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Review Paper

Emergence of MDR and XDR Tuberculosis Brought Forth New Strains and Challenges

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ABSTRACT

Tuberculosis, caused by Mycobacterium tuberculosis (MTB) can remain inactive in infected populations and can be reactivated to cause tuberculosis. Risk of MTB infection progressing to TB is highest in immunocompromised individuals, co-infected with HIV/AIDS, diabetes, or undergoing dialysis. Development of drug resistance by MTB, leading to multi-drug resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and other forms of TB are major challenges. HIV-infected individuals with MDR-TB and XDR-TB have extremely high mortality rates. India currently has the highest number of tuberculosis cases globally, including MDR TB and XDR-TB. 'NIKSHAY' tool used to track TB patients during COVID-19 for proper management and treatment. DOTS-Plus program has been implemented to control MDR-TB advocates for chemotherapy and directly observed therapy short course. Early detection and efficient administration of first-line drugs in every new patient can prevent the emergence of MDR-TB and XDR-TB. AIDS patients with tuberculosis are given highly active antiretroviral therapy (HAART) to prevent the spread of untreatable MDR-TB and XDR-TB. To control TB, World Health Organization recommends various approaches, including development of new techniques for early diagnosis, vaccines, and standardized drug distribution. To address this issue, it is crucial to promote social transformation, enhance governmental and global aid, implement DOTS, non-DOTS, and NGO programs, incorporate TB and HIV programs, sponsor research, enact regulatory legislation, and establish medical education programs and awareness among independent practitioners. Improvements in MDR-TB and XDR-TB surveillance, better laboratory capacity for detecting drug-resistant strains, improved infection control measures, and the development of new therapeutics are also urgently needed.

Introduction

Tuberculosis (TB) is the global primary cause of death over human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS) despite vaccination and chemotherapy(Koenig *et al*., 2020). The World Health Organization (WHO) declared Tuberculosis (TB) a public health emergency in 1993 and called for all nations to prioritize TB control efforts (Awasthi & Singh, 2021). WHO states recent cases ≈10.4 million and deaths ≈1.8 million due to TB every year (WHO, 2016). Most of these new cases (approximately 3 million) are currently unrecognized to the healthcare system, and several cases are not getting appropriate medication (WHO, 2016). TB affects India with the highest incidence (2.7 million) and number of deaths (0.4 million) in 2018 (RNTCP, 2019).

Tuberculosis is a contagious bacterial disease; caused by Mycobacterium tuberculosis (MTB) (Miggiano *et al*., 2020); spread among humans through the respiratory system and commonly affects the lungs (Perveen&Sharma, 2022). Fewer MTB infected individuals (about 10 percent) progress to severe TB disease in their lifespan; remaining infected individuals successfully control their disease and remain asymptomatic (Jilani *et al*., 2023). Major challenge of MTB pathogen is that it persists in an inactive state in various infected

populations for a long time and could be reactivated to TB (Salina & Makarov, 2022). The progression risk of MTB infection to TB is highest in immunocompromised individuals and in individuals, co-infected with HIV/AIDS (Azevedo-Pereira *et al*., 2023; Sharan *et al*., 2020).

TB problems become more severe due to co-infection with HIV/AIDS. However, the TB problem with HIV/AIDS co-infection represents merely 11 percent of the entire TB burden in some regions of Sub-Saharan Africa. Third-quarter of TB patients gets co-infected with HIV/AIDS in high burden of TB (Chiang *et al*., 2021). Attempts to control TB infection in such countries are overcome by the increasing number of TB cases occurring in correspondence to the HIV/AIDS epidemic (Behera, 2021).

Despite TB being a manageable infectious disease, ≈1.3 million populations were killed due to TB infection in 2012 (Chen *et al*., 2020). A serious cause of growing TB infection is developing drug resistance by the MTB. The two most powerful standard drugs (isoniazid and rifampicin) used for treatment of patients with drug-susceptible TB, which showed excellent recovery rates. Patients infected with strains resistant to isoniazid and rifampicin, called multidrug-resistant (MDR) TB, stands almost untreatable by standard first-line treatment (Parums *et al*., 2021).

Multidrug-resistant tuberculosis (MDR-TB)andextensively drug-resistant tuberculosis (XDR-TB)

MDR-TB refers to the resistance of Mycobacterium tuberculosis (MTB) strains to standard first-line anti-TB drugs like isoniazid (INH) and rifampicin. This resistance is increasing globally (Singh et al., 2020), leading to the emergence of extensively drug-resistant (XDR) TB that is insensitive to various second-line drugs and all current TB drugs (Uplekar *et al*., 2015; Dheda *et al*., 2014; Udwadia *et al*., 2012). The appearance of MDR TB and XDR TB is due to transmission rather than inadequate treatment (Shah *et al*., 2017).

XDR-TB refers to strains of the Mycobacterium tuberculosis (MTB) that are resistant to INH, rifampin, a second-line injectable drug (SLID; kanamycin, amikacin, or capreomycin), and any fluoroquinolone. MDR-TB strains and XDR-TB strains display resistance to the most potent anti-TB drugs available (Chowdhury *et al*., 2023). The outbreak of MDR-TB in New York City during the 1990s caught the world's attention, as did the rapid spread of XDR-TB across the globe (Loddenkemper *et al*., 2002).

The current challenges and threats of extensively drug-resistant tuberculosis

The emergence of XDR-TB strains suggests inadequate tuberculosis management, and preventing their emergence is a significant global health issue. This poses a challenge to tuberculosis control efforts worldwide, particularly in developing countries and those with limited resources, as well as in countries with a rising prevalence of HIV/AIDS (Jain & Mondal, 2008).

One of the biggest challenges in controlling tuberculosis globally is the persistent spread of multi-drug resistant TB (MDR-TB) and the difficulty in treating it. Seung *et al*. (2015), in 2012 there were approximately 450,000 new cases of MDR-TB and 170,000 deaths due to TB infection worldwide. MDR-TB was found in 3.8% of new TB patients and 20% of those who had a previous history of TB therapy. The highest percentage of MDR-TB cases was observed in Eastern European and Central Asian countries. About 20% of new TB cases were persistent MDR-TB and 50% of patients had a history of previous TB treatment. In 2011, Minsk, Belarus reported that 35% of new MDR-TB patients had previously been treated for TB infection, and 75% of those had received treatment before (Skrahina *et al*., 2012).

India and China have the highest and second-highest numbers of patients with multidrug-resistant tuberculosis (MDR-TB) in the world, respectively, and carry 50% of the global TB burden. In China, 10% of its 1.4 million TB patients have MDR-TB, with most MDR-TB patients never receiving treatment for TB (Zhao *et al*., 2012). MDR-TB is also becoming a growing challenge in South Africa, where the high prevalence of HIV has increased both the spread and severity of MDR-TB (Wells *et al*., 2007).

MDR-TB and XDR-TB posed a threat to the control of tuberculosis. A global project on anti-tuberculosis drug resistance surveillance was jointly launched (in 1994 in 35 countries) by the WHO and the International Union Against Tuberculosis and Lung Disease (WHO-IUATLD) to collect the data (1994-2009) from areas representing almost 60% of the global TB cases. WHO estimated 50 million people were infected with DR-MTB strains. Subsequently, WHO-IUATLD carried out second, third and fourth global drug resistance surveillances in 1996-99, 1999-2002 and 2002-2007 respectively in 114 countries and reported the emergence of 4,89,139 MDR-TB cases in 2006 (Prasad, 2010).

Special Administrative Regions (SARs) initially reported ≈ 200635 XDR-TB cases in 2006. Global surveillance reported that 4,40,000 cases of MDR-TB and extensively drug-resistant TB (5.4%) emerged globally in 2008 and caused ≈1,50,000 deaths. Cumulatively, 58 countries confirmed at least one XDR-TB case. M/XDR-TB emergence can be prevented by early detection and efficient administration of first line drugs in every new patient (Prasad, 2010).

Tuberculosis in compromised hosts

Tuberculosis is a serious illness that can spread easily; and is a particular threat to patients with weakened immune systems (immunocompromised), such as those who have undergone organ transplants. In fact, over half of transplant patients with tuberculosis

experience pulmonary TB, while 16% have extra-pulmonary disease and 33% contract TB altogether (Bumbacea *et al*., 2012). For individuals with diabetes mellitus (DM), the likelihood of contracting TB is even higher due to impaired immune function (Krishna & Jacob, 2021). Dialysis patients are also at increased risk for tuberculosis, with higher mortality rates and incidence rates compared to the general population. Often, these patients contract TB within a year of starting dialysis (Wakasugi *et al*., 2012). Individuals with AIDS and tuberculosis may experience temporary worsening of their TB symptoms about two weeks after starting highly active antiretroviral therapy (HAART) (Japanese, 2003). Although current treatments for TB are effective in controlling the spread of Mycobacterium tuberculosis, they can have serious side effects and do not prevent reinfection (Khan *et al*., 2019).

Management of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB)

MDR-TB being resistant to isoniazid, rifampicin and other drugs; destabilize global tuberculosis (TB) control. An efficient TB control approach, such as directly observed treatment, short course (DOTS), is necessary to prevent the emergence of MDR-TB. Effective management of MDR-TB should be undertaken by experienced clinicians and well equipped laboratories, and performed in vitro sensitivity testing of mycobacterial culture. Innovative approaches such as DOTS-Plus promised for the management of patients with MDR-TB appeared a hope for the future (Surendra *et al*., 2006). In most cases, many individuals with TB are asymptomatic, hence it becomes challenging to reduce transmission and incidence markedly (Royce*et al*., 2014; Bates *et al*., 2012).

The development of proactive approaches is crucial for successful TB control in healthcare systems. Over time, various approaches have been recommended by the WHO for global TB control. The earliest methods included the development of new techniques for early diagnosis, vaccines, treatment, and the distribution of standardized drugs (Schrager *et al*., 2018; Atun *et al*., 2005).

The strength of a country's healthcare system greatly impacts the success of TB control (Atun, 2012). In Low or Middle Income Countries (LMICs), TB control is often delayed due to imperfections in healthcare system management (Marais *et al*., 2010; Elzinga *et al*., 2004). TB infection can be acquired through inhalation, putting people of all social and economic statuses at risk in low, middle, and high-income countries. HIV/AIDS co-infection with TB is more prevalent in high-income populations in Africa (Gao *et al*., 2013).

Global challenges to TB control programs

In 1994, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (WHO-IUATLD) jointly launched a global project aimed at monitoring drug resistance in tuberculosis patients. Data was collected from areas representing almost 60% of global TB cases between 1994 and 2009. According to the WHO, around 50 million people were infected with drug-resistant strains of tuberculosis (Singh & Chibale, 2021).

Incorporating drug-resistant tuberculosis (DR-TB) into TB control programs has become a major challenge in the face of this growing health problem. Specifically, multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) are of particular concern. Among HIV-infected individuals, mortality rates are extremely high for those with MDR-TB and XDR-TB, exceeding 90% (Gandhi *et al*., 2012).

To successfully monitor and investigate the prevalence of MDR and XDR strains of tuberculosis, and to ensure the success of global TB control programs, it is essential to detect and monitor drug resistance and to analyze the susceptibility patterns of Mycobacterium tuberculosis (MTB) isolates against antituberculosis drugs (Seloma *et al*., 2023; Albarouni *et al*., 2014).

An approach called DOTS-Plus has been implemented since 1999 to control MDR-TB in low and middle income countries (Rachmat *et al*., 2023). This strategy involves the use of second line drugs within the DOTS framework. Poland also joined the global TB control programs in 1997 and conducted its first survey on primary and acquired drug resistance in tuberculosis cases (Sandhu., 2023). Over the past 30 years, Poland has conducted four surveys to monitor drug resistance in tuberculosis patients. Both MDR and XDR types of resistance have been identified in Polish tuberculosis patients (Zwolska *et al*., 2011).

India currently has the highest number of tuberculosis cases, including MDR TB, globally (Chatterjee *et al*., 2018). This is due to a variety of factors, such as the failure of the National Tuberculosis Programme, patients rejecting and not complying with treatment, lack of oversight for doctors in private practice, governmental policy disintegration and corruption, financial difficulties, and the expanding HIV epidemic (Thakur *et al*., 2020; Zhou *et al*., 2019). To address this issue, it is crucial to promote social transformation, enhance governmental and global aid, implement DOTS, non-DOTS, and NGO programs, incorporate TB and HIV programs, sponsor research, enact regulatory legislation, and establish medical education programs and awareness among independent practitioners (Udwadia, 2001).

The DOTS Plus project was launched by WHO to manage MDR-TB (Kibret *et al*., 2017). The laboratories need to be improved for accurate and timely detection of M/XDR-TB (Hoffner, 2013). The management of M/XDR-TB needs to be improved in order to reach the target set by the global TB control plan. Research should be conducted to develop diagnostics, medicines, vaccines, and better use of second-line drugs to treat the widespread MDR-TB (Prasad, 2010; Kant *et al*., 2010).

Tuberculosis management in India during the COVID-19 crisis

TB and COVID-19 both affect the human respiratory system and therefore it's important to test for both TB and COVID-19 simultaneously, especially in areas where TB is prevalent and social distancing is difficult. This can help reduce the risk of transmission in these hotspots (Luke *et al*., 2022).

During the extended lockdown period, many workers migrated back to their hometowns, so ICT-based tools like 'NIKSHAY' are being used to track TB patients under India's National Tuberculosis Elimination Programme (NTEP). Fortunately, TB control in India has made significant progress towards eradication (Behera & Behera, 2021; TB, 2021). Frontline healthcare workers can be trained to recognise the symptoms of TB and COVID-19 for proper management. Healthcare workers in the NTEP also understand how to control airborne infections (Awasthi & Singh, 2021).

Efforts to eliminate TB in India have gained significant momentum in recent years. Effective coordination between the central and state government health departments, non-governmental organizations, and private health sector representatives is necessary to develop and implement an integrated response for managing both COVID-19 and TB (Awasthi *et al*., 2021).

Diagnosis & Treatment

In countries with low to middle income, tuberculosis (TB) detection is usually done by examining stained smear samples of suspected patients through a microscope (Bhalla *et al*., 2013). However, this method can only identify about 50-60% of cases that are smear-positive. There are more sensitive techniques available for detecting TB, MDR-TB, and XDR-TB infections, but they are pricier (Vashistha *et al*., 2016). Delays in diagnosing and treating TB can lead to disease transmission, and unfortunately, the period between symptom onset and treatment initiation is often prolonged (Datiko *et al*., 2020). Although the BCG vaccine is widely used, its effectiveness varies by location and may not provide complete protection (Kuan *et al*., 2020). To eradicate tuberculosis in areas with high incidence rates, more potent vaccines will be necessary (Hawn *et al*., 2014).

Treating TB disease requires taking multiple drugs for several months, which can be difficult for patients and healthcare systems. This is especially true in low- and middle-income countries where resources are limited compared to the high disease burden. In certain regions, drug-resistant TB is on the rise, which requires longer and more expensive treatment regimens, making it even more challenging (Bloom *et al*., 2017).

For the past 40 years, the primary approach to tackling TB has been to offer diagnosis and treatment to people who are sick and visit health facilities. The idea is that if those with active TB are cured, mortality rates will decrease, disease prevalence will drop, transmission will decline, and therefore, the incidence of TB will decrease. However, the situation in many countries is more complicated, and the decrease in incidence has been slow, only around 1.5 percent per year, which is not satisfactory (Zheng *et al*., 2017).

Chemotherapy is a highly cost-effective treatment for tuberculosis (McKee &Atun, 2006). This evidence is important in promoting the WHO and Stop TB Partnership's directly observed therapy, short course (DOTS) strategy, which is a comprehensive approach to the diagnosis and care of patients with TB. The DOTS strategy advocates for standardised treatment, along with supervision and patient support, which may involve direct observation of therapy (DOT) by a healthcare professional (Karumbi & Garner 2015).

Over the past few decades, TB control has made significant progress thanks to worldwide investments and dedicated efforts. Research shows that global mortality from TB has decreased by 18.7% between 1990 and 2010, and by 22% between 2000 and 2015, saving approximately 49 million lives by 2015. The United Nations' Millennium Development Goals aimed to stop and reverse the increasing incidence of tuberculosis by 2015 (Bloom *et al*., 2017), and this objective has been accomplished to some extent in all six WHO regions and in most of the 22 high-burden countries worldwide. However, some countries still face significant challenges in controlling TB (Rahevar *et al*., 2018).

Recommendations for improving delivery strategies and strengthening health systems, including care, supply chain, and information systems. Because the current tools for combating TB are seriously inadequate, we conclude with sections on critical research and development and economic analyses of new interventions for diagnosis, treatment, and vaccines. Throughout, emphasis is placed on data or modeling of the economic costs and benefits, where available, of current or possible future interventions to combat this disease (Bloom *et al*., 2017).

In order to prevent the spread of untreatable XDR-TB, there is an urgent need for improvements in XDR-TB surveillance, better laboratory capacity for detecting drug-resistant strains, improved infection control, and the development of new therapeutics. Molecular testing can quickly identify MDR, and treatment options have expanded globally (Dheda *et al*., 2014). However, the outcomes for MDR and XDR-TB are worse than for drug-susceptible disease, despite multiple drugs and long-duration treatment regimens. Addressing challenges such as better management of toxicity, prevention of transmission, and identification and appropriate management of infected contacts will be crucial in the future (Seaworth & Griffith, 2017; Banerjee *et al*., 2008).

Conclusion

Tuberculosis (TB) is a deadly disease that causes millions of deaths every year, especially MDR-TB and XDR-TB that are resistant to many drugs. The World Health Organization (WHO) has recommended several approaches to tackle TB globally, including new techniques for early diagnosis, BCG vaccines, distribution of standardized drugs, highly active antiretroviral therapy (HAART), directly observed therapy (DOTS-Plus) program, and the use of ICT-based tools such as 'NIKSHAY' to track TB patients under India's National Tuberculosis Elimination Programme (NTEP). However, reinfection remains a challenge due to a lack of oversight of doctors in private practice.

To address this issue, the chapter proposes various strategies for dealing with TB in countries where the disease is widespread. These include actively searching for cases, improving healthcare systems, providing services in communities instead of hospitals, and investing in research for better diagnostic tools, treatment plans, and vaccines. Although many of these approaches were previously mentioned in WHO policies, they were not given much attention.

It is essential to improve laboratories for accurate and timely detection of M/XDR-TB. Research should be conducted to develop diagnostics, medicines, vaccines, and better use of second-line drugs to treat the widespread MDR-TB and XDR-TB. By adopting these strategies, we can effectively tackle the TB epidemic and save numerous lives across the world.

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