

A Systematic Literature Review of Mathematical Models for Coinfections: Tuberculosis, Malaria, and HIV/AIDS

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Abstract: Tuberculosis, malaria, and HIV are among the most lethal diseases, with AIDS (Acquired Immune Deficiency Syndrome) being a chronic and potentially life-threatening condition caused by the human immunodeficiency virus (HIV). Individually, each of these infections presents a significant health challenge. However, when tuberculosis, malaria, and HIV co-occur, the symptoms can worsen, leading to an increased mortality risk. Mathematical models have been created to study coinfections involving tuberculosis, malaria, and HIV. This systematic literature review explores the importance of coinfection models by examining articles from reputable databases such as Dimensions, ScienceDirect, Scopus, and PubMed. The primary emphasis is on investigating coinfection models related to tuberculosis, malaria, and HIV. The findings demonstrate that each article thoroughly covers various aspects, including model development, mathematical analysis, sensitivity analysis, optimal control strategies, and research discoveries. Based on our comprehensive evaluation, we offer valuable recommendations for future research efforts in this field.

Keywords: tuberculosis, malaria, HIV, AIDS, coinfection, model, systematics literature review

Introduction

Human immunodeficiency virus (HIV) is responsible for causing acquired immunodeficiency syndrome (AIDS).¹ The transmission of HIV occurs when infected individuals come into contact with certain bodily fluids, such as blood, semen, breast milk, and vaginal secretions.² Even though a cure for HIV is not available, the virus can be effectively managed through the use of antiretroviral (ARV) drugs, to control its progression.³ HIV epidemic significantly influences the prevalence of tuberculosis infections and⁴ the virus compromises the immune system, making individuals who are infected highly susceptible to different infectious diseases.⁵

Tuberculosis (TB) is transmitted through the air when infected individuals speak, sneeze, or cough, making it an airborne disease. It is caused by *Mycobacterium tuberculosis*, a bacterium that primarily targets the lungs but can also affect other.⁶ After successful treatment, individuals who have been declared cured can still be susceptible to reinfection. Failure to consistently take the prescribed medication for the designated duration can lead to the development of Multi-Drug Resistant Tuberculosis (MDR-TB), where the bacteria become resistant to drugs.⁷ Even individuals who are subjected to treatment can still transmit tuberculosis when the virus remains active in their bodies.⁸ According to the 2013 global report by the World Health Organization (WHO), approximately one-third of the population is affected by the infection. The 2020 global report stated that around 9.96 million individuals were estimated to have contracted tuberculosis in 2020.⁹ Furthermore, between 2000 and 2019, the diagnosis and treatment efforts saved the lives of approximately 63 million people.¹⁰ Among individuals coinfecting with HIV and tuberculosis, tuberculosis is the primary cause of mortality.¹¹ Globally, approximately 10.6 million individuals contracted tuberculosis in 2022, marking an increase from the estimated 10.3 million cases in 2021.

There is a possibility of a resurgence in the declining trend observed before the pandemic, anticipated to take place in either 2023 or 2024.¹²

Malaria is caused by a parasite called *Plasmodium*.¹³ Common signs of malaria consist of fever, muscle pain, fatigue, and chills. In severe instances, the illness can result in fatalities. The disease is a highly fatal contagious illness solely transmitted by *Anopheles* mosquitoes.¹² The transmission occurs when female mosquitoes infected with the *Plasmodium* parasite bite humans, passing on the infection.¹⁴ Female mosquitoes require blood meals to produce eggs.¹⁵ According to World Health Organization (WHO), the count of malaria-endemic countries reporting fewer than 10,000 cases has risen from 26 nations in 2000 to 47 in 2020. Moreover, the number of countries with fewer than 100 native cases has increased from 6 to 26.¹⁶ On a worldwide scale in 2022, an approximate 249 million cases of malaria were reported across 85 countries where malaria is prevalent. The incidence of malaria cases in 2022 stood at 58 per 1000 population at risk.¹⁷ Global initiatives are in progress to eliminate malaria, which involves the development of novel vaccines and the implementation of insecticides to prevent mosquito bites.

Based on this data, the imperative to take action becomes evident to mitigate the transmission risk and curb the dissemination of tuberculosis, malaria, and HIV.¹⁸ As we progress towards controlling and potentially eliminating malaria, HIV, and TB, mathematical models offer a robust framework for assessing the potential impact of interventions. They help identify areas requiring additional empirical research, prioritize crucial policy and research questions, and, most importantly, necessitate improved communication between modelers and those involved in experiments or fieldwork. This collaboration is essential to fine-tune questions, pinpoint critical data, and ensure that analytical work contributes to enhanced policies and effectively controls all three infections.¹⁹ This model divides the population into different compartments based on certain assumptions and characteristics.²⁰ Model can also serve to depict the occurrence of epidemic events involving interactions between two diseases. Using this model enables the estimation of individuals who are infected.^{21,22} Subsequently, through the application of optimal controls, effective recommendations can be identified to manage and curb the transmission of the disease.

In recent years, progress has been made in the development of coinfection model for tuberculosis, malaria, and HIV. This Systematic Literature Review is dedicated to compiling existing model related to coinfection of these diseases and evaluating the extent of research and its corresponding outcomes. Ultimately, the objective is to provide valuable recommendations for future investigations in this field.

Materials and Methods

The method employed for articles to be included in this systematic literature review is the Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA).²³ PRISMA involves three key stages: identification, screening, and eligibility. In the identification stage, articles pertinent to the research are searched in different databases using specific keywords. During, at the screening stage, all identified articles from multiple databases are consolidated and duplicated entries are removed. The remaining articles are subjected to relevance assessment base on title and abstracts. At this stage, the relevance of the title and abstract in question is adjusted to the keywords used to search for these articles in the previous stage. The article goes to the next stage if the title or abstract contains a combination of these keywords. However, if there is no combination of these keywords, then the article is categorized as irrelevant at this stage. Additionally, the accessibility is checked, and any articles that do not meet the criteria are excluded. Following the screening stage, the articles that pass the initial assessment proceed to the eligibility phase, where a comprehensive evaluation is conducted to ascertain their relevance. At this stage, the relevance of the article in question is adjusted to the research topic of the article to be reviewed, namely mathematical models of tuberculosis, malaria, and HIV/AIDS coinfection in the form of ordinary differential equations. The article goes to the next stage if it is appropriate to the topic. However, if it is inappropriate, the article is categorized as irrelevant at this stage. By following these stages, the selected articles serve as the research material for this systematic literature review, facilitating a thorough exploration of coinfection model for tuberculosis, malaria, and HIV.

This systematic literature review encompasses articles not only focusing on coinfection models involving all three diseases but also combinations of coinfections arising from pairs of distinct diseases. The infectious diseases under investigation in this article include tuberculosis, malaria, and HIV/AIDS. Hence, PRISMA was conducted four times with different keywords. Furthermore, the articles were searched on four databases, namely Dimensions, Scopus, PubMed, and Science Direct. The first PRISMA used keywords: (“Mathematical Model” OR “Mathematical Modelling” OR “Compartmental Model” OR “Transmission Model”) AND (“Coinfection” OR “Co-infection”) AND (“Tuberculosis” OR

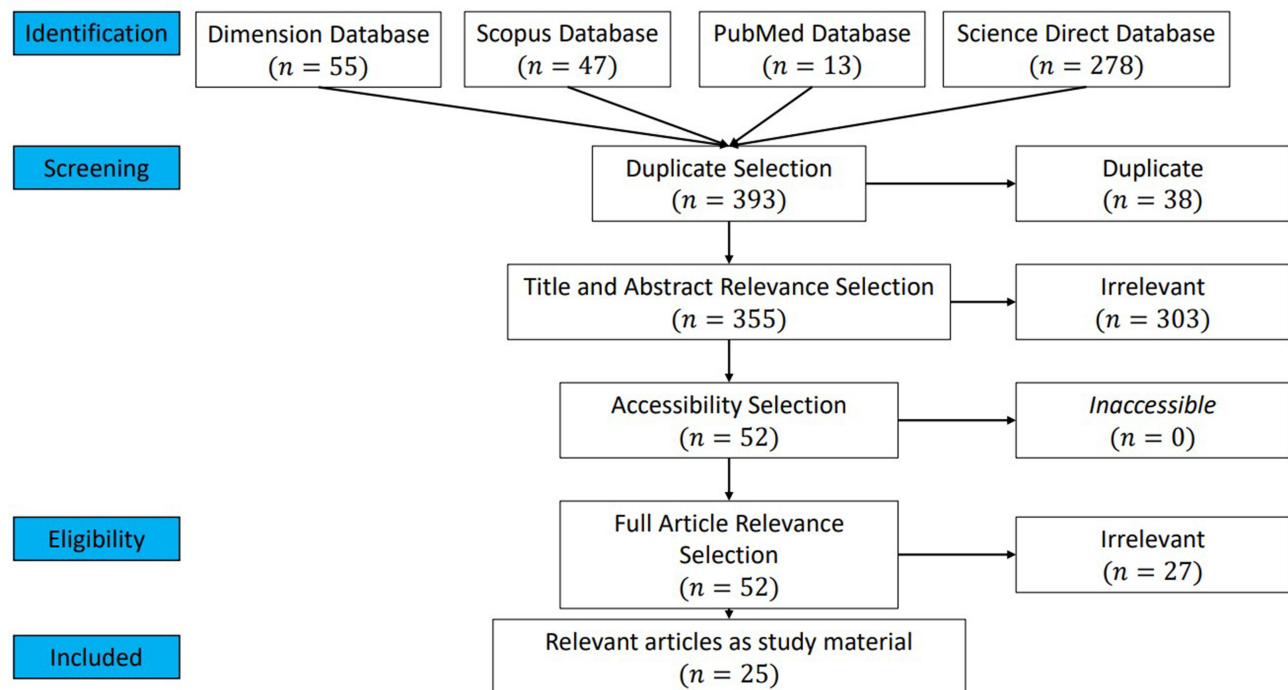
“TB”) AND (“AIDS” OR “HIV”). The second PRISMA used keywords: (“Mathematical Model” OR “Mathematical Modelling” OR “Compartmental Model” OR “Transmission Model”) AND (“Coinfection” OR “Co-infection”) AND (“Tuberculosis” OR “TB”) AND “Malaria”. Meanwhile, the third used keywords: (“Mathematical Model” OR “Mathematical Modelling” OR “Compartmental Model” OR “Transmission Model”) AND (“Coinfection” OR “Co-infection”) AND “Malaria” AND (“AIDS” OR “HIV”). The last PRISMA used keywords: (“Mathematical Model” OR “Mathematical Modelling” OR “Compartmental Model” OR “Transmission Model”) AND (“Coinfection” OR “Co-infection”) AND (“Tuberculosis” OR “TB”) AND “Malaria” AND (“AIDS” OR “HIV”).

The search limitation for this systematic literature review is as follows:

1. Research articles published in English language.
2. Research articles published between 1986 and 2024.
3. Research articles from Dimensions, ScienceDirect, Scopus, and PubMed databases.
4. The topic of the research article is the mathematical model of tuberculosis, malaria, and HIV/AIDS coinfection in the form of ordinary differential equations.

Duplication selection employed JabRef, while research topic mapping used VOSviewer. JabRef and VOSviewer were opensource software applications accessible to all users. JabRef enabled users to store their data in a simple text-based file format without being tied to any specific vendor. In contrast, VOSviewer was a software tool designed for creating and visualizing bibliometric networks.

Figure 1 showed the first PRISMA for articles on tuberculosis and HIV/AIDS coinfection models. A total of 55, 47, 13, and 278 articles were obtained from Dimension, Scopus, PubMed, and Science Direct, while 38 articles were duplicated. The screening process yielded 52 articles that proceeded to the eligibility stage. Subsequently, these 25 articles were deemed suitable for inclusion in this systematic literature review.



("Mathematical Model" OR "Mathematical Modelling" OR "Compartmental Model" OR "Transmission Model") AND ("Coinfection" OR "Co-infection") AND ("Tuberculosis" OR "TB") AND ("AIDS" OR "HIV")

Figure 1 PRISMA of Tuberculosis and HIV/AIDS.

Figure 2 showed the second PRISMA for articles on tuberculosis and malaria coinfection model. A total of 8, 3, 2, and 95 articles were obtained from Dimension, Scopus, PubMed, and Science Direct. After going through all stages of PRISMA, only 2 articles met the criteria for this systematic literature review.

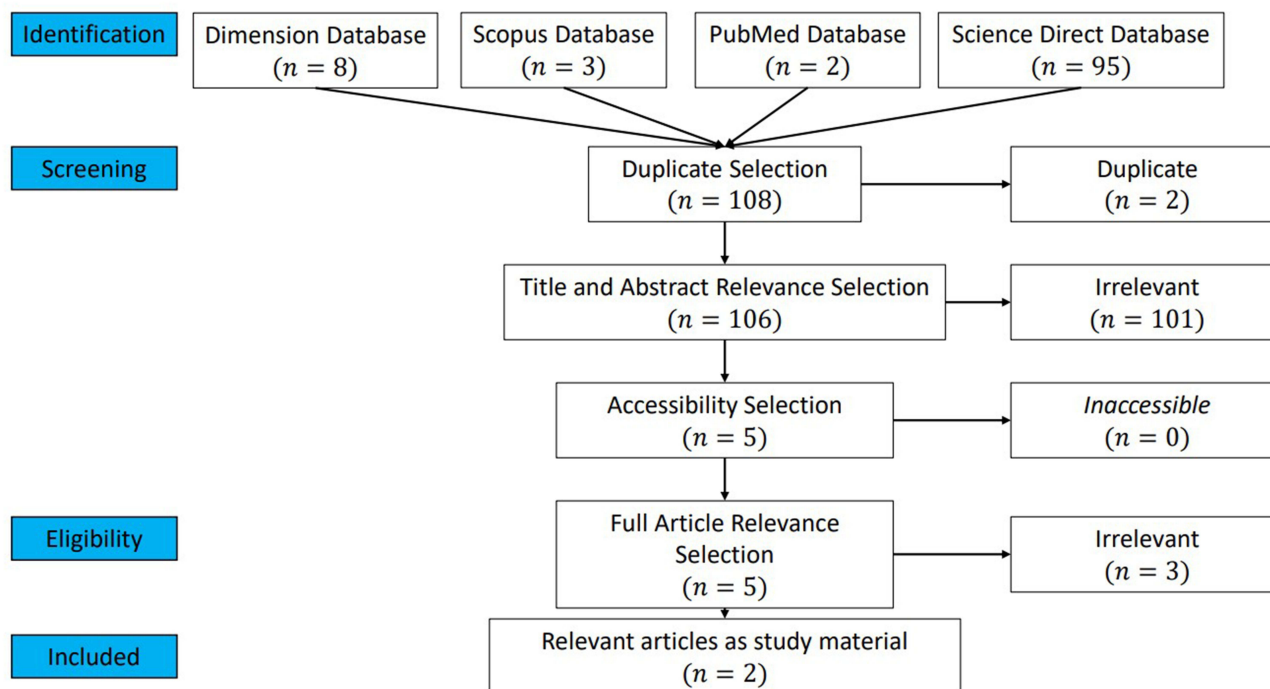
Figure 3 showed the third PRISMA for articles on malaria and HIV/AIDS coinfection model. A total of 22, 14, 7, and 122 articles were obtained from Dimension, Scopus, PubMed, and Science Direct were obtained, while 12 articles are duplicates. The screening result was 15 articles that proceed to the eligibility stage and only 7 articles were included in this systematic literature review.

Figure 4 showed the fourth PRISMA for articles on tuberculosis, malaria, and HIV/AIDS coinfection model. A total of 6, 1, 2, and 84 articles were obtained from Dimension, Scopus, PubMed, and Science Direct. After going through all stages of PRISMA, only 1 article met the criteria for this systematic literature review.

The articles retrieved from the four PRISMA searches were combined, and the keywords were mapped using VOSviewer. Figure 5 presented the resulting mapping, indicating connections between mathematical model, coinfection, HIV/AIDS, malaria, and tuberculosis. The circle shape represents the keywords contained in these articles. The bigger the circle, the more frequently the keyword appears in the articles. The lines connecting the circles illustrate the relationship between these keywords. The circle for the keyword HIV is larger than the circle for the keyword tuberculosis and the circle for the keyword malaria. This is because search results show that HIV co-infection is more common than tuberculosis or malaria. Based on the most occurrences, the keywords that appeared the most were “model” 80 times, “HIV” 73 times, “disease” 49 times, and “co-infection” 40 times. Meanwhile, “tuberculosis” and “malaria” appeared 29 and 22 times.

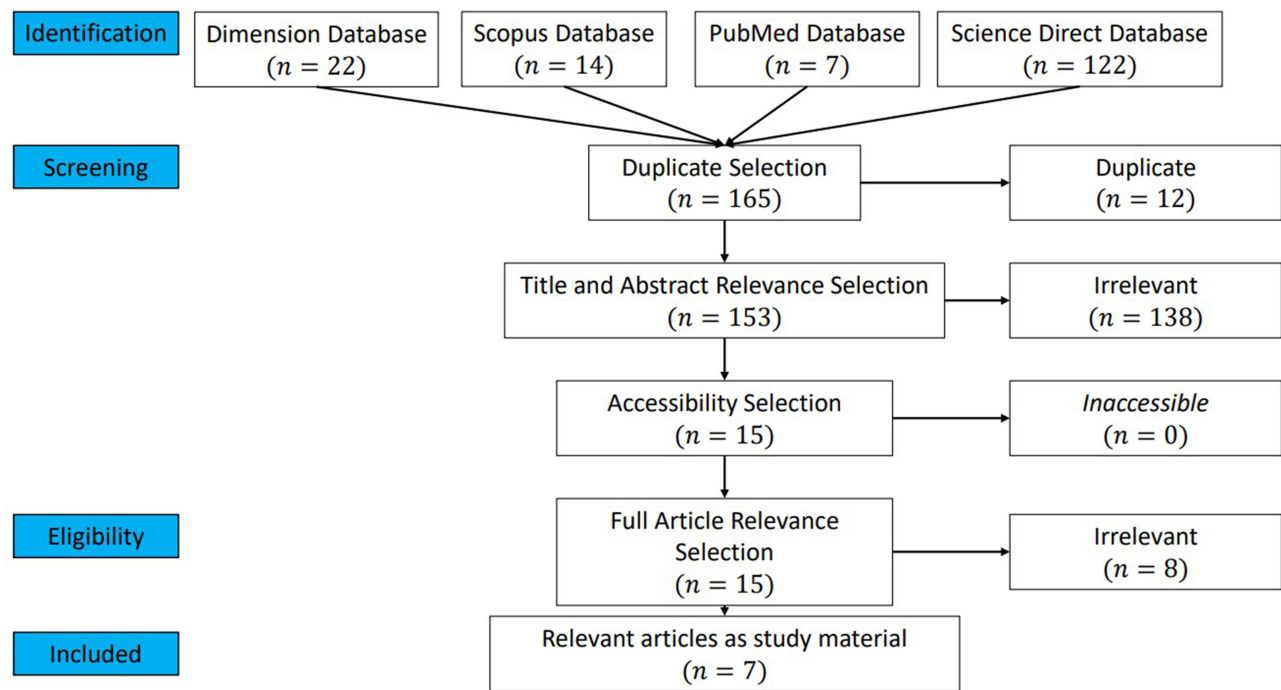
Results and Discussion

The articles derived from the analysis of the four PRISMA analyses were examined and assessed. The articles were scrutinized, focusing on aspects such as model construction, mathematical analysis, sensitivity analysis, and optimal



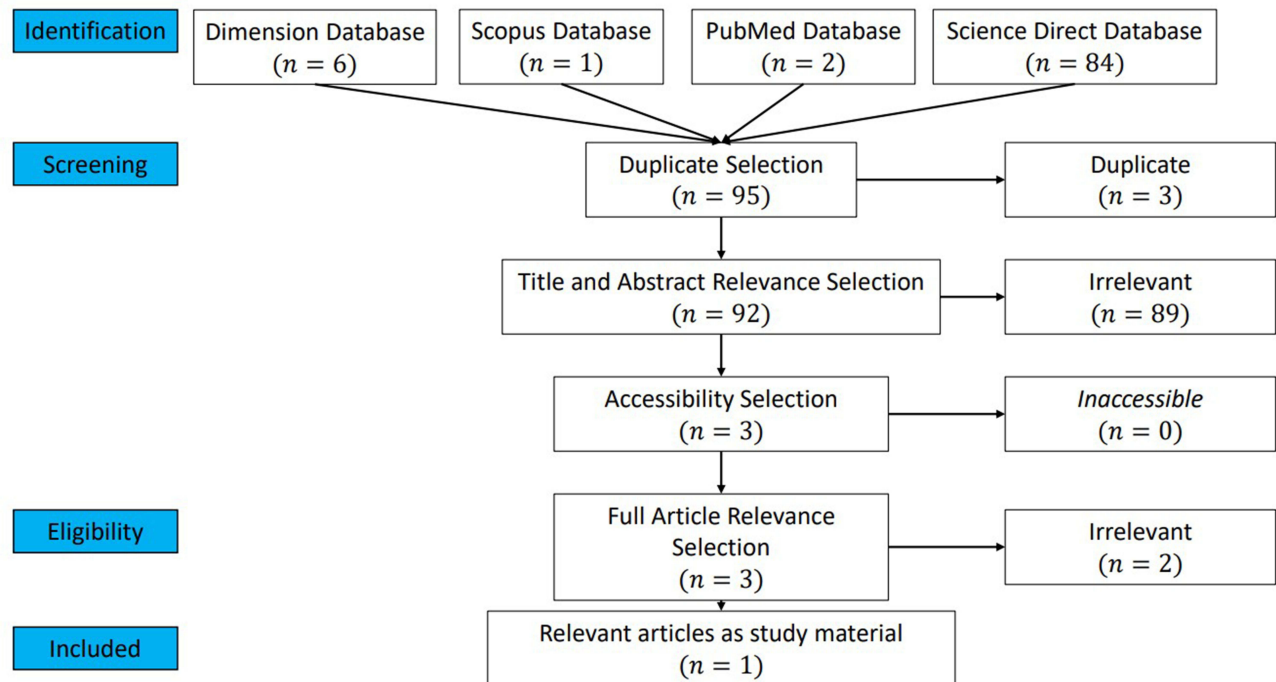
("Mathematical Model" OR "Mathematical Modelling" OR "Compartmental Model" OR "Transmission Model") AND ("Coinfection" OR "Co-infection") AND ("Tuberculosis" OR "TB") AND "Malaria"

Figure 2 PRISMA of Tuberculosis and Malaria.



("Mathematical Model" OR "Mathematical Modelling" OR "Compartmental Model" OR "Transmission Model") AND ("Coinfection" OR "Co-infection") AND "Malaria" AND ("AIDS" OR "HIV")

Figure 3 PRISMA of Malaria and HIV/AIDS.



("Mathematical Model" OR "Mathematical Modelling" OR "Compartmental Model" OR "Transmission Model") AND ("Coinfection" OR "Co-infection") AND ("Tuberculosis" OR "TB") AND "Malaria" AND ("AIDS" OR "HIV")

Figure 4 PRISMA of Tuberculosis, Malaria, and HIV/AIDS.

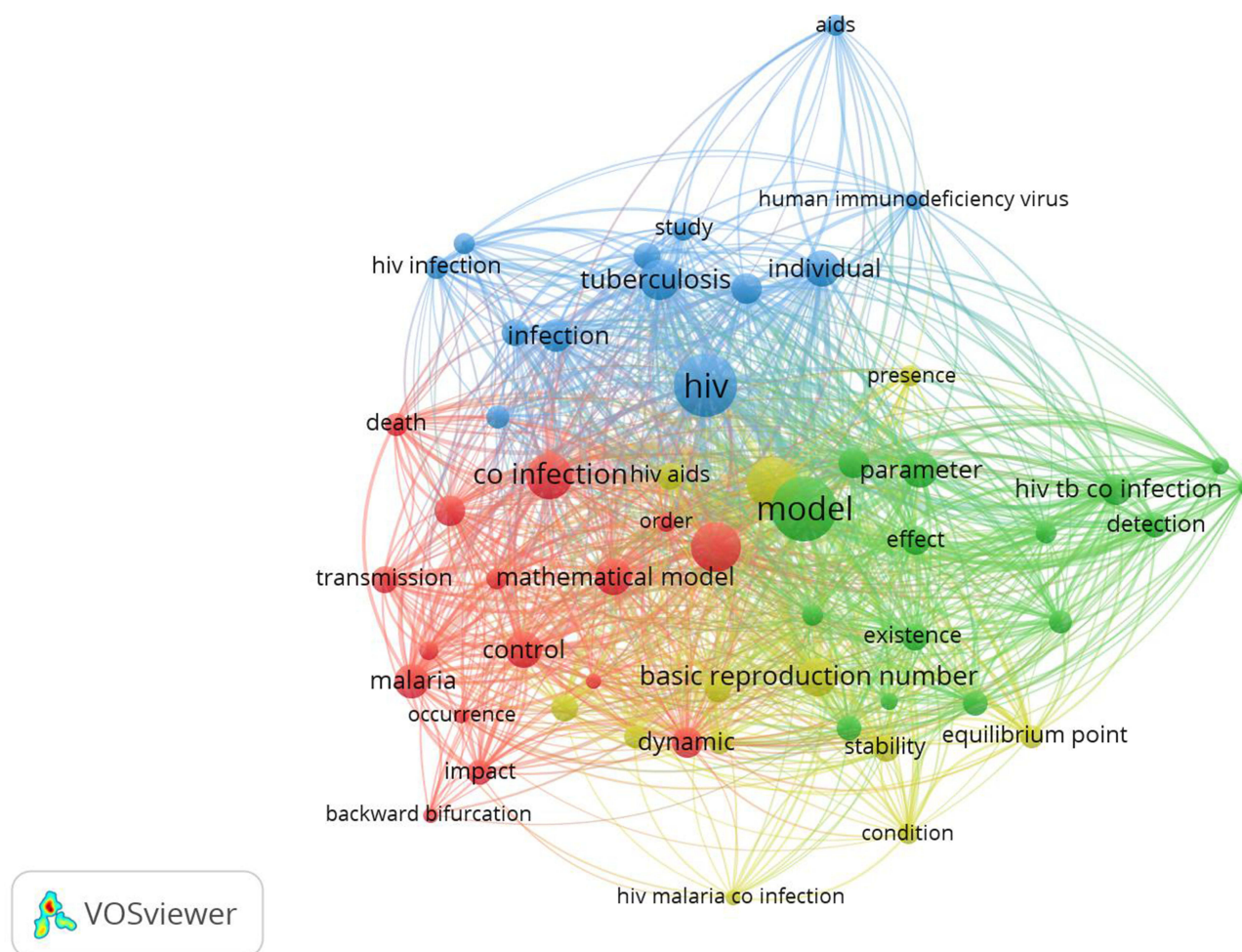


Figure 5 Mapping research topics using VOSviewer.

control. The outcomes were described, and a summary of the findings was provided. In conclusion, recommendations were offered to guide future research in potential areas of development. The objective of this systematic literature review addressed the following inquiries:

1. Which disease coinfection model does the article include?
2. Is the coinfection model mathematically analyzed?
3. What sensitivity analysis method is used in the article?
4. What controls are used in optimal control of coinfection model in the article?
5. How many compartments does the coinfection model consist of, and what are the compartments identified?
6. What are the research results obtained in the article?

Mathematical analysis can encompass various aspects of coinfection models, such as examining their fundamental properties, such as positivity, uniqueness, and invariant regions. This can also involve conducting local and global stability analyses. Additional analyses such as bifurcation may be incorporated. If the article does not discuss one of these analyses, then the article is said to be “No” on mathematical analysis, although all articles explain the formulation of mathematical models.

Sensitivity Analysis is a method for measuring uncertainty in a model. Sensitivity analysis in disease spread models can be used to determine how much influence parameter changes have on changes in basic reproduction numbers (\mathcal{R}_0) or compartments. Several sensitivity analysis methods can be used to analyze the model: index method for \mathcal{R}_0 and Partial Rank Correlation Coefficient (PRCC).

In models of tuberculosis, malaria, and HIV/AIDS coinfection, interventions in the form of various forms of control are often used to reduce the spread of these diseases. Mathematically, this control is used to create an objective function to minimize the spread of the disease. The solution can be found using optimal control theory. Optimal control theory is a subset of control theory focused on determining a control strategy for a dynamic system throughout a specific time frame, aiming to optimize an objective function. These articles were reviewed to find out what type of controls were used in each article.

In this systematic literature review, a total of 35 articles were examined from the four PRISMA analyses. The analysis aimed to gain insights into the coinfection scenarios involving tuberculosis-malaria, tuberculosis-HIV, malaria-HIV, as well as tuberculosis-malaria-HIV. Detailed information from all the articles was extracted, including author names, publication years, details of mathematical analysis, sensitivity methods, and the controls used in model, as shown in Table 1. The specifics regarding the compartments employed in model are available in Table 2. Detailed descriptions of the model parameters can be seen in the reference article. The research results of these articles will be briefly explained in this systematic literature review.²⁴

The only article about a coinfection model of tuberculosis and malaria based on the second PRISMA. Model formulation of malaria and tuberculosis coinfection can be seen in model (1). In model (1), the entire human population is categorized into various subpopulations: susceptible individuals denoted as $S(t)$, individuals currently exposed to malaria alone represented as $E_m(t)$, individuals exclusively infected with malaria noted as $I_m(t)$, individuals who have

Table 1 Detail of the Articles

(Name, Year)	Coinfection	Mathematical Analysis	Sensitivity Analysis Methods	Control	Reference
(Alzahrani, 2022)	Tuberculosis-Malaria	Yes	–	Long-Lasting Insecticide-Treated Nets (LLITN), Treatment Malaria, Treatment Tuberculosis, Indoor Residual Spraying (IRS), Prevention Tuberculosis	[24]
(Afolabi, 2021)	Tuberculosis-Malaria	Yes	Index to \mathcal{R}_0	–	[25]
(Barley, 2012)	Malaria-HIV	Yes	Index to \mathcal{R}_0	–	[26]
(Seidu, 2015)	Malaria-HIV	Yes	Index to \mathcal{R}_0	Condoms, Insecticide- Treated Nets, Malaria Treatment, Highly Active Antiretroviral Therapy (HAART), Mass Spraying	[27]
(Nyabadza, 2015)	Malaria-HIV	Yes	Index to \mathcal{R}_0	HIV Treatment, AIDS Treatment, Malaria Treatment	[28]
(Mohammed-Awel, 2017)	Malaria-HIV	Yes	Index to \mathcal{R}_0	Malaria Treatment, Insecticide- Treated Nets	[29]
(Fatmawati, 2018)	Malaria-HIV	Yes	Index to \mathcal{R}_0	Malaria Prevention, Malaria Treatment, Antiretroviral Therapy (ARV)	[30]
(Saha, 2019)	Malaria-HIV	Yes	–	HIV Treatment, Malaria Treatment	[31]
(Oladapo, 2023)	Malaria-HIV	Yes	Index to \mathcal{R}_0	–	[32]
(Massad, 1993)	Tuberculosis-HIV	No	Index to Variable	–	[33]
(Naresh, 2009)	Tuberculosis-HIV	Yes	–	Tuberculosis Treatment	[34]
(Bhunu, 2009)	Tuberculosis-HIV	Yes	–	–	[35]
(Gakkhar, 2012)	Tuberculosis-HIV	Yes	–	–	[36]

(Continued)

Table 1 (Continued).

(Name, Year)	Coinfection	Mathematical Analysis	Sensitivity Analysis Methods	Control	Reference
(Agusto, 2014)	Tuberculosis-HIV	Yes	Index to \mathcal{R}_0	Three Case Findings, Six Preventions Treatment Failure Tuberculosis,	[37]
(Kaur, 2014)	Tuberculosis-HIV	Yes	–	Tuberculosis Treatment, HIV Treatment, Tuberculosis Screening, HIV Screening	[38]
(Adewale, 2015)	Tuberculosis-HIV	Yes	Index to \mathcal{R}_0	HIV Treatment	[39]
(Bunwong, 2015)	Tuberculosis-HIV	No	–	–	[40]
(Kaur, 2015)	Tuberculosis-HIV	Yes	–	–	[41]
(Nthiiri, 2015)	Tuberculosis-HIV	Yes	–	–	[42]
(Mallela, 2016)	Tuberculosis-HIV	Yes	–	HIV Early Treatment, HIV Late Treatment	[43]
(Olopade, 2016)	Tuberculosis-HIV	Yes	–	–	[44]
(Bolarin, 2017)	Tuberculosis-HIV	No	–	HIV Treatment, Tuberculosis Treatment	[45]
(Awoke, 2018)	Tuberculosis-HIV	Yes	–	HIV Preventive Education, Tuberculosis Preventive Education, HIV Treatment, Tuberculosis Treatment	[46]
(Muthuri, 2018)	Tuberculosis-HIV	Yes	Index to \mathcal{R}_0	Tuberculosis treatment	[47]
(Tahir, 2019)	Tuberculosis-HIV	Yes	–	Tuberculosis Treatment, Tuberculosis Social Distancing, Infection Control at Health Care Center, MDR Tuberculosis Treatment - HIV ARV	[48]
(Tanvi, 2020a)	Tuberculosis-HIV	Yes	–	HIV-Tuberculosis Treatment	[49]
(Tanvi, 2020b)	Tuberculosis-HIV	Yes	–	HIV Detection, Tuberculosis Detection, HIV- Tuberculosis Detection	[50]
(Tanvi, 2020c)	Tuberculosis-HIV	Yes	–	Tuberculosis Treatment, Early HIV Treatment, Late HIV Treatment, IRIS Treatment	[51]
(Omale, 2021)	Tuberculosis-HIV	Yes	Index to \mathcal{R}_0	Tuberculosis Awareness Education, HIV Awareness Education, Tuberculosis-HIV Awareness Education	[52]
(Biswas, 2022)	Tuberculosis-HIV	Yes	–	Tuberculosis Vaccination, Tuberculosis-HIV Treatment	[53]
(Patchaimani, 2022)	Tuberculosis-HIV	Yes	–	Tuberculosis-HIV Treatment	[54]
(Adeyemo, 2023)	Tuberculosis-HIV	No	–	–	[55]
(Teklu, 2023)	Tuberculosis-HIV	Yes	Index to \mathcal{R}_0	Prevention HIV, Prevention Tuberculosis, Treatment HIV, Treatment Tuberculosis,	[56]
(Torres, 2023)	Tuberculosis-HIV	Yes	PRCC	–	[57]
(Singh, 2013)	Tuberculosis-Malaria- HIV	Yes	–	Malaria Treatment	[58]

Note: \mathcal{R}_0 Basic Reproduction Number.

Table 2 Compartments of the Models

(Name, Year) [Reference]	Number of Compartments	Tuberculosis	Malaria	HIV/AIDS	Vector	Coinfection	Others
(Alzahrani, 2022) ²⁴	11	Exposed, Infected, Treatment	Exposed, Infected	–	Susceptible, Exposed, Infected	Tuberculosis-Malaria	Susceptible, Recovered
(Afolabi, 2021) ²⁵	14	Vaccination, Exposed, Undetected, Detected, Recovered	Exposed, Infected, Recovered	–	Susceptible, Exposed	Exposed Tuberculosis- Malaria, Active Tuberculosis-Malaria, Recovered Tuberculosis- Malaria	Susceptible
(Barley, 2012) ²⁶	6	–	Infected	HIV Infected	Susceptible, Infected	HIV-Malaria	Susceptible
(Seidu, 2015) ²⁷	9	–	Infected	HIV Productive, HIV Non- Productive, AIDS Infected	Susceptible, Exposed, Infected	HIV-Malaria	Susceptible
(Nyabadza, 2015) ²⁸	13	–	Exposed, Infected	HIV Infected, AIDS Infected, HIV Treatment, AIDS Treatment	Susceptible, Exposed, Infected	Asymptomatic, AIDS- Malaria, Symptomatic, AIDS-Malaria, AIDS- Malaria Treatment	Susceptible
(Mohammed- Awel, 2017) ²⁹	8	–	Infected	HIV Infected	Susceptible, Infected	HIV-Malaria	Susceptible, Recovered (Temporary Immune to Malaria), Recovered (Infectious HIV)
(Fatmawati, 2018) ³⁰	7	–	Infected	HIV Infected, AIDS Infected	Susceptible, Infected	HIV-Malaria	Susceptible
(Saha, 2019) ³¹	9	–	Infected, Treatment	HIV Infected, HIV Treatment	Susceptible, Infected	HIV-Malaria Coinfected, HIV-Malaria Treatment	Susceptible
(Oladapo, 2023) ³²	14	–	Treated, Exposed, Infected, Recovered	HIV Latent, HIV Undetected, HIV Detected, HIV Treated,	Susceptible, Exposed, Infected	HIV-Malaria Exposed, Active HIV-Malaria	Susceptible
(Massad, 1993) ³³	16	Latent, Active, Infected,	–	HIV Infected, AIDS Infected, AIDS Complex	–	HIV-Latent Tuberculosis, HIV-Active Tuberculosis, HIV-Tuberculosis, AIDS- Latent Tuberculosis, AIDS- Active Tuberculosis,	Susceptible, Healthy Seropositive
(Naresh, 2009) ³⁴	5	Infected	–	HIV Infected, AIDS Infected	–	Tuberculosis-HIV	Susceptible

(Continued)

Table 2 (Continued).

(Name, Year) [Reference]	Number of Compartments	Tuberculosis	Malaria	HIV/AIDS	Vector	Coinfection	Others
(Bhunu, 2009) ³⁵	10	Exposed, Symptomatic, Recovered	–	HIV Asymptomatic, AIDS Infected,		Exposed Tuberculosis-HIV, Exposed Tuberculosis- AIDS, Symptomatic Tuberculosis-HIV, Symptomatic Tuberculosis- AIDS,	Susceptible
(Gakkhar, 2012) ³⁶	4	Infected	–	HIV Infected	–	Tuberculosis-HIV	Susceptible
(Agusto, 2014) ³⁷	21	Sensitive Latent, Sensitive Active, Treated Sensitive, Resistant Latent, Resistant Active, Treated Resistant,	–	HIV Infected, HIV Symptoms,	–	HIV-Sensitive Latent, HIV- Sensitive Active, Treated HIV-Sensitive, HIV- Resistant Latent, HIV- Resistant Active, Treated HIV-Resistant, AIDS- Sensitive Latent, AIDS- Sensitive Active, Treated AIDS-Sensitive, AIDS- Resistant Latent, AIDS- Resistant Active, Treated AIDS-Resistant,	Susceptible
(Kaur, 2014) ³⁸	6	Infected	–	HIV Infected, AIDS Infected	–	Tuberculosis-HIV, Tuberculosis-AIDS	Susceptible
(Adewale, 2015) ³⁹	9	Exposed, Undetectable, Detectable, Treatment, Recovered	–	HIV Exposed, HIV Undetectable, HIV Detectable, HIV Treatment	–	–	Susceptible
(Bunwong, 2015) ⁴⁰	6	Exposed, Active	–	HIV Infected	–	Exposed Tuberculosis-HIV, Active, Tuberculosis-HIV	Susceptible
(Kaur, 2015) ⁴¹	4	Infected	–	Infected	–	Infected	Susceptible
(Nthiiri, 2015) ⁴²	12	Protected, Asymptomatic, Symptomatic, Recovered		Protected, Asymptomatic, Symptomatic,		Tuberculosis-HIV Asymptomatic, Tuberculosis-HIV Symptomatic, Tuberculosis-AIDS Symptomatic, Tuberculosis-AIDS Asymptomatic	Susceptible
(Mallela, 2016) ⁴³	8	Infected	–	HIV Infected	–	Tuberculosis-HIV Coinfected, Initial Treatment, HIV- Tuberculosis, Late Treatment, HIV- Tuberculosis, Initial Treatment, HIV-Treatment Tuberculosis, Final Treatment, HIV-Treatment Tuberculosis	Susceptible

(Continued)

Table 2 (Continued).

(Name, Year) [Reference]	Number of Compartments	Tuberculosis	Malaria	HIV/AIDS	Vector	Coinfection	Others
(Olopade, 2016) ⁴⁴	15	Latent, Detected, Undetected, Treatment Fail, Recovered	–	HIV Latent, HIV Detected, HIV Undetected,	–	Latent Tuberculosis-HIV, Active Tuberculosis-HIV, Recovered Tuberculosis-HIV, Latent HIV-Tuberculosis, Aktif HIV-Tuberculosis	Susceptible
(Bolarin, 2017) ⁴⁵	6	Infected, Recovered	–	HIV Infected, AIDS Infected	–	Tuberculosis-HIV	Susceptible
(Awoke, 2018) ⁴⁶	13	Educated, Latent, Active, Treated,	–	Educated, HIV Asymptomatic, HIV Treatment, AIDS Infected,	–	Latent Tuberculosis-HIV, Active Tuberculosis-HIV, Tuberculosis-AIDS, Recovered Tuberculosis-HIV	Susceptible
(Muthuri, 2018) ⁴⁷	9	Latent, Infected, Treated	–	HIV-Infected, AIDS Infected		Exposed Tuberculosis-HIV, Tuberculosis-HIV, Treated Tuberculosis-HIV, Treated Tuberculosis-Treated HIV	Susceptible
(Tahir, 2019) ⁴⁸	9	Exposed, Active, Cured	–	HIV with AIDS symptoms, HIV without AIDS symptoms, HIV Treatment	–	Exposed Tuberculosis-HIV, Active, Tuberculosis-HIV	Susceptible
(Tanvi, 2020a) ⁴⁹	5	Infected	–	HIV Infected,	–	Tuberculosis-HIV	Susceptible, Recovered
(Tanvi, 2020b) ⁵⁰	11	Exposed, Active, Cured	–	HIV Infected, AIDS Infected, AIDS Treatment	–	Exposed Tuberculosis-HIV, Active, Tuberculosis-HIV, Exposed Tuberculosis-AIDS, Active, Tuberculosis-AIDS	Susceptible
(Tanvi, 2020c) ⁵¹	14	Exposed, Recovered, Infected, Initial Stage Treatment, Final Stage Treatment	–	HIV Infected, HIV Treatment	–	Exposed Tuberculosis-AIDS, Exposed Tuberculosis-HIV, Early Stage of Tuberculosis-ARV, Final Stage of Tuberculosis-ARV	Susceptible, IRIS, IRIS Treatment
(Omale, 2021) ⁵²	7	Infected, Treatment, Recovered	–	AIDS Infected	–	Tuberculosis-HIV Coinfected, Tuberculosis-HIV Treatment	Susceptible
(Biswas, 2022) ⁵³	10	Latent, Symptoms, Exposed	–	HIV Infected, HIV with AIDS Symptoms, AIDS Infected	–	Exposed Tuberculosis-HIV, Exposed Tuberculosis-AIDS,	Susceptible, Recovered
(Patchaimani, 2022) ⁵⁴	6	Infected	–	HIV Infected, AIDS Infected	–	Tuberculosis-HIV	Susceptible, Recovered
(Adeyemo, 2023) ⁵⁵	9	Infected, Death, Recovered	–	HIV Infected, Death, Recovered	–	Tuberculosis-HIV, Death	Susceptible

(Continued)

Table 2 (Continued).

(Name, Year) [Reference]	Number of Compartments	Tuberculosis	Malaria	HIV/AIDS	Vector	Coinfection	Others
(Teklu, 2023) ⁵⁶	14	Immune, Exposed, Fast Latent, Slow Latent, Active, Treated	–	HIV Acute, HIV Chronic, AIDS Infected, HIV Treatment,	–	Acute HIV-Tuberculosis, Infected HIV-Tuberculosis, Treated HIV-Tuberculosis	Susceptible
(Torres, 2023) ⁵⁷	14	High Risk Latent, Low Risk Latent, Symptomatic		HIV Treated, HIV Aware, HIV Unaware, AIDS Infected		Latent Tuberculosis- Unaware HIV, Latent Tuberculosis-Aware HIV, Tuberculosis-Unaware HIV, Tuberculosis-Aware HIV, Tuberculosis-AIDS, Tuberculosis-Treated HIV	Susceptible
(Singh, 2013) ⁵⁸	5	Infected	Infected	HIV Infected, AIDS Infected	–	–	Susceptible

recovered from both TB and malaria referred to as $Re(t)$, individuals exposed to TB marked as $E_{tb}(t)$, individuals infected with TB indicated as $I_{tb}(t)$, individuals infected with TB who are undergoing treatment as $T_{tb}(t)$, and individuals concurrently infected with both TB and malaria denoted as $I_{mt}(t)$. The author carries out a fundamental analysis of the model to prove that the model is well posed by establishing the positivity of the solution, invariance region, and stability of the equilibrium point locally and globally. The author also proves that model (1) experiences backward bifurcation. To obtain the best strategy for dealing with tuberculosis and malaria coinfection, the author used optimal control with five types of control and then carried out numerical simulations for several optimal control combinations.

$$\frac{dS}{dt} = \Lambda - \lambda_{tb}S - \lambda_mS - dS,$$

$$\frac{dE_m}{dt} = \lambda_mS - (\tau_m + d)E_m,$$

$$\frac{dI_m}{dt} = \tau_mE_m - (d + d_m + \gamma_m)I_m - \lambda_{tb}I_m,$$

$$\frac{dR}{dt} = \gamma_mI_m + \alpha_{tb}T_{tb} + \psi_{mt}I_{mt} - dR,$$

$$\frac{dS_v}{dt} = \Lambda_v - \lambda_vS_v - d_vS_v,$$

$$\frac{dE_v}{dt} = \lambda_vS_v - (d_v + \tau_v)E_v, \quad (1)$$

$$\frac{dI_v}{dt} = \tau_vE_v - d_vI_v,$$

$$\frac{dE_{tb}}{dt} = \lambda_{tb}S - (d + \epsilon_{tb})E_{tb} + (1 - \eta_{tb})\delta_{tb}T_{tb},$$

$$\frac{dI_{tb}}{dt} = \epsilon_{tb}E_{tb} + \eta_{tb}\delta_{tb}T_{tb} - (d + \gamma_{tb} + \sigma_{tb})I_{tb} - \lambda_mI_{tb},$$

$$\frac{dT_{tb}}{dt} = \gamma_{tb}I_{tb} - (d + \delta_{tb} + \sigma_{tb} + \alpha_{tb})T_{tb},$$

$$\frac{dI_{mt}}{dt} = \lambda_{tb}I_m + \lambda_m I_{tb} - (\varepsilon + d + \psi_{mt})I_{mt},$$

with $\lambda_{tb} = \frac{\beta_{tb}\sigma_{tb}I_{tb}}{N}$, $\lambda_m = \frac{\beta_m\sigma_m I_v}{N}$ and $\lambda_v = \frac{\beta_v\sigma_v I_m}{N}$.

Based on the results obtained from the third PRISMA, six articles discuss malaria and HIV coinfection.²⁷ Of the six articles, the article has detailed and coherent discussion content. The author divides the model into sub-models and then looks for the balance point and stability of each balance point, both local stability and global stability. Model formulation of malaria and HIV coinfection can be seen in model (2). In model (2), the human population is categorized into six distinct compartments, each mutually exclusive: susceptible $S_h(t)$, productive HIV-only infected individuals $I_{pa}(t)$, non-productive HIV-only infected individuals $I_{na}(t)$, AIDS patients $A(t)$, non-productive individuals infected with malaria only $I_{nm}(t)$, and individuals dually infected with both HIV and malaria $I_{nd}(t)$. Similarly, the vector population is divided into three exclusive compartments: susceptible mosquitoes $S_v(t)$, exposed mosquitoes $E_v(t)$, and infected mosquitoes $I_v(t)$. Model (2) also experiences backward bifurcation. The author also added 5 optimal controls and carried out numerical simulations to get the best control.

$$\frac{dS_h}{dt} = Q_h + r_2 I_{nm} - (\lambda_a + \lambda_m + \mu)S_h,$$

$$\frac{dI_{pa}}{dt} = r_1 I_{na} + r_3 I_{nd} - (\lambda_m + \delta_1 + \mu)I_{pa},$$

$$\frac{dI_{na}}{dt} = \lambda_a S_h - (\lambda_m + r_1 + \delta_2 + \mu)I_{na},$$

$$\frac{dI_{nm}}{dt} = \lambda_m S_h - (\lambda_a + r_2 + \psi_m + \mu)I_{nm},$$

$$\frac{dI_{nd}}{dt} = \lambda_m (I_{pa} + I_{na}) + \lambda_a I_{nm} - (r_3 + \delta_3 + \psi_m + \mu)I_{nd}, \quad (2)$$

$$\frac{dA}{dt} = \delta_1 I_{pa} + \delta_2 I_{na} + \delta_3 I_{nd} - (\psi + \mu)A,$$

$$\frac{dS_v}{dt} = Q_v - (\lambda_v + v + \mu_v)S_v,$$

$$\frac{dE_v}{dt} = \lambda_v S_v - (\delta_m + v + \mu_v)E_v,$$

$$\frac{dI_v}{dt} = \delta_m E_v - (v + \mu_v)I_v,$$

with $\lambda_a = \frac{\beta_a(I_{pa} + I_{na} + I_{nd})}{N_h}$, $\lambda_m = \frac{\beta_m \varepsilon \phi I_v}{N_h}$ and $\lambda_v = \frac{\beta_v \varepsilon \phi (I_{nm} + I_{nd})}{N_h}$.

Based on the results obtained from the first PRISMA, sixteen articles discuss tuberculosis and HIV coinfection.⁵² Of the sixteen articles, research on a comprehensive model of tuberculosis and HIV coinfection, starting from basic analysis to model simulations. Model formulation of tuberculosis and HIV coinfection can be seen in model (3). The overall population is divided into seven distinct classes: Susceptible individuals represented as $S(t)$, those infected with tuberculosis as $I_1(t)$, individuals who have both HIV and TB infections as $I_2(t)$, individuals with TB who are undergoing treatment as $T_1(t)$, individuals with both HIV and TB infections who are receiving treatment as $T_2(t)$, individuals affected by AIDS as $A(t)$ due to the progression of HIV-infected individuals who have chosen not to undergo treatment, and lastly,

individuals who have recovered from tuberculosis infection, denoted as $R_1(t)$. The author carries out a fundamental analysis of the model to prove that the model is well posed by establishing the positivity of the solution, invariance property, existence of the solution, and stability of the equilibrium point both locally and globally.

$$\begin{aligned}
 \frac{dS}{dt} &= \pi - \frac{\beta_1(1-u_1)SI_1}{N} - \frac{\beta_2(1-u_2)SI_2}{N} + \theta_1 R_1 - \mu S \\
 \frac{dI_1}{dt} &= \frac{\beta_1(1-u_1)SI_1}{N} - \frac{\beta_3(1-u_3)I_1 I_2}{N} - (\gamma + \sigma_1 + \mu)I_1 \\
 \frac{dI_2}{dt} &= \frac{\beta_2(1-u_2)SI_2}{N} - \frac{\beta_3(1-u_3)I_1 I_2}{N} - (1-\phi)I_2 - \phi I_2 - (\sigma_2 + \mu)I_2 \\
 \frac{dT_1}{dt} &= \gamma I_1 - (\eta + \sigma_3 + \mu)T_1, \\
 \frac{dT_2}{dt} &= \phi I_2 - (\theta_2 + \sigma_4 + \mu)T_2, \\
 \frac{dA}{dt} &= (1-\phi)I_2 + \theta_2 T_2 - (\sigma_5 + \mu)A \\
 \frac{dR_1}{dt} &= \eta T_1 - (\theta_1 + \mu)R_1
 \end{aligned} \tag{3}$$

According to the fourth PRISMA, only one article constructs a model from tuberculosis, malaria, and HIV coinfection.⁵⁸ Model formulation of malaria and tuberculosis coinfection can be seen in model (4). The entire population is categorized into five distinct classes, which include the susceptible $S(t)$, individuals with treatable malaria infections $I_1(t)$, those with mTB infections $I_2(t)$, the HIV-infected population $I_3(t)$, and the class of people living with AIDS $A(t)$. Model (4) considers one-way infection from malaria or mTB infection to malaria-HIV coinfection and mTB-HIV coinfection. In addition, this model also does not consider coinfection between malaria and mTB. The author analyzes local stability, performs several numerical simulation cases, and concludes that malaria and mTB infection significantly increase HIV/AIDS infection. From this information, this model still has many things that can be developed.

$$\begin{aligned}
 \frac{dS}{dt} &= Q - \frac{\beta_1 SI_1 + \beta_2 SI_2 + \beta_3 SI_3}{N} - dS + \lambda_1 I_1 + \lambda_2 I_2 \\
 \frac{dI_1}{dt} &= \frac{\beta_1 SI_1}{N} - \frac{\beta_4}{N} I_1 I_3 - dI_1 - \lambda_1 I_1, \\
 \frac{dI_2}{dt} &= \frac{\beta_2 SI_2}{N} - \frac{\beta_5}{N} I_2 I_3 - dI_2 - \lambda_2 I_2, \\
 \frac{dI_3}{dt} &= \frac{\beta_3 SI_3}{N} + \frac{\beta_4}{N} I_1 I_3 + \frac{\beta_5}{N} I_2 I_3 - dI_3 - \epsilon I_3, \\
 \frac{dA}{dt} &= \epsilon I_3 - dA - \alpha A.
 \end{aligned} \tag{4}$$

Table 1 provides an overview of the included articles, showing 7, 25, 2, and 1 article on malaria-HIV coinfection model, tuberculosis-HIV coinfection model, tuberculosis-malaria and tuberculosis-malaria-HIV coinfection model.^{33,40,45} The authors did not incorporate mathematical analysis into their articles.³³ One of this research featured highly intricate model that posed challenges for mathematical analysis.^{26–30,37,39,52} Furthermore, articles performed a sensitivity analysis on model, employing an indexing method to assess the impact on basic reproduction number. Basic Reproduction

Number \mathcal{R}_0 is a threshold value that can reference whether a disease will spread or be eliminated from a population. Sensitivity analysis of a parameter is carried out to see how the parameter influences changes in \mathcal{R}_0 .⁵⁷ Other Article use PRCC method to analyze the sensitivity of the parameter. Obtaining trustworthy data poses a common challenge in mathematical biology. Although specific parameter values are available in other articles, some parameters had to be estimated. Consequently, it is crucial for the estimation of \mathcal{R}_0 to exhibit relatively low sensitivity to these parameter values.²⁶ Example of sensitivity analysis result, if HIV infection predominantly influences \mathcal{R}_0 , a 10% reduction in the transmission rate is approximately mirrored by a 10% decline in \mathcal{R}_0 . However, a 10% reduction in the death rate results in a 7% rise in \mathcal{R}_0 for Malawi and an 8% increase for sub-Saharan Africa.³⁰ Other article result, increasing infection rate for malaria by 10%, increases the reproduction number by 5%. Thus, increasing natural death rate δ by 10% decreases the basic reproduction number by 10%.³³ Other articles employed sensitivity analysis with an indexing method applied to different variables. In general transmission model, sensitivity analysis employs an index for \mathcal{R}_0 . The more modest the sensitivity of a parameter to its \mathcal{R}_0 , the more accurate the estimated value of that parameter. For some cases, the results of sensitivity analysis are used as a reference for selecting parameters to be controlled using optimal control theory. This can prove the influence of these parameters on the spread of disease in the population.

Optimal control plays a crucial role in determining the most appropriate and efficient interventions for model. Several articles employ these methods, incorporating different types of prevention and intervention controls.^{28,31,34,38,39,45,49,58} Certain articles determine the best strategy to reduce infection by altering parameter values.^{26,33,40} However, some articles did not incorporate any control measures in their analysis.

Table 2 illustrates that model with the³⁶ lowest and³⁷ highest number of compartments consist of 4 and 21 compartments, respectively. Despite the complexity of their model, the authors conducted mathematical and sensitivity analyses, and utilized optimal control to obtain results.

The presented articles have yielded recommendations for mitigating the transmission of tuberculosis, malaria, and HIV.²⁴ The integration of Long-Lasting Insecticide-Treated Nets (LLITN), malaria treatment, tuberculosis treatment, Indoor Residual Spraying (IRS), and tuberculosis prevention proves to be effective in reducing the spread of tuberculosis, malaria, as well as their coinfection.

The results obtained for the malaria-HIV coinfection model differ. According to³⁰ article, the most effective method to diminish malaria-HIV coinfection involves the combination of malaria prevention measures and antiretroviral (ARV) treatment. However,³¹ article obtained the result that treating malaria and HIV individually proved to be more effective in reducing infection compared to administering combined treatment.²⁸ The escalation of HIV/AIDS prevalence due to coinfection with malaria, highlights the significance of treatment in mitigating this interplay, particularly for individuals already affected by AIDS.²⁶ The mortality rate rises with coinfection and doubles when the infectivity escalates by 30%.²⁷ The most cost-effective control to inhibit the spread of HIV-Malaria coinfection is prevention. Furthermore,²⁹ significant reductions or potential eradication of HIV prevalence can be achieved by ensuring high bed-net coverage, a high rate of malaria treatment to effectively minimize the incidence of malaria-HIV coinfection.

The outcomes derived from coinfection model of tuberculosis and HIV exhibit variations.⁴⁰ The infections exert a significant impact on the population due to the presence of a hidden population with tuberculosis infection.³³ Tuberculosis and HIV are intricately interconnected with each other, while AIDS is influential on tuberculosis infection. Likewise,³⁴ the presence of tuberculosis infection can expedite the progression of HIV, potentially leading to more rapid development of AIDS.

In terms of optimal control,³⁶ article implemented effective isolation measures to restrict the contact and transmission of infections within the population, to eliminate tuberculosis-HIV coinfection. Furthermore,³⁷ the integration of case findings and prevention treatment failure of tuberculosis proved to be effective in reducing the spread of tuberculosis and HIV.³⁸ Screening plays a crucial role in managing and containing the transmission of HIV and tuberculosis.³⁹ Individuals with weakened immune systems are more vulnerable to contracting HIV and tuberculosis. The overall burden arising from coinfection can be minimized by employing well-selected strengths and initiating antiretroviral therapy (ARV).⁴³ Additionally, maintaining a higher early treatment rate compared to the late treatment rate throughout the entire treatment program is essential.⁴⁵ Early detection of HIV and tuberculosis cases and the prompt initiation of treatment can effectively decrease the rate of infection, slow down the progression of HIV infected individuals toward AIDS, and reduce the occurrence of coinfection.⁴⁶

The combination of prevention and treatment gives good results from economic and epidemiological perspectives. In addition,⁴⁹ vaccination leads to rapid recovery in individuals.⁴⁸ Optimal detection and integrated therapy, administered at the appropriate time, also yield superior clinical outcomes.⁵⁰ The optimal result can be obtained by combining all the detection or one of tuberculosis or HIV only for a longer period.

To decrease the prevalence of infection and fatalities caused by the disease, it is necessary to implement all control measures collectively and at an optimal level. However,⁵¹ this method carries the potential risk of inducing immune reconstitution inflammatory syndrome (IRIS) in infected individuals.⁵² Enhancing awareness through education results in a decline in the cumulative occurrence of new cases of coinfection within a population.⁵³ The most effective method to minimize infection, maximize the rate of recovery, and control the disease progression is through a combination of vaccination and treatment.

Based on the method employed to search for articles, only one addresses coinfection model involving tuberculosis, malaria, and HIV. However,⁵⁸ this model refrains from employing vectors as compartments, and the management of malaria and tuberculosis can potentially decelerate the progression of HIV.

Some coinfection models consider the effects of prevention and intervention in various forms. Prevention is in the form of Net insecticides and mass spraying to reduce mosquito populations. There is also in the form of education and use of condoms or in any form without specifying the prevention. Meanwhile, intervention can take the form of treatment for malaria and tuberculosis or various therapies for HIV/AIDS. Based on these articles, prevention and intervention significantly influence the dynamics of disease spread. Prevention and intervention in various forms can be used as optimal control in reducing the spread of disease in a population.

Mathematical models of coinfection between tuberculosis, malaria, and HIV/AIDS can be used to help in deciding intervention policies that must be implemented to suppress the spread of these diseases.¹¹ One of the important mathematical models in the spread of infectious diseases is the use of country-specific dynamic models to estimate the incidence and mortality of TB in that period 2020–2022. Estimates for 2020–2022 were generated utilizing a dynamic model tailored to each country, considering the impact of disruptions to tuberculosis diagnosis and treatment caused by the Covid-19 pandemic. Determining the burden of TB during the Covid-19 pandemic and its aftermath poses challenges, and the current approach involves the use of country- and region-specific dynamic models, particularly for many low- and middle-income countries. These models also used by WHO.⁵²

Article use data relevant to Kogi state of Nigeria to study the coinfection of tuberculosis and HIV. Analytical results supported by numerical simulation prove that educational awareness campaigns and treatment can reduce the burden of tuberculosis, HIV, and the coinfection of tuberculosis and HIV.⁴⁰ Article use population and health statistic from the Ministry of Interior, the Ministry of Public Health, Thailand and the World Health Organization to estimate the parameter value of the model. The extended duration of latent TB infection means that newly infected cases do not exhibit clinical symptoms immediately. Consequently, these cases remain unnoticed for a considerable period. To account for this delay, the development of a time-delay differential equation model becomes essential.²⁶

Global parameter estimates were derived from data collected in sub-Saharan Africa. The complete biological interactions between the malaria parasite and HIV are not yet fully understood. However, it is plausible that coinfection might result in a magnitude increase in the parasite or viral load. Future research endeavors should involve parameter fitting to data. Exploring coinfection at a cellular level would be needed as well.

Conclusion

In conclusion, a comprehensive search was conducted for articles using four different databases and specific sets of keywords. The selection process involved removing duplicated articles, assessing titles and abstracts, checking accessibility, and evaluating the relevance of entire article. Furthermore, the search yielded a total of 761 articles with the specified keywords. After completing the selection process, 35 articles were identified for analysis in systematic literature review. The articles covered different aspects, including model construction, mathematical analysis, sensitivity analysis, optimal control, and research findings. Valuable research and findings were also presented, contributing to the field of tuberculosis, malaria, and HIV coinfection model. Infectious diseases are a global health problem, especially deadly diseases such as tuberculosis, malaria and HIV/AIDS. This can become a more crucial health problem when coinfection

occurs between these diseases. Mathematical models of tuberculosis, malaria, and HIV/AIDS coinfection can find the most effective intervention policies in reducing the spread of disease. Several studies on tuberculosis, malaria, and HIV/AIDS coinfections have been carried out in several countries using mathematical models and parameter estimation using data resulting from collaboration with local departments. For example, in Nigeria, Thailand, and Africa. This research produced several optimal solutions to reduce the spread of disease, including educational awareness campaign and treatment. Mathematical models of disease spread can produce recommendations for the government to create policies to reduce the spread of disease. However, there was still potential for further development of coinfection model by considering factors such as lifestyle, hospitalization, traditional treatment, and bacterial or virus evolution. Future research can also carry out parameter fitting estimation methods or use time delay models. Even the research object can be modified, namely from distribution at the human level to distribution at the cellular level.

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Disclosure

The authors declare no conflicts of interest in this work.

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