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Systematic Review

Mathematical Models of Tuberculosis Disease and Environmental Factors: A Systematic Review

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ABSTRACT

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB) that enters the body through the respiratory system and is mainly spread through the air. Multiple factors can lead to TB infection, involving complex interactions between individual, environmental and social factors. This article aims to provide a systematic overview of the environmental factors affecting TB incidence and a mathematical model of TB epidemiology. The sources of articles used are Google Scholar, PubMed, and Scopus from 2018-2023. Environmental factors that increase the risk of TB transmission include meteorological factors (temperature, rainfall, wind speed, and air pollution) and residential environmental factors related to physical parameters such as ventilation, natural lighting, room humidity, and occupancy density. Mathematical modeling of TB spread helps understand the dynamics of infection, identify key factors affecting spread, and develop effective prevention and control strategies to reduce the prevalence and impact of TB in the community. In developing mathematical models of TB epidemiology, two important aspects are considered: adding TB compartments that can survive in the environment due to meteorological factors, and considering the influence of aspects of the TB patient's living environment related to physical parameters on the rate of disease transmission in the model.

INTRODUCTION

Tuberculosis (TB) remains a frightening scourge on global public health. Millions of new cases of TB emerge each year, making it the second deadliest infectious disease after HIV/AIDS, as confirmed by the World Health Organization (World Health Organization, 2023a). The burden of TB disease is high, with a significant impact on individuals, families, and health systems worldwide (Jarde et al., 2022).

Globally, in 2023, an estimated 10.6 million people worldwide had TB, a slight decrease from 10.7 million in 2022. About 1.5 million people died from TB in 2023, making it the second-highest infectious cause of death after COVID-19. These data confirm that TB remains a serious health threat, especially in low- and middle-income countries. Eight countries account for more than half of global new TB cases, namely: India, Indonesia, China, South Africa, the Philippines, Nigeria, Pakistan, and Tanzania. Southeast Asia has the highest TB burden, followed by Africa. Challenges faced in the fight against TB include underfunding of TB programs, inadequate access to TB diagnosis and treatment, especially for drug-resistant TB (DR-TB) and multidrug-resistant TB (MDR-TB), stigma, and discrimination against people with TB that prevent them from seeking treatment and support (World Health Organization, 2023b). Although there have been significant advances in the diagnosis and treatment of TB, the spread of the disease continues to be an issue of concern.

The spread of pulmonary tuberculosis is not only influenced by individual characteristics such as age, nutritional status, and comorbidities but also by various environmental factors. These factors, such as poor sanitation, high population density, which can increase contact between individuals, thereby increasing the likelihood of pulmonary TB transmission through droplets produced when coughing or sneezing, unhealthy air quality, and limited access to health services, significantly increase the risk of pulmonary TB transmission in various regions (World Health Organization, 2023a; Zumla & Maekawa, 2011; Alvi et al., 2020). Studies that discuss tuberculosis in relation to the environment include (Heriyani et al., 2013; Saraswati et al., 2018; Alauddin, 2020; Ghadimi-Moghadam, 2020; Zhang et al., 2022). Furthermore, poor air quality, especially due to indoor and outdoor air pollution, can increase the risk of pulmonary TB infection and disease.

Understanding the interplay between individual and environmental factors in the spread of pulmonary TB is essential for designing effective intervention strategies. Mathematical models, such as agent-based models and compartmental models, can be used to simulate the dynamics of lung TB transmission under various environmental conditions. These models help predict the impact of different interventions, such as improved access to clean water and sanitation, reduced population density, and improved air quality, on the transmission rate and disease burden of pulmonary TB.

Mathematical models of epidemiology have become an important tool in understanding and forecasting trends in the spread of TB in the population. However, research specifically exploring the role of environmental factors in the development of these models is limited. Therefore, this study aims to conduct a systematic review of the existing literature for identifying and evaluating epidemiological mathematical models that consider environmental factors in modeling the spread of TB. By including environmental factors in epidemiological models, we can improve our understanding of the complexity of TB spread and design more effective interventions to control TB disease in the future, as well as provide valuable insights for researchers and practitioners in the field of public health.

The importance of systematic reviews is crucial to understanding and developing mathematical models for tuberculosis. Although various models have been developed to map and predict the spread of TB, there is a need for a thorough, systematic review that examines the effectiveness and applicability of these approaches in the context of epidemiology. A systematic review will provide a synthesis of evidence from multiple studies, allowing researchers and policymakers to understand the strengths and weaknesses of each mathematical model (Petticrew & Roberts, 2006). By collecting and analyzing data from various studies, this systematic review is expected to not only help in evaluating existing models but also provide insights for further research or the development of new models.

Several studies have reviewed articles related to TB in various aspects. Harris et al., (2016) reviewed articles with a primary focus on epidemiological models involving TB vaccines and how they can contribute to future TB elimination efforts. Shaweno et al., (2018) reviewed and analyzed methods used in spatial analysis of TB epidemiology. Overall, this article aims to provide guidance on the use of spatial analysis methods in TB research and to improve TB control strategies through a better understanding of TB distribution and risk factors. Martinez et al., (2020) conducted a systematic review and meta-analysis of the data. The aim of this article is to evaluate the risk of developing TB in children following close contact with a TB case and highlight the urgent need for better prevention and early detection strategies to reduce the burden of TB in the pediatric population.

The purpose of this study is to compile a systematic review of the factors affecting the spread of pulmonary TB using mathematical models used in TB epidemiology, with special attention to the influence of environmental factors on its spread. The results of this systematic review are expected to provide valuable insights for public health policy development and improve the precision of epidemiological models in the global fight against pulmonary TB.

MATERIALS AND METHODS

A systematic literature review is a method to create a synopsis of a large amount of information and a means to contribute to answering questions about what works and what does not, and many other types of questions as well. The article search was conducted using an article title approach in the form of medical subject headings for health themes and mathematical modeling in the field of epidemiology and using keywords in the search into categories related to TB (refer to Table 1), namely: 1. Factors associated with TB, 2. Mathematical Models of TB Epidemiology (System of Differential Equations, SIR Model, SEIR Model), 3. Other mathematical model analysis, 4. Optimal control of TB disease.

Questions:

1) How are climate change and environmental factors related to the epidemiology of tuberculosis?
2) How is the spread of TB modeled mathematically?
3) How is the control of TB spread modeled mathematically?

The general objective of this study is to explore the relationship between climatic or environmental factors and TB incidence as well as mathematical models of TB disease spread using an epidemiological approach. We prepared an inclusive list of keywords and their combinations to search the literature based on the review question. We used the "Publish or Perish" application in collecting literature, and the time span of the literature we collected was from 2018 to 2023. The articles studied were those indexed by Google Scholar, Pubmed, and Scopus. As shown in Table 1, we assessed 1869 articles, consisting of 790 articles assessed from Google Scholar, 424 from PubMed, and 655 from Scopus.

Table 1: Number of articles in Google Scholar, PubMed, and Scopus

No.	Keywords (title)	Number of Article (Th. 2018-2023)		
		Google Scholar	PubMed	Scopus
1	Climate, tuberculosis	200	80	200
2	Tuberculosis Environmental	200	196	200
3	TB Mathematical Model	200	136	200
4	Optimal control TB mathematical model	190	12	55
Sub total		790	424	655
Total		1869		

The following were the inclusion criteria:

(a). Articles published in peer-reviewed journals
(b). Articles that examine the influence of the environment and climate change on TB cases
(c). Articles examining mathematical models of the TB epidemic through several modeling approaches in the form of differential equations or statistics
(d). Articles examining optimal control in mathematical models of TB
(e). An article published in English.

The following were the exclusion criteria:

(a). There are duplicate articles.
(b). Blog posts
(c). The article discusses the combination of two diseases (TB and other diseases) in the model.
(d). The article has nothing to do with TB.
(e). Does not include humans as the study population and MTB as the agent.
(f). The article is published in a language other than English

RESULTS AND DISCUSSION

Based on Table 1, inclusion criteria, and exclusion criteria, the selection process in the systematic review of articles was as follows:

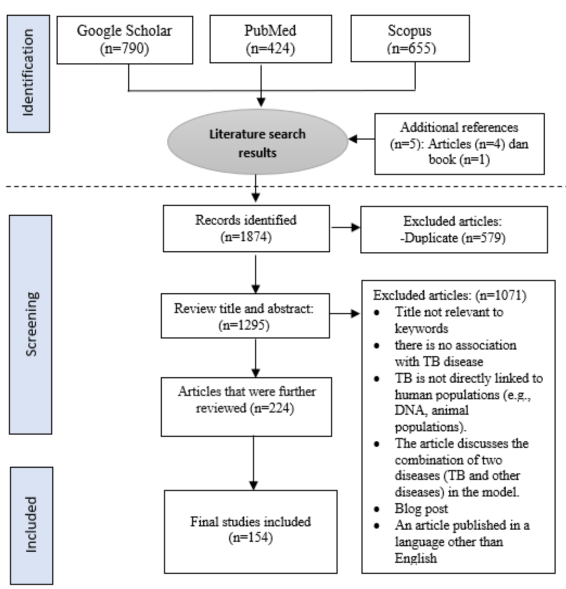

Figure 1: Flow chart of the selection process in the systematic review of articles

As presented in Figure 1, we reviewed 154 original research articles. The results of the literature review obtained a discussion of the factors that affect TB disease, a review of the mathematical model of TB epidemology, a review of the mathematical model of TB related to the environment, and optimal control of TB problems.

The classification of articles that have been reviewed is presented in Figure 2.

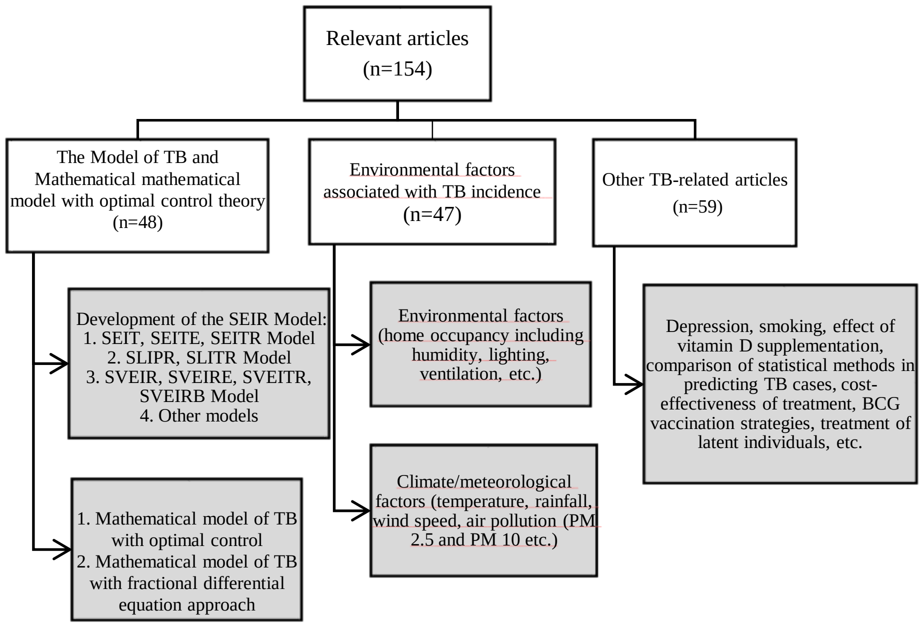

Figure 2: Classification of reviewed articles

The flow chart in Figure 2 illustrates the distribution of 154 relevant articles related to tuberculosis (TB) into three main categories: mathematical models of TB, environmental factors associated with TB incidence, and other TB-related articles. The Model of TB and Mathematical Model with Optimal Control Theory consist of SEIR Model Development, Mathematical Model of TB with Optimal Control, and Mathematical Model of TB with Fractional Differential Equation Approach. Articles in this category discuss the development of various mathematical models used to predict and control the spread of TB. The optimal control approach is used to find the best strategy to reduce the spread of TB. Environmental Factors Associated with TB Incidence consist of home environmental factors (living conditions including humidity, lighting, ventilation, etc.), climate and meteorological factors (temperature, rainfall, wind speed, air pollution, etc.). This category includes articles that examine how environmental factors, both indoors and outdoors (meteorology), affect TB incidence. Other TB-related Articles contains articles covering a variety of other topics related to TB, such as psychological factors (depression), smoking habits, the benefits of vitamin D, and the evaluation of TB treatment and prevention methods and strategies.

Factors that influence the spread of TB disease

Meteorological factors play an important role in determining air quality in an area. Atmospheric conditions are largely determined by various meteorological factors, such as wind speed and direction, humidity, air temperature, air pressure, and surface height. Besides being influenced by the number of pollutant sources, meteorological parameters also affect the levels of pollutant gases in the air, so environmental conditions cannot be ignored. Wind speed, air temperature, and air humidity are some of the meteorological parameters that can affect the levels of pollutant gases in the air. Wind speed determines how much polluted air is initially mixed, and the irregularity of wind

speed and direction determines the rate of spread of contaminants when carried in the wind direction. This factor determines how polluted an area will be and how quickly contaminant levels are depleted due to mixing with environmental air.
The study by Laeremans et al. examined the short-term effects of physical activity, air pollution, and their interaction on the cardiovascular and respiratory systems. In this study, physical activity in urban environments can lead to an increased inhalation of air pollutants. Furthermore, inhalation of air pollution triggers a decline in lung function, while physical activity acts as an acute bronchodilator, potentially providing a protective effect (Laeremans et al., 2018). Furthermore, Albers et al. investigated the effect of using firewood for cooking on latently infected individuals. As a result, the use of fuel for cooking tended to be more influential in moving from the infected state to pulmonary TB than to complex TB infection (Mouafo et al., 2023).

Pollutants can be divided into two main categories: primary pollutants, which are generated directly from vehicular traffic, industrial emissions, and household heating. Meanwhile, secondary pollutants, such as ozone, are usually the result of chemical reactions occurring in the atmosphere. Particulate matter (PM) in the air, both from primary and secondary sources, is a major cause of the increase in global mortality due to pollution. Particularly, particles with an aerodynamic diameter of 2.5 μm (PM2.5) and ultra-fine particles (PM0.1) are considered harmful because they can penetrate gas exchange in the alveolar space and can also enter the systemic blood circulation. Cardiovascular disease is emerging as a greater human health threat caused by air pollution (Mannucci, 2013). Furthermore, Polezer et al. study used artificial neural networks to assess the effect of PM2.5 on respiratory diseases. Based on this, air pollution has an impact on or influence on respiratory diseases (Polezer et al., 2018).

Respiratory diseases and TB are closely related, as both attack the human respiratory system. Pulmonary TB is closely related to respiratory problems. Studies examining the impact of air pollution on TB cases include: Peng et al. analyzed the relationship between long-term exposure to PM2.5 and deaths caused by specific causes in a group of TB patients in China from 2003 to 2013. The results stated that long-term exposure to PM2.5 increased the risk of death from TB and other diseases among TB patients (Peng et al., 2017). Other studies in line include (Ibironke et al., 2019), controlling ambient air pollution can help reduce mortality caused by TB. Furthermore, Yao et al. concluded that exposure to ambient air pollution (PM2.5, PM10, O3, and CO) is associated with an increased risk of multi-drug-resistant TB (MDR-TB) (Yao et al., 2019). Ding et al. (2020) described the impact of air pollution on pulmonary TB transmission in Jiangsu, China. This study evaluated the relationship between air pollution through the air quality index (AQI), PM2.5, and PM10 and the number of TB cases. The results obtained showed that long-term exposure to PM2.5 was closely related to the spread of TB disease (Ding et al., 2020). Wang's research in 2021 investigated the impact of meteorological factors and air pollutants on tuberculosis in Shijiazhuang, China. The results obtained showed that the impact of PM10 air pollutants had an effect on TB cases. While SO2 pollutants, which were Wang's main research, were found to have no effect on TB cases (Wang, 2021). The results of these studies can be seen as complementary to the results obtained by Peng et al. and may provide a scientific basis for TB prevention and control (Peng et al., 2017). Feng et al. showed a potential association between outdoor exposure to PM2.5, NO2, and O3 and the risk of pulmonary TB (Feng et al., 2022).

Other studies on TB cases associated with meteorological factors include Zhang et al., (2019), which showed that there is a positive correlation between TB incidence and annual average rainfall, and Zhang & Zhang, (2019), which concluded that temperature and wind speed have a positive effect on TB incidence. Furthermore, Xu et al., (2021) explained that average temperature and relative humidity are factors that influence the TB epidemic, so that they can be a practical reference for improving the TB warning system. Meanwhile, the article by Maharjan et al. concluded that TB is affected by many factors, especially climate change (such as temperature, humidity, and rainfall) (Maharjan et al., 2021).

In addition to meteorological and climatic factors, several studies mention that pulmonary TB is closely related to environmental factors in the homes of people with pulmonary TB. Amaliah et al. showed that there was a significant relationship between the physical environment of the house and the incidence of tuberculosis (Amaliah et al., 2022). Aditama et al., (2019) concluded that there is a significant relationship between ventilation, lighting, humidity, occupancy density, and floor type with the incidence of pulmonary TB In addition, Tanjung et al., (2021) explained that there is a relationship between income, ventilation, floor conditions, humidity, and lighting and the incidence of pulmonary TB. Humidity was the most dominant variable associated with TB incidence. Based on this study, an understanding of the physical environmental factors of home occupancy that potentially affect pulmonary TB cases is expected to help in designing effective interventions for the prevention and control of this disease in the community.

Figure 3, a flow chart of factors affecting TB disease, is given below.

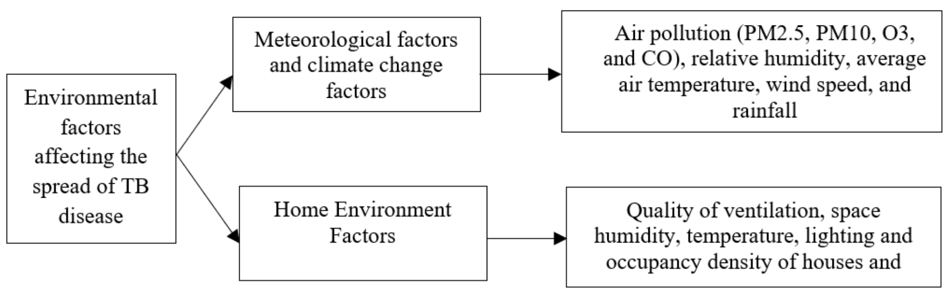

Figure 3: Environmental factors affecting the spread of TB disease

Figure 3 is a diagram illustrating the various environmental factors that contribute to the spread of tuberculosis (TB). These environmental factors consist of two main categories: meteorological and climate change factors, and home environment factors. Meteorological and climate change factors that affect the spread of TB include: air pollution (such as PM2.5, PM10, O3, and CO) are particulates and pollutant gases that can make individuals more susceptible to TB infection; relative humidity is the level of air humidity that can affect the survival of airborne TB bacteria; average air temperature is a higher or lower than normal temperature that causes TB bacteria to survive longer in certain environmental conditions; wind speed also helps spread TB bacteria through the air; and rainfall patterns can affect environmental humidity and, indirectly, affect the survival of TB bacteria. Home environmental factors include the physical conditions of the residence that may affect the risk of TB transmission. These factors include: good quality ventilation is essential to reduce indoor bacterial concentrations; indoor humidity can affect the resistance of TB bacteria; comfortable and stable indoor temperatures can help reduce the risk of transmission; good lighting, especially sunlight, can kill TB bacteria; and crowded homes have a higher risk of TB transmission due to close contact between individuals.

Overview of mathematical models of the TB epidemology

Mathematical models of epidemiology are mathematical tools used to model and understand the spread of a disease in a population. These models allow researchers to describe the dynamics of the spread of infectious and non-infectious diseases and to predict the spread of such diseases with various prevention and control strategies. These models are generally built using systems of differential equations that describe the interactions between various compartments in the population. The compartments formed in the model include susceptible, infected, and recovered individuals. An understanding of epidemic modeling often begins with studying the classic SIR model first proposed by Kermack and McKendrick in 1927 (Affandi et al., 2023).

SIR epidemic models play an important role in helping us understand the spread of disease in a population (Martcheva, 2015), The development of SIR models takes into account factors such as contact rates between individuals, disease transmission rates, incubation periods, immunity, and preventive interventions such as vaccination or quarantine. Some epidemiology mathematical models for the spread of an infectious disease are in the form of SIR, SIS, and SEIR. From these models and their development, equations can be created that can describe the conditions for the spread of an infectious disease or epidemic, including TB.

The tuberculosis disease spread model by Khajanchi et al., (2018) is a development of the SEIR model. The model aims to look at the role of exogenous reinfection and endogenous reactivation. The model consists of four compartments: susceptible (S), exposed (E, infected but not infectious), infectious (I), and recovered (R, still susceptible). The results suggest that the rate of disease transmission and the exogenous re-infection rate play an important role in changing the qualitative dynamics of TB spread.

Research by Wangari et al. (2018) suggested a mathematical model for the spread of TB, namely the SLIPR model. Subpopulation L in the model is divided into two groups, namely early latents and late latents. Subpopulation P is made up of individuals treated with isoniazid preventive therapy. This model examines the possibility that people who recover from active TB and people treated with preventive therapy have different levels of immunity. The reinfection rate in the subpopulation treated with preventive therapy is most instrumental in the qualitative changes in TB dynamics. In contrast, the reinfection rate in cured individuals (previously treated with active TB) plays a minor role. Furthermore, Yu (2018) extended the SEIS mathematical model to account for MDR-TB (multi-drug resistant). In this model, it is assumed that drug resistance can arise due to infection or as a consequence of treatment (not being treated properly for various reasons). From the simulation results, it can be explained that an increase in the detection rate will lead to a significant decrease in the infected population in 20 years. Drug resistance arises due to the inappropriate use of antibiotics in chemotherapy. Gonmwan and Okuonghae modeled the spread of TB. The model investigates the impact of the diagnosis and treatment of latent and active TB infections on the dynamics of disease transmission in a population (Egonmwan & Okuonghae, 2019).

Lestari (2018) created the SEIR Model by taking vaccination factors into account and making the assumption that healthy individuals will become immune to MTB upon vaccination. Calculate the equilibrium point, the fundamental reproduction number, assess the stability of the equilibrium point, and run numerical simulations using data from the Yogyakarta region using the model that was created. Based on the model simulation results, a control plan is required to limit the spread of infection by determining the ideal proportion of vaccination that has to be administered to susceptible populations. Furthermore, in their research, Nkamba et al., (2019) put forward the SVELI Model (Susceptible, Vaccinated, Early Latent, Late Latent, Infectious). The global stability was analyzed using the Lyapunov-Lasalle method to see the dynamic behavior of the model. Then, numerical simulations of the model were conducted using Cameroonian TB data to support the analytical results. The results show that vaccination coverage is not sufficient to control TB. Furthermore, high effective contact rates have a high impact on the spread of TB. In a similar study by Mengistu & Witbooi, (2019) results showed a positive effect of vaccination efforts in newborns and treatment of latent and active TB patients on TB control.

In the research of Ullah et al., they developed the SEIR model into a SLITR model (S. Ullah et al., 2019). This model does not involve the vaccination compartment, and global stability analysis is shown through the Lyapunov function. Then the sensitivity analysis of the model and the corresponding graphical results of various model parameters on tuberculosis transmission and prevalence were presented. From the numerical results and sensitivity analysis of the model, it is found that the spread of tuberculosis disease can be minimized by increasing the treatment rate of infected individuals, decreasing the effective disease transmission rate, and increasing the rate of individuals leaving the treated class and re-entering the infected class. Research by Ullah et al., (2020) developed the SEITR Model by considering the presence of imperfect treatment, and Khan et al., (2019) developed the SEITR model by dividing compartment E into slow and fast exposed classes. Research by Ayinla et al., (2021) developed the SVEITR model and considered the infected compartment, which consists of two diagnosed and undiagnosed compartments.

Several studies have developed TB epidemic models involving optimal control theory, which is used to understand the dynamics of TB spread in the population and determine the most effective control strategy. Using optimal control theory, we can design interventions that minimize the impact of TB on the population while considering resource and cost constraints. Such studies include those involving distance control, latent case tracing control (Kim & Jung, 2018; Kuddus et al., 2020) chemoprophylaxis effort control, and infectious treatment control to increase the number of cured individuals (Temgoua et al., 2018; Baba et al., 2020), treatment and media awareness (Kar et al., 2019), public awareness campaign control, treatment effort, and prevention control against incomplete treatment (Abimbade et al., 2020), considering three different treatment regimens at different stages of TB (Khatua et al., 2021), vaccine control, treatment of Latin TB, and active TB (Gao & Huang, 2022). Furthermore, the TB epidemic model with control in the form of the SEIR model was developed by Upadhyay et al. by considering treatment control using two functions, namely Holling type II and III treatment levels. As a result, the application of Holling type II treatment is the most effective way to prevent the spread of TB disease (Upadhyay et al., 2019).

The TB epidemic model can also be developed into a mathematical model in the form of fractional differential equations and is known as the fractional model. The model involves the use of fractional calculus to extend the conventional epidemic model. These fractional models introduce fractional-order derivatives in the equations to describe the dynamics of disease spread, which can provide a more accurate picture of the dynamics of complex and heterogeneous systems. This allows for more precise predictions and more in-depth analysis of the spread of TB disease. Researchers who developed fractional models for TB disease spread include (Khan et al., 2018; Ullah et al., 2018; Ullah et al., 2020; Rahman, 2021; Zhang, 2021). Olaniyi combined the fractional model with four time-dependent controls, namely advocacy efforts against infection and re-infection, vaccination control, prophylaxis against latent infection, and treatment control (Olaniyi, 2023). Furthermore, Oshinubi et al. simulated the Caputo fractional tuberculosis outbreak model using the Adams-Bashforth-Moulton approach to investigate the impact of treatment and vaccine rates. The simulation results obtained show that increasing vaccination and, especially, the availability of treatment for infected people can reduce the prevalence and burden of tuberculosis in the human population (Oshinubi et al., 2023).

A mathematical model of TB epidemiology associated with environmental factors

The mathematical model of Fröberg et al., (2019) was established with the aim of identifying contacts between new latent and remote latent tuberculosis individuals. The estimation of latent TB individuals is based on case transmission rate, exposure time, and environmental factors. Research by Cai et al., (2021) formulated a mathematical model of TB epidemology that takes into account the impact of a bacteria-contaminated environment on the dynamics of TB transmission. This model develops the SEIR model and adds one compartment, namely the concentration of TB bacteria in the surrounding environment (TB bacteria are assumed to survive on doorknobs, towels, handkerchiefs, toys, utensils, bedding, and so on). Furthermore, Li & Wang's research developed the Sulayman et al. model by adding a new compartment in the form of the number of TB virus concentrations in the environment due to exposure to infected people (Derny et al., 2023; Sulayman et al., 2021). The addition of one compartment to the model was done on the basis that TB bacteria have been found to survive in various natural and artificial environments for months to years (Ding et al., 2020).

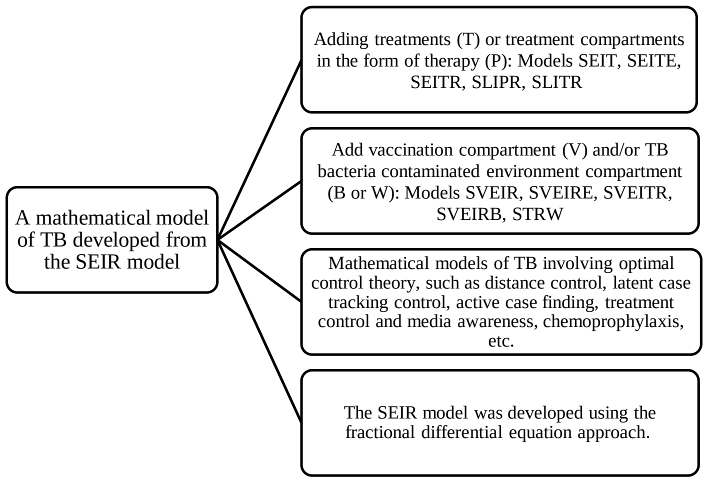

Figure 4: Development of a Mathematical Model of TB Disease Spread

The model was then developed by taking into account many aspects as presented in Figure 4, including: adding a treatment compartment; adding a TB bacteria concentration compartment in the environment; a mathematical model of TB involving optimal control theory, such as distance control, latent case-finding control, active case-finding, treatment control and media awareness, chemoprophylaxis, and others, and the SEIR model developed into a fractional model.

CONCLUSION

Meteorological factors strongly influence air quality and pollutant levels that impact respiratory health, including TB. Long-term exposure to air pollution, especially PM2.5, increases the risk of death and affects the spread of TB. In addition, residential environmental factors also have a significant effect on TB transmission. This study demonstrates the importance of controlling air pollution and improving physical environmental conditions in homes for effective prevention and control of the spread of TB in the community. The TB epidemiology models that have been studied are basically SEIR models. Various modifications and extensions of the SEIR model are expected to more accurately model the spread of TB and the effectiveness of different interventions. Further research and control strategies should focus on the integration of environmental factors in TB epidemiologic models. This approach allows researchers and policymakers to test different TB control strategies under various conditions.

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