, 2003).

2.4 Tuberculosis drug issues: prices, fixed-dose combination products and second-line drugs

Access to tuberculosis drugs depends on multiple factors. Selection of a standard list of TB drugs to procure is the first step. This paper reviews the advantages and disadvantages of procuring and using fixed-dose combination (FDC) products for both the intensive and continuation phases of treatment. The major advantages are to prevent the emergence of resistance, to simplify logistic management and to reduce costs. The major disadvantage is the need for the manufacturers to assure the quality of these FDCs by bioavailability testing. The paper reports on the inclusion of second-line TB drugs in the 1999 WHO Essential Drug List (EDL). The need to ensure that these drugs are used within established DOTS-Plus programs is stressed. The price of TB drugs is determined by many factors, including producer prices, local taxes and duties as well as mark-ups and fees. TB drug prices for both the public and private sectors from industrialized and developing countries are reported. Price trends over time are also reported. The key findings of this study are that TB drug prices have generally declined in developing countries while they have increased in developed countries, both for the public and private sectors. Prices vary between countries, with the US paying as much as 95 times

the price paid in a specific developing country. The prices of public sector first-line TB drugs vary little between countries, although differences do exist due to the procurement methods used. The price of tuberculin, a diagnostic agent, has increased dramatically in the US, with substantial inter-country variations in price. The paper suggests that further research is necessary to identify the reasons for the price disparities and changes over time, and suggests methods which can be used by National Tuberculosis Programme managers to ensure availability of quality assured TB drugs at low prices.

In this study, to determine current US and international TB drug prices and how they have changed over time, a number of data sources were consulted. For the US private sector prices in 1999 and over time, the Red Book was used. The actual prices paid by an institution may be rebated from this price. While this publication does include Health Care Financing Administration (HCFA) prices, these were not included, as access to these drugs at these prices is limited. Average prices of all producers for their largest pack sizes were calculated.

Ensuring the reliable supply of assured quality TB drugs at the best possible price is the aim of any TB program. With the changes occurring in FDCs becoming available and strongly advocated and the emergence of MDR-TB, program managers will need to become more competent in drug management. However the outlook is promising. FDCs will simplify drug management and should, when incorporated into a DOTS program, prevent the emergence of MDR-TB. International prices for TB drugs have fallen and stabilized at a level where it should be possible for most countries to purchase their needed drugs (Laing & Mcgoldrick, 2000).

2.5 The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis

There is considerable exigency to take all necessary steps to cure tuberculosis cases and prevent further emergence of drug-resistant tuberculosis. The most important of these steps is to ensure that the treatment, particularly of sputum smear-positive cases, is adequate and that patients adhere to their treatment by supervised, direct observation of drug-taking according to the standardized regimens. Use of fixed-dose combinations (FDCs) of tablets against tuberculosis is now being recommended by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) as an additional

step to ensuring proper treatment. FDCs simplify the prescription of drugs and the management of drug supply, and may also limit the risk of drug-resistant tuberculosis arising as a result of inappropriate drug selection and monotherapy. Only FDCs of proven quality and proven rifampicin bioavailability should be purchased and used. In most situations, blood levels of the drugs are in adequate because of poor drug quality rather than poor absorption. This is true irrespective of the human immunodeficiency virus(HIV) infection status of the tuberculosis patients (otherthan those with overt acquired immunodeficiency syndrome, with CD4 counts <200 cells/mm3). Currently, WHO, IUATLD and their partners are developing strategies for ensuring that only quality FDCs are used in tuberculosis programmes. A simplified and effective protocol for assessment of rifampicin bioavailability has been developed, and laboratories are being recruited to form a supra national network for quality assurance of FDCs. Standardization of FDC drug formulations has been proposed, which limits rifampicin-containing preparations to nine (including a four-drug FDC and three paediatric FDCs).

FDCs and the DOT strategy Although it simplifies both prescribing and drug taking, the use of FDCs does not eliminate the need for direct observation of treatment (DOT). Whether FDCs or single-drug tablets are used, the other components of the WHO/IUATLD recommended strategy for tuberculosis control remain vital for successful tuberculosis control. Particularly, the information system used in modern tuberculosis control programmes should be maintained so that the effects of a change in treatment policy to use FDCs can be properly monitored. Thus, FDCs are promoted as an integrated part of good service delivery, helping to ensure that the treatment given is of good quality. FDCs of good quality facilitate accurate dose delivery, and ensure cure when given as directly observed treatment. However, inadequate doses, especially of rifampicin, may also lead to treatment failure and drug resistance. Thus, if FDCs are given unsupervised, patients can interrupt treatment repeatedly, and this may lead to emergence of drug resistance. The risk is best avoided by giving FDCs as directly observed treatment, at least during the initial phase of treatment (Blomberg, *et al*, 2001).

2.6 The background and rationale for a new fixed-dose combination for first-line treatment of tuberculosis in children

In 2010, the World Health Organization revised the recommendations for the treatment of tuberculosis (TB) in children. The major revision was to increase isoniazid, rifampicin and pyrazinamide dosages according to body weight in children.

However, national tuberculosis programmes faced unforeseen challenges in implementing the revised recommendations. The main difficulty was to adapt the revised dosages for the treatment of children with drug susceptible TB using available fixed-dose combinations (FDCs). A more suitable FDC for the intensive and continuation phases of treatment has now been developed for planned implementation in 2015. This paper explains the background and rationale for the development of a new FDC tablet for children with drug susceptible TB.

In response to the challenges created by the 2010 dose revision,40 an informal consultation was organised by the WHO and held in May 2012 in Stellenbosch, South Africa. A range of experience and expertise was represented, including global experts in pharmacokinetics, formulation and regulatory process for antituberculosis medication in children.Important decisions to inform the future development and implementation of a suitable FDC were to recommend RHZ 75:50:150 as the preferred FDC and to widen the recommended range for INH to 7– 15 mg/kg. These recommendations were supported by pharmacokinetic and safety data. The data also provides an example of a suitable weight-band table for the implementation of the new FDC (Graham, Grzemska & Gie, 2015).

2.7 Treating Tuberculosis: Time to Introduce Fixed-Dose Drug Combinations

Tuberculosis has been an elusive infectious disease. In India, two deaths occur every three minutes due to tuberculosis. As modern antituberculosis therapy (ATT) can cure all patients, these deaths can be prevented. But it is imperative that these patients take ATT for the prescribed duration (minimum of six months). Hence, adherence to treatment plays an important role in the success of the treatment. The Revised National Tuberculosis Control Programme (RNTCP) of India is based on Directly Observed

Treatment-Short course (DOTS) strategy. The RNTCP was launched as a national program in 1997 and the entire country was covered under DOTS by March 2006. Even though the treatment is directly observed, there are defaulters under this strategy too. This is of concern as it can lead to the serious issue of multidrug-resistant tuberculosis (MDR TB).The main success of the program is the strict adherence to the treatement. The factors affecting adherence can be grouped as patient factors, disease factors, and medication characteristics. A few of the factors hindering the success were identified and rectified in the recent past. Presently, a category I tuberculosis patient should take six tablets and one capsule (two tablets each of isoniazid, pyrazinamide, and ethambutol, and one capsule of rifampicin) available as a combination pack for a single-day treatment. Even though DOTS is an effective strategy to improve compliance, the pill burden of the current regimen hinders compliance and, thereby, the success of the treatment.

Introducing FDCs for the treatment of tuberculosis seems to be a promising solution to the problem. Incorporating FDCs into the present regimen would offer the following benefits:

- The pill burden is drastically reduced, thereby increasing acceptability by the patient.
- Selection of a particular drug from the combination pack and the consequent monotherapy leading to the development of drug-resistant forms can be reduced.
- Logistic difficulties such as ordering, storage, handling, and delivery of the drug can be reduced by FDCs (Manikandan, 2012).

2.8 Fixed-dose combination drugs for tuberculosis: application in standardized treatment regimens

Short-course chemotherapy is highly efficacious in treating tuberculosis (TB). However, the length (>/=6 months) and complexity (three or four different drugs) of the treatment makes adherence difficult.

This paper reviews that erratic treatment not only fails to cure patients but also creates chronically contagious cases, who may excrete drug-resistant TB bacteria. The Directly Observed Treatment Short-course (DOTS) strategy recommended by WHO provides a

comprehensive organisational and infrastructural framework for the rational use of diagnosis, drug supply, as well as case and programme management services, in TB control. WHO and other organisations recommend fixed-dose combination formulations (FDCs) as a further step to facilitate the optimal drug treatment of TB. Using FDCs in TB control will simplify the doctor's prescription and patient's drug intake, as well as the drug supply management of the programme.

By preventing monotherapy and facilitating the ingestion of adequate doses of the constituent anti-TB drugs, FDCs are expected to help prevent the emergence of drug resistance. This article presents the international recommendations for the use of FDCs in TB programmes. The fundamental issue is to obtain drug supplies of good quality.

A laboratory network for quality testing, including bioavailability testing of FDCs exists, and the recently established Global TB Drug Facility (GDF) supplies quality TB drugs, including 4-drug FDCs, to countries requesting assistance. This articles deals with the requirements for a successful transition to FDC-based treatment. It emphasises the need for appropriately revised programme documentation (programme manual, training modules, treatment guidelines and forms), training of staff at all levels, carefully calculated drug needs, and a plan for the exhaustion of existing stocks of loose tablets and the phasing-in of FDCs at all levels of the programme at the same time. Loose drugs for individualised treatment of patients with adverse effects should be kept at district or central health institutions (Blomberg & Fourie, 2003)

2.9 Fixed-dose combinations of anti tuberculous medications to prevent drug resistance

The treatment of tuberculosis requires at least two drugs to retard the development of drug resistance. Unfortunately, patients may take only one drug (monotherapy) when more than one is prescribed.

This paper emphasizes that Fixed-dose combinations with two or more antituberculous drugs in one capsule or tablet are available to prevent this. In the United States, these drugs are Rifamate (Marion Merrell Dow), which contains isoniazid plus rifampin, and Rifater (Marion Merrell Dow), which contains isoniazid plus rifampin and pyrazinamide. Because these preparations make monotherapy impossible, they are clearly preferable to

individual drugs. In the United States in 1993, however, only 15% to 18% of rifampin was sold in the form of fixed-dose combinations. To correct this deficiency, fixed-dose combinations should be widely promoted and accepted as a primary way to prevent drug-resistant tuberculosis.

There are two caveats regarding these preparations. First, many fixed-dose combinations, especially those in developing countries, achieve inadequate blood levels of one or more of the component drugs, especially rifampin.

The authors recommended the application of drugs only to preparations with proven bioavailability. Second, because the name Rifamate is similar to the name rifampin, mistakes in prescribing and dispensing can result in the patient receiving rifampin alone when Rifamate is intended. A name change from Rifamate to a highly distinctive name such as Rif-Isoniazid is needed to prevent such occurrences (Moulding, Dutt & Reichman, 1995).

2.10 Trends in drug-resistant tuberculosis after the implementation of the DOTS strategy in Shenzhen, China, 2000-2013

The DOTS strategy has been regarded as the most cost-effective way to stop the spread of tuberculosis (TB) since its launch by the World Health Organization.

The main objective of this study was to estimate the effects of DOTS by tracking long-term trends in multidrug-resistant TB (MDR-TB).

A retrospective cohort study was conducted from 2000 to 2013 to analyse trends in resistance to anti-tuberculosis drugs and the effect of DOTS-based treatment in Shenzhen, China, using the $\chi 2$ test.

An overall MDR-TB rate of 4.2% was observed between 2000 and 2013, with an annual reduction of 0.16%. From 2000 to 2013, trends in resistance to isoniazid (INH), rifampicin (RMP) and MDR-TB declined significantly in new TB patients ($P < 0.01$), but not in retreatment cases. Sputum smear conversion rates after 2 months of treatment decreased significantly, in particular after 2007, in new and retreatment cases.

INH and RMP resistance and MDR-TB rates declined significantly, suggesting that DOTS-based programmes were successful in reducing drug resistance in new cases but not in retreatment cases. The decreasing sputum smear conversion rates may have been due to an increase in the number of migrants. These two findings suggest that TB is unlikely to be completely eliminated by 2050 in Shenzhen (Zhu *et al,* 2017).

2.11 A Four-Drug Fixed-Dose Combination Regimen for TB

In this study, a total of 1585 adults with apparent pulmonary TB were randomized to receive daily isoniazid, rifampin, ethambutol, and pyrazinamide — either as an FDC or as separate drugs — for 8 weeks. All patients were then switched to isoniazid/rifampin for 16 weeks. Treatment was directly observed in both groups.

Three analyses were conducted: planned modified intent-to-treat (ITT; 1348 patients), post hoc modified ITT (1305), and per-protocol (1170). The latter two analyses showed that, at 18 months, the FDC regimen was noninferior to the separate-drugs regimen. Adverse events were similar between the groups in both incidence and severity, but treating physicians were more likely to discontinue study medications for such events in the FDC group than in the separate-drugs group (10 patients vs. 3 patients).

These findings indicate that a four-drug FDC regimen (although not available in the U.S.) can be safe and effective for initial treatment of pulmonary TB. The use of an FDC regimen should aid adherence to early therapy, although it will make sorting out and managing adverse drug events more complicated (Lienhardt, *et al,* 2011)

2.12 Measuring Progress in TB Control in China

Between 1990 and 2010, the prevalence of smear-positive tuberculosis decreased from 170 to 59 per 100,000 population.

In 2001, China issued a new national tuberculosis (TB) control program that expanded the directly observed treatment, short-course (DOTS) program covering half the country's population, implemented in the 1990s, to include the entire population by 2005. In a longitudinal analysis, investigators from the Chinese CDC compared results from national TB prevalence surveys done in 1990, 2000, and 2010.

The prevalence of smear-positive TB was 59 per 100,000 in 2010, down from 170 per 100,000 in 1990 and 137/100,000 in 2000. Between 1990 and 2000, the TB prevalence in provinces that had not instituted the DOTS program showed little change (180 to 174/100,000). Prevalence of bacteriologically positive TB in 2010 (116/100,000 overall, down from 221/100,000 in 1990 and 178/100,000 in 2000) remained substantially higher in males than in females (183 vs. 64/100,000), in rural than in urban populations (163 vs. 73/100,000), and in western provinces than in central or eastern ones (212 vs. 124 or 66/100,000). Prevalence was highest in the oldest age group studied (346/100,000 among individuals aged ≥60) and lowest in the youngest (59/100,000 in those aged 15–29).

The authors credit the improvement in tuberculosis control to expansion of the directly observed treatment, short-course program to cover the entire country and expansion of free treatment to include all patients with active pulmonary TB (instead of only those with smear-positive infection). They note that improved socioeconomic conditions probably also contributed to the decrease in TB prevalence. They acknowledge the need for more attention to regions and groups — notably, western provinces and rural populations — with consistently higher rates of infection. As noted by editorialists, China had >900,000 TB cases notified in 2012, and as such was a major contributor to the global TB burden. This study confirms the feasibility of doing TB prevalence surveys, even in a country as large as China (Wang *et al*, 2014).

2.13 Regarding the role of DOTS in tuberculosis treatment and control

Directly Observed Therapy Short course (DOTS) is composed of five distinct elements: political commitment; microscopy services; drug supplies; surveillance and monitoring systems and use of highly efficacious regimens; and direct observation of treatment.

The difference in the way the term 'DOTS' as defined by WHO and interpreted by many observers has led to some misunderstanding. WHO generally uses the term to mean the five components of DOTS. But the word 'DOTS' is an acronym for Directly Observed Therapy Shortcourse. Many workers therefore interpret DOTS purely as direct supervision of therapy.

DOTS is not an end in itself but a means to an end. In fact it has two purposes, to ensure that the patient with tuberculosis (TB) completes therapy to cure and to prevent drug

resistance from developing in the community. The main criticism of DOTS rightly derives from the fact that some properly conducted randomized, controlled trials of directly observed therapy with or without the other components have shown no benefit from it. The problem is that it is impossible to design a study of modern directly observed therapy against the previous self-administered, poorly-resourced programs.

As soon as a study is implemented, the attention to patients in the control (non-directly observed therapy) arm inevitably improves from the previous non-trial service situation. What is of concern is that in some trials less than 70% cure rates were achieved even in the direct observation arm.

With no new drugs or adjuvant treatment available to bring the length of treatment down to substantially less than 6 months, DOTS offers the best means we have at our disposal for TB control (Davies, 2003).

2.14 Success with the DOTS strategy

BRAC has been implementing a tuberculosis programme in Bangladesh with directly observed therapy since 1984, well before the World Health Organization announced a "breakthrough" in tuberculosis control in 1997 through the directly observed therapy short-course (DOTS) strategy.

For the first decade of operation, the BRAC programme relied on a 12-month treatment regimen, but from 1995 an 8-month short-course regimen was introduced.

Since the start of short-course treatment, a consistent and satisfactory cure rate has been reported (Mushtaque & Chowdhury, 1999).

2.15 Fixed-Dose Combination Drugs for Tuberculosis

Short-course chemotherapy is highly efficacious in treating tuberculosis (TB). However, the length (≥6 months) and complexity (three or four different drugs) of the treatment makes adherence difficult.

This article presents the international recommendations for the use of FDCs in TB programmes. The fundamental issue is to obtain drug supplies of good quality. A

laboratory network for quality testing, including bioavailability testing of FDCs exists, and the recently established Global TB Drug Facility (GDF) supplies quality TB drugs, including 4-drug FDCs, to countries requesting assistance. This articles deals with the requirements for a successful transition to FDC-based treatment. It emphasises the need for appropriately revised programme documentation (programme manual, training modules, treatment guidelines and forms), training of staff at all levels, carefully calculated drug needs, and a plan for the exhaustion of existing stocks of loose tablets and the phasing-in of FDCs at all levels of the programme at the same time (Blomberg & Fourie, 2003).

2.16 Effectiveness of RHZE-FDC (fixed-dose combination) compared to RH-FDC + Z for tuberculosis treatment in Brazil: a cohort study

In 2009, Brazil was the sole high-burden country to use three drugs [rifampin (R), isoniazid (H) and pyrazinamide (Z)] as the standard treatment for sensitive tuberculosis, with RH in fixed-dose combination (FDC). In December 2009, the country has adopted the FDC four-drug regimen including ethambutol (E).

The rationale was the expectation to reduce default and resistance rates, by increasing adherence to treatment and avoiding monotherapy. However, there is no consensus on the superior effectiveness of the RHZE-FDC regimen over RH-FDC + Z. In particular, few studies evaluated its influence on default and smear negativation rates.

In this research, the authors have conducted a historic cohort study to assess the effectiveness of RHZE-FDC for the treatment of tuberculosis in Brazil, measured by the rates of treatment default and smear negativation in the second month of treatment, using secondary data from the national information system known as SINAN-TB.

The study have shown that RHZE-FDC had a protective effect against treatment default compared to RH-FDC + Z, reducing it by 14%. However, it was not possible to show an effect of the RHZE-FDC on the rate of second month smear negativation. In addition to the regimen, other well-studied individual characteristics, such as older age (over 38 years) and higher education occupation were also protective against default.

Their analysis of a cohort database in a high burden country showed that compared to RH-FDC + Z, RHZE-FDC reduces the default rates, independently of other influencing individual or health service factors (Braga & Trajman, 2015).

2.17 Preliminary results of an operational field study to compare side-effects, complaints and treatment results of a single-drug short-course regimen with a four-drug fixed-dose combination (4FDC) regimen in South Sulawesi, Republic of Indonesia

This study was conducted in Health centres in the South Sulawesi Province, Republic of Indonesia. The main objective of this research was to compare complaints, side-effects and treatment outcome in new smear-positive patients treated with a single-drug short-course (National TB Programme (NTP)) regimen with those treated with a four-drug fixed-dose combination (4FDC) regimen. The study was a prospective study in which patients are randomly allocated to the NTP or the 4FDC regimen. Preliminary results of the first 360 patients (162 treated with the NTP regimen and 198 with the 4FDC regimen) show that two patients, treated with the NTP regimen, developed jaundice. During the intensive phase of treatment, gastro-intestinal and muscle–joint complaints of any duration and gastro-intestinal complaints lasting for 2 consecutive weeks or more were more frequent in patients treated with the NTP regimen. Sputum conversion was 89% in patients treated with the NTP regimen and 94% in those treated with the 4FDC regimen. Nine-five per cent of patients, both regimens, were cured.

The results so far show that complaints during the intensive phase of treatment are less frequent among patients treated with the 4FDC regimen. The lower dose of pyrazinamide might be the reason. Treatment results are excellent for both regimens (Gravendeel, *et al,* 2003)

2.18 Weight gain in patients with tuberculosis treated under directly observed treatment short-course (DOTS)

This study was conducted in India. The main objective was to identify the effects of weight gain among. TB patients at the end of treatment on different factors such as socio-economic and demographic characteristics, smoking and drinking habits, treatment under supervision, the type of DOTS centres and problems in taking drugs.

This study has shown that among 1557 smear-positive TB patients registered under DOTS programme, the changes in weight ranged from a loss of 4 kgs to a gain of 20 kgs at the end of TB treatment; the average change in weight was 3.22 kgs. The gain in weight at the end of treatment was associated with age (<45 years), DOT at government centres, no problems in taking drugs as reported by patients and cure rate. In conclusion, the findings showed that there is an association between gain in weight with DOT at government centres and cure of patients (Vasantha,*et al*, 2009)

2.19 Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: A four year retrospective study

A study was carried out regarding whether the Treatment of multidrug-resistant tuberculosis (MDR-TB) requires the use of expensive and toxic second-line anti-tubercular drugs which are given for a longer duration. Adverse drug reactions (ADRs) of second-line antitubercular drugs affect compliance and thereby treatment outcome. We set out to analyze ADRs and treatment outcome of MDR-TB patients receiving directly observed treatments plus therapy.

This study was a retrospective study of registered MDR-TB cases at district tuberculosis center during 2010-2014 was performed. Data regarding sociodemographic profile, diagnosis, and treatment as well as ADRs were recorded and evaluated. ADRs were evaluated for causality, severity assessment, management aspects, and impact on treatment outcome.

Results: In total 147 ADRs were reported among 72 cases. Most commonly observed ADRs were gastrointestinal (24.5%) followed by self-reported weakness (21.23%), psychological (14.38%), joint pain (14.38%), and respiratory symptoms. Discontinuation of the drugs due to ADRs was required in 36 (24.48%) events. ADRs were significantly

associated with nontreatment adherence and defaulter outcome. Cure rate was higher in MDR-TB cases with ADRs (59.72%) than MDR-TB cases without ADRs (30.18%). The study concludes that Attention needs to be paid for timely recognition and treatment of ADR with minimum modification of treatment regimen. Equal attention should be paid to MDR-TB without ADR cases to raise over all cure rate (Dela, *et al*, 2017).

2.20 Treatment outcome of tuberculosis patients under directly observed treatment short course and its determinants in Shangla, Khyber-Pakhtunkhwa, Pakistan: A retrospective study.

Tuberculosis (TB) is one of the leading causes of morbidity and mortality in Pakistan. Assessment of TB treatment outcomes, monitoring and evaluation of its risk factors in Directly Observed Treatment Short Course (DOTS) are among the major indicators of the performance of a national TB control program. Even though Pakistan ranks 5th among the 22 high-TB burden countries, there are no available data in this regard.

The methodology used was Institution-based retrospective study was conducted to determine the treatment outcome of TB patients and investigate associated risk factors at District Head Quarter Hospital Shangla, Khyber-Pakhtunkhwa, Pakistan. Two-year record (January 2011 to December 2012) of TB clinic of the hospital was reviewed. A total of 493 patients' complete information was reviewed in the study period, of these, 42.19% were smear-positive pulmonary TB (PTB), 35.09% were smear-negative PTB, and 22.72% were extra-PTB (EPTB). The overall prevalence of smear-positive PTB was 42.19% (95% confidence interval [CI]: 37.9-46.2). Records of the treatment outcome showed that 192 (38.94%) were cured, 276 (55.98%) completed treatment, 13 (2.6%) defaulted, 9 (1.8%) died, 1 (0.2%) treatment failure, and 1 (0.2%) had transferred to other facilities. The overall mean treatment success rate of the TB patients was 94.93%. TB age and TB form or baseline smear were significantly associated with unsuccessful treatment outcome. The risk of unsuccessful outcome was significantly lower among TB patients age.

The treatment success rate was high and match the World Health Organization criteria. To sustain the effective implementation of DOTS in the area, effective management, and diagnosis should be given for EPTB (Ahmad *et al*, 2017)

Justification of the Study

Tuberculosis has been a major public health problem in worldwide and Bangladesh is one of the high burden countries with high incidence and prevalence rates.
There is considerable exigency to take all necessary steps to cure tuberculosis cases and prevent further emergence of drug-resistant tuberculosis. The most important of these steps is to ensure that the treatment, particularly of sputum smear-positive cases, is adequate and that patients adhere to their treatment by supervised, direct observation of drug- taking according to the standardized regimens. Use of fixed-dose combinations (FDCs) of tablets against tuberculosis is now being recommended by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) as an additional step to ensuring proper treatment.

Fixed Dose Combinations simplify the prescription of drugs and the management of drug supply, and also limit the risk of drug-resistant tuberculosis arising as a result of inappropriate drug selection and monotherapy.
Directly Observed Treatment Short course (DOTS) is composed of five distinct elements: political commitment; microscopy services; drug supplies; surveillance and monitoring systems and use of highly efficacious regimens; and direct observation of treatment. This is an effective way to ensure complete drug administration for TB patients and reduces the chance of drug resistant.

Tuberculosis is also seen as an alarming issue in North Eastern region of the country, in Kanaighat Upazila of Sylhet district, where there are low socio economic community working in Tea gardens and low lands. Therefore this upzilla was chosen to conduct this study.

According to WHO, fixed dose combinations (FDC) is recommended for any type of TB cases with a recommended regimen in order for the patient to completely get cure from the disease. The role of Directly Observed Treatment (DOT) is an important factor to ensure the proper doses and time of treatment. The purpose of the study is the use of fixed dose combinations in TB cases and the effectiveness use of DOT during the treatment.

Objective of the study

i. The primary objective of this study is to identify the use of fixed dose combination for complete cure of Tuberculosis patients.

ii. The use of DOT to ensure proper counseling and drug intake in correct dose and time and within the treatment regimen provided by physicians.

iii. Outcome of anti TB treatment with FDC and follow-up of DOT.

CHAPTER - 3

Methodology

3.1 Study Area

This study was conducted in kanaighat Upazila, a sub district of Sylhet, Bangladesh.

3.2 Type of study

This is a descriptive study aimed to determine the use of Fixed Dose Combination (FDC) tablets for treatment of Tuberculosis and the role of DOT in TB treatment.

3.3 Total number of participant

A total number of 50 participants were selected for this study.

3.4 Inclusion Criteria

1. A registered TB patient
2. Patient who has taken 4FDC during their course of treatment

3.5 Exclusion criteria

1. Patient unwilling to participate in the study
2. Patient with incomplete records
3. A Multi drug resistant (MDR) TB case

3.6 Procedure

A standard questionnaire and patient consent form was prepared. Respective Data was collected from kanaighat Upazila Health Complex (DOTS center). Consent was taken from the patient before starting the interview. Some patients were interviewed in health complex on spot when they came to the center to take anti TB drugs or for a follow-up. Some patients were interviewed at their home while those who had completed their treatment had been interviewed during an advocacy program "Cured TB patients orientation" in the health complex.

Each registered TB patient has a treatment card which is an asset of the government and is preserved in the DOTS center where they are liable and responsible by HEED Bangladesh. Necessary permission was taken from respective department prior to use these treatment cards for data entry. Treatment details were taken from those cards and

pictures of those cards were taken and preserved for further use (with consent from the patient).

All the patients were randomly selected (irrespective of their age, sex, treatment month and cured date) and a blind serial were given to them for future references.

3.7 Data Analysis

Data analysis was done using the software SPSS version 19.

3.8 Study Period

This study period will be from May 2017 to October 2017.

CHAPTER – 4

Results

4.1 Gender distribution

There were 50 patients in our study. Out of them, 66% (33) were male and 34% (17) were female

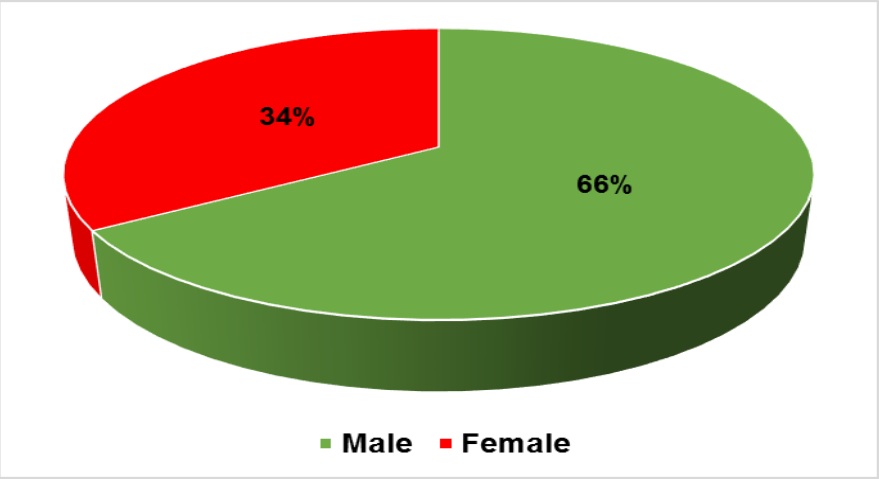


Figure 4.1. Percentage of gender distribution

4.2 Age of the patients

The age of the patients were categorized into 5 groups: less than 18 years, 18-34 years, 35-49 years, 50-65 years, 65+ years. In the pie chart beside, there are only 2 patients (4%) less than 18 years and 6 patients (12%) above 65 years. Most of the patients fell into the age group 50 - 65 years (ie 17 patients, 34%).

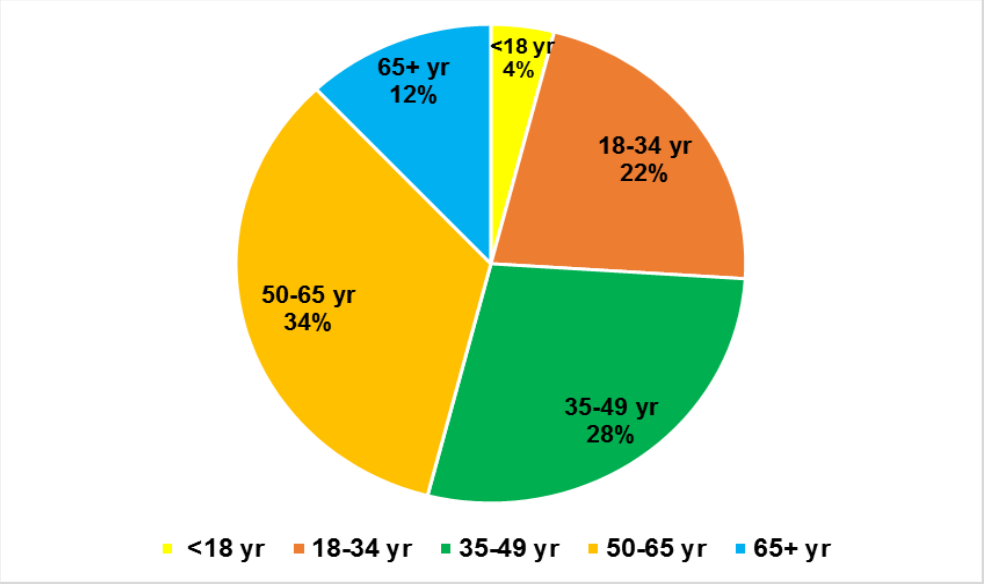


Figure 4.2: Age groups

4.3 Monthly income of patients

The chart below shows that most of the patients 64% have come from a very low socio economic status, with an average monthly income below 5000 taka.

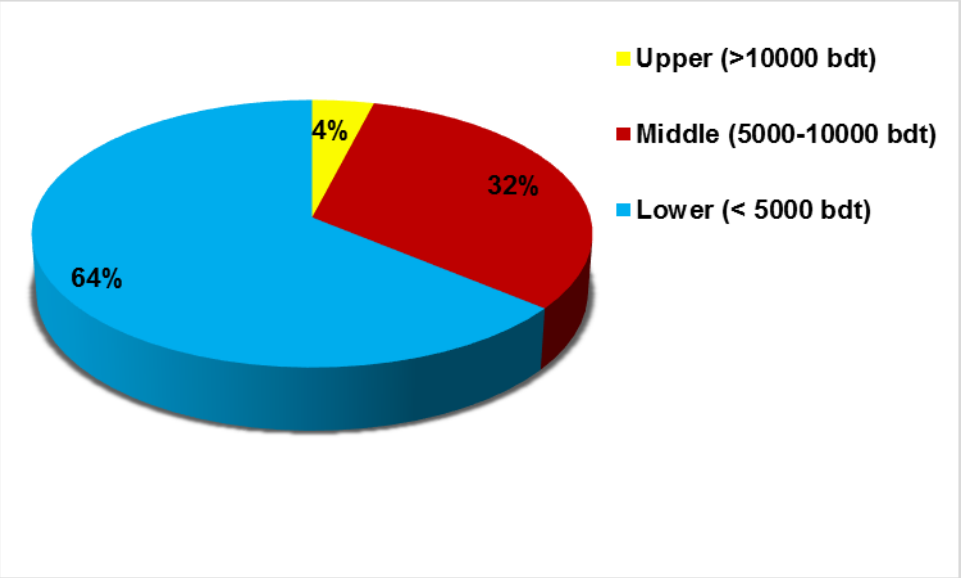


Figure 4.3: Monthly income of patients

4.4 Occupational history

Most of the patients, 42% were farmer and 30% female patients were housewives (88% of total female patients).

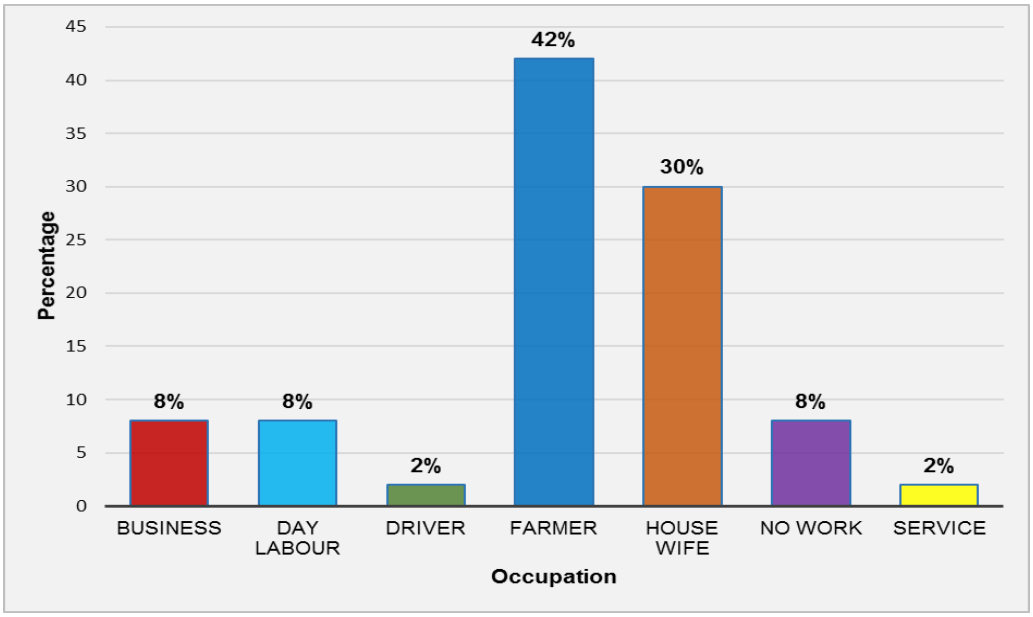


Figure 4.4: Occupational history

4.5 Number of family members living in same house

The family members of each patient was recorded and tabulated in 3 groups, ie less than 5 members, 5-8 members, more than 8 members. 60% had a family of 5-8 members.

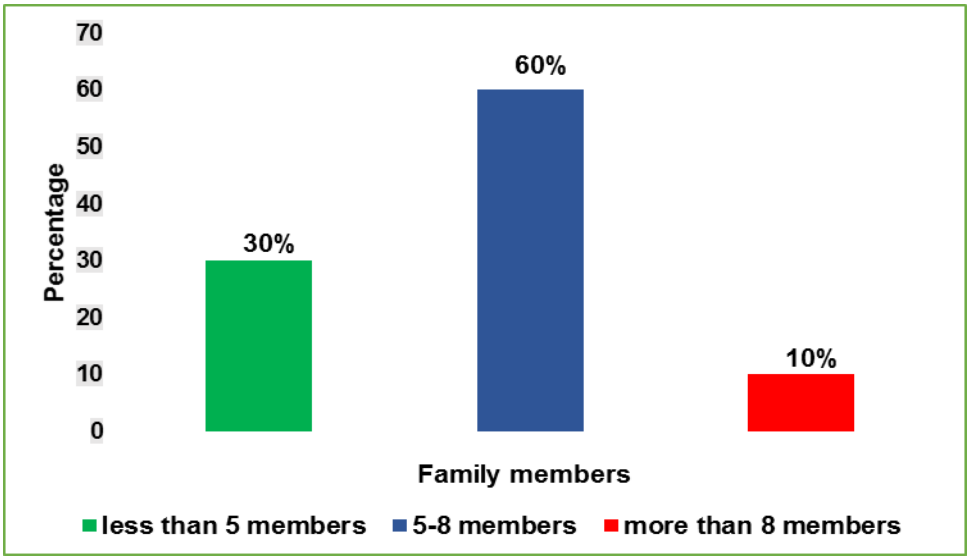


Figure 4.5: Family members

4.6 Protein intake per month

The chart beside shows that most of the patients interviewed had protein intake of two times a month 52%.

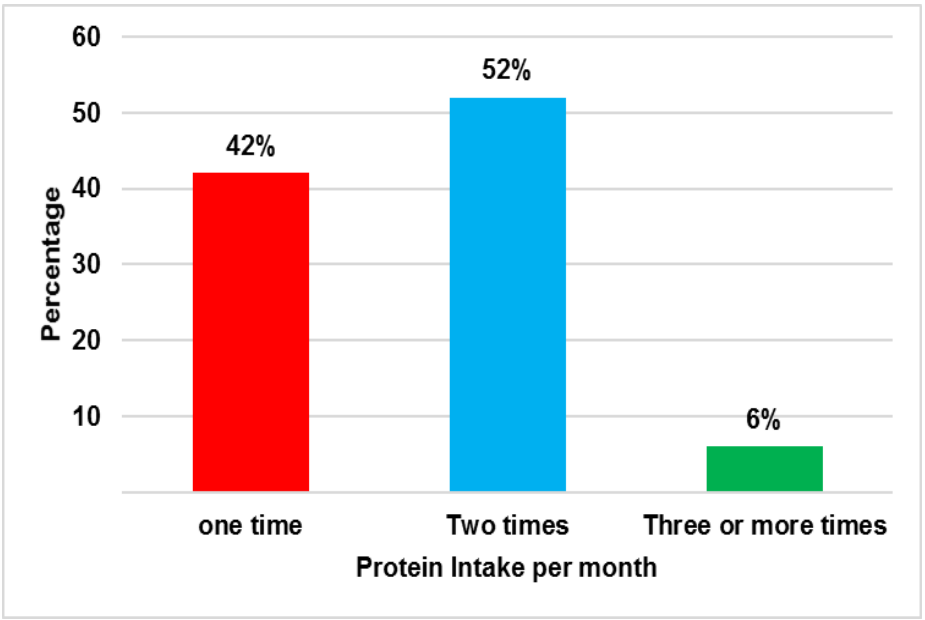


Figure 4.6: Protein intake per month

4.7 Distance from health center

Kanaighat is a large upazilla where the health complex is situated at one corner (in sadar union) but the rest of the unions are very far away from the health center. So I have recorded the distance patient has to come from their home to the health center for treatment and follow-up.

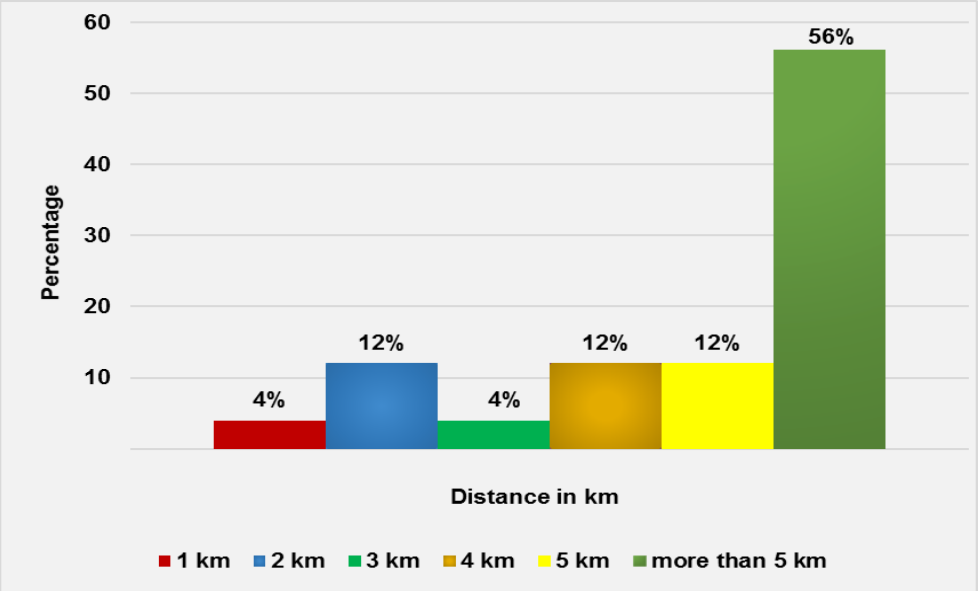


Figure 4.7: Distance from health center

Most of the patients (56%) have come a long way from their home, ie more than 5 km to the health center. The rest of the patients have homes nearer to the health center.

4.8 History of close contact

The pie chart below shows that 86% patients had no history of contact with TB. Only 14% had some history of contact with TB within the family.

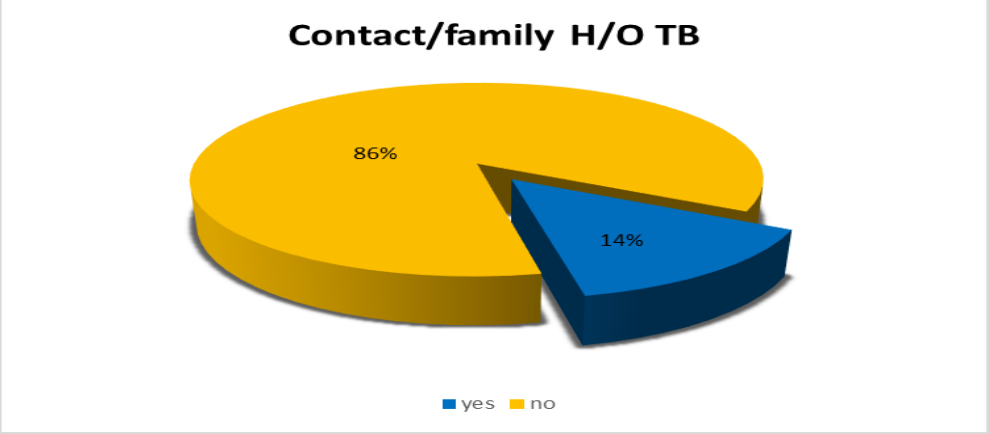


Figure 4.8: Contact/ Family History of TB

4.9 BCG vaccination status

The following figure shows that only 6% patients had given BCG vaccination while patients 94% had no immunization history with BCG.

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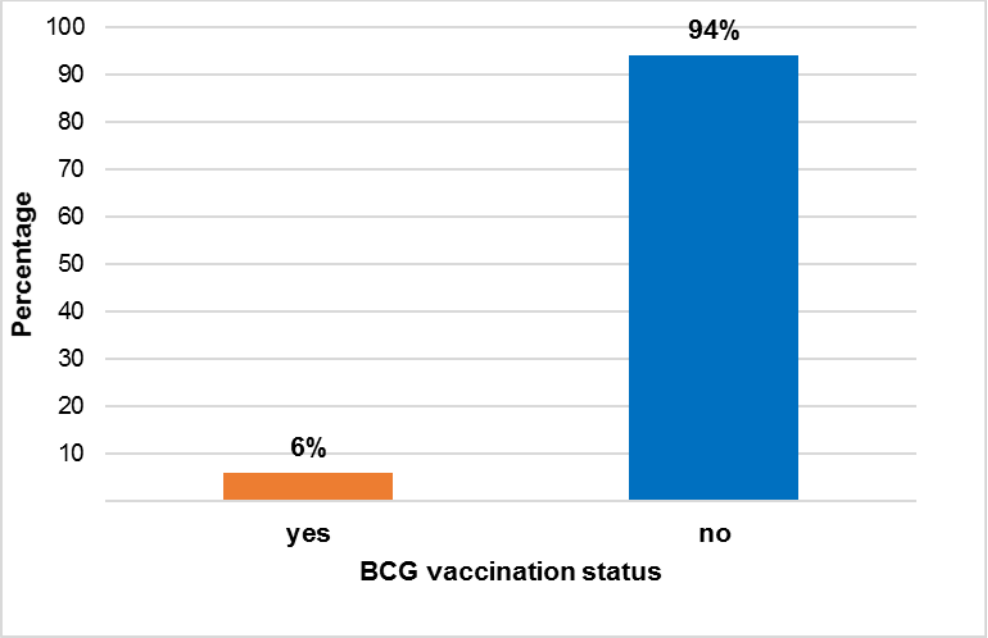


Figure 4.9: BCG vaccination status

4.10 Smoking/drug/alcohol abuse history

About 38% patients were smoker and 62% were non-smokers. None of them had any history of drug abuse or alcohol intake.

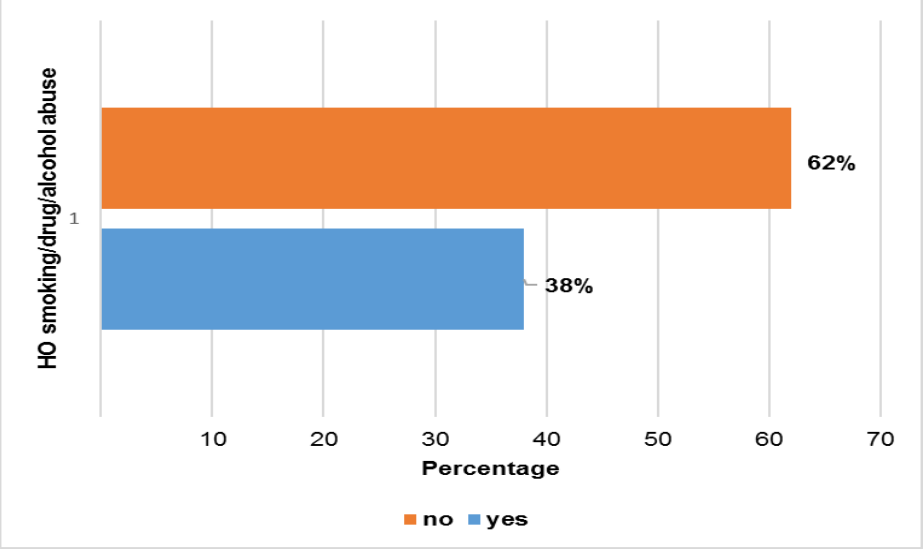


Figure 4.10: History of smoking/drug/alcohol abuse

4.11 Household condition

The household condition was divided into 3 groups according to the condition of the build of patients' house; Brick build & Tin shade, Brick build & Asbestos, Mud ,bamboo & straw. 94% patients were living in Brick build & Tin shade houses. While 6% living in Brick build + Asbestos.

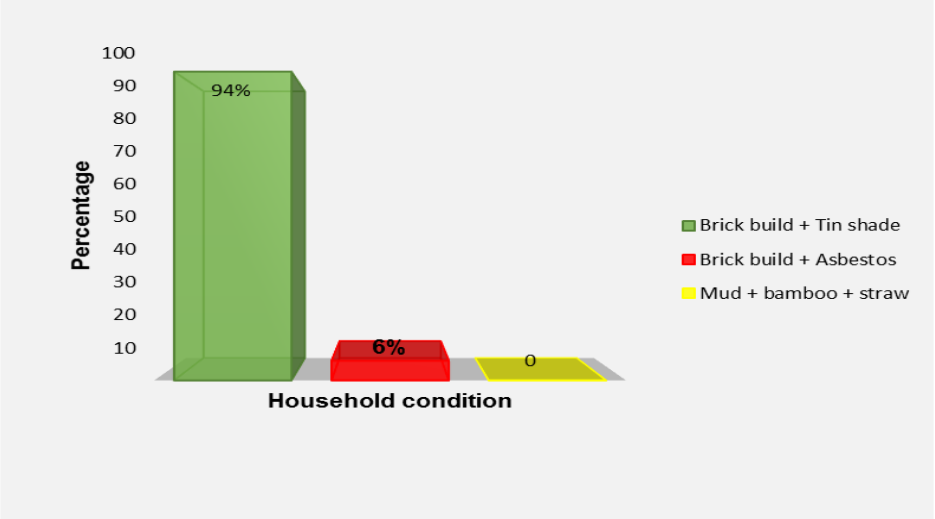


Figure 4.11: Household condition

4.12 Symptoms presented by patients

The symptoms presented by the patients during their first assessment period were cough for more than 3 weeks (96%), production of sputum (92%), blood streak sputum (48%), unexplained weight loss (76%), low grade fever (96%), loss of appetite (96%), fatigue (74%), night sweat (34%), shortness of breath (54%).

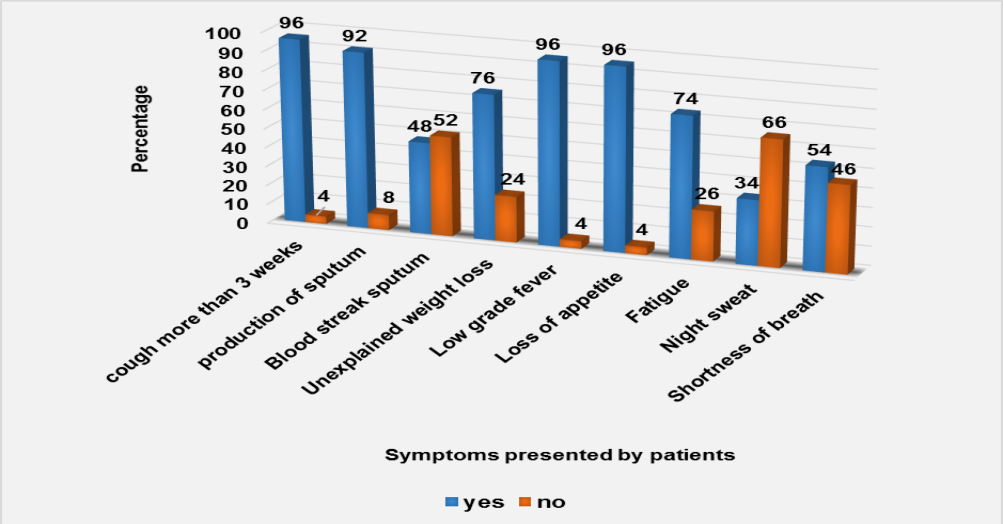


Figure 4.12: Symptoms presented by patients

The most common symptoms were cough for more than 3 weeks along with production of sputum, low grade fever and loss of appetite. Even though other symptoms were also common among each patients (if not all).

4.13 Tests done for confirmation of Tuberculosis

The tests done by the patients for diagnosis of TB mainly divided into 4 groups: Sputum for AFB, Xpert for MTB/RIF, X-Ray Chest, Others. In the category 'Others', patients were advised for some other tests for excluding other diseases, these tests included MT test, CBC with ESR, RBS, FNAC of pleural aspirate, Urine R/E, serum creatinine etc.

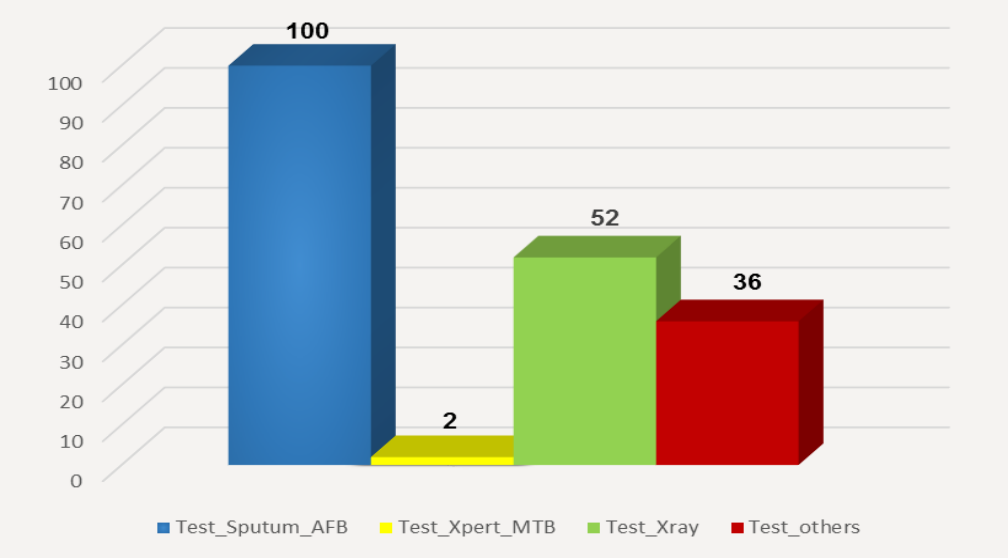


Figure 4.13 Tests done for diagnosis of TB (as in percentage)

All patients 100% had done sputum for AFB, which is the Gold standard test for diagnosis of Tuberculosis. Only 2% patient had done Xpert for MTB/RIF. 52% patients had done X-Ray chest while 36% patients had done other tests.

4.14 Confirmation of Diagnosis

Patients who were positive for sputum microscopy (AFB) is termed as Bacteriologically confirmed Tb case, those who were AFB negative or extra-pulmonary cases termed as Clinically diagnosed (these are confirmed by X Ray chest /other tests).

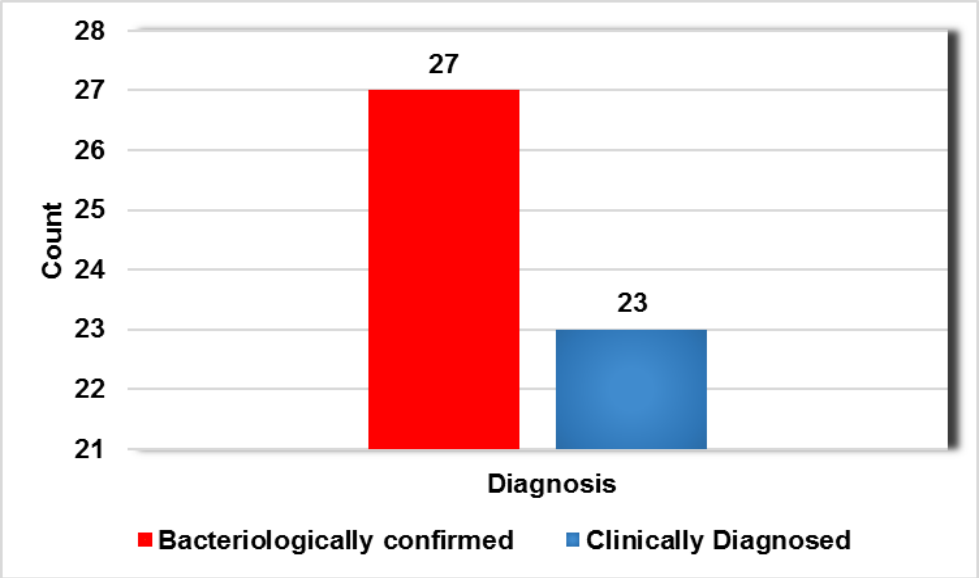


Figure 4.14.1: Confirmation of diagnosis (frequency)

Of all the patients in this study, 27 were diagnosed as smear positive (also known as bacteriologically confirmed), whereas 23 were clinically diagnosed. Out of these clinically diagnosed, there are smear negative and extra-pulmonary tuberculosis cases.

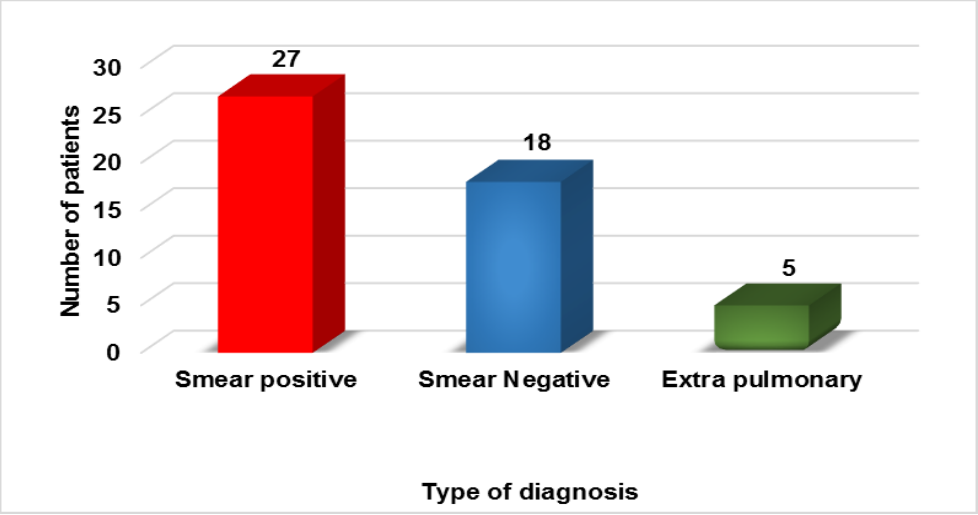


Figure 4.14.2: Type of diagnosis (frequency)

The chart explains that out of 23 clinically diagnosed cases 18 patients were diagnosed with smear negative whereas only 5 patients were diagnosed with extra-pulmonary Tuberculosis.

4.15 Gender Vs type of TB

The type of Tuberculosis cases is compared with the gender. The graph below explains that male dominance is prominent for both smear positive and negative (34% and 28% respectively) cases but females are slightly more in case of extra-pulmonary tuberculosis.

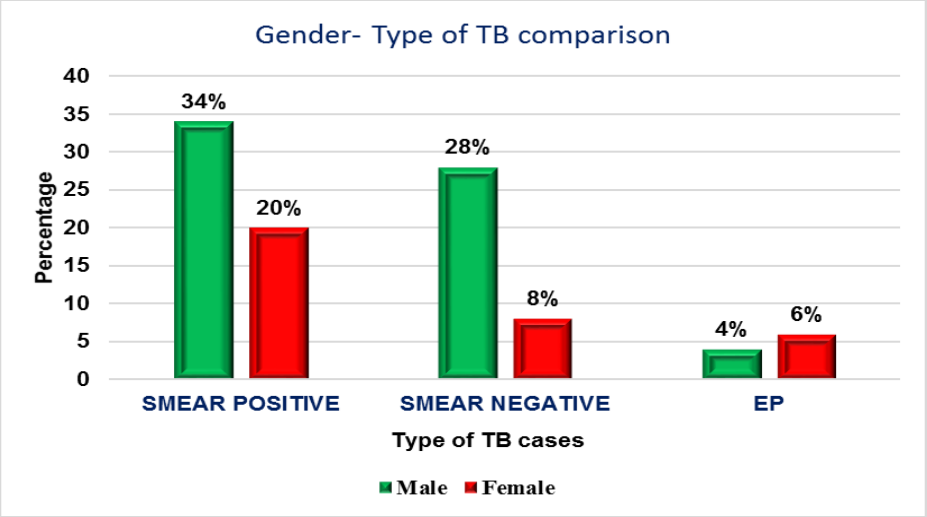


Figure 4.15: Gender Vs type of TB

4.16 Household condition and type of TB

The graph shows that most of the patients were living in brick built and tin shade houses (48% smear positive, 34% smear negative and 12% EP)

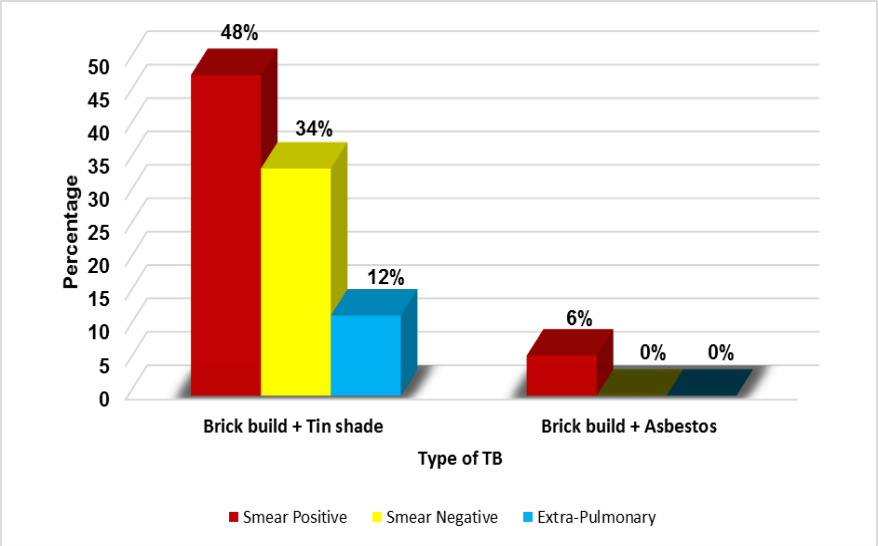


Figure 4.16: Household condition and type of TB

4.17 Treatment

The treatment of each patient depends on the type of TB and weight of individual patients. According to guideline (National guidelines and operational manual for Tuberculosis control, 5th edition), all patients (new case) will start Category 1 according to weight. In our study, all patients were registered as 'new cases' and Category 1 started.

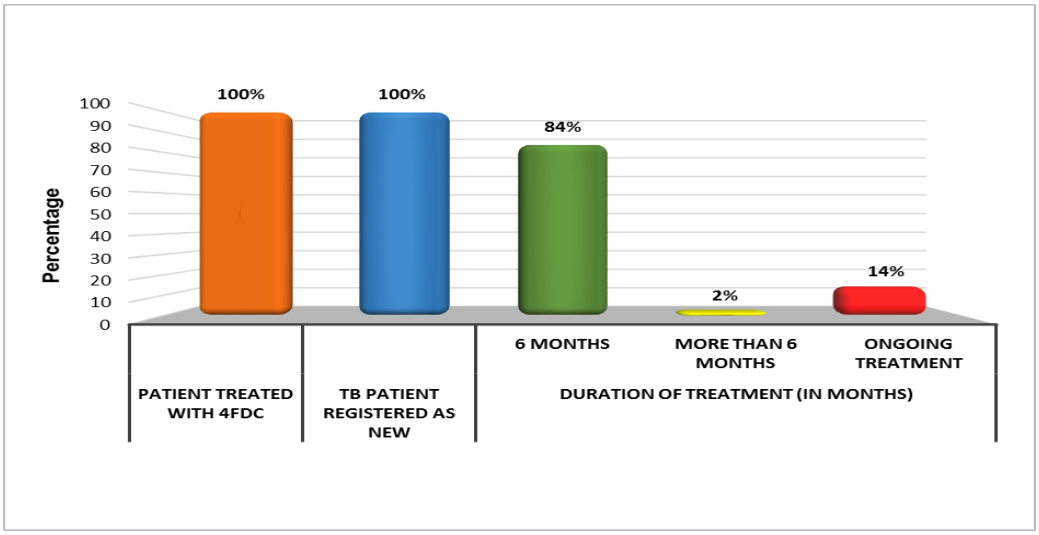


Figure 4.17: Treatment and duration

All patients have started their treatment with 4 FDC (Fixed dose combination), ie: rifampicin 150 mg + isoniazid 75 mg + pyrazinamide 400 mg + ethambutol 275 mg, and the minimum duration of treatment were 6 months with regular follow-up of patients. The graph above describes that 84% patients have completed their treatment in 6 months whereas 2% patient needed treatment more than 6 months. 14% patients were having ongoing treatment.

4.18 Comparison between number of tablets consumed and weight of patient

According to the national guideline (National guidelines and operational manual for Tuberculosis control, 5th edition), there are 4 weight groups where the number of tablets (Fixed dose combinations, FDC) that a patient should take is standardized for both intensive and continuous phase. These weight groups are:

30-37 kg------- 2 tablets required

38-54 kg------- 3 tablets required

55-70 kg------- 4 tablets required

>70 kg----------5 tablets required

Weight beyond these boundaries will be calculated as mg/kg body weight according to guideline.

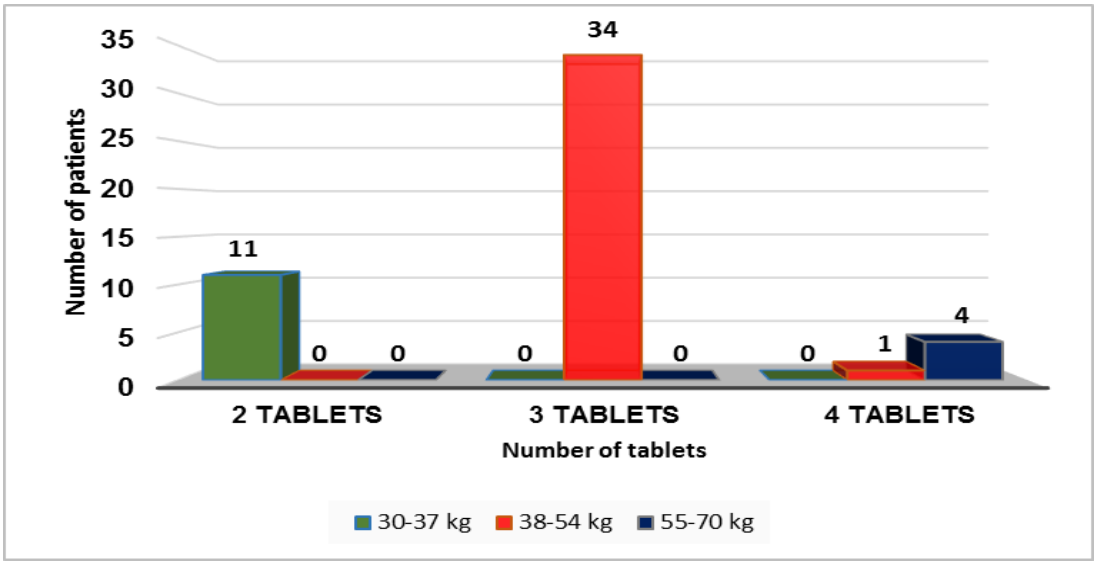
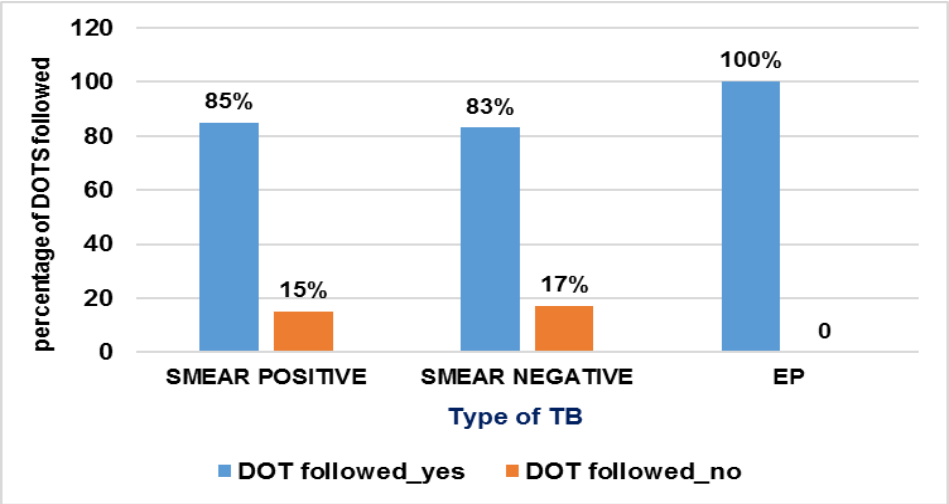


Figure 4.18: Comparison between no of tablets consumed & weight of patient

Almost all the patients have taken their anti-TB drugs with correct dosages according to the weight of the patient, except 1 patient who has taken one tablet more (ie 4 tablets instead of 3) (and hence fell into the group 55-70 kg). We did not had any patients whose weight was above 70 kg.

4.19 Directly Observed treatment (DOT)

One of the most important indicator for effective treatment of Tuberculosis is to ensure treatment with DOT. Each patient were asked whether DOT was properly followed during his or her entire course of treatment and who their DOT provider was and their answers were recorded. The following chart summarizes their record according to the type of TB cases.



4.19.1: DOT following status according to type of TB

The chart shows that 85% of smear positive cases followed DOT according to guideline where 15% has not followed. Similarly, 83% of smear negative cases has followed DOT whereas 17% did not followed. There were 100% DOT done by extra-pulmonary cases.

The figure below compares between the percenatage of gender who has followed DOT according to the guideline. Among 33 male patients, 82% followed DOT whereas 18% did not. Similarly, Out of 17 female patients 94% have followed DOT whereas 6% patient did not.

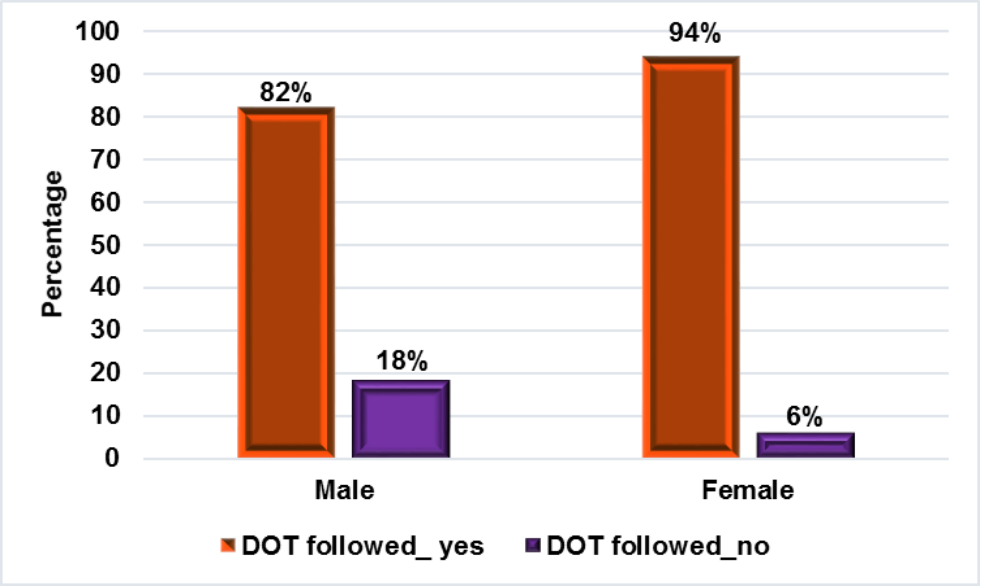


Figure 4.19.2: DOT followed vs Gender

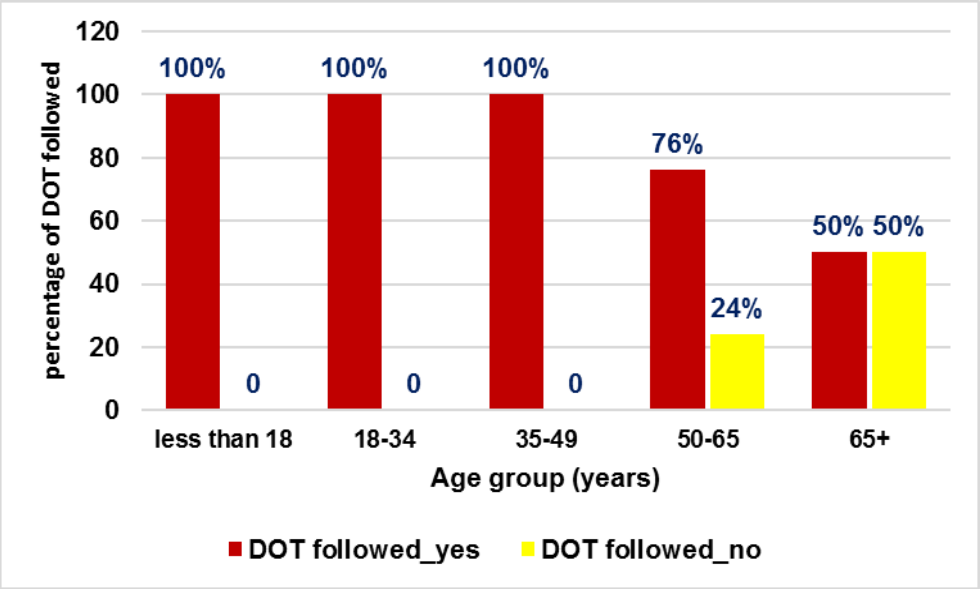


Figure: 4.19.3: Relationship between DOT and age group of patients

It shows that DOT were followed 100% below the age of 49 years.There were 76% patients in age group 50-65 years who followed DOT whereas 24% patients did not. Only 50% patients aged more than 65 followed DOT according to the guideline.

4.20 Outcome

The outcome chart below has been divided into 4 groups: **Diagnosis** (no of patients being diagnosed as smear positive, smear negative and EP), **Cured** (no of patients declared cured at the end of the treatment), **Treatment completed** (no of patients of smear negative/ EP/ smear positive whose sputum follow-up was not done at end of the treatment) and **Ongoing treatment** (ongoing treatment is NOT an outcome as they were still having treatment).

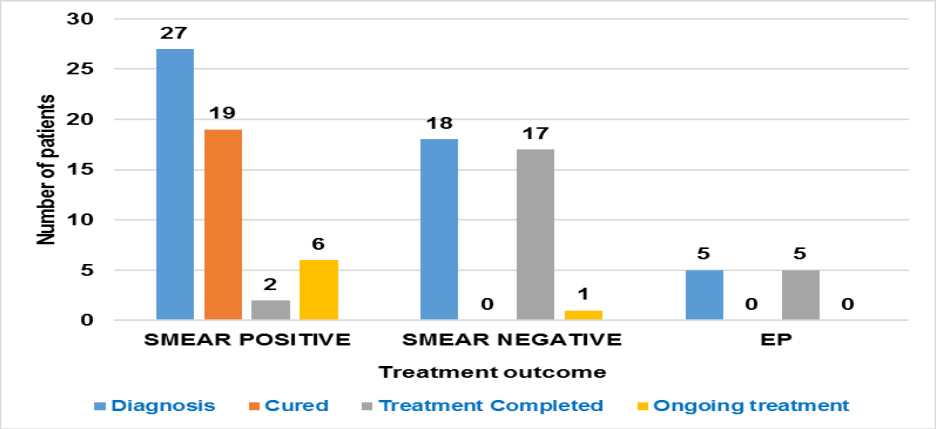


Figure 4.20.1: Treatment outcome

Out of 27 smear positive patients, 19 patients have been declared as cured whereas 2 patients declared as treatment completed. There were 6 patients in ongoing treatment. Out of 18 smear negative patients, 94% have been declared as treatment completed and 6% patient was on treatment. Out of 5 extra-pulmonary cases, all 5 have been declared as treatment completed. Hence, the treatment completion rate among them was 100 %.

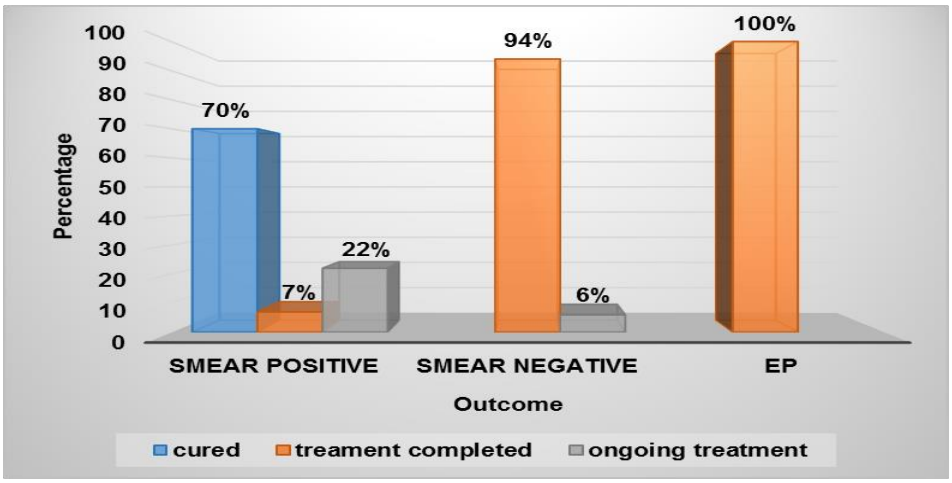


Figure 4.20.2: Treatment outcome (percentage)

4.21 DOT not followed vs Sputum conversion on 1st follow-up

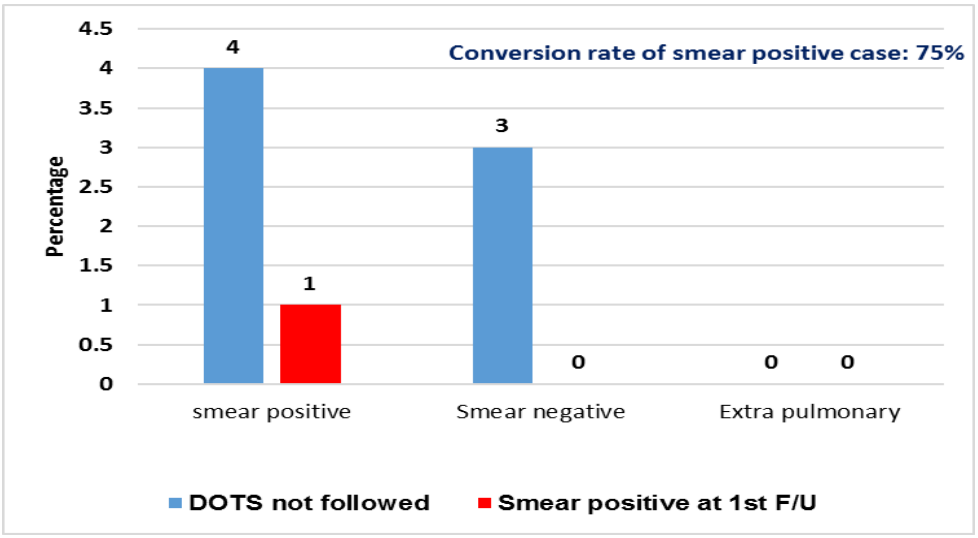


Figure 4.21: DOT not followed vs sputum conversion on 1st Follow-up

Four smear positive cases did not follow DOT according to guideline. Sputum conversion were 75% among them. Only 1 patient (25%) had no conversion on 1st follow up.

4.22 Sputum conversion Rates

Sputum conversion is one of the important indicators of prognosis of the Tuberculosis treated with anti-TB drugs.The graph shows that out of 27 smear positive cases, 19 of them has been converted during 1st follow-up. Conversion rate is 70%. The rest 8 patients were converted during the later stage of treatment.

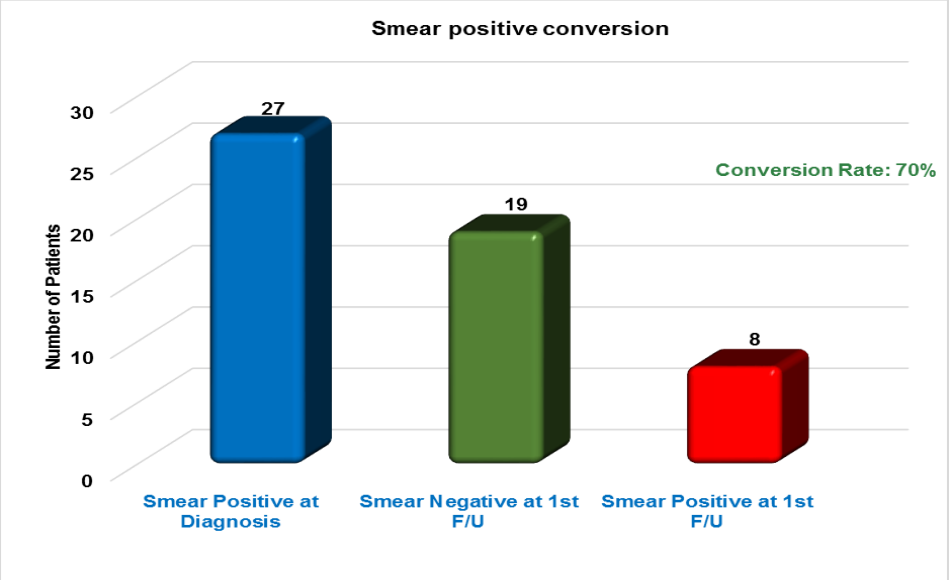


Figure 4.22.1: Sputum conversion on 1st Follow-up of smear positive case

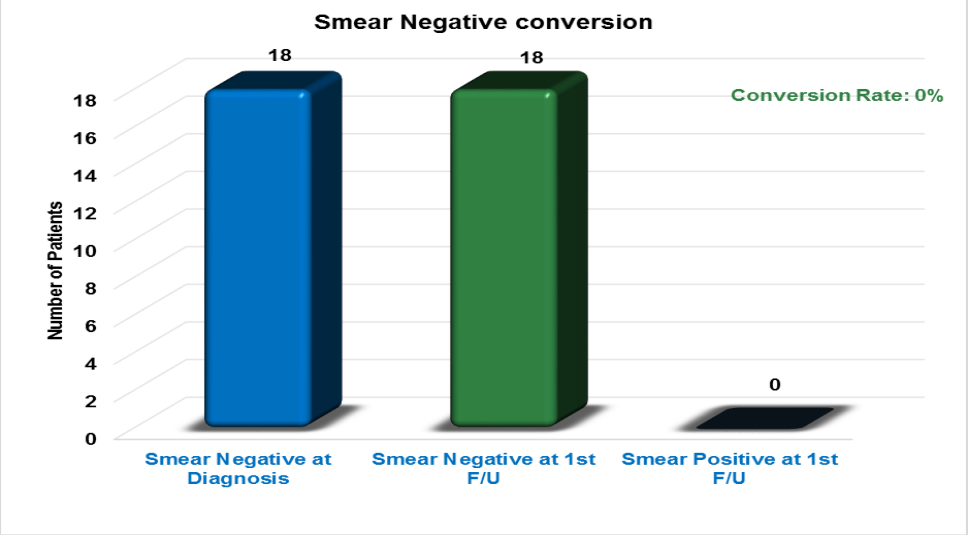


Figure 4.22.2: Sputum conversion on 1st Follow-up of smear negative case

The smear negative cases has a zero percent conversion rate, which means that all smear negative cases did not have a sputum positive result on 1st follow-up (at 2months).

4.23 Weight comparison among smear positive, smear negative and Extra- pulmonary cases

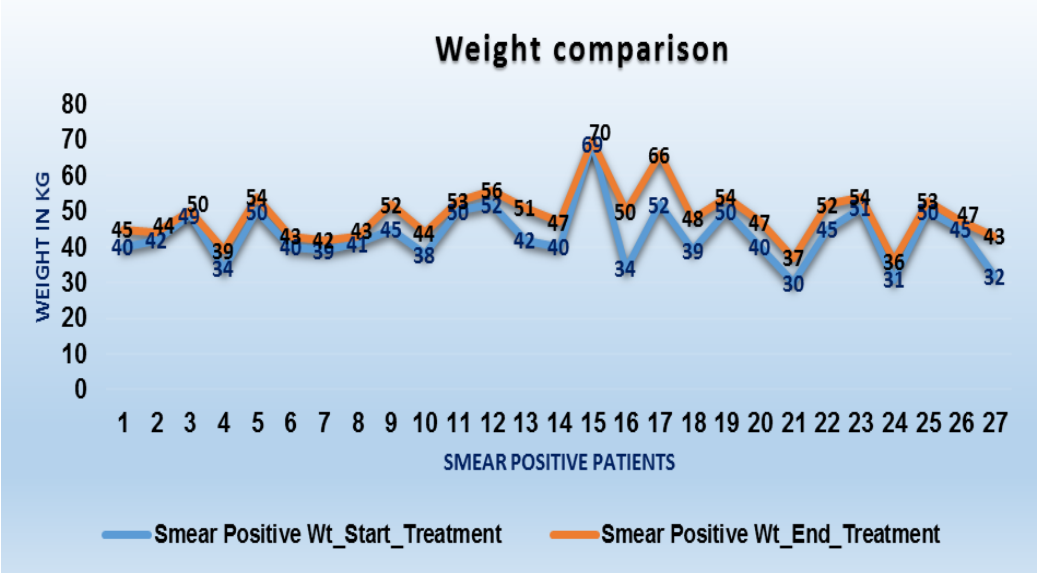


Figure 4.23.1: weight comparison of smear positive cases

There is a significant increase of weight of all smear positive cases at the end of treatment when compared to their previous weight (start of treatment). Smear negative cases also shows that there is an increase in weight in almost all cases at the end of treatment when their weight was compared to the weight during the start of treatment.

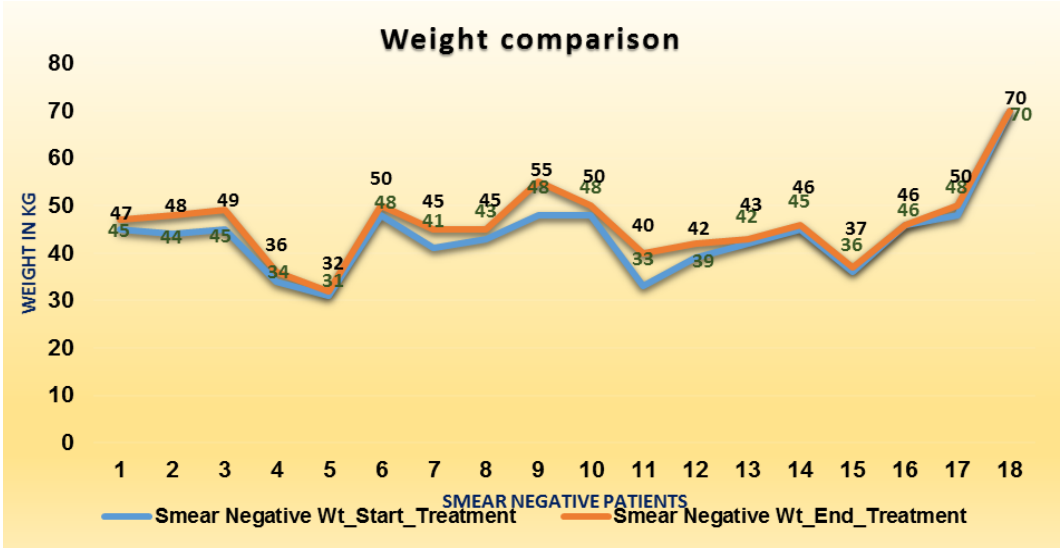


Figure 4.23.2: weight comparison of smear negative cases

The weight comparisons in extra-pulmonary cases has also shown a similar result, there was a small increase in weight all patients at the end of the treatment, except one patient whose weight was unchanged during the treatment course.

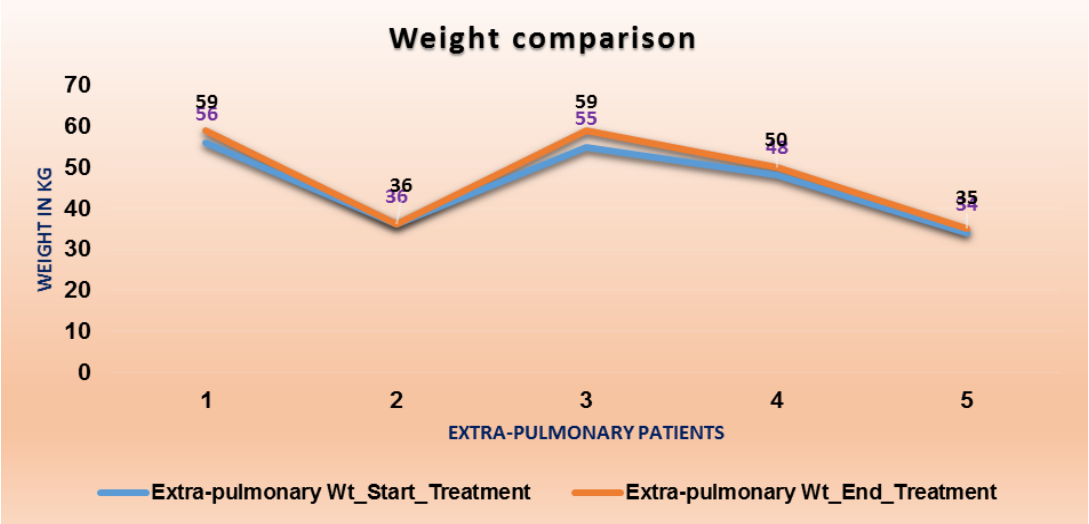


Figure 4.23.3: weight comparison of extra-pulmonary case

4.24 Side effects of treatment

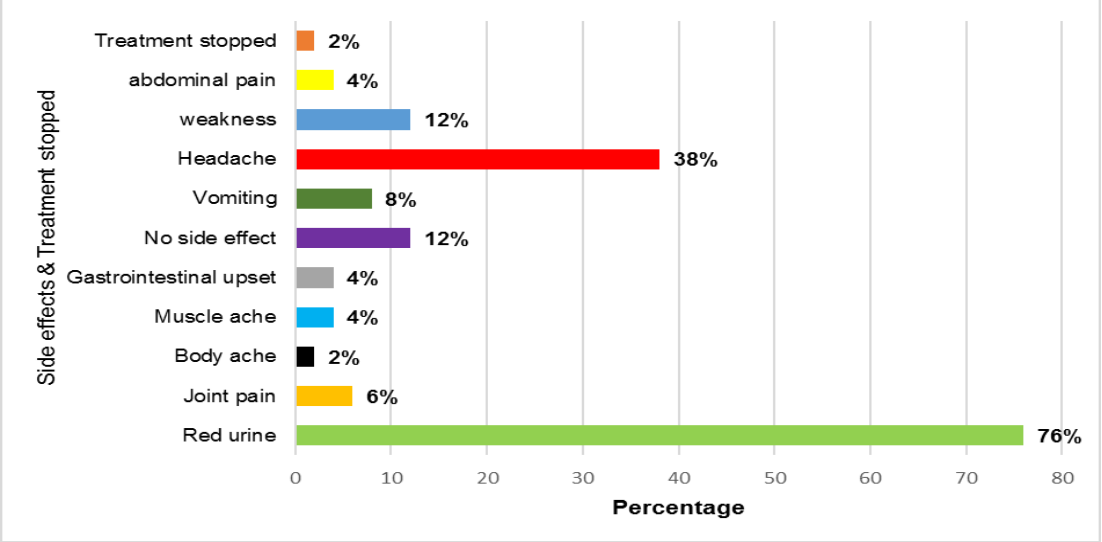


Figure 4.24: Side effects of treatment

The most common side effect was red urine (76%), headache (38%) was also common along with minor other side effects. Only 2% patients had stopped the treatment due to side effects.

CHAPTER – 5

Discussion

Tuberculosis is a major public health problem in high burden countries and Multi drug resistant Tuberculosis increases the risk many folds as patient compliance to anti-TB drugs decreases. Due to inadequate treatment with Fixed doses combination tablets (FDC) and reduction in DOT follow-up, a patient can easily become resistant to these drugs which eventually become difficult to treat further.

The result in our study has shown some positive outcomes which narrows the conclusion regarding the rationale use of fixed dose combination tablets and the role of DOT in TB Control Programme.

There were 50 patients in our study, most of the patients infected with tuberculosis is in between 50-65 years (34%). This shows that tuberculosis is affected mainly at an older age, increases the risk above 60 years of age. A similar study was conducted in China where the prevalence of TB patient was highest among oldest age group and lowest among young age group (Wang L *et al*.2014). The same study has also concluded that the males are more affected with TB than females, specially in smear positive cases in rural area which is close to our study (34% male vs 20% female).

In our study, we have found that smear positive cases were 54%, where smear negative cases were 36%. A similar result was observed in a previous study carried out in Bangladesh (Kumaresan *et al*, 1998)

All patients in our study were treated with Cat 1 and DOT followed. The result have shown that the sputum conversion rate was higher among those who had taken the drugs following DOT (75%). A study was conducted in Uganda where they have found similar result and their success rate also increased to 74% after implementation of DOT (Adatu *et al*, 2003) .

About 86% of all the patients enrolled in our study had followed their treatment regimen under Directly observed treatment (DOT). Those who did not followed DOT (14%) were mainly aged patient and the main reason for not following might be distance from health center and their physical condition. Almost all the patients had their weight increased at the end of treatment completion with 4FDC. Similar result were also found in one study that were carried in India where the findings showed that there is an association between gain in weight with DOT at government centers and cure of patients (Vasantha, 2009).

In outcome of the patients, we have found that 70% of the patients with smear positive were cured, 7% treatment completed. We could not calculate the rest 22% patient who were under treatment. Hence the cured rate is 90.5% for smear positive cases who had completed the treatment regimen. A study in Indonesia have shown that 94% was the cured rate with

4FDC (Gravendeel, *et al*, 2003) while a study in Bangladesh between 1993-1995 showed that the cure rate among smear positive is 75% with use of 4FDC and DOT (Kumaresan *et al*, 1998).

The conversion rate of smear positive cases was 70% on first follow-up.

Another study has also proved that there is a consistent and satisfactory cured rate after implementation of DOTS strategy in Bangladesh. (Mushtaque,& Chowdhury, 1999)

There were a few side effects of patients who had anti-TB drug, out of them patients complained with red urine (76%) and headache (38%) most along with weakness, abdominal pain, gastro intestinal upset, vomiting and muscle ache. Only 2% patient have stopped treatment due to side effect. A study was carried out in Indonesia where similar results were found except they have found a few patients with jaundice (Gravendeel, *et al*, 2003).

CHAPTER – 6

Conclusion

In conclusion, the result of this study has shown a very good outcome when patients get treated with anti-TB drugs as a fixed doses combination. The use of 4FDC is rational and helps Tuberculosis patients to cure completely with TB disease and simultaneously reduces any chance of spreading the disease to the community if these tablets are consumed at a prescribed dose, according to weight for an extended period of time (regimen) and under supervision of a DOT provider. This study also proved that there is a relationship between good outcome of a patient who had consumed anti-TB drugs and followed DOT according to guideline.

The percentage of DOT not followed was very low, and mainly aged patients failed to follow DOT according to guideline. The reason could be due to the distance from health center and their physical condition.

Smear positive patients who had taken correct dose of FDC and under directly observed treatment (DOT) had a better sputum conversion rate during the first follow-up at 2 months and was cured completely. Similarly, smear negative patients who has taken 4FDC and DOT followed was cured completely.

Hence, the use of Fixed dose combination tablets for treatment of tuberculosis patients is rational and the role of DOT and DOTS strategy is very important in Tuberculosis Control program, specially in a high burden country like Bangladesh.

CHAPTER – 7

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