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Review Article

Tuberculosis: a narrative review on epidemiology, risks, implications, preventions and treatments

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ABSTRACT

Tuberculosis (TB) is an airborne disease that generally affects the pulmonary portion of the human body leading to severe coughing, fever and chest pain. It is caused by a bacterium known as *Mycobacterium tuberculosis*, which kills human beings each and every year globally more than the death toll of combined HIV and malaria. However, it is preventable, treatable, and curable. The world is suffering due to this dreaded disease with an approximate number of 11 million TB cases and 1.6 million deaths annually. Tuberculosis increases the public health attention because of its high mortality rates after HIV/AIDS. World Health Organisation (WHO) and Centre for Chronic Disease Control (CCDC) are the leading organizations playing an important role to combat against TB by publishing proper health guidelines and treatments through reliable awareness campaigns whenever there is sudden outbreaks of TB, COVID-19 and related diseases. A wide range of research findings, clinical reports and new treatment methods like multi-drug therapy have been developed to combat TB. It is still necessary to develop new research and innovative ideas and proper implementations of the treatment and prevention guidelines of WHO and CCDC to fight against this fatal disease. In countries having higher increase of populations due to immunosuppressed chronic diseases like HIV, diabetes and pandemics like COVID-19, eradication of TB infection is a very difficult and challenging task. This mini review is based on the critical analyses of the data available from the official websites of WHO (Global Tuberculosis Report), CCDC, and search engines like Medline, PubMed, Google Scholar, and research findings of selected articles, textbooks were used as additional sources which are cited in the reference section.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, Prevention, Multi-drug therapy, Drug resistance

INTRODUCTION

Until the emergence of COVID-19 pandemic, Tuberculosis (TB) was described as, "the most destructive pathogen on the planet" and was ranking above HIV/acquired immune deficiency syndrome. It is actually a leading global public health problem, with high morbidity and mortality in humans. Tuberculosis is caused by *Mycobacterium tuberculosis* (MTB) and other various trains of the mycobacteria. Generally, it affects the pulmonary portion but slowly spreads to other parts of the human body if remains untreated in the right time which will ultimately result in death. TB can also affect other parts of the body, such as the brain, the kidneys, and the bones. Sudden weakness feelings, weight loss, fever, and frequent night sweating are the general symptoms of TB. Persons suffering from TB infected lungs will face problems of chest pain, coughing, sometimes coughing up blood. When the infected person speaks, coughs or sneezes, TB germs are transmitted into the air. These germs can remain active in the air for several hours. Persons who inhale the air containing the tiny droplets of

TB germs can become infected leading to a chain like chemical reactions. It the chain is not terminated at certain stage everybody will suffer from latent TB infection. This mini review focusses on epidemiology, risks, implications, preventions and treatments along with a short history of the origin of TB.

ORIGIN AND EPIDEMIOLOGY

Tuberculosis was detected as a fatal disease of mankind thousands of years ago. A good number of research findings on the evolutionary origins of the Mycobacterium tuberculosis established that the most recent common ancestor of the complex was a human-specific pathogen.[1-5] Richard Morton used the word "tubercles" instead of tuberculosis as associated with various pulmonary symptoms in 1689 and J. L. Schonlein had started using the term "tuberculosis" in 1839.[1,2] Robert Koch isolated the bacillus causing TB as *Mycobacterium tuberculosis* in 1882 and he was awarded Nobel prize in 1905 for his outstanding works in physiology and medicinal research. Other suspicious strains of this mycobacteria are *M. bovis, M. microti* and *M. africanum.* Among these three again *M. bovis* has been reported having a wider host range and is the main cause of tuberculosis in other animal species.[6,7] Milk, milk products or meat containing Mycobacterium bovis are the sources of TB infection when consumed by man or animals.[8] Approximately, 6% of tuberculosis deaths in humans was reported in the pre-antibiotic era due to *M. bovis*.[9]

Drug-resistant tuberculosis is another threat to the global control of the disease. The emergence of multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) is increasing in some regions of the world. The increase of drug-resistant TB demands accurate and reproducible drug susceptibility testing (DST) methods. In 2015, the World Health Organization (WHO) proposed a strategy to end TB crisis by emphasizing on the activities of early, rapid, and accurate identification of Mycobacterium tuberculosis (Mtb) and the determination of drug susceptibility in the treatment and management of this disease.[10]

The death toll due to tuberculosis reached maximum in the late 1700s and early 1800s in Western Europe and the United States, and 100 to 200 years later, it had spread in full force to Eastern Europe, Asia, Africa, and South America.[1-2] The epidemic expanded over the next two centuries and almost all Western Europeans became infected with *M. tuberculosis*, and about one in four deaths were due to tuberculosis.[11] Approximately one-third of the world population is infected with *Mycobacterium tuberculosis*, resulting in more than eight million new cases and two million deaths annually. For almost half a century, TB remains the leading cause of preventable deaths in the world today.

The infection rate in the last decade is still increasing. According to Global Tuberculosis Report published by WHO during the period of 1997-2023, TB infections are approximately 1% of the global population each year.[12] The number of people newly diagnosed with TB fell from 7.1 million in 2019 to 5.8 million in 2020, and reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. By 2021, the number of new cases each year was decreasing by around 2% annually. About 80% of people in many Asian and African countries test positive, while 5–10% of people in the United States test positive via the tuberculin test. In 2022, an estimated 10 million people developed active TB, resulting in 1.3 million deaths, the second highest infectious disease death count after COVID-19.

A pictograph has been drawn depicting the global distribution of TB infected persons in the year 2022, where eight countries accounted for more than two thirds of global TB cases as: India (27%), Indonesia (10%), China (7.1%), Philippines (7%), Pakistan (5.7%), Nigeria 4,7%), Bangladesh (3.6%) and Democratic Republic of Congo (3.0%) (Figure 1). This pictograph is based on the Global Tuberculosis Report published by WHO in 2023.[12]

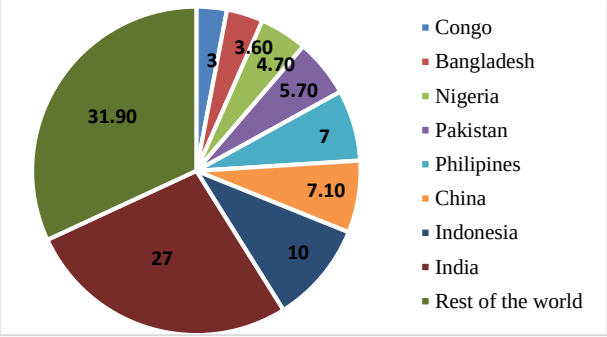

Figure 1: Infection percentage of TB as on 2022 in eight countries.

RISK FACTORS

Co-infection

The highest immunosuppressive risk factor for developing active TB disease is considered as the human immunodeficiency virus (HIV).[13,14] For patients coinfected with TB and HIV, the chances of reactivation of latent infection of TB increases with the rapid TB progression following primary infection or reinfection with TB.[15] Many clinical experiments revealed that diabetes patients have three times higher risk of contracting TB compared to non-diabetic individuals.[16] Even though the biological association of TB and diabetes is not fully understood, many research findings suggest that diabetes depresses immune responses, which in turn facilitates infection with *Mycobacterium tuberculosis* which progresses TB symptoms. During the initial stages of TB diagnosis, diabetes is always checked as the first step.[17-19] Among the comorbidities of COVID-19, the most severe cases are its coinfection with TB. Their symptoms may overlap as each disease belongs to the same category

of acute respiratory distress syndromes (ARDS) and increase mortality rates.[20] In fact, during the outbreak of Covid-19, many challenging research activities have been reported and simultaneous treatment of both the diseases for reducing the mortality and risks.[21,22]

Age factor

There had been reports on infection of TB in paediatric stages which might be due to contact with known TB cases, exposure to smoke, over-crowding in the houses, and poor household conditions particularly in low- and middle-income countries.[23] TB infection is higher in the elderly persons compared to younger and paediatric stages and eventually the mortality rate due to tuberculosis remains higher in elderly patients.[24] Reactivation of lesions that have remained dormant or latent TB infection are the root cause of increase in infection rate in the elderly groups. Changes in the immune system due to aging process actually reactivates the lesions. Even though, all age groups are at risk, adults in in their most productive years have been the soft targets of TB.[24] There have been reports that 80% of TB cases and deaths are in low and middle-income countries.[25]

Gender factor

The latest reliable data of TB (2023) published by WHO reported that men/boys are significantly more at risks of contracting and dying from TB more than females/girls.[26] There have been reports of social mixing as a probable factor for TB transmission from African countries.[27] Men face a higher risk of developing TB disease than women due to risk factors such as smoking and intravenous drug use that are more common among males. The male to female ratio in patients of pulmonary tuberculosis was 2:1. A large number of patients (65–68%) were in the young and reproductive age group. Again, among the male groups, one-fifth patients were found in the elderly age groups.[28]

Apart from HIV, diabetes and COVID-19 co-infection, there are many risk factors associated with TB infection are malnutrition (biological factors), tobacco smoking, alcoholism (behavioural factors), poverty, overcrowding and poor housing (socio-economic factors).[29,30]

IMPLICATIONS

TB bacteria initially attacks the lungs; however, progression will occur by attacking any part of the body such as the kidney, bones and spine, brain and nervous system.[26] The infected patients will not show any sickness initially. However, at the later stage sickness signs due weak immune systems of various organs will be developed. In fact, two TB-related conditions exist: latent TB infection (LTBI) and TB disease. If not treated properly, TB disease can be fatal. The most common indication for tuberculosis-related intensive care unit (ICU) admitted patients is acute respiratory failure due to pneumonia or acute respiratory distress syndrome (ARDS) followed by septic shock with multiple organ dysfunction, adrenal insufficiency, and neurological involvement, especially tubercular meningitis.[25]

Long lasting or permanent lung damage may happen if the TB infected lungs are not treated properly or treatment is discontinued without consulting physicians or due. Patients who couldn't afford the treatment charges, psychological problems may arise. TB patients may be rejected by family and friends or lose their jobs. In some societies particularly in low income and uneducated countries, TB patients are taken as damaged for life or unmarriageable. Such discrimination can result in anxiety, depression, and reduction in the quality of life. The family of the infected person also is at a high risk of contracting the contagious disease. Also, the social stigma attached to the disease can't be ignored. The effect of TB on society and our country India is such that it affects the National Economy at the macro level mainly due to decreased workforce. This leads to lower per capita income and a lower GDP. India is one of the most populated TB affected country with two deaths occurring in every three minutes from. As derived from Figure 1 based on the Global Tuberculosis Report of WHO, India accounts for about a quarter of the global tuberculosis burden.[31] Lack of awareness of health guidelines, illiteracy, superstitious mind and poverty are powerful determinants of tuberculosis. Living and working in poorly ventilated, unhygienic and crowded environments are directly related risk factors of tuberculosis.[32] Inhalation of tiny droplets from the coughs or sneezes of an infected person will transmit to other unaffected persons.

TREATMENT

Symptoms

Weight loss, weakness, and malaise appear to be less common in tuberculosis infected persons which makes difficult to predict the symptom at early stage. However, for HIV-infected patients, diagnostic specimens from any suspected site of disease should be examined for mycobacteria. Analysis of pleural fluid biopsy of persons suffering from pleural tuberculosis can give positive results. In several cases of extrapulmonary tuberculosis which involves the joints and bones, increases with increasing age and is equally frequent in men and women. In central nervous system tuberculosis; meningitis is encountered more than solitary or multiple tuberculomas. Angina patients suffering from chest pain have chances of tuberculosis infection and special observation is required.[33]

Chemotherapy

Several drugs particularly antibiotics are available for fighting against the TB bactericidal activities. Isoniazid (H), rifampin (R), ethambutol (E), pyrazinamide(Z) and streptomycin (S) are the essential first-line anti-

tuberculosis drugs.[10,26] Aminoglycosides (kanamycin, amikacin), quinolones (ciprofloxacin, ofloxacin, levofloxacin), ethionamide or prothionamide, cycloserine, para-aminosalicylic acid (PAS) and polypeptide (capreomycin) are the second-line anti-tuberculosis drugs.[34] Isoniazid and rifampicin are the most effective drugs in preventing the emergence of resistance to other drugs. Streptomycin and ethambutol are weaker but nevertheless effective drugs.[35] After the discovery of streptomycin by S. A. Waksman who was awarded Nobel prize in 1952, many significant advanced methodologies have been developed with reports of 100% successful results.[36] Series of randomised clinical trial reports by Tuberculosis Research Centre in Chennai and British Medical Research Council in Africa established new principles of antituberculosis chemotherapy.[36,37]

One problem in TB treatment by chemotherapy was drug resistant by *Mycobacterium tuberculosis*. Multidrug-resistant TB (MDR TB) is caused by TB bacteria that are resistant to at least isoniazid and rifampin, the two most potent TB drugs.[38] The most important way to prevent the spread of drug-resistant TB is to take all TB drugs exactly as prescribed by the health care provider. No doses should be missed and treatment should not be stopped early. People receiving treatment for TB disease should tell their health care provider if they are having trouble taking the drugs. Extensively drug-resistant TB (XDR-TB) is a rare type of multidrug-resistant tuberculosis (MDR TB) that is resistant to isoniazid, rifampin, a fluoroquinolone, and a second-line injectable (amikacin, capreomycin, and kanamycin) OR isoniazid, rifampin, a fluoroquinolone, and bedaquiline or linezolid.[39] Another advance form of treatment in severe cases of XDR-TB is repurposing of drugs by interchanging with new drugs derived from the approved and established drugs. Mostly antibiotics such as linezolid, moxifloxacin, levofloxacin, clofazimine and meropenem are applied in this treatment.[40] With the advance of medical and pharmaceutical sciences, nowadays TB is considered as curable provided the proper treatments are executed at the right time.

PREVENTION

Some of the major preventive measures are briefly discussed herein with the following sub-headings:

Covering nose and mouth

Tuberculosis transmission in hospitals is a big threat for the staffs working and patients admitted in the hospitals. Surgical face masks used by patients with TB are believed to reduce transmission but have not been strictly tested.[41] Inhalation of TB bacilli during breathing process causes in spreading TB. Thus, respiratory precautions like a face mask and social distancing, in addition to handwashing, can help in reducing the worldwide TB infections. Avoiding handshakes and hugging, close room meetings, casual social gatherings and travel, and the use of face masks may represent a simple way to reduce TB transmissions, especially in those areas which have limited resources but widespread TB.[42] Hospital staffs and relatives visiting infectious TB patients should follow the proper respiratory protection guidelines of the hospital for TB control. Wearing of surgical masks by the admitted patients in the presence of others, especially of hospital staff, and whenever outside the isolation room should be mandatory.[43]

N95 masks had been recommended to use by every person during the pandemic COVID-19 whenever they go out of the rooms or houses which was really useful in healthcare workers in in preventing TB infections. While N95 masks cost 30 times more than surgical masks, preventing TB exposure among healthcare workers significantly outweighs the cost disadvantage.[44]

Mechanical ventilation

Mechanical ventilation is considered as the most effective way to treat respiratory failure which supports to relieve symptoms in acute phase and to gain opportunity for the later treatment.[45] Multiple organ failure and consolidation on chest radiographs are the two factors which increases the mortality rate of in-hospital patients which actually results due to lack of proper mechanical ventilation.[46] Patients in advanced stages are recommended to admit in 6–12 air-changes/hour room with good ventilation according to TB infection control guidelines, However such facilities are found in limited numbers in TB wards in most of the general hospitals.[47]

Table 1. Preventive measures of TB.

S. no.	Methods	Requirements	Benefits
1.	Covering nose and mouth	Wearing of surgical masks like N95 masks	Prevention of spreading the disease due to inhalation of TB bacilli.
2.	Mechanical ventilation	Recommend 6–12 air-changes/hour room ventilation	Supports to relieve symptoms in acute phase and to gain opportunity for the later treatment
3.	Ultraviolet light	Kills tuberculosis bacteria, thus inhibiting the growth or division of it	Ultraviolet lights could reduce the spread of tuberculosis in hospital wards and waiting rooms by 70%.

Ultraviolet light

Germicidal or Ultraviolet-C (UVC) light kills tuberculosis bacteria, including drug-resistant strains, by damaging their DNA so they cannot infect people, grow or divide. Upper-room ultraviolet germicidal ir-radiation (UVGI) systems are considered a supplement or adjunct to other TB infection-control measures (e.g., ventilation) in settings where persons with undiagnosed TB could potentially contaminate the air (e.g., waiting rooms, emergency rooms, corridors, central areas).[48-49] Mass spreading of tuberculosis in hospital wards and waiting rooms can be reduced with the help of Ultraviolet lights. Ultraviolet therapy has been reported to be very effective in destroying bacteria and promoting wound healing. Another additional application of UV therapy is in fighting against the drug resistant bacteria.[50] Table 1 summarizes the three preventive methods of TB.

CONCLUSION

Tuberculosis still remains a deadly disease and a global health issue of the world in spite of the development of newer methodologies for diagnosis and treatments. Like COVID-19, TB is also a worldwide pandemic based on the Global Tuberculosis Reports of WHO. Increase of immunosuppressed populations due to HIV, COVID-19, diabetes or any other infections also hampered the various efforts to eradicate TB. Combination of clinical, radiographic, microbiological, histopathologic methods and appropriate multidrug therapy are successful programs in TB treatment. Some issues like poverty, inadequate health centres/clinics, hospitals with poor infrastructures, unhygienic hospital wards, insufficient funds in health care programs and drug resistance are the major obstacles in fighting the TB disease. Public health management strategies such as diagnosis, contact investigation, and testing of persons who came into close contact with patients with active TB should be implemented in the affected areas. Quick screening of this disease at field level followed by diagnostic tests and short course of chemotherapy are the preventive programs to be executed to end this TB crisis.

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