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Mathematical Modelling and Analysis for the Co-infection of Viral and Bacterial Diseases: A Systematic Review Protocol

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Abstract

Introduction: Breaking the chain of transmission of an infectious disease pathogen is a major public health priority. The challenges of understanding, describing and predicting the transmission dynamics of infections have led to a wide range of mathematical, statistical and biological research problems. Advances in diagnostic laboratory procedures with the ability to test multiple pathogens simultaneously mean that co-infections are increasingly being detected, yet little is known about the impact of co-infections in shaping the course of an infection, infectivity, and pathogen replication rate. Particularly, the apparent synergistic effects of viral and bacterial co-infections that present the greatest threats in public health due to their lethal nature and complex dynamics.

Objective: In this systematic review, we will explore and synthesise the mathematical epidemiological modelling of viral-bacterial co-infections and the role of simultaneous pathogen interactions in shaping transmission dynamics, severity, and control of infectious diseases.

Methods and analysis: MEDLINE through PubMed, Web of Science, medRxiv and Scopus will be systematically searched for studies published between January 2010 to date. Three reviewers will screen articles independently for eligibility and quality assessment will be performed using the TRACE (Transparent and Comprehensive Ecological modelling) standard modelling guide. Data will be extracted using an Excel template in-line with the Preferred Reporting Items for Systematic Review & Meta Analysis (PRISMA) guidelines. This systematic review will apply the SWiM (Synthesis without Meta-analysis) approach in its narrative synthesis coupled with tables and figures to present data obtained. The synthesis will highlight key dynamical co-infection model features such as assumptions, data fitting and estimation methods, validation, and sensitivity analyses, optimal control analyses, and impact of co-infections.

Ethics and dissemination: Ethics approval will not be sought for this systematic review. The output of this study will be submitted for publication in a peer reviewed journal.

PROSPERO registration number: CRD42023481247

Strengths and limitations of this study

- This systematic review highlights the impact of coinfections in shaping disease burden, transmission, severity, and control strategies.
- This review informs the gaps in the coinfection modelling literature and highlight the need to rigorously develop models that could guide public health policies.
- This is the first review study to focus on viral-bacteria co-infection epidemic modelling formulation, assumptions, and underscore the transmission peculiarities.
- This systematic review describes the complexity and discusses the implications of viral-bacterial co-infections.
- This systematic review considers only studies published between January 2010 to date, which may hamper generalisability.
- This systematic review investigates only mechanistic mathematical co-infection epidemic modelling approaches, which may create bias.

Introduction

Co-infection refers to the simultaneous infection by two or more pathogens[1] or the presence of multiple strains of the same infection in a host, as seen in the case of influenza viruses.[2-4] On the other hand, they can occur as multiple infections by varied diseases within same host or between different hosts.[5-8] Over the years, diligent vaccinations and use of anti-biotics have significantly prevented deaths and helped combat transmission of viral-bacterial infectious diseases. However, viral and bacterial infections remain a major public health threat since they are lethal and predisposes the most vulnerable population to infections.[9] For instance, childhood viral-bacterial diseases like pneumonia and diarrheal infections remain the main causes of mortality in infants and children, while SARS-COV-2, HIV, Tuberculosis (TB), Influenza and hepatitis are among the major killer viral-bacterial infections in adults globally. According to World Health Organization (WHO) viral and bacterial infections of the respiratory system lead with a global burden (6.2%) followed by diarrheal infections, which account for a burden (4.8%).[9] The synergism of viral-bacterial co-infections has remained lethal leading to extensive theoretical and clinical research on the mechanisms behind their transmission dynamics.[10] The ecological epidemiology of infectious pathogen interactions and coexistence in the host species can be complex and their combined effects on disease transmission, clinical outcomes and public health intervention measures remain poorly understood.[11-13]

Many human and animal populations acquire infections with either bacterial or viral pathogens.[14 15] Studies on the 2009 pandemic Influenza A(H1N1) in the United States found that within six days of influenza infection, a bacterial co-infection occurred with an increased risk of death for critically ill patients.[16] Similarly, epidemiological studies have reported Influenza (viral) and Streptococcus pneumoniae (bacterial) co-infections occurring during flu season with influenza potentially weakening the immunity of individuals which predisposes them to bacteria like streptococcus pneumoniae infections.[14] Additionally, HIV and TB co-infections have been reported with HIV infected individuals experiencing advanced immunosuppression which renders patients weaker and unable to fight off TB bacteria, predisposing HIV-positive patients with higher vulnerability to catching a TB infection.[17] Therefore, viral-bacterial co-infections are of great public health concern due to the risk factors they present in altering the severity, incidences and mortalities. [14]

Despite co-infection models having vital implications in public health policy, epidemiology and pathogen evolution, few studies have addressed their complexity and implications in forecasting disease dynamics. Limited systematic reviews have focused on co-infection mathematical epidemiological modelling design, quality, and applications. Recent systematic reviews have assessed the impact of co-infections in disease dynamics and have focused on specific co-infections such as HIV-hepatitis, HIV-TB and Ebola-malaria co-infections.[11 12 14-20] Some significant and interesting reviews on the impact of coinfections have focused on respiratory tract infections[10 16], aquatic animals[21] and modelling within-host coinfections.[22]

Given the vital significance and potential for wide application of co-infection studies in public health, understanding the dynamics of simultaneous coexistence of infectious pathogens is crucial to improving the practicability of the co-infection modelling.[23] Transition and interaction framework between classes in a co-infection model may be complex[22], especially in cases where infections present multiple strains or pathogens in a host. Dynamical co-infection epidemiological models are effective tools for highlighting a more comprehensive understanding of infectious disease spread, precise prediction and transition dynamics.[24] The models can highlight the causal factors, expected size and duration of an epidemic outbreak, and the extent of resource strain and disease case fatalities associated with the outbreak.[25] It is expected of a mathematical model to provide realistic predictions for disease dynamics.[24]

This systematic review aims at providing an extensive exposition and diagnostics of existing bacterial-viral co-infection epidemiological models of infectious diseases that were published from January 2010 till date. In detail, we will particularly focus on the co-infection model formulation, assumptions, analysis, modelling techniques and data integration while assessing its significance and identifying potential research gaps which might be of interest to mathematical epidemiologists and public health policy makers. The co-infection modelling framework has the potential to guide policies on management and control strategies for emerging and re-emerging infectious diseases.

Research objectives and questions

This systematic review is aimed at performing a critical review of dynamical co-infection epidemiological modelling and assess the key features of co-infection models. Its focus is primarily on modelling techniques applied (assumptions,

modelling designs, data fitting, and model analysis and control strategies). It will identify research gaps in co-infection modelling mechanism that may help advance the models to further realism and enhance effective description and forecasting of disease dynamics. Specifically, this systematic review is aimed at addressing the following questions:

1. How do parameters change in a co-infection model? Does catching a viral pathogen increase, decrease the risk in acquiring a bacterial infection or is it insignificant and vice versa? Do viral/bacterial pathogen co-infections lead to a higher risk of disease severity?
2. Does a co-infection alter infectiousness and mortality rates? How are co-infections and mortalities epidemiologically modelled?
3. What is the impact(s) of co-infections in shaping the infectious disease spread dynamics?
4. What are the mathematical modelling approaches employed to describe the dynamics? What research gaps exist in the modelling approaches?
5. How are surveillance data integrated in a co-infection model? What reasonable data inputs/assumptions might be necessary to predict or forecast co-infection disease dynamics? What are the challenges in parameter estimation of a co-infection model?
6. How can co-infection mathematical models be robustly formulated, analysed, tested, and evaluated in a manner that is biologically meaningful and relevant for provision of guidance on urgent response policy and mitigation of an infectious disease outbreak?

Rationale

The spread dynamics of pathogens in humans and animals can be 5influenced by co-infections, which may ultimately lead to insignificant, beneficial, or detrimental health outcomes.[11] The interactions between two or more infectious disease pathogens in host species can have serious outcomes, particularly in vulnerable immunosuppressed individuals such as HIV-positive patients who are at a higher risk of experiencing increased severity or dying due to co-infections.[11]

Co-infection models offer a way to understand and describe infectious disease spread dynamics and provide both short-term and long-term forecasts through integration of biological features, behavioural and environmental epidemiological factors that shape the burden, transmission, surveillance, prevention, and control strategies. The last decade has witnessed an increased interest in epidemiological modelling due to its

potential of integrating both ecological epidemiology and mathematics under a data, knowledge, and strategic decisions framework to explain the transmission and control strategies of infectious diseases.[26]

Due to the complex nature of interaction of pathogens for co-infection models, the theoretical design framework remains a fundamental and pivotal issue that shapes the reliability of parameters estimated, practicability of intervention measures and realistic forecasting[27], particularly applying methods that account for scarcity of data which may hamper the biological basis and justifiability of assumptions, integration with data, model analysis, and their impact in informing policies in public health.[27 28] There is a need to review the key aspects of co-infection modelling to understand the milestones achieved, significance and research gaps and opportunities in their development that may improve their modelling framework and relevance in informing policy on control interventions and improved health outcomes.

Methods and analysis

Study protocol design

This review will be developed in line with the approach reported in the Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P).[29 30] The protocol checklist provided in PRISMA-P has been followed. We will perform a systematic review for co-infection epidemiological modelling to highlight the milestones and significance it holds in description of disease dynamics while noting the gaps in their modelling.

Eligibility criteria

The following inclusion criteria will apply: (1) Full text research articles written in English on infectious disease mathematical epidemiology, published from January 2010 till date and a study will be selected if it is investigating viral-bacteria co-infections of infectious diseases using mathematical epidemiological modelling approaches such as deterministic, stochastic, and fuzzy logic modelling. (2) Studies focusing on within host, between host and multiple strain co-infections. The exclusion criteria will include: (1) articles focused on mono-infection mathematical modelling, clinical experiments and surveys and case studies; (2) duplicate studies, books and book chapters, review protocols, and systematic reviews.

Studies search criteria.

The outline for a search strategy provided in PRESS peer review guidelines will be used in this systematic review.[31] The search will be done in MEDLINE through PubMed, Web of Science, medRxiv and Scopus from November 2023 to April 2024 to identify epidemiological co-infection model studies from January 2010 to date.

The search items will be combined via Boolean operations 'AND' and 'OR' coupled with words and/or synonyms formed by a combination of statements in 4 main categories as follows: mathematical approach or term, co-infection, epidemic, and modelling terms. We will apply a search algorithm in each database as follows: ("mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "Fuzzy") AND ("co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation") AND ("epidemiological" OR "epidemic" OR "infectious disease" OR "transmission") AND ("model" OR "modeling" OR "modelling"). A summary of the search criteria is provided in Table 1.

Table 1: The search algorithm to retrieve viral-bacterial co-infection models.

Set	Terms/Items
1	"mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
2	"co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
3	"epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
4	"model" OR "modeling" OR "modelling"
Search strategy	1 AND 2 AND 3 AND 4

Study selection

The studies found via the search algorithm across the considered databases will be assembled in Endnote (Version 20.4.1) referencing tool and further imported to Rayyan (https://www.rayyan.ai/) an online systematic review web tool[32]. This web systematic review tool is designed to help reviewers screen titles, abstracts, reduce risk of bias and aid data extraction process[33]. Three reviewers will initially screen the titles and abstracts in accordance with the eligibility criteria to select potential studies that meet the inclusion threshold. Discrepancies on inclusion such as: (1) both reviewers are unsure; (2) one reviewer recommends while the other is unsure; (3) one reviewer recommends inclusion while the other recommends exclusion, will be resolved through a discussion with the help of a third reviewer to reach consensus. The PRISMA diagrammatic structure of the study selection outline will be applied. The next phase involves a review of the full texts and data extraction for selected studies.

Quality assessment and risk of bias

The risk of bias assessment in a dynamical co-infection epidemic models may seem difficult to assess due to lack of measurement for bias in models, considerations of modelling approach and

type of models are the main recognizable features.[34] The quality of selected co-infection modelling articles will be assessed for good dynamical modelling standard practice, refer[35-37] for the guidelines highlighting the components of an epidemiological model which include; model formulation, description, data fitting, evaluations, simulations, analysis, validation and output corroboration.

Data extraction process

Data extraction will be done using a standard excel template while applying the standard PRISMA data collection guidelines.[38] Data extraction will be done by TY with the help of two reviewers to verify the quality of data extracted.

Data Items

The following features of the selected articles will be extracted as illustrated in Table 2.

Table 2: Description of data items to be extracted on the coinfection models.

Details	Description/examples
Research articles	Title, hyperlink, journal, author, settings, publication year (ranging from 2010 to date)
Model description	Structure of co-infections (within host, between host or multiple strain coinfections) Modelling approach (Deterministic, stochastic, or fuzzy logic) Type of model (ordinary, fractional order, age-structured or spatio-temporal) Host species (human, animal)
Co-infection/co-dynamics	Co-infection diseases: we will record which disease(s) the model considered (e.g., rotavirus/cholera, Typhoid/Tuberculosis, HIV/Tuberculosis/pneumonia etc.) Modelling of coinfection infectivity (increase, decrease or no change)
Key assumptions	Mortality assumption (additive, not additive) Transition to a co-infection class (from mono-infections to co-infected: infectivity modelled as increasing, decreasing or no change) Co-infection transitions and infectivity assumptions are biologically meaningful and justifiable (yes, no, or partially)
Data fitting	Parameter estimation: e.g., incidence rates, pathogen ingestion rates, recovery rates and mortality rates (Literature, epidemiological data, or laboratory data) Data availability (yes or no). In cases where data was not used, we will denote 'none'. Articles applying two or more data sources will be denoted 'multi-data'.
Intervention measures	Intervention strategies to manage and control infectious diseases (non-pharmaceutical (washing, sanitation, good hygiene), treatment, vaccinations, screening, isolations and quarantine, education campaigns, vector control, antimicrobial stewardship, personal protection etc.)
Model evaluation	Sensitivity analyses (yes or no) Model validations (yes or no) Findings on impact(s) of coinfections on disease severity (increase, decrease or no effect)

Data synthesis strategy

We will provide a summary of the included studies in tabular form and critically assess using the TRACE standard ecological modelling guideline to characterize the models.[35] Subsequently, a narrative synthesis of the findings will be provided. The summary will highlight the following key co-infection model features: modelling approaches, assumptions, parameter estimates and simulations, intervention strategies, impact of co-infections, model validation and sensitivity analysis, research gaps and opportunities for future studies. Due to lack of data for meta-analysis this systematic review will apply SWiM guideline [39] in its narrative synthesis.

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Author Contributions

TY- conceptualisation, design of the protocol and draft manuscript. EA-Y, SR, JC and UM - supervision, contribution to the plan of search strategy, data extraction and data analysis, review and editing.

All authors read and approved the final manuscript.

Acknowledgements

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Ethics and dissemination

Ethics approval will not be sought for this systematic review since it will be based on published work. The output of this study will be submitted for publication in peer reviewed epidemiology journals.

Funding

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Data availability

All data generated and used during this study will be included in the published review article.

Competing interests None to declare.

Patient and public involvement Patients and/or the public were not involved in the formulation, or conduct, or reporting, or dissemination plans of this research.

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Abstract

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Methods and analysis: MEDLINE through PubMed, Web of Science, medRxiv and Scopus will be systematically searched for studies published between January 2010 to October 2024. Three reviewers will screen articles independently for eligibility and quality assessment will be performed using the TRACE (Transparent and Comprehensive Ecological modelling) standard modelling guide. Data will be extracted using an Excel template in-line with the Preferred Reporting Items for Systematic Review & Meta Analysis (PRISMA) guidelines. This systematic review will apply the SWiM (Synthesis without Meta-analysis) approach in its narrative synthesis coupled with tables and figures to present data obtained. The synthesis will highlight key dynamical co-infection model features such as assumptions, data fitting and estimation methods, validation, and sensitivity analyses, optimal control analyses, and impact of co-infections.

Ethics and dissemination: Ethics approval is not required for a systematic review. The output of this study will be submitted for publication in a peer reviewed journal.

PROSPERO registration number: CRD42023481247

Strengths and limitations of this study

- This systematic review will apply the Transparent and Comprehensive Model Evaluation (TRACE) approach with standardized ecological modelling guide.
- This review will address gaps in the coinfection modelling literature and methods by comprehensively analysing research findings, complexities and developments in mathematical and modelling techniques.
- This is the first review study to focus on viral-bacteria co-infection epidemic modelling formulation, its assumptions, and transmission peculiarities.
- This systematic review considers only studies published between January 2010 to October 2024, which may hamper generalisability.
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forecasting disease dynamics. Limited systematic reviews have focused on co-infection mathematical epidemiological modelling design, quality, and applications. Recent systematic reviews have assessed the impact of co-infections in disease dynamics and have focused on specific co-infections such as HIV-hepatitis, HIV-TB and Ebola-malaria co-infections.[11 12 14-20] Some significant and interesting reviews on the impact of coinfections have focused on respiratory tract infections[10 16], aquatic animals[21] and modelling within-host coinfections.[22]

Given the vital significance and potential for wide application of co-infection studies in public health, understanding the dynamics of simultaneous coexistence of infectious pathogens is crucial for improving the practicability of the co-infection modelling.[23] Transition and interaction between classes in a co-infection model may be complex[22], especially in cases where infections present multiple strains or pathogens in a host. Dynamical co-infection epidemiological models are effective tools for highlighting a more comprehensive understanding of infectious disease spread, precise prediction and transition dynamics.[24] The models can highlight causal factors, expected size and duration of an epidemic outbreak, and the extent of resource strain and disease case fatalities associated with the outbreak.[25] It is expected of a mathematical model to provide realistic predictions for disease dynamics.[24]

This systematic review aims to provide an extensive exposition and diagnostics of existing bacterial-viral co-infection epidemiological models that were published from January 2010 to October 2024. A study by Rigaud et al., 2010 [40] concluded that diverse within host assemblages make co-infection predictions difficult. This suggests 2010 was the period when the complexity of co-infection dynamics was being recognised. In particular, we will focus on the co-infection model formulation, assumptions, analysis, modelling techniques and data integration while assessing the significance and potential research gaps which might be of interest to mathematical epidemiologists and public health policy makers. The co-infection modelling framework has the potential to guide policies on management and control strategies for emerging and re-emerging infectious diseases.

Research objectives and questions

In this systematic review, we will explore and synthesise the mathematical epidemiological modelling of viral-bacterial co-infections and the role of pathogen interactions in shaping transmission dynamics, severity, and control of infectious diseases. Its focus is primarily on modelling techniques (assumptions, modelling designs, data fitting, and model analysis and control strategies). It will identify research gaps in co-infection modelling mechanisms that may help advance the models to further realism and enhance effective description and

forecasting of disease dynamics. Specifically, this systematic review is aimed at addressing the following questions:

1. How do parameters change in a co-infection model? Does catching a viral pathogen increase, decrease the risk of acquiring a bacterial infection or is it insignificant and vice versa? Do viral/bacterial pathogen co-infections lead to a higher risk of disease severity?
2. Does a co-infection alter infectiousness and mortality rates? How are co-infections and mortality rates epidemiologically modelled?
3. What is (are) the impact(s) of co-infections in shaping the infectious disease spread dynamics?
4. What are the mathematical modelling approaches applied to describe the dynamics? What research gaps exist in the modelling approaches?
5. How are data integrated in a co-infection model? What reasonable data inputs/assumptions might be necessary to predict or forecast co-infection disease dynamics? What are the challenges in parameter estimation of a co-infection model?
6. How can co-infection mathematical models be robustly formulated, analysed, tested, and evaluated in a manner that is epidemiologically meaningful and relevant for provision of guidance on urgent response policy and mitigation of an infectious disease outbreak?

Rationale

The spread dynamics of pathogens in humans and animals can be influenced by co-infections, which may ultimately lead to insignificant, beneficial, or detrimental health outcomes.[11] The interactions between two or more infectious disease pathogens in host species can have serious outcomes, particularly in vulnerable immunosuppressed individuals such as HIV-positive patients who are at a higher risk of experiencing increased severity or dying due to co-infections.[11]

Co-infection models offer a way to understand and describe infectious disease spread dynamics and provide both short-term and long-term forecasts through integration of biological features, behavioural and environmental epidemiological factors that shape the burden, transmission, surveillance, prevention, and control strategies. The last decade has witnessed an increased interest in epidemiological modelling due to its potential of integrating both ecological epidemiology and mathematics under a data, knowledge, and strategic decisions framework to explain the transmission and control strategies of infectious diseases.[26]

Due to the complex nature of interaction of pathogens for co-infection models, the theoretical design remains a fundamental and pivotal issue that shapes the reliability of parameters estimated, practicability of intervention measures and realistic forecasting[27], particularly applying methods that account for scarcity of data which may hamper the biological basis and justifiability of assumptions, integration with data, model analysis, and their impact in informing policies in public health.[27 28] There is a need to review key aspects of co-infection modelling to understand the milestones achieved, significance and research gaps and opportunities in co-infection model development that may improve their framework and relevance in informing policy on control interventions and improved health outcomes.

Methods and analysis

Study protocol design

This review will be developed to facilitate reporting in line with the Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P).[29 30] The protocol checklist provided in PRISMA-P was used in drafting and appraising the review protocol. We will perform a systematic review for co-infection epidemiological modelling to highlight the milestones and significance it holds in description of disease dynamics while noting the gaps in their modelling.

Eligibility criteria

The following inclusion criteria will apply: (1) Full text research articles written in English on infectious disease mathematical epidemiology, published from January 2010 to October 2024 and a study will be selected if it is investigating viral-bacteria co-infections of infectious diseases using mathematical epidemiological modelling approaches such as deterministic, stochastic, and fuzzy logic modelling. (2) Studies focusing on within host, between host and multiple strain co-infections. The exclusion criteria will include: (1) articles focused on mono-infection mathematical modelling, clinical experiments and surveys and case studies; (2) duplicate studies, books and book chapters, review protocols, and systematic reviews.

Studies search criteria

The outline for a search strategy provided in PRESS peer review guidelines will be used in this systematic review.[31] The search will be done in MEDLINE through PubMed, Web of Science, medRxiv and Scopus from November 2023 to October 2024 to identify epidemiological co-infection model studies from January 2010 to October 2024. The search items will be combined via the Boolean operations 'AND' and 'OR' coupled with words and/or synonyms formed by

a combination of statements in 4 main categories as follows: mathematical approach or term, co-infection, epidemic, and modelling terms. We will apply a search algorithm in each database as follows: ("mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "Fuzzy") AND ("co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation") AND ("epidemiological" OR "epidemic" OR "infectious disease" OR "transmission") AND ("model" OR "modeling" OR "modelling"). A summary of the search criteria is provided in Table 1.

Table 1: The search algorithm to retrieve viral-bacterial co-infection models.

Set	Terms/Items
1	"mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
2	"co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
3	"epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
4	"model" OR "modeling" OR "modelling"
Search strategy	1 AND 2 AND 3 AND 4

Study selection

The studies found via the search algorithm across the considered databases will be assembled in Endnote (Version 20.4.1) referencing tool and further imported to Rayyan (https://www.rayyan.ai/) an online systematic review web tool[32]. This web systematic review tool is designed to help reviewers screen titles, abstracts, reduce the risk of bias and aid the data extraction process[33]. Three reviewers will initially screen the titles and abstracts in accordance with the eligibility criteria to select potential studies that meet the inclusion threshold. Discrepancies on inclusion such as: (1) both reviewers are unsure; (2) one reviewer recommends while the other is unsure; (3) one reviewer recommends inclusion while the other recommends exclusion, will be resolved through a discussion with the help of a third reviewer to reach consensus. The PRISMA diagrammatic structure of the study selection outline will be applied. The next phase involves a review of the full texts and data extraction for selected studies.

Quality assessment and risk of bias

The assessment of the risk of bias in a dynamical co-infection epidemic model may seem difficult to assess due to lack of measurement for bias in models, considerations of modelling approach and type of models are the main recognisable features.[34] The quality of selected co-infection modelling articles will be assessed for good dynamical modelling standard practice, refer[35-37] for the guidelines highlighting the components of an epidemiological model which include; model formulation, description, data fitting, evaluations, simulations, analysis, validation and output corroboration.

Data extraction process

Data extraction will be done using a standard excel template while applying the standard PRISMA data collection guidelines.[38] Data extraction will be done by TY with the help of two reviewers to verify the quality of data extracted.

Data Items

The following features of the selected articles will be extracted as illustrated in Table 2.

Table 2: Description of data items to be extracted on the coinfection models.

Details	Description/examples
Research articles	Title, hyperlink, journal, author, settings, publication year (ranging from 2010 to October 2024)
Model description	Structure of co-infections (within host, between host or multiple strain coinfections) Modelling approach (Deterministic, stochastic, or fuzzy logic) Type of model (ordinary, fractional order, age-structured or spatio-temporal) Host species (human, animal, or both)
Co-infection/co-dynamics	Co-infection diseases: we will record which disease(s) the model considered (e.g., rotavirus/cholera, Typhoid/Tuberculosis, HIV/Tuberculosis/pneumonia etc.) Modelling of coinfection infectivity (increase, decrease or no change)
Key assumptions	Mortality assumption (additive, not additive) Transition to a co-infection class (from mono-infections to co-infected: infectivity modelled as increasing, decreasing or no change) Co-infection transitions and infectivity assumptions are biologically meaningful and justifiable (yes, no, or partially)
Data fitting	Parameter estimation: e.g., incidence rates, pathogen ingestion rates, recovery rates and mortality rates (literature, simulated data, epidemiological data, or laboratory data) Data availability (yes or no). In cases where data was not used, we will denote 'none'. Articles applying two or more data sources will be denoted 'multi-data'.
Intervention measures	Intervention strategies to manage and control infectious diseases (non-pharmaceutical (washing, sanitation, good hygiene), treatment, vaccinations, screening, isolations and quarantine, education campaigns, vector control, antimicrobial stewardship, personal protection etc.)
Model evaluation	Sensitivity analyses (yes or no). If yes, we asses nature of sensitivity (local or global) analysis and sensitivity approaches (graphical or numerical).

	Model validations (yes or no). If yes, we determine the number of infections validated (one or both or multiple (more than two infections)) and determine type of datasets (simulated or surveillance data). For surveillance data, we further determine the datasets (incidence, vaccinated, hospitalized or death case counts). Studies which use two or more datasets simultaneously in the validation will be denoted 'multi-data'. In addition, we state the setting which the model is validated (city or country or state or multi-states) Findings on impact(s) of coinfections on disease severity (increase, decrease or no effect)

Data synthesis strategy

We will provide a summary of the included studies in tabular form and critically assess them using the TRACE standard ecological modelling guideline to characterize the models.[35] Subsequently, a narrative synthesis of the findings will be provided. The summary will highlight the following key co-infection model features: modelling approaches, assumptions, parameter estimates and simulations, intervention strategies, impact of co-infections, model validation and sensitivity analysis, research gaps and opportunities for future studies. Due to lack of data for meta-analysis this systematic review will apply SWiM guideline [39] in its narrative synthesis.

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Author Contributions

TY- conceptualisation, design of the protocol and draft manuscript. EA-Y, SR, JC, and UM - supervision, contribution to the plan of search strategy, data extraction and data analysis, review, and editing.

All authors read and approved the final manuscript.

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Ethics and dissemination

Ethics approval is not required for a systematic review since it will be based on published work. The output of this study will be submitted for publication in peer reviewed epidemiology journals.

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Data availability

All data generated and used during this study will be included in the published review article.

Competing interests None to declare.

Patient and public involvement Patients and/or the public were not involved in the formulation, or conduct, or reporting, or dissemination plans of this research.

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Studies Search Criteria.

Below is a detailed search strategy for the systematic review protocol, outlining the databases, filters and limits that can be used in the search for studies on viral-bacterial co-infections.

Databases to be used:

- MEDLINE through PubMed
- Web of Science
- MedRxiv
- Scopus (platform: Elsevier)

Search terms:

The search will use Boolean operations 'AND' and 'OR' with specific keywords related to mathematical approaches and co-infections. The search terms will be categorised into four main groups:

- **Group 1:** "mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
- **Group 2:** "co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
- **Group 3:** "epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
- **Group 4:** "model" OR "modeling" OR "modelling"

Combined search strategy

The search will be conducted using the following search algorithm:

- **Search query:** (Group 1) AND (Group 2) AND (GROUP 3) AND (Group 4)

Filters and limits:

- **Publication date:** Studies published from January 2010 to October 2024.
- **Language:** Articles published in English.
- **Document type:** Limit to research articles focusing on mathematical epidemiology related to viral-bacterial co-infections.
- **Exclusion criteria:** Articles focused on mono-infection mathematical modelling, clinical experiments, surveys, case studies, duplicate studies, books, book chapters, review protocols, conference papers and review, letter, editorial, and systematic reviews.

Implementation

- Each database will be searched using the combined search query and the results will be imported into a reference management tool (Endnote) for further screening.

This detailed search strategy will be included as a supplementary file to ensure transparency and reproducibility in the systematic review process.

BMJ Open

Mathematical Modelling and Analysis for the Co-infection of Viral and Bacterial Diseases: A Systematic Review Protocol

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Mathematical Modelling and Analysis for the Co-infection of Viral and Bacterial Diseases: A Systematic Review Protocol

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Abstract

Introduction: Breaking the chain of transmission of an infectious disease pathogen is a major public health priority. The challenges of understanding, describing, and predicting the transmission dynamics of infections have led to a wide range of mathematical, statistical, and biological research problems. Advances in diagnostic laboratory procedures with the ability to test multiple pathogens simultaneously mean that co-infections are increasingly being detected, yet little is known about the impact of co-infections in shaping the course of an infection, infectivity, and pathogen replication rate. This is particularly true of, the apparent synergistic effects of viral and bacterial co-infections that present the greatest threats in public health due to their lethal nature and complex dynamics. This systematic review is aimed at performing a critical review of co-infection modelling and assess the key features of the models.

Methods and analysis: MEDLINE through PubMed, Web of Science, medRxiv and Scopus will be systematically searched in November 2024 for studies published between January 1980 to December 2024. Three reviewers will screen articles independently for eligibility and quality assessment will be performed using the TRACE (Transparent and Comprehensive Ecological modelling) standard modelling guide. Data will be extracted using an Excel template in accordance with the Preferred Reporting Items for Systematic Review & Meta Analysis (PRISMA) standard reporting guidelines. This systematic review will apply the SWiM (Synthesis without Meta-analysis) approach in its narrative synthesis coupled with tables and figures to present data obtained. The synthesis will highlight key dynamical co-infection model features such as assumptions, data fitting and estimation methods, validation, and sensitivity analyses, optimal control analyses, and impact of co-infections.

Ethics and dissemination: Ethics approval is not required for a systematic review since it will be based on published work.

PROSPERO registration number: CRD42023481247

Strengths and limitations of this study

- This systematic review will apply the Transparent and Comprehensive Model Evaluation (TRACE) approach with standardized ecological modelling guide.
- A comprehensive analysis of research findings, formulation complexities and developments in co-infection modelling techniques will aim to address critical gaps in existing literature.
- To the best of our knowledge, this review is the first to explore viral-bacteria co-infection epidemic modelling formulation, its underlying assumptions, and transmission peculiarities.
- This systematic review considers only studies published between January 1980 to December 2024, which may hamper generalisability.
- This systematic review investigates only mechanistic mathematical co-infection

epidemic modelling approaches, which may create bias.

Introduction

Co-infection refers to the simultaneous infection by two or more pathogens[1] or the presence of multiple strains of the same infection in a host, as seen in the case of influenza viruses.[2-4] On the other hand, they can occur as multiple infections by different pathogens within the same host or between different hosts.[5-8] Over the years, vaccination campaigns and use of anti-biotics have significantly prevented deaths and helped combat transmission of viral-bacterial infectious diseases. However, viral and bacterial infections remain a major public health threat since they are lethal and predisposes the most vulnerable population to infections.[9] For instance, childhood viral-bacterial diseases like pneumonia and diarrheal infections remain the main causes of mortality in infants and children, while SARS-COV-2, HIV, Tuberculosis (TB), Influenza and hepatitis are among the major killer viral-bacterial infections in adults globally. According to the World Health Organization (WHO) viral and bacterial infections of the respiratory system lead with a global burden of 6.2% followed by diarrheal infections, which account for a burden of 4.8%.[9] The synergism of viral-bacterial co-infections has remained lethal leading to extensive theoretical and clinical research on the mechanisms behind their transmission dynamics.[10] The ecological epidemiology of infectious pathogen interactions and coexistence in the host species can be complex and their combined effects on disease transmission, clinical outcomes and public health intervention measures remain poorly understood.[11-13]

Many human and animal populations acquire infections with either bacterial or viral pathogens.[14 15] Studies on the 2009 pandemic Influenza A(H1N1) in the United States found that within six days of influenza infection, a bacterial co-infection occurred with an increased risk of death for critically ill patients.[16] Similarly, epidemiological studies have reported Influenza (viral) and Streptococcus pneumoniae (bacterial) co-infections occurring during flu season with influenza potentially weakening the immunity of individuals which predisposes them to bacteria like streptococcus pneumoniae infections.[14] Additionally, HIV and TB co-infections have been reported with HIV infected individuals experiencing advanced immunosuppression which weakens patients and makes them unable to fight off TB bacteria,

predisposing HIV-positive patients with higher vulnerability to catching a TB infection.[17] Therefore, viral-bacterial co-infections are of great public health concern due to the risk factors they present in altering the severity, incidences and mortalities. [14]

Despite co-infection models having vital implications in public health policy, epidemiology and pathogen evolution, few studies have addressed their complexity and implications in forecasting disease dynamics. Limited systematic reviews have focused on co-infection mathematical epidemiological modelling design, quality, and applications. Recent systematic reviews have assessed the impact of co-infections in disease dynamics and have focused on specific co-infections such as HIV-hepatitis, HIV-TB and Ebola-malaria co-infections.[11 12 14-20] Some significant and interesting reviews on the impact of coinfections have focused on respiratory tract infections[10 16], aquatic animals[21] and modelling within-host coinfections.[22]

Given the vital significance and potential for wide application of co-infection studies in public health, understanding the dynamics of simultaneous coexistence of infectious pathogens is crucial for improving the practicability of the co-infection modelling.[23] Transition and interaction between classes in a co-infection model may be complex[22], especially in cases where infections present multiple strains or pathogens in a host. Dynamical co-infection epidemiological models are effective tools for highlighting a more comprehensive understanding of infectious disease spread, precise prediction and transition dynamics.[24] The models can highlight causal factors, expected size and duration of an epidemic outbreak, and the extent of resource strain and disease case fatalities associated with the outbreak.[25] It is expected of a mathematical model to provide realistic predictions for disease dynamics.[24]

This systematic review aims to provide an extensive exposition and diagnostics of existing bacterial-viral co-infection epidemiological models that were published from January 1980 to December 2024. We will focus on the co-infection model formulation, assumptions, analysis, modelling techniques and data integration while assessing the significance and potential research gaps which might be of interest to mathematical epidemiologists and public health policy makers. The co-infection modelling framework has the potential to guide policies on management and control strategies for emerging and re-emerging infectious diseases.

Research objectives and questions

In this systematic review, we will explore and synthesise the mathematical epidemiological modelling of viral-bacterial co-infections and the role of pathogen interactions in shaping transmission dynamics, severity, and control of infectious diseases. Its focus is primarily on

modelling techniques (assumptions, modelling designs, data fitting, and model analysis and control strategies). It will identify research gaps in co-infection modelling mechanisms that may help advance the models to further realism and enhance effective description and forecasting of disease dynamics. Specifically, this systematic review is aimed at addressing the following questions:

1. How do parameters change in a co-infection model? Does catching a viral pathogen increase, decrease the risk of acquiring a bacterial infection or is it insignificant and vice versa? Do viral/bacterial pathogen co-infections lead to a higher risk of disease severity?
2. Does a co-infection alter infectiousness and mortality rates? How are co-infections and mortality rates epidemiologically modelled?
3. What is (are) the impact(s) of co-infections in shaping the infectious disease spread dynamics?
4. What are the mathematical modelling approaches applied to describe the dynamics? What research gaps exist in the modelling approaches?
5. How are data integrated in a co-infection model? What reasonable data inputs/assumptions might be necessary to predict or forecast co-infection disease dynamics? What are the challenges in parameter estimation of a co-infection model?
6. How can co-infection mathematical models be robustly formulated, analysed, tested, and evaluated in a manner that is epidemiologically meaningful and relevant for provision of guidance on urgent response policy and mitigation of an infectious disease outbreak?

Rationale

The spread dynamics of pathogens in humans and animals can be influenced by co-infections, which may ultimately lead to insignificant, beneficial, or detrimental health outcomes.[11] The interactions between two or more infectious disease pathogens in host species can have serious outcomes, particularly in vulnerable immunosuppressed individuals such as HIV-positive patients who are at a higher risk of experiencing increased severity or dying due to co-infections.[11]

Co-infection models offer a way to understand and describe infectious disease spread dynamics and provide both short-term and long-term forecasts through integration of biological features, behavioural and environmental epidemiological factors that shape the burden, transmission, surveillance, prevention, and control strategies. The last decade has witnessed an increased interest in epidemiological modelling due to its potential of integrating both ecological

epidemiology and mathematics under a data, knowledge, and strategic decisions framework to explain the transmission and control strategies of infectious diseases.[26]

Due to the complex nature of interaction of pathogens for co-infection models, the theoretical design remains a fundamental and pivotal issue that shapes the reliability of parameters estimated, practicability of intervention measures and realistic forecasting[27], particularly applying methods that account for scarcity of data which may hamper the biological basis and justifiability of assumptions, integration with data, model analysis, and their impact in informing policies in public health.[27 28] There is a need to review key aspects of co-infection modelling to understand the milestones achieved, significance and research gaps and opportunities in co-infection model development that may improve their framework and relevance in informing policy on control interventions and improved health outcomes.

Methods and analysis

Study protocol design

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P) 2015 checklist.[29 30] The review has been registered in PROSPERO.

Eligibility criteria

The following inclusion criteria will apply: (1) Full text research articles written in English on infectious disease mathematical epidemiology, published from January 1980 to December 2024 and a study will be selected if it is investigating viral-bacteria co-infections of infectious diseases using mathematical epidemiological modelling approaches such as deterministic, stochastic, and fuzzy logic modelling. (2) Studies focusing on within host, between host and multiple strain co-infections. The exclusion criteria will include: (1) articles focused on mono-infection mathematical modelling, clinical experiments and surveys and case studies; (2) duplicate studies, books and book chapters, review protocols, and systematic reviews.

Studies search criteria

The outline for a search strategy provided in PRESS peer review guidelines will be used in this systematic review.[31] The search for articles from databases (PubMed, Web of Science, Scopus and medRxiv), selection of studies, data extractions and synthesis will be done comprehensively from November 2024 to April 2025 to identify epidemiological co-infection model studies from January 1980 to December 2024. The search items will be combined via the Boolean operations 'AND' and 'OR' coupled with words and/or synonyms formed by a

combination of statements in 4 main categories as follows: mathematical approach or term, co-infection, epidemic, and modelling terms. We will apply a search algorithm in each database as follows: ("mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "Fuzzy") AND ("co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation") AND ("epidemiological" OR "epidemic" OR "infectious disease" OR "transmission") AND ("model" OR "modeling" OR "modelling"). A summary of the search criteria is provided in Table 1 and a detailed version for each database available in search strategy (supplementary file).

Table 1: The search algorithm to retrieve viral-bacterial co-infection models.

Set	Terms/Items
1	"mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
2	"co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
3	"epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
4	"model" OR "modeling" OR "modelling"
Search strategy	1 AND 2 AND 3 AND 4

Study selection

The studies found via the search algorithm across the considered databases will be assembled in Endnote (Version 20.4.1) referencing tool and further imported to Rayyan (https://www.rayyan.ai/) an online systematic review web tool[32]. This web systematic review tool is designed to help reviewers screen titles, abstracts, reduce the risk of bias and aid the data extraction process[33]. Three reviewers will initially screen the titles and abstracts in accordance with the eligibility criteria to select potential studies that meet the inclusion threshold. Discrepancies on inclusion such as: (1) both reviewers are unsure; (2) one reviewer recommends while the other is unsure; (3) one reviewer recommends inclusion while the other recommends exclusion, will be resolved through a discussion with the help of a third reviewer to reach consensus. The PRISMA diagrammatic structure of the study selection outline will be applied. The next phase involves a review of the full texts and data extraction for selected studies.

Quality assessment and risk of bias

The assessment of the risk of bias in a dynamical co-infection epidemic model may seem difficult to assess due to lack of measurement for bias in models, considerations of modelling approach and type of models are the main recognisable features.[34] The quality of selected co-infection modelling articles will be assessed for good dynamical modelling standard practice, refer[35-37] for the guidelines highlighting the components of an epidemiological model which include; model formulation, description, data fitting, evaluations, simulations, analysis, validation and output corroboration.

Data extraction process

Data extraction will be done using a standard excel template while applying the standard PRISMA data collection guidelines.[38] Data extraction will be done by TY with the help of two reviewers to verify the quality of data extracted.

Data Items

The following features of the selected articles will be extracted as illustrated in Table 2.

Table 2: Description of data items to be extracted on the coinfection models.

Details	Description/examples
Research articles	Title, hyperlink, journal, author, settings, publication year (ranging from 1980 to 2024)
Model description	Structure of co-infections (within host, between host or multiple strain coinfections) Modelling approach (Deterministic, stochastic, or fuzzy logic) Type of model (ordinary, fractional order, age-structured or spatio-temporal) Host species (human, animal, or both)
Co-infection/co-dynamics	Co-infection diseases: we will record which disease(s) the model considered (e.g., rotavirus/cholera, Typhoid/Tuberculosis, HIV/Tuberculosis/pneumonia etc.) Modelling of coinfection infectivity (increase, decrease or no change)
Key assumptions	Mortality assumption (additive, not additive) Transition to a co-infection class (from mono-infections to co-infected: infectivity modelled as increasing, decreasing or no change) Co-infection transitions and infectivity assumptions are biologically meaningful and justifiable (yes, no, or partially)
Data fitting	Parameter estimation: e.g., incidence rates, pathogen ingestion rates, recovery rates and mortality rates (literature, simulated data, epidemiological data, or laboratory data) Data availability (yes or no). In cases where data was not used, we will denote 'none'. Articles applying two or more data sources will be denoted 'multi-data'.
Intervention measures	Intervention strategies to manage and control infectious diseases (non-pharmaceutical (washing, sanitation, good hygiene), treatment, vaccinations, screening, isolations and quarantine, education campaigns, vector control, antimicrobial stewardship, personal protection etc.)
Model evaluation	Sensitivity analyses (yes or no). If yes, we asses nature of sensitivity (local or global) analysis and sensitivity approaches (graphical or numerical).

	Model validations (yes or no). If yes, we determine the number of infections validated (one or both or multiple (more than two infections)) and determine type of datasets (simulated or surveillance data). For surveillance data, we further determine the datasets (incidence, vaccinated, hospitalized or death case counts). Studies which use two or more datasets simultaneously in the validation will be denoted 'multi-data'. In addition, we state the setting which the model is validated (city or country or state or multi-states) Findings on impact(s) of coinfections on disease severity (increase, decrease or no effect)

Data synthesis strategy

We will provide a summary of the included studies in tabular form and critically assess them using the TRACE standard ecological modelling guideline to characterize the models.[35] Subsequently, a narrative synthesis of the findings will be provided. The summary will highlight the following key co-infection model features: modelling approaches, assumptions, parameter estimates and simulations, intervention strategies, impact of co-infections, model validation and sensitivity analysis, research gaps and opportunities for future studies. Due to lack of data for meta-analysis this systematic review will apply SWiM guideline [39] in its narrative synthesis.

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Author Contributions

TY- conceptualisation, design of the protocol and draft manuscript. EA-Y, SR, JC, and UM - supervision, contribution to the plan of search strategy, data extraction and data analysis, review, and editing. Guarantor: Timothy Yano is the guarantor for this study.

All authors read and approved the final manuscript.

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Ethics and dissemination

Ethics approval is not required for a systematic review since it will be based on published work. The output of this study will be submitted for publication in peer reviewed epidemiology journals.

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Data availability

All data generated and used during this study will be included in the published review article.

Competing interests None to declare.

Patient and public involvement Patients and/or the public were not involved in the formulation, or conduct, or reporting, or dissemination plans of this research.

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Studies Search Criteria.

Below is a detailed search strategy for the systematic review protocol, outlining the databases, filters and limits that can be used in the search for studies on viral-bacterial co-infections.

Databases to be used:

- MEDLINE through PubMed
- Web of Science
- MedRxiv
- Scopus (platform: Elsevier)

Search terms:

The search will use Boolean operations 'AND' and 'OR' with specific keywords related to mathematical approaches and co-infections. The search terms will be categorised into four main groups:

- **Group 1:** "mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
- **Group 2:** "co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
- **Group 3:** "epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
- **Group 4:** "model" OR "modeling" OR "modelling"

Combined search query: (Group 1) AND (Group 2) AND (GROUP 3) AND (Group 4)

Table 1 below provides a detailed description of the search criteria for each specified database using the search terms and the combined search strategy.

Table 1: Summary for search query, filters and limits for each database

Database	**Scopus (https://www.elsevier.com/products/scopus)**	
1	Search query in the search bar	[Title/Abstract/Keywords] ("mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy") AND [Title/Abstract/Keywords] ("co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation") AND [Title/Abstract/Keywords] ("epidemiological" OR "epidemic" OR "infectious disease" OR "transmission") AND [Title/Abstract/Keywords] ("model" OR "modeling" OR "modelling")
	Filters and limits	Publication year (1980-2024) and limit to language (English) and document type (article).
	Exclusion	Exclude: conference paper, review, case studies, book, book chapter, short survey, letter, editorial and conference review.
	MEDLINE through PubMed (https://pubmed.ncbi.nlm.nih.gov/)	

2	Search query in the search bar	(“mathematical” OR “dynamical” OR “deterministic” OR “stochastic” OR “fuzzy”) AND (“co-infection” OR “co-dynamics” OR “dual infection” OR “co-circulation”) AND (“epidemiological” OR “epidemic” OR “infectious disease” OR “transmission”) AND (“model” OR “modeling” OR “modelling”)
	Filters and limits	Publication year (1980-2024) and limit to language (English) and document type (article).
	Web of Science (https://www.webofscience.com/)	
3	Search query in the search bar	Topic Search ((“mathematical” OR “dynamical” OR “deterministic” OR “stochastic” OR “fuzzy”) AND (“co-infection” OR “co-dynamics” OR “dual infection” OR “co-circulation”) AND (“epidemiological” OR “epidemic” OR “infectious disease” OR “transmission”) AND (“model” OR “modeling” OR “modelling”))
	Filters and limits	Publication years (1980-2024) and limit to languages (English) and document types (article).
	MedRxiv (https://www.medrxiv.org/)	
4	Search query in the search bar	Search for term "(“mathematical” OR “dynamical” OR “deterministic” OR “stochastic” OR “fuzzy”) " AND title "(“co-infection” OR “co-dynamics” OR “dual infection” OR “co-circulation”)" AND abstract or title "(“epidemiological” OR “epidemic” OR “infectious disease” OR “transmission”)" AND full text or abstract or title "(“model” OR “modeling” OR “modelling”)"
	Filters and limits	Date posted: 01 January 1980 and 31 December 2024
5	Timeframe	1980/01/01 to 2024/12/31

Exclusion criteria: Manually review the results and exclude mono-infection mathematical modelling articles, clinical experiments, surveys, case studies, duplicate studies, non-English studies, books, book chapters, review protocols, conference papers and review, letter, editorial, and systematic reviews.

This detailed search strategy will be included as a supplementary file to ensure transparency and reproducibility in the systematic review process.

BMJ Open

Mathematical Modelling and Analysis for the Co-infection of Viral and Bacterial Diseases: A Systematic Review Protocol

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Mathematical Modelling and Analysis for the Co-infection of Viral and Bacterial Diseases: A Systematic Review Protocol

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Abstract

Introduction: Breaking the chain of transmission of an infectious disease pathogen is a major public health priority. The challenges of understanding, describing, and predicting the transmission dynamics of infections have led to a wide range of mathematical, statistical, and biological research problems. Advances in diagnostic laboratory procedures with the ability to test multiple pathogens simultaneously mean that co-infections are increasingly being detected, yet little is known about the impact of co-infections in shaping the course of an infection, infectivity, and pathogen replication rate. This is particularly true of the apparent synergistic effects of viral and bacterial co-infections, which present the greatest threats in public health because of their lethal nature and complex dynamics. This systematic review protocol is the foundation of a critical review of co-infection modelling and an assessment of the key features of the models.

Methods and analysis: MEDLINE through PubMed, Web of Science, medRxiv and Scopus will be systematically searched between 1 December 2024 and 31 January 2025 for studies published between January 1980 to December 2024. Three reviewers will screen articles independently for eligibility, and quality assessment will be performed using the TRACE (Transparent and Comprehensive Ecological modelling) standard modelling guide. Data will be extracted using an Excel template in accordance with the Preferred Reporting Items for Systematic Review & Meta Analysis (PRISMA) standard reporting guidelines. This systematic review will apply the SWiM (Synthesis without Meta-analysis) approach in its narrative synthesis coupled with tables and figures to present data. The synthesis will highlight key dynamical co-infection model features such as assumptions, data fitting and estimation methods, validation, and sensitivity analyses, optimal control analyses, and the impact of co-infections.

Ethics and dissemination: Ethics approval is not required for a systematic review since it will be based on published work. The output of this study will be submitted for publication in a peer-reviewed journal.

PROSPERO registration number: CRD42023481247

Strengths and limitations of this study

- This systematic review will apply the Transparent and Comprehensive Model Evaluation (TRACE) approach with a standardized ecological modelling guide.
- A comprehensive analysis of research findings, formulation complexities and developments in co-infection modelling techniques will aim to address critical gaps in existing literature.
- To the best of our knowledge, this review will be the first to explore viral-bacterial co-infection epidemic modelling formulations, their underlying assumptions, and transmission peculiarities.
- This systematic review considers only studies published between January 1980 to December 2024, which may hamper generalisability.

- This systematic review investigates only mechanistic mathematical co-infection epidemic modelling approaches, which may create bias.

Introduction

Co-infection refers to the simultaneous infection of a host by two or more pathogens[1], which can include multiple strains of the same infection in a host, as seen with influenza viruses,[2-4] or infections by different pathogens within the same host or between different hosts.[5-8] Over the years, vaccination campaigns and use of anti-biotics have significantly prevented deaths and helped to combat the transmission of viral-bacterial infectious diseases. However, viral and bacterial infections remain a major public health threat since they can be lethal and predispose the most vulnerable population to further infections.[9] For instance, childhood viral-bacterial diseases like pneumonia and diarrheal infections remain the main causes of mortality in infants and children, while SARS-COV-2, HIV, Tuberculosis (TB), Influenza and hepatitis are among the major lethal viral-bacterial infections in adults globally. According to the World Health Organization (WHO) viral and bacterial infections of the respiratory system lead with a global burden of 6.2% followed by diarrheal infections, which account for a burden of 4.8 %.[9] The synergism of viral-bacterial co-infections has remained lethal, leading to extensive theoretical and clinical research on the mechanisms behind their transmission dynamics.[10] The ecological epidemiology of infectious pathogen interactions and coexistence in the host species can be complex and their combined effects on disease transmission, clinical outcomes and public health intervention measures remain poorly understood.[11-13]

Many human and animal populations acquire infections with either bacterial or viral pathogens.[14 15] Studies on the 2009 pandemic Influenza A(H1N1) in the United States found that within six days of influenza infection, a bacterial co-infection occurred. The critically ill patients who developed bacterial co-infections faced an increased risk of death.[16] Similarly, epidemiological studies have reported Influenza (viral) and Streptococcus pneumoniae (bacterial) co-infections occurring with influenza during flu seasons, potentially weakening the immunity of individuals which predisposes them to bacteria like streptococcus pneumoniae infections.[14] HIV and TB co-infections are common, with individuals infected with HIV often experiencing advanced immunosuppression. This weakened immune response increases their susceptibility to catching a TB infection.[17] Therefore, viral-bacterial co-infections are of great

public health concern due to the risk factors they present in altering the severity, incidences and mortalities.[14]

Despite co-infection models having vital implications in public health policy, epidemiology and pathogen evolution, few studies have addressed their complexity and implications in forecasting disease dynamics. Limited systematic reviews have focused on co-infection mathematical epidemiological modelling design, quality, and applications. Recent systematic reviews have assessed the impact of co-infections in disease dynamics and have focused on specific co-infections such as HIV-hepatitis, HIV-TB and Ebola-malaria co-infections.[11 12 14-20] Some significant and interesting reviews on the impact of coinfections have focused on respiratory tract infections,[10 16] aquatic animals[21] and modelling within-host coinfections.[22]

Given the vital significance and potential for wide applications of co-infection studies in public health, understanding the dynamics of simultaneous coexistence of infectious pathogens is crucial for improving the practicability of the co-infection modelling.[23] Transition and interaction between classes in a co-infection model may be complex,[22] especially in cases where infections present multiple strains or pathogens in a host. Dynamical co-infection epidemiological models are effective tools for highlighting a more comprehensive understanding of infectious disease spread, precise prediction and transition dynamics.[24] The models can highlight causal factors, expected size and duration of an epidemic outbreak, and the extent of resource strain and disease case fatalities associated with the outbreak.[25] It is expected of a mathematical model to provide realistic predictions for disease dynamics.[24]

This systematic review aims to provide an extensive exposition and diagnostics of existing bacterial-viral co-infection epidemiological models that were published from January 1980 to December 2024. The study duration was chosen after reviewing the historical emergence of significant viral and bacterial infections known to cause co-infections. For instance, the HIV/AIDS epidemic (1980s), the SARS-COV (2002) and H1N1 influenza (2009) pandemic, which were pivotal moments in infectious disease history that may have influenced co-infection studies. We considered a time frame from January 1980 to December 2024, a duration of 44 years that may give a comprehensive view of the evolution of co-infection studies and capture trends over time. The studies allow us to capture both historical and recent co-infection studies like HIV and tuberculosis, influenza and pneumonia, or COVID-19 and secondary bacterial infections among others. We will focus on the co-infection model formulation, assumptions, analysis, modelling techniques and data integration while assessing the

significance and potential research gaps which might be of interest to mathematical epidemiologists and public health policy makers. The co-infection modelling framework has the potential to guide policies on management and control strategies for emerging and re-emerging infectious diseases.

Research objectives and questions

In the planned systematic review, we will explore and synthesise the mathematical epidemiological modelling of viral-bacterial co-infections and the role of pathogen interactions in shaping transmission dynamics, severity, and control of infectious diseases. Its focus is primarily on modelling techniques (assumptions, modelling designs, data fitting, and model analysis and control strategies). It will identify research gaps in co-infection modelling mechanisms that may help advance the models to further realism and enhance effective description and forecasting of disease dynamics. Specifically, this systematic review is aimed at addressing the following questions:

1. How are parameters interrelated in a co-infection model? Does catching a viral pathogen increase or decrease the risk of acquiring a bacterial infection, or is it insignificant and vice versa? Do viral/bacterial pathogen co-infections lead to a higher risk of disease severity?
2. Does a co-infection alter infectiousness and mortality rates? How are co-infections and mortality rates epidemiologically modelled?
3. What is (are) the impact(s) of co-infections in shaping the infectious disease spread dynamics?
4. What are the mathematical modelling approaches applied to describe the dynamics? What research gaps exist in the modelling approaches?
5. How are data integrated in a co-infection model? What reasonable data inputs/assumptions might be necessary to predict or forecast co-infection disease dynamics? What are the challenges in parameter estimation of a co-infection model?
6. How can co-infection mathematical models be robustly formulated, analysed, tested, and evaluated in a manner that is epidemiologically meaningful and relevant for provision of guidance on urgent response policy and mitigation of an infectious disease outbreak?

Rationale

The dynamics of pathogen spread in humans and animals can be influenced by co-infections, which may ultimately lead to insignificant, beneficial, or detrimental health outcomes.[11] The interactions between two or more infectious disease pathogens in host species can have serious

outcomes, particularly in vulnerable immunosuppressed individuals such as HIV-positive patients who are at a higher risk of experiencing increased severity or dying due to co-infections.[11]

Co-infection models offer a way to understand and describe infectious disease spread dynamics and provide both short-term and long-term forecasts. This is done through integration of biological features, behavioural and environmental epidemiological factors that shape the burden, transmission, surveillance, prevention, and control strategies. The last decade has witnessed an increased interest in epidemiological modelling due to its potential of integrating both ecological epidemiology and mathematics under a data, knowledge, and strategic decisions framework to explain the transmission and control strategies of infectious diseases.[26]

Due to the complex nature of interaction of pathogens for co-infection models, the theoretical design remains a fundamental and pivotal issue that shapes the reliability of estimated parameters, practicability of intervention measures and realistic forecasting,[27] particularly applying methods that account for scarcity of data which may hamper the biological basis and justifiability of assumptions, integration with data, model analysis, and their impact in informing policies in public health.[27 28] There is a need to review key aspects of co-infection modelling to understand the milestones achieved, their significance, and research gaps and opportunities in co-infection model development that may improve their framework and relevance in informing policy on control interventions and improved health outcomes.

Methods and analysis

Study protocol design

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P) 2015 checklist.[29 30] The review has been registered in PROSPERO.

Eligibility criteria

The following inclusion criteria will apply: (1) Full text research articles written in English on infectious disease mathematical epidemiology, published from January 1980 to December 2024. The choice of English as the language for this review was primarily influenced by the research team's proficiency in English as well as resource constraints such as time and funding that language translation may demand. A study will be selected if it is investigating viral-bacterial co-infections of infectious diseases using mathematical epidemiological modelling approaches such as deterministic, stochastic, and fuzzy logic modelling. (2) Studies focusing

on within-host, between-host, and multiple-strain co-infections. The exclusion criteria will include: (1) articles focused on mono-infection mathematical modelling, clinical experiments, and surveys and case studies; (2) duplicate studies, books and book chapters, review protocols, and systematic reviews.

Studies search criteria

This systematic review will use the outline for a search strategy provided in PRESS peer review guidelines.[31] The search for articles from databases (PubMed, Web of Science, Scopus and medRxiv), selection of studies, data extractions and synthesis will be done comprehensively from December 2024 to April 2025 to identify epidemiological co-infection model studies from January 1980 to December 2024. The search items will be combined via the Boolean operations 'AND' and 'OR' coupled with words and/or synonyms formed by a combination of statements in 4 main categories as follows: mathematical approach or term, co-infection, epidemic, and modelling terms. We will apply a search algorithm in each database as follows: ("mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "Fuzzy") AND ("co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation") AND ("epidemiological" OR "epidemic" OR "infectious disease" OR "transmission") AND ("model" OR "modeling" OR "modelling"). A summary of the search criteria is provided in Table 1 and a detailed version for each database is available in search strategy (supplementary file).

Table 1: The search algorithm to retrieve viral-bacterial co-infection models.

Set	Terms/Items
1	"mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
2	"co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
3	"epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
4	"model" OR "modeling" OR "modelling"
Search strategy	1 AND 2 AND 3 AND 4

Study selection

The studies found via the search algorithm across the considered databases will be assembled in the Endnote (Version 20.4.1) referencing tool and further imported to Rayyan (https://www.rayyan.ai/), an online systematic review web tool[32]. This web systematic review tool is designed to help reviewers screen titles and abstracts, reduce the risk of bias, and aid the data extraction process[33]. Three reviewers will initially screen the titles and abstracts in accordance with the eligibility criteria to select potential studies that meet the inclusion threshold. Discrepancies on inclusion such as: (1) both reviewers are unsure; (2) one reviewer recommends while the other is unsure; (3) one reviewer recommends inclusion while the other recommends exclusion, will be resolved through discussion with the help of a third reviewer to reach consensus. The PRISMA diagrammatic structure of the study selection outline will be applied. The next phase involves a review of the full texts and data extraction for selected studies.

Quality assessment and risk of bias

The assessment of the risk of bias in a dynamical co-infection epidemic model may seem difficult to assess due to lack of measurement for bias in models. Considerations of modelling approach and type of models are the main recognisable features.[34] The quality of the selected co-infection modelling articles will be assessed for good dynamical modelling standard practice, referring to guidelines[35-37] highlighting the components of an epidemiological model which include; model formulation, description, data fitting, evaluations, simulations, analysis, validation and output corroboration.

Data extraction process

Data extraction will be done using a standard Microsoft Excel template while applying the standard PRISMA data collection guidelines.[38] Data extraction will be done by TY with the help of two reviewers to verify the quality of data extracted.

Data Items

The following features of the selected articles will be extracted as illustrated in Table 2.

Table 2: Description of data items to be extracted on the coinfection models.

Details	Description/examples
Research articles	Title, hyperlink, journal, author, settings, publication year (ranging from 1980 to 2024)
Model description	Structure of co-infections (within-host, between-host, or multiple-strain coinfections) Modelling approach (deterministic, stochastic, or fuzzy logic) Type of model (ordinary, fractional order, age-structured or spatio-temporal)

	Host species (human, animal, or both)
Co-infection/co-dynamics	Co-infection diseases: we will record which disease(s) the model considered (e.g., rotavirus/cholera, Typhoid/Tuberculosis, and HIV/Tuberculosis/pneumonia) Modelling of coinfection infectivity (increase, decrease or no change)
Key assumptions	Mortality assumption (additive, or not additive) Transition to a co-infection class (from mono-infections to co-infected: infectivity modelled as increasing, decreasing or no change) Co-infection transitions and infectivity assumptions are biologically meaningful and justifiable (yes, no, or partially)
Data fitting	Parameter estimation: e.g., incidence rates, pathogen ingestion rates, recovery rates and mortality rates (literature, simulated data, epidemiological data, or laboratory data) Data availability (yes or no). Cases without data will be denoted by 'none.' Articles applying multiple data sources will be denoted as 'multi-data.'
Intervention measures	Intervention strategies to manage and control infectious diseases (non-pharmaceutical (washing, sanitation, good hygiene), treatment, vaccinations, screening, isolations and quarantine, education campaigns, vector control, antimicrobial stewardship, and personal protection)
Model evaluation	Sensitivity analyses (yes or no). If yes, we assess the nature of sensitivity (local or global) analysis and sensitivity approaches (graphical or numerical). Model validations (yes or no). If yes, we determine the number of infections validated (one or both or multiple (more than two infections)) and determine the type of datasets (simulated or surveillance data). For surveillance data, we further determine the datasets (incidence, vaccinated, hospitalized or death case counts). Studies using multiple datasets for validation will be denoted 'multi-data.' In addition, we state the setting in which the model was validated (city or country or state or multi-states) Findings on impact(s) of coinfections on disease severity (increase, decrease or no effect)

Data synthesis strategy

We will provide a summary of the included studies in tabular form and critically assess them using the TRACE standard ecological modelling guideline to characterize the models.[35] Subsequently, a narrative synthesis of the findings will be provided. The summary will highlight the following key co-infection model features: modelling approaches, assumptions, parameter estimates and simulations, intervention strategies, impact of co-infections, model validation and sensitivity analysis, research gaps and opportunities for future studies. Due to insufficient data for meta-analysis, this systematic review will use the SWiM guidelines [39] in its narrative synthesis.

Ethics and dissemination

Ethics approval is not required for a systematic review since it will be based on published work. The output of this study will be submitted for publication in a peer reviewed epidemiology journal.

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Author Contributions

Timothy yano- conceptualisation, design of the protocol and draft manuscript. Ebenezer Afrifa-Yamoah, Steven Richardson, Julia Collins, and Ute Mueller - supervision, contribution to the plan of search strategy, data extraction and data analysis, review, and editing. Guarantor: Timothy Yano is the guarantor for this study.

All authors read and approved the final manuscript.

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Data availability

All data generated and used during this study will be included in the published review article.

Competing interests

None to declare.

Patient and public involvement

Patients and/or the public were not involved in the formulation, or conduct, or reporting, or dissemination plans of this research.

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Studies Search Criteria.

Below is a detailed search strategy for the systematic review protocol, outlining the databases, filters and limits that can be used in the search for studies on viral-bacterial co-infections.

Databases to be used:

- MEDLINE through PubMed
- Web of Science
- MedRxiv
- Scopus (platform: Elsevier)

Search terms:

The search will use Boolean operations 'AND' and 'OR' with specific keywords related to mathematical approaches and co-infections. The search terms will be categorised into four main groups:

- **Group 1:** "mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy"
- **Group 2:** "co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation"
- **Group 3:** "epidemiological" OR "epidemic" OR "infectious disease" OR "transmission"
- **Group 4:** "model" OR "modeling" OR "modelling"

Combined search query: (Group 1) AND (Group 2) AND (GROUP 3) AND (Group 4)

Table 1 below provides a detailed description of the search criteria for each specified database using the search terms and the combined search strategy.

Table 1: Summary for search query, filters and limits for each database

Database	**Scopus (https://www.elsevier.com/products/scopus)**	
1	Search query in the search bar	[Title/Abstract/Keywords] ("mathematical" OR "dynamical" OR "deterministic" OR "stochastic" OR "fuzzy") AND [Title/Abstract/Keywords] ("co-infection" OR "co-dynamics" OR "dual infection" OR "co-circulation") AND [Title/Abstract/Keywords] ("epidemiological" OR "epidemic" OR "infectious disease" OR "transmission") AND [Title/Abstract/Keywords] ("model" OR "modeling" OR "modelling")
	Filters and limits	Publication year (1980-2024) and limit to language (English) and document type (article).
	Exclusion	Exclude: conference paper, review, case studies, book, book chapter, short survey, letter, editorial and conference review.
	MEDLINE through PubMed (https://pubmed.ncbi.nlm.nih.gov/)	

2	Search query in the search bar	(“mathematical” OR “dynamical” OR “deterministic” OR “stochastic” OR “fuzzy”) AND (“co-infection” OR “co-dynamics” OR “dual infection” OR “co-circulation”) AND (“epidemiological” OR “epidemic” OR “infectious disease” OR “transmission”) AND (“model” OR “modeling” OR “modelling”)
	Filters and limits	Publication year (1980-2024) and limit to language (English) and document type (article).
	Web of Science (https://www.webofscience.com/)	
3	Search query in the search bar	Topic Search ((“mathematical” OR “dynamical” OR “deterministic” OR “stochastic” OR “fuzzy”) AND (“co-infection” OR “co-dynamics” OR “dual infection” OR “co-circulation”) AND (“epidemiological” OR “epidemic” OR “infectious disease” OR “transmission”) AND (“model” OR “modeling” OR “modelling”))
	Filters and limits	Publication years (1980-2024) and limit to languages (English) and document types (article).
	MedRxiv (https://www.medrxiv.org/)	
4	Search query in the search bar	Search for term "(“mathematical” OR “dynamical” OR “deterministic” OR “stochastic” OR “fuzzy”) " AND title "(“co-infection” OR “co-dynamics” OR “dual infection” OR “co-circulation”)" AND abstract or title "(“epidemiological” OR “epidemic” OR “infectious disease” OR “transmission”)" AND full text or abstract or title "(“model” OR “modeling” OR “modelling”)"
	Filters and limits	Date posted: 01 January 1980 and 31 December 2024
5	Timeframe	1980/01/01 to 2024/12/31

Exclusion criteria: Manually review the results and exclude mono-infection mathematical modelling articles, clinical experiments, surveys, case studies, duplicate studies, non-English studies, books, book chapters, review protocols, conference papers and review, letter, editorial, and systematic reviews.

This detailed search strategy will be included as a supplementary file to ensure transparency and reproducibility in the systematic review process.