"COMPARISON OF PREDISPOSING FACTORS TOWARDS THE DEVELOPMENT OF DRUG SUSCEPTIBLE AND DRUG RESISTANCE PULMONARYTB RE-TREATMENT CASE

Dissertation submitted in partial fulfilment of the
requirements for the Degree of

DOCTOR OF MEDICINE

TUBERCULOSIS & RESPIRATORY MEDICINE

Branch - XVIII

2015-2018

DEPARTMENT OF TUBERCULOSIS & RESPIRATORY MEDICINE

Government Stanley Medical College & Hospital

Chennai-600 001

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI-600 032

April 2018

CERTIFICATE

This is to certify that the dissertation on “Comparison of predisposing Factors towards the development of drug susceptible and drug resistance pulmonaryTB re-treatment cases” is a record of research work done by **Dr.G.K.BALAJI** in partial fulfilment for M.D. (TUBERCULOSIS & RESPIRATORY MEDICINE) Examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in April 2018.The period of study is from October 2016 to July 2017.

Dr.R.SRIDHAR,M.D, DTRD.,
Professor& Head of the Department,
Department of Tuberculosis &
Respiratory Medicine,
Stanley Medical College,
Chennai- 600 001.

Dr. PONNAMBALAM NAMASIVYAM
M.D,D.A.,
Dean,
Stanley Medical College,
Chennai- 600 001.

CERTIFICATE BY GUIDE

This is to certify that the dissertation on **"Comparison of predisposing Factors towards the development of drug susceptible and drug resistance pulmonary TB re-treatment cases"** is a record of research work done by **Dr.G.K.BALAJI** in partial fulfilment for M.D. (TUBERCULOSIS & RESPIRATORY MEDICINE) Examination of the Tamil Nadu, Dr. M. G .R. Medical University to be held in April 2018.The period of study is from October 2016 to July 2017.

DR.R.SRIDHAR, M.D, DTRD.,
Professor & Head of the Department,
Department of Tuberculosis &
Respiratory Medicine,
Stanley Medical College & Hospital,
Chennai-600 001.

DECLARATION

I hereby declare that the dissertation entitled "**Comparison of predisposing Factors towards the development of drug susceptible and drug resistance pulmonary TB re-treatment cases"** submitted for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch XVIII, TUBERCULOSIS & RESPIRATORY MEDICINE is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai
Date: 26.09.16

Signature of the Scholar
(Dr.G.K.BALAJI)

ACKNOWLEDGEMENT

Language with all elaborations seems to be having limitation especially when it comes to expression of feelings. It is incapable of conveying in words all the emotions and feelings one wants to say.

It would take pages to acknowledge everyone who, in one way or another has provided me with assistance, but certain individuals deserve citation for their invaluable help.

I would like to express my heartfelt thanks to **Dr. PONNAMBALAM NAMASIVYAM,M.D,DA**., Dean, Stanley Medical College and Hospital for giving me permission to conduct this study.

I find words insufficient to express my deep sense of gratitude for my esteemed and revered teacher, my chief **Prof.Dr.R.SRIDHAR, M.D, D.T.R.D,** Head of the Department, Dept. of Tuberculosis & Respiratory Medicine, Stanley Medical College and Superintendent, Govt. Hospital of Thoracic Medicine, Tambaram Sanatorium, for his ever-inspiring guidance and personal supervision.

The finest privilege in my professional career has been the opportunity to work under his inspirational guidance.

I thank Associate professor **Dr.V.VINOD KUMAR M.D,(CHEST), DNB**. For his constant encouragement and guidance throughout my postgraduatecourse.

I would like to express my sincere thanks and heartful gratitude to Associate professor **DR.D.NANCY GLORY M.D.,** for her constant support, enthusiasm and valuable guidance throughout my work.

Words fall short in expressing my sincere gratitude for other eminent teachers in our department, who helped me in my work **Dr.S.Kumar M.D, Dr.G.Allwyn Vijay M.D, Dr. S.P.Vengadakrishnaraj D.T.C.D,DNB, Dr.K.Maheswaran M.D.**

I express my sincere thanks to all the assistants in our department for their support. I heartfully thank my senior **Dr.P.Anand,M.D** and junior colleagues for their enthusiasm and involvement for completing this study.

I have no words to express my sincere and heartfelt gratitude to my father and my mother who always supported me throughout my life as a student, guided me to solve my problems and helped me to face all kind of difficulties. Their love, affection and support enabled me to reach this stage of life. This work is dedicated to my beloved father who dedicated his entire life for wellbeing of me and my family.

I will always be grateful to my dear wife **DR.B.MEENATCHI** for being cooperative, for sharing my enthusiasm and dismay and constantly supporting my ambitions and struggle. This work would not have been possible without her support in my difficult times.

Last but definitely not the least, I would like to thank all the patients who cooperated with me throughout my work.

Finally it is endowment of spiritualism and remembrance of almighty for all that I achieved.

CONTENTS

COMPARISON OF PREDISPOSING FACTORS TOWARDS THE DEVELOPMENT OF DRUG SUSCEPTIBLE ANDDRUG RESISTANCE PULMONARY TB RE-TREATMENT CASES

DEDICATE TO MY

PROFESSOR'S

INTRODUCTION

Multiple drug- resistant tuberculosis[1] (MDR-TB) is emerging as a growing threat to TB control programs in many countries and accounts for3.5%of all newly diagnosed patients worldwide. The potentially serious impact of MDR-TB (TB strain resistant to at least isoniazid and rifampicin) has long been recognized; drug resistance is a major threat to tuberculosis (TB) control programs worldwide. multidrug resistant TB (MDR-TB) is defined as a simultaneous resistant to atleast rifampicin(RMP) and isoniazid (INH) patients infected with MDR strains are less chance to be cured from TB particularly if they are co-infected with HIV or suffer from other immuno suppressive diseases. MDR-TB is associated with a two to four fold period of treatment, psychological problems, economic wastage, poor treatment adherence and consequently treatment failure.

Globally, 3.5% of new TB cases and 20.5% of previously treated cases are estimate to have MDR-TB[2]. In developing countries,due to poverty, migration and HIV infection, MDR-TB is associated with spread and persistent high incidence. However, the problem is of special concern because, expensive treatment, with only 65%-75%efficacy, and may have side effects.

In perspective of the public health, a study on the identification of risk factors linked to MDR-TB at the onset of therapy,among new cases, is

important to identify patients vulnerable to getting infection with MDR-TB strains.

This is necessary for breaking the transmission cycle of MDR-TB. This will further reduce the cost treatment, as well as improve the implementation of the DOTS- based RNTCP.

REVIEW OF ARTICLES

Tuberculosis[3] is as old as mankind TB is a most common cause of death due to a single infectious agent worldwide in adults. In 1993, WHO took unprecedented step and declared TB to be a global emergency According to recent estimates 10.4 million was infected with mycobacterium tuberculosis worldwide. TB[4] is a principally a disease of poverty with 95% cases and 98% of deaths occurring in developing countries. Though disease was known since ancient times, organisms causing TB was identified only a century ago by Robert Koch on march 24, 1882 Until middle of 20th century there was no definitive treatment available for TB till the availability of streptomycin, Isoniazid, PAS, in mid 1940's predictable curative treatment became reality

EPIDEMIOLOGY

It has been estimated prevalence of 2-10 million[5] TB cases with 2 million new cases occurring every year. India has the second higher MDR TB in the world after chinadrug resistance surveys in several statesindicates prevalence of MDR-TB in India 2-3 percent among new cases, about 15-20% among re-infection, the RNTCP is scaling up the number of culture and DST laboratory nationwide along with treatment .Despite of these achievements India's efforts to control TB and MDR TB still suffer from few laboratories slow diagnostic tools, and inadequate management of treatment.

India[6] ranks second in harbouringmultidrug resistant cases out of expected 99,000 cases among 50,000 cases are recorded from treated pulmonary TB cases. In a study in Hyderabad every three patient among 10 retreatment cases are being developed having MDR TB who need treatment with second the anti-TB drugs. The emergence of résistance to anti-tuberculosis on general and MDR-TB in particular as became major health problem of prime concern in number of countries and major bottleneck ineffective TB control and management of MDR TB is a challenge which requires prolonged use of expensive second line drugs with significant toxicity[3]mismanagement of MDR-TB may lead to development of extensively drug resistant TB, a virtually untreatable TB, which has been recorded in 45 countries[4] the economic, social and health status of countries and communities could be threatened by virtually untreatable TB among the breadwinners, parents and economically productive age. The disease is not only medical problem or a public health problem but is also critical social problem of great magnitude, Baseline adequate information on epidemiological, social, economic cultural factors and their interactions is required for its control and effective treatment[4].

PULMONARY TUBERCULOSIS

Pulmonary TB is the most frequent organ of TB worldwide. Lungs account for a majority of both primary and post-primary forms of TB.

Miliary TB invariably affects both lungs symmetrically.Further, Pulmonary TB is a major source of infection. In addition to the elegant studies of Rich [7], Medlar [8] based his observations on 1332 un-excepected deaths in New York and further evaluated 17000 necropsy records with reference to Pulmonary TB. The Indian perspective is available from the study based on 1680 autopsies by Nayak and co-workers at New Delhi [9].

PRIMARY PULMONARY TUBERCULOSIS

Classical features of Primary complex in the lung [Ghon complex] are a small [usually less than one centimetre] often inapparent parenchymal lesion [Ghon lesion or Ghon focus] coupled with enlarged, ipsilateral hilar and less commonly paratracheal nodes.The lymph nodes are generally much larger than the parenchymal focus. As has been repeatedly indicated, the location of the parenchymal lesion is usually towards the middle of the lung [upper part of the lower lobe or the lower region of the middle or upper lobe depending on the side]. Certain sites such as the apical Segment of the lower lobe or upper portion of right middle lobe are described as likely sites of primary infection, however, no part of the lung is exempt[10].

A single Ghon's complex was identified in 58 per cent and multiple in 16 percent of the cases studied by Medlar[10]. In one case, five foci were identified, one in each different lobe. In 26 percent cases, the complex was incomplete because either a parenchymal or lymph nodal component was not

demonstrated. A typical primary or Ghon's focus is single, two millimetres or more in size and located within one centimetre of the pleura of the collapsed lung. A majority of the primary foci calcify and a minority show caseous necrosis [85% and 15 % respectively].

Lymph node enlargement is easily identified in a large majority [87%]. In order to demonstrate the tubercle, it may be necessary to make serial slices in about three-fourths of the cases whereas in the remaining the lesions are readily apparent. Bilateral adenopathy is uncommon except with left-sided primary foci[11]. Massive lymphadenopathy is reported especially in the poorly nourished.

PROGRESSION OF TUBERCULOSIS

The Natural history of TB in the human host is influenced by age sex, mycobacterial virulence, infecting dose, natural and acquired resistance, resulting in a tendency of the disease to follow a pattern of progression according to Wallgren's timetable[11]. Interplay of these factors and the likely mode of spread of the bacillus result in different manifestations.Early in the course of, disease, tuberculin conversion after primary infection may result in mild illness. In the first few years there is increased susceptibility to military spread and meningitis.

Miliary disease and meningitis follow within two to nine months in 10 per cent of children under two years of age, although these forms can be seen at any age. Segmental lesion [epituberculosis] is an early sequel in infants and in a minority of adolescents and young adults generally within two to nine months of primary infection. Pleural effusion,which follow primary TB, is also seen as sequel of the Post-primary pulmonary disease.

Progression to post-primary TB is more likely if primary infection is acquired in the later years of young adulthood than in childhood. In child infection the post-primary disease is delayed until adolescence. Extra-pulmonary organ TB is variable. Cervical lymphadenitis may be early but, skeletal and renal TB, usually present very late. This progression is only a broad direction and not absolute.

Further Changes of the Primary Complex

The primary complex may heal or progress further. Progression occurs in a small proportion of cases. Early dissemination is common but may not necessarily result in concurrent illness. The spread of infection from the primary lesion is by a variety of ways, such as, direct extension into adjacent tissue or by endobronchial, lymphatic or vascular pathways for a disseminated spread.

Endobronchial spreal of liquefied caseous material is a cause of ipsilateral or contralateral acinar pneumonia. Implantation of mycobacterium in the mucosa of the upper airway can result in laryngotracheal, oral or middle ear TB. Swallowing infective sputum can also lead to TB and ulceration of the intestinal mucosa. Ipsilateral hilar lymph node spread is especially prominent in primary infections. Perforation of a bronchus by an enlarged caseous lymph node followed by endobronical spread can result in massive segmental or lobular pneumonia. From regional lymph nodes bacilli can disseminate through lymphatics to the pleura, spine and other viscera. Haematogenous disseminations can occur through the thoracic duct after lymph node involvement or by direct extension of the lesion into branches of the pulmonary vein.

HEALING

Healing of the primary lesions is the rule. The caseous focus is gradually replaced by reticulin and collagen desposition. Eventually, hyalinization, and calcification are common [up to 85%]. Subsequent demonstration of these lesions may be difficult. However, aminority of patients may demonstrate radiologically a residual hyalinised scar or calcification at the site of the primary [Ghon] lesion, in the lung parenchyma and in the hilar or paratracheal lymph nodes a combination referred to as the healed primary [Ghon] complex.

EARLY GENERALIZATION

Early generalization or dissemination is an invariable accompaniment of primary TB [detailed above]. The primary infection is accompanied by early lymphohaematogeneous spread within hours or days from the site of initial implantation[12]. It is felt that occult mycobcteraemia is probably common before acquired immunity and thus may seed many sites in the body especially where the bacilli favoured to remain viable[13].

With the sites of these seedings have already been mentioned, one aspect needs to be highlighted here. Huebschmann [1928] [7] observed a group of nodular lesions in one or both apices of the lung that occasionally follow primary TB in children. These foci are so small that special techniques may be necessary to demonstrate them. These Huebschmann foci heal and cause no further disease. It is likely that Simon foci which are larger, single or multiple apical caseous nodules with a tendency to calcification are exaggerated form of these smaller foci. The importance of Simon foci lies in the pathogenesis of post-primary TB[7]. Ina minority of the cases haematogenous dissemination results in military TB.

LIQUEFACTION AND PROGRESSIVE PRIMARY TUBERCULOSIS

Liquefaction of solid caseous foci is thought to be related to the onset of DTH with the release of hydrolytic enzymes by macrophages [12].

Liquefaction may result in a caseous mass that may include the enlarged lymph nodes. Within the liquefied area there are multiplying tubercle bacilli and, therefore, there is a risk of transmission of disease. Due to the liqueactive necrosis there is extensive parenchymal destruction and caviation, which is generally a little less than the size of the original caseous mass. The cavity may communicate with an airway and thus promote bronchial spread to other parts of the lung, larynx and the alimentary tract. An acute fatal bronchopneumonia may result. In some of these case the inflammatory reaction is neutrophilic, like in the case of bacterial pneumonia, but AFB are demonstrable.

Due to such a reaction, the diagonosis may be missed. Discharge of the liquefied material through the adjacent pleura results in pleural effusion, pneumothorax or empyema. Caseous lymph nodes may similarly discharge liquefied contents into the bronchus.

Progressive primary TB directly follows the primary lesion. There occurs an extended primary focus or TB bronchopneumonia. cavitation may ensue. Cavitaion and progressive primary disease are more likely in infancy, at puberty and in the elderly. There is a tendency for progressive primary TB to involve lesions that are apical. This location is similar to that of post primary TB.

LOBAR AND SEGMENTAL LESIONS

As a consequence of spread along the submucosal lymphatics of bronchi, tubercle formation with ulceration of bronchial mucosa at times is followed by complete necrosis of the bronchus. Within the bronchus a cold abscess may developed and can be seen on the radiograph as a rounded or elongated shadow. Bronchial lesions are rare but my result in narrowing of the lumen. Extrinsic compression from enlarged lymph nodes in a relatively more likely cause of bronchial obstruction. The lobe or segment subtended by the obstruction maybe the seat of obstructive hyperinflation, atelectasis, secondary (non-TB) pneumonia, TB pneumonia, and disseminated intra-alveolar epithelioid cell granulomas. Atelectasis most commonly affects the anterior segment of the upper lobes and right middle lobe. Endobronchial TB is a complication of primary TB in children [13]. Residual bronchostenosis and bronchiectasis may occur as later complications.

Hilar and mediastinial lymph nodes may very rarely cause impaired venous return severe enough to cause superior mediastinal syndrome. Such lymph nodes may result in tracheal obstruction at the thoracic inlet, rupture into mediastinum and pointing abscess into the supraclavicular fossa, erosion of blood vessel, invasion of pericardium, compression of or erosion into the oesophagus and the formation of various fistulae.

EPITUBERCULOSIS

Epituberculosis is a rare but more frequent in infants and children than in adults. It is a benign lesion appearing as a dense homogenous shadow on chest radiographs, typically wedge-shaped, extending from the hilum to the pleura. The lesion is frequently large rather sharply defined and has the appearance of an area of consolidation. Clinical symptoms are few and the shadow generally clears after several months.

Residual changes are infrequent and radiographs may show slight abnormal marking or calcifications. The radiographic appearance is relatively dramatic and sinister, in contradiction that occur in TB. Hence eliasberg and newland suggested the term "epituberculosis" which implied a non-tuberculosis consolidation in a TB lung[7].The current view is that it is either resolving TB pneumonia or an atelectasis produced by obstruction of a bronchus by a TB lymph node or by a primary pulmonary lesion.

A combination of the two is possible. Since the shape of the shadow is highly suggestive of involvement of a portion of lung tissue supplied by a bronchus, rich studied several cases and found that a caseous lymph node had perforated the bronchial wall, discharge its contents and resulted in aspiration of the material. It is understandable that the caseous material is poor bacilli, otherwise the lesion would be a progressive bronchopneumonia. The resulting consolidation could be partly due to a "hypersensitive" reaction to contents of

the lymph node (a positive "pulmonary tuberculin test, if such a term is acceptable).the alveoli in such cases would resemble pneumonia with epithelioid cells and few or no AFB. There is also sufficient evidence to suggest the atelectasis theory and relief of atelectasis by interventional bronchoscope. A combination may occur. Since encroachment by an enlarged lymph node is a common accompaniment, therefore, these lesion are common in children[7].

PRIMARY TUBERCULOSIS IN ADULTS

The radiological and other features of adult primary TB are essentially similar to childhood primary disease [13].primary TB poses diagnostic problems in adults. Prominent hilar and mediastinal glands and caseation are less frequent in adults except in patients with AIDS. Also, bronchial obstruction and dissemination are less common. As in children, endobronchial TB may occur as a sequelae of adjacent parenchymal disease from which submucosal lymphatic spread leads to mucosal ulceration hyper plastic polyp formation or fibrostenosis with atelectasis of the subtended lobe[14].

POST PRIMARY PULMONARY TUBERCULOSIS:

In contrast to primary TB, the localization of post-primary pulmonary TB is a apical or sub-apical. This area has been referred to as the 'vulnerable region' by medlar[8]. This site probably relate to the relatively higher oxygen

tension in the region resulting from the effect of gravity on the ventilation-perfussion ratio in the upright lung. Presently, evidence suggests that this is possible because of better survival of the bacillus at this region as the higher oxygen tension has an unfavourable effect on the macrophage and thereby permits intracellular growth[15].

This may also influence progressive primary disease that is more frequent in the apical and posterior segments of the upper lobe. Higher vascularity and consequently increased oxygen tension may determine the preferential multiplication of bacilli at other sites also, such as ends of long bones, vertebrae and the renal cortex.

Similarly, mitral stenosis, which result in higher pulmonary arterial pressure and increased apical blood flow, confers a protective effect. The reverse in true for pulmonary stenosis[94]. Lowered blood flow may also be associated with decreased lymph flow and thus lesser antigen clearance.

The great majority of these cases represent recrudescence of dormant tubercle bacilli occurring several years after the primary infection or even decades after primary infection. As has been mentioned earlier, there is a haematogenous seeding of the apical and sub-apical regions of the lungs, following primary infection

This is the endogenous pathway resulting in reactivation TB . However, there is evidence to suggest that a bronchial spread from an index case may be the route of infection. This is the exogenous pathway resulting in re-infection TB. The organisms may reach by either pathways[7]. Infection with other related species of myco-bacteria may also have the same result.

The pathological lesions seen in post-primary pulmonary TB are enumerated in table, based on the findings of Medlar[8] and Nayak et al[9].

LESIONS IN POST- PRIMARY PULMONARY TUBERCULOSIS

- **Pulmonary lesions:**
  1.Lobular Pneumonia
  2.Nodular Pneumonia
  Small Nodule
  Large Nodule
  Healed Nodule
  3.Fibrocaseous Tb
  With Cavity
  Without cavity
  4.Tuberculosis bronchopneumonia
- **Bronchial lesions:**
  1.Bronchial inflammation
  2. Endobronchial TB
  3.Bronchiectasis

- **Whole lungTB**
- **Millary TB**
- **Complications:**

1.Haemoptysis

2.Aspergilloma

3.Amyloidosis

4.Carcinoma

5.Oral cavity and upper respiratory tract TB pleural lesions.

EARLY LESIONS

The earliest lesion is probably an apical or sub-apical lobular pneumonia. These lesions are not well documented because it is believed that the pneumonia gives way to a granuloma rapidly. An outline of the alveolar reticulin framework in the centre of some of these granulomas may suggest such a transition [9].

It may be mentioned that in 1925, Assmannn drew attention to the fact that the earliest lesions clearly visible in clinical TB consist of infiltrates not at the apex, nut at the sub-apical and infraclavicular region. These infilitrates are known as Assmann infiltrates or foci[5]. The histological counterpart of these lesions is not known.

NODULAR LESIONS

Nodular lesions (coin lesions, tuberculomas) are localized, well-defined are as of TB wherein the adjacent pulmonary parenchyma is usually normal or may show some scarring. A small nodule is less than a centimetre in diameter whereas the large nodule is larger than a centimetre in diameter. Grossly, nodules are white to yellow in colour and may vary in consistency from soft lesions that are largely necrotic to firm or hard lesions that are fibrosed or calcified. Small nodules have a central area of caseation, are surrounded by epithelioid cells and giant cells and are encapsulated by a fibrous wall. Large nodules are similar but show more caseation and less encapsulation. Healed nodules are of the size of small nodules and are fibrosed or hyalinised or calcified. Anthracotic pigment may be identified in any nodule[9].

Active nodules especially of the small sixe are predominantly located in the apical and sub-apical regions and may be single or multiple. The reverse is true for healed nodules. It appears that small nodules give rise to larger ones and nodular TB may expand to form fibrocaseous lesions. It may be mentioned that (these nodules are not related to Ghon's focus. The location and the absence of accompanying enlarged lymph nodes should provide a clue. Acid-fast bacilli could be demonstrated in seven per cent of small nodules and 29 percent of large nodules [82].

FIBROCASEOUS TUBERCULOSIS

Fibrocaseous TB includes lesions that reveal well known features of TB such as caseation, consolidation, liquefaction and fibrosis. Grossly, various patterns are seen. The apical and posterior segments of the upper lobes are predominantly involved. Lymph node involvement is slight in comparison to primary TB. Retraction of lung parenchyma is associated often with pleural thickening. In some cases the lung may have an appearance of bronchopneumonia due to consolidation. At times the caseous areas stand out amidst the black background of antharacotic pigmentation. The most striking feature is the presence of one or more cavites. Cavities may assume varying sizes and may be so large as to result in a severe loss of lung paraencyma. The wall of the cavity may be lined by TB granulation tissue or show varying fibrosis.

Often the thick walls of cavities seen on radiographs are found to be accounted for by a rim of consolidation of the adjacent lung. Communication may or may not have been established with a bronchus. These findings have implications on auscultation of the chest process allows the arteries to obliterate. The caeseous material may Traversing the wall or the lumen along fibrous bands, are bronchi and branches of pulmonary artery. Fortunately in most instances the chronic soften the wall of the arteries giving rise to

Rasmussen's aneurysms. These may give rise to haemoptysis that may be fatal.

Microscopically variable caseous necrosis, extensive fibrosis, numerous palisades of epithelioid cells and fibroblasts together with Langhans giant cells are seen. Areas of consolidation may show caseous pneumonia or even a neutrophilic response. Microscopic cavities may be identified in such pneumonic foci. Cavities are lined by necrotic TB granulation tissue and show fibrosis. Occasional cavities may be lined in part by columnar or squamous epithelium. Acid-fast bacilli can be demonstrated more frequently in fibrocaseous lesions than in nodular TB. Acid-fast baclilli were found more frequently in cavitary lesions (88%) in comparison to non-cavitary lesions (77%)[5].

Smaller cavities may heal. Healing in general results in fibrosis and cicatrisation extending between the upper pole of the hilum and the apex, thus elevating the hilum on that side. This causes volume loss on the ipsilateral side. Simultaneously the upper mediastinum would be pulled towards the side of the lesion distorting the trachea and giving a characteristic radiological appearance. Modern treatment, however, allows rapid closure of cavities, which leaves little evidence of disease on chest radiographs. Serious complications resulting from pulmonary TB are uncommon now except when the disease has been neglected and becomes chronic and progressive.

OTHER LESIONS

Tuberculosis bronchopneumonia and military TB are a consequence of a large dose of virulent organisms disseminating through the bronchus or the blood stream, respectively. It is obvious that the host immunity may be compromised. The lesions have been described earlier.

BRONCHIAL LESIONS

Despite being closely associated with the lung parenchyma, bronchi not appear to be frequently affected in pulmonary TB[19]. In a majority of cases, the inflammation is non-specific and typical granulomas may not be seen. In some cases endobronchial TB, as discussed under primary pulmonary TB, may follow post-primary lesions [20] and this is characterized by bronchial inflammation ulceration, granuloma, small pseudopolyps and eventual healing by fibrosis. Bronchostensosis may give rise to post-stenotic dilatation of the bronchus.

Bronchiectasis directly attributable to pulmonary TB is rare. In those instances when this is found it usually occurs in the upper lobe and is relatively asymptomatic. Along with bronchostensosis it predisposes to secondary infection, haemoptysis and atelectasis.

Extension of TB to the pleura is common. Pericardial TB may follow pleuritis or by lymphatic spread from a pulmonary focus.

CHRONOLOGY OF IMMUNOPATHOGENESIS OF TUBERCULOSIS

Pulmonary TB [20,21]can be marked with four distinct phases following mycobacterium tuberculosis infection. Each of these phases determined by the homeostasis between the bacillary factors and host immune status including both innate and adaptive immunity (cellular as well as hormonal). First, following inhalation of mycobacterium tuberculosis, depending on their intrinsic microbicidal capability alveolar macrophages ingest the pathogen and destroy them. However, bacilli often evade initial destruction by phagocytes and continue to multiple inside them ending in their disruptions to cause fresh infection of the bystander macrophages.

This heralds the second phase, characterized by recruitment of blood monocytes and other inflammatory cells to the primary disease site, the lung in most instances. Monocytes ingest the bacilli and differentiate into macrophages, but fail to eliminate there completely. This stage is marked by logarithmic growth of the pathogens with little tissue destruction. Following this, antigen specific T-cell are recruited to that activate the monocytoid cells leading to either of these two types of gaint cell epitheliod and mult-nucleted langhans' type gaint cells. This is the third stage of granuloma formation, which aims at walling off the infection from the rest of the body and prevent dissemination of bacilli, thus contains infection. This stage of latency, which

disruptsunder conditions of failing immune surveillance and give rise to endogenous reactivation of dormant foci culminating in post-primary TB which is characterized by cessation necrosis (fourth phase). In summary, after entry into the body, mycobacterium tuberculosis encounters a series of host defense mechanisms with final outcome depending on the balance between bacillary growth and extent of host immunity. Essentially, all these phases of TB infection involve various arms of innate and acquired immunity sequentially in an orchestrated manner.

MECHANISM OF DRUG RESISTANCE:

Tuberculosis cavity usually contains 10^7 to 10^9 bacilli. Mutations causing resistance to isoniazid occur in about 1 in 10^6 replications, and the mutations causing resistance to rifampicin occur in about 1 in 10^8 replications,and the overall the probability of spontaneous mutations causing resistance to both isoniazid and rifampicin would be 10^6 x 10^8 which is equal to 1 in 10^{14} replications. Patients with extensive cavitary pulmonary TB, the chance of the development of spontaneous dual resistance to rifampicin and isoniazid is very common and this forms the basis for administration of multiple drugs for the treatment of TB.

MOLECULAR BASIS OF MULTIPLE DRUG-RESISTANCE

Predominantly, the molecular basis of drug resistance could be traced to mutations in genes coding for drug target proteins [23]. However, as an efficient pathogen, mycobacterium tuberculosis is equipped with several defence strategies, including a complex cell wall, drug efflux pumps and multi-functional proteins.

RIFAMPICIN

Resistance of rifampicin is a relatively rare event[24] and leads to selection of mutants that are already resistant to other components of shout-course treatment. Therefore, rifampicin resistance is often regarded as an excellent surrogate marker for MDR-TB. The association of the ribonucleic acid (RNA) polymerase beta subunit gene (rpoB) with resistance to rifampicin has been documented previously and subsequent reports from various groups have confirmed this association in clinical isolates of mycobacterium tuberculosis. Introduced in the early 1970s, rifampicin is a lipophilic ansamycin and its efficacy as an antituberculosis drug lies in its ability to diffuse across the hydrophobic cell envelope [24]. The ‘ansa’ designation denotes an aromatic centre that is bridged on both the ends by an aliphatic chain. The conformational relationship between the aromatic nucleus and the aliphatic chains is very important for microbiological activity, probably because of the interaction of the drug with its target.

It is a potent inhibitor of DNA dependent RNA polymerase. The RNA polymerase is a multisubunit protein consisting of a core enzyme having four polypeptide chains. The holoenzyme has an additional subunit delta that allows promoter recognition for initiation of transcription. The subunits alpha, beta, beta' and delta are coded by the rpoA, rpoB, rpoC and rpoD genes, respectively). Rifampicin binds to the beta subunit involved in the initiation and elongation of transcription.

RIFAMPICIN RESISTANCE

The molecular mechanism of rifampicin resistance has been thorough studied in Escherichia Coli and supplemented with genetic studied in early 1980s .mutation occurring in a discrete region of rpoB gene were identified and correlated with rifampicin resistance by several investigators [25]. This agnate region of mycobacterium tuberculosis rpoB was first cloned and sequenced by Telenti et al [26] on the basis of sequances information available from rpoB gene of mycobacterium leprae [26].

They identified a total of 15 distinct mutations clustered in a 23-amino acid stretch (69 bases).of the 15 mutations,eight were in the conserved amino acid residue 526 or 531 of the rpoB gene. Kapur et al [26] sequenced 121 rifampicin-resistant strains and concluded that 90 % of the rifampicin-resistant strains had sequence alteration in the 69 base pair(bp) hotspot that

was present within the 350 bp region showing considerable polymorphism amongst the rifampicin-resistant strains.

These earlier efforts led to a surprising discovery that certain mutations were relatively more abundant in one set of population than the other,and pointedto geographic partitioning and strain divergence amongst the rifampicin-resistant strains. Subsequent work has documented several other novel mutations that have been added to the list of mutations in the rpoB gene in rifampicin-resistant strains.

A study from Japan[27] established for the first time a relationship of these mutations to the level of resistance demonstrated by the strains. Isolates with mutations in codons 513,526,and 531 had high levels of drug resistance indicated by minimum inhibitory concentration (MIC) levels of greater than or equal to 50 microgram/ml. In contrast, amino acid substitutions located at position 514,521 or 533 resulted in low-level resistance (MIC<TO 12.5microgram/ml). It is important to mention here than in some of the rifampicin- resistant strains studied earlier, no mutation either in the rpoB hotspot or its flanking region were found, suggesting that there must be supplementary molecular mechanisms associated with the rifampicin-resistance.

ISONIAZID

Isonicotonic acid hydrazide (isoniazid), one of the key drugs for the treatment of TB is considered to be an ideal antimicrobial agent because of its low cost, excellent intracellular penetration, bioavaibility, and a narrow spectrum of action.

ISONIAZID RESISTANCE

Isoniazid is a pro-drug and is converted into active yet an unstable eletrophilic intermediate that inhibits the biosynthesis of cell wall mycolic acids. It was observed that complete deletion of katG led to the development of high-level resistance (MIC>50microgram/ml). furthermore, it was found that a subset of isoniazid-resistant strains of mycobacterium tuberculosis had intact katG.24 isoniazid-resistant isolates were analysed for insertions, deletions and substitution mutations in the katG locus. The mutations in the 5' region.

STREPTOMYCIN

The antibiotics aminoglycosides, macrolides and tetracylines target translation machinery of the pathogen. Streptomycin is an aminocyclitol glycoside that binds to 16S ribosomal RNA (rRNA OPERONS including 16S rRNA, and therefore mutations in one copy can be compensated by the active products of other copies. But slow growing mycobacteria like mycobacterium

tuberculosis or mycobacterium leprae have a single copy of 16S rRNA, implying that any mutation in these genes would confer resistance to streptomycin[28].

It is importance in mycobacterium tuberculosis arises due to alteration of the target than drug itself. Mutations in two target genes are associated with streptomycin resistance in mycobacterium tuberculosis, the 16S rRNA and ribosomal protein S12. The latter is involved in the translation machinery indirectly where it stabilizes the quaternary 'pseudoknot' structure of 16S rRNA Therefore, any mutation in 12 can result in altered structure of 16S rRNA preventing binding of streptomycin, thus, conferring resistant.

PYRAZINAMIDE

Pyrazinamidase led to the discovery of mycobacterium tuberculosis pyrazinamidase (pnc A)that had both pyrazinamidase and nicotinamidase activate. The mutations mapped onto mycobacterium tuberculosis pncA from clinical isolates, nucleotide insertions and deletions.

FLUOROQUINOLONES

Fluoroquinolones target the bacterial DNA gyrase, an ATP- dependent type II DNA topoisomerase that catalyses the negative supercoiling of DNA. This enzymes is made up of four units(alpha2 beta2)that are encoded by the

gyr A and gyrB genesrespectively. Fluoroquinolones bind to the gyrase and inhibit the supercoiling of DNA.

MOLECULAR MECHANISM UNDERLING ANTITUBERCULOSIS DRUG RESISTANCE

SL.NO.	DRUG	GENES INVOVLED IN RESISTANT
1.	Group 1 first-line oral antituberculosisagents isoniazid	Enoyl acly carrier protein (acp)reductase (inhA), catalase-peroxidase (katG),alklyl hydroperoxidase reductase (ahpC), oxidative stress regulator(oxyR) beta-ketocyl carrier protein systhase (kas A)
2.	i)Rifampicin ii)Pyrazinamide iii) ethambutol	i)RNA polymerase subunit B(rpoB) ii)Pyrazinamidase (pncA) iii)Aabinosyl transferase (emb A, emb B, and emb C)
3.	Group 2 injectable antituberculosis agents streptomycin	Ribosomal protein subunit 12 (rpsl) 16s ribosomal RNA (rrs), aminoglycoside phosphotransferase gene (strA)
4.	i)capreomycin ii)Group 3 fluoroquinolones	i)haemolysin(tlyA) ii)DNA gyrase (gyr A and gyr B).

Since Robert Koch's discovery of mycobacterium tuberculosis in 1882, microscopic detection of the bacilli in clinical specimens has remained the mainstay of tuberculosis diagnosis in developing nations. However, in human immunodeficiency virus (HIV) era microscopic diagnosis has certain drawbacks (i) a low clinical sensitivity of the technique in HIV-associated TB; and (ii) lack of access to quality microscopy services in HIV endemic areas.

Recently, a number of exciting technologies are being developed for rapid and improved diagnosis of TB including HIV-associated TB. These include improvements in microscopy, growth-based detection and subsequent strain characterization including drug susceptibility testing (DST), antigen detection, molecular detection and recently described interferon release assays (IGRAs).

CLINICAL SPECIMENS: COLLECTION AND TRANSPORTATION

In pulmonary TB, sputum is the specimen of choice. If TB of any other organ of the body is suspected, specimen should be from specific organ or system such as urine for renal TB and cerebrospinal fluid (CSF) for TB meningitis. Mycobacterium tuberculosis is in abundance in lesions showing rapid caseation.

Sputum

The specimen is collected in a sterile container. It is a common misassumption that as mycobacterial specimens are decontaminated before culture, cleanliness of the container is not important. Unsterilized containers may be contaminated with environmental mycobacteria.

To facilitate the choice of container, following sp0ecifications are recommended for a container: (i) widemouthed so that the patient can expectorate easily inside the container without contaminating it from outside; (ii) volume capacity of approximately 25 ml; (iii) made of transparent material in order to observe specimen volume and quality without opening the container; (iv) screw capped to obtain a water-tight seal, to reduce the risk of leakage during transport; (v) easily-labeled to allow p0ermanent identification; and (vi) rigid, to avoid breakage during transit.

An ideal container is the 28 ml universal container, which is a heavy glass, screw capped bottle. This container is reusable after thorough cleaning and sterilization. The identification number can be permanently engraved on the bottle cap.

In TB diagnosis, care must be taken to obtain adequate and satisfactory specimens to the laboratory are important to ensure that the results are accurate and reliable.

Collection Procedure

It is best to obtain a sputum specimen early in the morning before the patient has eaten, since food particles in smears make them difficult to examine[29]. For collecting a good sputum specimen, the patient must be given clear instructions [2]. Aerosols containing mycobacteria may be formed when the patient coughs to produce as sputum specimen. Patients should, therefore, produce specimens either outside in the open air or away from other people and not in confined spaces such as toilets.

Because of the intermittent excretion of tubercle bacilli, three specimens should be collected for diagnosis as follows: (i) one spot specimen when the patient first attends the health service; (ii) one early morning specimen (preferably the next day); (iii) one spot specimen when the early morning specimen is being submitted for examination. These should not be pooled but should be sent to the laboratory as separate specimens.

If a patient has a productive cough, obtaining a sputum specimen is a fairly straightforward procedure. The patient is given a container on his first attendance. He should be instructed with demonstration by actual actions such as: (i) to inhale deeply two to three times; (ii) to cough out deep from the chest; (iii) to open the container and spit the sputum into the bottle; (iv) to avoid saliva or nasal secretions; and (v) to close the container.

A good sputum specimen should be thick, purulent and of sufficient quantity at least 5 ml. The details of the patients name, address, age, sex and bottle number are to be recorded in a form/card and sent to the laboratory with the specimen. Specimens should be transported to the laboratory as soon as possible after collection. If refrigerated or kept in as cool a place as possible to inhibit the growth of unwanted micro-organisms. If refrigerator is not available and specimen is to be transported in hot climate then it should be preserved by adding equal volume of one per cent acetyl pyridinium chloride in two percent saline.

Collection of Specimens Other Than Sputum

Fibreoptic Bronchoscopy

Fibreoptic bronchoscopy has been extensively used to ascertain the diagnosis in patients who produce inadequate sputum or do not produce sputum at all, and in those with smear-negative pulmonary TB. Various bronchoscopic specimens such as bronchial washings, brushings, bronchoalveolar lavage (BAL) fluid and transbronchial lung biopsy have been evaluated and found to be useful [30].

Gastric Lavage

Gastric Lavage has often been used for the diagnosis of pulmonary TB in young children instead of sputum. Young children seldom produce

adequate sputum and secretions from the respiratory tract are often swallowed. Gastric lavage reveals the organism in 30 to 40 percent of the cases and the yield may be greater in infants with extensive disease[31]

Gastric lavage should be performed early in the morning, when the patient has been fasting for the preceding eight hours. Securing the specimen at this time would minimize the dilution of the bronchial secretions swallowed during the night by saliva or tears. Inhalation of superheated nebulized saline prior to gastric lavage has been reported to increase the bacteriologic yield.

Following insertion of nasogastric tube, the stomach contents are aspirated. Then a small amount of sterile distilled water, (not more than 50 to 70 ml), is instilled through the nasogastric tube and the aspirate is added to the first collection. As gastric acidity is poorly tolerated by Mycobacterium tuberculosis, the gastric aspirate should be immediately neutralized either with 10 percent sodium carbonate added by dropper to just pink (pH7) indicated by phenol red, or with 40 percent anhydrous sodium phosphate to green with bromothymol blue as an indicator.

Urine

The first few milliliters of urine should be allowed to flush the external urethra. Thereafter, clean-voided total volume of the first early morning urine

specimen on three consecutive days is collected in a sterile container and transported to the laboratory as early as possible.

Cerebrospinal Fluid

About 5 to 10 ml of CSF should be collected for culture in a sterile vial.

Serous Fluids

The largest possible volume of pleural, pericardial, synovial and ascetic fluid is procured for culture and 1 ml of 3.8 percent sodium citrate solution per 4 ml of specimen or 1 ml of 1:1000 heparins per 50 ml of fluid is added to prevent clotting of the serous fluid.

Tissue

Tissue biopsy specimens of lymph nodes, liver etc., are aseptically collected in a viral containing normal saline and transported to the laboratory immediately. Tissue in formalin should never be sent for culture.

Pus and bronchial secretions should be collected in sufficient quantities when possible to enable the concentration of mycobacteria. Bone marrow aspirates, which are generally free of rapid growing non-acid fast bacteria, can be directly inoculated on to the Lowenstein Jensen (L-J) medium.

Urine, CSF, Synovial or other fluids which are collected aseptically need to decontamination. For other specimens, sodium hydroxide in the final concentration of two percent in the diluted specimen is the most commonly used liquefying agent and digestant. The decontaminated specimen is concentrated by sedimentation in a refrigerated centrifuge at 3000 g for 30 minutes. The sediment is used for inoculating media and preparation of smears while the supernatant can be used for biochemical and/or immunological investigations.

DIRECT DEMONSTRATION OF MYCOBACTERIA BY STAINING TECHNIQUES

Use of microscopy in diagnosis of TB is of paramount importance, as culture takes a long time before the results are ready. Microscopy is also helpful in the detection of open or infectious cases. Stained smears are examined directly from the sputum and after concentration [32].

The tubercle bacilli are gram positive though they do not take the stain readily. Mycobacteria retain the primary stain even after decolourization with acid alcohol; hence the term “acid fast”. A counter-stain is employed to highlight the stained organisms for easier recognition. There are several methods of determining the acid fast nature of mycobacteria. In the carbol-fuchsin (Ziehl-Neelsen) procedure, acid fast organisms appeared against a blue background.

Acid fastness is based on the integrity of the cell wall beaded or barred forms are frequently seen in Mycobacteruium tuberculosis while Mycobacteruium bovis stains more uniformly. In younger cultures, no acid fast rods and granules have been reported.

The mycobacterial cell wall is complex in nature. It has high lipid content, which accounts for about 60 percent of the cell wall weight. The cell wall has several distinct layers. The inner layer overlying the cell membrance is composed of peptidoglycan (murein).

External to the murein is a layer of arabinogalactan, which is covalently linked to a group of long chain fatty acids termed mycolic acid, This form a dense palisade, arranged in rope like structure, which gives the cell wall its thickness and is largely responsible for acid fastness.

It has been shown that at least 10000 bacilli per ml of sputum are required for direct microscopy to be positive. The sensitivity can be further improved by examining more than one specimen form a patient.

Examination of two specimens will, on an average, detect more than 90 percent of cases and the addition of a third specimen increases the percentage to approximately 95 to 98 percent. A negative smear, however, does not exclude the diagnosis of TB as some patients harbor fewer numbers

of bacilli which cannot be detected by direct microscopy. A poor quality specimen or smear may also produce negative results.

New glass slides should be used for making smears as acid fast bacilli(AFB) are not always removed from the old slides. Only those reagents and diluents should be used which have been shown to be free of environmental mycobacteria to avoid false positive smears. Direct examination is performed by selecting a purulent looking portion of sputum and spreading it thinly on a glass slide with a bacteriological loop or a wooden stick.

The watery part of sputum is less likely to contain bacilli. The AFB are seen as bright red rods against the blue, green or yellow background (depending upon the counterstain used in staining). A negative result does not exclude TB. As recommended by World Health Organization (WHO), before declaring a slide negative it is essential that at least 100 fields are examined taking over at least 10 minutes. Smear can be graded according to the number of bacilli seen.

OTHER STAINING METHODS USING CARBOL FUSHSIN

Other staining methods using carbol fushsin for light microscopy include the cold staining methods (such as, kinyoun's or with Gabett's

solution). The performance of these techniques might have been overestimated.

Carefully planned studies have shown that the quantity of bacilli seen with a cold stain method is generally less than that with the conventional Ziehl-neelsen(Z-N) staining method, which might pose a problem in paucibacillary specimens.

The Gabett's solution has advantage only for experienced technicians who have to stain large numbers of smears, since it consists of only two steps (acid and methylene blue combined). However, the background colour with this method with this method is often not satisfactory.

GRADES ACCORDING TO THE NUMBER OF BACILLI SEEN WITH ZIEHL-NEELSEN STAINING:

NO.OF AFB	FIELDS	REPORT
None	Per 100 oil immersion field	Negative
1-9	Per 100 oil immersion field	Scanty(report exact number)
10-99	Per 100 oil immersion field	1+
1-10	Per oil immersion field(examine 50 fields)	2+
>10	Per oil immersion field (examine 20 fields)	3+

FLUORESCENT STAINING

Ziehl-Neelsen staining is a time consuming process for staining as well as examination. The WHO has recommended that the maximum number of Z-N smears examined by a microscopist in a day should not exceed 20. If more than this number of examinations is attempted, visual fatigue will lead to a deterioration of reading quality

On the other hand, proficiency in reading the Z-N smears can only be maintained by examination at least 10-15 Z-N smear per week,i.e., an average of two to three smears per day.

Establishment of fluorescence microscopy is recommended where more than 50 smears are examined per day, and if electricity is continuously available. Under such circumstances fluorescence microscopy might be cost-effective. Additional requirements in training and economic considerations (capital investment and maintenance) need to be taken into account before introducing fluorescence microscopy.

Fluorescence staining utilizes basically the same approach as Z-N staining, but carbol fuchsin is replaced by a fluorescent dye (auramine-O, rhodamine, auramine rhodamine, acridine orange etc.), the acid for decolourisation is milder and the counterstain, though not essential, is useful to quench background fluorescence.

Both sensitivity and specificity of fluorescence microscopy are comparable to the characteristics of the Z-N technique. The most important advantage of the fluorescence technique is that the slides can be examined at a lower magnification, thus allowing the examination of a much larger area per unit of time. In fluorescence microscopy, the same area that needs examination for 10 minutes with a light microscope can be examined in two minutes.

To increase the sensitivity of microscopic examination, various methods for concentrating the bacillary content of sputum and other clinical specimens are used. The most widely used method which concentrates the bacilli without inactivating them is Petroff's method

PETROFF'S METHOD

In this method, the sputum is incubated with an equal volume of four percent sodium hydroxide at 37 degree C with frequent shaking till it becomes clear. This takes an average of 15 to 20 minutes. It is centrifuged at 3000 rpm for 30 minutes. The deposit is neutralized with dilute hydrochloric acid using neutral red as an indicator. This deposit can be used for making microscopy, culture and other diagnostic tests.

Value of Smear Examination in Extra-pulmonary Specimens

Specimens form extra pulmonary sources, such as urine, CSF and other body fluids are centrifuged and the deposit is stained and examined.

The benefit of microscopy in these specimens is limited because of their paucibacillary nature and it is, therefore, recommended that the extra-pulmonary specimens be referred for culture and other molecular techniques.

Gastric Washings

Examination of direct smears of gastric lavage should be avoided, as the results could be misleading, The AFB are frequently present in food and water and hence in the stomach. There is no way of distinguishing such organisms from tubercle bacilli on microscopy and positive results must be regarded with suspicion.

Laryngeal Swabs

Direct smear examination of laryngeal swabs is not much useful. A negative result cannot rule out TB and whenever possible, the material obtained should be subjected to mycobacerial culture.

Pus and Thick Aspirates

Direct smears of pus and other body fluids, should be made thin. Thick smears tend to float off the slide and even if they are retained, the AFB may

be difficult to see after staining. Problems may arise if a large amount of blood is present in the specimen since blood may sometimes produce acid fast artifacts.

Pleural and Pericardial Fluid

The pleural and pericardial fluids should be centrifuged and smears should be prepared from the sediment. Again, these should be thin otherwise they may float off the slide.

Cerebrospinal Fluid

Smears from CSF are rarely positive and sediment from the CSF should rather be cultured. If a smear is desired, two parallel marks about 10 mm long and 2 mm apart should be made on a clean glass slide. A loopful of the sediment is spread between these marks are the smear is allowed to dry. Another loopful of the sediment is then spread over the first. When this is dry, the process may be repeated depending on how much sediment is available. This procedure clearly marks the area to be searched for AFB. It is desirable that two independent readers examine the smears. The clots should be saved for culture.

Urine

Smears of centrifuged urine deposits are most unreliable and should be avoided. Non-tuberculous mycobacteria (NTM) are sometimes present in the urine, either when it is voided or as a result of poor collection techniques. The presence of AFB in urine should be viewed with suspicion.

Isolation of Mycobacteria By Culture

Culture examination, on the other hand, detects fewer bacilli and increases the number of TB cases found, often by 30 to 50 percent. Culture methods provide definitive diagnosis by establishing the viability and identity of the organisms. Further, in order to distinguish between different mycobacterial species as well as to perform drug susceptibility tests, culture examination becomes a necessity.

Compared to other bacteria, which typically reproduce within minutes, Mycobacterium tuberculosis proliferates extremely slowly (generation time 18 to 24 hours). Further, growth requirements of mycobacteria are such that they will not grow on primary isolation in simple chemically defined media. Hence, culture methods for mycobacteria are expensive and require considerable infrastructure and technical expertise.

Cultures are very sensitive for the detection of tubercle bacilli and may detect as few as 10 to 100 bacilli per ml of sputum. The culture is considered as gold standard . Most commonly used medium is L-J medium. It contains eggs, asparagines, glycerol and some mineral acids.

Cultural Characters

The growth appears in about two weeks but may be delayed up to six to eight weeks. Optimum temperature for growth is 37 degree C; growth does not occur below 25 degree C and above 40 degree C. Optimum PH for growth is 6.4 to 7.0. Increased carbon dioxide (CO2) tension (5% to 10%) enhances growth. Human strains grow more luxuriantly in culture (eugenic) than do bovine strains (dysgenic). The addiction of a low percentage of glycerol to the medium encourages the growth of human strains but not that of bovine strains, which may in fact be inhibited.

Culture Media

Various types of media are commonly used have been summarized

Colony Characteristics

On solid media human type of tubercle bacilli give rise to discrete, raised, irregular, dry and wrinkled colonies which are creamy white to begin

with and then develop buff colour. By contrast, the bovine type grows as flat, white, smooth, moist colonies which “break up” more readily when touched.

Tubercle bacilli will grow on top of liquid medium as a wrinkled pellicle if the inoculums is carefully floated on the surface and flask left undisturbed otherwise they will grow as floccules throughout the medium. However, a diffuse growth can be obtained by adding a wetting agent such as Tween 80. Virulent strains tend to form long serpentine cords in the liquid media while virulent strains grow in a more dispersed fashion.

The clinical specimen as such, or after concentration, is inoculated onto two bottles of L-J medium and incubated at 37’C. Cultures are examined initially after three to four days to rule out the presence of rapid growing mycobacteria and contaminant fungi and bacteria. Thereafter, cultures are examined twice weekly. A negative result is given, if no growth appears after eight to twelve weeks. If growth is obtained, then a Z-N stained smear made from the same is examined and routine biochemical tests put up.

All cultures should be examined 18 to 72 hours after inoculation to detect gross contaminants. Thereafter cultures are examined weekly, up to eight weeks on a specified day of the week. With doubtful cultures, the acid-fastness should be confirmed by Z-N staining. A very small amount of growth is removed from the culture using a loop and gently rubbed into one drop of sterile saline on a slide.

At this point the ease with which the organisms emulsify in the liquid should be noted; as tubercle bacilli do not form smooth suspensions, unlike some other mycobacteria. The smear is allowed to dry, fixed by heat and stained by the Z-N method.

Animal Inoculation

Guinea pig inoculation was once a popular way of diagnosing TB but should now be regarded as obsolete. It has been clearly demonstrated that the use of this animal offers no practical advantage over in vitro culture. In addition to human considerations, animal inoculation is costly and generates many biohazards. However, in some laboratories it is still used.

Immunodiagnosis

Antibody detection tests:

Various antigens have been evaluated for detection of antibody to mycobacterium tuberculosis. The A60 is the most extensively used antigen for both pulmonary and extrapulmonary, adult and childhood TB. Immunoglobulin(Ig) G (IgG) and IgM detection has been evaluated. In various studies the sensitivity of these tests has ranged between 30 to 100 % . A variety of commercial kits are available primarily in developing countries. However, all them lack adequate sensitivity and specificity.

Tests are also available which use purified antigens mainly 38kDa and 30kDa. The former is very specific and the latter is highly immunogenic and more sensitive. Antibody detection by enzyme linked immune-sorbent assay (ELISA) or other serological tests are of limited use since less than 70% of patients produce specific antibody in high levels. Moreover, presence of antibody does not indicate current disease or past infection. Accordingly, presence of antigen may be a better indicator of the disease than the antibody.

However, antigen quantity in circulation is usually very limited and masked by the antibody and hence difficulty to detect. Though various tests have been attempted, there is none that can be recommended and is widely used.

A recent WHO study found that TB rapid diagnostic tests currently available in the market vary widely in performance, with some products showing a high lot-to-lot and reader-to-reader variability. At less than80%, the specificity was poor in the majority of products when tested in TB suspected cases from endemic settings. Those tests with a better specificity (over 90%) had poor sensitivity, detecting fewer than 40% of TB patients. The tests performed even worse in HIV co-infection samples the conclusion of a review of several studies showed that none of the assays perform well enough even to replace microscopy.

ANTIGEN DETECTION TEST

Lipoarabinomannan Urine Test

The tests detect lipoarabinomannan (LAM) in urine as a surrogate marker for mycobacterium tuberculosis infection.

Lipoarabinomannam is a component of the TB bacterial cell wall. The test exists in ELISA and simplified “tube” format. Clinical trials to develop a dipstick format are ongoing. The simplified tube format is apparently robust and does not require cold chain.

Flow – Through Filter Tests

These tests rely on detection of mycobacterium tuberculosis in sputum or body fluids with a polyclonal antibody, using a flow-through device.

NUCELIC ACID AMPLIFICATION TESTS

Nucleic Acid Probes

Deoxyribonucleic acid (DNA) hybridization technique detects small numbers of mycobacterium tuberculosis with no cross hybridization with non-mycobacterial respiratory pathogenswith sensitivity equivalent to smear examination by Z-N staining.

POLYMERASE CHAIN REACTION

Polymerase chain reaction (PCR)is extremely sensitive and specifictechnique[32]. A protocol for detection of insertion element IS6110 was described and it gave a positive result in nine out of the fifteen TB pleural effusions, while a PCR for conserved region was positive in only three of these patients.

However, it was also reported that when different specimens from the same patient were tested, positive results were obtained intermittently [33].

Initially developed PCR could detect as low as 10 bacilli in the specimen. Recent modifications have enabled DNA extracted from a fraction of a bacilli to be detected after suitable amplification.

The DNA ligase functions to link two stands of DNA together to continue a double strand segment. The seal can reliable take place only if the ends are complementary and are an exact match. In ligase chain reaction (LCR), the fragmented primers are four in number and are added in excess. Results from PCR and LCR tests are available in three days as compared to culture which takes six weeks. Its power can, however, be its greatest weakness as even the smallest amount of contaminating DNA can be amplified, resulting in misleading results.

AMPLIFIED MYCOBACTRIUM TUBERCULOSIS DIRECT TEST

Amplified mycobacterium tuberculosis direct test is specific test for mycobacterium tuberculosis complex. It is an isothermal transcription mediated amplification (TMA) test in which the target is the mycobacterial 16SrRNA.the entire process is performed at 42 degree C.

The test is highly specific, and gives result within three hours. This is the first test to be approved by the FDA for smear positive respiratory specimens. Similarly, other PCR test systems that target 16SrRNA including the real time assays have been developed.

Efforts are being made to simplify the nucleic acid testing systems. In loop mediated isothermal amplification (LAMP), mycobacterium tuberculosis DNA is amplified directly from clinical samples. A positive result in signalled by a colour reaction visible to the naked eye.

Overall, sensitivity of nucleic acid amplification tests (NAAT) is higher when test is applied to the respiratory sample as opposed to other body fluids [34].

Geno Type Assays

Two geno type assays are commercially available. The first is for TB diagnosis(Geno type myco bacteria assay), the second for detection of rifampician and isoniazid resistance (geno type MTBDRassay).

Isolation is commonly done by PCR amplification of the 16S-23S ribosomal DNA spacer region followed by hybridization of the biotinylated amplified DNA products with 16 specific oligonucleotide probes. The specific probes are immobilized as parallel lines on a membrane strip.

Polymerase Chain Reaction Sequencing

Specific mycobacterium tuberculosis genetic material is amplified and sequenced, allowing the DNA to be "read". This is a gold standard and most widely used method for defining genetic resistance for drug sensitivity testing. It has been commonly used for characterising mutations in the rpoB gene in rifampicin resistant strains and to detect mutations responsible for other antituberculosis drugs.

Drug Susceptibility Testing

The DST tests should be performed in the following instances: (I) for relapse or treatment cases; (ii) To change the drug regimens when drug resistance is suspected; and (iii)undertaking drug resistance surveillance studies in a region/country.

- Direct method
- Indirect test
    1. Absolute concentration method
    2. Resistance ratio method
    3. proportion method

- Microscopic-observation drug-susceptibility assay(MODS).

BIOLOGICAL AND IMMUNOLOGICAL MARKERS

- Adenosine deaminase and interferongamma.

DIAGNOSIS OF MDR TB

CONVENTIONAL METHODS

Traditionally Lowenstein Jenson(LJ) culture has been used for drug sensitivity testing using i) absolute concentration method ii) resistance ratio method iii) proportions method .In resistance ratio method MIC of isolated is expressed as multiple of MIC of standard susceptible strains.

In proportion method ratio of number of colonies growing on drug content medium to number of colonies in drug free medium is compared.

Modern methods

Radiometric methods have been developed for rapid drug susceptibility testing of M. Tuberculosis. In the BATEC-46(Becton Dickinson THIZ medium contains palimitic acid labelled with radioactive (C14 palimitic acid) detects radioactive carbon dioxide as mycobacterium metabolise these fatty acid [23,24]

The mycobacterium growth indicator tube is rapid non-radioactive method oxygen sensitive compound restriction fragments length polymorphism has facilitated elucidation of molecular epidemiology of TB. LCR (ligase chain reaction) involves the use of DNA ligase, Luciferase reporter assay is a moral reporter gene assay system fast plaque TB-RIF a rapid detection tests Genetic mechanism.

The line probe assay(lipA;INNO genetic NA) has been based on reverse hybridisation method consist of PCR amplitude of segment of rpo B genetic followed by denaturisation and hybridisation of bio tiny PCR amp icons to capture probes bound to micro cellulose strip.

The emergence of MDR-TB is a threat for population of resource limited countries, low socio economic states of the people, high prevalence of infectious diseases and cases to well-equipped health care facilities worsens the effect of MDR-TB further more poor treatment outcomes, longer treatment higher treatment cost and many more complication makes MDR-TB complex diseases.

Prevalence of MDR TB in cat II TB patient was high and these patients are at high risk of amplified resistant, in this view of high risk of MDR-TB among cat II retreatment.

This study was carried out to compare the various factors among the drug susceptible in the drug resistant and compare the factors which might to contribute towards the development of multi drug resistant tuberculosis, which may help identify various risk factor for development of MDR-TB, helps in the treatment of drug susceptible and drug resistance case

MDR Worldwide

Though studies published from the developing world suggested that drug resistance was a potential problem[35] it was emergence of MDR-TB on USA in 1990 attracted the global extent of problem of drug resistant tuberculosis is evident on the report by WHO International Union agent Tuberculosis and long disease (IUATLD) global prefect on anti-tuberculosis drug resistant surveillance between 1994 and 1997.

In this study drugresistantce was found to be prevalent in 35 countries suggesting it to be global problem therefore WHO – UATLD [36,37] survey was extended to define the problem further between 1996 and 1999 patient and 58 countries surveyedfor newly diagnosed patients, frequency of resistance to, at least one anti-tuberculosis drug ranged from 1.7% in urguay to 36.9 in Estonia, china(10.8%), Russian oblast of Ivano(9%), Results of resistance survey from 64 countries together with data predicted of 72 others suggested, new cases of MDR TB occurred worldwide constituted 3.2% of all new cases.

Isoniazid the most powerful mycobactecidal drug available ensures early sputum conversions and helps in decreasing the transmission of TB. Rifampicin by its mycobactericidal and sterilizing activities is crucial for preventing relapse thus isoniazid and rifampicin are keystone drugs in management of TB. While resistance to either isoniazid and rifampicin may be managed with other first IM-drugs resistance to both isoniazid and rifampicim is MDR-TB demands treatment with second line drugs.

These drugs have limited sterilizing capacity and are not suitable for short course chemotherapy thus patient with MDR-TB required prolong treatment, in less effective and more toxic drugs.

Primary resistance is that which has not resolved from the treatment of the patient with the drugs concerned. It included resistance in wild strains which have never came in contact with the drugs (natural resistance) and the resistance occurring as result of exposure of the strain to the drug but in another patient. Initial resistance is the resistance in patient who give a history of never having chemotherapy of includes both primary resistance and resistance by previous treatment concerned by patient [38].

The terms acquired resistance has often been used with implications that resistance has developed due to exposure of strain to anti-tuberculosis drugs and consequent selecting out of resistant mutant bacilli.

However some of drug some of drug resistant isolated in previously treated patient may actually represent primary resistance among patient who remains incurred if initial drug susceptibility testing has not been done[39]. The term resistance among previously treated patient would be a more approximate term than acquired drug resistance[40]susceptible strains are those that have not been exposed to main anti-tuberculosis drugs and respond to this drugs in a uniform manner.

Resistant strains differ from the sensitive strain in their capacity to grow in presence of higher concentration of drug. Wild strains are those that have never been exposed to drug naturally resistant strains are wild strains resistant to drug without having a contact to it.

Various factors have been implicated in the

CAUSATION OF MDR-TB

1. Genetic factors

Though there is some evidence to postulate host genetic predisposition as the basis for the developments of MDR-TB, it has conclusion [41, 42]. In a recent study from India patient with HLADRB113 and DRBI 14 were found to have two fold increases risk of developing MDR-TB. Partly 84-34 found that susceptibility history of MDR-TB in Korean patient was strongly associated with HLA DRBI 08032-DQBI 0601 haplotype.

The exact role of the factors is not known. It is likely that these loci or alleles linked with then play a permissive role of increasing susceptibility to development of MDR-TB.

FACTORS RELATED TO PREVIOUS ANTI-TUBERCULOSIS TREATMENT

Incomplete and inadequate treatment, review of published literature strongly suggested that the most powerful predictor of the presence of MDR-TB is the history of treatment of tuberculosis.

TB patient in India get treated with DOTS regimens, not only theory of Revised National Tuberculosis Control Programme (RNTCP) but also receive treatment from private medical practitioners, irregular treatment is commonest mean of acquired drug resistant organism[43].

Mahumoudi and Isman.et al[44] observed that among the 35 patients with MDR patients errors in management decision occurred in 28 patients, at an average of 3.93 errors per patients. The most common error is addition of single drug to regimen, failure to identify persisting or acquired drug resistance, initiation of an adequate primary regimen when the patient appear to be detoriate clinically.

Inadequate treatment complaints

Poor compliance with treatment is also an important factor in the development of acquired resistance. In a study conducted in South India[45]45% of patients receive short course (n-2306) and 35% of those receiving standard chemotherapy (n+1051) completed 80 percent of treatment, non- compliance with prescribed treatment is often underestimated by the physician and is difficult to predict.

The drug defaulter, just like placebo reactor is not a consistent or readily identified person [46]. In west demographic factors given as age, sex, marital status, socio economic status have been not found to like degree of compliance on the one hand certain factors such as psychiatric illness, alcoholism, drug addiction and homelessness do predict non-compliance.

This may not be entirely true in Indian context and the relevance of these factors in Indian scenario merits the further study.[47]Santha etal.studied the risk factors associated with default,failure death among TB patients treated in TB patients, In this study in multivariate analysis higher default rates were associated with irregular treatment, male sex, history of previous treatment, alcoholism. Higher death rates were independently associated with weight less than 35kg.

Jhonson et al[48] found high incidence of drug resistance in previous treatment defaulters. The various reason for default included travel to different places, symptom relief, adverse drug reaction and inability to effort treatment, Good reliable laboratory support is not accessible in developing nations. Unfortunately these are the areas where MDR-TB is major health hazard.

This program of tuberculosis control was assessed in a sputum positive tuberculosis. Drug resistance data on admission were available for 131 patient and 55 percent of patients had of mycobacterium tuberculosis resistant to one or more drugs mortality drug treatment was 11 percent and 13 percent treatment was successful in 54 percent of patient, in 71 percent of treatment completing patients. Similar observations were made in another study with results of treatment with first line drugs enrolled with WHO and IUALTDS global project on drug resistance surveillance.

This data suggest that short course chemotherapy based on first line drugs inadequate for some patients with drug resistant TB[49]. Although DOTS strategy is basis of good control of TB, the strategy should be modified in some settings to identify drug resistant cases source and to make use of second line drugs in approximate treatment.

PREDICTORS FOR DEVELOPMENT OF MDR-TB

Certain factors have been documented to associated with development of MDR-TB. In a analysis to identify determinants of drug resistance, population based data a, new and previously treated patient with TB collected within an international drug surveillance networks were studied [50].

Of the 9,615 patient 85.5% were new cases compared with old cases, patients who received treatment in the past were more likely to have resistance to anti-tuberculosis drugs. Multivariate analysis revoked that prior anti-tuberculosis treatment but not HIV positivity.In Saudi Arabia previous history of anti-tuberculosis treatment young age were found to risk factors.

In a study from[51]henan province, past history of tuberculosis, poor compliance to treatment, low socio economic status and body mass under contributors to risk of developing MDR-TB. In most of published study previous history of the tuberculosis and past history of anti-tuberculosis treatment have been implicated in the cause of MDR-TB. Parketal reported that extra pulmonary involvement was risk factor for shorter survival while a cavitation lesions on initial chest film treatment was high risk factor.

Predictor's survival in patient MDR-TB

DOTS is key in the tuberculosis control strategy. In population where MDR-TB is endemic the outcome of short course regimen

uncertain.unacceptable Failure rates have been reported and resistance to additional agent may induced[51].

As a consequence there has been cause for well factor of DOTS programme to provide addition service. The WHO has also established greenlight committee in attempt to promote access to and rational use of second give anti-tuberculosis drugs and treatment of MDR-TB [52].

Nutritional enhancement

Tuberculosis is a wasting disease, the degree of cachexia is most profound where MDR-TB occurs in patient with HIV co-infecteion; while the mechanism involved in weight loss are not well known, current evidence points to tumour (TNF-alpha) to be the cytokines responsible for phenomenon.

Though definitive evidence is not yet available it is generally believed that malnourished patients are as greater risk of developing post-operative complications[53]. Nutritional assessment and regular monitoring of nutritional state by a discussion are essential for the successful management of MDR-TB Patients.

There are limited data's are available on the risk factors for multidrug resistant tuberculosis. Various factors that might contribute towards the development of multidrug resistant tuberculosis was analysed in various

studies all over the world. Larger studies showed involvement age, gender, education, economy, defaulter, alcoholism towards the development of MDR TB. Age distribution pattern in many study showed peak levels of defaulting are in the >45 year [54].

In another study in ODISHA[55] towards factors for sourceful outcome in pulmonary tuberculosis showed factors such as young age, high income, high education, regular treatment favours for the positive outcome of disease. Determinate of MDR TB published in IRS annul congress 2012 showed a positive correlation of MDR TB with previous treatment.

Similar study in eastern, Ethiopia analysed risk factors for un-successful tuberculosis treatment outcome[56] showed association unsuccessful treatment with age, previous history of treatment, HIV-TB co-infection.

In other study[57] done in kuwait towards determinants of defaulter and MDR TB suggested association of history of defaulter Low education, male sex, homelessness, smoking, Alcohol, drug based towards development of MDR TB.

In case control study of diabetes and other risk Factor for multi drug resistant tuberculosis in a Mexican population[58]. The important finding in this study was Association between diabetes and MDR TB (47.2%). In onestudy by Gimenez et al DM associated with a Higher frequency of cavities among

diabetics possible explanation for the increased frequency of MDR-TB among DM-TB Patients include a) to maintaince phase of anti-TB treatment b) higher mycobacterial burden in DM-TB patients.

Results from national survey of south Africa[59] for the determinate of multi drug resistant TB patients showed resistance cases were consistenly high in previous treated cases, the role of HIV as an independent risk factor for MDR remains inconculsive. A case control study by addis abba[60]showed high prevalence of MDR among retreatment cases, male, smoker, alcohol. The study also showed important finding very low association of HIV towards the development MDR TB. Thailand study also showed insignificant association of HIV with MDR[61].

In France being HIV positive was associated with primary MDR TB but it was not associated with secondary MDR TB [62]. Risk factor of multi drug resistant in urban Allahabad[63] again confirmed association of MDR TB with males, previously treated cases substance abuse, and with associated co-morbidities, in controversy to other studies it showed association of MDR with young age.

Similar study from henan province case control study [64] compared the various factor involved with development MDR TB assured the association of previous treatment, male sex, low education, unemployment, smoking, lack of awareness towards the development with significant (C OR 95%,P value).

The study also recommended associations of HIV-TB co-infections for the association factors associated with treatment defaulter by tuberculosis patient in morocco showed smoker, alcoholic associated with development of MDR Or(95% CI).

Relapsed case 4.49 (1.87 -10.1) <.001

Chronic smoker 2.10 (1.07 -4.14) 0.03

Alcohol user 2.92 (1.04 -8.19) 0.04

Risk[65] factors for multidrug resistant TB showed once again association of prior treatment, economy, illiterate. This study significantly associated HIV towards the development of MDR in contrary to other studies.

Variables COR (95%CI) ADR (95%) P-value

History of Previous Treatment			
Yes	20.5	21	0.001
No	1.00	1.00	
Infected with HIV			
Yes	2.46 (1.33-4.55)	3.1	0.46
No	1.00	1.00	

Another[66]Study showed prevalence of MDR among category II patient was about 20.4 % tuberculosis among HIV patient in India was3-5% in new cases 15-20% in retreatment cases) which was again showed in various study in India withabove background we carriedout our study to determine predisposing factor forMDR TB.

AIM OF STUDY

To Compare the predisposingFactors towards the developmentof drug susceptible anddrug resistance pulmonary TBre-treatment cases. To analyse the factors which might contribute the development multidrug resistant tuberculosis.

OBJECTIVES

To determine factors leading to development multidrug resistant tuberculosis.

METHODLOGY

1. Title of the study	:	Comparison of predisposingFactors towards the developmentof drug susceptible and drug resistance pulmonaryTBre-treatment cases.
2. Site of Investigation	:	GHTM
3. Principal Investigator		
a) Name	:	Dr. G.K.BALAJI
b) Qualification	:	M.B.B.S M.D(Post graduate in T.B & RD)
c) Institution	:	Govt. Stanley Medical College Hospital
4. Co-investigators	:	Dr. SRIDHAR (MD CHEST,DTRD)
a) Name	:	Dr. VINODKUMAR (MD CHEST,DNB)
		Dr. NANCY GLORY(MD CHEST)
		Dr. VENKADAKRISHNARAJ(DTCD,
		DNB(CHEST)
		Dr. MAHESWERAN (M.D CHEST).
5. Aim/Goal of the study	:	To evaluate the factors contributing to development MDR TB

6. Primary Objectives	:	To compare and analyses various risk factors associatedwith pulmonary TB defaulters towards development of MDR TB
7. Secondary Objectives	:	Identifying the risk factors and avoiding it. To prevent development of MDR TB.
8. Hypothesis/Research question	:	What are the risk factor towards developmentMDR TB
9. Study design	:	Type of study -prospective
10. Work plan /Timeline	:	Approx time for sample collection –10 months Study data analysis one month.
11. Ethical Clearance	:	The various investigations and procedures that will be used in this study will be as per protocol. The identity of each patient will be kept confidential. This study will not violate medical ethics in anyway
12. Study population	:	Pulmonary TB retreatment casesand MDR patientsin GHTM
14. Inclusion criteria	:	1) All patients with pulmonary TB retreatment and MDR cases. 2) Age > 15 years

14. Exclusion criteria	:	1) Patients with only extrapulmonary TB 2) Age < 15 years 3) Patients who are moribund, sick and unableto produce sputum. 4) Patients who are not willing to participate in the study
15. Collection of clinical samples/data	:	Specify type 1. Recruitment as perInclusioncriteria 2. Symptom diagnosis 3. Chest radiograph 4. Sputum AFB smear 5.CB-NAAT result 6. Culture results
16. Methodology	:	Technique Sample size-100 Source of the study population –GHTM Study design-Prospective.

To find the relationship between commonly associated risk factor such as:

1. Age<15, 15-45,>45
2. Gender
3. Education-illiterate , literate
4. Economic status

   - 3000/month

   -> 3000/month
5. History of contact with MDR
6. HIV status
7. Diabetic status
8. Alcohol consumption, smoking, cavitation in chest x-ray
9. Category of treatment

   - defaulter

   - treatment failure

   - relapse

   - new case
10. Treatment history :

    Towards the development of MDRTB among TB retreatment cases

11. Laboratory investigations:		Chest Xray, Sputum Smearfor AFB,DST Tridot for HIV,CD4 count, FBS, PPBS, LPA.
12. Statistical analysis	:	As per standard statistical method.
13. Involvement of other centres	:	NIL
14. Requirement of Funds	:	NIL
15. Conflict of interest if any:		NIL
16. Significance of the study:		Identifying the risk factors associated withDevelopment of MDR helps to prevent the MDR TB.

RESULTS AND OBSERVATION

COMPARISON OF DRUG SENSITIVE AND DRUG RESISTANT PULMONARY TUBERCULOSIS RETREATMENT CASES

Results

Descriptive statistics

Among Defaulter, frequency of default,

Inferential statistics

Association of frequency of default and resistance

COMPARISON OF DRUG SENSITIVE AND DRUG RESISTANTPULMONARY TUBERCULOSIS RETREATMENT CASE TOWARDS DEVELOPMENT OF MDR

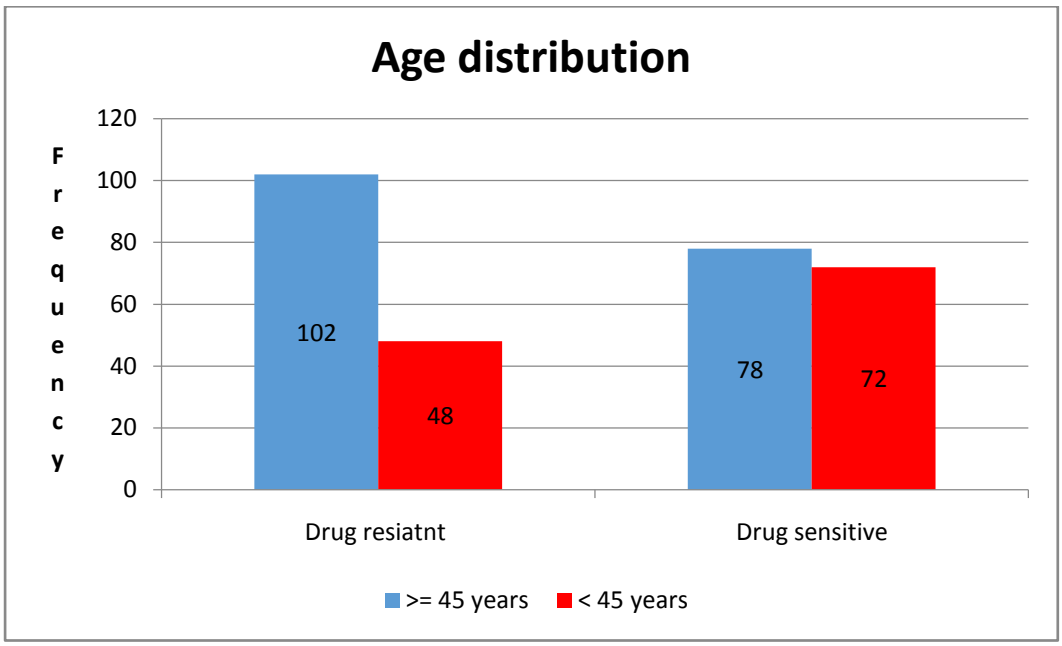
S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Age Group	≥45 years	102	68%	78	52%
		< 45 years	48	32%	72	48%

Descriptive statistics

Result:

Charts / Figures

Comparison of frequency distribution of age in two groups.



Inferential statistics

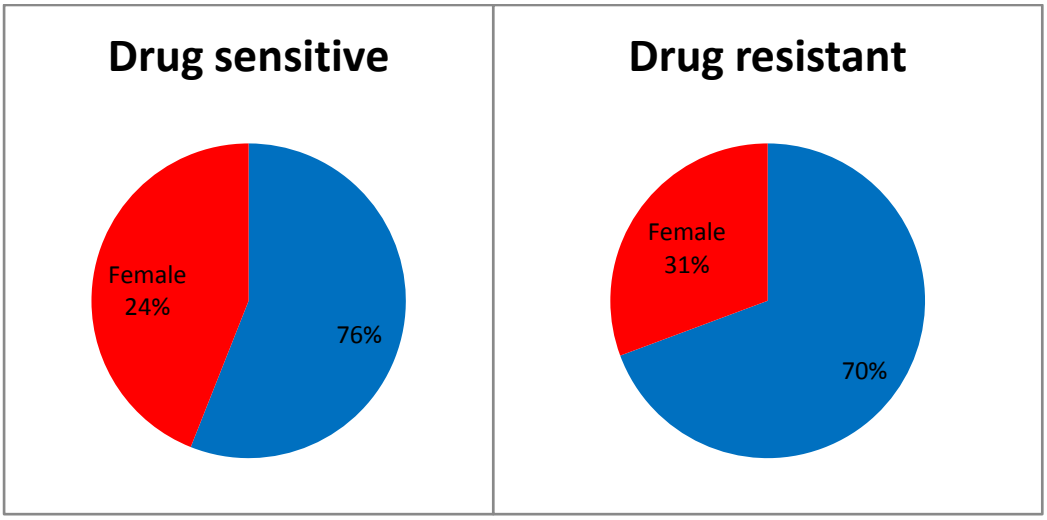
S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Age Group	≥ 45 years	78	48	0.00	2.29 (1.43 – 3.68)
		< 45 years	72	102		

Sex distribution

Drug resistant group

Drug sensitive group

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
2.	Sex	Male	104	69.3%	114	76%
		Female	46	30.7%	36	24%



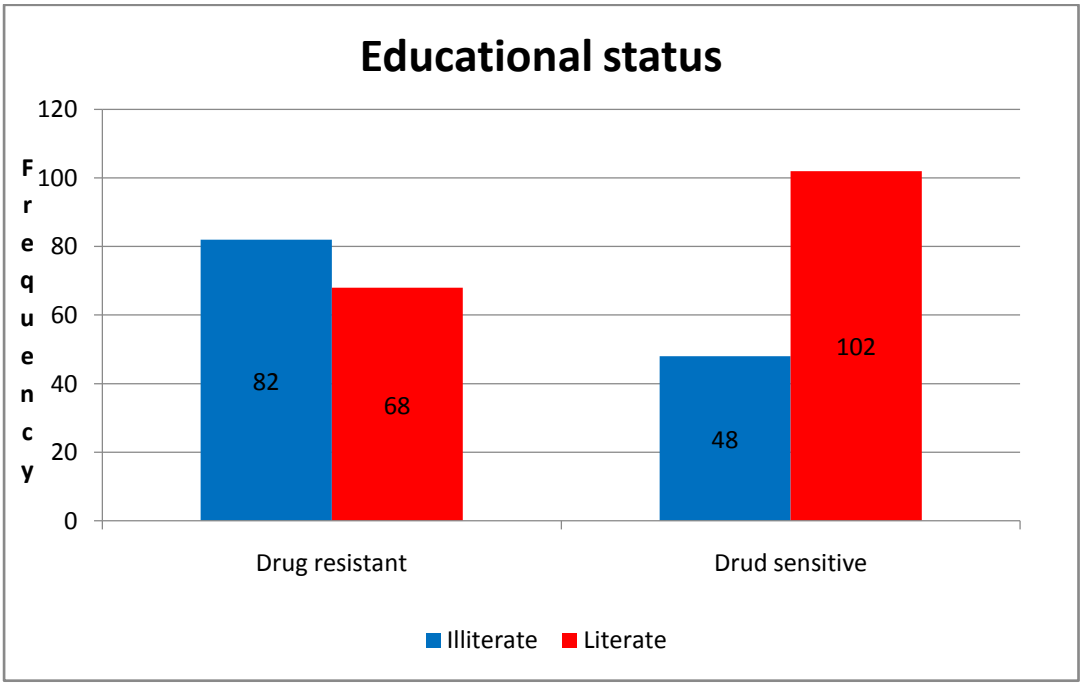
S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Sex	Male	104	84	0.01	1.77 (1.10 – 2.86)
		Female	46	66		

Inferential statistics

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
3.	Education	Illiterate	82	54.6%	48	32%
		Literate	68	45.3%	102	68%

Descriptive statistics

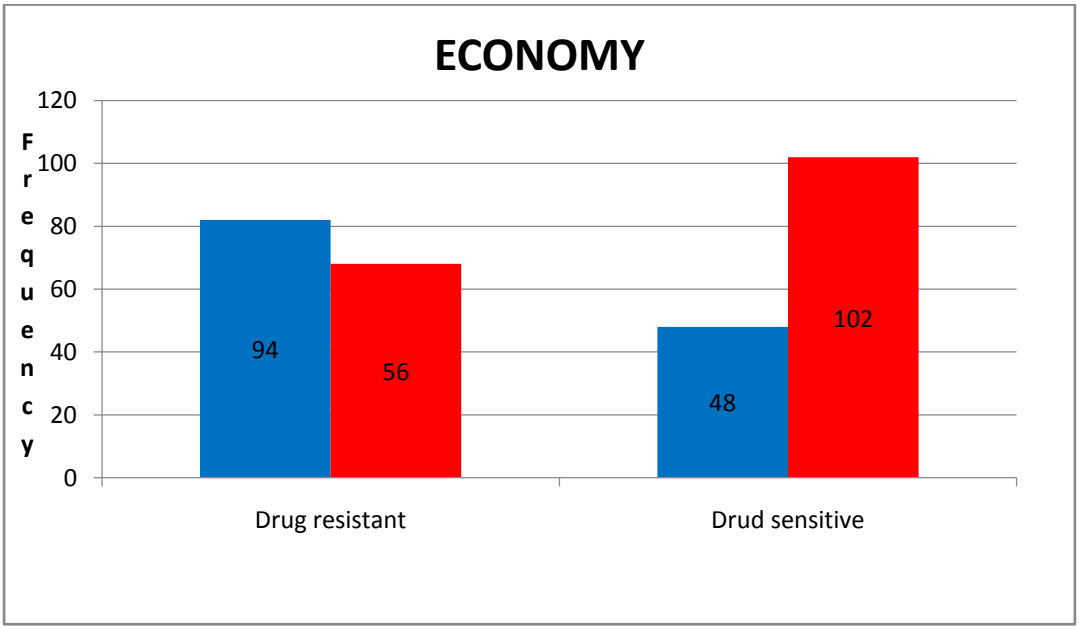
Results



S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Education	Illiterate	82	48	0.00	2.55 (1.59 – 4.1)
		Literate	68	102		

Inferential statistics

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Economy	<3000	94	62.6%	48	32%
		>3000	56	37.3%	102	68%



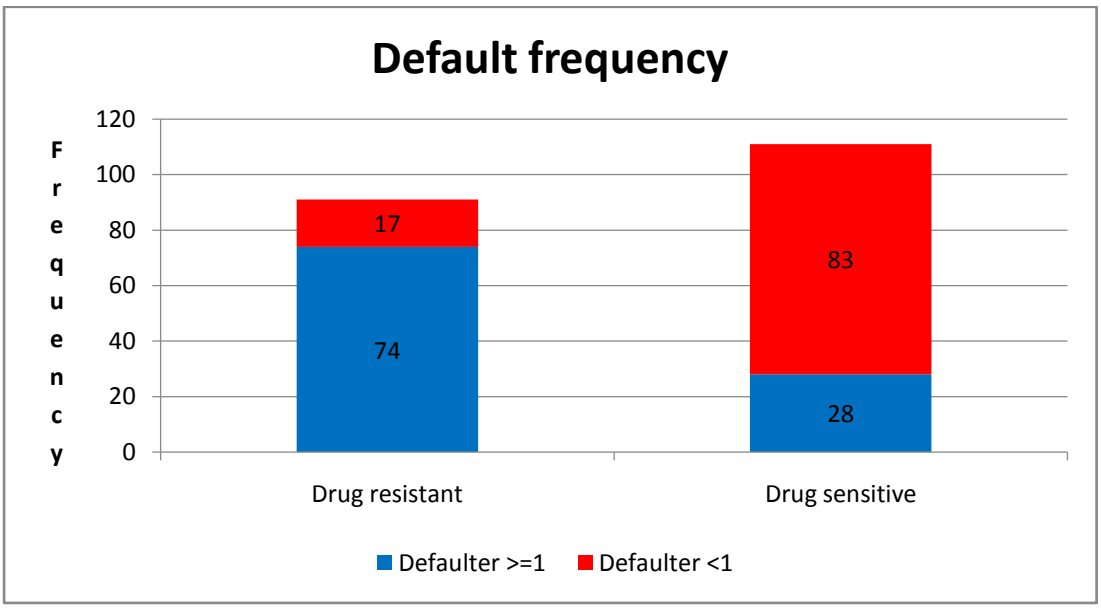
Descriptive statistics

Results

S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Economy	<3000	94	48	0.00	2.55

		>3000	56	102		(1.59 – 4.1)

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Treatment History	New case	6	4%	0	0%
		Defaulter	91	60.6%	111	74%
		Relapse	41	27.3%	34	22.6%
		Treatment failure	12	8%	5	3.3%



S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Treatment History	New case	6	0	0.009	
		Defaulter	91	111		

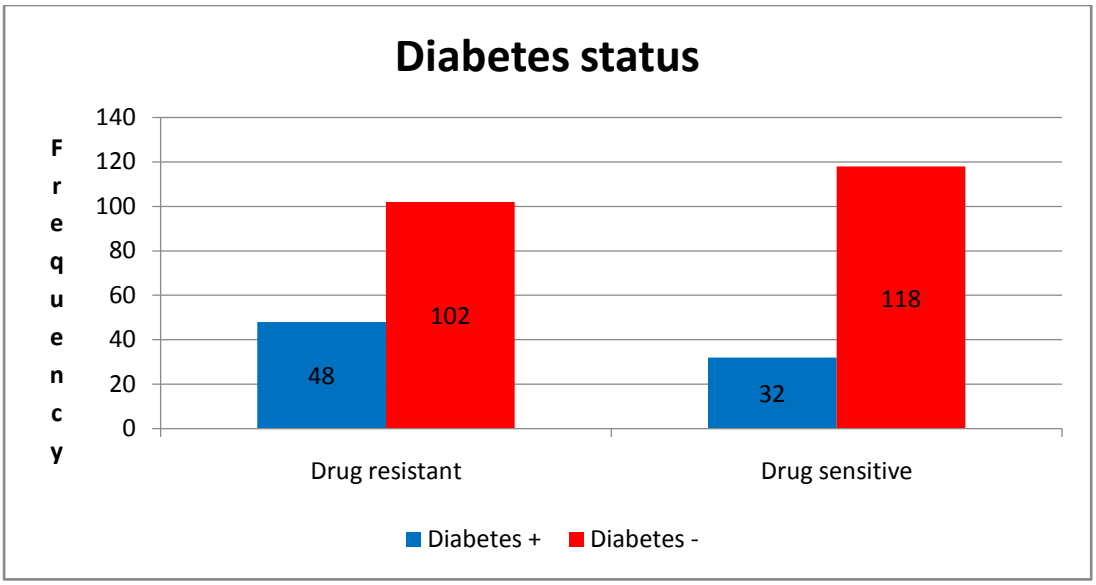
		Relapse	41	34		
		Treatment failure	12	5		

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Diabetes history	+	48	32%	32	21.3%
		-	102	68%	118	78.6%

Inferential statistics

Descriptive statistics

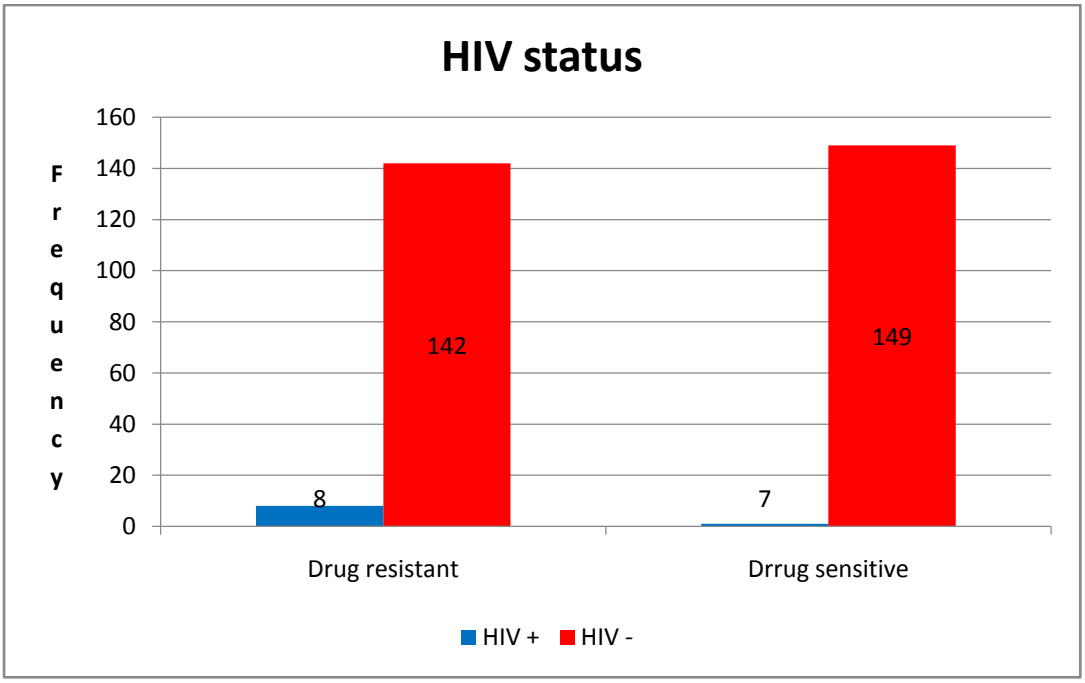
Results



S. No.	Variable	Drug resistant group	Drug sensitive group	Chi square test	Odds ratio with confidence

			(n=150)	(n=150)	P value	limits
1.	Diabetes history	+	48	32	0.03	1.73 (1.03 – 2.93)
		-	102	118		

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	HIV status	+	8	5.3%	7	4.6%
		-	142	94.7%	143	95.3%



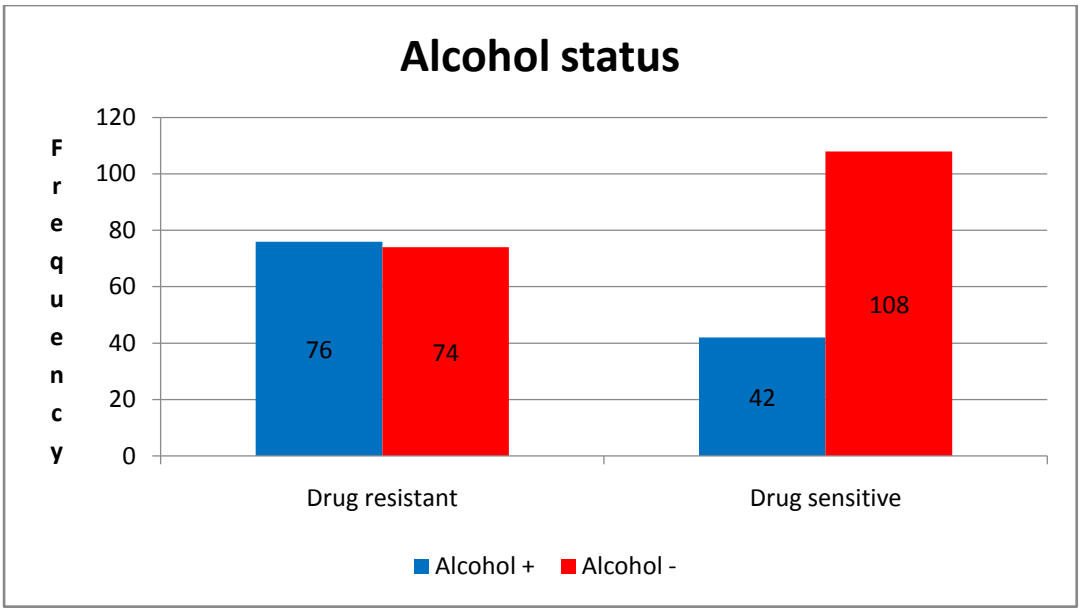
Inferential statistics

S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	HIV status	+	8	7	0.01	8.39
		-	142	143		

Descriptive statistics

Results

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Alcohol history	+	76	50.6%	42	28%
		-	74	49.4%	108	72%



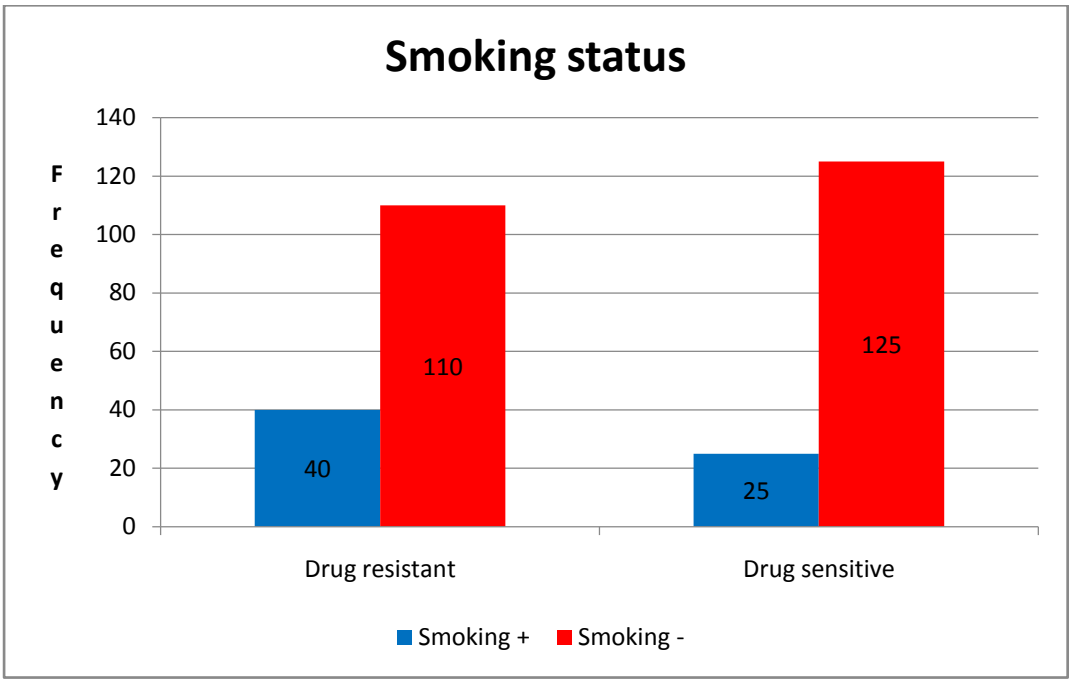
S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Alcohol history	+	76	42	0.00	2.6 (1.6 – 4.2)
		-	74	108		

Inferential statistics

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Smoking history	+	40	26.6%	25	16.6%
		-	110	73.3%	125	83.3%

Descriptive statistics

Results



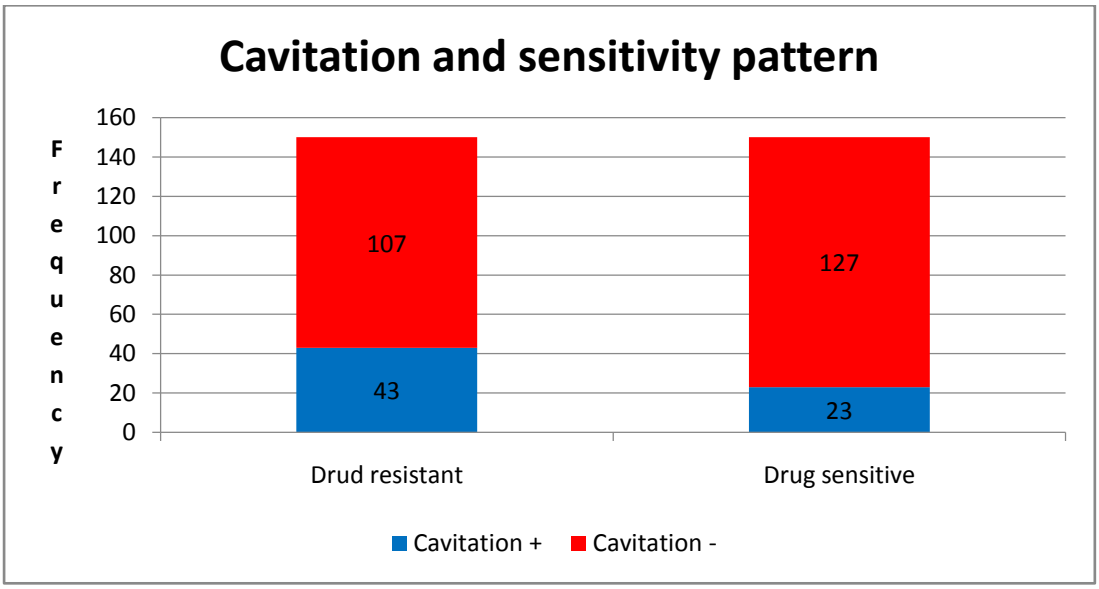
S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
9.	Smoking history	+	40	25	0.03	1.8 (1.0 – 3.2)
		-	110	125		

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Cavitation	+	43	28.6%	23	15.3%
		-	107	71.3%	127	84.6%

Inferential statistics

Descriptive statistics

Results



Inferential statistics

S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Cavitation	+	43	23	0.00	2.21 (1.25 – 3.95)
		-	107	127		

COMPARISON OF DRUG SENSITIVE AND DRUG RESISTANT PULMONARY TUBERCULOSIS RETREATMENT CASE TOWARDS DEVELOPMENT OF MDR

Results

Descriptive statistics

S.No.	Variable		Drug resistant group (n=150)		Drug sensitive group (n=150)	
			Frequency	Proportion	Frequency	Proportion
1.	Age	≥ 45 years	102	68%	78	52%

	Group	< 45 years	48	32%	72	48%
2.	Sex	Male	104	69.3%	114	76%
		Female	46	30.7%	36	24%
3.	Education	Illiterate	82	54.6%	48	32%
		Literate	68	45.3%	102	68%
4.	Treatment History	New case	6	4%	0	0%
		Defaulter	91	60.6%	111	74%
		Relapse	41	27.3%	34	22.6%
		Treatment failure	12	8%	5	3.3%
5.	Diabetes history	+	48	32%	32	21.3%
		-	102	68%	118	78.6%
6.	HIV status	+	8	5.3%	7	4.6%
		-	142	94.7%	149	99.3%
7.	Alcohol history	+	76	50.6%	42	28%
		-	74	49.4%	108	72%
8.	Smoking history	+	40	26.6%	25	16.6%
		-	110	73.3%	125	83.3%
9.	Cavitation	+	43	28.6%	23	15.3%
		-	107	71.3%	127	84.6%

Among Defaulter, frequency of default

S.N	Variable	Drug resistant group (n=150)	Drug sensitive group (n=150)

o.			Frequency	Proportion	Frequency	Proportion
1.	Defaulter frequency	>1	74	82.2%	28	25.2%
		≤ 1	17	18.8%	83	74.7%

Association of frequency of default and resistance

S.No.	Variable		Drug resistant group (n=91)	Drug sensitive group (n=111)	Chi square test P value	Odds ratio with confidence limits
1.	Defaulter frequency	>1	74	28	0.00	12.7 (6.5 – 25.6)
		≤ 1	17	83		

Inferential statistics

S.No.	Variable		Drug resistant group (n=150)	Drug sensitive group (n=150)	Chi square test P value	Odds ratio with confidence limits
1.	Age Group	≥ 45 years	102	78	0.00	2.29 (1.43 – 3.68)
		< 45 years	48	72		
2.	Sex	Male	104	84	0.01	1.77 (1.10 – 2.86)
		Female	46	66		
3.	Education	Illiterate	82	48	0.00	2.55 (1.59 – 4.1)
		Literate	68	102		
4.	Treatment History	New case	6	0	0.009	
		Defaulter	91	111		
		Relapse	41	34		
		Treatment failure	12	5		
5.	Diabetes history	+	48	32	0.03	1.73 (1.03 – 2.93)
		-	102	118		
6.	HIV status	+	8	7	0.01	8.39
		-	142	143		
7.	Alcohol history	+	76	42	0.00	2.6 (1.6 – 4.2)
		-	74	108		
8.	Smoking history	+	40	25	0.03	1.8 (1.0 – 3.2)
		-	110	125		
9.	Cavitation	+	43	23	0.00	2.21 (1.25 – 3.95)
		-	107	127		

DISCUSSION

In our study we found factors which are predominant in drug resistant pul.TB cases,Which are evidenced by so many previous studies as discussed earlier, statistical analysis and percentage of patients among the drug resistant and drug susceptible retreatment cases show team association of these factors towards development of drug resistant Tuberculosis.

Drug resistant pul.TB patients were predominantly >45 years about 68% ,among drug susceptible pul.TB patient were years 52%.descriptive statistical analysis show with p value of 0.00 and CL of (2.29).

Drug susceptible and drug resistant pul.TB retreatment cases has the male predominant ,which can been seen as about 69.3%&76%, which shows predominant of drug susceptible and drug resistant TB among males which can be attributed to various coexistent factors like alcohol, smoking, occupational history which leads increased defaults among the male patient which again leads to development of MDR TB.

In a similar fashion we found that literate person among drug resistant TB patients around 45.3% while illiterate around 54.6%, majority of literate patient were seen in drug sensitive patient which again reveals literacy and awareness about treatment of pulmonary TB has causal relationship with development of MDR TB.

Economy of patient does have role among causation of drug resistant pulmonary TB patient, Although patient with poor income can be seen predominately on both drug susceptible and drug resistant cases. Most of drug resistant pulmonary TB patients 72% were seen with very low income which might attribute to increase in frequency of default.

The most important factor in our study we observed is that strong association of frequency of default among drug resistant cases. Most of retreatment cases who had less frequency of default fell into category of Drug susceptible retreatment cases, while those frequency of default more than 2 times were predominantly seen among drug resistant pul.TB

Defaulter >2 were 60.6% among drug resistant patient, most of patient had defaulter frequency greater than 2, while drug sensitive most of patient had decreased frequency of default when compared to drug susceptible retreatment cases.

Similarly we observed marginal increase in drug resistant cases among diabetes mellitus 32%, while drug sensitive were about 21.3% inferential statics showed that diabetes mellitus might contribute to development of drug resistant cases with p value of 0.03 with OR (cl) 1.73 (1.02-2.93).

Interesting observation we had was very low frequency of HIV patients among drug resistant pulmonary TB retreatment cases, which favours toward lesser degree of association of HIV towards development of drug resistant cases.

Association of alcohol and smoking had significant role towards development of drug resistant retreatment cases. Although in our study we had almost equal number of non alcoholic (49.4%) and alcoholic (50.6%) as drug resistant cases. Most of non alcoholic were drug sensitive retreatment case whohad decreased frequency of default which strongly favors towards the development of drug resistant cases, similar observation were also made among smokers.

As so many previous study revealed, we also found to have increased frequency of drug resistant retreatment cases with cavities in the chest x-ray predominance of patient with lung cavities in cxr was suggestive of association of lung cavities towards development of drug resistant cases which can be explained poor penetration of drug in the cavities increased loads of bacilli in cavities .

In our study we observed increased proportion drug resistant cases were seen in group > 45 yrs, male, illiterate, with poor income. Most of them were smoker, alcoholic, we also observed predominance of diabetes, lung cavities incxr among drug resistant cases. Most of drug resistant cases had

strong predisposition towards frequency of default of pulmonary TB treatment. As frequency of default increases, we found increase multidrug resistant TB. Persons with HIV-TB remained same both groups.

CONCULSION

In our study comparing the drug susceptible and drug resistant pul.TB re-treatment cases. We found factors like Age >45, male, TB treatment defaulter > 1 times, diabetes milletus, alcohol and smoking,dominates in drug resistant re-treatment cases. Early identification persons with this risk factor, giving extra care and follow up can reduce prevalence of MDR which is about 20.3%in re-treatment cases.

Special care, nutrition, health workers follow up, for these person at risk will definitely help in controlling multidrug resistant TB and its economic, social burden.

Alcoholic de-addiction centre along with sanatorium type of care for these patients with risk factors, can definitely reduce multi drug resistant tuberculosis, can help the humanity towards pathway of END TB strategy.

BIBLIOGRAPHY

1. World Health Organization Tuberculosis fact sheet http//www.who.int/gtb/publications/fact sheet.
2. Sharma sk, Mohan A. Multi drug resistant tuberculosis. Mediquest 1995;13:14-29
3. Grange JM, Zulma A. The global emergency of Tuberculosis JR Soc Health 2002;122;78-81
4. Mohan A Sharma SK.Epidemiology In Sharma SK Mohan A editors. Tubercuosis.
5. Raviglione MC Snider DE.Global epidemiology of Tuberculosis JAMA 1995;273;2
6. Corbett EL, Watt CJ, Walker N, The growing burden of tuberculosis.Arch Intern Med 2003; 163.
7. Wain H. the story behind the word. Illinois: Charles.Thomas; 1958.
8. Russell DG. Who puts the tubercle in tuberculosis? Nat Rev microbial 2007;5:39-47.Epub 2006 Dec 11.
9. Zumla A, james GD. Granulomatous infections: Etiology and classification. Clin infect Dis 1996;23:146-58.
10. Rook GAW, al attiyah R.Cytokines and Koch phenomenon. Tubercle 1991;72:13-20.
11. Walksman SA. The conquest of tuberculosis. Berkley: university of California press;1964.

12. Morrison A,Gyure KA, Stone J, Wong k, MC Evoty, Koeller K, et al. mycobacterial spindle cell pseudotumor of the brain: a case report and review of the literature. Am J Surg pathol 1999;23:1294-9.

13. Le Gall, Loeiullet L, Delaval P,Thoreux PH, Desures B, Ramee MP.Necrotising sarcoid granulomatosis with and without extrapulmonary involvement. Pathol Res Pract 1996;192:306-13.

14. Brady JG, schutze GE, Siebert R, Horn HV, Marks B, Parham DM. Detection of mycobacterial infections using the dieterle stain. Pediatr Dev pathol 1998; 1:309-13.

15. Gutierrez-Cancela MM, Garcia Marin JF. Comparison of ziehl-neelsen staining and immunohistochemistry for detection of mycobacterium bovis in bovine and caprine tuberculous lesions.J comp pathol 1993;109:361-70.

16. Dinnes J, Deek J,kunst H, GIBSON A,Cummins E,Waugh N, etal. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health technol assess 2007;33:850-8.

17. Kaplan MH, Armstrong D, Rosen p. tuberculosis complicating neoplastic disease: a review of 201 cases. Cancer 1974;33:850-8.

18. Mettler CC. history of medicine. Philadelphia :the Blakiston company;1947.

19. Ghon A. The primary lung focus of tuberculosis in children (translation by king DB). London:Churchill; 1916.

20. Smith DW. Bacillemia in primary tuberculosis. Ann Intern Med 1971;75:479-80.

21. Van Crevel R, Ryan l, Van der merr. Innate immunity to mycobacterium tuberculosis Clin Microbiol 2002;15:294-304

22. Schlesinger LS Bellinger.Phagocytosis of mycobacterium tuberculosis is mediated by human monocyte.J Immunol 1990;144:277-80.

23. Ramaswamy s,JM.molecular genetic bases of antimicrobial agent resistance in mycobacterium tuberculosis Tuber Lung Dis1998; 79:3-29. 1987;68(supp12):5-18.

25. Ovchinnikov YA monastyrskaya GS gubanaov VV,et al.Mol Gen Genet1984;196:536-8

26. Telenti A,Imboden P,Marchesi F,Lowrie D, et al. detection of mutations in M.Tuberculosis Lancet 1993;341:647-50.

27. Taniguchi H, Araamaki H,Nikaido Y, et al. Rifampicin resistance FEMS Microbiol Let 1996;15:103-8.

28. Bercovier H, Kafri O, sela S.Mycobacteria posess small number of ribosomal RNA genes.

29. AmericanThoracic society and centre for disease control. SDiagnostic standard and classification of tuberculosis.Am Rev Respir 1990;149:264-7

30. Mohan A, Pande JN,Sharma SK, Rattan A, Guleria R, Khilnani GC.BAL in Pulmonary TB .QJM 1995;88:269-76.

31. Lincoln EM,Harris LC,Bovornkilli.Endobronchial tuberculosis in children.AM Rev 1958;77;39-61

32. American Thoracic society Diaganostic standard and classification of tuberculosis in adults and children. AM J Dis Child 1969;117: 1376-95.

33. Shoemaker SA.FisherJH,Techniques of DNA.AM REV Respir Dis 1985;131:760-3.

30. Indian council of medical research. Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India.Part I. findings in urban clinics among patients giving no history of previous chemotherapy. Indian J Med 1968;56:1617-30.

31. Anti-tuberculosis drug resistance in the world. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance. WHO/TB/97.229. Geneva: world health organization; 1997.

32. Dye C, Espinal MA, Watt CJ, Mbiaga C, Williams BG. Worldwide incidence of multidrug- resistant tuberculosis.J Infect Dis 2002;185:1197-202.

33. Vareldzis BP, Grosset J, de kantor I,crofton J,Laszlo A, Felten M, et al. Drug resistant tuberculosis: laboratory issues. World health organization recommendationstuber lung Dis 1994;75:1-7.

34. Frieden TR, sterling T, pablos-mendez A, Kilburn JO, Cauthen GM, Dooley SW. the emergence of drug- resistant tuberculosis in new York city. N Engl J Med 1993;328:521-6.

35. Indian council of medical research. Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with systems at chest clinics In India. Part II. Findings in urban clinics among patients giving no history of previous chemotherapy. Indian J Med Res 1969;57:823-35.

36. WHO(world health organisation) THE STOP TB strategy,building on and enhancing DOTS to meet TB related MDG Swizterland Geneva.

37. Marlucia da silva garrido, maria lucia penna,Tomas M. Factors associated with tuberculosis default plos one volume issue 6 e 39134.

38.Bastian I, rigouts L, Van Deum A, portaels F. directly observed treatment, short-course strategy and multidrug-resistant tuberculosis: are any modifications required? Bull World health organ 2000;78: 238-51.

39. Park MH, song EY, park HJ, Kwon SY, Han sk, shim YS. HLA – DRBI and DQBI gene polymorphism is associated with multidrug-resistant tuberculosis in Korean patients. Hum Immunol 2002;63: S33.

40. Mahmoudi A. Iseman MD.Pitfalls in the care of patients with tuberculosis.Common errors and their association with the acquisition of drug resistance. JAMA1993;270:65-8.

41. Datta M. Radhamani MP, Selvaraj R. Paramasivan CN, Gopalan BN, Sudeendra C, et al. critical assessment of smear- positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme. Tuber lung Dis 1993; 74:180-6.

42. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi P, et al. risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. Int J Tuberc lung Dis 2002;6:780-8.

43. Janson J, Kagal A, Bharadwaj R, factors associated with drug resistance in pulmonary tuberculosis. Indian J chest Dis allied sci 2003;45:105-9.

44. Janmeja AK, raj B. acquired drug resistance in tuberculosis in harayana, India. J assoc physicians India 19981;46:194-8.

45. Espinal M, dye C, Raviglione M, Kochi .Rational ‘dots plus’ for the control of MDR-TB.Int J tuberc lung Dis 1999;3:561-3.

46. Espinal MA, Laserson K, Camacho M, Fusheng Z, kim SJ, Tlali RE, et al. determinants of drug resistant tuberculosis: ananylsis of 11 countries. Int J Tuberc lung Dis 2001;5:887-93.

47. SharmaSK, Turga KK, Balamurugan A, Saha PK, Pandey RM, Jain NK, etal. Clinical and genetic risk factors for the development of multidrug- resistant tuberculosis in non- HIV infected at a tertiary care center in India: a case control study. Infect genet evol 2003;3:183-8.

48. Bastian I, rigouts L, Van Deum A, Portaels F. directly observed treatment, short-course strategy and multidrug-resistant tuberculosis: are any modifications required? Bull World health organ 2000;78:238-51.

49. Gupta R, Cegielski JP, Espinal MA, Henkens M, Kim JY, Lambregts-van weezenbeek CS, et al. increasing transparency in partnerships for health- introducing the green light committee.tropMed Int health 2002;7:970-6.

50. Jouveshomme S, Dautzenberg B, bakdach H, Derenne JP. Preliminary results of collapse therapy with plombage for pulmonary disease caused by multidrug-resistant mycobacteria.Am J Respir crit care med 1998;157:1609-15.

51. Gupta R,esinal M, stop TB working group on dots-plus for MDR-TB. A prioritised research agend for DOTS-plus for multidrug- resistant tuberculosis (MDR-TB). Int J tuberc lung Dis 2003;7:410-4.

52. Pomerantz M, Madsen L,Goble M, Iseman M. Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections.Ann thorac surg 1991;52:1108-11.

53. Dinnes J, Deeks J,Kunst H,et al, A systematic review of rapid diagnostic ; Study on default and its factor among tuberculosis journal of health review January-april2015 volume2 issue 1

54. Tariku Dingeta anmante,Tekabe Abdosh Ahemed.Risk factors for unsuccessful tuberculosis treatment outcome Ethiop. J. 2014;28(1):17-21

55. QingZhang,Mohamed Gaafer, Ibrahim bayouny The Scientific world journal volume 2014 article id 672825.

56. Alejandro Gomez,Martin magna-Aquino.Diabetes and other risk factor forMDR TB in a Mexican population.Archives of Medical Research 46(2015)142-48.

57. K Weyer,J Lancaster, J Levin.Determinants of multi drug resistant tuberculosis in southafrica.SAMJ November 2007,97,no,11.

58. Seamawit Hipra,Girmay Medhir,Determinants of multidrug-resistant tuberculosis in patients in ADDIS ABABA.Hipra et.al. BMC public health 2013 13;782.

59. Charoen chuchottwan,Vipa Thanacharwet. Risk factors of multidrug resistant tuberculosis Plos one/ journal.pone.0139986.

60. Schwobel v, Decludt D, Vincent j; multidrug resistant tuberculosis in france BMJ 1998 317:630-631.

61. Jamil Razzi,Shiv Prakash,Kurshid Praveen.Risk factors of multidrug resistant tuberculosis in urban Allahabad.Razzi et. Al. Int J Community Med Public health 2017 jul:4(7).

62. K.Slama N.Tachfouti. Factors associated with treatment default by tuberculosis in fez,Morroco EMJH.VOL 9 No 8.

63. Aysun Sengul, Uiku Akturk. J infect Dev Ctries 9 (8);821-828.

64. Tuberculosis and Hiv in India N Engl J Med 2007; 356:1198-1199.

ANNEXURES

PROFORMA

1. Age	:	18-25 yrs
		25-45 yrs
		>45 yrs
2.Sex	:	Male
		Female
3.Education	:	Illiterate
		Literate
4.Montly income	:	<3000/month
		>3000/month
5.Smoking	:	Smoker- No. of Cigarettes/ Day
		Non-smoker
6.Alcoholic consumption	:	Yes
		No
7.HIV status	:	Negative
		Positive
8.Diabetic status	:	Non-diabetic
		Diabetic-controlled, uncontrolled.
9.a)Treatment history	:	Previously untreated
		Treated

b)Number of previous treatment	:	0-2
		2 and above
c)Category of treatment	:	Defaulter
		Treatment failure
		Relapse
		New case
d)Irregular treatment	:	Intensive phase
		Continuous phase
10.History contact with MDR	:	
11.Cavitations of cxr	:	Yes
		No
12.Other co-morbidities	:	Hypertension
		IHD
		Kidney disease
		Liver disease
13.Others if any	:	
14.Investigation	:	Sputum smear for AFB
		Cxr
		Tridot for HIV,CD4
		LPA

CONSENT FORM

I Mr / Mrs / Miss / _____ have understood the procedure read by the Doctors. I in my whole conscious awareness give consent for the procedure. I understand that the procedure is done in good faith for the best therapeutic results possible. I fully understand the consequences of the procedure. I can resign from the study at any point of time.

Signature

Name :

Date and Time :

Signature of Researcher :

_¯ J¨¦uÀ £iÁ®

Bµõ´a] |ø»¯® : Aµ_ ö{g\P ÷{õ´ ©¸zxÁ©øÚ uõ®£µ® \õÚ÷hõ¶¯®, ö\ßøÚ.

£[S ö£Ö£Áº ö£¯º :

£[S ö£Ö£Áº Gs. :

£[S ö£Ö£Áº ( ) CuøÚUSÔUPÄ®

÷©÷» SÔ¨¤h£mkÒÍ B´Âß ÂÁµ[PÒ GÚUS ÂÍUP¨£mhx.

GßÝøh¯ \¢÷uP[PøÍ ÷PmPÄ®, AuØPõÚ uS¢u ÂÍUPøÍ¨ ö£ÓÄ® Áõ´¨£ÎUP¨£mhx. {õß C¢u B´ÂÀ ußÛaø\¯õPzuõß £[÷PØQ÷Óß. G¢u PõµnzvÚõ÷» G¢u Pmhzv¾® G¢u \mh]UP¾US® Em£hõ©À Â»QU öPõÒÍ»õ® GßÖ AÔ¢x öPõs÷hß.

C¢u B´Ä -»® QøhUS® uPÁÀPøÍ²® £¶÷\õuøÚ ¬iÄPøÍ²® ©ØÖ®]Qaø\ öuõhº£õÚ uPÁÀPøÍ²® ©¸zxÁº £¯ß£kzv öPõÒÍ \®©vUQ÷Óß.

÷{õ¯õÎUPõÚ uPÁÀ £iÁ®

©v¨¤ØS¶¯ I¯õ,

E[PÒ Â¸¨£vß ÷£¶À C¢u B´ÂÀ £[S÷PØS®£i Aß¦hß ÷PmkU öPõÒQ÷Óõ®. C¢u B´ÂÀ Bµõ´a] ÷{õUPzxUPõP uõ[PÒ £¶÷\õuøÚUS Em£kzu £kÃºPÒ uS¢u]Qaø\ u[PÐUS öuõh[P¨£k®. C¢u B´ÂÀ £[÷PØP Â¸¨£® C¸¢uõÀ J¨¦uÀ £iÁzøu £izx¨£õºzxU øPö¯õ¨£® Ck®£iU ÷PmköPõÒQ÷Óß.

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Comparison of predisposing factors towards the development of Drug susceptible and Drug resistance Pulmonary TB Re-treatment cases.

Principal Investigator : Dr. G K Balaji

Designation : PG MD (TB & RD)

Department : Department of TB & RD
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 26.09.2016 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE,
CHENNAI-600 001.

URKUND

Urkund Analysis Result

Analysed Document: Epidemiology.docx MDR TB THESIS.docx (D31238252)
Submitted: 10/12/2017 7:14:00 AM
Submitted By: balajigk7@gmail.com
Significance: 5 %

Sources included in the report:

TheseMathysVanessa.pdf (D12966816)
13 Saravana Ethinder M.pdf (D17227915)
A COMPARATIVE STUDY ON ZIEHL NEELSEN STAINING AND IMMUNOHISTOCHEMICAL ANALYSIS IN SUSPECTED TUBERCULOUS LESIONS.docx (D31146810)
Mrs. Pranali Pingle Life Science.pdf (D29556121)
Gaurav Garg_Pharmacy Thesis_07-Jan-2017.pdf (D24767480)
THESIS COMBINED.docx (D22977108)
tuberculosis report.pdf (D14079217)

Instances where selected sources appear:

34

MASTER CHART

DRUG RESISTANT

SL. NO.	NAME	AGE	SEX	EDUCATION	NEW CASE	TREATMENT HISTORY			CAVITATION ON CHEST XARY	HIV	DIABETIC	SMOKING	ALCOHOLIC
						DEFAULTER	RELAPSE	TREATMENT FAILURE					
1	RAJAN	52	M	ILLITERATE					NO	NO	yes	NO	NO
2	BABU	39	M	ILLITERATE			RELAPSE		NO	NO	No	NO	YES
3	PALANIVEL	47	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
4	PUSHPARAJ	48	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
5	DHANARAJ	53	M	LITERATE		DEFAULTER			YES	NO	yes	NO	YES
6	JAYASHANKAR	41	M	LITERATE	New case				YES	NO	No	NO	NO
7	BOOPATHY	60	M	ILLITERATE		DEFAULTER			YES	NO	yes	NO	NO
8	MANIVELAN	51	M	LITERATE		DEFAULTER			NO	NO	No	NO	NO
9	RANGAN	54	M	LITERATE		DEFAULTER			NO	NO	No	NO	YES
10	KALAISELVAM	64	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
11	CHANDRASEKAR	49	M	LITERATE		DEFAULTER			NO	NO	No	NO	YES
12	NEELAKANDAN	54	M	LITERATE		DEFAULTER			NO	NO	yes	NO	YES
13	VIJAYAKUMAR	50	M	LITERATE			RELAPSE		NO	NO	yes	NO	NO
14	GUNASEELAN	49	M	LITERATE		DEFAULTER			NO	NO	No	NO	NO
15	THIRUSEVAM	47	M	ILLITERATE		DEFAULTER			NO	NO	No	YES	NO
16	MOORTHY	50	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	NO
17	ADHIMOOLAM	50	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
18	ARAVINDHAN	35	M	LITERATE			RELAPSE		YES	NO	No	NO	YES
19	ANGAMUTHU	63	M	ILLITERATE		DEFAULTER			NO	NO	yes	YES	YES
20	MUTHUKUMARAN	51	M	ILLITERATE			RELAPSE		NO	NO	No	YES	YES
21	KUMARASAMY	60	M	ILLITERATE		DEFAULTER			NO	NO	No	YES	YES
22	SAMBANDHAM	69	M	ILLITERATE				TREATMENT FAILURE	NO	NO	No	NO	YES
23	SEKAR	58	M	ILLITERATE		DEFAULTER			NO	NO	yes	YES	NO
24	SUBRAMANI	49	M	LITERATE				TREATMENT FAILURE	NO	NO	No	NO	YES
25	MANIMARAN	56	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
26	GOPALAN	69	M	ILLITERATE				TREATMENT FAILURE	NO	NO	No	NO	YES
27	GOVINDAN	47	M	ILLITERATE		DEFAULTER			YES	NO	yes	YES	YES

28	ELUMALAI	67	M	LITERATE				TREATMENT FAILURE	NO	NO	No	YES	YES
29	FIROZUDDIN	46	M	ILLITERATE		DEFAULTER			NO	NO	No	YES	YES
30	ISMAIL	52	M	LITERATE			RELAPSE		NO	NO	No	YES	YES
31	SAMINATHAN	64	M	LITERATE		DEFAULTER			NO	NO	No	YES	YES
32	ABDULLAH	51	M	LITERATE			RELAPSE		NO	NO	yes	NO	YES
33	SHANMUGASUNDARAN	41	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
34	SOUNDARAJAN	57	M	ILLITERATE				TREATMENT FAILURE	NO	NO	No	NO	YES
35	IBAN	32	M	LITERATE			RELAPSE		NO	NO	yes	YES	YES
36	HARI	38	M	ILLITERATE		DEFAULTER			YES	NO	yes	NO	YES
37	HAMEED ALI	39	M	LITERATE			RELAPSE		NO	NO	No	YES	YES
38	NAGARAJ	50	M	LITERATE		DEFAULTER			YES	NO	No	YES	YES
39	NANDAKUMAR	43	M	LITERATE			RELAPSE		NO	NO	No	YES	YES
40	NARAYANASAMY	71	M	LITERATE		DEFAULTER			NO	NO	No	NO	NO
41	MANAVALAN	72	M	LITERATE				TREATMENT FAILURE	NO	NO	No	NO	NO
42	MAHESHWARAN	31	M	ILLITERATE		DEFAULTER			NO	NO	yes	YES	NO
43	PARTHIBAN	28	M	LITERATE			RELAPSE		YES	NO	No	YES	YES
44	POOVARAN	46	M	ILLITERATE		DEFAULTER			YES	NO	No	YES	NO
45	RAJESH	29	M	LITERATE		DEFAULTER			YES	NO	No	NO	YES
46	SAMEER	34	M	LITERATE		DEFAULTER			YES	NO	No	NO	NO
47	SHEIK MOHAMMED	50	M	ILLITERATE	New case				NO	NO	No	NO	NO
48	DHANDAPANI	43	M	LITERATE		DEFAULTER			NO	NO	No	YES	NO
49	KAMALA	50	F	LITERATE		DEFAULTER			NO	NO	No	NO	YES
50	KRISHNAVENI	52	F	ILLITERATE			RELAPSE		NO	NO	yes	NO	YES
51	SIVAKUMAR	31	M	ILLITERATE		DEFAULTER			YES	NO	No	YES	NO
52	CHITRA	27	F	ILLITERATE			RELAPSE		NO	NO	No	NO	YES
53	SHANTHA	47	F	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
54	SELVAKUMAR	29	M	LITERATE			RELAPSE		NO	NO	No	YES	YES
55	GURUMOORTHY	49	M	LITERATE		DEFAULTER			NO	NO	No	YES	YES
56	TAMILSELVAN	46	M	ILLITERATE			RELAPSE		NO	NO	yes	YES	NO
57	SELVAKUMARI	47	F	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
58	UMAPATHY	44	M	LITERATE			RELAPSE		YES	NO	yes	YES	YES
59	THANGAMANI	43	F	ILLITERATE		DEFAULTER			YES	NO	No	NO	YES
60	RUKMANI	41	F	LITERATE			RELAPSE		YES	NO	No	NO	YES

61	GODHANDAN	44	M	ILLITERATE		DEFAULTER			YES	NO	yes	NO	YES
62	KANNIYAPPAN	59	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
63	MURUGESAN	47	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
64	PARTHASARATHY	39	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
65	MUNIYANDI	48	M	ILLITERATE				TREATMENT FAILURE	NO	NO	No	NO	YES
66	MUTHUKUMARAN	26	M	LITERATE			RELAPSE		NO	NO	No	NO	NO
67	VADIVEL	32	M	LITERATE			RELAPSE		NO	NO	No	NO	NO
68	VEERASAMY	53	M	LITERATE		DEFAULTER			YES	NO	No	YES	NO
69	DHANASEKAR	33	M	ILLITERATE			RELAPSE		NO	NO	No	YES	YES
70	KALIMUTHU	55	M	ILLITERATE		DEFAULTER			NO	NO	No	YES	NO
71	PICHANDI	63	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
72	PURUSOTHAMMAN	32	M	ILLITERATE			RELAPSE		NO	NO	No	NO	YES
73	PACHAIYAPPAN	50	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
74	THANGARASU	43	M	ILLITERATE		DEFAULTER			YES	NO	No	YES	NO
75	KANAGARAJ	40	M	ILLITERATE	New case				NO	NO	No	YES	NO
76	MUBARAK ALI	41	M	LITERATE		DEFAULTER			YES	NO	yes	YES	NO
77	SENTHIL	36	M	LITERATE			RELAPSE		YES	NO	No	YES	NO
78	KALIYAMOORTHY	58	M	LITERATE		DEFAULTER			YES	NO	yes	YES	YES
79	GANESAN	32	M	LITERATE			RELAPSE		YES	NO	No	YES	YES
80	ANBARASU	29	M	LITERATE		DEFAULTER			NO	NO	No	YES	YES
81	PERIYASAMY	68	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
82	JAYARAM	41	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
83	SENTHILKUMAR	38	M	ILLITERATE		DEFAULTER			YES	NO	No	NO	YES
84	SURESHKUMAR	26	M	ILLITERATE			RELAPSE		NO	NO	No	NO	NO
85	SAMIKANNU	59	M	ILLITERATE		DEFAULTER			YES	NO	yes	NO	NO
86	RAMKUMAR	23	M	LITERATE			RELAPSE		NO	NO	No	YES	NO
87	SATYAMOORTHY	44	M	LITERATE		DEFAULTER			YES	NO	No	YES	NO
88	MANIKANDAN	49	M	ILLITERATE		DEFAULTER			YES	NO	yes	NO	YES
89	KRISHNAN	50	M	LITERATE				TREATMENT FAILURE	YES	NO	No	NO	YES
90	LOGU	38	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
91	SIVAKUMAR	36	M	LITERATE		DEFAULTER			NO	NO	No	NO	NO
92	SUDHAKAR	38	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
93	KUMAR	45	M	LITERATE	New case				NO	NO	No	YES	NO

94	RAMAN	37	M	ILLITERATE		DEFAULTER			NO	NO	No	YES	NO
95	MARIAMMAL	60	F	ILLITERATE				TREATMENT FAILURE	NO	NO	yes	YES	NO
96	SELVAM	44	M	LITERATE		DEFAULTER			NO	NO	No	YES	NO
97	PANNEERSELVAM	50	M	ILLITERATE			RELAPSE		NO	NO	yes	NO	NO
98	ARUMUGAM	40	M	LITERATE		DEFAULTER			YES	NO	No	YES	NO
99	GOVINDARAJ	49	M	LITERATE		DEFAULTER			YES	NO	yes	NO	NO
100	DEVAKI	59	F	ILLITERATE				TREATMENT FAILURE	NO	NO	yes	NO	NO
101	DURAI	44	M	LITERATE			RELAPSE		NO	NO	yes	NO	YES
102	VARADHARASU	57	M	ILLITERATE				TREATMENT FAILURE	YES	NO	No	NO	YES
103	KANNAN	39	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
104	ANNADURAI	32	M	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
105	RAJAMANIKAM	72	M	LITERATE			RELAPSE		NO	NO	No	NO	NO
106	RAJAMMBAL	64	F	LITERATE		DEFAULTER			YES	NO	No	NO	NO
107	RAJASEKAR	22	M	ILLITERATE			RELAPSE		YES	NO	No	NO	NO
108	RAJAM	41	F	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
109	MANI	34	M	LITERATE		DEFAULTER			YES	NO	No	NO	NO
110	MUNIYANDI	68	M	LITERATE		DEFAULTER			YES	NO	No	NO	NO
111	MUNUSAMI	54	M	LITERATE		DEFAULTER			NO	NO	yes	NO	NO
112	SARAVANAN	32	M	ILLITERATE			RELAPSE		NO	NO	No	NO	NO
113	MALAR	21	F	ILLITERATE			RELAPSE		NO	NO	No	NO	YES
114	SANGEETHA	24	F	ILLITERATE			RELAPSE		NO	NO	No	NO	YES
115	RUBY	35	F	LITERATE			RELAPSE		YES	NO	yes	NO	YES
116	VALLI	46	F	LITERATE		DEFAULTER			YES	NO	No	NO	YES
117	VANITHA	36	F	LITERATE			RELAPSE		NO	NO	yes	NO	YES
118	CHITRA	37	F	ILLITERATE			RELAPSE		YES	NO	No	NO	YES
119	PRIYANKA	26	F	ILLITERATE			RELAPSE		YES	NO	yes	NO	NO
120	ARUNA	28	F	LITERATE			RELAPSE		YES	NO	No	NO	NO
121	REVATHY	32	F	LITERATE			RELAPSE		NO	NO	No	NO	NO
122	REGAVALLI	48	F	LITERATE		DEFAULTER			NO	NO	No	NO	NO
123	USHA	41	F	LITERATE		DEFAULTER			NO	NO	No	NO	NO
124	SUDHA	49	F	ILLITERATE			RELAPSE		YES	NO	No	NO	NO
125	PANDYAMMA	54	F	ILLITERATE		DEFAULTER			YES	NO	No	NO	NO
126	GANESAN	43	M	ILLITERATE			RELAPSE		NO	NO	No	NO	NO
127	RAVIKUMAR	46	M	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES

128	SINGAMUL	41	M	ILLITERATE			RELAPSE		NO	NO	No	NO	YES
129	SAILAJA	46	F	ILLITERATE		DEFAULTER			YES	NO	No	NO	YES
130	RAGINI	41	F	ILLITERATE			RELAPSE		YES	NO	No	NO	YES
131	KIRUBAKIRI	43	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
132	ANJALAI	39	F	ILLITERATE		DEFAULTER			NO	NO	No	NO	YES
133	KOTHAI	45	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	NO
134	SULOCHANA	50	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	NO
135	PUNIDHA	39	F	LITERATE				TREATMENT FAILURE	NO	NO	No	NO	NO
136	PACHAIYAMMAL	60	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	NO
137	BATHMA	52	F	LITERATE	New case				NO	NO	No	NO	YES
138	RAJESWARI	41	F	ILLITERATE	New case				NO	NO	No	NO	NO
139	JOTHI	36	F	ILLITERATE		DEFAULTER			NO	NO	No	NO	NO
140	BAKIYAM	57	F	LITERATE		DEFAULTER			NO	NO	yes	NO	NO
141	KANNAMMAL	55	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	NO
142	KASTHURI	56	F	LITERATE		DEFAULTER			NO	NO	No	NO	NO
143	SAROJA	59	F	LITERATE		DEFAULTER			NO	NO	yes	NO	YES
144	AMIRTHAVALLI	43	F	LITERATE		DEFAULTER			NO	NO	No	NO	YES
145	RANJITHAM	48	F	LITERATE		DEFAULTER			NO	NO	yes	NO	YES
146	RANIAMMAL	64	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	YES
147	SEETHALAKSHMI	32	F	LITERATE		DEFAULTER			NO	NO	No	NO	NO
148	MANIARASI	39	F	LITERATE		DEFAULTER			NO	YES	No	NO	NO
149	CHELLAMMAL	66	F	ILLITERATE		DEFAULTER			NO	NO	yes	NO	NO
150	PARAMESWARI	44	F	LITERATE		DEFAULTER			NO	NO	yes	NO	NO

DRUG SENSITIVE

SL. NO.	NAME	AGE	SEX	EDUCATION	TREATMENT HISTORY				CAVITATION ON CHEST XARY	HIV	DIABETIC	SMOKING	ALCOHOLIC
					NEW CASE	DEFAULTER	RELAPSE	TREATMENT FAILURE					
1	SARAVANAN	42	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	NO
2	CHELLADURAI	39	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
3	SUSEELAN	41	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
4	CHINNAMANI	48	M	ILLITERATE		DEFAULTER			NO	NO	YES	YES	NO
5	SELVARAJ	53	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	YES
6	ALAGIRI	41	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	YES
7	VASU	32	M	ILLITERATE		DEFAULTER	RELAPSE		YES	NO	NO	NO	NO
8	NATHAMUNI	51	M	ILLITERATE		DEFAULTER			NO	NO	YES	NO	NO
9	SURIYAPERUMAL	54	M	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
10	KAVIARASU	40	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	YES
11	BOOPALAN	49	M	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
12	MANIMARAN	54	M	LITERATE				TREATMENT FAILURE	NO	NO	YES	NO	NO
13	AROGYA DHASS	43	M	ILLITERATE					NO	NO	NO	NO	NO
14	ISAI SELVAN	32	M	ILLITERATE		DEFAULTER			NO	NO	NO	YES	YES
15	SARANGAM	47	M	LITERATE		DEFAULTER	RELAPSE		NO	NO	YES	NO	NO
16	SINGAMUTHU	50	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
17	ACHUDHANAND	42	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	YES
18	NANDHAGOPAL	35	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
19	PALLAVAN	63	M	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
20	PERIYANDI	51	M	ILLITERATE				TREATMENT FAILURE	NO	NO	NO	YES	YES
21	SUBBURAYAN	60	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
22	SUBRAMANI	69	M	LITERATE			RELAPSE		YES	NO	YES	NO	NO
23	MALLAN	58	M	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
24	DILLIBABU	39	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
25	SYED ALI	56	M	ILLITERATE		DEFAULTER			NO	NO	YES	NO	NO
26	DAKSHINA	69	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
27	VIJAYAKUMAR	47	M	ILLITERATE			RELAPSE		NO	NO	NO	YES	YES
28	VIKRAM	23	M	ILLITERATE		DEFAULTER			NO	NO	YES	NO	NO
29	KARTHIKEYAN	39	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO

30	RAMMOORTHY	52	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	YES
31	JEYASHANKAR	64	M	ILLITERATE		DEFAULTER			NO	NO	NO	YES	NO
32	SANTHAKUMAR	31	M	ILLITERATE		DEFAULTER			NO	NO	YES	NO	YES
33	KUMARESAN	41	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
34	SUDHAKARAN	41	M	ILLITERATE		DEFAULTER			NO	NO	NO	YES	NO
35	KARUNAKARAN	32	M	ILLITERATE			RELAPSE		NO	NO	YES	NO	NO
36	KATHIRVEL	38	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
37	PATTABIRAMAN	39	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
38	THYAGARAJAN	50	M	ILLITERATE		DEFAULTER			NO	NO	NO	YES	NO
39	BAKIYANATHAN	43	M	LITERATE		DEFAULTER			YES	NO	YES	NO	NO
40	ADHIKESAVAN	71	M	LITERATE			RELAPSE		NO	NO	NO	NO	YES
41	SULAIMANN	72	M	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
42	MOHAN	31	M	LITERATE			RELAPSE		NO	NO	YES	NO	NO
43	SUNDHARBABU	28	M	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
44	MARIMUTHU	43	M	LITERATE			RELAPSE		NO	NO	NO	NO	NO
45	ANANDHARAJ	29	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	YES
46	ARULSELVAM	34	M	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
47	SIVAKUMAR	50	M	ILLITERATE		DEFAULTER			NO	NO	YES	NO	NO
48	PONNRASU	43	M	LITERATE			RELAPSE		NO	NO	NO	NO	NO
49	KRISHNA	32	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	NO
50	BHARANI	52	M	ILLITERATE			RELAPSE		NO	NO	NO	YES	NO
51	ELANGOVAN	31	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	YES
52	BASHA	27	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
53	NAGESWARAN	44	M	ILLITERATE		DEFAULTER			YES	NO	NO	NO	NO
54	PARAMESHWAR	29	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
55	SANTHANAM	39	M	ILLITERATE		DEFAULTER			NO	NO	NO	YES	NO
56	KOTI	46	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	YES
57	JANARTHANAN	47	M	LITERATE			RELAPSE		NO	NO	YES	NO	NO
58	ARUN	44	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	YES
59	KUPPUSAMY	43	M	ILLITERATE		DEFAULTER			NO	NO	YES	NO	NO
60	KANRAYAN	41	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	YES
61	JABARDHASS	44	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	NO
62	LINGESWARAN	35	M	ILLITERATE			RELAPSE		NO	NO	NO	NO	YES
63	LOGANATHAN	47	M	ILLITERATE		DEFAULTER			YES	NO	NO	NO	NO

64	MANICKAM	39	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
65	NITHYARAMAN	48	M	LITERATE			RELAPSE		NO	NO	NO	NO	YES
66	NAGARJUNAN	26	M	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
67	HAMEED	32	M	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
68	RIYAZ KHAN	39	M	LITERATE				TREATMENT FAILURE	NO	NO	YES	NO	NO
69	ASIF ALI	33	M	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
70	IJAZ MOIDHEEN	55	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
71	KALAIVANAN	29	M	LITERATE		DEFAULTER			YES	NO	NO	YES	NO
72	THILLAIRAJ	32	M	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
73	RAJA	23	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
74	BALAKRISHNAN	43	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
75	DHANAPAL	40	M	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
76	PREMNATH	41	M	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
77	RAMALINGAM	36	M	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
78	DEVARAJ	58	M	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
79	ANNADURAI	48	M	LITERATE			RELAPSE		NO	NO	NO	NO	YES
80	VELURAJ	29	M	LITERATE			RELAPSE		NO	NO	NO	NO	NO
81	SETHURAMAN	68	M	LITERATE			RELAPSE		NO	NO	NO	YES	YES
82	JOTHI KRISHNAN	41	M	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
83	CHANDRAN	38	M	LITERATE		DEFAULTER			NO	YES	NO	NO	NO
84	RAJA	26	M	LITERATE			RELAPSE	TREATMENT FAILURE	NO	NO	NO	NO	NO
85	SANTHINI	34	F	LITERATE		DEFAULTER			NO	NO	YES	NO	YES
86	KOTESWARI	23	F	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
87	KOMALA	33	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
88	KALAIVANI	26	F	LITERATE		DEFAULTER			YES	NO	YES	NO	NO
89	AMULU	44	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
90	LALITHA	38	F	LITERATE			RELAPSE		NO	NO	NO	NO	NO
91	LOKESWARI	36	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
92	SAMEERA BHANU	38	F	LITERATE			RELAPSE		NO	NO	NO	NO	NO
93	PUSHPALAKSHMI	45	F	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
94	PANCHAVARNAM	37	F	LITERATE		DEFAULTER			NO	NO	YES	NO	YES
95	AMUDHA	28	F	LITERATE		DEFAULTER			NO	NO	NO	YES	YES
96	CHANDRAKALA	44	F	LITERATE		DEFAULTER			YES	NO	NO	NO	NO

97	LAKSHMI	38	F	LITERATE					NO	NO	NO	NO	NO
98	LOGAMMAL	40	F	ILLITERATE		DEFAULTER			NO	NO	YES	NO	YES
99	VIJAYARANI	49	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
100	SUJATHA	44	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
101	SRIVANI	44	F	LITERATE			RELAPSE		NO	NO	NO	YES	YES
102	JEYASHREE	57	F	ILLITERATE		DEFAULTER			NO	NO	NO	NO	NO
103	AMBIKA	39	F	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
104	AMARAVATHI	32	F	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
105	ARULSELVI	21	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
106	KALPANA	38	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
107	KANAGAVALLI	22	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
108	MENAGA	41	F	LITERATE			RELAPSE		YES	NO	YES	NO	NO
109	NOORJAHAN	34	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
110	ASARAF FATHIMA	26	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
111	MERY	54	F	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
112	LATHA	32	F	LITERATE		DEFAULTER			YES	NO	YES	NO	NO
113	UMA	21	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
114	SIVAKAM	46	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
115	SAMPOORNA	35	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
116	PAVITHRA	24	F	LITERATE		DEFAULTER			YES	NO	NO	YES	NO
117	RAJALAKSHMI	36	F	LITERATE			RELAPSE		NO	NO	NO	NO	NO
118	RAMADEVI	37	F	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
119	DEIVANAI	32	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
120	PREMA	28	F	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
121	LEELAVATHY	32	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
122	REKHALAKSHMI	31	F	LITERATE		DEFAULTER			YES	NO	NO	YES	NO
123	SIVASHAKTHI	41	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
124	SURYAKALA	49	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
125	SHEELA	30	F	LITERATE			RELAPSE		NO	NO	NO	NO	YES
126	JENABAAI	43	F	LITERATE		DEFAULTER			NO	NO	NO	YES	NO
127	YAMUNA	46	F	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
128	GANGA	41	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
129	JAMUNA	46	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
130	PRABHA	41	F	LITERATE		DEFAULTER			NO	NO	YES	NO	NO

131	PADHMINI	43	F	LITERATE			RELAPSE		NO	NO	NO	YES	YES
132	SUSEELAMMAL	56	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
133	JANAKI	45	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
134	VAIDHESWARI	50	F	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
135	ANANDHI	39	F	LITERATE			RELAPSE		NO	NO	NO	YES	NO
136	SELVARANI	60	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
137	SAVITHRI	52	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
138	MULLAIRANI	41	F	LITERATE		DEFAULTER			YES	NO	YES	NO	NO
139	MANJULA	36	F	LITERATE				TREATMENT FAILURE	NO	NO	NO	NO	NO
140	GOMATHY	57	F	LITERATE		DEFAULTER			NO	NO	YES	NO	NO
141	HEMAVATHY	44	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
142	SARALA	59	F	LITERATE			RELAPSE		NO	NO	NO	YES	NO
143	SILAMBARASI	39	F	LITERATE		DEFAULTER			YES	NO	YES	NO	NO
144	RASHIDHA	43	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
145	FARIDHA	48	F	LITERATE		DEFAULTER			NO	NO	NO	NO	YES
146	PONNI	64	F	LITERATE		DEFAULTER			YES	NO	NO	NO	NO
147	VASANTHI	32	F	LITERATE		DEFAULTER			NO	NO	NO	NO	NO
148	DILLIRANI	39	F	LITERATE			RELAPSE		NO	NO	NO	NO	NO
149	PARIMALA	66	F	LITERATE		DEFAULTER			NO	NO	NO	YES	YES
150	DHAYALAMMAL	55	F	LITERATE		DEFAULTER			YES	NO	YES	NO	NO