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A Novel Model of "Remedy and Elimination of Tuberculosis"

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ABSTRACT OF THE DISSERTATION

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ABSTRACT

Tuberculosis (TB), is one of the top ten causes of death worldwide. TB is commonly linked to poverty and creates poverty as it is the single largest cause of death in the 15-49-year-old age group in South-East Asia (WHO, 2017). It is also linked to the HIV population, and its leading cause of death. TB is effected by socio-economic factors, cultural factors, and health policy. My goal of this dissertation is to identify systematic approaches that shall support the mission set by World Health Organization (WHO): to eliminate TB globally by the year 2050. Measures might include addressing social barriers and improving implementation of tools which may increase the likelihood of achieving elimination. Looking at the high incidence rate of TB, this dissertation aims to research and find foundation for this disease in countries and especially in South-East Asia, more specifically India. TB is a severe health crisis in India with one third of its population suffering from this infectious disease.

TB is associated with socioeconomic factors such as levels of poverty and under nutrition while HIV and smoking are a result of co-infections. (WHO, 2017). My goal is to provide a systematic approach in the identification of factors which if modified could lead to increased preventive measures, diagnosis and treatment. This can be done by looking at the history of tuberculosis, diagnostic tests and global impact related to public health with a focus for the newer diagnostic tests that could potentially help reduce the burden of this disease.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACET – Advisory Council for the Elimination of Tuberculosis

BCG- bacillus of Calmette and Guerin

BMRC-British Medical Research Center

CDC – Centers for Disease Control and Prevention

CDI – Communicable Disease Investigators

DOTS – Directly Observed Therapy Short Course

DST-Total drug susceptibility testing

DR-Drug Resistance

HIV-human immunodeficiency virus

ICMR-Indian Council of Medical Research

MDG-Millennium Development Goal

MIC-Minimum inhibitory concentration

MDR -Multidrug-resistant

NTI-National Tuberculosis Institute

SEAR- Southeast Asian Region SEAR

SEAA-Southeast Asian area

TB – Tuberculosis

TCP – Tuberculosis Control and Refugee Health Program

TRC- Tuberculosis Research Center

VDOT – Video Directly Observed Therapy

WHO – World Health Organization

XDR-Extensively drug-resistant

LIST OF FIGURES

Figure 6. Positive tuberculin tests **Pg 32**

The Mantoux tuberculin skin test (TST), which was used to test for M. tuberculosis infection for latent infections by measuring induration in a tuberculin skin test.

From: http://CRITICALCARENURSE Vol 29, No. 2, APRIL 2009 Tuberculosis: Pathophysiology, Clinical Features, and Diagnosis Nancy A. Knechel, RN, MSN, ACNPccn.aacnjournals.org

Figure 7. Schematic illustrating the model structure **Pg 39**

Infections are stratified by smear, drug sensitivity, HIV co-infection and history of previous treatment. TB care stages (diagnosis and treatment) are stratified by public and private sectors. 'FL' and 'SL' denote first- and second-line treatment, respectively. Outgoing dashed lines indicate the loss of patients from the care-seeking pathway. These patients reenter the care-seeking pathway after a given delay, represented by the incoming dashed line at top right. The red lines indicate the effects of Xpert: that is, to bypass the interval for suspecting and testing for MDR-TB, and to enable wider uptake of upfront drug sensitivity testing. Individuals who are cured are assumed to be non-infectious until death, relapse or reinfection. In the latter two cases, they re-enter the infected, pre-care seeking compartment**.** **New Technology for detecting TB both for drug resistant and latent TB infection** Components of the post-research-and-development process for promising new tuberculosis (TB) diagnostic technologies. QA, quality assurance.

From: The Potential Impact of Up-Front Drug Sensitivity Testing on India's Epidemic of Multi-Drug Resistant Tuberculosis, Kuldeep Singh Sachdeva,Neeraj Raizada etal, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0131438

Figure 8. Components of the post-research-and-development process for promising new tuberculosis (TB) diagnostic technologies. QA, quality assurance. **Pg 50**

From:https://academic.oup.com/cid/article/50/Supplement_3/S173/318342/New-Diagnostic-Tests-for-Tuberculosis-Bench

Susan E. Dorman. Clinical Infectious Diseases, Volume 50, Issue Supplement_3, 15 May 2010, Pages S173–S177.

LIST OF TABLES

A Novel Model of “Remedy and Elimination of Tuberculosis”

Chapter1

Tuberculosis

1.1Introduction

Tuberculosis (TB) is an antique human disease of mankind and has co-evolved with humans for many several thousand years (Hirsh AE, 2004). Still, after millennia TB remains a global concern (Sandhu GK,2011). As the world's leading infectious disease, TB is thus approximately as old as humankind itself and indications of this deadly infection have been seen in fossils of Homo erectus skeletons (Daniel TM,2006). Historically, TB is known as a disease of the poor and underprivileged. As estimated by World Health Organization (WHO) in 2016, most of the 2 million people who die of the disease annually reside in undeveloped countries or in urban neighborhoods of wealthier countries (Millet JP,2013). TB has been around for many centuries and it has learned to adapt and survive in human hosts (Rothschild BM,2001). The diagnostics, antibiotics and the other advances to date have not had an impact on TB incidence rates (WHO,2014). A major barrier to TB is societal and I hypothesize that without concerted efforts to tackle the social barriers and the impact of poverty, the rates of TB will never reach elimination (Courtwright A,2010). With modification to social barriers and the development of new policies and adjustment to existing ones, I hypothesize that the decline in TB rates will accelerate (Ortblad KF,2015)

1.1.1 Disease Definition

TB is considered a communicable disease infecting lungs aerobically by the bacilli, *Mycobacterium tuberculosis* (*M. tb*). There are few members of the Mycobacterium complex which can also cause TB such as: *Mycobacterium bovis, Mycobacterium microti* and *Mycobacterium africanum*. However, in humans, *Mycobacterium microti* is not known to cause TB. *Mycobacterium africanum* and bovis infections are found to be rare (Frank W,2009).

For centuries, risk factors such as indoor air pollution, tobacco smoke, malnutrition, overcrowded living conditions, and excessive alcohol intake were related to TB (Schmidt CW,2008). Now, scientists are presenting substantial evidence to affirm these relationships; leading some TB disease experts to reason that control programs must confront fundamental risk factors to limit the spread of the TB disease. There are various chronicles on TB

addressing the sources and ramifications of the infection, the social discriminations and amending the public health structure for those affected by TB (Chakrabarti B,2007).

1.2 History of Tuberculosis

The starting of the Silk Road some 2,000 years ago facilitated the transmission of infections as trade and trade routes were being established between Asia, Europe, and North America (Fanning EA,1998). The plague of Antoninus brought Rome small -pox and Europe faced bubonic plague, which later was commonly called the Plague of Justinian. The fourteenth century saw the Black Death, which killed millions of people as new routes from Central Asia like China brought goods like furs, which were the flea, infested. It appeared as I researched that trade routes were opening globally, and with it bringing in human pathogens, which traveled attached to goods and travelers increasing their microbial microorganism's habitat more and more (Knobler S, 2006).

The travelling of these disease leading microorganisms and microbes attached to humans from place to place led towards the discovery in 1882 by Robert Koch of *Mycobacterium tuberculosis* that caused TB. This further in 1905, on his novel discovery led him towards the Nobel Prize in physiology and medicine (Nobelprize.org, 2010).

Evidence of TB has been observed in human remains dating back for thousands of years. The remains were found by molecular methods such as radioactive dating in a fossil skeleton of an extinct animal called the Pleistocene bison (Rothschild BM, 2001). The history of TB (Daniel TM,2006) dates back to 1689 when a well-known scientist named Dr. Richard Morton investigated and found that TB was related to pulmonary diseases with some of the symptoms observed were related to tubercles. Hippocrates thought of TB as a disease (DanielTM,2015) which was fatal with coughing producing a thick white phlegm or blood and fever (Zumia ,2013). Until 1820, TB could be related to many onsets of diseases but in1839, the condition was finally given the name of "tuberculosis" by J. L. Schönlein. In 1882, Robert Koch discovered the bacillus that caused TB, *Mycobacterium tuberculosis which* earned him *a* Nobel Prize in 1905 in physiology and medicine. (Nobelprize.org, 2010)). Koch's discovery of the bacilli containing a very exclusive coating of protein further led to the diagnostic stain called the Zeihl Neelson stain. The bacilli were observed under the red acidic dye and were further classified as acid-fast bacilli (AFB) (HuberJB,1907) *"The tubercle bacillus is an index by inversion of the real progress of the human race. The claim of civilization to*

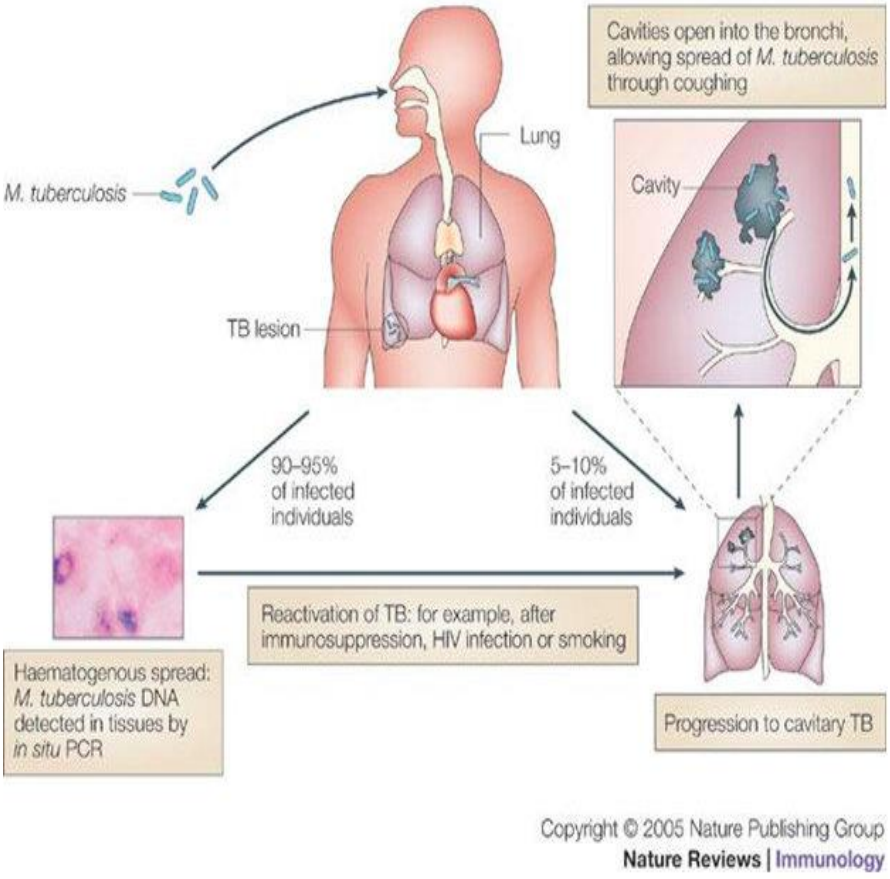
dominate human life may be fairly judged. It was correctly determined that TB will decrease with the substantial advancements of civilization, and the disease will as surely increase as civilization retrogrades" (Boire NA, 2013)

Though it has taken many years, the discovery of antibiotics with activity against *M.tb* ushered in new health initiatives by countries as a first step to move forward against this global pandemic. Unfortunately, despite these advances TB has survived in human communities from ancient to modern time. (Hershkovitz C,2017). As written by Charles Dickens, the famous novelist, *"Tuberculosis is a kind of suffering* (Atlantic,2016*) in which death and life are so strangely blended, that death takes the glow and hue of life, and life the gaunt and grisly form of death."* Paul Edward Farmer, a renowned physician, and anthropologist (Farmer P, 1996), remarked: *"What the American population thinks is very important for the future of good health. You can't have a public health without a public health system."*

An understanding of a disease is not only based on medical knowledge, but public health of the global community and societies who have different views and regulations on fighting the disease. The gathered knowledge only enhances the methods to control the disease in societies. The two key participants' knowledge and medicine play an important role and continue to push forward advancements in human awareness towards finding a cure for elimination and survival.

1.3.1 Pathophysiology of Tuberculosis

A brief outline of the development of TB is shown below in Figure 1, which starts with infection by *M. tb* and inadequate containment by the immune system. Patients infected with *M. tb* who have no clinical, bacteriologic, or radiographic evidence of active TB are said to have latent TB infection (Dye C, 2006). Active TB may occur from reactivation of previously latent infection or the progression of primary disease. As seen in Fig.1.1 (Rook, GAW,2005), inhalation of *M. tb* has various consequences. The process starts first by the inhalation of the droplet nuclei, next comes the potential of latent infection, third, the progression to active disease which can be primary progression soon after infection, or the reactivation of disease which can occur years later.



I. Pathophysiology of tuberculosis

Figure1.1. The Pathophysiology of Tuberculosis (Graham AW,2005)

There are many stages of TB infection – 1. Inhalation - the bacteria is inhaled. 2. Bacterial multiplication. 3. T-Cell activation 4. Tubercle Formation 5. Cavitation and Tubercle break-down. *M.Tb* is oblong shaped when viewed under microscopy, decolorizing on acid stains, thus being described as an acid fast bacillus (Koch R,1982). Upon infection it has been shown to reside in white blood cells called macrophages. Since it is an airborne disease, bacteria are carried by droplet nuclei expelled when a patient with TB coughs. Once inhaled, incubation may take weeks, and once infection is established, the body's immune system is unable to clear the bacteria, and years later the infected person may develop active TB which in turn continues the transmission to others. It has been suggested that in some people the bacilli can be cleared fully; however, in at least a third of those infected, bacilli will lay dormant for some time not inducing any visible infection or symptoms.

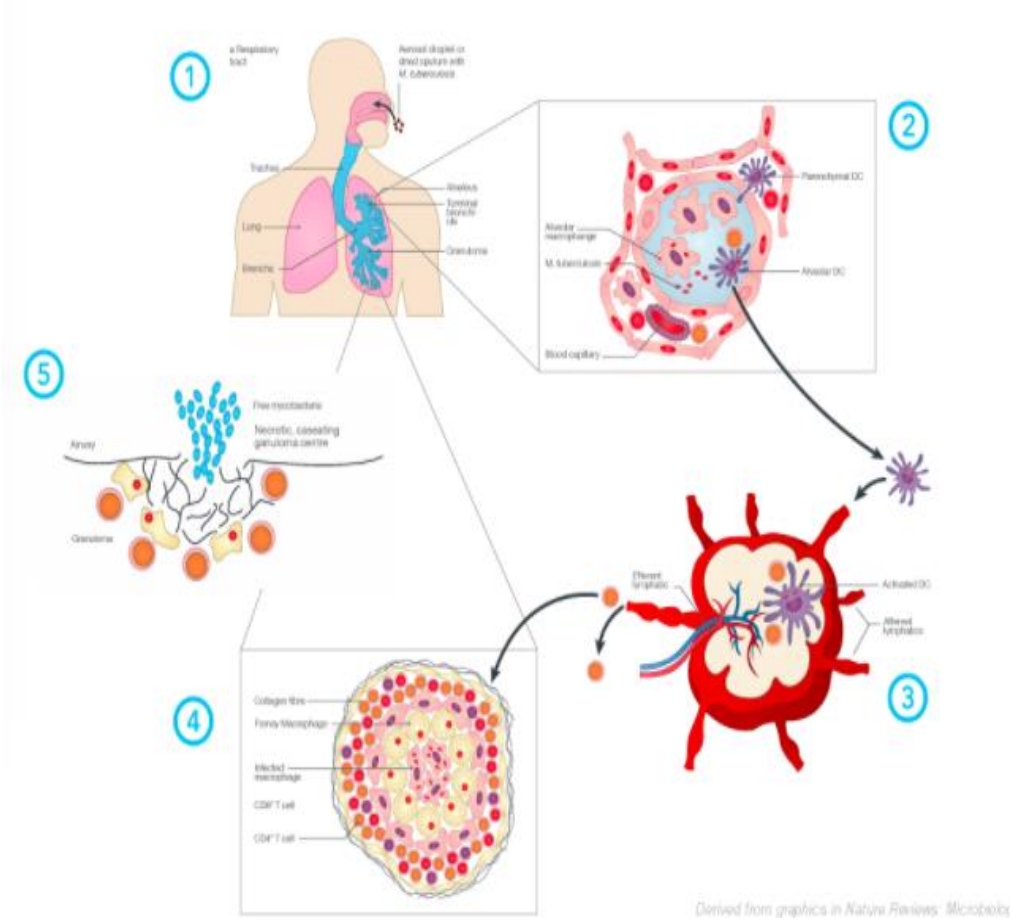


Figure 1.2 How Tuberculosis Works and Cycle of Bacterial Infection (Nature Review)

1.3.2 Etiology of Tuberculosis

Studies have shown that *Mycobacterium bovis* infects humans through food sources of meat, poultry, and unpasteurized milk products. (Prasad HK, 2005). In earlier decades from 1931 to 1937 in South England, it was observed that *Mycobacterium bovis* resulted in approximately 6% of human deaths (Hardie RM, 1992). Organs that were affected commonly include the lungs and the lymph reticular system, but also the the gastrointestinal system, and occasionally, the nervous system, the skin, and the liver (Rotimi A, 2017). Today, 9 million new cases and about 2 million deaths yearly are attributed to TB. (Harries AD, 2006). Therefore, understanding the etiology of TB becomes important so new advancements in medicine can be possible and discovered leading towards new directions of cure.

1.4 Classification of TB by American Thoracic Society and CDC

Classification systems have been developed to standardize the various forms of TB, assigning a category to all forms from exposure to disease. The ranking prepared by the American Thoracic Society (ATS 2000) is based on a five-point scale, prioritizing those who need medical attention first given the disease is communicable and of public health importance. Institutions and immigration agencies also apply such categories as part of institutional screenings and immigration screening. The rate of TB is high in immigrants originating from countries where the incidence rate can be as high as 200 times more than in the US. As such, US-bound immigrants from high incidence countries are screened as part of immigration processes. Epidemiologic studies show that immigrants in the US retain their risk for tuberculosis and experience progression to disease at the high levels of the incidence reported in their country of origin. Moving to United States also can destabilize immigrant families resulting in poor economic conditions, with unstable housing and unstable employment, which compounds their risks for progressing to TB disease (McKenna MT, 1995).

1.5 Classification of Tuberculosis

As outlined in the (American Thoracic Society) American Review of Respiratory 1990: there are five classifications of grading TB:

*"*0. *No TB exposure, not infected. Persons in this class have no history of exposure and a* negative reaction to the tuberculin skin test.

1. TB exposure, no evidence of infection. Persons in this class do have a history of exposure to *M. tb.* If there has been close exposure within 3 months, follow-up is required, and preventive action necessary.

2. TB infection, no disease. Persons in this class have a positive reaction to the tuberculin skin test, negative bacteriologic studies (if done), and no clinical or radiographic evidence of TB. Preventive chemotherapy may be indicated in some persons of this group.

3. TB: clinically active. Class 3 includes all patients with clinically active TB whose diagnostic procedures are complete. If the diagnosis is still pending, the person should be classified as a TB suspect (Class 5). To fit into Class 3, a person must have clinical and radiographic evidence of current TB. This is established most definitively by isolation of *M.tb*. In the absence of a positive culture for *M. tb*, persons in this class must have a positive reaction to

the tuberculin test. A person who had past TB and who currently has clinically active disease belongs in Class 3. A person remains in Class 3 until treatment for the current episode of disease is completed. The following characteristics further define this group:

4. TB: not clinically active. This classification is defined by a history of previous episode(s) of tuberculosis or abnormal stable radiographic findings in a person with a positive reaction to tuberculin skin test, negative bacteriologic studies (if done), and no clinical and/or radiographic evidence of current disease. Persons in Class 4 may never have received chemotherapy, may be receiving prevention chemotherapy, or may have completed a previously prescribed course of chemotherapy. If the current clinically active disease has not been ruled out, especially in persons not adequately treated in the past, this person should be classified as a tuberculosis suspect (Class 5) until diagnostic evaluation permits classification as Class 3 or Class 4.

5. TB suspect (diagnosis pending). Persons should be so classified when a diagnosis of TB is being considered, whether or not treatment has been started, until diagnostic procedures have been completed. Persons should not remain in this class for more than three months. When diagnostic procedures have been completed, the person should be placed in one of the introductory classes."

This classification system formalizes an approach to screening and classifying patients suspected of having TB and thereby increases the opportunity to receive appropriate diagnostics and therapies, which may be less readily available in their country of origin. With this system used in classifying TB, it becomes a biomedical standard for physicians who are either directly or indirectly addressing the concerns of the population as they treat nationally and globally. Not only that, the above classification helps immigrants and refugees if detected to get treatment of which they are unaware of in their country. As Charles Dickens the novelist mentioned, *"a disease that 'medicine never cured, wealth never warded off.' It is the consequence of gross defects in social organization, and of errors in individual behavior. Man can eradicate it without vaccines and drugs by integrating biological wisdom into social technology, into the management of everyday life."*

1.6 Global Statistics of Tuberculosis and Impact

A 2016 World Health Organization published report declared that "in 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among

women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases" (WHO 2016). Due to TB being an airborne pathogen, the disease can involve all family members in a household, and transmit further in communities and the general public, which is why it is a disease of public health importance. Despite the gains in TB control and the decline in both new cases and mortality, TB still accounts for a huge burden of the worldwide morbidity and mortality. The bulk of the global burden of new infection rate and TB death is reported in six developing countries, India, Indonesia, China, Nigeria, Pakistan, and South Africa. According to the WHO, India alone reported 60% of TB deaths worldwide in 2015, (WHO, 2017). India has the largest burden of TB where approximately 2.2 million people develop TB each year from the 8.6 million cases reported by WHO every year with a dying rate of 220,000 every year. Though TB can affect all types of population, countries such as India, reports more cases of TB. This is due to the high levels of poverty. Also called as slum dwellers these people are usually the first ones to bear the brunt of this catastrophic disease (Oxlade O, 2012).

1.7Aim of Thesis and Research

My aim and research is to 1) identify social barriers to receiving excellent TB care, 2) determine which ones are modifiable and 3) which have the greatest impact on the TB epidemic worldwide.If social barriers can be modified through development of new policies or changes to existing ones, the long term global ambition of TB elimination will be more likely to be achieved.

This research will enable one to locally and globally find ways for TB elimination with newer and developing diagnostic tests moving it towards a decline. This dissertation is aimed at observing the problems of TB related to public health in several parts of the developing world with findings based on a novel model of "remedy and elimination of tuberculosis" that has ended as a global health threat. Numerous remedies and technologies have been developed as we move in the 21st century, though TB has been announced in previous decades as "the disease of death" it moves towards cure and elimination with new technologies and drug regimens. It has become necessary to find better and more efficient cures for this disease and to educate the global community and health policymakers, that with a combination of knowledge and invention in medicine, better treatments can be developed which will benefit not only patients but end the global impact of this disease. Therefore, it is the duty of scientists and

health facilities to discover holistic remedies thus globally giving people the right to live a happy life with respect to the standards of good health. If the standard of living is controlled in the developing countries the treatment and elimination of TB automatically gets under control.

According to Article 25 (United States Constitution) in the United Nations Universal Declaration of Human Rights: *"Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control."* Looking at the incidence rate and distribution of disease in developing countries my study shall discuss one of the poverty-stricken countries where geographic distribution with relation to poverty has affected in raising the death rate into the millions.

Chapter 2

Epidemiology of Tuberculosis

2.1. Introduction

Today *M. tb* accounts for one of the major health problems and is a leading concern internationally. TB is linked to HIV population, which is one of the reasons leading towards a high mortality rate. The impact of TB worldwide is often reported in terms of morbidity and mortality, but the broader effect on society, communities, individuals and families is poorly described or understand, but nonetheless, these impacts are very real. My goal of this dissertation is to identify measures which support the mission set by World Health Organization (WHO): to eliminate TB globally by the year 2050.

In this day and age it has become necessary to find new cures for TB and its status to be addressed globally. Though in developing nations when compared to other infectious diseases. TB seems to be spreading faster compared to others infectious diseases. Countries need to come together to virtually stop this untreatable disease (Lallanilla, M,2013). As said by Anthony Fauci, TB, *"is now the leading cause of death from infectious disease worldwide,"* who is the director of the National Institute of Allergy and Infectious Diseases. It has spread

globally, and as its strains are becoming resistant to an increasing number of antibiotics, it further is getting difficult to finish this disease as approximately 2 million deaths happen every year" (Atlantic, 2016).

2.2 Global Incidence

TB is a global disease. Even in the United States, there continues to be nearly 10,000 cases of TB annually. According to the CDC, nearly 2/3rd of the cases in the US are identified in foreign-born populations, with the remaining 1/3rd in US-born populations. The epidemiology of TB in the United States also has associations with unstable housing and poverty, in addition to comorbid conditions that weaken immunity and lead to disease progression (CDC,2011).

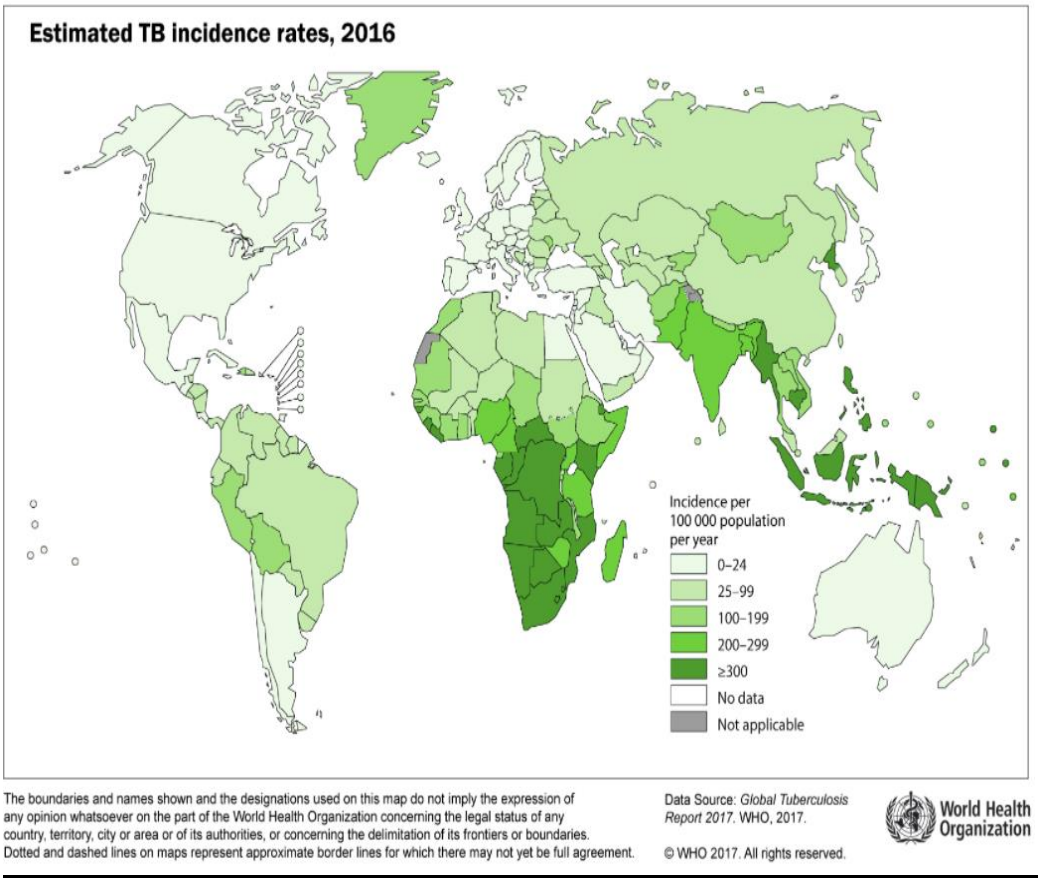


Figure2. Map: Estimated tuberculosis incidence rates. (WHO 2016)

Clinical Trials and short course TB drug - therapy with the bringing in by WHO, the Directly Observed Therapy Short Course (DOTS) theory (WHO, 2001) has brought good results since 1990. These efforts have impacted that global incidence rate for TB, which according to the WHO has fallen by 1.5% every year, in parallel

with decreasing rates of mortality. From the time when it began to be observed that the active TB rate was one person per second the World Health Organization (WHO) decided to declare TB as a health emergency during the year 1993(WHO 1993).

TB seems to have affected lives globally as it has made its entry in the body biologically. Innovative ideas such as new interventions involving TB patients, providers, and health policy makers are needed to control this vast spreading global disease. Since these new technologies are being developed it is still noticeable that health care organizations have begun to play an essential role but still seems to be far behind when it comes to potential future care. Individual attention is though provided but still the social aspect of this growing disease, is ignored as early diagnosis is not predictable. This has led to increase in the incidence rate of morbidity due to obstructed drug opposition as seen in Figure1b below (WHO, 2013). International organizations like World Health Organization (WHO) and the World Bank are working cohesively against the fight for the elimination of TB. Still one wonders at the global unification and how the disease started millennia ago.

2.3 Globalization and countries burdened with Tuberculosis

"Globalization" - the term brought attention towards trade among countries during the start of the Silk Road centuries ago, but today international migration is more fluid now than ever before, which means that TB is likely to continue to transmit worldwide unless more enhanced measures and better tools are used to screen migrating populations for disease.

TB was becoming noticeable in global countries because it was being seen that the European region had a low MDR-TB cases as compared to other countries (WHO, 2009). It was observed that an approximately 10 percent cases of TB are in the European region. The Eastern Mediterranean region did not have many known of TB cases. Similarities were seen in the United States but with a low incidence rate of TB.

The Southeast Asian Region (SEAR) (WHO, 2009b) has 20% of infectious diseases because more than thirty percent of the population is poor with a health care system which is unreachable due to poor infrastructure. My opinion looking at the reviewed literature makes me decipher that in controlling such a significant population and helping in the development worldwide health care will not be possible without noticeable progress in making a positive health care policy for all these countries whose population is exposed to TB disease (WHO, 2009). Health

policies need to be for public health. It is well said by theorist like Michel Foucault (Foucault M, 1980) a renowned thinker and historian that "*a return of knowledge*" is necessary. This being due to the fact that though we gain it artificially by reading books and methods, this type of behavior cannot be applied towards helping people. They are not a theory of life but an individual where money and books cannot buy. "*This is moreover subjugated knowledge, which has been in books for years and is being used in making documents for health policies for countries."* (Pg.82).

He challenged that this power is sporadically manipulated by people/groups as acts of dictatorship, viewing it as scrambled and universal. Power has become a part of a social structure that permeates into society, and is inconsistently fluid and arbitrated, as it is applied by conventional methods of knowledge and scientific facts. According to Foucault sometimes power gets silenced by rules and regulations, which deem to be insufficient to help in causes related to people and their health care. Sometimes, therefore, the countries are left untouched, and the communities flourish in cities catching the fine line of survival with their old customs. This explanation when applied to TB one can see that public policy holders are in power of regulations and policies where health is concerned. They are unable to see new methods and procedures and still want reform through ancient old policies on health following the customs and bringing the country to a halt globally. Thus concluding politicians need to be open to new changes and developments happening in scientific research.

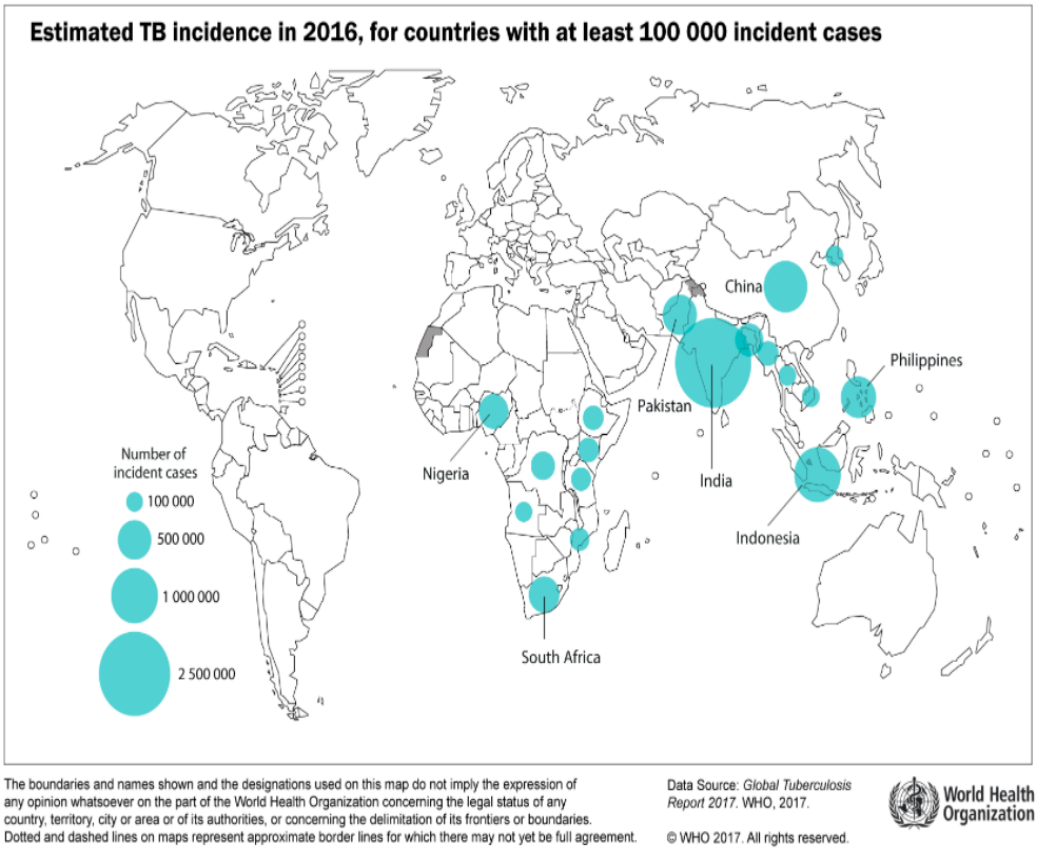


Figure 3. Estimated Incidence of New TB Cases as of 2016 (WHO, 2016)

Current technologies developed modified this in 2016 because the Xpert MTB/RIF Ultranow was designed by Cepheid in collaboration with Rutgers with support from Australia and the Netherlands. The Assay has been re-designed in the form of liquid culture in a faster sensitive way by showing ten times more than the previous instrument made in 2010. More than 130 countries are using the Xpert technology for detection of *MDR-TB* cases. Studies done in a multicenter involving ten sites of low and middle-income countries using this Xpert Ultranow was seen to help in the early detection of TB cases. The study conducted by FIND and the NIAID-sponsored Tuberculosis Clinical Diagnostics Research Consortium was seen that the sensitivity in detecting *MDR-TB* was 17% higher than Xpert MTB/RIF (Albert H, 2016).

2.4 INDIA & TUBERCULOSIS

India being such a vast country comprising of 121 crore Indians, where about 83.3 crore reside in rural live in rural regions while the rest of 37.7 crore are found to be residing in urban areas. India is a country having the maximum number of deaths related by TB during 2016 (WHO,2016) which being approximately being 423,000 TB patients. This has resulted India to become the world's number one in TB related deaths. Approximately 40 percent of India's population suffer from latent TB. mostly coming through the private sector of the country. 2016 also made India to have the largest number of MDR-TB patients which were approximately about 147,000 of people. It is seen that India sees approximately TB cases 850,000 every year which have been not detected or diagnosed or treated. This being due to the fact that standard of care in India is very poor. Shortage of drugs being one of the major factors for such a vast population suffering from TB being one of them. The quality of care and diagnosis is so far behind for TB patients in India as the anti drug regimes for sufferers is slow and at least two months behind in diagnosis of TB. Lack of drug regimes and follow up are the leading cause seen to be for TB increase in India (WHO,2016).

Historic literature of India, the Upanishads and Puranas mention TB to be present in the population (WHO, 2010). TB in India developed in a couple of stages: Before independence or the early period, before tests like taking chest and lungs pictures came; thirdly after–independence, and lastly the current time when WHO and World Bank programs were formulated. WHO started assisting by laying out rules in the control of this disease all over world. India, as a poor developing country, saw the significant sufferings in villages and suburbs as their infrastructure was not strong enough to face these challenges of this vast disease. The non-presence of drugs and chemo agents was one of the drawbacks that were being met in controlling for TB in poverty areas.

TB treatment in India is given by private sector health officials and in the public sector by Indian government developed program Revised National TB Control Program (RNTCP). Though medicines are free for treating TB patients still the awareness is not present in the population and treatment is taken by private sector health officials. TB testing in India is usually done by few diagnostic methods like the 1. Microbiological confirmation by producing sputum by patients.2. Chest X-ray is another screening test used to diagnose TB among patients (CDC, 2016).

In 1961, the Indian government formulated a program called the District Tuberculosis Center (DTC) in Andhra Pradesh, in the district of Anantapur. This program was formatted by the government and initiated schemes to control TB in the community, which were also economical for the TB population (Agarwal SP, 2005). These initiated schemes were beneficial in the control of TB and other cities nearby wanted to also invest in the program but due to less staff following a medicinal regime was not possible (ICMR, 1959). Thus in 1962 the first TB disease center model was founded and was called the National TB disease Control Program (NTCP). To stop this expansion, definite programs and methods were needed and that even fast to end this growing epic of disease. Though today with advancement in technology and drugs, there is still a great need for these TB patients to be treated as humans and get the full medicine course irrespective of the money which they are unable to afford due to poverty.

Type of TB mostly India faces is MDR-TB, which was drastically observed in the city of Mumbai in India (N Mistry,2012) having the second largest in TB population. 320, 000 of the annual deaths in India could be divided in 17.6percent to be communicable infectious deaths and 3.5% mortality (Central TB Division 2011). The high rate of TB in a city like Mumbai was seen to be resulting due to numerous factors as shown in the study done by (K Gupta, 2009). It was observed that environment malnutrition and failure led to the spread of TB, as the extensive population did not have enough water, while pollution in the atmosphere caused pulmonary risk and lastly with concentration in a high population density in housing led towards some of the factors for TB being spread (Major B, 2005).

India

POPULATION 2016 **1 324 MILLION**

Estimates of TB burden,[a] 2016

	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	423 (324–534)	32 (24–40)
Mortality (HIV+TB only)	12 (6.6–19)	0.92 (0.5–1.5)
Incidence (includes HIV+TB)	2 790 (1 440–4 570)	211 (109–345)
Incidence (HIV+TB only)	87 (56–125)	6.6 (4.3–9.4)
Incidence (MDR/RR-TB)[b]	147 (95–199)	11 (7.2–15)

Estimated TB incidence by age and sex (thousands),[a] 2016

	0–14 years	> 14 years	Total
Females	107 (47–167)	897 (391–1 400)	1 000 (437–1 570)
Males	120 (52–188)	1 660 (725–2 600)	1 780 (778–2 790)
Total	227 (99–355)	2 560 (1 120–4 010)	2 790 (1 440–4 570)

TB case notifications, 2016

Total cases notified	1 936 158
Total new and relapse	1 763 876
— % tested with rapid diagnostics at time of diagnosis	17%
— % with known HIV status	72%
— % pulmonary	84%
— % bacteriologically confirmed among pulmonary	63%

Universal health coverage and social protection

TB treatment coverage (notified/estimated incidence), 2016	63% (39–120)
TB patients facing catastrophic total costs	
TB case fatality ratio (estimated mortality/estimated incidence), 2016	0.17 (0.09–0.27)

TB/HIV care in new and relapse TB patients, 2016

	Number	(%)
Patients with known HIV-status who are HIV-positive	39 815	3%
— on antiretroviral therapy	39 123	98%

Drug-resistant TB care, 2016

	New cases	Previously treated cases	Total number[c]
Estimated MDR/RR-TB cases among notified pulmonary TB cases			84 000 (72 000–95 000)
Estimated % of TB cases with MDR/RR-TB	2.8% (2–3.5)	12% (10–13)	
% notified tested for rifampicin resistance	20%	67%	580 438
MDR/RR-TB cases tested for resistance to second-line drugs			22 492
Laboratory-confirmed cases			MDR/RR-TB: 37 258, XDR-TB: 2 464
Patients started on treatment[d]			MDR/RR-TB: 32 914, XDR-TB: 2 475

Treatment success rate and cohort size

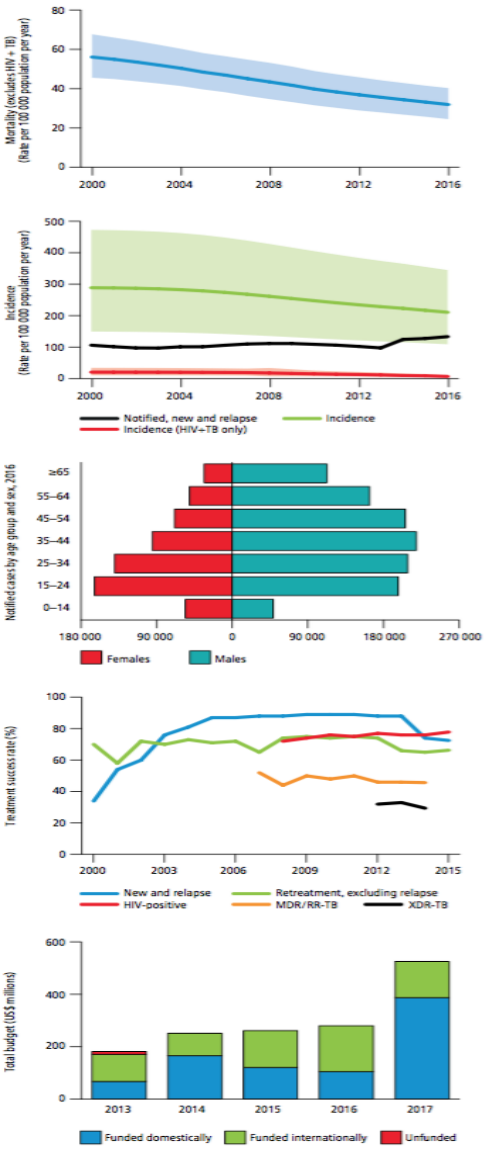
	Success	Cohort
New and relapse cases registered in 2015	72%	1 656 233
Previously treated cases, excluding relapse, registered in 2015	66%	69 823
HIV-positive TB cases registered in 2015	78%	44 191
MDR/RR-TB cases started on second-line treatment in 2014	46%	22 524
XDR-TB cases started on second-line treatment in 2014	29%	1 397

TB preventive treatment, 2016

% of HIV-positive people (newly enrolled in care) on preventive treatment	5%
% of children (aged < 5) household contacts of bacteriologically-confirmed TB cases on preventive treatment	1.9% (1.7–2)

TB financing, 2017

National TB budget (US$ millions)	525
Funding source:	74% domestic, 26% international, 0% unfunded



Data are as reported to WHO. Estimates of TB and MDR/RR-TB burden are produced by WHO in consultation with countries. Estimates are rounded and totals are computed prior to rounding.
[a] Ranges represent uncertainty intervals. Estimates of TB incidence and mortality for India are interim in nature, pending results from the national TB prevalence survey planned for 2018/2019.
[b] MDR is TB resistant to rifampicin and isoniazid; RR is TB resistant to rifampicin.
[c] Includes cases with unknown previous TB treatment history.
[d] Includes patients diagnosed before 2016 and patients who were not laboratory-confirmed.

Data for all countries and years can be downloaded from www.who.int/tb/data

Figure 4. Estimated TB Burden- India as of 2016 by the Global Tuberculosis Report 2017 (ANNEX2)

Chapter 3

Poverty, Stigma and Tuberculosis

3.1 Introduction

TB is a disease linked with poverty. According to World Bank one- sixth of humanity that is about a billion people survive on less than a dollar a day (World Bank,). According to WHO report of SEAR (2008) the habitats are living in urban slums and challenging environmental conditions like overcrowding and poor nutrition, the population becomes defenseless towards TB which takes them towards social and monetary instability. This leads one to think that it's the poor and disadvantageous people who die first (Courtwright A ,2010).

3.1Tuberculosis and Poverty

Socially economic factors like poverty as one can say becomes a burden globally as disease and death are distributed in health variations in a country (Heijinders M,2006). Considering one of the developing countries like India it was seen that it faced at least one-third of the global burden of TB every year due to population overload. Population living in overcrowding areas like slums as was termed were exposed to TB but the treatment regime was not adequate to cover the exposed population. Treatment drugs was given to only 600 patients with TB, out of 100,000 exposed. (Municipal CorporationReport,2009). This showed that the availability of drugs was not adequate or TB sufferers did not follow the regimen given to fulfill the course for a cure. Not only the above factors but monetary and inadequate cleanliness (Gupta, K, 2009) was found also to be the leading factors for the high rate of TB patients in Mumbai. (Chowgule R.V. 1998). Therefore, conditions of living, overcrowding, hygiene, and food become significant factors where groups of people and their health is concerned which further leads towards deterioration in the control of any disease (Garner P,1993). As said by Tom Frieden the former director of U.S. Centers for Disease Control and Prevention (CDC), *"stopping TB requires a government program that functions every day of the year, and that's hard in certain parts of the world, and partly it's because of who TB affects: It tends to affect the poor and disenfranchised most."*

As seen globally and branded TB to be a disease of poverty, sometimes it proves right when one observes countries like India and its neighboring high scale overcrowded cities to be exposed to bacteria where the air pollution, overcrowding and improper health care treatments play an important part in the downfall of a country.

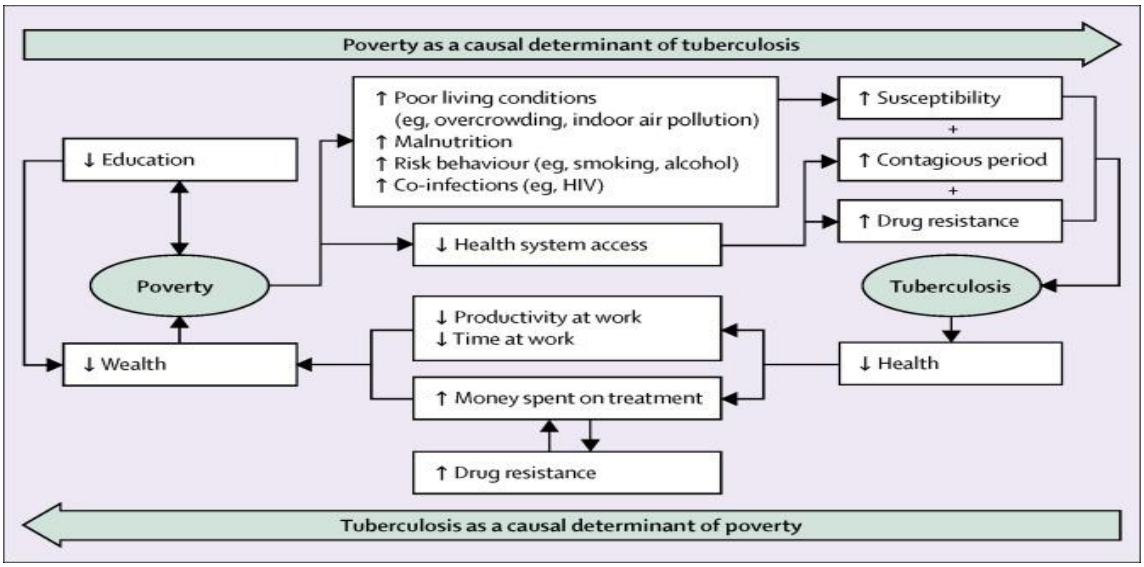


Figure 5. The cycle of poverty and Tuberculosis (Ortbald,KF,2015)

3.2 Tuberculosis and Stigma

Knowing about TB and studying the significance of the disease now becomes more important to me because it is necessary to educate the poverty class people of lower and middle-income countries and make them aware the remedies that they can do to safeguard their lives. Data 2013 shows that had 70% of reported cases in TB from at least 40% from areas, which were economically poor while 44% of TB sufferers, did not have employment (Central TB 2014). 2014 World Health Organization (WHO) united with the European Respiratory Society (ERS)) in Munich and formed an eight priority clause action to be applied with countries which were having low incidence reports of TB (WHO, 2014). With the growing need for TB control in 2015, the Sustainable Development Goals (SDGs) aims for 2030 have been taken up by the United Nations to end the TB epidemic. TB was governed by biomedical research and priority as a social factor was never given to it as stated in the study done by Macq (Macq 2006) “It is striking to see that stigma is at the center of global strategies to fight AIDS and it is so little present in the international priorities of TB control” (page 351).

Discovery of this disease in ancient decades was signified as a disease of consumption from the Greek word phthisis or white plague where there were no remedies or care, and people knew they would not survive. They became to be known as untouchables and were isolated from places socially. It was a social stigma to be infected by TB. This seclusion of individuals by communities and the stigma impacted TB patients, their families and communities in complex ways critically hindered patients from seeking and receiving appropriate care including curative treatments (Craig, 2016). The TB sufferers lost their social identity and self. It disrupted them emotionally and psychologically. TB had been up till now treated more using biomedical approaches, one had never explored the cultural aspect of it, which comprised of social setbacks, economically or monetarily aspect with the contribution of the family being the most important. The attitude of people suffering TB in the 19th century remarked by a specialist in TB was (Porto A, 2007*)"Having tuberculosis was a defect. When there was a case of tuberculosis in the family, it was kept a secret, then: "So-and-so has a spot in his lung, or something of the sort…"* Nobody talked about tuberculosis it was not mentioned. When a man was engaged and found out that his fiancée got tuberculosis, he would cancel the wedding. "

3.3 Drawbacks towards Tuberculosis in countries and Financial Strains

It was seen that many drawbacks were met by organizations like WHO and World Health Bank as they started their humanitarian work towards the benefit of saving the mankind suffering from TB. Sometimes they faced limitations in the countries, which had fixed theories, government rules, and sometimes the poverty of the country with no proper health care or drug availability brought them back to the goal where they had started. Moreover, though TB was being given so much importance and consideration in providing ways in terms of care, still it did not reach the way public health was defined to help the suffering countries. This being due to the fact of unawareness of policy makers on policies being inadequate and unaccountable due to the various cultural norms each country possessed. WHO declared TB as a global epidemic as reports indicated at least 15 countries to be having the highest rate of TB. Some of the few countries like Africa, India, China, Indonesia and Bangladesh have the highest incidence rate with *M. tb* (WHO,2010; Sandhu GK, 2011) on its one- third of their global population.

Data showed that South Africa had drug-resistant TB that was very common in its population (WHO,2010; Sandhu GK, 2011). This being since though thousands of people who were developing TB could be falling into the

category of the drug- resistant strains. Though another leading cause that came to light was the body being exposed to HIV was suddenly becoming a prominent factor towards TB. Since with not much availability of monetary funds, problems of availability of drugs was an added factor for the recovery from TB. The population exposed to TB was tired, exhausted, malnourished, depleted of energy that to afford the full course of antibiotics was not feasible for their body to take it. Moreover, elements of poverty led towards the way of living leading towards overcrowding in areas making one believe that living conditions could also play an important role in the development of resistance.

Chapter 4

India and TB data

4.1 Methodology and Study Section Data

This section summarizes data collection and data analysis that is used for framing this thesis. This thesis is exclusive as it employs qualitative secondary data with TB patients in India and globally. The explanation of the data collection progression mainly outlines techniques used by other researchers in the Causes of Tuberculosis Transmission while researching study samples in India and global countries. It's a novel method for detecting cases of TB which are previously affected and along with the new diagnosis.

4.2 Data Collection in India

The Multi-drug resistance (MDR) TB poses a significant task in controlling in India and worldwide not because DOTS theory set by WHO is working but because the presence of multiple private sectors which are not organized. With the coming in of World Health Assembly (WHA) approving the End -TB strategy with the goal of decreasing TB deaths by 95% and the new diagnosis cases by 90% between 2015 and 2035 (Kuldeep SS,2015) is a challenge being faced in India. Another accurate diagnosis of *M. tb* test can be undertaken when there is presence of sputum and rifampicin, a method used along with the regular quick drug susceptibility testing (DST) method but utilized when TB has been diagnosed (Sachdeva KS,2015).

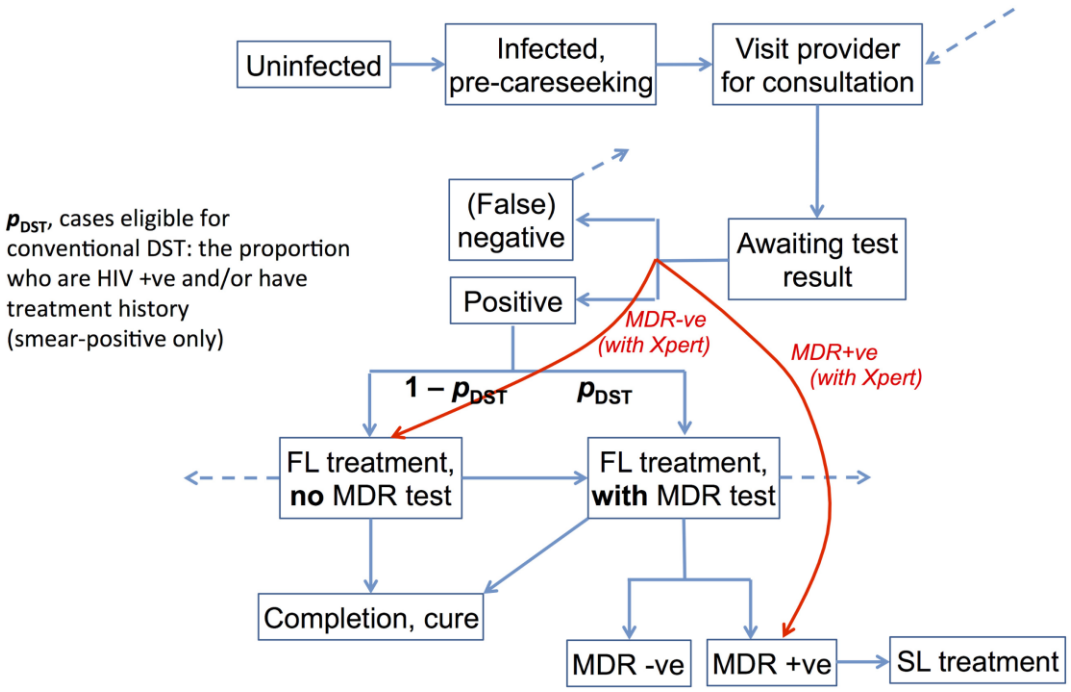


Figure 6. Schematic illustrating the model structure (Kuldeep SS, 2015)

"Infections are stratified by smear, drug sensitivity, HIV co-infection and history of previous treatment. TB care stages (diagnosis and treatment) are stratified by public and private sectors. 'FL' and 'SL' denote first- and second-line treatment, respectively. Outgoing dashed lines indicate the loss of patients from the care seeking pathway. These patients re-enter the care seeking pathway after a given delay, represented by the incoming dashed line at top right. The red lines indicate the effects of Xpert: that is, to bypass the interval for suspecting and testing for MDR-TB, and to enable wider uptake of upfront drug sensitivity testing. Individuals who are cured are assumed to be non-infectious until death, relapse or reinfection. In the latter two cases, they re-enter the infected, pre-care seeking compartment."

The results of this study done in India showed that this high sensitive diagnostic testing along with DST impacted in the cases of MDR-TB. TB diagnosis especially in the public sector could contribute towards 180,000 cases of MDR-TB (95% CI 44187 – 317077 cases) between 2015 and 2025 as it moved to 75% in three years with all TB cases considered. (Kuldeep SS, 2015).

4.3 Technology Impact on Data Collection

Today technological innovations are providing opportunities for improving TB control in India while bringing new opportunities to the vast, diverse population of India. Still the present limitations socially and economically made it complicated to overcome this bridge. Though the outcomes with an effort can bridge the gap of diagnosis of MDR-TB patients quicker still the effect of these programs should be addressed to the public health in a manner that is understandable thus overcoming the social barriers that bind India in this fight against TB.

To study awareness of TB, a survey in northern part of India at the community level with different age groups of youth was done to check awareness of the TB disease and data was collected. Using two KAP survey groups 2010–2011 (baseline) and 2012–2013 (midline) related to at least thirty cities in India was observed. Though 11percent of the population was aware of the cough symptoms but at least 7percent were on baseline towards knowledge and test on tuberculosis. This brought a conclusion that though the knowledge of TB was on treatment and tests still the conception of TB disease being communicable if shared food or water is taken was still lacking (Thapa B, 2016).

Some limitations observed were the geographical factors, socio-economic and cultural information, as well as the uneducated class, which kept certain misconceptions to be held tight with custom views and prejudices of each family. This showed that there would be many parts of global developing countries that the community is unaware of the social setbacks with this disease. It becomes necessary, therefore, to educate them on all parts of this communicable disease on symptoms awareness, diagnosis and the free treatments available.

The attitudes of the young towards the disease and the disease that was associated with HIV in some country population, was a stigmatism for some who did not want to be cured. The cultural differences in countries showed that they preferred social isolation as to moving towards the remedial therapy. Age was one of the factors that led in some of the nations towards attitudes and health consciousness towards the disease. Many countries still consider that TB sufferers are a stigma socially. With this conception, it becomes necessary to find ways and remedial measures for these developing countries to look upon people who suffer from TB and not label them as social outcast as found in Africa, Ethiopia or Malaysia.

Various notions and research articles focus on TB data by organizations, but mostly the etiology and social barrier seems to be the cause of high prevalence in developing countries. TB is named as a species of boundary suggesting though it is thought as a clinical infestation, still public health considers it as a social outcast in underdeveloped countries or as an immigrant disease. Moreover, epidemiologists consider distribution and location aspect of the country when thinking of TB which acts in boundaries of the health policies.

As mentioned by Starr, (Starr,1982) boundaries exist as one analyzes health care to be more political and the public health, which should be towards public more private. This creates functioning boundaries towards TB leading one to various cultural distributions that cause the disease. According to Starr, there can be four types of limitations but the fifth one, the visionary becomes the main one when applied to TB.

It is a challenge as organizations portray the numbers and sometimes policyholders are unable to challenge and depend on the institutions. The policyholders are caught in between regulations, social norms of the country or sometimes ignorance of the disease, as they are not the sufferers. Not understanding the socio-economic condition of the TB sufferer, it is difficult to control and understand the behavior, race or the individual responsibility that comes with the disease. It is necessary, as Starr says, that the doctors and patient, each has to be visionary when outlying the treatment plan as it needs to be beneficial even if sometimes the medicine or treatment is not followed correctly.

Chapter 5

Stages and Tests of Tuberculosis

5.1 Introduction

TB results in countries sometimes having limited therefore it becomes necessary to organize a set of rules for the diagnosis so even the low income people can have the right treatment of care. Medical history, patient questionnaires or direct history first was used in the diagnosis of TB. The symptoms were obtained about cough for three weeks. Symptoms of fever, chills, night sweats, weight loss or fatigue were considered.

5.2 Stages of Tuberculosis

TB has a latent phase and an active phase (RevolV, 2006). More recent publications have suggested that TB is more of a spectrum from infection to disease, than a simple two stage pathogen. To

understand entirely how TB was infecting and what types and stages there were on infection with the facts behind the active and latent stages of the person's immune system was important. Moreover, it was necessary to comprehend how this all shaped up in behavior and risk factors.

As I researched I found that there were a couple of stages of TB which included the initial infection, then the early primary or active disease next came the late primary or and lastly the latent disease. This can be seen in Table 1 below. 1) Primary Tuberculosis (PT) usually happens in unexposed persons. The microorganism can be active only in 5% persons infected. But *M. tb* bacteria sometimes becomes dormant in the immune system of people for numerable years and shows no signs of infection or disease. (Goyot-Revol V, 2006). When this happens, it is referred as the latent infection because the T cells form a granuloma along the macrophages, which do not allow it to spread (Jensen PA, 2005). But sometimes as years pass by it becomes active TB as it resurfaces again whenever the immune system suddenly becomes active when in contact with diseases like HIV, renal failure or chemotherapy moving the disease progress towards active TB. (Frieden TR 2003). Reports have indicated that about 10% patients who have latent infection get reactivated. (CDC Surveillance reports, 2006), resulting in a weak immune system (Thrupp L, 2004).

Table 1: Differences in the stages of tuberculosis

Table 1 Differences in the stages of tuberculosis

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

2) Primary pulmonary TB (PPTB) can only be detected by various tests as shown above in Table 1. This type of disease is usually very insufficient and spreads through the lungs towards the lymphatic system causing fever and pain. It is usually asymptomatic since its detection is very poor

3) Primary Progressive TB (PPT) advances in the active TB population though it is found to be less than 10% present in TB sufferers. Signs and symptoms are usually with fatigue, losing weight instantly, fever and night sweats. (CDC,2009). Soon it changes the body system with increasing coughs, which start giving out white infectious sputum in the patients (Ddungu H, 2006). The white leukocytes are seen to be increasing in white blood cell as infection increases. Thus, increase in disease symptoms may lead to dyspnea because of reduced lung diffusion (Paton NI, 2004).

4) Extra-pulmonary TB (EPT) is usually present in patients whose immune system has been suppressed and occurs more likely in more than 20 % population. The infection increases and affects the nervous system which could lead to meningitis and ultimately might result in death (Frieden TR, 2003). Sometimes this advance stage mycobacteria infection goes into the blood stream and is termed as miliary TB leading towards different organs of the body to be infected. (Wang JY, 2007). A) Miliary TB advances quickly in the system and is not easily diagnosed, as the symptoms sometimes are broad. (American Thoracic Society, 2000). Another form of extra-pulmonary TB is the b) lymphatic TB, which is a frequent advancement in many patients resulting in cervical adenopathy and also other locations like the bones and joints could also get this type of TB. (CDC, 2009).

5.3 Discovery of Medicines for Treating Tuberculosis

As *M. tb* got discovered need for medicines to treat TB was needed. Discovery of a substance that killed a microorganism, which caused syphilis by Paul Ehrlich, a German scientist in 1910, led towards the belief that if more substances were developed treatment for TB would be possible (Nobel prize, 2010). This initiated in 1935, the discovery of Prontosil, which contained sulfur for treating bacterial infections by a German scientist named Gerhard Domagk (Schrag SJ, 1977). He was awarded the Nobel Prize in Medicine in 1939(Nobel Prize 2010). New drugs were needed to treat TB. 1943 brought in the discovery of antibiotic streptomycin by an American scientist, Selman Waksman, who showed that the fungus *Streptomyces griseus* produced a substance called streptomycin that had some resistance towards TB (Schatz AB, 1944). After many tests on animals, it was finally tried on a woman

suffering with TB in 1944, was cured of the disease. This discovery of treatment led Domagk towards the Nobel Prize in Medicine 1952. Soon this drug started becoming resistant to tuberculosis and in 1943 discovery of another drug called para-aminosalicylic acid (PAS) which when combined with streptomycin showed that the bacteria infecting TB were not becoming resistant (Lehman, J, 1946). Lastly, with the discovery of drug called isoniazid, by Domagk, in 1953 again followed and thus came in medicines for TB oriented disease. 1960 brought in ethambutol which was better tolerated than para-aminosalicylic acid (PAS) (Thomas JP, 1961). Coming in of the 1967 period chemotherapeutic agents started coming on board for helping Tuberculosis patients. Agents like Rifampicin and Pyrazinamide were discovered in 1959 for short-term chemotherapy (SCC) for tuberculosis thus helping in the treatment of TB to nine and six months respectively (Chakrabarty S, 2015)). The discovery the drug Rifampicin became the first anti -TB disease drug to be used against TB as treatment in 1966(Maggi N, 1966). Since these drugs were becoming effective no new drugs were discovered, and 2012 brought in the discovery of two new drugs Delamanid and Bedaquiline to be used for MDR-TB treatments (Otsuka, 2015)

Drug	Year of discovery	Mode of action
Streptomycin (S)	1944	Inhibition of protein synthesis
Pyrazinamide (P)	1952	Converted to pyrazinoic acid (inhibit protein and RNA synthesis)
* Isoniazid (INH) or (I)	1952	Inhibit mycolic acid synthesis (reduce NAD content)
Ethambutol (E)	1961	Slow inhibition of RNA synthesis (affect lipid and cell wall metabolism)
* Rifampicin (R)	1965	Inhibition of RNA synthesis (bind to bacterial DNA-dependent RNA polymerase)

Table.2 Discovery of drugs and their use (Yew, 2007)

- Means effective treatment
- WHO recommended dosage of medicines for active new TB patients (WHO,2010f)

Chemotherapy agents	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg)	Maximum (mg)	Dose and range (mg/kg)	Daily maximum (mg)
Isoniazid (INH)	5 (4–6)	300	10 (8–12)	900
Rifampicin (R)	10 (8–12)	600	10 (8–12)	600
Pyrazinamide (P)	25 (20–30)	–	35 (30–40)	–
Ethambutol (E)	15 (15–20)	–	30 (25–35)	–
Streptomycin[a] (S)	15 (12–18)		15 (12–18)	1000

Table.3. Recommended doses of first-line anti-tuberculosis drugs for adults (WHO, 2010f)

5.4 Diagnostic Tests and Vaccines of Tuberculosis

One of the most commonly used microbiologic tests to detect TB remains the acid-fast staining technique, which relies on smear microscopy. Though this test was easy, it has a very low sensitivity and many sputum smears were needed for its detection of TB. Another important assay for detection of TB was the skin test, the Mantoux tuberculin skin test (TST) or the TB blood test can which was used to test for *M. tuberculosis* infection for latent infections. The detection was done by an intradermal injection in hand of a 0.1 ml solution five tuberculin units in purified protein derivative (PPD). Once injected after 48 or 72 hours it was read to see that it did not swell or was having redness as a positive sign of TB detection measurements as seen in Figure 6 and Table 4. below (Knechel NA,2009). Though this test for detection is good it had limits because it did not detect various species of bacteria (GoldrickBA, 2004).

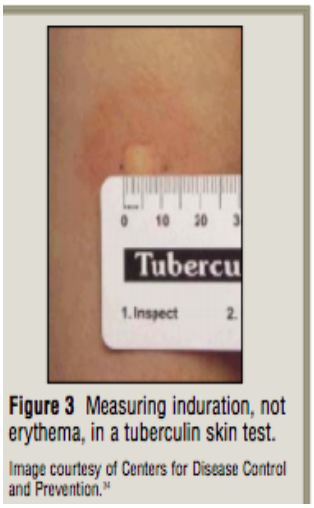


Figure 3 Measuring induration, not erythema, in a tuberculin skin test.

Image courtesy of Centers for Disease Control and Prevention.[34]

Table 3 Positive tuberculin skin tests

Diameter of induration	Considered positive for
≥5	Persons at high risk for tuberculosis: Patients with chronic diseases (eg, infection with human immunodeficiency virus) Persons with recent exposure to tuberculosis Patients with findings on radiographs suggestive of tuberculosis Employees of hospitals and long-term care facilities
≥10	Persons at risk for tuberculosis: Injectable drug users Persons in close living conditions Persons born in countries with high prevalence of tuberculosis
≥15	Persons who do not belong to either of the other groups

Figure 7. Positive tuberculin tests: The Mantoux tuberculin skin test (TST) which was used to test for M. tuberculosis infection for latent infections by measuring induration in a tuberculin skin test (Knechel NA,2009)

Table 4. Positive tuberculin tests: The Mantoux tuberculin skin test (TST) which was used to test for M. tuberculosis infection for latent infections (Knechel NA,2009)

Since the skin test was right for latent tuberculosis infection, another assay was detected called the interferon Gamma Release assay also commonly known as the QuantiFERON-TB test. The detection was done by incubating whole blood with an antigen and used an immunosorbent assay to measure how much the white blood cells released interferon-γ in detection tuberculosis (Leylabadlo HE,2016). Radiological tests like imaging of Chest X-Ray were taken as WHO required chest radiography to see any lesion present in lungs or chest. The pattern found were related to clinical history or TB treatment if ever was done.

5.4 Discovery of Diagnostics and Tests associated with Tuberculosis

Table 2 Diagnostic tests for identifying tuberculosis

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

Table 5. Diagnostic tests for identifying tuberculosis (Frieden TR, 2003)

Vaccines Developed for TB first was the BCG Bacille Calmette-Guérin (BCG) discovered in 1920 by two French scientists Albert Calmette and Camille Guerin (Rowland R,2011). This vaccine is nationally in developing countries especially for children especially so as to safeguard children from getting TB meningitis (Kntechel NA,2009). This vaccine is nationally in developing countries especially for children especially so as to safeguard children from getting TB meningitis. More clinical trials are being done to develop vaccines like H56, which is made up of Ag85B, ESAT-6 and Rv2660 antigens, and is used as post infection entering phase I/IIa (Billeskov,R 2016).

As it was necessary to learn how the TB disease was being categorized and deduced in different patient population, for me, it became essential to understand how the diagnostics tests were used and how each population was decided from these tests. It was necessary to know about each test then understand the impact of this disease given to the patient community and how it was essential to recognize the categories so future role of health cares in deciding treatment would become easy.

5.5 Evolution of Sanitorium, Technologies, and Medicines

As the tests for diagnosis were being used in detecting TB an evolution in Europe by Hermann Brehmer to open the first sanitorium of high altitude in Görbersdorf, in the Silesian mountains, Poland **(**DanielTM,2011) so that treatment of pulmonary tuberculosis would benefit the physical life of the patient with a healthy diet and exercise program. This had become necessary as explained by Starr (Starr,1982) in his book on social medicine that to remain healthy comes from within, and that decision was to be taken by the individual if he needed to be healthy. According to him all TB clinics were becoming clinics of knowledge, not only giving medicine but also educating all on

the role of hygiene thus moving towards a better public health scenario in Britain and United States. The introduction of technologies and medicines with programs in educating public awareness of the causes of TB has been encouraged by organizations like WHO and who have been working cohesively (World Bank, 1993). Though it is necessary to look at the socio-economic way of living as one of the factors, developing a healthy life should be encouraged controlling TB in all under -developed countries. So it is not just discovering drugs or medicines but taking charge of the living conditions too at the individual end and educating them of the good and bad of the disease.

Chapter 6

Development of Public Health and Strategies and Constraints for Elimination of tuberculosis

6.1 Introduction

After learning about the different tests and different strains of TB, I now recognized how TB has affected the globe and its elimination is a challenge that must be met. I choose to take this challenge and be a part of the elimination and a determination of the leading causes that are stopping it.

Research in the developing countries, concerning the impact that was being caused as displayed in the figures below, brought about a better understanding as to how the microorganism has moved globally creating such a huge health concern.

6.2 History of Public Health

After getting a better understanding about TB, I now know why TB has been getting so much attention globally, not only because awareness is needed to eliminate this disease, but because it is socially considered a disease of the poor. It is stigmatized to the extent that people are put in isolation because they carry the communicable infection or are labeled as untouchables, thus making it such a dreaded disease.

Also, as I moved ahead with my thesis, in order to outline my thesis topic on remedies and elimination of TB, it was necessary to understand first and foremost what was public health and why it became so important globally. As researched, 1920 brought forward the definition of Public Health by Charles-Edward Amory Winslow

(Winslow CE,1920), who became the founder of Yale Public health school, defined public health and helped shape the system on health care policies that became local and national and internationally. According to him,

> *"Public health is the science and art of preventing disease, prolonging life and promoting physical health and efficacy through organized community efforts for the sanitation of the environment, the control of communicable infections, the education of the individual in personal hygiene, the organization of medical and nursing services for the early diagnosis and preventive treatment of disease, and the development of social machinery which will ensure every individual in the community a standard of living adequate for the maintenance of health; so organizing these benefits in such a fashion as to enable every citizen to realize his birthright and longevity". (p. 30)* (Winslow, 1920) Winslow's definition of public health became the standard tool for health policies and involved social factors along with doctors and statisticians as it educated them in taking care of health.

6.3 Theories of Foucault and TB

By understanding this history, it would better frame the judgment that the underlying public policies in eliminating and remedial measures for the TB disease were sufficient or not and if any changes were needed to be brought to help me in framing my research accordingly. The first theory that came to mind was the French philosopher, Michael Foucault (Foucault M,1975). According to him, *"society was subject to a process of medicalization and described the extent to which the medical eye exerted ever more control over matters of everyday life."*

6.3.1 Discovery of Medicine in Countries

According to Foucault public health goes back to the eighteenth century when social medicine was more used. Foucault described social medicine to be actually present-day medicine and was being used for an individual body.

Countries like Germany became responsible for developing the state of medicine considering the body of the patient first. Unlike Germany, France developed the urban medicine where the patient was individualized and kept separate. Finally, as Foucault mentioned, Britain, in the 19th century, brought in the development of labor force

in medicine, where compulsory vaccination were necessary, because the sufferers had reduced labor force and the wealthy wanted to be clear of the disease.

While all this was being discovered in other countries, 1904 brought in the first National Association for the Study and Prevention of Tuberculosis with Edward Livingston Trudeau (Shampo MA,2010) as the President. He was diagnosed with TB and to cure himself he moved towards the mountains where his health got better. Seeing this he developed the theory of "rest cure" with the cold mountain air which led towards an opening by him of a TB sanatorium in 1905 at Saranac Lake, United States, called the Adirondack Cottage Sanatorium. This was the first preventive therapy that did not require hospital visits or timed scheduled medication. According to them, the patient was put in the open air with fresh high altitude air good for the lungs, and given plenty of rest and a proper diet. It was the first public policies to address the TB control.

The National Association soon changed to National Tuberculosis and Respiratory Disease Association (NTRDA) in 1968. And their mantra became "*It's a matter of life and breath, "When you can't breathe, nothing else matters."*

Another change in the TB Association resulted in being called, "*Fighting for Air*" (Jones,1969). This led to public health's formation of a person's individual's space, their hygiene and taking care their own body and it all was so termed under public health.

Public health involved many ideas, not only from individual patients but also from public interventions. Similarly, TB control needed help in funding by local and community groups set by the WHO partnering with local chapters that would follow protocol of state and federal agencies and help stabilize the TB epidemic.

TB was being linked to a biomedical perception where all the rules and policies were made to shape this bacillus both medically and bio-medically. Foucault explained this in his chapter of Medical Perception Birth of a Clinic -1963 (Foucault M,1963) where he brought in the term 'medical gaze' as he focused how the French revolution brought about the changes of medicine. This was the era when physicians stopped being aides of bureaucracy and started taking responsibility for health reforms, thereby moving away from superstitions and involving themselves in dual observations of pathology and physiology.

According to Foucault*, "Facilitated by the medical technologies that frame and focus the physicians' on the*

theory of observation of a patient's body with respect to how the human body worked. And optical grasp of the patient, the medical gaze abstracts the suffering person from her sociological context and reframes her as a "case" or a "condition." The "medical gaze" explained the bond between a physician and a patient showing how the patient was dependent on the knowledge of the doctor. Thus, the gaze became an observation for doctors as they looked at the patient, and the description of the disease as it changed during checkups, which soon became the start in the development of the medical technology. This innovation altered the idea of medicine, and the terminology gave way to specialization through the medical gaze. Developed by Foucault, changes were then brought by the French Revolution as it inferred on drugs that changed the outlook on science.

This was observed and found to be valid in TB because the disease in the body functioned as a separate body and the condition in the person was affected by social and regional as well as economic characteristics.

This theory was found correct as I studied TB! If the birth of the clinic by Foucault was similar to the way the disease had been developed then the development after its emergence of antibiotic treatments and drug discoveries held true. It was now noticeable, as I did my research, that the thinking power towards medicine was different where human health was concerned. The doctors and the health care communities were privatized and needed more money. They went through enormous disagreements as to how the role of medicine would to be managed; primarily in the case of TB because of various factors that played its part socially and geographically.

6.4 Remedial Measures developed and Limitations for eliminating TB

Shortage of TB drugs was an important part in the treatment and care. The hospitals sometimes had few loads of medicines which could not cover the cities TB affected population. Companies that produced drugs were not safe as their production was of low quality as they were not licensed. My curiosity increased when I saw the companies and particularly, the unregulated companies that produced drugs decades ago had not invested heavily in drugs unless they were highly profitable as seen in today's pharmaceutical market this century.

TB is a disease that requires a complex drug regimen and though the drugs are given at affordable prices still the poverty of the country sometimes makes it impossible even to afford it by the TB sufferer. Also the prices of medicines and production of drugs by not licensed companies could change at any time as the companies produce drugs that are to their benefit or support profits on their production. This makes it difficult for TB sufferers sometimes

to support their regime of treatment in cities which are poor in the country. (Harries AD, 2011). This type of unregulated distribution, even from the Food and Drug Administration, led to the production of TB drugs to be inconsistent. Foucault's (Foucault M,1975) view of medicine, having shifted towards private medical care, was coming true. As the 19th and 20th century progressed, one saw the public health being divided into four categories: personal hygiene, sanitary scientific ideas, seclusion and a new way of public health. All of which was more of a concern to some individuals as opposed to a group. Each had its own way of explaining what public health meant and an understanding of diseases and how one could become their manager individually.

Health proposals for public cleanliness and health started to come forward during these centuries. Each playing an active part, were informing schools and organizations the creation of laws that were being made to get better informational data for public health. Spitting laws were being made to control spitting on public streets. The children were being taught public hygiene and women associations started formed resulting in better welfare for women. But even then, the TB control was lacking the full initiative that was needed for public health to become first and foremost.

Though the rate of incidences of the disease were somewhat lowered coming into the 20th century, the idea of isolating patients suffering from TB was softening as new drug therapies were coming on board. The purpose of the sanatoria was now becoming subjective due to health officials' opinions. The idea of bringing it home to TB patients was not working because the officials were personal in making one realize that the hygiene and cleanliness were needed and refused the concept of the sanatoria as a remedy towards disinfection not being utilized (McCarthy OR,2001).

During this time, the free clinics that were started during the 50's, were closing as hospitals and private hospitals were coming up to face this disease. It was not a social dilemma but was becoming an individual priority. This led to the start of the World Health Organizations (WHO) in 1990, the Directly Observed Therapy, Short-course (DOTS**) (**WHO, 2009) which was to be looked after by care givers for individuals' who would take their medicine regularly.

Moving ahead and having my questions and further into the study, I wanted to know how today's TB model could be accountable to control the population globally, geographically and/or socially. The big question in my mind

was that since there is such a vast disagreement in health policies towards global health and public awareness being so weak, how can it be accountable for the vast amount of population discrimination in giving treatment or trying to give the best of health care.

The poverty areas of the population where immigrants or societies are undocumented, illegal residents suffering from TB suffered this discrimination. I searched for these questions that were unanswerable because there was no form or methodology present in any country that could document the TB ratio of these people and there was no way that help could be given to such persons of socially disowned population. This gave way to an understanding that globally there was nothing that could be documented or made to help these people to control TB.

A theory was needed that would not only help globally but approach the problem in such a way that not only this disease could be controlled, but the old cultural barriers could be broken when it related to society and thousand age -old norms and beliefs.

As I got my answer, now the question on my thesis was suddenly becoming different. Was a cure needed to help these TB sufferers or was it a necessary prevention to control TB? I was getting an answer from the global research data and then comparing it with local hospitals, it appeared, that because of so much red tape and regulations in global countries, health care was left far behind when public health was concerned. Social norms and regulations of a country played an important part in developing and eliminating infectious disease

This was mainly due to the socioeconomic conditions that were hampering the cure rate. Factors like ethnic background, living conditions of the sufferer and having responsibilities of supporting the family were a few reasons that made the TB patient unable to take medicines for their cure. And the most important part was being played by the individuals' will to survive in such conditions of TB depending on the stage of the illness. After a good understanding of TB and public health interventions, I researched the literature to see how the data and technology as of today are being utilized to decrease the burden of TB, not only in India but globally.

Chapter 7

Dissertation Conclusion

The *Mycobacterial tuberculosis* bacilli have a distinctive quality as being challenging to reject itself by the human immune system and therefore give resistance to treatment by medicines. This is mainly due to its existence intercellular organism, its structural features and slow replication that makes it a difficult micro- organism.

Today, a major factor that brings concern is TB's relationship with HIV which has led to being a significant contributing factor in the development of TB globally with very low survival rate. One cannot fail to notice an increase of the TB rate among the poor and weak in society especially in suburban countries with maximum prevalence with the HIV infected population requiring challenging remedies to be overcome. Remedies for an elimination of TB now are necessary for countries where the TB burden is high due to the vast Human immunodeficiency virus (HIV) population. Based on my thesis studies now we have an improved understanding of TB and its complications and barriers that it faces as it develops globally. Numerous studies on the TB disease have been seen to be conducted that have drawn attention towards the cause and effect, public health transformation, biomedical research activities, and finally the impact on the individuals globally and socially. Based on these various study points analyzing the TB disease means understanding the public health support with the policies made by WHO along with the development of targeted research to know better how this disease took form across the local and global population.

One can see the many divisions of tuberculosis from its starting leading towards its consequences especially on social injustices regarding public health reform and day to day developments. A prime example could be in the biomedical research being developed to help the people and societies being affected by this disease. We can conclude that that these factors must be understood across global and local communities. Looking at the many ways of classifying tuberculosis it can be defined in a societies day to day routine of the people whose lives have been influenced not only socially, medically, but also resulted in different aspects of politics also.

Development of biomedical models can be seen to help in progressing the elimination of TB being used globally and medically in solving this problem of persons suffering from active disease of TB. This has helped in

finding cures and easy remedies in poverty stricken countries where the instruments are not sufficient for detecting TB and controlling it globally. This paper focused on the different aspects of countries which were economically poor and its impact on individuals socially, politically, and economically which seemed be the main foundation of this disease.

Since public health and policies are dependent on frameworks and standardized procedures finding goals at a native level becomes important because in the diagnosis and treating individuals suffering with TB requires many individuals on different levels who have to collaborate and understand the scope of TB.

My thesis is primarily concentrating on "A novel model of "remedy and elimination of tuberculosis", which for me is needed to include facts like how TB disease etiology works, and with consideration of the incidence of the disease globally, the clinical physiology behind the mycobacterium and finally seeing the diagnostic methods that were used in identifying each stage.

Limitations in following with compliance the drug regime which is long by TB patients leads towards burdens of the country. The need for elimination of TB by countries require newer methods to be developed which can be a short - term therapy rather than long-term compliance of treatment so as not to create problems both nationally and at local levels. Countries with their rules and regulations sometimes are unable to give proper care and treatment to TB patients thus falling behind in the appropriate standard of care. It has been observed that policy health makers are sometimes not aware of the crisis and the bindings of the country and the strict cultural society norms resists them in making helpful policies that can safeguard the suffering patient.

Many times, it has been seen that rural based health systems do not have proper medication to support these TB patients and end up with medications, that have expired for the treatment regime for patients (Almeida D,2003). This results in weaker infrastructure not only of the country but health policies, that shapes the future of the country. Local funding gets dropped due to lack of programs in some states, which leads to disease overload and budget restrictions and good health care just diminishes. This further leads especially in poor countries the will of the

sufferer to give up on life as he is ignorant about tests and treatments that could result in a cure if funding were available.

Newer methods are required for controlling TB because the increasing incidence of MDR-TB is very unexpected. This was observed because the MDR-TB infections increased due to the presence of latent MDR-TB infections which were ignored at initial stage of diagnosis and became active moving towards increased numbers of mortality (WHO 2009). Strategies are needed to be developed to detect this latent TB infection at the early stage in order to eliminate TB at initial stages in the population. Based on my thesis, a new strategy is available for controlling the growth of MDR-TB. The use of Xpert technology is an easier way of early detection of TB. More production of predictive markers like mycobacterial should be developed to be used as diagnostic tests along with production of vaccines. This would make blood or skin testing much quicker, reducing the time needed for preventive therapy (Esmail H, 2014).Another measure for early detection and treatment can be through public health importance, to each individual timely, irrespective of social status or costs, and explaining the course of medicine to be taken continuously though difficulties and side effects may be involved in the process.

Another method for control during latent infections is to start remedial measures with preventive therapy utilizing a nine months' period of isoniazid or a three month course of Rifampicin. A combination of both the unaffected populations with or without HIV would be the use of on the spot diagnostic tests with a single dose of prophylactic. Various methods can be used but I think it would beneficial by developing short tests that are predictive for a shorter period of time like twelve months and perhaps in between if symptoms developed positive then the exposed TB individual can be transitioned into treatment. These types of regular checkups and tests would be helpful in high burden countries, that have TB and HIV patients significantly in their population.

My thesis data suggests the new method in controlling MDR-TB in India will help to consider new sources of new TB infections and also adapting the disease control based transmission generated TB infections. This use of Xpert could be a turnaround number increasing MDR cases and finishing detection of TB finally. This would help in early diagnosis of TB which would move towards treatment early bridging the gap between care and control. Therefore, it is necessary to develop and bring in new diagnostic tests to improve patient and public health. WHO's

new program of STOP TB is trying to come forward with simple procedures that can detect TB both for drug resistant and latent TB infection.

In the run towards developing new drugs by pharmaceutical companies for TB, many antibacterial compounds have been identified but the major task is which can be used and which are cost effective for these developing countries, as monetary impact becomes a leading cause for remedial measures and therapeutic delivery among patients. Secondly, designing first of clinical trials before coming into market becomes a duty as to what type of disease population would work immediately. Therefore, new therapeutic ways and remodeling the public health along with policies will turn TB cure a past into an upcoming future globally. Support groups should be started when new technology gets introduced in order to make aware the patient of possibilities of cure. New ways to help the community should be considered so that TB stigmatism branding the society is removed.

Therefore, strategic planning in Figure 9. is necessary to pay attention to studies, which will not only benefit the community but also as a whole help policy maker to use these upcoming tests for TB detection. (Dorman SE,2010)

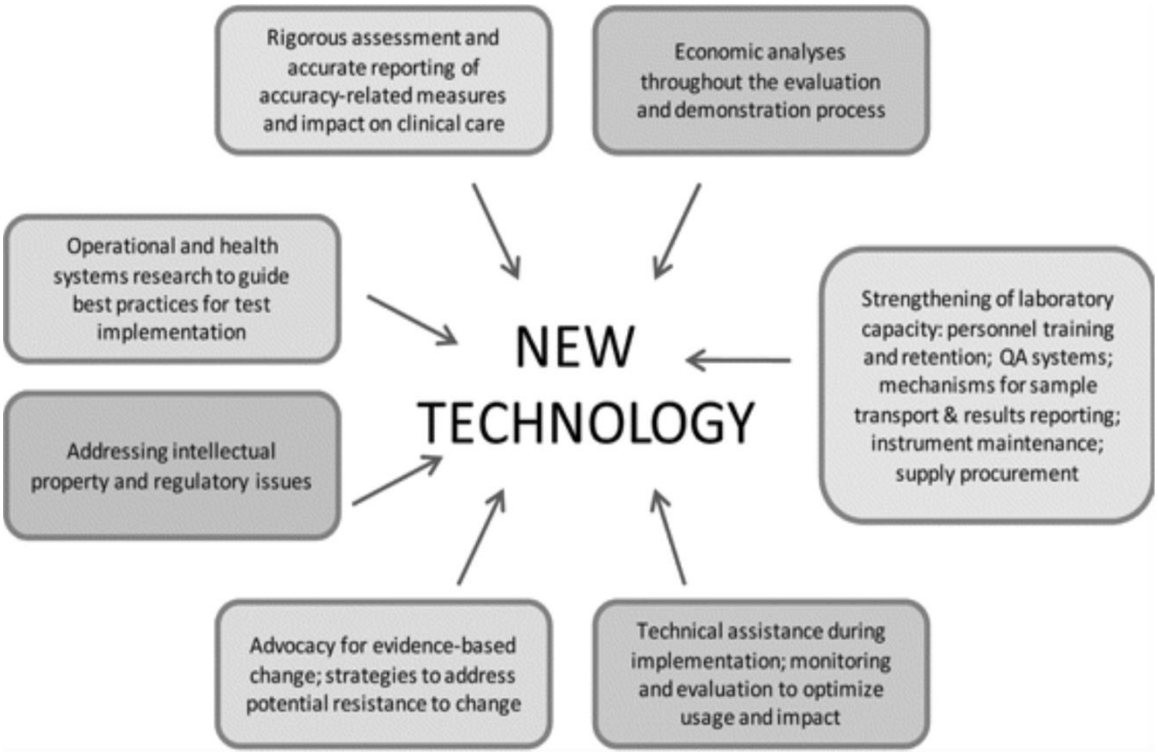


Figure 8. Components of the post-research-and-development process for promising new tuberculosis (TB) diagnostic technologies. QA, quality assurance (Dorman S,2010)

It's important to realize that if infrastructure is good in a country then health care flourishes; if is poor, it leads to various difficulties to overcome. It is necessary to learn the etiology of the disease if any changes are needed to be brought about as it is important to look at various factors when deciding on a change. Social and ethnic factors can be a result which has led to certain factors of the disease to increase in an individual's body, or it might be monetary responsibilities that overshadow treatment. Social responsibilities or age could be a reason but most important is the presence of adequate medicines in health care facilities that have not expired and do not pose a threat of being too expensive.

All of these socioeconomic factors need to be looked at before making a commitment to finishing TB globally. Since public health policies are not diverse, it becomes necessary to start from there, as maybe some regulations are not meant to be involved and need a change. Even when addressing the local community factors regarding this disease, it becomes important to see the diarchy ladder and see if it needs to be dismantled so the common man has all benefits at arms' reach. Therefore, all boundaries need to be observed when approaching TB elimination.

An important aspect that needs to be addressed is the DOT program; hallmark or gold standard for TB detection set by WHO, the Strategy for Tuberculosis Control, Directly Observed Therapy, and Short-course (DOTS) program commonly used to control TB (Bossuyt.PM,2003). This program has made a lot of progress as it goes beyond clinics and straight to the home of the individual suffering in order to help them manage drug and sickness routinely. Even though it's helping many latent infected individuals, sometimes it comes across social barriers. This program is questionable to me because for many developing countries, it does not help, the reason being a more philosophical test, because it requires lots of work from the care nurse or care giver assigned to the patient.

Next, social customs and barriers cannot make it move forward because of restrictions in some countries because of certain challenges of the caregiver. The selective policy just on active TB should be monitored, but is questionable geographically and culturally.

The prevention therapy as marked does not fit all individuals because not all patients get active TB all the time so this biomedical approach becomes useless.

It has been seen non-adherent patients who are lost to follow-up and do not complete their treatment are categorized as “done”. This is not the case and in reporting to the WHO, programs must report numbers of patients lost to follow-up (Hailu H,2015). However, sometimes a relapse happens and the individual is back into therapy and unknowing had the six-month drug regime stopped, this would not have happened. Thus, it is important for public health policies to made in such a way that it is adaptable where it is needed.

Sometimes the drug needs to be continued to the patient and not stopped or sent back to work once he is cured. This is an important factor, which will stop re-activation of TB in many. Also, as programs are being made for active diseases some strategies and drug interventions should start for latent infections as well. My research shows that mostly all policies lead towards active TB so patients who are just being diagnosed should be able to come to clinics for free checkups monthly.

Therefore, it is necessary to open regulations, to such an extent the public health and educate local chapters and ask for help in making the infrastructure strong for that country.

Health importance should become a priority for all and not for a few. Treatment and benefits should be given to all. To accomplish something, it should be a unified goal of the managers, administrators, physicians, and government holders. As shown in my research, TB is beyond the factor of treatment, it crosses certain limitations, which need to be crossed if it needs to be eradicated by 2050.Therefore short term strategies should not be considered by policy holders for TB population but aim towards fully decreasing the load of this disease by programs which are feasible and less complicated for every individual to follow during treatment. The bringing in of WHO’s plan of “STOP TB” is an idea to finish the health concern with TB by 2050 in this global world (WHO, 2009). Controlling TB globally requires all countries to join in this two-step method, first the early detection along with giving proper health care treatment to patients suffering from TB and finally incorporating new methods and new inventions to fight the strains that are infecting TB patients which can change the outcome. Also developing vaccines that could safeguard from getting TB could reduce the transmission of infection and lessen the disease globally.

As seen from my research and information, one can conclude that it's a long way to eliminate this disease. Few words from the famous poet Robert Frost who wrote the poem - Stopping by Woods in 1923 reminds us "… *miles to go before I sleep*", thus we have to really cover lots of miles and countries to defeat this deadly disease.

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