Tuberculosis and Co-infection with HIV-AIDS

Tuberculosis and Co-infection with HIV-AIDS:

Its History, Cause and Spread

Edited by

Pranveer Singh

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Dedicated to my Parents (Mummy & Papa)
and Grandparents (Baba & Aazi)

TABLE OF CONTENTS

PREFACE

Epidemiology deals with the distribution pattern, cause, and effect of disease in a population. It analyzes the causative and risk factors for a disease over a period of time, so as to arrive at preventive measures and policy on the part of stakeholders. The science of epidemiology involves the collection, design, and analysis of statistical data, and some mathematical modeling to draw meaningful interpretation. Major sub-disciplines of epidemiology include forensic epidemiology, occupational epidemiology, investigation of the root causes of disease, outbreak, surveillance, screening, and biomonitoring.

Tuberculosis is a highly contagious disease. It is usually communicated from person to person, via droplets containing infectious particles. Tuberculosis infection is airborne, and follows person to person communication. Drug-resistant tuberculosis (DR-TB) is posing a serious threat to tuberculosis control measures in India. Tuberculosis coupled with co-infections, like HIV, in an immune-compromised individual, complicates the pathological state of the infected person. Tuberculosis is difficult to diagnose in an individual with HIV by conventional diagnostics, and cannot be cured by conventional therapy. This may pose challenges for the control of TB and HIV epidemics.

Madhya Pradesh is home to one of the largest tribal populations in India. Tribal people, owing to lack of awareness, lack of education and poor socio-economic conditions, fall prey to diseases like tuberculosis, which is a poor man's disease. Tribal people resort to 'black magic', witchcraft, or sometimes traditional medicine, but avoid modern allopathic treatment, which further aggravates the disease. This also makes the affected person a potential reservoir, transmitting the disease to others. Therefore, it is very important to carry out an epidemiological survey to address the issues involved with respect to tuberculosis in particular, which has now switched to drug resistant TB (MDR/XDR-TB) and HIV-AIDS co-associated with TB.

Current epidemiological study has focused on the selected regions of Madhya Pradesh, based on previous records of TB and HIV prevalence,

and looks into socio-economic, historical factors, as well as clinical factors, responsible for the emergence, prevalence and control of TB. The strategy involves meta-analysis and statistical analysis of previously available and current data, laboratory analysis, and mathematical modeling to study its projection and control. The main objectives include; studying the historical background and overview of tuberculosis in the identified regions of Madhya Pradesh; studying the efficacy of modern TB diagnostics coupled with herbal treatment protocols under traditional healers by tribes within the study area; studying the epidemiology of tuberculosis, including rate of incidence, prevalence, and spread; and study of the epidemiology of HIV and associated co-infection, particularly tuberculosis, including distribution and gender-based relationships. Results have clearly shown the efficacy of combined treatment which includes modern diagnostics, coupled with treatment using herbal medicine. Trends and seasonality analysis have established a season-dependent peak and fall, and a definite trend of tuberculosis infection in Madhya Pradesh. The epidemiology of HIV+TB has established gender-based prevalence, and also distribution across different blocks and sub-divisions of the Anuppur district of Madhya Pradesh.

LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immuno Deficiency Syndrome
ANC	Ante Natal Care
ART	Antiretroviral Therapy
BAL	Broncho Alveolar Lavage
BCG	Bacilli Chalmette Guerin
BMHRC	Bhubaneswar and Bhopal Memorial Hospital and Research Center
BRAC	Bangladesh Rural Advancement Corporation
BSI	Botanical Survey of India
CDC	Center for Disease Control and Prevention
C&DST	Culture and Drug Susceptibility Testing
CIMAP	Central Institute of Medicinal and Aromatic Plants
CP	Continuation Phase
CSF	Cerebrospinal Fluid
CT	Compound Tomography
DMC	Designated Microscopy Centers
DR	Drug-Resistant
DR-TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Testing
DOTS	Directly Observed Treatment Short-Course
DOTS	Direct Observed Treatment Strategy
EPTB	Extra Pulmonary Tuberculosis
EQA	External Quality Assessment
XDR	Extensively Drug Resistant
FIND	Foundation for Innovative New Diagnosis
HAART	Highly Active Antiretroviral Therapy
HDI	Human Development Index
HIS	Health Information System
HIV	Human Immune Virus
ICMR	Indian Council of Medical Research
INH	Isoniazid
IUATLD	International Union against Tuberculosis and Lung Disease
IVDU	Intravenous Drug Users
LCC	Leprosy Coordinating Committee

LPA	Line Probe Assay
LTBI	Latent TB Infection
LTB	Latent Tuberculosis
MCI	Medical Council of India
MDR-TB	Multi-Drug Resistant Tuberculosis
MOTC	Medical Officer TB Control
MOTT	Mycobacteria Other Than Tuberculosis
NGOs	Non-Governmental Organization
NTM	Non Tuberculosis Mycobacterium
NTP	National Tuberculosis Programme
NTI	National Tuberculosis Institute
NRLS	National Reference Laboratories
NIRT	National Institute for Research of Tuberculosis
NITRD	National Institute of Tuberculosis and Respiratory Disease
OI	Opportunistic Infection
PMDRT	Programmatic Management on Drug-Resistant Tuberculosis
PTB	Pulmonary Tuberculosis
PWB	Patient Wise Box
RMP	Rifampicin
RNRC	Regional Medical Research Center
RNTCP	Revised National Tuberculosis Control Programme
RRDR	Rifampin Resistance Determining Region
SCC	Short Course Chemotherapy
SNP	Single Nucleotide Polymorphism
STS	Senior Tuberculosis Supervisor
TB	Tuberculosis
TDR	Tropical Disease Research
TFRI	Tropical Forest Research Institute
TST	Tuberculin Skin Test
TU	Tuberculosis Units
UMTS	Union Mission Tuberculosis Sanatorium
UNAIDS	United Nations Acquired Immunodeficiency Syndrome
WHO	World Health Organization
WHA	World Health Assembly

CHAPTER I

EPIDEMIOLOGY OF TUBERCULOSIS: HIV-AIDS CO-INFECTION

PRANVEER SINGH, RAMSEVAK KACHHI, VIKAS KUMAR SAKET

Abstract

Tuberculosis caused by the bacterium *Mycobacterium tuberculosis* is a highly contagious disease. It usually communicates from person to person, via droplets containing infectious particles. Tuberculosis has threatened the human race since its inception, due to its social and economic aspects, in addition to its medical and physiological morbidity. Tuberculosis has become more pathogenic and less curable, in its drug-resistant TB (DR-TB) forms, and with the co-associated infection of HIV-AIDS. Tuberculosis usually affects the lungs, but other organs may also be affected. Where the lungs are the site of infection, tuberculosis is known as pulmonary tuberculosis (PTB), however, if other parts (brain, bones, glands, etc.) are affected, it is known as extrapulmonary tuberculosis (EPTB). Countries with the highest burden of tuberculosis and HIV invariably have higher numbers of tuberculosis cases, as observed in the Asian and African continents. India shares 20 percent of the global tuberculosis burden, with the highest number of tuberculosis cases for an individual country. Madhya Pradesh, housing the largest tribal population, is particularly vulnerable to the combined threat of HIV+TB, due to the lack of education, awareness, and other socio-economic factors. India, with its improvised initiatives of RNTCP and DOTs, has considerably limited the prevalence of HIV and TB. The need of the hour is an indomitable political will to develop health policies which are largely based on empirical data and technical know-how for positive intervention.

1.1 Background

Tuberculosis is thought to be the oldest disease of man, believed to be as old as the history of humankind (Rosenblatt 1973, Dye et al. 2008). Since the beginning of human life, tuberculosis continues to be the major cause of human morbidity and mortality (Agrawal et al. 2012). There are innumerable diseases which have surfaced alongside tuberculosis in humans, but over the course of time, these have either been completely eradicated, or tamed. However, tuberculosis has continued to be a great killer since the beginning of human civilization (Wirth et al. 2008). The impact of tuberculosis has encompassed the social, as well as the economic domains of human life, since time immemorial.

Vedas (*vide infra*) references this disease, referring to it as an ancient scourge, and 'rajayakshma' (meaning 'wasting disease'). Hippocrates (460-377 BC) has named this disease as 'phthisis', which, in Greek, means 'to consume/to spit and to waste away' (Garrison 1921, Flick 1925, Webb 1936, Canci et al. 1996, Daniel 2006). Around 460 BC, tuberculosis was also associated with the term 'consumption', meaning 'wasting of the body' due to pulmonary tuberculosis (PTB). Hebrew references this disease as 'schachepheth', meaning 'waste away' which can be found in the Bible (Rosenblatt 1973, Daniel 2011). However, Prof. J.L. Schonlein coined the term 'tuberculosis' for the first time (Rosenblatt 1973). The word 'tuberculosis' has its origin in the Latin word 'tubercula', which refers to 'a small lump'. Since the time of J.L. Schonlein, who gave a name to the disease, numerous names have been employed by various workers to refer to tuberculosis (Flick 1925, Dubos et al.1952, Waksman 1964, Gutierrez et al. 2005). Oliver Wendell Holmes called it 'white plague' (Dubos et al. 1952).

Tuberculosis, in its acute and progressive stage, was referred to as 'galloping consumption' (Grigg 1958, Rubin 1995). Pulmonary TB (PTB), or tuberculosis of the lungs, has been referred to as *Tube pulmonali*, while abdominal tuberculosis is referred to as *Tabesmesenterica* (Nuland 1988). Tuberculosis cervical lymphadenitis is referred to as 'scrofula', 'king's evil', and 'stroma', while the term *Lupus vulgaris* is reserved for cutaneous TB, (Zink et al. 2001).

1.2 Tuberculosis in Ancient Times

It is generally believed that TB first originated in cattle, before humans contracted the disease via zoonosis (Pearce-Duvet 2006). TB has references in Vedas, where it is referred to as 'Rajayakshma'.

Muncamitvahavisajivanayakam
Agnatayakshmadutarajayakshma (RV, X, 116, 11)

In Krishna *Yajurveda Samhita,* there is a reference to the way Soma (Moon) had contracted 'Yakshma' (Samhita et al. 1973). Later, 'Yakshma' has evolved into 'Rajayakshma' owing to the royal (Kingship and ruler) status of Soma. In Sanskrit also, this disease is referred to as 'Rajayakshma', 'Ksayah', and 'Sosa' (*Vagabhata, Ast-s and Ast-hrd, Nidan V, 1-2)* and *(CharakaSamhita, Chikitsasthanam VII, 11)* (Debnath et al.1998).

Pathological changes of TB were first reported, and described in holistic detail, in the skeletal remains of Neolithic man. Empirical evidence for TB lesions of bone was reported in Egyptian mummies from 3400 B.C. (Meachen 1936, Cave 1939, Nerlich et al. 1997). Causative bacterium for TB, the *Mycobacterium tuberculosis* has been demonstrated in the mummy of a five-year-old child (Zimmerman 1979, Crubezy et al. 1998). Ancient Chinese literature has referred to this disease as 'lung cough' or 'lung fever', giving a remote reference to the disease as tuberculosis. A reference for TB can also be found in the code of Hammurabi of the Babylonian era.

Greek academicians Homer (800 B.C), Hippocrates, Aristotle (384-322 B.C), Plato (430-347 B.C), Galen (129-199), and Vegetius (420), have extensively referred to a disease similar to tuberculosis, which was referred to as 'consumption' (Kapur et al. 1994). AI Razi (850-953) and IbnSina (980-1037), the famous Arabic physicians, have correlated lung activities with skin ulcers (Morse et al. 1964). Literature of the Middle Ages is replete with evidence of the healing touch of monarchs to cure 'scrofula' (King's Evil). King Charles II was claimed to have cured an astounding number of patients of 'scrofula' through his divine healing touch around 1629 BC (Wilson 1990, Evans 1994). London used to provide death certificates for the disease, referring to it as 'consumption', suggesting tuberculosis. In ancient times, people were divided about the contagious nature of TB, and there was a school of thought that was vehemently opposed to the idea of TB being contagious. The Republic of Lucca is credited with pioneering the legislation aimed at controlling TB.

This has given a fillip to the slew of such legislation in countries like Italy and Spain (Dubos and Dubos 1952, Formicola et al. 1987, Canci et al.1996, Rothschild 2003).

Benjamin Marten, an English physician, provided an elaborate hypothesis about TB in his seminal study *A New Theory of Consumption.* He opined that certain species of 'animalcule', or microscopically small creatures, cause tuberculosis. He further suggested that once these organisms gain entry to the body, they can generate lesions and symptoms of the disease (Webb 1936, Mensforth et al. 1978, Rubin 1995, Brosch et al. 2002).

1.3 Tuberculosis in Arts and Literature

'Youth grows pale, and specter thin, and dies'
John Keats, *Ode to a Nightingale*

TB has been extensively described in literature and works of fiction. The immortal dramatist William Shakespeare described a 'consumptive lover' in his play *Much Ado about Nothing* and 'scrofula' in *Macbeth* (Webb 1936, Vickers 2007). Charles Dickens has also described the pains of Little Blossom in *David Copperfield*, while Thomas Mann, in *The Magic Mountain* gives a detailed sketch of a TB sanatorium (Webb 1936, Saville et al. 2002). Characters like Little Eva in Harriet Beecher's Stowe's *Uncle Tom's Cabin,* Milly Theale in Henry James' *The Wings of the Dove,* and Marguerite Gautier in Alexander Dumas' *La Dame Aux Camellias* are also described as having suffered from tuberculosis (Webb 1936, Lintz 2005).

Tuberculosis is a democratic disease, and it can happen to anyone, irrespective of class, caste, or status. However, by and large, it is a 'poor man's disease'. Innumerable personalities, statesmen, writers, poets, performers, and artists have been known to contract tuberculosis (Webb 1936, Moore 1993, Rubin 1995, Gaskell 2009). Tuberculosis consumed the families of Ralph Waldo Emerson and Henry David Thoreau. Many famous Indians, like mathematician Shrinivasa Ramanujan, writer Munshi Premchand, and Kamla Nehru, have also died of tuberculosis. The list is not inclusive, as many more Indians have succumbed to tuberculosis (Webb 1936, Mohan et al. 2009, Daniel 2011).

1.4 Tuberculosis at a Glance

Tuberculosis, since its inception, has refused to die, and relentlessly threatens the human race, owing to its social and economic impact. This is

in addition to its medical and physiological morbidity. Even in the current scenario, when humans have perceptibly conquered different aspects of life through scientific prowess, they have not been able to halt the aggressive and progressive march of tuberculosis. In fact, tuberculosis has become more pathogenic and incurable, in its new form as drug-resistant TB (DR-TB). Its new-found company in the human immunodeficiency virus (HIV), leading to acquired immunodeficiency syndrome (AIDS), has made it one of the worst of the scourges which have the potential of wiping out the human race, if allowed to progress unchecked (Getahun et al. 2010). To some extent, the developed world has claimed to control the disease by improving the human development index (HDI), but developing countries, which house the majority of the population, continue to grapple with the brutal onslaught of tuberculosis. Realizing its killing potential, in 1991, the World Health Assembly (WHA) passed a resolution recognizing TB as a major global public health problem, and set out twin targets for a national tuberculosis program, the first being the detection of 70 new smear-positive patients, and the second, providing a conclusive cure for 85 percent of similar cases, so as to rejuvenate global TB programmes (Walker et al. 1981, World Health Organization 1991, Whalen et al. 1995). Following this, the World Health Organization (WHO) declared TB a 'global emergency' in 1993, citing its lethal potential (Grange et al. 2001). The directly observed treatment strategy (DOTS) was unveiled in 1994, and has become the globally recommended strategy for tuberculosis control, adopted all over the world and establishing itself as a standard protocol for tuberculosis cure (Bayer et al.1995, Sharma et al. 2009).

1.4.1 Tuberculosis Epidemiology

Tuberculosis is a highly contagious disease. It usually communicates from person to person via droplets containing infectious particles. Tuberculosis infection is air-borne and follows person-to-person communication. The tendency to contract the disease is directly correlated with the index case, the bacillary burden in sputum, and frequency of cough in the index case (Comstock et al. 1974). Social factors include overcrowding, lower socio-economic status, and unhygienic, unsanitary living conditions which all play a role in acquiring the infection. It is caused by the bacterium *Mycobacterium tuberculosis* (Boire et al. 2013). Tuberculosis usually infects and affects the lungs, but other organs may also be affected. Where lungs are the site of infection, tuberculosis is referred to as pulmonary tuberculosis (PTB), however, if other parts (brain, bones, glands, etc.) are affected, then it is called extrapulmonary tuberculosis (EPTB) (Sakula

et.al. 1982, Saket et al. 2017). In India, the mortality caused by tuberculosis is higher than that of any other infectious disease. World Health Organization (WHO) TB statistics for India estimated there were 2.2 million cases for India, out of a global incidence of 9.6 million in 2015 alone (WHO 2015). According to an estimate, of the total tuberculosis cases of around 14 million, 3.5 million are sputum positive. One million sputum positive cases are added every year (Mishra and Mulani 2013).

1.5 The Mycobacteria

Mycobacterium is the main causative organism of tuberculosis. The generic name *Mycobacterium* was coined and introduced by Lehmann and Neumann in 1896 (Lehmann and Neumann 1896). The fungus (Myco)-like appearance of the bacterium has given it a name, *Mycobacterium*. Genus *Mycobacterium* is the only member in the family *Mycobacteriaceae* and the order *Actinomycetales*, with over 150 species of the genus (Runyon 1959, Central TB Division New Delhi 2008).

Mycobacteria are aerobic, non-motile bacteria-possessing capsules, but they do not form endospores. The cell wall is comparatively thicker, waxy, and rich in mycolic acid/mycolates. The cell wall is further supplemented with a hydrophobic mycolate layer and a peptidoglycan layer, held together by arabinogalactan. The optimum temperature for growth varies from 25°C to 50°C. *Mycbacteria* are classical acid fact organisms, taking Fite's stain, Ziehl-Neelsen stain, and Kinyoun stain (Figure 1) (Bhamidi 2009). *Mycobacterium* usually resists decolorization by a weak mineral acid after staining with one of the aryl-methane dyes, which constitutes very important characteristics of the bacterium. However, acid fastness is not unique to *Mycobacteria*, as *Nocardia* species and bacterial spores also display acid fast character. The genus *Mycobacterium* can better be defined based on the chemical structure of the mycolic acid and its antigenic structure (Runyon 1959, Grange et al. 1997, Chapman 1982, Cosma et al. 2003, Appelberg 2006).

The World Health organization (WHO) has classified *Mycobacterium tuberculosis* in risk group III, owing to its air-borne infectious route. The number of TB bacilli required to infect a person is known as the 'quantum of infectious dose' and is as low as 10 TB bacilli, indicating its infection potential. The infectious TB bacilli form aerosols and can circulate in the environment as moist droplets (Bhatia 2009).

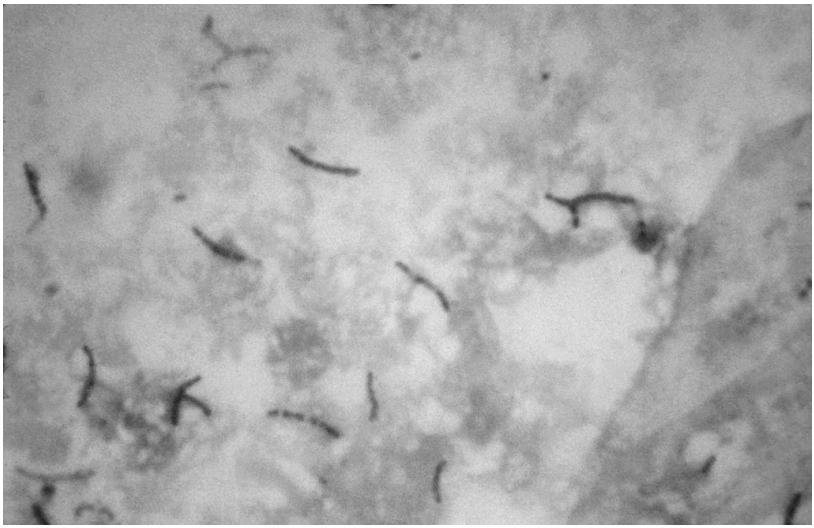

Fig. 1-1 Tuberculosis bacilli in Ziehl-Neelsen stain

1.5.1 Clinical and Taxonomic Classification

There may be anonymous, unclassified, tuberculoid, paratubercle or non-tuberculosis *Mycobacteria* (NTM), or *Mycobacteria* other than tuberculosis (MOTT). Runyon has classified these into several groups (Figure 2) (Runyon 1959, Marais et al. 2010). Clinical classification of *Mycobacterium* facilitates diagnosis and treatment. It could be classified into *Mycobacterium tuberculosis complex (MTBC)* which includes *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* and *M. leprae*, which causes Hansen's disease, or leprosy. *Non-tuberculous Mycobacterium* (NTM) can cause pulmonary disease which resembles tuberculosis, lymphadenitis, skin disease, or disseminated disease (Figure 2, Table 1) (McCann et al. 2009).

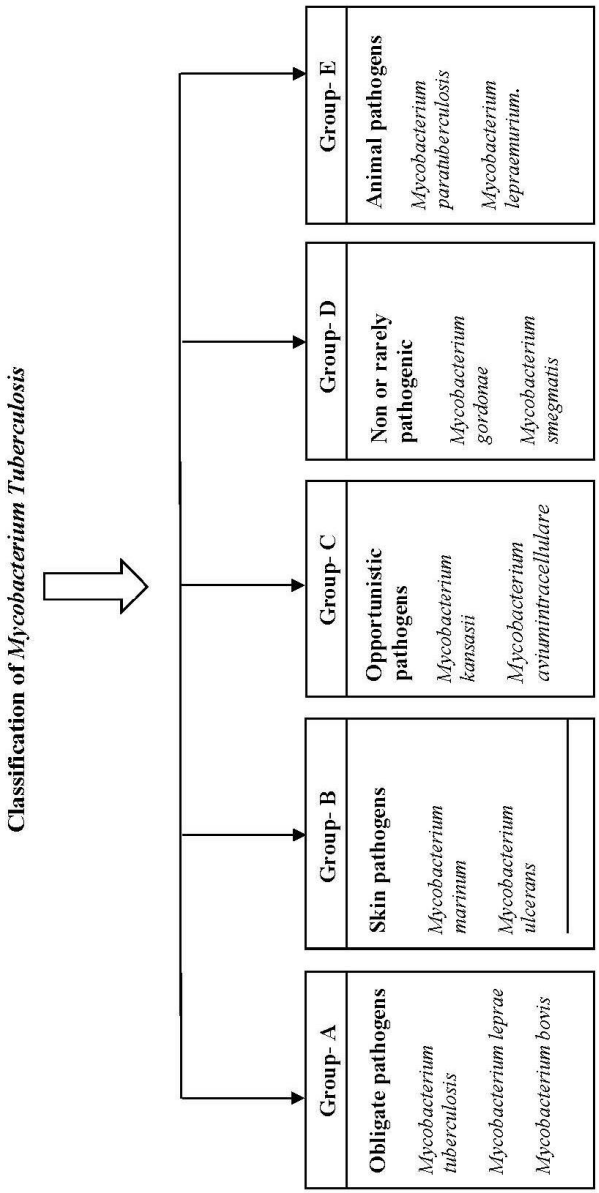

Fig. 1-2 Schematics of classification of *Mycobacterium Tuberculosis*

Table 1-1 Types of tuberculosis, affected organs and causative organisms

S.No.	Type of Tuberculosis	Affected organ	Causative organism
1.	Pulmonary tuberculosis	Lungs	*Mycobacterium tuberculosis*
2.	Lower lung field tuberculosis	Lungs	*Mycobacterium tuberculosis*
3.	Endo-bronchial tuberculosis	Tracheobronchial tree	Mycobacterium tuberculosis
4.	Pleural effusion tuberculosis	Pleural cavity	Mycobacterium tuberculosis
5.	Silico-tuberculosis	Upper mid and lower lobe of lung	Mycobacterium tuberculosis
6.	Abdominal tuberculosis	Gut, peritoneum, abdominal lymph nodes, and rarely liver, spleen and pancreas	Mycobacterium tuberculosis
7.	Neurological tuberculosis	Central nervous system, meninges, sylvian fissures, basal cisterns, brainstem, and cerebellum, spinal cord, nerve roots	*Mycobacterium tuberculosis*
8.	Musculo-skeletal tuberculosis	Spine, hip, knee, intervertebral disks in the dorsolumbar regions, cervical vertebrae, craniovertebral junction, sacrum, sacroiliac joints, Ribs, pelvic bones, small bones of foot, long bones, sternoclavicular joint, sternum and bursae	*Mycobacterium tuberculosis* complex (MTBC)

9.	Cardiac tuberculosis	Endocardium	*Mycobacterium tuberculosis*
10.	Cutaneous tuberculosis	Skin	*Mycobacterium tuberculosis, Mycobacterrium bovis*
11.	Lymph node tuberculosis	superficial lymph nodes, posterior and anterior cervical chains or the suprascapular fossae but others like submandibular, periauricular, inguinal and axillary groups	*Mycobacterium tuberculosis*
12.	Ocular tuberculosis	Eyes	*Mycobacterium tuberculosis*
13.	Mammary tuberculosis	Breast	*Mycobacterium tuberculosis*
14.	Genitourinary tuberculosis	Kidney and genital organs	*Mycobacterium tuberculosis*
15.	Tuberculosis in pregnancy	Lungs, bones, kidneys, uterus, spine, nervous system and brain	*Mycobacterium tuberculosis*
16.	Disseminated and miliary tuberculosis	Lungs, liver and spleen	*Mycobacterium tuberculosis*
17.	Drug-Resistant tuberculosis	Lungs and other parts of body	*Mycobacterium tuberculosis*

1.6 Types of Tuberculosis

The type of tuberculosis depends on the organ affected, such as pulmonary tuberculosis, lower lung field tuberculosis, endo-bronchial tuberculosis, pleural effusion tuberculosis, silico-tuberculosis, abdominal tuberculosis, neurological tuberculosis, heart tuberculosis, musculo-skeletal tuberculosis, cutaneous tuberculosis, lymph node tuberculosis, ocular tuberculosis, breast tuberculosis, tuberculosis in pregnancy, female genital tuberculosis, genitourinary tuberculosis, tuberculosis in chronic renal failure, disseminated

and miliary tuberculosis, tuberculosis and human immunodeficiency virus infection, tuberculosis in children, and drug-resistant tuberculosis (Table 1) (Rylance et al. 2010). The main types can be classified as pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (PTB).

1.6.1 Pulmonary Tuberculosis (PTB)

Pulmonary tuberculosis (PTB) is a chronic and highly contagious disease caused by the *Mycobacterium tuberculosis. Mycobacterium africanum* and *Mycobacterium bovis* are the other *mycobacteria* which can lead to PTB. Patients having PTB with cavity lesions act as a reservoir of infection. These patients are sputum smear-positive. Coughing from an infected person produces tiny infectious droplets. Usually, a single cough produces 3000 droplets nuclei which can persist in the air for a long period of time (Rouillon et al. 1976). These infectious nuclei can survive in the dark for long periods. However, proper ventilation removes these infectious nuclei. Direct exposure to sunlight quickly kills the bacilli. There are several factors that increase the risk of exposure to the individual. The two most important factors which increase the exposure risk and disease communication, are the concentration of droplets nuclei in the contaminated air, and the quantum of time over which air is inhaled. However, the possibility of transmission of infection from a sputum smear-negative person is considerably lower. Infection with the *Mycobacterium bovis* is quite rare in the Indian scenario, due to their habit of boiling milk before use (Keers 1978).

The lung is an important site of infection, and infectious droplets gain access to the lung through inhalation of air contaminated with the *Mycobacterium* droplets nuclei which have been coughed up by an infected person. An infected person is sputum smear-positive who has either not received the treatment, or has left the treatment midway through the disease. The initial contact with the bacilli produces few observable signs or symptoms (Fregnan and Smith 1962). This is followed by a localized infection in the peripheral part of the lung. However, four to six weeks later, tuberculin hypersensitivity, coupled with mild fever and other morbidity, sets in. In most of the patients, the process is restrained by local and systemic defenses. However, the rupture that the sub-pleural primary pulmonary tuberculosis focuses on the pleural cavity may result in the development of TB pleurisy with effusion (Mohan et al. 1995).

Pulmonary tuberculosis (TB) can be further divided, into primary TB, and post-primary tuberculosis (TB). The main bases of classification of the two types of PTB are the nature of the lesion, the site of involvement, lymphadenopathy, and pleural involvement. However, the classification is not accurate, as there is substantial overlap in the symptomatic findings reported in both forms of tuberculosis (Schaaf et al.1995).

1.6.2 Primary Tuberculosis

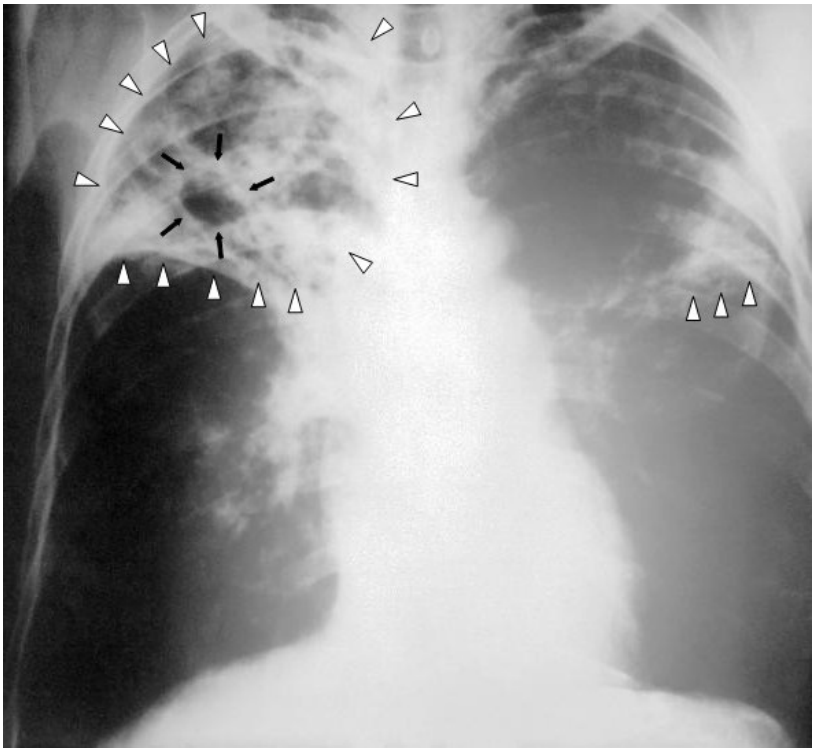

Fig. 1-3 Chest X-ray of a patient diagnosed with advanced stage of tuberculosis

Primary PTB comprises 23 to 34 percent of all reported adult cases of tuberculosis. Primary PTB incorporates lung parenchyma, lymph nodes, tracheobronchial tree, and pleura. However, the chest radiograph may appear normal in up to 15 percent of cases. The primary parenchymal lesion is visible in the area of consolidation (Volmink et al. 2003). The lesions may incorporate the whole lobe of the lung, primarily due to

endobronchial obstruction. Consolidation next to a fissure may show sharp margins (Figure 3). PTB is often indistinguishable from pneumonia as far as consolidation is concerned. However, the absence of universal toxicity, coupled with lymphadenopathy and/or failure to respond to conventional antibacterial therapy, may aid in diagnosing tuberculosis etiology (Frieden and Sbarbaro 2007).

1.6.3 Post-Primary Tuberculosis

The majority of post-primary PTB occurs due to a relapse of the infection acquired in an individual's past life. Occasionally, disease results from the initial infection by the bacterium in individuals vaccinated with bacilli chalmette guerin (BCG) (Anderson and Doherty 2005). Primary and post-primary PTB show substantial overlap on a chest radiograph. However, post-primary TB can be distinguished by the tendency for upper lobe involvement, proclivity for cavitation, and infrequent lymphadenopathy (Ducatti et al. 2006).

1.7 Drug Resistant Tuberculosis (DR-TB)

DR-TB is a serious threat to tuberculosis control programs. The first World Health Organization International Union against Tuberculosis and Lung Disease (WHO-IUATLD) anti-tuberculosis drug resistance surveillance was carried out in 1994, in around 35 countries, which reported the median prevalence of primary and acquired multi-drug resistance to be 1.4 percent, and 13 percent respectively (Abu-Raddad et al. 2009). The WHO-IUATLD has carried out drug surveillance for the second, third, and fourth time via global drug resistance surveillances in 1996-99, 1999-2002, and 2002-2007 respectively, in many more countries (WHO/IUATLD 1996). This drug resistance information was based on drug resistance from 114 countries, where no such survey had been carried out, and therefore no such information was previously available. The survey has estimated a staggering 489,139 cases of MDR-TB which emerged in 2006, of which China and India shared around 50 percent of the global DR-TB burden (Reid et al. 2006). Drug-resistant tuberculosis (DR-TB) is posing a serious threat to tuberculosis control measures in India. However, so far, no countrywide surge/prevalence data are available. Estimates of DR-TB in HIV-co-infected patients are likewise unknown. Undiagnosed and untreated DR-TB among HIV-infected patients contributes substantially to tuberculosis-related mortality and morbidity (Saket et al. 2017).

1.7.1 Multi Drug Resistant Tuberculosis (MDR-TB)

MDR-TB occurs when a patient develops resistance to, at least, isoniazid (INH) and rifampicin (RMP), the two most powerful first-line anti-tubercular drugs. Isolated cases that show multiple-resistance to any other combination of anti-TB drugs, but not to INH and RMP, cannot be considered as MDR-TB. MDR-TB usually develops when treatment is stopped midway, or the treatment regimen is not completed or followed properly (Ramchandran et al. 2009, 2010, Pai et al. 2010). In such cases, the level of anti-TB drug to kill 100 percent of the bacteria is low. To aggravate the issue further, tuberculosis usually occurs in immune-compromised high HIV-prevalence settings, where HIV/TB goes undiagnosed via conventional laboratory infrastructure, thereby affecting timely diagnosis and treatment. Also, circumstantial delays in current drug-susceptibility testing (DST) methods lead to clinical deterioration and subsequent transmission of MDR and XDR-TB. Inaccurate diagnosis in private clinics, and limited health service providers, such as under-qualified doctors, pose a serious threat to the control of tuberculosis (Murray et al. 1989, 1993, Saket et al. 2017).

A person infected with TB acts as a potential reservoir of infection, and can possibly infect 10-15 people annually. India, with its highest tuberculosis burden, accounts for about one-third of globally reported cases. About 40 percent of the Indian population is infected with tuberculosis bacilli, a majority of them having latent tuberculosis, and thus acting as a reservoir of infection for those coming into contact (National Framework for Joint HIV/TB Collaboration Activities 2009). Incomplete treatment, due to long periods of hospitalization, and the cost involved (300-700 Rs per day for up to 50 weeks), may lead to drug-resistant (DR) TB in its two most dangerous forms, such as multi-drug resistant TB (MDR-TB) or extensively-drug resistant TB (XDR-TB) (Styblo 1980).

An epidemiological survey was conducted among adults and children, at ART centers, between 2005 and 2013 in Greater Mumbai (Styblo 1989). All the suspected cases were subjected to smear microscopy, culture (phenotypic liquid culture MGIT) and drug-susceptibility-testing (DST) against first and second-line TB-drugs. This was done to determine DR-TB prevalence, and the pattern of resistance for new and previously treated, culture-positive TB-cases. The outcome of this retrospective, an observational study, has led to the categorization of the resistance pattern into four categories, viz. MDR-TB, pre-XDR-TB, XDR-TB, and XXDR-TB (Johnston et al. 2009, Boehme et al. 2010, Chen et al. 2011).

1.7.2 Issues Related to MDR-TB

MDR-TB is mostly an issue in developing countries, due to the prevailing socio-cultural and economic conditions. This situation exists in India as well. Epidemiological studies and surveys do not reflect the actual picture, or the status of the infection and prevalence of DR-TB, particularly MDR and XDR forms. The advent and circulation of DR-strains have crippled existing healthcare provision pertaining to tuberculosis. Further, the emergence of new DR-forms has outpaced the development of drugs and vaccines for them. The combined threat of new resistant forms has made tuberculosis, otherwise a curable infection, a formidable challenge for healthcare and health service providers. TB continues to pose a serious threat to the survival of the human race, despite positive intervention from healthcare providers. Tuberculosis continues to be a global challenge, despite the efforts of the World Health Organization, and centers for disease control and prevention (WHO/CDC) at the global level which aim to eradicate it. Incomplete treatment regimens, partially cured or relapsed cases, non-adherence, and poor drug availability, are the major causes of drug resistance (DR) cases. Re-infection in cases of tuberculosis, from a similar strain or new strain, is possible, as the first episode of infection does not lead to lifelong immunity (Velayati et al. 2009).

1.8 Geriatric Tuberculosis

Tuberculosis shows different epidemiological patterns in high and low incidence countries. For instance, young adults show high epidemic peaks, and the elderly show low epidemic peaks in high incidence countries. For low incidence countries, the TB burden increases with the advancing age of patients (Dutta and Stead 1992, Doherty et al. 2006). Also, older people are more prone to adverse reactions to anti-TB drugs (Davies 1994).

1.8.1 Types

In elderly patients, TB lymphadenitis, TB pleural effusion, TB of bones and joints, genitourinary TB, and TB meningitis are more common. Older people contract TB infection largely due to **exogenous infection,** or re-infection that is acquired from an external source, while **endogenous reactivation** is due to the quiescent lesions in pulmonary or extra-pulmonary regions. Endogenous reactivation is the predominant cause of TB in elderly people. This is particularly true when the rate of transmission is low in the community. In that case, increased TB cases in older age can

only be attributed to the reactivation of latent infection (Nagami and Yoshikawa 1984). However, when transmission is high in the community, then infection is largely due to exogenous reinfection. This might be true in developed countries which receive a huge influx of refugees and asylum seekers, making elder people with weakened immunity vulnerable to TB infection. This delays the transmission of TB from a community (Canetti et al. 1972). Elderly patients remain asymptomatic, due to lack of fever or a persistent cough and other systemic symptoms. This delays diagnosis and palliative therapy.

1.8.2 Diagnostic Limitations

Hematological TB parameters are found to be similar in young and elderly patients. Serum biochemistry is also similar in both, except for mild elevation of alkaline phosphatase and liver enzymes, which could be due to asymptomatic involvement of the liver by TB (Umeki 1989, Lee et al. 2005, Das et al. 2007, Gupta 2014). Although, the treatment regimen is similar for young adult and elderly patients, compliance is less from elderly people on account of forgetfulness, dementia, poor eyesight, and lack of motivation to go for treatment, on account of infirmity and old age. Therefore, medication under DOTS is highly recommended for elderly people (Yoshikava 1992, WHO 2003).

1.8.3 Treatment Challenges

Elderly patients having pneumonia and not responding to the antibiotics are the usual suspects for TB. Elderly patients may not cough up enough sputum for microscopic analysis. Therefore, if the clinical suspicion is high, and the sputum smear is negative (false negative), more invasive protocols such as laryngeal swab, fibreoptic bronchoscopy, and examination of various bronchoscopic secretions and gastric aspirate, may be examined for diagnostic purposes (Stead 1981, Chan et al. 1992). Similarly, a negative tuberculin skin test (TST) may not rule out a TB diagnosis. In such cases, efforts should be made to take microbiological or histopathological specimens, such as fine needle aspiration, cytology material from the lymph nodes, cold abscess, and other body fluids and secretions, depending upon the clinical situation, for diagnostic purposes (Stead 1981, Chan et al. 1992).

1.9 Pediatric TB

Tuberculosis in children is mostly an exogenous infection. It reflects the rate of ongoing transmission in the community, and indirectly provides an index of adult TB (Chintu 2007, Rekha and Swaminathan 2007). The epidemiology of paediatric TB essentially reflects the epidemiological pattern of adult TB. TB is one of the major causes of mortality in children in both developing and developed countries. Mortality occurs largely due to meningeal and miliary TB in early childhood (Datta and Swaminathan 2001). Paediatric TB adds 10 percent to the total TB burden. However, this may go up to 40 percent in high incidence communities (Donald 2002, Mandalakas and Starke 2005).

Paediatric TB infection is more prevalent in developing nations, with the annual risk ranging from 2 to 5 percent. India shows an annual risk of 1.5 percent of paediatric TB. Around 40 percent of children contract TB at less than one year of age. If left untreated, it may escalate into lymphadenopathy or segmental lesion (Miller and Seale 1963, Comstock et al. 1974, Enarson 1995, Munoz and Starke 2000, Chadha 2005, Chadha et al. 2005).

1.10 Molecular Diagnostics

The pace with which drug resistance is developing requires rapid development of new diagnostics to outpace it. This will complement tuberculosis control programs in an effective manner. The latest developments in phenotypic drug susceptibility testing incorporate *mycobacterium* growth indicators and phage-based assays. These methods can provide results on phenotypic resistance in 2 to 10 days. However, the culture of viable bacilli poses a serious health hazard to laboratory personnel, and therefore requires stringent biosafety measures. Numerous PCR-based molecular techniques have revolutionized the pace of detection of drug resistance, thus neutralizing the limitations associated with it (Boehme et al. 2010, Saket et al. 2017).

Non-synonymous single nucleotide polymorphism (SNPs), and the number conferring resistance, pose a challenge to the development of genotypic drug susceptibility-determining protocols (Migliori et al. 2012, Saket et al. 2017). These issues are partially addressed by analyzing the prominent non-synonymous single nucleotide polymorphism (SNPs), though with low sensitivity and specificity. However, lack of downstream processing, which could lead to the identification of non-synonymous single nucleotide polymorphism (SNPs) within the PCR amplified domain

(e.g., hybridization to immobilized oligonucleotides, microarray, dot blot hybridization, denaturing high-performance liquid chromatography, and DNA sequencing), has further acted as a severe roadblock (Saket et al. 2017). These steps are complicated to perform, and being multistep processes, could increase the chances of cross-contamination, resulting in inaccurate diagnosis (Jacobson et al. 2010). It has been shown that the analysis of conformational changes created by non-synonymous single nucleotide polymorphism (SNPs) in a heteroduplex could be used to determine rifampin susceptibility (Anh et al. 2000). Further, thermal denaturation profiles of heteroduplexes could also lead to the enhanced detection of non-synonymous single nucleotide polymorphism (SNPs) that leads to resistance in *M. tuberculosis*. Since the thermal denaturation profile of DNA is largely dependent on the nucleotide content of the fragment, any change in the sequence would alter the thermal denaturation profile. The altered thermal denaturation profile could be detected by analyzing the binding efficiency of fluorescent dye to DNA fragment at variable temperature. However, a transversion point mutation (A:T and G:C) cannot be detected by this protocol, as this mutation has very little effect on the overall thermal denaturation profile. This limits the efficiency of point mutation detection (transition and transversion) analyzing the thermal denaturation profiles of DNA duplexes having DNA fragments, with, and without, change into heteroduplex and homoduplex, respectively (Mohan et al. 2009, Jacobson et al. 2010).

Caminero et al. (2001) have devised a protocol for determining rifampin resistance by analyzing the unique thermal denaturation profile of the rifampin resistance-determining region (RRDR) of the *rpoB* gene. Mono-resistance to rifampin is a rarity, as it is mostly accompanied by isoniazid resistance, thereby providing the rifampin resistance profile as a possible biomarker for suspected MDR-TB and XDR-TB cases (Eisenach et al. 1988, Dale et al. 2001, Saket et al. 2017).

1.11 Treatment

Chemotherapy for TB was initiated with the discovery of streptomycin in 1994. However, this monotherapy soon led to TB bacilli developing resistance to streptomycin. Later, combined therapy involving streptomycin with para-aminosalicylic was found to be effective in drug-resistant cases. This was further improved by the advent of isoniazid, which formed the basis for primary chemotherapy in the 1950s and 1960s. Therefore, the standard regimen comprised of streptomycin, isoniazid and para-