Minireview Article

Challenges forMathematical Modeling of Multidrug Resistant Tuberculosis in Sub Saharan Africa

ABSTRACT

Background: In sub-Saharan Africa, where there are inadequate diagnostic and reporting facilities, limited data availability hinders the accurate estimation of key parameters in mathematical models of multi-drug-resistant tuberculosis. Furthermore, gaps in knowledge about multi-drug resistant tuberculosis (MDR-TB) dynamics add another layer of complexity to these modeling efforts.

Methods: We analyzed databases such as google scholar, PubMed, scopus, Web of Science etc, using relevant keywords to identify relevant articles on challenges for mathematical modeling of multi-drug resistant tuberculosis in sub Saharan Africa covering the period from 2010 to the present.

Results:This review highlights the epidemiology of multidrug resistant tuberculosis in sub Saharan Africa and the limitations in mathematical modeling of multi-drug resistant tuberculosis (MDR-TB) in the region.

Conclusion: Accurate diagnosis and reliable data are crucial barriers to effective modeling. The review also underscores the potential of machine learning techniques to improve data quality and address issues related to incomplete data, suggesting that these methods could become essential components of future mathematical models.

Keywords: Mathematical modeling, tuberculosis, multidrug-resistant tuberculosis, sub-Saharan Africa

1. INTRODUCTION

1.1 Background on Tuberculosis (TB)

Tuberculosis (TB) emerged as the first infectious disease to be identified as a threat to global health by the World Health Organization (WHO) in 1993 [1]. *Mycobacterium tuberculosis* is the bacterium responsible for tuberculosis [2]. Prior to the emergence of coronavirus disease (COVID-19), tuberculosis was the leading cause of mortality across the globe. According to a recent report, TB remains one among the top-ten causes of mortality worldwide [3]. In 2022, TB claimed about 1.3 million lives, including 167,000 individuals living with human immunodeficiency virus (HIV). Globally, Africa accounts for only 15% of the world's population, yet it bears a high burden of TB. For each 100 new TB cases and 100 TB-related deaths recorded across the globe, Africa accounts for 23% and 31%, respectively [4]. Also, the rise in TB cases is associated with poverty, decline in healthcare infrastructure, and accessibility, and a high prevalence of HIV infection [5].

1.2 Mathematical Modeling in Epidemiology

The dynamics of tuberculosis involve complex interactions between the human host and *Mycobacterium tuberculosis*, exacerbated by factors such as the HIV epidemic, drug-resistant TB, and unhealthy lifestyles, such as malnutrition and smoking [6]. Mathematical models are used in epidemiology to understand such interactions between the host organism and disease-causing agents. They can help identify the parameters that have the most influence and are most controllable, as well as help narrow thoughts on the crucial mechanisms that shape the epidemiology of an infectious disease [7].

The general approach to modeling requires translation of epidemiological scenarios into a mathematical problem. Based on the scientist's knowledge of the system, the modeling approach usually starts with a detailed description of the processes. A precise epidemiological question guides the translation into mathematical equations. Only those features that are pertinent to the particular epidemiological inquiry in mind are included in the model. Once developed, the model is then examined to either estimate parameters, yield crucial quantities that control the general behavior of the solutions, fit to existing data, or determine the relative importance of each parameter to the solution by means of simulation. The findings are then translated back, and evaluated in the context of the epidemiological situation and perhaps look for the solution to the initial inquiry [8].

2. OBJECTIVES OF REVIEW

This review identifies the key factors that hinder the mathematical modeling of multidrug-resistant tuberculosis (MDR-TB) in Sub-Saharan Africa, and examines potential strategies to address these challenges.

3. METHODS

A minireview was conducted to analyze relevant publications on mathematical modeling of MDR-TB in Sub-Saharan Africa by searching electronic databases (like Scopus, Google Scholar, etc.), covering the period from 2008 to the present, using the following keywords: 'tuberculosis,' 'mathematical modeling,' 'multi-drug resistance,' 'Africa,' and 'sub-Saharan Africa.'

4.Result and DISCUSSION

4.1 The Present State of Epidemiological Evidence of Multidrug-Resistant Tuberculosis in Sub-Saharan Africa.

MDR-TB occurs when a TB bacterium develops resistance to at least two of the most potent first-line antibiotics utilized to treat TB, which are rifampin and isoniazid. It is a major hindrance to TB control efforts [9, 10]. This is a more difficult and costly tuberculosis to treat compared to drug-susceptible TB [11]. There were 186,772 reported instances of multidrug-resistant tuberculosis, with 156,071 patients under medical care globally [11]. The region of sub-Saharan Africa remains at the forefront in combating this global ailment, bearing an enormous share of multi-drug resistant tuberculosis [12, 13]. There are 30 countries with high MDR-TB prevalence, 8 of these countries are found in Sub-Saharan Africa and are conisdered high burden countries for MDR-TB, as presented in ***Figure 1***below.

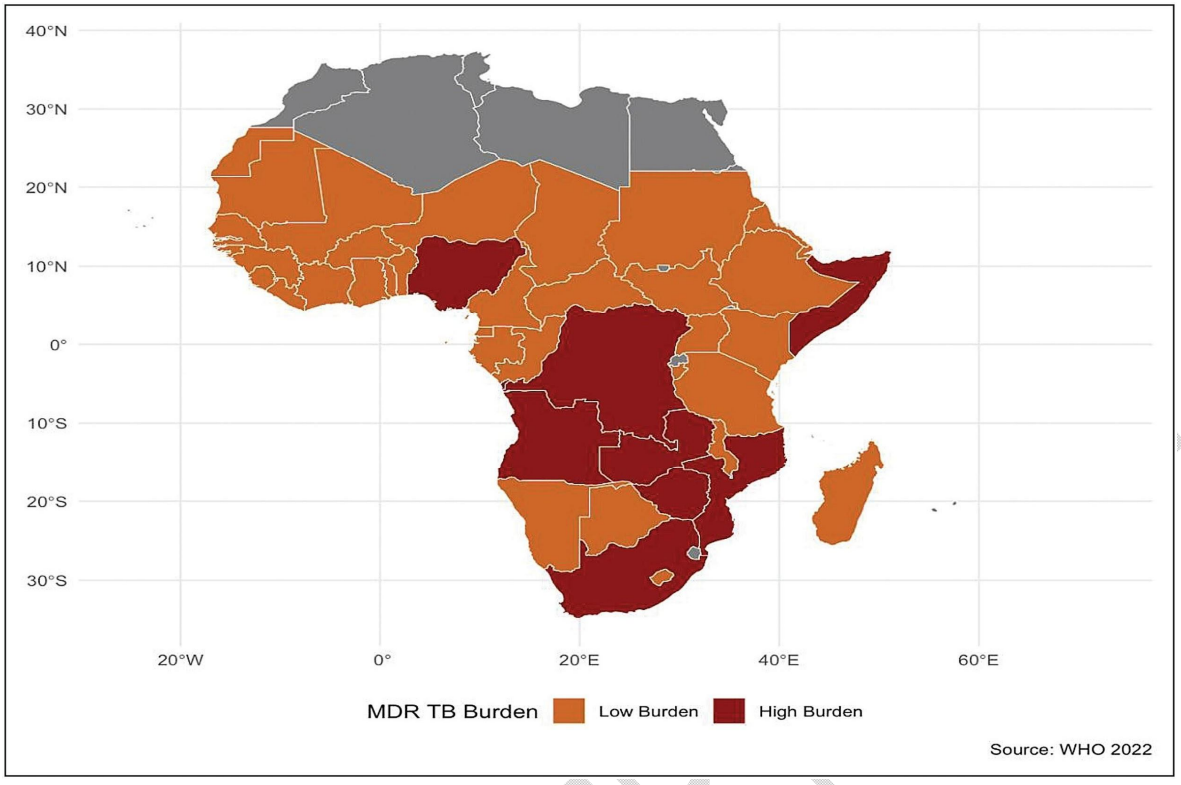

Figure 1: Highly worried countries with Multidrug-Resistant TB in Sub-Saharan African in 2022 (WHO, 2022 report).

In recent times, there are specific changes in incident cases in Sub-Saharan Africa countries that are worth pinpointing. Figure 2 shows the estimated number of incident cases of multidrug-resistant/rifampicin-resistant TB in Sub-Saharan Africa from 2015 to 2021. The figure depicts the challenges over 7 years (2015-2021) in the eight most affected countries in Sub-Saharan African, and this demonstrates the variability of incidences of multidrug-resistant TB in the future and the requirement of strong strategies on the particular country [14]. There are eight out of the 30 worried countries with high multidrug-resistant/rifampicin-resistant TB, and six of the countries, namely Mozambique, Congo-DRC, South Africa, Nigeria, Zambia, and Zimbabwe are reported to have a high incidence of HIV/AIDS and multidrug-resistant TB in Sub-Saharan Africa [15,16]. Thus, in terms of the number of co-infections involving multidrug-resistant TB and HIV, sub-Saharan Africa is leading globally. However, the above studies have revealed that the sub-Saharan African region is poorly reporting the problems of multidrug-resistant TB, and it is estimated that data comes from 50% of the nations, and majority of these data are from Southern and East Africa [17, 18].

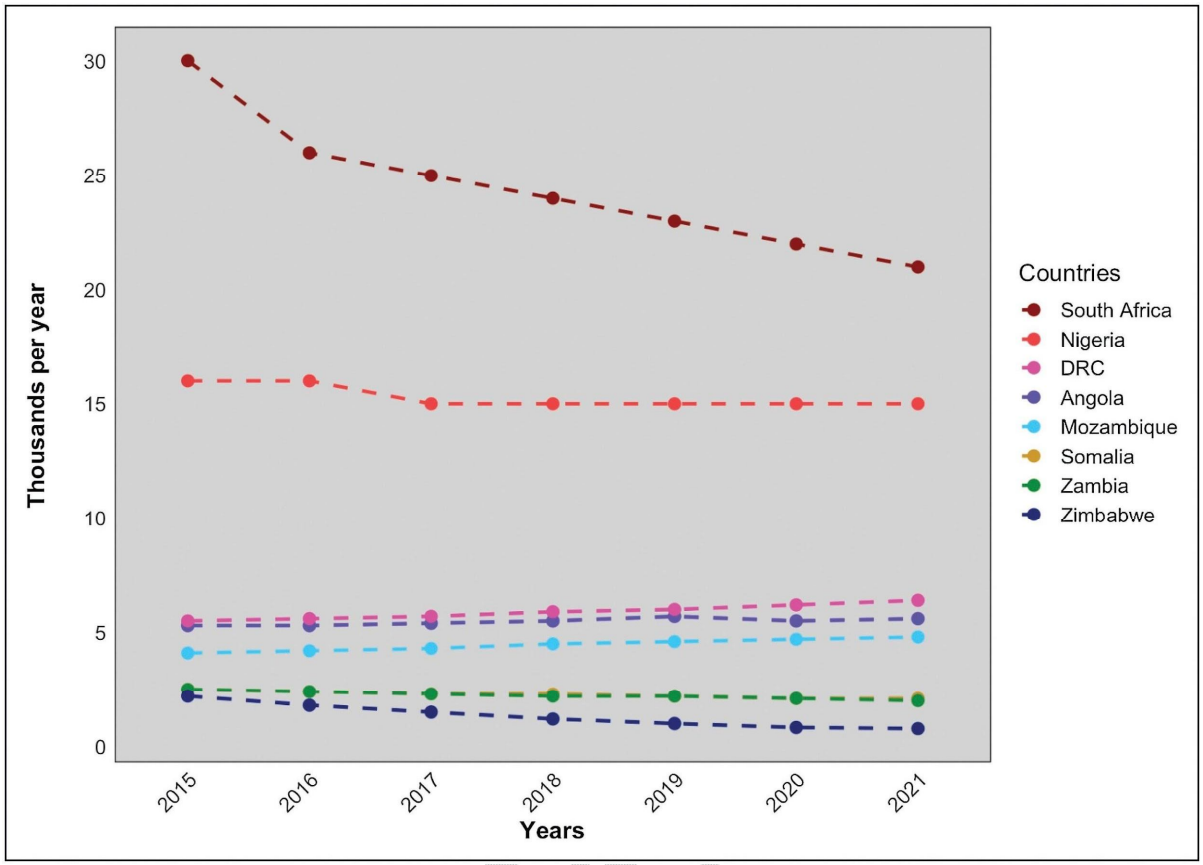

Figure 2: The estimated number of incident cases of multidrug-resistant/rifampicin-resistant TB of Country-specific trends from 2015-2021 (WHO, Report 2022).

4.2 Diagnostic Challenges and Treatment.

The main reason for the rising multidrug-resistant TB prevalence in Sub-Saharan Africa, is evidently treatment defaulting [19]. As a result, there is a problem of timely diagnoses and delayed commencement of the necessary treatment. Current data suggest that there's a substantial gap when it comes to diagnosing tests and the general application of the tools [17]. Regarding treatment, the picture is quite worrisome as it concerns the ability to catch up with the goals set by the World Health Organization End TB Strategy. Although the introduction of brief program regimens is a positive progress, the treatment rate for multidrug-resistant TB in Africa remains at only 59%, suggesting that more improvements are needed to enhance treatment outcomes [20].

4.3 Mathematical Models in TB Research

The fundamental idea about disease transmission models is the description of temporal progression of the outbreak in mathematical terms [7]. To capture dynamics of infectious diseases, a biological knowledge of the pathogen and a statistical description of the available data are needed in addition to mathematical frameworks [21].

Mathematical models are an approximate quantitative description of some actual or hypothetical real-world scenario expressed in mathematical language [22]. The most widely used mathematical epidemiological model is the *SIR* model [23], which divides a population into either "susceptible," "infected" or "recovered and immune." Susceptible individuals (S) can contract the disease.Infectiousindividuals (I) can transmit to vulnerable populations. Recovered individuals (R) are those who have been infected and recovered from the disease. An increase in the infected population decreases the susceptible population [24].

SIR is a predetermined model based on a set of differential equations that can be used to simulate the dynamics of different states of individuals in a population [7].The simplest version of SIR models are designed to not consider some demographic factors - for example, no death, no birth, no migration, and no re-infection can be assumed [23]. Different versions incorporate different factors.

Compartment models can be used to divide a population into subpopulations based on tuberculosis status where susceptible persons who are exposed to tuberculosis are at risk of becoming infected[24].

Figure 3 A basic Tuberculosis transmission model.

4.4 Modeling Multidrug Resistant-Tuberculosis in sub-Saharan Africa

Several mathematical models have been created to investigate the dynamics of multi-drug resistant tuberculosis (MDR-TB) in sub-Saharan African countries, and to predict future trends.

Dowdy *et al.* [25] designed a compartmental difference-equation model to analyze the TB/HIV epidemic among adults in South Africa by fitting it to epidemiological data from World Health Organization. The TB model population was divided into compartments based on the disease status (susceptible, latent infection, diseased, or cured), TB drug susceptibility (nonresistant, MDR, or XDR), TB infectivity (less or highly infectious), and HIV status (positive or negative). They estimated that culturing and performing DST in 85% of previously treated cases and 37% of new cases could prevent 46.6% of MDR-TB deaths, and avert 7,721 MDR-TB cases in South Africa over a decade.

Salvatore *et al.* [9] developed a deterministic compartmental model of adult TB transmission in South Africa, projecting that MDR-TB incidence will account for 5% of total incident TB by 2040 under the assumption of consistently lower efficiency of MDR-TB transmission compared to drug-susceptible TB. They however emphasize the limited understanding of actual trends in MDR-TB transmission efficiency and the uncertainty surrounding future MDR-TB epidemics in the country [9].

Mengistu and Witbooi [26] developed a compartmental model to identify MDR-TB transmission dynamics in Ethiopia, aiming to determine the most effective strategies for tackling MDR-TB in the region. Their findings indicate that the treatment of drug-susceptible tuberculosis is the most effective method for halting MDR-TB transmission in Ethiopia.

In the mathematical modeling analysis conducted by Menzies *et al.* [27], a correlation was identified between the high estimates of rifampicin-resistant tuberculosis (RR-TB) burden and the simultaneous prevalence of TB and HIV in Southern African countries. The association between RR-TB with HIV is particularly pronounced, of which HIV-infected patients are estimated to experience 40 times more disability-adjusted life years from RR-TB compared to HIV-uninfected individuals. This is due to the accelerated progression of TB among people living with HIV. The significant overlap between TB and HIV

epidemics is aggravated by low income status and poor healthcare facilities, which hinder positive treatment outcomes for patients coinfected with RR-TB and HIV [27].

Wotale*et al.* [28] modeled the time until death for patients with multidrug-resistant tuberculosis at Saint Peter's Specialized Hospital in Ethiopia using parametric shared frailty models.

4.5 Challenges in Mathematical Modeling of Multidrug Resistant-Tuberculosis

However, gaps remain in the understanding of the MDR-TB dynamics in sub-Saharan Africa using mathematical models. One of the challenges faced is the limited amount of quality data. This is caused by poor diagnostic and reporting facilities in this region. Thus, it can be really hard to estimate the parameters of those mathematical models. Trying to incorporate this uncertainty into the models often results in complexity [21], coupled with the fact that parameter selection is a meticulous task. For example, the No Deficit model developed by Salvatore *et al* [9] was inadequately supported by empirical data in South Africa leading to nonuniformity in projection when compared to reports from previous reports.

Also, the knowledge gap in the dynamics of MDR-TB imposes another challenge in mathematical modeling [29, 9]. For instance, the mechanisms of reactivation and mixed strain are not completely understood. As a result, the complexities of mixed infection are often omitted in mathematical modeling of MDR TB [29]. Such omissions can affect the predictive accuracy of mathematical models. A better understanding of these dynamics of multi-drug resistant TB in sub-Saharan Africa will enhance the efficiency of mathematical models in making predictions [9].

Prioritizingtargeted investments in MDR-TB interventions should be emphasized, such as expanding the availability and accessibility of drug susceptibility testing (DST), enhancing case finding efforts, improving MDR-TB treatment regimens, and securing dedicated political and economic support, given the potential for significant future spread of MDR-TB [9].

4.6 Future Directions in Multidrug Resistant-Tuberculosis Modeling

In sub-Saharan Africa, a region characterized by limited amounts of quality data on MDR-TB, and gaps in documentation of MDR-TB cases, machine learning techniques can help improve data quality and make up for incomplete data thus increasing prediction accuracy of mathematical models. Such an integration of machine learning (ML) predictions or parameters into mathematical models to simulate the future spread and effects of MDR-TB in Sub-Saharan Africa will be of great impact. The development of efficient mathematical models of MDR-TB can also help provide information about the efficiency of drugs and vaccines [30]. This can have a great impact on the development and optimal distribution of new medication and vaccines of tuberculosis in sub-Saharan Africa. However, there is much need for proper MDR-TB surveillance and testing systems in Sub-Saharan Africa [31] since the true burden of drug-resistant TB is largely missed in Africa with only 30% diagnosed [17].

5. CONCLUSION

This review emphasizes the need for precise diagnostics, reliable data, and sophisticated modeling techniques to tackle MDR-TB effectively in sub-Saharan Africa. The results reveal that the primary challenges in developing robust mathematical models for MDR-TB in this region are the limited and poor-quality data and significant knowledge gaps.

To overcome these challenges, it is recommended that sub-Saharan Africa establish robust MDR-TB surveillance systems. Enhanced data quality will drive more MDR-TB research, bridging existing gaps in knowledge and data. Existing literature suggests that targeted strategies, such as improved diagnostic testing and tailored treatments, can significantly decrease MDR-TB prevalence and mortality in the region.

Furthermore, addressing incomplete data and boosting model accuracy through machine learning techniques to predict missing information could greatly improve model effectiveness. It is also crucial to

integrate the efforts of modelers with clinicians and policymakers to develop and implement comprehensive strategies to combat MDR-TB in sub-Saharan Africa.

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