A Review on Tuberculosis Risk in India

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Abstract:
Airborne diseases are constantly gaining attention from researchers. Tuberculosis is an airborne disease through coughing, innate reflex, and generally inborn reflex such as viruses and bacterial infections. Our review is aimed to establish the risk and etiology behind Tuberculosis in Indian public health. The study was carried out using a database like Google scholar, pub med, science direct, research gate, and Elsevier with no time-bound. The study includes numerous parameters to establish Tuberculosis risk, including epidemiology, fatality, care in India's public sector, drug-resistant pulmonary Tuberculosis, and a national tuberculosis control program. Although by review, it was revealed that Uttar Pradesh and other states of the Indian Nation are affected by TB greater or lesser extent, and it can be controlled with evidence-based approaches and preventable measures.

Index Terms- Airborne disease, Tuberculosis, Public health, Epidemiology.

Running title: Study on burden of Tuberculosis patient.

INTRODUCTION

Airborne infections are diseases caused by pathogens and circulated through the air, which remains a significant public health concern. Many airborne infections are transmitted directly (host-host) and indirectly (host-source-host) through actions like coughing, innate reflex, and generally inborn reflex such as viruses (measles, influenza) and bacterial infections. Mycobacterium tuberculosis (M. tuberculosis) invades the human host by aerosol and establishes infection within the respiratory systems by harming host immunity. These bacteria live and multiply in the macrophages, therefore avoiding the natural defense system in the patient's blood serum. Following M. tuberculosis aerosol exposure, three clinical outcomes are possible: bacillus resistance or early clearance, asymptomatic or latent M. tuberculosis infection (LTBI) that can last for years, or symptomatic 'active tuberculosis,' which includes pulmonary disease that can lead to further transmission[1]. There is much significance registered for M. tuberculosis inhalation, i) fail to register an infection, ii) Become infected but not clear the infection, iii) Despite successfully containing the infection, bacilli are still present in the absence of symptomatic disease (latent TB infection), or iv) develop progressive tuberculosis Environmental, host, and pathogen variables are all thought to be risk factors for tuberculosis susceptibility [2].

Tuberculosis (TB) has been linked to significant morbidity and mortality and continues to be a significant global health issue. Despite possibilities for current diagnostic and therapeutic procedures for tuberculosis, millions of people continue to suffer and die due to the disease. Nearly a quarter of the world's tuberculosis patients live in India. If left untreated, this illness has a greater than 50% mortality rate. India has the most significant number of tuberculosis and multidrug-resistant tuberculosis patients globally. In 2015, India had the largest estimated TB burden globally (2.8 million patients) and Rifampicin-resistant or multidrug-resistant Tuberculosis (130 000 cases). In 2019, an estimated 9500 HIV-positive people and 436,000 HIV-negative people died from Tuberculosis (TB). The Government of India has implemented a national strategic plan (2017-2015) that aims to eliminate Tuberculosis (TB) by 2025. On a serious note, Tuberculosis elimination means that for every 10-lakh people, there should be just one case of Tuberculosis [5].

Mycobacterium is produced during necrosis and can infect or disseminate to new macrophages. However, the bacteria are destroyed along with the macrophage after apoptosis. Mycobacterium can survive and even multiply in infected macrophages before specific T-cells activate the adaptive immune response. IFN-α produced by activated T-cells plays an essential role in TB protection. IFN-α is essential for macrophage activation and mycobacterial killing within the cell. TNF- is a cytokine produced by macrophages, dendritic cells, and T cells. It is involved in granuloma formation, macrophage induction, and immunoregulation. Therefore, patients using TNF suppressing agents are at increased risk of infection and reactivation. The hallmark of mycobacterial infection is tuberculoma or granuloma. A tuberculous granuloma is an organized aggregation of immune cells and debris on a microscopic level. They continue to be able to phagocytize mycobacteria [3].

Tuberculosis is classified into several forms, including Pulmonary TB, Pleural Tb, Skeletal TB, Brain TB, Bladder and Kidney TB, Joint TB, Gastrointestinal Tract TB, and Military Tuberculosis. Latent TB does not have symptoms. Instead, a skin or blood test is used to identify it. Active tuberculosis symptoms include Coughing for more than three weeks, chest pain, hemoptysis, feeling tired all the time, nocturnal hyperhidrosis, rigor, fever, anorexia, and weight loss. To avoid clinical relapse, anti-tuberculosis therapy includes the swift killing of actively proliferating bacilli, preventing acquired drug resistance, and sterilizing contaminated host tissues. Official guidelines recommend at least 6 months of combination antibiotic therapy to attain these objectives. The development of multidrug-resistant tuberculosis (MDR-TB), characterized as resistance to the first-line medications isoniazid and rifampicin, as well as extensively drug-resistant tuberculosis (XDR-TB), defined as MDR-TB and as well as fluoroquinolone resistance and at least one injectable second-line drug, poses significant challenges to global tuberculosis control efforts [4].

Tuberculosis (TB) is the leading cause of death from communicable diseases worldwide. Despite significant progress in the past decades, the elimination of TB seems a far-off reach at the current rate of progress. Hence, spreading knowledge about the disease to everyday people and the safety measures are necessary. Therefore, we decided to review Tuberculosis to spread awareness about the disease. The designed study contains detailed research about the epidemiology studies (states), national family health survey/NGO, and risk factors associated with Tuberculosis [6].

MATERIALS AND METHOD

The keywords Airborne disease, Tuberculosis, Public health, Epidemiology were used to search peer reviewed paper to collect the literature using Google scholar, science direct, pubmed and Elsevier with 10 years time bound.

RESULT AND DISCUSSION

Systemic review of epidemiology study

India has the world's most significant TB burden, with an anticipated incidence of 26.9 lakh cases in 2019 (WHO). In 2019 24 lakh cases of TB were reported in India, i.e., over a 12% increase compared to the data obtained in the year 2018. The most significant increase of cases was seen in the private sector, contributing 6.79 lakh notifications in 2019, approximately 28% of total notifications. This is an increase of 25% compared to 2018 when we compare the private sector data alone. Given below is a table(table.1) showing different states of India and the number of TB incidents reported in the year 2019, and the percentage it contributes to the total TB burden of India (Fig 1) [7].

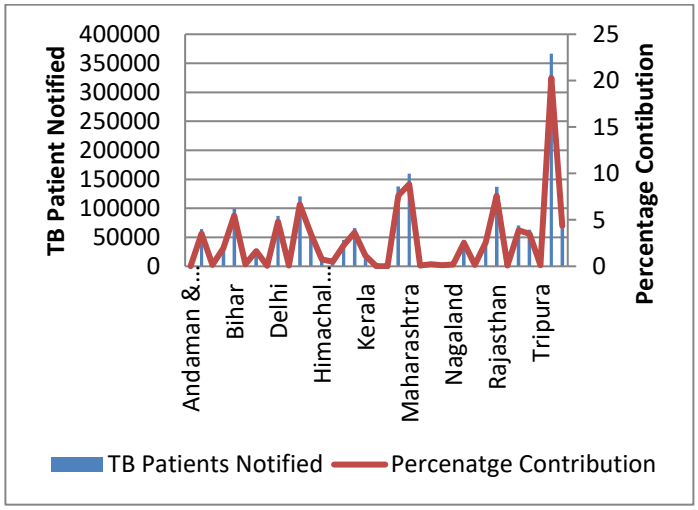

Fig. 1: Graphical Representation of the Number of TB patients notified in different states and union territories of India & Percentage contribution of each state to the TB notification in 2021.

The five states contribute over half of the total notifications every year since they are some of the bigger states geographically and population-wise, namely 1. Uttar Pradesh (20%), 2. Maharashtra (9%), 3. Madhya Pradesh (8%), 4. Rajasthan (7%) and 5. Bihar (7%).

Tuberculosis case fatality in India

The WHO "End TB Strategy" ambitioned the global reduction of case fatality ratio (CFR) below 5%. India is responsible for a third of all Tuberculosis (TB) deaths worldwide. This systematic review estimated the CFRs of Indian patients with tuberculosis during and after treatment. At the country level, the CFR is calculated as the number of TB fatalities divided by the number of incident cases in the same year, represented as a percentage. To meet the aim of reducing mortality by 75% by 2025. The WHO recommends a Global Tuberculosis CFR of less than 5%. The search tactic focused on the convergence of terms related to tuberculosis death and India. The databases Medline (1946–Present), Embase (1947–Present), and Global Health (1973–Present) were searched on January 8, 2019. To limit the data to when up to the minute DOTS treatment was vastly accessible across India, the papers were restricted to those published in 2006 or later. Of the 218 relevant studies identified, 211 provided treatment phase CFRs. Most patients (92.4%) were managed in the public sector. Treatment phase CFRs were more in number for pediatric (no. of patients = 27, 6.50%), drug-resistant (no. of patients = 43, 14.06%) and HIV-affected (no of patients = 35, 10.91%). Case fatality is a crucial indicator of the quality of Tuberculosis care[8].

On paper, India's treatment CFRs appear to meet WHO targets, but several important patient groups stay unstudied, and most methodologies are plagued by methodological errors and are therefore unfeasible. Therefore, a higher quality of reporting on the patient result is necessary to improve the database in this field.

TB Cascade of care in India's public sector

The "cascade of care" is a valuable paradigm for visualizing case detection and retention issues to prioritize interventions. A valuable result of the cascade is 1-year TB recurrence-free survival. This statistic shows whether patients finished treatment and whether it was of excellent quality, as poor adherence

raises the likelihood of TB relapse or death after treatment. The TB India reports include treatment results for all kinds of tuberculosis, except for those who have a negative smear for retreatment. However, MDR TB patients' results are not published until three years after the treatment has begun because of the long treatment duration. Since treatment results for MDR TB patients reported in 2013 were published in the 2016 TB India report, 2013 is the earliest year for which a TB cascade of care, comprising patients with all types of TB, can be developed[9].

The revised National TB Control Programme (RNTCP) covers about half of India's patient population, mainly the public sector. Data from numerous officials WHO report and India's national TB program were utilized to enumerate different steps of India's TB cascade of care in 2013. In 2013, out of 27 lakhs prevalent TB patients in India, 72% were evaluated at government Tuberculosis health facilities; 60% were capably diagnosed with TB; 53% began TB treatment; 45% completed TB treatment, and approximately 39% achieved the optimal outcome of 1-year recurrence-free survival. Patients with a prior history of tuberculosis (retreatment patients) and those with TB resistant to the two most effective drugs (MDR TB) have much poorer outcomes than other TB patients. Increased identification and diagnosis of new patients using newer TB diagnostic tests may be the most critical intervention for improving patient outcomes in specific kinds of TB, such as 1. smear-negative TB and 2. multi-drug-resistant TB. Medication adherence may be the greatest way to avoid a return of other types of TB, such as smear-positive TB. To improve the accuracy of the TB cascade and assess progress toward TB reduction, well-designed research must be conducted at several sites in India's National TB program and the private sector. Furthermore, increasing case identification, particularly in the private sector, is required to improve India's TB care cascade results [10]

Prevalence of drug-resistant pulmonary Tuberculosis in India

The rise of Mycobacterium tuberculosis strains resistant to vital first-line medicines has posed a danger to tuberculosis (TB) control efforts (drug-resistant Tuberculosis or DR-TB). The World Health Organization (WHO) predicted 480,000 incident multidrug-resistant tuberculosis (MDR-TB; resistance to both isoniazid and rifampicin) infections worldwide in 2015. India, the Russian Federation, and South Africa accounted for 45 percent of all notified combined MDR-TB and rifampicin-resistant (RR-TB) cases in 2015, with an estimated 79,000 MDR-TB cases.[9].

From 1995 to 2015, researchers studied the incidence of DR-TB and India's geographical diversity in resistance patterns. For clarity, distinct forms of resistance are referred to as follows. [9]

• DR-TB consists of two types of resistance: mono resistance (to a single first-line antitubercular medication) and poly resistance (too numerous first-line antitubercular treatments) (resistant to more than one 1st line anti- TB drug other than isoniazid and rifampicin)

• MDR: Isoniazid and rifampicin resistant.

- Pre- XDR: MDR + resistant to fluoroquinolone or 2nd line injectables. However, not both
- XDR: MDR + resistant to fluoroquinolone + resistant to 2nd line injectables (capreomycin, kanamycin, amikacin) [9].

The study was performed based on two essential variables

1. By decade: Decade 1 (1995–2005) represented the early years of RNTCP deployment, whereas Decade 2 (2006–2015) covered the later years of RNTCP implementation [11].

2. By region: Jammu and Kashmir, Himachal Pradesh, Punjab, Uttaranchal, Haryana, Delhi, Rajasthan, Uttar Pradesh, Bihar, and Jharkhand were included in North India. South India includes Andhra Pradesh, Karnataka, Kerala, and Tamil Nadu; West India includes Gujarat, Maharashtra, and Goa; and East and central India includes West Bengal, Orissa, the northern states, Chhattisgarh, and Madhya Pradesh [12].

As a result, over 40% of 45,076 suspected isolates tested positive for any 1st line anti-TB drug. Furthermore, the rise of MDR-TB was seen more in previously treated TB patients, i.e., in decade 1(29.8%) and decade 2(35.8%) in comparison to that of freshly diagnosed cases [decade 1(4.1%) and decade 2(5.6%)].

According to the results acquired from a region-based study, the Western States of India reported the highest rate of DR-TB (57.8%) and MDR-TB (39.9%) during decade 2. The prevalence of pre-XDR TB was 7.9%, with fluoroquinolone resistance (66.3%) being the most common. The rate of XDR-TB was 1.9% over two decades of study. The results indicate a considerable rise in the prevalence of different types of drug-resistant TB in India; hence, it puts forward a considerable challenge to the health management system and calls for a more structured nationwide surveillance of TB to make India's TB accessible [2][9].

Revised National Tuberculosis Control Program

The RNTCP, abbreviated as the **Revised National Tuberculosis Control Program,** is the Program launched by the Government of India to eliminate Tuberculosis in India. Recently, it was renamed as National Tuberculosis Elimination Program (NTEP) in 2020 to eliminate Tuberculosis in India by 2025. DOTS (Directly Observed Treatment Short-course) strategy was put up under the RNTCP in 1997. By 2006, the DOTS strategy successfully achieved nationwide coverage [13]. By 2015, the DOTS aimed to attain and maintain an 85 percent cure measure amid new sputum positive (NSP) patients and a case identification measure of at least 70% of the projected NSP cases in a specific population. RNTCP is the 2nd most extensive Tuberculosis Control Program in the world. The RNTCP has more than 16,000 microscopy centers and more than 600,000 DOTS providers[14]. In some larger cities with limited health infrastructure, the RNTCP has funded specialized full-time staff for microscopy and treatment observation. In these urban areas, approximately one laboratory technician and one treatment observer (TB Health Visitor) are funded and hired to provide services for each 100,000-population covered. In some rural areas with large vacancies, the program has funded laboratory technicians as a temporary measure. To make the RNTCP more accessible to tribal and marginalized groups, they developed a Tribal Action Plan, which was implemented with the additional Tuberculosis (TB) Unit and Designated Microscopy Centre (DMC) in tribal and remote areas of the country, more staff were recruited under the Tribal Action Plan, higher rates of salary were offered to the contractual staff to encourage them to work in remote areas.

Under the DOTS program, diagnosis is made by sputum microscopy; treatments are directly observed, as the name suggests. Standardized regimens and methods are used for recording and reporting. Every patient visiting health centers with coughing symptoms for more than two weeks is directed to submit their sputum. The sputum undergoes three sputum smear examinations over two days. Patients are treated with anti-tuberculosis treatment if two smears are positive for acid-fast bacilli. If all the smears are negative, one to two weeks of broad-spectrum antibiotics is prescribed. If one of the smears is positive or the symptoms persist, a chest radiograph is done, and the patient is evaluated. Diagnosis and treatment are free of charge to the patient. Recording and reporting are performed according to WHO

recommendations, with the progress and outcome of the patient recorded and reported quarterly[15].

RNTCP provides Health care to TB patients in the three-tier system of sub-centers, Primary Health Centres, Community Health Centres, and urban areas through the Urban Health Centers. The basic principles of the RNTCP are 1. To ensure adequate funds, staff, and other vital inputs, 2. Diagnosis as per WHO guidelines, 3. Regular undisrupted supply of anti-tuberculosis medicine, 4. Direct observation of every dose of treatment in the intensive phase and at least the first of three doses each week in the continuation phase of treatment, 5. Systemic monitoring, supervision, and cohort analysis; one additional paramedic staff for uninterrupted treatment [11]. Some of the Scholars cited that even after decades of the implementation of the RNTCP, there is still a lack of awareness among the public of this country. Due to the lack of awareness, more than half of the TB patients are either treated in private sectors or are left untreated. Most private practitioners do not have appropriate training programs and adequate information, due to which the TB patients are receiving inadequate treatments. The main critical limiting factor of the RNTCP was the health services' ability to diagnose a large enough number of cases and treat them.

Pediatric TB Management under RNTCP

Pediatric Tuberculosis has received lower priority than adult TB in national TB programs as it is considered non-infectious and challenging to diagnose. In contrast to National TB programs, RNTCP has accorded high priority to Pediatric Tuberculosis since the inception of the program in the country. The project was implemented in 4 major cities of India, namely Chennai, Delhi, Hyderabad, and Kolkata, where the population is over 30 million, to provide all pediatric presumptive TB cases free of cost Xpert testing. Children coming with signs and symptoms of TB in any public or private health facilities were given an option of prescribing free of cost Xpert testing. Xpert testing was performed on specimens like gastric aspirate /lavage (GA/GL), bronco-alveolar lavage (BAL), CSF, sputum, lymph node aspirate, etc. Samples were collected at the referral facilities, which had a link with Xpert testing laboratories in the city. Sputum smear examination was done as per the guidelines of RNTCP, and Xpert testing was done according to the project diagnostic algorithm. More than 40000 pediatric TB cases were provided access to Xpert testing. More than 90% of the cases were from public health facilities, were among them, the proportion of male patients was higher. Higher rifampicin resistance was found in children in the age group of 10-14 years. To simplify the diagnosis and treatment of Tuberculosis in pediatrics, RNTCP, in consultation with the Indian Academy of Pediatrics (IAP), has found a new algorithm for diagnosing pulmonary TB among children. There were three key treatment components. 1. Same as adults, Tb was classified, categorized, registered, and treated with intermittent short-course therapy, given under DOTS, 2. Children are assigned 6 pre-treatment weight bands and are treated according to their weight band-wise doses. 3. Uninterrupted good quality "ready to use" patient wise boxes containing the complete course of anti-tuberculosis drugs are made available to every patient registered. RNTCP suggests that physicians working in public and private health facilities diagnose and treat patients according to program guidelines [16].

Combined Efforts of RNTCP and NGOs

Since the 1990s, WHO has been showing keen interest in bringing the Private medicinal practitioners and public health facilities under one goal of improving the health of populations based on mutually agreed roles and principles. RNTCP has begun to encourage the development of private-public partnerships to assist in the rapid expansion of the DOTS strategy. The research was conducted in the Bhor Tuberculosis Unit in the Pune district of Maharashtra by the Pune-based NGO, which

facilitated creating the linkage and monitoring of the project. Meetings were held between Private medicinal Practitioners (PMPs) and public health facilities to create the study process, determine the evaluation methods, and develop the referral system. The model was introduced in October 2001. The staff from the NGO monitored the referrals from the PMPs, they also went through with the data of RNTCP, and it was later validated with the various software to make sure that the data had been appropriately provided. They used different indicators for different approaches Process indicators were implemented to check the links between the two sectors. Moreover, outcome indicators were also introduced to check the project's overall outcome. However, as the project was withdrawn, many PMPs denied continuing this partnership as the infrastructure public health sectors were not up to the mark, and the delayed production of the examination results discouraged the patients visiting the PMPs. Also, the process was challenging to process and sustain, as without the help of an NGO, monitoring the linkage between the two sectors was burdensome to the RNTCP [17].

From the research done in various parts of India, it was evident that several NGOs were growing and flourishing in areas where the public health facility program was falling apart. Declining of the National program and the flourishing of the NGOs were occurring mainly because the NGOs implemented their projects in the designated areas, and they were focused on bringing the notification rates down for the area where NGOs mainly believed in counseling the people of the area regarding the disease. National programs, on the other hand, implement the same strategy all over the Nation due to which people in the remote areas do not understand the concept, and due to the fear of stigmatization, they depend primarily on the home remedies, which brings down the person health so does same with the success of National TB program of the country.

National Health Family Survey

During the National Health Family Survey -2 from 1998 to 1999, it was found that the poorest of people are the ones who are more affected by Tuberculosis [6]. They are furthermore pushed towards poverty because of Tuberculosis. Apart from poverty, the gender difference plays a significant role in society, and women are more affected due to TB due to the factors like malnutrition, ill health, HIV infection, repeated childbirth, fear, and stigma associated with Tuberculosis. As per the research conducted in the northern state of India Chandigarh in the year 2002, where the sex ratio was 818females per 1000males, the notification rates of the TB in the retreatment groups before the age of 20 years are higher in females, which may be due to cultural seclusion practices, socialization patterns, nutrition, etc. In countries with low income, women often have lower socioeconomic status giving them reduced access to locate and reach appropriate health services as the decision of treatment is made by the male member of the senior member of the family who tends to be earning [18]. A comparison between age and sex-specific prevalence and notification rates suggested that low notification rates in females are due to the epidemiological factors rather than the differential access to health care. However, it has been observed that even though males have a higher TB notification rate, women have been found to have an increased incidence of extrapulmonary Tuberculosis compared to men. Marital status has made a significant difference for females. Treatment seeking of females who never married or separated is significantly higher (about 80 percent) than currently married (about 50 percent) females. This is because of the gender difference prevailing in society. Married females are more likely to have restrictions from other household members, especially husbands and in-laws. Improving the economy and reducing poverty are relatively long-term goals. It may take several years to bring down the poverty level, increase living standards, or provide better housing. However, education is vital for a better future, especially for females who are traditionally

prohibited from making independent decisions in their favor [19].

During the NFHS-4 2015-2016, trained personnel were sent as an interviewer to the households covering all 640 districts in 29 states and 7 Union Territories [5]. Any adult family member with the ability to provide information about the households was chosen as a respondent. Information like whether the patient is taking treatment from public health services or private sectors. Other information includes gender, age, education, wealth, residence, household structure, and type of hospital family members go for treatment. Statistical analysis was conducted based on the responses. As a result, around 8500 self-reported cases were identified among 28 lakhs usual residents in the household covered during the survey. The differences of about 50.46 to 837/ 100,000 population self-reported cases were found among different states and union territories [11].

ASSOCIATION OF TB WITH RISK FACTORS

Despite several efforts to ameliorate Tuberculosis's case identification and treatment conformity, it remains a significant health problem globally. It is the single highest curable infectious disease in today's world. It usually affects the lungs and is transmitted from person to person via droplets. Those at risk of developing this disease include poorly nourished individuals and those with poor immune defenses, such as those infected with HIV, diabetes, alcoholics, patients with leukemia, and patients receiving immunosuppressive therapies. HIV infection, male sex, comorbidities such as diabetes, family history of TB, lack of a Bacillus Calmette–Guerin (BCG) scar, smoking, alcohol usage, single marital status, overcrowding, and poor socioeconomic position are all reported TB risk factors [20] [21].

The key risk factors for the association of TB are as follows

Immunosuppressive Conditions

HIV co-infection is the most potent immunosuppressive risk factor for developing active TB disease. HIV co-infection greatly enhances the likelihood of reactivating latent tuberculosis infection and accelerates TB development following primary or reinfection with the disease. HIV co-infection worsens TB illness, and TB co-infection speeds up HIV replication in afflicted organs such as the lungs and pleura. Through enhanced systemic immunological activation, Tuberculosis also hastens HIV development. As a result, co-infection accelerates disease development and increases mortality in patients for various reasons. Individuals with immune-mediated inflammatory disorders (IMID) have an increased risk of developing active tuberculosis (TB), particularly after using TNF—alpha inhibitors to treat various autoimmune illnesses. In addition, many of these illnesses have been linked to an increased risk of infection, particularly tuberculosis (TB), in locations where the disease is prevalent [22].

Malnutrition

According to studies, malnutrition (including micro- and macro-deficiency) has been linked to an increased risk of tuberculosis (TB) due to a weakened immunological response. [1]. In addition, because of decreased appetite and alterations in metabolic pathways, Tuberculosis can cause malnutrition. The relationship between malnutrition and tuberculosis was proven in BCG vaccination trials undertaken in the United States in the late 1960s, with estimates indicating that malnourished children are twice as likely to contract tuberculosis as their well-fed peers [7].

Socioeconomic and Behavioral Factors

Rapid urbanization in emerging nations and their socioeconomic level (SES) has also impacted individuals' vulnerability to infection. [23]. The burden of tuberculosis follows a clear socioeconomic gradient both between and within nations, with the poorest countries facing the most significant risk.

People with poor socioeconomic status are more likely to be exposed to the risk factors mentioned above, which increases their TB risk[24]. Because of cramped living circumstances, co-infection with HIV, and injectable drug misuse, marginalized people, including prisoners, have a higher risk of contracting tuberculosis. While lower-income people are more likely to smoke, there is no clear link between lower-income people with alcohol, HIV, or diabetes [19].

Tobacco Smoke

Bates and colleagues found that smokers had a higher relative risk of TB disease (RR = 2.3–2.7) than nonsmokers in a meta-analysis of 24 studies on the effects of smoking on TB and that there was clear evidence that smoking caused TB infection and disease, with an increased risk of death in people with active TB. In addition, biological variables such as poor mucosal secretion clearance, lower alveolar macrophage phagocytic capacity, diminished immunological response, and lymphopenia produced by nicotine in cigarettes have been linked to increased susceptibility to pulmonary tuberculosis [21].

Alcohol

Alcohol has long been recognized as a substantial risk factor for tuberculosis (TB) infection, and a meta-analysis of molecular epidemiological data has shown that it is a risk factor for clustering in both high- and low-incidence countries. [25]. Furthermore, a systematic review and case-control studies discovered that those who use more than 40 g of alcohol per day and have an alcohol use issue had a much greater risk of active TB. Changes in the immune system, mainly signaling molecules involved in cytokine production, have also been linked to increased cancer risk [26].

A short Introduction to and risk factors associated with MDR-TB

In many countries, multidrug-resistant tuberculosis (MDR-TB) is an increasing danger to TB control initiatives, accounting for 5% of all newly diagnosed patients. MDR-TB (TB strains resistant to at least isoniazid and rifampicin) has long been known as a serious problem; however, the issue is of particular concern because second-line drugs, which are required for treatment, are frequently unavailable, are significantly more expensive than first-line drugs, have only 65-75 percent efficacy, and have side effects that may necessitate hospitalization. [9]. Research risk assessment variables were connected to MDR-TB at the commencement of therapy, among new cases, is relevant from the standpoint of public health policy to identify patients at risk of infection with MDR-TB strains. Patients with MDR-TB strains have a poor response to first-line therapy. Similarly, there is a considerable risk of amplifying resistance among MDR-TB patients if treated with first-line drugs. Early detection of new cases infected with MDR-TB strains can help avoid patient and healthcare delays caused by the system in treatment beginning, and those patients can be placed on a different, more appropriate regimen. This is required to break the MDR-TB transmission cycle. This will further reduce the cost of treatment and improve the implementation of the treatments. MDR-TB is linked to factors including young age, migration, unemployment at the time of diagnosis, poor nutritional condition (based on low BMI), history of drunkenness, homelessness, comorbidities like diabetes, HIV/AIDS, etc. In India, after thorough studies, there was a higher risk of MDR-TB in the people belonging to older age groups [10].

COVID-19 pandemic threats and challenges for MDR-TB services and management

The COVID-19 pandemic poses a unique threat to healthcare delivery to patients with multidrug-resistant tuberculosis (MDR-TB) and threatens to undermine global control efforts. According to the WHO's Global TB Report for 2020, the reallocation of human, financial, and other resources from TB treatment and prevention to the COVID-19 response has resulted in fewer TB case notifications in more

than 200 countries (WHO, 2020a Report). For example, three of the highest TB-burden countries, India, Indonesia, and the Philippines, had TB notifications fall by up to 30% from January to June 2020, compared with the same period in 2019 because of health services disruptions caused by the COVID-19 pandemic [27].

Drug interactions & adverse drug events in MDR-TB patients

All anti-tubercular drugs (ATD) cause adverse drug reactions (ADRs). Because of the negative consequences, patients with multidrug-resistant tuberculosis (MDR-TB) have greater morbidity and mortality. Lower consequences of adverse events leading to permanent discontinuation included levofloxacin, moxifloxacin, bedaquiline, and clofazimine. Three second-line injectable (SLI) medicines, para amino-salicylic acid (PAS), and linezolid have a significantly high rate of adverse effects resulting in permanent cessation. In Indian studies, adverse events to second-line ATD vary from 47% to 58%.4,5 Spontaneous ADR reporting by global studies showed common ADRs related to second-line anti-TB drugs [9].

Risk factors associated with ADRs with Anti TB drugs

Geriatric, Malnutrition, Pregnancy, and lactation, Alcohol addiction**,** Liver failure**,** Chronic renal failure**,** HIV infection**,** Disseminated TB**,** Allergy/atopy**,** Anemia**,** Diabetes Mellitus**,** Family history of ADRs**,** Patients receiving intermittent treatment**,** Patients receiving treatment for other comorbidities, in addition to anti-TB drugs [2].

CONCLUSION

The present study was designed to study the epidemiology of Tuberculosis in India. The study was considered in the 29 states & 8 union territories using an epidemiology study, Revised National Tuberculosis Control Program, National Health Family Survey, and Associative Risk Factors of Tuberculosis [17].

In today's India, WHO-assisted TB control program across the country. The Government of India, in collaboration with the World Health Organization (WHO) and the Swedish International Development Agency (SIDA), reviewed the national program and concluded that it had managerial flaws, insufficient funding, and an over-reliance on X-rays, resulting in improper treatment management and detection [10]. As a result, WHO designated Tuberculosis a worldwide emergency in 1993, developing the DOTS plan and recommending all nations adopt it [11]. DOTS (directly observed short treatment course) Program soon became the fastest-expanding and the most extensive program globally in terms of patients initiated on treatment; and the second-largest population coverage. Between 1995 and 2008, 36 million TB patients were effectively treated in DOTS programs worldwide, eliminating 6 million fatalities. In addition, For the first time in 2007, the treatment success rate (86%) attained in DOTS cohorts worldwide exceeded the global objective of 85 percent[28].

Although the DOTS Programme may seem like a great success, it is too early to say that we are heading in the right direction towards the "End TB Strategy." To support the above statement, we must first look at how a vast country like India's health sector functions and how the people of the country from various economic classes function after being diagnosed with TB. Unregulated private health care leading to widespread irrational use of first-line and second-line anti-TB drugs becomes a significant challenge in the rural parts of India among the poor population. Various factors deviate India from hitting the common target of ending TB: overpopulation, illiteracy, spreading HIV, and corrupt administration. Under the Systemic Review of Epidemiology Study, we have found that India has a higher Case fatality Rate (CFR) of Tuberculosis which is around 10% of the total

fatalities in India, which the WHO has declared under the 'End TB Strategy' that ideal CFR is 5%. Most of the TB fatalities in India are associated with other risk factors like HIV, MDR-TB, and XDR. Under RNTCP, the DOTS strategy introduced by the WHO was being practiced and implemented with all the guidelines in all the TB units of the country [29]. Despite that, most private medicinal practitioners did not follow the guidelines issued by the RNTCP. Notification rates in India do not match the actual ground data as most patients rely on the Private health sector. Also, there is a lack of a system where private and public health sectors can submit their data on a single platform. The current requirement in India is for a more structured treatment protocol for being diagnosed with TB. The private and public health sectors must provide the same treatment at a similar cost [11]. Since the data from the private sector is not structured and feasible for any study, the annual report is largely dependent on public sector data, which fails to provide the required transparency. The government should work upon something that allows the private and public sector records to be collected either online or offline for us to get a clearer view or more of the ground-level report [29].

The current investigation concluded the various parameters affecting Tuberculosis and its epidemiology. Only in 2019 utter Pradesh was the most affected by TB. The WHO estimates that about 780,000 people in Uttar Pradesh have Tuberculosis. However, the state only has 280,000 patient records. This means that 500,000 people have gone unidentified, jeopardizing the federal government's goal of eliminating Tuberculosis by 2025.

Tuberculosis is a huge public health concern in India, and much effort is being put into diagnosing and treating the disease to reduce the overall disease burden in the country. However, there is still a suboptimal quality of TB care, particularly in the private sector. Improvement of quality of care should be a priority for India. India still has a long way to go until completely eradicates Tuberculosis. Moreover, we look forward to providing as much information as possible to help battle tuberculosis through this study.

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Conflict of interest

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