Mathematical Models for Tuberculosis Disease Transmission in Southeast Asia: A Systematic Literature Review

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Abstract: Research on tuberculosis (TB) continues to be a primary focus, given its status as a serious threat to global health, including in the Southeast Asia region. Enhancing understanding of the TB transmission model is imperative, with the main objectives of this study being (1) identifying developed models, (2) describing the study methodologies employed, and (3) identifying proposed interventions within these models. By applying for a Systematic Literature Review following the 2020 PRISMA guidelines, we successfully collected 872 articles from the Scopus database, specifically focusing on those studying TB spread through compartmental mathematical models. However, only 21 articles met the eligibility criteria for further analysis utilizing the meta-synthesis analysis method. Each article was then thoroughly analyzed to identify its characteristics and research context. Various interventions proposed in each model were evaluated, identified, and summarized to understand the potential for model development in future research. The entire content of the articles discusses the role of mathematics in analyzing TB models and transmission studies, with various interventions explained in detail. The results of the analysis indicate that the mathematical modelling of TB transmission can be enhanced by developing models with direct and indirect interventions for the human population. Various approaches in tuberculosis transmission dynamics, including compartmental models and spatial modelling techniques, are highlighted in this research. Evaluating the effectiveness of interventions and control measures implemented in the models also serves as a focal point to assess their impact on TB spread. This review contributes to synthesizing existing knowledge, identifying research gaps, and highlighting opportunities for future advancements in mathematical modelling for TB control strategies in the Southeast Asia region.

Keywords: Tuberculosis disease, Mathematical models, Systematic literature review

Introduction

Tuberculosis (TB) remains a significant global health challenge, posing hurdles to healthcare systems worldwide. This infectious disease is caused by Mycobacterium tuberculosis, primarily affecting the lungs but potentially impacting other body parts and spreading to others through respiratory droplets in the air (Campo & Kawamura, 2017). *Mycobacterium tuberculosis* plays a crucial role in granuloma formation and maintenance, ensuring disease dissemination and preventing its progression to severe illness (Russell, 2007). Its transmission involves numerous factors, including respiratory illness, bacilli release, environmental survival, and host defenses, with gaps in knowledge and limited animal models (Turner et al., 2017). Despite significant progress

in prevention and treatment, TB continues to afflict millions each year, especially in resource-limited settings where factors such as poverty, population density, and lack of healthcare access contribute to its transmission and persistence. Understanding TB transmission is vital for developing effective control strategies and reducing its burden on global public health systems. Hence, it is crucial to explore various aspects of TB transmission, including its routes, risk factors, and the importance of early detection and intervention in controlling its spread.

In Southeast Asia, TB prevalence remains high, with thousands of new cases reported annually. The WHO Southeast Asia Region accounted for 45% of new TB cases and 50% of global TB deaths in 2021, significantly supporting global TB efforts (Bhatia et al., 2023). Moreover, poor TB detection in Southeast Asia, where a third of cases go undetected or untreated outside national health programs, could hinder the region's goal to reduce TB prevalence and deaths by half from 1990 levels by 2015 (Padma, 2010). Thus, a deep understanding of TB transmission in Southeast Asia is crucial for designing effective intervention strategies. Efforts to raise public awareness about the importance of early detection, easier access to healthcare services, and promoting healthy lifestyles are critical steps in addressing the TB burden in this region. Therefore, it is important to delve into greater detail about the factors influencing TB transmission in Southeast Asia and the strategies that can be adopted to reduce its impact on public health.

Mathematical modelling is a valuable tool in understanding, analyzing, and forecasting real-world phenomena in various fields, including epidemiology and infectious disease control, aiding in constructing and utilising epidemiological models (Garnett, 2002). Mathematical models represent a system, process, or relationship using mathematical concepts and equations. By translating complex phenomena into mathematical language, we can gain insights, make informed decisions, and solve problems efficiently. In this exploration of mathematical modelling, we will delve into the various applications and methodologies behind its creation. From differential equations describing celestial motion to optimization models guiding business strategies, mathematical modelling bridges theoretical understanding and practical solutions.

As previously established, the complex transmission of Tuberculosis (TB) poses a barrier to effective control and prevention strategies. In the effort to understand and address this public health threat, mathematical modelling emerges as a powerful tool. By summarizing the intricate interactions among biological, social, and environmental factors, mathematical models offer invaluable insights into TB transmission patterns and the impact of interventions. In the realm of mathematical modelling in the context of TB, we explore various approaches, assumptions, and outcomes that shape our understanding of disease spread. Through the lens of mathematical abstraction, we unravel the dynamics of TB transmission within populations, providing insight into key factors such as transmission routes, latent periods, and host susceptibility.

In the complex landscape of public health, the battle against tuberculosis (TB) in Southeast Asia poses a serious challenge. With diverse demographics, socioeconomic factors, and varying healthcare infrastructures, this region has become a complex environment in which to understand and address the spread of this infectious disease (Pramono, 2021). In this endeavor, mathematical modeling emerges as a vital ally, offering a systematic approach to uncovering the complex dynamics of TB transmission. TB transmission models exhibit considerable discrepancies regarding the progression of the disease to active TB, with 40% of outcomes being more than double or less than half of empirical estimates (Menzies et al., 2018). This systematic literature review embarks on a journey through the broad realm of mathematical models used to analyze TB transmission dynamics in Southeast Asia. Through careful analysis and synthesis of existing research, this study aims to provide a comprehensive overview of the methodologies, findings, and insights gained from mathematical modelling efforts in this region. By delving into various mathematical models, ranging from compartmental models to agent-based simulations, this review seeks to uncover fundamental patterns of TB transmission dynamics across different settings, populations, and epidemiological contexts in Southeast Asia. Through the lens of mathematical abstraction, we strive to understand the complex interactions among factors influencing TB spread, including demographic characteristics, healthcare access, treatment adherence, and social determinants of health.

Furthermore, this review seeks to evaluate the strengths, limitations, and gaps in existing mathematical modelling approaches, providing insights into areas ready for further investigation and refinement. By synthesizing various studies, we hope to draw conclusions that can form the basis for developing and implementing TB control and eradication interventions in Southeast Asia. Essentially, this systematic literature review is a collective effort to harness the power of mathematical modelling as a guide in the fight against TB in Southeast Asia. By uncovering the intricate web of TB transmission dynamics, we aim to pave the way for evidence-based strategies that have the potential to reduce the TB burden and protect the health and well-being of communities in this region. Research on mathematical modelling for tuberculosis (TB) has been extensive.

Therefore, we aim to enhance understanding of TB transmission models by identifying developed models, explaining the research methodologies used, and identifying proposed interventions in these models. Hopefully, this review contributes to synthesizing existing knowledge, identifying research gaps, and highlighting opportunities for future advancements in mathematical modelling for TB control strategies in the Southeast Asia region.

Method

This section outlines the research methodology, the PRISMA method. The PRISMA method, also known as Preferred Reporting Items for Systematic Reviews and Meta-Analyses, is a manuscript methodology that must undergo a selection process. Using this strategy, article elements included in the database are identified through analysis (Moher et al., 2009; Stovold et al., 2014). It addresses the basic research questions used to find, select, and evaluate related research to understand the research problem.

Table 1. Eligibility criteria

No.	Inclusion criteria	Exclusion criteria
1.	Article published between 2013 and 2023.	The articles are not in English.
2.	Journal articles only	The articles are not open-access
3.	Published as final peer review	The articles are not in Southeast Asia

Articles were found using the keywords "Mathematical Model" AND "Tuberculosis" in the Scopus database. A maximum of 872 results were available for selection, with publication years restricted between 2013 and 2023. We summarized this field's latest advancements using references encompassing current research. We identified 21 articles relevant to these terms through this technique for general understanding. Figure 1 illustrates the selection process.

As depicted in Figure 1, the article under analysis underwent a series of stages before publication, including identification, screening, and selection. The initial stage involved limiting the years and using predetermined keywords to retrieve 872 articles from the Scopus database. In the second round, 872 items were examined, with 843 disqualified according to the specified inclusion and exclusion criteria (see Table 1). During this screening process, the primary focus was on articles conducted or affiliated with the Southeast Asian region.

The remaining articles passed through thorough analysis in the third step. In the final phase, an analysis was conducted to address the research question. This analysis was carried out on 29 publications selected for systematic review. Before conducting the analysis, the abstracts of each article were carefully reviewed to identify relevant themes or subthemes. Subsequently, each article was investigated further to gather more in-depth data aligned with the research objectives. Thus, 21 articles were selected for further examination within the framework of this study. These stages demonstrate meticulous and systematic efforts to ensure that the selected articles meet the established criteria and are relevant to the research question.
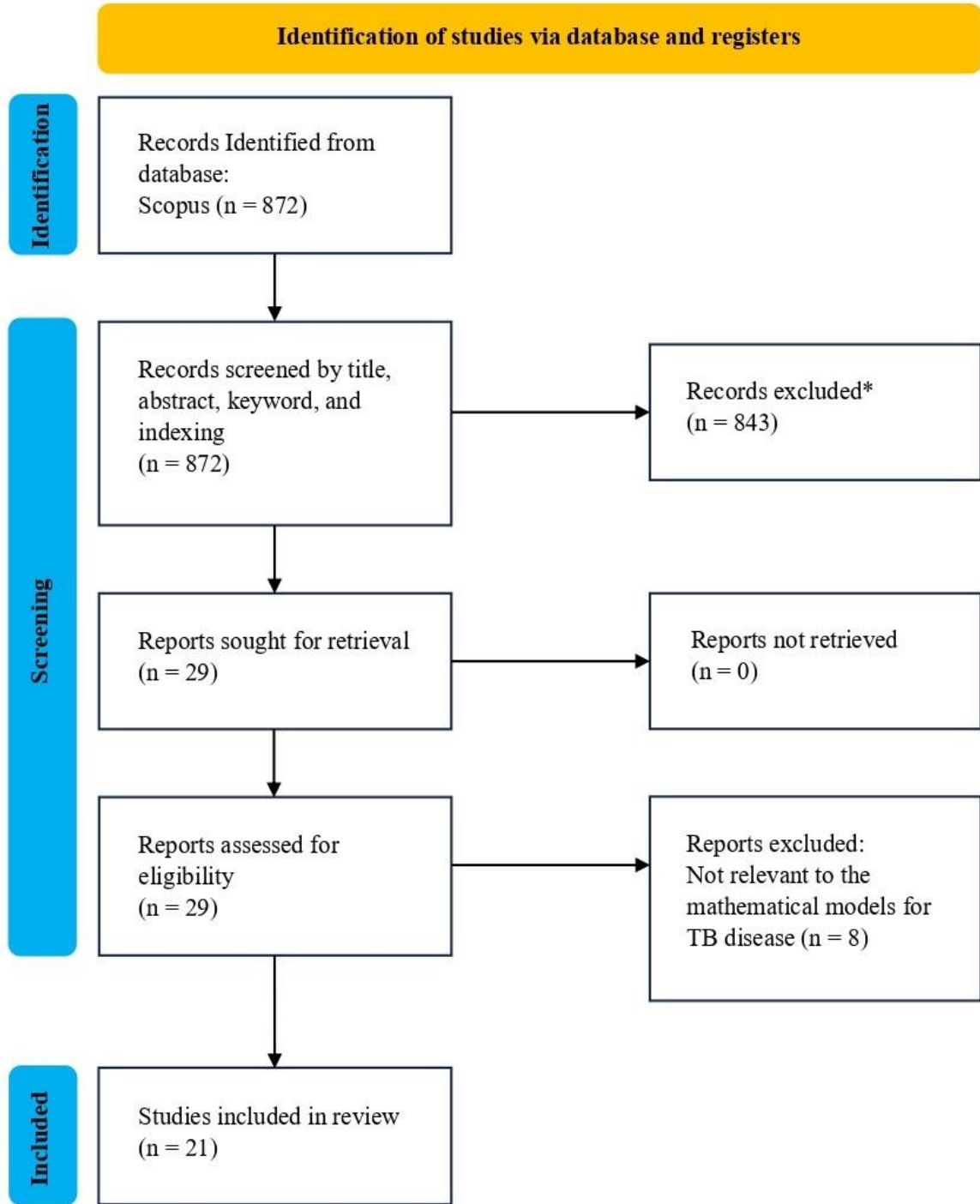
Results and Discussion

Identifying Models

The first mathematical model to simulate the spread of tuberculosis was introduced by (Waaler et al., 1962). They divided the population into three classes based on the epidemiological characteristics of the disease. This model provided a mathematical representation of the TB spreading process and laid the foundation for an initial understanding of the disease dynamics. Subsequently, the model by (Revelle et al., 1967) was further developed by (Revelle et al., 1967) using a system of nonlinear ordinary differential equations.

The resulting model introduced the concept that the spread of tuberculosis depends on the proportion of its prevalence, providing a more accurate depiction of how the number of infected individuals in the population influences TB spread. Over time, this model continued to evolve and was utilized to discuss strategies for controlling the spread of tuberculosis. This included research on the effectiveness of various interventions such as anti-TB immunization programs, sanitation programs, and treatment. By employing these models, researchers could predict the impact of various control strategies and identify the most effective approaches to reducing TB transmission in communities. Essentially, these models provide an important mathematical framework for understanding and addressing the spread of TB and guiding the development of more effective policies and

interventions to control this disease. We explored all identified papers, including authors, compartment notation, and whether they were analyzed mathematically (see Table 2). Table 3 explains the notation of each compartment. The aim is to introduce the entire article and obtain some basic information for further exploration

Identification of studies via database and registers

Identification

Records Identified from database:
Scopus (n = 872)

Screening

Records screened by title, abstract, keyword, and indexing
(n = 872)

Records excluded*
(n = 843)

Reports sought for retrieval
(n = 29)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 29)

Reports excluded:
Not relevant to the mathematical models for TB disease (n = 8)

Included

Studies included in review
(n = 21)

*Note:
1. The publication does not comprise the final article (n = 218).
2. The publication does not include the journal source type (n = 5).
3. The publication is not in English (n = 12).
4. The publication is not open access (n = 198).
5. The publication does not originate from Southeast Asia (n = 410).

Figure 1. The flowchart of the selection process.

Table 2. Identification of compartments on articles

Name, Year	Cited	Analyzed Mathematically	Compartment	Interventions
Ahmadin & Fatmawati, (2014)	14	Yes	$S_1, I_S, I_r, R_1, S_2, I_2, R_2$	Treatment
Vinh et al., (2018)	2	No	$U, L, ExPTBn, PTBn, U_h, L_h, ExPTBn_h, PT_h$	-
Aldila et al., (2019)	9	Yes	$x_1, x_2, x_3, y_1, y_2, y_3, y_4$	Medical mask intervention, Quarantine on cattle
Gomes et al., (2019)	9	No	U_i, P_i, I_i, L_i	-
Fatmawati et al., (2020)	43	Yes	$S_C, L_C, I_C, S_A, L_A, I_A$	-
Kabunga et al., (2020)	27	Yes	$S, L_e, L_f, I, R_1, R_2, T, K$	Prevention, Screening, Treatment
Kim et al., (2020)	17	No	S, E, I, L	Educational health campaigns, Treatment, Quarantine, Isolation
Han et al., (2021)	4	No	DS and MDR	Treatment
Kasbawati et al., (2021)	1	Yes	S, E, I, I_h, R	Treatment
Rahman et al., (2021)	49	Yes	$\mathbb{S}, \mathbb{E}, \mathbb{I}, \mathbb{T}, \mathbb{R}$	Treatment
Sulayman et al., (2021)	21	Yes	S, V, E, I, R, E	Vaccination
Weerasuriya et al., (2021)	15	No	-	Vaccination, Therapy
Biswas et al., (2022)	1	Yes	$S, L_T, I_H, H_S, E_{TH}, E_{HT}$	Vaccination, Treatment
Inayaturohmat et al., (2022)	7	Yes	$S, I_C, I_T, I_{TC}, Q, T, R$	Isolation, Treatment
Nuraini et al., (2022)	3	Yes	$S, Q_1, E_{co}, I_{co}, R_{co}, Q_2,$	Quarantine
Qu et al., (2022)	9	Yes	S, E, I, T, R	-
Singh et al., (2023)	5	Yes	S, E_H, E_C, I, R	-
Chukwu et al., (2023)	3	Yes	S, E, I, R	-
Muhafzan et al., (2023)	1	Yes	S, I, T, R	Treatment
Tamhaji & Hamdan, (2023)	-	Yes	B, S, E, I, R	Vaccination
Vo et al., (2023)	-	No	SROI	The economic evaluation of healthcare interventions

Table 2 provides details of the identities of 21 new relevant articles. From the data, it can be inferred that the work by (Rahman et al., 2021) is the most frequently cited, with 49 citations. Meanwhile, the studies conducted by (Tamhaji & Hamdan, 2023; Vo et al., 2023) have never been cited in the recorded literature. The article by (Vinh et al., 2018) developed a mathematical model depicting Tuberculosis (TB) transmission by dividing the population into two groups, namely G1 (non-hyper-susceptible) and G2 (hyper-susceptible). In the model they presented, it was assumed that the transition of individuals from G1 to G2 occurs uniformly across TB-affected regions. As a result, the resulting model has 14 compartments depicting transmission dynamics, which appear complex even though G1 and G2 essentially have similar characteristics. Additionally, (Nuraini et al., 2022) has developed a mathematical model explaining the impact of COVID-19 quarantine on TB and Diabetes Mellitus cases. This article also involves the formation of 12 compartments in its model, indicating high complexity in its resolution.

Table 3. Notations description

Notations	Description	Additional
$\mathbb{S}, S, S_1, S_2$	Susceptible population/individuals	-
S_C	Susceptible children	-
S_A	Susceptible adults	-
x_1	Susceptible cattle	-
y_1	Susceptible human who has direct contact with cattle	-
z_1	The susceptible human who has no direct contact with cattle	-
$\mathbb{E}, E$	Exposed population/individuals, high-risk latent	-
E_H	Exposed Tuberculosis	-
E_C, E_{co}	Exposed COVID-19/coronavirus	-
E_{TH}	infected with HIV (pre-AIDS) exposed to TB	-
E_{HT}	AIDS individuals exposed to TB	-
E_{T0}	Exposed to TB only	-
x_2	Exposed cattle	-
y_2	Exposed human who has direct contact with cattle	-
z_2	Exposed human who has no direct contact with cattle	-
$\mathbb{I}, I, I_2$	Infectious population/individuals	-
I_C, I_{co}	Infectious children, Infectious with COVID-19/coronavirus	-
I_A	Infectious adults	-
I_T, I_{tb}	Infectious with tuberculosis	-
I_{TC}	Individuals coinfected with COVID-19 and tuberculosis	-
I_s	infected sensitive	-
I_r	resistant to the class of anti-TB drugs	-
I_H	Infectious with HIV only	-
I_h	Infectious and hospitalized	-
I_i	Active tuberculosis disease	-
x_3	Infectious cattle	-
y_3	Infectious human who has direct contact with cattle	-
z_3	Infectious human who has no direct contact with cattle	-
$\mathbb{T}, T$	Treatment, Transferred	-
$\mathbb{R}, R, R_1, R_2$	Recovered population/individuals	-
R_h	Recovered hyper-susceptible	-
R_T	Recovered with temporal immunity	-
R_{co}	Recovered coronavirus	-
R_{tb}	Recovered tuberculosis	-
y_4	Recovered human who has direct contact with cattle	-
z_4	Recovered human who has no direct contact with cattle	-
L_C	Latent TB children	-
L_A	Latent TB adults	-
L_e	Latent early	-
L_f	Latent late	-
L	Low-risk latent	-
L_i	Latent infection	-
L_h	Latent hyper-susceptible	-
L_T	Latent TB with no HIV	-
L_{tb}	Latent tuberculosis	-

K	People who stop treatment	-
V	Vaccinated	-
B	BCG vaccinated	-
DS	Drug-susceptible	DS refers to cases of TB that are susceptible to standard treatment with commonly used anti-TB drugs.
MDR	Multidrug-resistant	MDR refers to cases of TB that are resistant to standard treatment with the most used anti-TB drugs.
SROI	the Social Return on Investment	SROI is a method for measuring values that are not traditionally reflected in financial statements, including social, economic, and environmental factors.
Q	Isolated with COVID-19 infection	-
Q_1	Quarantined susceptible	-
Q_2	Quarantined infected coronavirus	-
S_T	Symptomatic TB	Symptomatic TB refers to the stage of (TB) infection where an individual exhibits noticeable symptoms of the disease.
H_S	HIV infected displaying AIDS symptoms	-
H_{DT}	AIDS individuals dually infected with TB	-
D_{tb}	Diagnosed tuberculosis	-
D_{dm}	Diabetes without complications	-
C_{dm}	Diabetes with complications	-
U_i	Uninfected	-
U_h	Uninfected hyper-susceptible	-
P_i	Primary infection	Primary infection is a subpopulation that is infected for the first.
$ExPTBn$	Active extra-pulmonary TB new cases	-
$PTBn$	Active pulmonary TB new cases	-
$ExPTBr$	Active extra-pulmonary TB relapsed cases	-
$PTBr$	Active pulmonary TB relapsed cases	-
$ExPTBn_h$	Active extra-pulmonary TB new cases of hyper-susceptible	-
$PTBn_h$	active pulmonary TB new cases hyper-susceptible	-
$ExPTBr_h$	Active extra-pulmonary TB relapsed of cases of hyper-susceptible	-
$PTBr_h$	Active pulmonary TB relapsed cases of hyper-susceptible	-

Out of the 21 included articles, five of them (Chukwu et al., 2023; Fatmawati et al., 2020; Muhafzan et al., 2023; Qu et al., 2022; Rahman et al., 2021) incorporate their analyses using fractional models. This fractional model approach offers a robust framework for investigating TB transmission dynamics, predicting disease outcomes, optimizing intervention strategies, understanding complex transmission dynamics, and evaluating public health policies. The integration of fractional models with TB analysis in this context is expected to significantly contribute to designing more effective intervention strategies and estimating the impact of these interventions more accurately. On the other hand, three other articles (Inayaturohmat et al., 2022; Nuraini et al., 2022; Singh et al., 2023) evaluate the impact of the COVID-19 pandemic on TB cases. Reviewing this impact is important to understand how TB is managed during the pandemic, considering shifting priorities and limited healthcare resources. Analysis of how to address TB amidst the COVID-19 pandemic is crucial in formulating appropriate strategies to mitigate the dual impact of both diseases.

The development of these models is highly dependent on the assumptions used and the complexity of the problem under investigation. Therefore, more complex models may emerge in the future tailored to more complicated or specific issues. Advances in understanding disease dynamics, better data availability, and the development of mathematical and computational modeling techniques may enable the development of more sophisticated models.

In the context of infectious diseases such as tuberculosis, where factors such as variability in individual immunity, changes in social behavior, and population interactions play crucial roles in disease spread, more complex models may be required to account for all these variables accurately. Thus, ongoing research will continue to drive the development of more advanced models tailored to the complexity of the problems being studied, with the hope that these models will provide deeper insights and more effective solutions in addressing complex public health issues.

Identifying Research Methodology

The mathematical analysis in the mentioned articles represents a crucial approach to understanding the dynamics of diseases and the effectiveness of health interventions. In 15 out of the 21 papers, the authors employ various mathematical theories to analyze the epidemiological models under study. The aim of this analysis is to gain a deeper understanding of the positivity of solutions (i.e., whether the model solutions state the existence and uniqueness of solutions), solution constraints (such as whether the model solutions are bounded within a certain range), disease-free equilibrium points (i.e., situations where there are no disease cases), disease equilibrium points (i.e., situations where the disease persists), as well as the local and global stability of these equilibrium points (Aldila et al., 2019; Kabunga et al., 2020; Sulayman et al., 2021; Tamhaji & Hamdan, 2023). Additionally, several additional analyses have been conducted, such as bifurcation analysis to understand qualitative changes in system behavior when parameters change (Kabunga et al., 2020; Singh et al., 2023), and the utilization of continuous-time Markov chain models to account for uncertainty and stochasticity in the system ((Kasbawati et al., 2021)). Optimal control theory is utilized in several articles to analyze conditions where optimal control can be achieved by considering the associated control costs (Ahmadin & Fatmawati, 2014; Biswas et al., 2022; Singh et al., 2023).

While not all articles apply analytical approaches, some rely on primary data to simulate population dynamics (Han et al., 2021; Kim et al., 2020; Vinh et al., 2018), while others only use secondary data. Economic analyses are also outlined in several articles, including the economic evaluation of tuberculosis treatment models by community health workers and the importance of considering risk inequality in TB policy development (Ahmadin & Fatmawati, 2014; Quang Vo et al., 2023).Furthermore, the epidemiological, cost-effectiveness, and budgetary impacts of new vaccines for multidrug-resistant tuberculosis are also investigated (Weerasuriya et al., 2021).

Overall, the mathematical analysis and modeling in these articles provide valuable insights into understanding the dynamics of specific diseases and the effectiveness of different health interventions. They combine various mathematical methods and analytical approaches to generate a better understanding of the factors influencing disease spread and the effects of various health policies. Thus, these articles make significant contributions to the fields of epidemiology and public health, providing a foundation for the development of more effective interventions in disease control.

Identifying Interventions

Mathematical models for understanding and controlling the spread of tuberculosis (TB) have become a major focus in public health research. By considering the various interventions available, researchers are attempting to develop effective strategies to address this problem. Treatment is one of the most used interventions in TB control (Ahmadin & Fatmawati, 2014; Biswas et al., 2022; Han et al., 2021; Inayaturohmat et al., 2022; Kabunga et al., 2020; Kasbawati et al., 2021; Kim et al., 2020; Muhafzan et al., 2023; Rahman et al., 2021). Research has consistently confirmed that treatment is the best approach to immediately stop the spread of the disease. The focus of these interventions is to provide treatment to the infected population to stop the immediate spread of the disease. However, although treatment is an important step, it cannot completely prevent the spread of the disease. Therefore, preventive measures are very important in reducing the risk of infection. One preventive measure that has been widely studied is the use of medical masks to prevent transmission of TB through air and breathing (Aldila et al., 2019).

The safety of the human population is a major concern in studying the TB phenomenon. This is why some researchers have begun focusing on development models considering direct preventive measures against human populations. Vaccination, for example, has been shown to be effective in reducing the risk of infection in human populations (Biswas et al., 2022; Sulayman et al., 2021; Tamhaji & Hamdan, 2023; Weerasuriya et al., 2021). However, it is important to remember that although vaccination can be effective, no measure has yet been able

to eliminate this disease. Therefore, researchers also considering other preventive measures such as educational campaigns (Kim et al., 2020), quarantine (Aldila et al., 2019; Kim et al., 2020; Nuraini et al., 2022), and isolation (Inayaturohmat et al., 2022; Kim et al., 2020) to help increase public awareness and reduce the spread of TB.

Apart from that, health checks and screening are also important in early detection of TB infection (Kabunga et al., 2020). These measures should not be ignored as they can help break the chain of disease spread and provide timely treatment to infected individuals. By considering these various interventions, mathematical models can be an invaluable tool in planning effective strategies for controlling the spread of TB and protecting human populations from the risk of serious infection.

All articles are annotated to obtain the identity of the article and annotated to understand the research better. Based on 49 citations, some articles with more citations than others confirm that their investigative findings are useful for further research functions or even applied to real conditions. The model in each article is studied mathematically to obtain its behavior analytically and numerically. Various interventions are considered in the model to control diseases and analyze system behavior. This includes controlling and preventing infections in humans and vectors in the system both directly and indirectly.

Conclusion

The results of the analysis indicate that mathematical modeling of TB transmission can be enhanced by developing models with direct and indirect interventions for the human population. Various approaches in tuberculosis transmission dynamics, including compartmental models and spatial modelling techniques, are highlighted in this research. Evaluating the effectiveness of interventions and control measures implemented in the models also serves as a focal point to assess their impact on TB spread. This review contributes to synthesizing existing knowledge, identifying research gaps, and highlighting opportunities for future advancements in mathematical modeling for TB control strategies in the Southeast Asia region.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

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