nature portfolio

Peer Review File

Integrating Artificial Intelligence with Mechanistic Epidemiological Modeling: A Scoping Review of Opportunities and Challenges

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This is a nicely written paper on AI and infectious diseases

The focus on the paper is on predictive algorithms, but little space is dedicated to comparisons of methods for infectious disease modelling. ML methods tend not to perform better than mechanistic ones, and their utility is still being debated.

I have a concern that restriction to ML and DL and excluding statistical models would be very limiting. In geostatistics, gaussian processes are popular but never refered to as deep learning models. Similarly the whole field of optimal control includes some machine learning aspects but do not refer to them as such. I worry restriction to these eligible terms is limiting. Similarily defining a mechanistic model is challenging and should be explained better - ODEs are clear a class, but renewal equations? hawkes processes? these would be mechanistic models, but would they be excluded?

60% of the studies are on COVID, i worry this really makes this paper about how AI can help respiratory viral illnesses.

line 194 - is the LASSO really ML or a statistical method (again referencing my earlier point). I mean its just linear regression + shrinkage.

line 189 - i think more should be discussed about the type of ensemble modelling, stacking or averaging etc. These make a big difference to performance.

line 192 - LSTM models are good at temporal dependencies, when these are complex, like sentences where the first word matters hugely. In noisy time series, they rarely perform better than ARIMAs. Transformer methods might be better

line 199 - What metrics are used? is calibration included? what about uncertainty - these are all super important to consider for forecasting

line 258 - "Neural networks, with their ability to approximate complex functions", trees do better on tabular data and many methods can approximate complex functions.

line 275 - what are "AI-enhanced Bayesian frameworks" this is a term ive never heard.

line 277 - this description of neural networks approximating the posterior being variational inference is very poor - the goal of variational inference is to approximate a conditional density of latent variables given observed variables through optimisation (the Elbo)

line 346 - people use tree based approaches because they work so well

minor comments

1) line 20 - is the focus on predictive only? this should be made clear in the title
2) line 36 - is the scope on viral illnesses or other pathogens? this should also be made clear to the reader at the onset
3) line 44 - this is not accurate, many parameters in models are time varying, such as the reproduction number or rate of transmission. Also parameters such as the generation time are constantly updated with new variants and over time and hence are not constant. However in the projection window perhaps, but we would not expect the generation interval to change over a matter of days. Other parameters that we expect to vary are modelled as such.
4) line 48 - i do not understand why these data cannot be incorporated into a mechanistic model? linear terms are easy to add for most parameters

Reviewer #2

(Remarks to the Author)
This scoping review provides a detailed analysis of the various methodological approaches used in integrating AI techniques with mechanistic epidemiological modelling. However, I found the title misleading as it does not specify the focus on mechanistic models, which led me to expect a broader discussion on all types of epidemiological models, including statistical and data-driven approaches. These models also contribute to the vast body of epidemiological research. While the authors clarify in the Methods section that non-mechanistic models were outside the scope of this review, I strongly recommend amending the title for clarity, as the abstract makes it clear the study is centred on AI integration with mechanistic models only.

The review significantly contributes to the field by advancing our understanding of the current state of the art of integrated models which combine AI predictive power with the explainability of mechanistic models. The study is original, highlighting the strengths and weaknesses of specific methods, while identifying knowledge gaps and opportunities for future research.

The study's conclusions are supported by the comprehensive review process, with sufficient detail provided in the Methods and appendices. However, the conclusions in the Abstract are somewhat vague and could be more specific. For example, the cited "promising methodologies" (line 26) are not identified, and "collaborative efforts across disciplines" (lines 28-29) could be further detailed. The Discussion section provides better clarity on these points, particularly in the final paragraphs (lines 451-529). They are also more clearly summarised in the Conclusion (lines 538-542) and can be used to improve the Abstract.

The point raised in the Discussion regarding the limited use of satellite imagery (lines 475-485) could be better explained by the exclusion of statistical and data-driven epidemiological models in this review. Previous studies have successfully integrated these and other data streams into AI-powered predictive epidemiological models, demonstrating their potential for enhancing disease prediction (see https://doi.org/10.1371/journal.pntd.0010509 and https://doi.org/10.1016/j.lanepe.2022.100370 for examples).

The methodology is adequate and follows standard scoping review protocols by the Joanna Briggs Institute and the PRISMA-ScR guidelines. Sufficient detail is provided to ensure the work can be reproduced. Overall, the study meets the expected standards for publication.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I thank the authors for their very detailed revisions. I really appreciate appendix 2, I am sorry if i missed this in the previous submission. I have no remaining concerns and really like this paper!

Response to Reviewers

We would like to thank the reviewers for providing insightful comments that were important in our revision of the manuscript. We have taken these comments into full consideration and addressed them in the revised manuscript. Below, we detail our responses to these comments.

All revised portions are marked in red in the revised manuscript. The main comments and our specific responses are detailed below.

REVIEWER COMMENTS

Reviewer #1:

REVIEWER COMMENTS 1-1: This is a nicely written paper on AI and infectious diseases. The focus on the paper is on predictive algorithms, but little space is dedicated to comparisons of methods for infectious disease modelling. ML methods tend not to perform better than mechanistic ones, and their utility is still being debated.

Response: Thank you for your positive feedback and for raising the important point about comparing modeling methods. While we acknowledge the ongoing debate regarding the relative advantages of machine learning (ML)/deep learning (DL) and traditional mechanistic models, the focus of this scoping review was to explore studies that leverage the advantages of both sides to advance the field of epidemiological modeling. Given that the utilization of mechanistic models integrated with ML/DL models is still in its infancy, in this scoping review, we identified and synthesized the literature on this emerging field. As a performance comparison of mechanistic and ML/DL models falls outside the scope of our review, we have noted it in our exclusion criteria (Appendix 1: "Comparing the performance of AI techniques and mechanistic epidemiological models"). We have clarified this further in the Eligibility criteria section of the main text (copied below).

In the Discussion section, we also provide a general assessment of the applicability of identified models based on data requirements, demonstrated performance, and generalizability. However, due to the vast heterogeneity in application areas, modeling objectives, and datasets used across identified studies, conducting a comprehensive performance comparison of mechanistic, purely AI, and integrated models was not feasible in this review. As you pointed out here and in Comments 1-6, the utility of ML methods (as well as other purely AI and integrated models) compared to traditional mechanistic models is still under investigation, and ML/DL models may not always outperform traditional statistical methods.

We highlighted this as a critical area for future research in the Discussion section. To ensure a more comprehensive discussion, we revised it to further highlight (i) the ongoing debate on the relative advantages of different modeling approaches and (ii) the

need for future research examining their comparative performance and limitations to guide effective model selection. The revised parts are copied below.

Methods, Eligibility criteria:
"We define "integrated models" as those combining mechanistic epidemiological models with AI techniques specifically for transmission analysis and disease intervention optimization. Studies that constructed AI techniques as alternative modeling methods, compared the performance of AI techniques with mechanistic models, or used mechanistic models solely to generate validation/testing datasets for AI techniques were not considered eligible under this definition."

Discussion:
"Finally, while this review identified a diverse range of methodological frameworks, many studies lacked rigorous evaluations of robustness, sensitivity, and generalizability—all crucial for real-world application. Addressing these deficiencies in performance evaluation is essential to increase model transparency and reliability, ultimately fostering public trust and facilitating wider adoption of these models. Moreover, the proliferation of methodological frameworks raises important questions about the relative performance of integrated, purely AI, and traditional mechanistic models. While integrated models often outperform simple mechanistic models (e.g., classical SIR systems), they may not surpass those that capture sufficient realism for practical decision-making. Additionally, although traditional statistical models fall outside the scope of AI techniques considered in our review, their integration into mechanistic epidemiological models remains valuable.[38] However, comparisons between these integrated approaches, especially those incorporating traditional statistical models versus those based on ML/DL, are rarely discussed. For example, while LSTM networks, with their ability to capture temporal dependencies, were frequently used in AI-augmented epidemiological models to predict dynamic model parameters, traditional statistical models such as autoregressive integrated moving average (ARIMA) models may be more robust when faced with noisy and scarce time series data.[301] Therefore, future research is needed to rigorously examine the limitations and comparative utility of AI-assisted and well-established traditional disease transmission models to guide effective model selection."

REVIEWER COMMENTS 1-2: I have a concern that restriction to ML and DL and excluding statistical models would be very limiting. In geostatistics, gaussian processes are popular but never refered to as deep learning models. Similarly the whole field of optimal control includes some machine learning aspects but do not refer to them as such. I worry restriction to these eligible terms is limiting. Similarily defining a mechanistic model is challenging and should be explained better - ODEs are clear a class, but renewal equations? hawkes processes? these would be mechanistic models, but would they be excluded?

Response: Thank you for your comments on the restrictions and clarifications of search terms. Our scoping review aims to explore the emerging research on integrated models, where new methodologies are rapidly developed, offering promising potential for

addressing epidemiological challenges, but a comprehensive synthesis of the literature is currently lacking. We finalized the scope of this review and defined the eligibility criteria based on this rationale.

First, we focus specifically on ML and DL models because their integration with mechanistic epidemiological models represents a newer area with rapid growth yet fragmented explorations. While traditional statistical models, some of which may be considered AI methods, are important, their integration with mechanistic models, especially for parameter inference and model calibration, is well-established and extensively covered in existing literature. Numerous statistical techniques, such as maximum likelihood estimation, filtering methods, and Gaussian process emulation, have been widely adopted for these purposes. Given the extensive existing literature and reviews on these established methods, another summary would offer limited added value.

We also appreciate you highlighting the overlap between ML/DL, statistical methods, and optimal control theory. These fields share common foundations, and their boundaries are becoming increasingly blurred. For example, Gaussian processes, linear regression, and time series models can be considered both statistical and ML models, and reinforcement learning has its roots in optimal control theory although traditional optimal control methods are rarely classified as ML/DL. However, including all statistical models and theories that provide the groundwork for ML/DL would make this scoping review unmanageably broad, hindering our ability to provide an in-depth analysis of the emerging integrated models. To maintain a focused scope, we included DL models (which are based on neural networks) and ML models that (i) have limited but growing integration with mechanistic epidemiological models and (ii) are more commonly referred to as "ML" than "statistical" models. Since there is no explicit rule for determining common usage or reference, the final inclusion or exclusion of a study was determined through discussion among the review team. This collaborative approach ensures a consistent and well-defined scope for our review. Importantly, although traditional statistical and optimal control methods are not considered eligible AI models, those coupled with DL models were included to capture the advancements at the intersection of DL and traditional techniques. This includes, for example, Bayesian neural networks (e.g., study #94 in Appendix 5) and neural optimal control methods (e.g., study #201 in Appendix 5). We further clarified the rationale for our review's scope (Introduction) and eligibility criteria for AI models included in this review (Appendix 1). We also guided readers interested in statistical models to relevant research (Introduction).

Second, we define mechanistic models as those grounded in the known governing laws and physical principles of disease transmission. This differs from empirical models, which primarily focus on data fitting without necessarily explaining the underlying causes of observed patterns. Seven types of mechanistic models are commonly used in epidemiological modeling: compartmental models, individual/agent-based models, metapopulation models, cellular automata, renewal equations, chain binomial models,

and branching processes. Our initial focus was on the first four types, which share a core concept of dividing the population into distinct health states with defined transition rates. We appreciate you highlighting renewal equations and Hawkes processes, which also represent infection dynamics mechanistically but were outside our initial scope. In the revised manuscript, we further refined the definition of mechanistic models (Introduction) and expanded our search and inclusion criteria (Methods) to ensure the inclusion of all seven model types. The expansion resulted in the inclusion of two additional studies and we updated the report accordingly. The revised parts are copied below.

Introduction:
"Mechanistic models, grounded in the known governing laws and physical principles of disease transmission, have been widely used to investigate various infectious diseases, including respiratory infections,[6–8] sexually transmitted diseases,[9,10] and vector-borne diseases.[11,12] Unlike empirical models, which primarily focus on data fitting without necessarily incorporating the underlying causes of observed patterns, mechanistic models aim to explain how and why epidemics unfold."

"Integrated models, which combine the data-mining capabilities of AI techniques with the explanatory power of mechanistic models, are gaining significant attention. Despite the wide spectrum of AI methods, current integrations with mechanistic epidemiological models are predominantly limited to traditional statistical models, particularly for parameter inference and model calibration.[38–41] Explorations on emerging ML and DL techniques, though promising and rapidly expanding, remain fragmented due to the complexity of these techniques and interdisciplinary communication challenges. Bridging this gap is crucial to fully harnessing the power of AI to advance epidemiological modeling."

Methods, Overview:
"We conducted a scoping review to synthesize the literature on the integration of AI techniques, specifically ML and DL models, with mechanistic epidemiological models of infectious disease dynamics."

Methods, Eligibility criteria:
"Seven types of mechanistic models, commonly used in epidemiological modeling, were considered eligible for this review: compartmental models, individual/agent-based models, metapopulation models, cellular automata, renewal equations, chain binomial models, and branching processes."

Appendix 1:
"Our review included seven types of mechanistic models commonly used in epidemiological modeling: compartmental models, individual/agent-based models, metapopulation models, cellular automata, renewal equations, chain binomial models, and branching processes. Other epidemiological models were not considered eligible. Eligible AI techniques in our review included DL models (which are based on neural

networks) and ML models that (i) have limited but growing integration with mechanistic epidemiological models and (ii) are more commonly referred to as "ML" than "statistical" models. Since there is no explicit rule for determining common usage or reference, the final inclusion or exclusion of a study was determined through discussion among the review team. This collaborative approach ensures a consistent and well-defined scope for our review."

"Not using eligible AI techniques or mechanistic epidemiological models

- **Using ineligible AI techniques, such as gradient-based or heuristic optimization algorithms, statistical models (e.g., linear regression models, time series models, Gaussian processes, maximum likelihood estimation, and filtering methods), fuzzy logic systems, automatic differentiation, and matrix factorization"**

Appendix 2:

Search terms

AI	Epidemic modeling	Modeling	Infectious disease	Infectious agents	Spreading
"artificial intelligence"	"epidemic model*"	"mathematical model*"	epidemi*	virus*	spread*
"machine learning"	"epidemics model*"	"simulation model*"	pandemic*	viral	transmissi*
"deep learning"	"epidemiological model*"	"stochastic model*"	endemic*	parasit*	transmit*
"reinforcement learning"	"transmission model*"	"deterministic model*"	"communicable disease*"	pathogen*	propagat*
"natural language processing"	"compartmental model*"	"differential equation*"	borne AND disease*	bacter*	
"neural network*"	"compartment model*"	"agent based model*"	emerg* AND disease*	microb*	
"decision tree*"	"chain binomial epidemic*"	"individual based model*"	infect*	fung*	
"random forest*"		"computational model*"	contagio*	protozo*	
"support vector machine*"		"disease model*"	outbreak*	helminth*	
"long short term memory"		"dynamic model*"	vaccin*	worm*	
"language model*"		"dynamics model*"	epizootic*	disease*	
		"mechanistic model*"	enzootic*	strain*	
		"mechanism model*"	panzootic*	variant	
		"metapopulation model*"	zoono*	variants	
		"meta population model*"			
		"renewal equation*"			
		"renewal process*"			

		"chain binomial process*"			
		"chain binomial model*"			
		"branching process*"			

PubMed (December 6, 2023: 1382 hits)

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OR
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AND
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Embase (Ovid) (December 6, 2023: 3342 hits)

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Web of Science (December 6, 2023: 2003 hits)

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Scopus (December 6, 2023: 4574 hits)

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IEEE Xplore

AI AND Epidemic modeling (Part 2) (December 6, 2023: 0 hit)

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AI AND Modeling AND Infectious disease (Part 3) (December 6, 2023: 1 hit)

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AI AND Modeling AND Infectious disease (Part 4) (December 6, 2023: 0 hit)

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AI AND Modeling AND Infectious agents AND Spreading (Part 2) (December 6, 2023: 0 hit)
("All Metadata":"artificial intelligence" OR "All Metadata":"machine learning" OR "All Metadata":"deep learning" OR "All Metadata":"reinforcement learning" OR "All Metadata":"natural language processing" OR "All Metadata":"neural network" OR "All Metadata":"neural networks" OR "All Metadata":"decision tree" OR "All Metadata":"decision trees" OR "All Metadata":"random forest" OR "All Metadata":"random forests" OR "All Metadata":"support vector machine" OR "All Metadata":"support vector machines" OR "All Metadata":"long short term memory" OR "All Metadata":"language model" OR "All Metadata":"language models" OR "All Metadata":"language modeling" OR "All Metadata":"language modelling")
AND
("All Metadata":"renewal equation" OR "All Metadata":"renewal equations" OR "All Metadata":"renewal process" OR "All Metadata":"renewal processes" OR "All Metadata":"chain binomial process" OR "All Metadata":"chain binomial processes" OR "All Metadata":"chain binomial model" OR "All Metadata":"chain binomial models" OR "All Metadata":"chain binomial modeling" OR "All Metadata":"chain binomial modelling" OR "All Metadata":"branching process" OR "All Metadata":"branching processes")
AND
("All Metadata":virus OR "All Metadata":viruses OR "All Metadata":viral OR "All Metadata":parasit* OR "All Metadata":pathogen* OR "All Metadata":bacter* OR "All Metadata":microb* OR "All Metadata":fung* OR "All Metadata":protozo* OR "All Metadata":helminth* OR "All Metadata":worm* OR "All Metadata":disease OR "All Metadata":diseases OR "All Metadata":strain OR "All Metadata":strains OR "All Metadata":variant OR "All Metadata":variants)
AND
("All Metadata":spread OR "All Metadata":spreads OR "All Metadata":spreading OR "All Metadata":spreaded OR "All Metadata":spreadable OR "All Metadata":transmission OR "All Metadata":transmissibility OR "All Metadata":transmissible OR "All Metadata":transmit OR "All Metadata":transmits OR "All Metadata":transmitting OR "All Metadata":transmitted OR "All

Metadata":transmittable OR "All Metadata":propagate OR "All Metadata":propagates OR "All Metadata":propagation OR "All Metadata":propagated OR "All Metadata":propagating)

ACM Digital Library (Full-Text collection)
AI AND Epidemic modeling (Part 2) (December 6, 2023: 0 hit)
Title/Abstract: "artificial intelligence" OR "machine learning" OR "deep learning" OR "reinforcement learning" OR "natural language processing" OR "neural network" OR "neural networks" OR "decision tree" OR "decision trees" OR "random forest" OR "random forests" OR "support vector machine" OR "support vector machines" OR "long short term memory" OR "language model" OR "language models" OR "language modeling" OR "language modelling"
AND
Title/Abstract: "chain binomial epidemic" OR "chain binomial epidemics"

AI AND Modeling (Part 4) (December 6, 2023: 1 hit)
Title/Abstract: "artificial intelligence" OR "machine learning" OR "deep learning" OR "reinforcement learning" OR "natural language processing" OR "neural network" OR "neural networks" OR "decision tree" OR "decision trees" OR "random forest" OR "random forests" OR "support vector machine" OR "support vector machines" OR "long short term memory" OR "language model" OR "language models" OR "language modeling" OR "language modelling"
AND
Title/Abstract: "renewal equation" OR "renewal equations" OR "renewal process" OR "renewal processes" OR "chain binomial process" OR "chain binomial processes" OR "chain binomial model" OR "chain binomial models" OR "chain binomial modeling" OR "chain binomial modelling" OR "branching process" OR "branching processes"

REVIEWER COMMENTS 1-3: 60% of the studies are on COVID, i worry this really makes this paper about how AI can help respiratory viral illnesses.

Response: Our review provides a comprehensive overview of integrated models applied across the full spectrum of infectious diseases, aiming to critically assess the current research landscape and identify gaps and promising future directions. To achieve this, we adopted an inclusive search strategy encompassing all infectious disease types, including respiratory, sexually transmitted, vector-borne, water-borne, and others (Appendix 2).

Our review reveals a research landscape that is currently concentrated on direct transmission (especially COVID-19). Despite this focus, these models offer valuable insights into common modeling challenges across disease types, such as model calibration, parameter estimation, and capturing the non-linear impacts of interventions. In the Discussion section, we also moved beyond this focus to discuss how to expand the horizon and unlock the full potential of AI-powered methods. We discussed the challenges of applying existing integrated models designed for COVID-19/direct transmission to other transmission routes and highlighted the importance of considering the unique challenges posed by different diseases. The revised manuscript now includes

more concrete examples and suggestions for future model improvement to facilitate broader applications. The revised parts are copied below.

Discussion:

"Fourth, our review reveals a research landscape that is currently concentrated on direct transmission (especially COVID-19). The dominance of COVID-19 research is likely attributable to the vast amounts of data collected and shared during the pandemic. However, such extensive data may not be available for less prevalent or local diseases, particularly in low- and middle-income countries with limited surveillance capabilities. The practicality and scalability of most methodological frameworks depend on the availability of abundant, high-quality data, which is often lacking. For instance, GNN-based methods require individual-level contact networks that are frequently unavailable. Therefore, it is crucial to invest in both enhanced disease surveillance and research to improve modeling techniques capable of handling incomplete and noisy data.

Moreover, this narrow focus on direct transmission raises concerns about their generalizability to diseases with indirect transmission routes. While these models offer valuable insights into common modeling challenges faced across disease types—such as model calibration, parameter estimation, and capturing the non-linear impacts of interventions—their lack of consideration of more complex transmission mechanisms hinders their full potential. For example, models for vector-borne diseases should account for the vector population dynamics and the interactions between vector and human populations. Similarly, models for water-borne diseases require a detailed representation of environmental factors, such as sanitation infrastructure and contamination pathways, and human behavioral factors, such as hygiene practices and access to clean water sources. Traditional mechanistic models, constrained by simplified assumptions and parameter uncertainties, face challenges in fully capturing these complexities. By leveraging AI's ability to integrate diverse data, learn complex patterns, and generate accurate predictions, integrated models can potentially enhance our understanding of underlying transmission mechanisms, optimizing a balance between model simplification and realism. This enables the application of integrated models to a broader spectrum of infectious diseases, each with unique challenges requiring tailored AI solutions."

REVIEWER COMMENTS 1-4: line 194 - is the LASSO really ML or a statistical method (again referencing my earlier point). I mean its just linear regression + shrinkage.

Response: Thank you for your comments. LASSO was not considered an eligible AI technique in our review (as explained in our response to Comments 1-2). This paper was included because it utilizes an agglomerative hierarchical clustering method, which is an eligible AI technique in our review. We have revised this sentence to avoid any misunderstanding. This modified sentence is copied below.

Results

"One study used a hierarchical clustering approach to group regions with similar disease activity patterns, partially determined by epidemiological models.[53] This approach allowed for the identification of regions with synchronized disease activity and the generation of cluster-based predictions."

REVIEWER COMMENTS 1-5: line 189 - i think more should be discussed about the type of ensemble modelling, stacking or averaging etc. These make a big difference to performance.

Response: Thank you for your comments. We have described the specific ensemble method used in each study. The modified part is copied below.

Results

"Six studies employed ensemble learning frameworks that combined forecasts from AI and epidemiological models to improve forecasting performance.[57–62] Long short-term memory (LSTM) networks–the most frequently used method–are adept at learning temporal dependencies from time-series data, thereby complementing mechanistic models in generating robust forecasts. Of these six studies, four used weighted averaging to combine forecasts based on historical model performance;[57–59,61] one utilized stacking, where an LSTM-based meta-model was trained to learn the optimal way to integrate forecasts from epidemiological models;[60] and one employed boosting, where a neural network learned to correct errors in the epidemiological model's forecasts.[62]"

REVIEWER COMMENTS 1-6: line 192 - LSTM models are good at temporal dependencies, when these are complex, like sentences where the first word matters hugely. In noisy time series, they rarely perform better than ARIMAs. Transformer methods might be better

Response: Thank you for raising this point about the performance of LSTM networks with noisy time series. We acknowledge that while LSTM networks are good at capturing complex temporal dependencies, their performance can be sensitive to data noise. In such cases, traditional statistical models such as ARIMA may be more robust. However, as stated in our response to Comments 1-1, a comparison of model performance is outside the scope of this review. Although we did not provide a detailed analysis of this aspect, we have highlighted in the Discussion section that the choice of model should depend on data characteristics and that ML/DL models may not always outperform traditional statistical methods. The revised part is copied below.

Discussion

"Additionally, although traditional statistical models fall outside the scope of AI techniques considered in our review, their integration into mechanistic epidemiological models remains valuable.[38] However, comparisons between these integrated approaches, especially those incorporating traditional statistical models versus those based on

ML/DL, are rarely discussed. For example, while LSTM networks, with their ability to capture temporal dependencies, were frequently used in AI-augmented epidemiological models to predict dynamic model parameters, traditional statistical models such as autoregressive integrated moving average (ARIMA) models may be more robust when faced with noisy and scarce time series data.[301]"

REVIEWER COMMENTS 1-7:

- line 258 - "Neural networks, with their ability to approximate complex functions", trees do better on tabular data and many methods can approximate complex functions.
- line 346 - people use tree based approaches because they work so well

Response: Thank you for your comments. We have revised the sentences to provide a more neutral and objective description of AI models, focusing on the observed usage frequency in the reviewed studies. The revised sentences are copied below.

Results
"Neural networks were the most frequently used surrogates (10 of 13 studies)."
"Most (13 out of 16) studies adopted tree-based models."

REVIEWER COMMENTS 1-8: line 199 - What metrics are used? is calibration included? what about uncertainty - these are all super important to consider for forecasting

Response: Thank you for your comments. These metrics are "outbreak situation metrics" (such as the number of infected premises during an outbreak of foot-and-mouth disease) instead of metrics used for assessing model performance. We have revised this sentence to avoid misunderstanding. The revised sentence is copied below.

Results
"Two studies leveraged tree-based methods, trained on synthetic datasets generated by epidemiological models, to discern the relationship between early-phase outbreak situation metrics and future epidemic outcomes.[55,56]"

REVIEWER COMMENTS 1-9: line 275 - what are "AI-enhanced Bayesian frameworks" this is a term ive never heard.

Response: Thank you for your comments. We have changed the term to "Bayesian neural networks."

REVIEWER COMMENTS 1-10: line 277 - this description of neural networks approximating the posterior being variational inference is very poor - the goal of variational inference is to approximate a conditional density of latent variables given observed variables through optimisation (the Elbo)

Response: Thank you for your clarification on the description of variation inference, we have revised the description accordingly. The revised sentence is copied below.

Results

"Bayesian neural networks leverage the capabilities of neural networks in handling high-dimensional data to enhance parameter inference in Bayesian approaches, including variational and simulation-based inference. These approaches attempt to approximate the posterior distribution of model parameters given observed data, especially when faced with intractable likelihood or marginal likelihood. One study employed variational inference to jointly infer unknown parameters and latent diffusion processes in the epidemiological model.[185] An RNN formed part of the variational approximation of the joint posterior distribution of the parameters and diffusion processes, conditional on the observed data. This approximation was optimized by maximizing the evidence lower bound (ELBO). Three studies utilized simulation-based inference techniques to approximate the posterior when the likelihood, implicitly defined by epidemiological models, was intractable.[184,186,187] These techniques include neural density estimation methods and neural network-based approximate Bayesian computation.[188]"

REVIEWER COMMENTS 1-11: line 20 - is the focus on predictive only? this should be made clear in the title

Response: Thank you for your comments. All ML and DL models, including predictive (e.g., LSTM), descriptive (e.g., clustering), and generative models (e.g., GAN), were considered eligible in our review. We appreciate you highlighting its point. We have modified this sentence to clarify the scope of our review.

Abstract

"Integrating prior epidemiological knowledge embedded within mechanistic models with the data-mining capabilities of artificial intelligence (AI) offers transformative potential for epidemiological modeling."

REVIEWER COMMENTS 1-12: line 36 - is the scope on viral illnesses or other pathogens? this should also be made clear to the reader at the onset

Response: Thank you for your comments. As mentioned in our response to Comments 1-3, our search strategy encompasses all infectious disease types, including viral infections, bacterial Infections, and others. We have modified this sentence and clarified our scope in the Abstract. The revised parts are copied below.

Introduction

"Mechanistic models, grounded in the known governing laws and physical principles of disease transmission, have been widely used to investigate various infectious diseases,

including respiratory infections,[6–8] sexually transmitted diseases,[9,10] and vector-borne diseases.[11,12]"

Abstract

"This scoping review provides a comprehensive overview of emerging integrated models applied across the spectrum of infectious diseases."

REVIEWER COMMENTS 1-13: line 44 - this is not accurate, many parameters in models are time varying, such as the reproduction number or rate of transmission. Also parameters such as the generation time are constantly updated with new variants and over time and hence are not constant. However in the projection window perhaps, but we would not expect the generation interval to change over a matter of days. Other parameters that we expect to vary are modelled as such.

Response: Thank you for your comments. We have revised these sentences to improve their accuracy. The revised sentences are copied below.

Introduction

"First, the reliability of these models depends heavily on the accuracy of estimated parameters governing transmission dynamics.[5,13,14] However, current models are often constrained by simplifications and data availability. For example, disease transmissibility, though modeled as dynamic, is frequently calibrated using lagged and potentially incomplete death or hospitalization data. Similarly, human contact patterns, crucial for understanding transmission, are often assumed to be static due to limited access to high-quality, real-time data. Furthermore, the impact of interventions is typically modeled using linear terms, failing to fully capture the complex interplay between public responses and pathogen evolution."

REVIEWER COMMENTS 1-14: line 48 - i do not understand why these data cannot be incorporated into a mechanistic model? linear terms are easy to add for most parameters

Response: Thank you for your comments. We have revised these sentences to improve their accuracy. The revised sentences are copied below.

Introduction

"Second, despite the wealth of epidemiological knowledge encoded in unstructured and multimodal data sources (e.g., satellite imagery, social media, electronic health records), their incorporation into mechanistic models has largely relied on manual feature extraction, hindering the effective utilization of the richness of these data.[15–17]"

Reviewer #2:

REVIEWER COMMENTS 2-1: This scoping review provides a detailed analysis of the various methodological approaches used in integrating AI techniques with mechanistic epidemiological modelling. However, I found the title misleading as it does not specify the focus on mechanistic

models, which led me to expect a broader discussion on all types of epidemiological models, including statistical and data-driven approaches. These models also contribute to the vast body of epidemiological research. While the authors clarify in the Methods section that non-mechanistic models were outside the scope of this review, I strongly recommend amending the title for clarity, as the abstract makes it clear the study is centred on AI integration with mechanistic models only.

Response: Thank you for your suggestion to refine the title and clarify the emphasis of our review on mechanistic models. We have now revised the title to "Integrating Artificial Intelligence with Mechanistic Epidemiological Modeling: A Scoping Review of Opportunities and Challenges."

REVIEWER COMMENTS 2-2: The review significantly contributes to the field by advancing our understanding of the current state of the art of integrated models which combine AI predictive power with the explainability of mechanistic models. The study is original, highlighting the strengths and weaknesses of specific methods, while identifying knowledge gaps and opportunities for future research.

Response: We sincerely appreciate your positive comments and recognition of the importance of this work.

REVIEWER COMMENTS 2-3: The study's conclusions are supported by the comprehensive review process, with sufficient detail provided in the Methods and appendices. However, the conclusions in the Abstract are somewhat vague and could be more specific. For example, the cited "promising methodologies" (line 26) are not identified, and "collaborative efforts across disciplines" (lines 28-29) could be further detailed. The Discussion section provides better clarity on these points, particularly in the final paragraphs (lines 451-529). They are also more clearly summarised in the Conclusion (lines 538-542) and can be used to improve the Abstract.

Response: We appreciate your feedback and agree that the abstract could be more specific. We revised the abstract to more clearly identify the "promising methodologies" and provide further detail on "collaborative efforts across disciplines," drawing on the more detailed explanations provided in the Discussion and Conclusion sections, as you suggested. The revised part is copied below.

Abstract:

"Our review highlights the practical value of integrated models, including advances in disease forecasting, model parameterization, and calibration. However, key research gaps remain. These include the need for better incorporation of realistic decision-making considerations, expanded exploration of diverse datasets, and further investigation into biological and socio-behavioral mechanisms. Addressing these gaps will unlock the synergistic potential of AI and mechanistic modeling to enhance understanding of disease dynamics and support more effective public health planning and response."

REVIEWER COMMENTS 2-4: The point raised in the Discussion regarding the limited use of satellite imagery (lines 475-485) could be better explained by the exclusion of statistical and data-driven epidemiological models in this review. Previous studies have successfully integrated these and other data streams into AI-powered predictive epidemiological models, demonstrating their potential for enhancing disease prediction (see https://doi.org/10.1371/journal.pntd.0010509 and https://doi.org/10.1016/j.lanepe.2022.100370 for examples).

Response: Thank you for pointing out this important point. We agree that the limited use of satellite imagery in integrated models can be further elucidated by clarifying the scope of our review. Therefore, we revised the Discussion section to acknowledge the potential of integrating satellite imagery within other modeling paradigms. The revised part is copied below.

Discussion:

"For example, the transmission of climate-sensitive vector-borne diseases is influenced by a variety of climate and environmental factors. However, existing mechanistic models often utilize basic weather data, such as temperature, rainfall, and humidity.[11,288] These data, primarily collected by meteorological institutions, can be limited by spatial coverage and temporal resolution. Satellite imagery presents a valuable supplement, offering real-time, high-resolution data for a wide range of climate and environmental variables.[47,289] Previous studies have shown the potential of integrating satellite data into disease surveillance and forecasting models, utilizing purely AI approaches.[290–292] This highlights the ability of AI to extract rich information from satellite data, enabling mechanistic models to build more comprehensive and dynamic representations of abiotic and biotic drivers of disease transmission."

REVIEWER COMMENTS 2-5: The methodology is adequate and follows standard scoping review protocols by the Joanna Briggs Institute and the PRISMA-ScR guidelines. Sufficient detail is provided to ensure the work can be reproduced. Overall, the study meets the expected standards for publication.

Response: Thank you again for your positive feedback.