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SEIRS research map COVID-19 vaccines: analysis of trends, findings, and challenges of mathematical models

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ABSTRACT

The control of the COVID-19 pandemic requires mathematical models that are able to accommodate complex immune dynamics, especially *waning immunity* phenomena and vaccination interventions. This study conducted a *Systematic Literature Review* using the PRISMA protocol to map trends, findings, and methodological challenges in SEIRS-Vaccination modeling. Of the 80 articles identified in the initial stage, 56 articles met the inclusion criteria and were analyzed. Furthermore, 11 articles were selected through *purposive sampling techniques* as representative samples for in-depth comparative analysis of five main methodology categories: Deterministic (ODE), Optimal Control, Fractional Order, Data Assimilation/Stochastic, and Spatial. The results of the literature synthesis reveal a significant paradigm shift from classical deterministic models that focused on stability analysis R_0 static towards a more adaptive model. Specifically, this study identifies the use of the *Ensemble Kalman Filter* for estimation of dynamic parameters and Optimal Control Theory for resource allocation strategies as the dominant methodological trends. The model's findings consistently validate that vaccination rate is the most sensitive intervention parameter, but its long-term effectiveness is highly dependent on the duration of immunity. The study concludes the need to develop a hybrid model that integrates stochastic approaches and optimal control to generate more precise policy recommendations in the future.

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1. INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a massive impact on global health, economic stability, and the social order [1, 2]. In response, the global scientific community raced to develop pharmaceutical interventions, with vaccination being the primary strategy to control the spread of the virus and reduce mortality [3, 4]. The mass vaccination program was launched in the hope of achieving herd *immunity* and restoring normality.

However, the hope of rapid eradication faces complex biological challenges. The emergence of various new variants (VoC), as well as scientific evidence showing the phenomenon *of waning immunity* [5 - 7], changed the control paradigm. This phenomenon indicates that the immunity acquired, both from natural infections and vaccinations, is not permanent and decreases over time. This opens up the risk of reinfection and breakthrough infections, which have the potential to trigger the next wave of the pandemic [8, 9].

To understand the complex dynamics between viral spread, vaccination interventions, and impermanent immunity, epidemiological mathematical modeling becomes a very important analytical tool [10, 11]. Classic compartment models, such as the standard SIR (Susceptible-Infectious-Recovered), which assume permanent post-recovery immunity, are no longer sufficient to capture the reality of COVID-19.

Classic compartment models, such as the standard SIR (Susceptible-Infectious-Recovered), which assume permanent post-recovery immunity, are no longer adequate to capture the reality of COVID-19. This is because this assumption contradicts clinical evidence that shows that the body's immunity to SARS-CoV-2 can decrease over time (*waning immunity*), allowing for reinfection. Therefore, the focus of this research shifted to the SEIRS (Susceptible-Exposed-Infectious-Recovered-Susceptible) model [12]. This model explicitly inserts the groove from the Recovered (R) compartment back to the Susceptible (S) at a certain rate, which represents the loss of immunity. Many researchers later expanded this framework to specifically include vaccination interventions, which gave birth to various model variants such as SEIR-V, SVEIR, or SEIRS-V [13 - 15].

A literature review of dozens of existing articles shows that there is no single approach in SEIRS-Vaccination modeling. There is a significant diversity of methodologies, each of which has a different focus and assumptions. These research trends can be categorized into several key approaches, including:

1. Deterministic Model (ODE): Analyzes stability, R_0, and the impact of vaccination strategies with the Common Differential Equation approach [16, 17].
2. Fractional Order Model: Using fractional calculus to model memory effects on transmission dynamics [18, 19].
3. Optimal Control Model: Seeking the best (optimal) vaccination allocation strategy to minimize infections and costs [20, 21].
4. Spatial Model (PDE); Analyzing the geographical spread (diffusion) of the disease and vaccination between regions [22, 23].
5. Stochastic Model and Data Assimilation: Incorporate elements of uncertainty (noise) or use *real-time observational data* (such as *the Ensemble Kalman Filter*) to dynamically correct model parameters [24, 25].

Fundamental differences in methodology, parameter assumptions (e.g., vaccination efficacy, fading immunity rate), and analysis focus (global stability, estimation of R_t, or resource allocation) result in a rich yet fragmented research landscape.

Therefore, this study aims to systematically categorize, analyze, and synthesize the findings from the SEIRS modeling literature (and its variants) in the context of COVID-19 vaccination. Through this systematic review, it is hoped that dominant methodological trends, key quantitative findings related to vaccination effectiveness, and consistent modeling challenges can be identified. This study ultimately aims to present a comprehensive "research map" to provide guidance for researchers and policymakers in understanding the mathematical model landscape for the COVID-19 pandemic.

2. METHOD

2.1 Research Approach

This study uses a *Systematic Literature Review (*SLR) approach, or more specifically, a *Systematic Mapping Study*. The aim is to comprehensively identify, categorize, and synthesize the existing academic literature on SEIRS mathematical modeling (and its variants) that specifically includes vaccination interventions for the COVID-19 pandemic.
This methodology is designed to answer the main research question: "What is the methodology landscape, key findings, and challenges in the mathematical modeling of SEIRS-COVID-19 vaccination?" This review process adopts the PRISMA framework [26] to ensure transparency and *repeatability of* the selection process.

2.2 Search Strategy and Selection Criteria

The process of collecting articles is carried out in two stages: identification and screening.
Identification: Literature searches are conducted on major academic databases, including *Scopus, Web of Science, PubMed/MEDLINE, Google Scholar,* as well as *pre-print servers* such as *arXiv* and *medRxiv* to cover the latest research. The search is limited to articles published between January 1, 2020, and early 2024. Keyword combinations used include (but do not include): ("COVID-19" or "SVEIR" or "SEIQR") and ("vaccination" or "vaccine" or "immunization").
Screening and *Eligibility*: The initial search yielded a total of 80 articles (as we have collected) that are generally relevant. These articles are then manually screened based on strict inclusion and exclusion criteria.

a. Inclusion Criteria:

1) The article must be a primary mathematical model (using ODE, PDE, SDE, or other computational approaches).
2) The model must be based on the SEIR or SEIRS framework (including variants such as SEIQR, SEIAR, SVEIR, etc.).
3) The model should explicitly include vaccination as a parameter, compartment, or control variable.
4) The context of the research must be specific to the COVID-19 pandemic.
5) Articles must be *full-text* accessible (including reputable *peer-reviewed* and *pre-print* journals).

b. Exclusion Criteria:

1) Articles that are not a primary model (e.g., review articles, editorials, or philosophical criticism articles).
2) The SEIR model focuses only on non-pharmaceutical interventions (NPIs) such as *lockdowns,* masks, or *social distancing* [27, 28].

3) Non-COVID SEIR/SIRS models (e.g., for influenza, measles, or other diseases) [29, 30].
4) A model where the 'V' does not stand for Vaccination (e.g., *Viral load* in wastewater) [31].

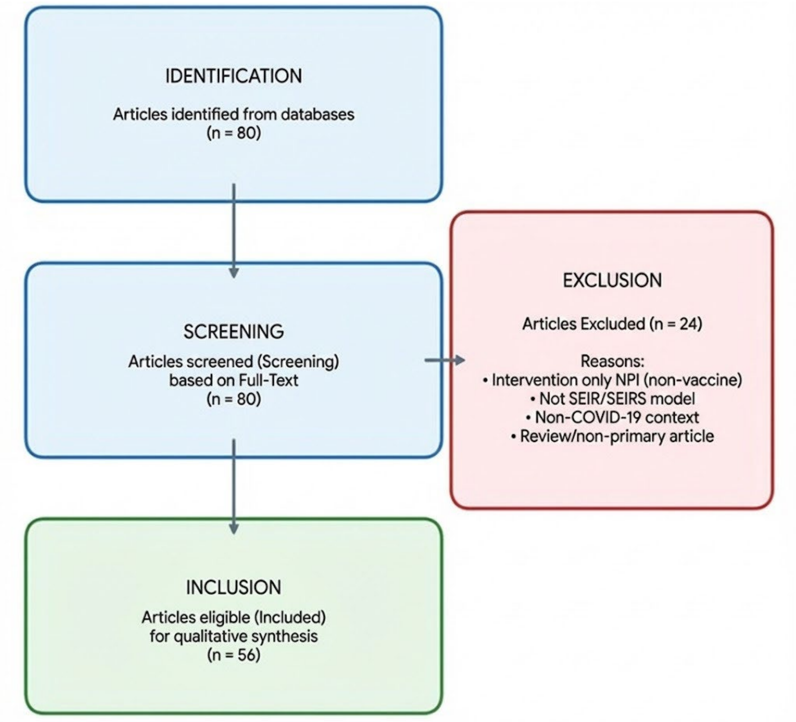

Figure 1. Prism Flowchart SEIRS Research Map-COVID-19 Vaccination

The results of the literature selection showed a high level of relevance in the initial search, where 70% (56 out of 80) of the identified articles successfully met the strict inclusion criteria. The elimination of the remaining 24 articles was carried out to ensure the validity of the focus of this research. The majority of excluded articles were studies that only modeled non-pharmaceutical interventions, such as quarantine or social distancing, without explicitly including vaccination parameters, or used a model approach that was neither SEIRS nor SEIR compartment-based.

This rigorous screening process resulted in 56 articles that met all the inclusion criteria and formed the basis for the analysis in this study.

2.3 Extra Data and Synthesis Analysis

All 56 articles that passed were analyzed, and data were extracted based on five main dimensions, which were inspired by the initial draft of the study:

Core methodology: Mathematical approaches used (e.g., Deterministic-ODE, Optimal Control, Fractional Order, Data Assimilation/Stochastic, Special-PDE).

1) Model Structure: The specific compartment used (e.g., additions V for Vaccination, A for Asymptomatic, Q for Quarantine, or age-structured sub-compartments).
2) Vaccination Implementation: How vaccination is modeled (e.g., as a content rate v from $S \rightarrow V$, Speed Control $u(t)$, or as a transfer $S \rightarrow R$).
3) Waning Immunity: There is a relapse from $R \rightarrow S$ or $V \rightarrow S$.
4) Key Findings: The most sensitive parameters, the values R_0 or R_{eff} that are calculated, and key policy conclusions.

The extracted data is then qualitatively synthesized to identify patterns and trends. From this synthesis, we identify 5 main categories of methodology that are dominant in the literature. For in-depth comparison and the compilation of the "Research Map" in this article, two representative articles were selected from each category (a total of 11 core articles) to be analyzed in detail in the Results and Discussion section.

3. RESULTS AND DISCUSSION

A systematic analysis of 56 relevant articles identified significant methodological diversity. Research trends show a shift from classical deterministic models to more complex approaches to addressing pandemic-specific challenges, such as data uncertainty, new variants, and optimal intervention strategies.

To map this landscape in detail, 11 representative articles were selected using purposive sampling techniques. The selection of this sample was based on the representative criteria of the five main methodological categories identified, in which the two best articles from each category were taken to ensure the balance of the analysis, plus one non-pharmaceutical intervention model as a comparative control of validity. The literature selection process in this study follows the Systematic Literature Review (SLR) protocol with the PRISMA flow. In the initial identification stage, as many as 80 potential articles were collected from various leading academic databases, covering the publication time span from the beginning of the pandemic to the present. All of these articles then went through the screening and eligibility stages thoroughly. 24 articles were excluded (eliminated) because they did not meet the inclusion criteria that had been set. The main reasons for exclusion include: articles that only model non-pharmaceutical interventions (NPIs) without including vaccination parameters, the use of models that are not based on the SEIR/SEIRS framework, or the context of studies that are not specific to the COVID-19 pandemic. After the elimination, 56 articles were declared eligible (included) for further analysis. These 56 articles are grouped into five main methodological categories and synthesized to produce this research map. The comparative findings are presented in Table 1.

3.1 Comparative Research Map of the SEIRS-COVID-19 Vaccine Model

Table 1. SEIRS Model Comparative Research Map- COVID-19 Vaccination

Category	Article (Author, [citation])	Model Structure & Intervention (Vaccination, v)	Key Methodology	Focus Analysis & "Solution Formula" Key
Deterministics (ODE)	Y. A. Terefe and T. A. Tegegn [2]	SEIR Age-Structured (16 age groups). $v_i(t)$: Vaccination rate per age group i	Deterministic ODE, Parameter Estimation	Impact estimation R_t and death. Focus on vaccine allocation priority strategies (e.g., targeting the elderly vs. spreaders).

	Y. Hou and H. Bidkhori [3]	SEIRS-V (S-E-I-R-S with compartment V). v: Vaccination rate (S→V).α: It's a quick powder ($R \to S$ and $V \to S$).	ODE Deterministic , Stability Analysis.	Stability analysis globally uses the Lyapunov function. Focus on R_0 and R_v (Reproductive number with vaccination).
	Misri et al. [1] (Comparison of NPIs)	SEIR (6 compartments). Intervention u: Rate of hand sanitizer use (S_1→ S_2, I_1→I_2).	Deterministic ODE Stability Analysis.	Equilibrium stability analysis (disease-free & endemic) using the Next Generation Matrix (NGM) to R_0 .
Control Optimal (ODE)	Y. Hou and H. Bidkhori [4]	SEIR (7 compounds). Control u_v (t): Vaccination rate (S→V). Control u_m(t): Use of masks.	Optimal Control Theory, Pontryagin Maximum Principle (PMP).	Look for $u_v(t)$ optimal to minimize *I*, and the cost of the "Formula of completion" is the Hamilton system and control characteristics.
	N. Nadia et al. [5]	SEIR (7 compartments). Control $u(t)$: Vaccination rate.	Optimal Control Theory (PMP), Sensitivity Analysis.	Determine the Optimal Vaccination strategy (Constant vs. gradual) and parameter sensitivity.
Order Fractional	N. Saidi and A. Radid [6]	SEIRS (with non-linear incidence). v: Vaccination rate (S→R).α: It's a fast-paced (R→S).	Fractional Calculus (Caputon D^α). Global Stability Analysis.	Using the Lyapunov function for fractional systems. Focus on how the order (memory effect) affects the stability of the model.
	Pan et al. [7]	SEIR (6 compartments). Control u_1 (t): Vaccination rate.	Hybrid: Fractional Calculus (Caputon D^α)	Looking for a strategy $u_1(t)$ and $u_2(t)$ optimal for fractional order

		Control $u_2\ (t)$: Pengobatan.	+ Optimal Control (PMP).	models. Shows better control over $\alpha < 1$.
Data Assimilation / Stochastic	Sun et al. [8]	SEIR-H-R-D: (The model is deterministic, but updated with data).	Data assimilation (Ensemble Kalman Filter - EnKF).	Dynamic parameter estimation (R_t). Using daily observation data (cases, deaths) to correct the state of the model in real-time.
	Tello et al. [9]	Special SEIR (PDE) Intervention $v(t)$: Vaccination rate (discussed in Remark 2).	State Observer for PDE systems.	Real-time estimation of unobserved compartments (e.g., E and I using observed data (e.g., R).
Spatial (PDE)	Bounkaicha & Allali [10]	SEIRS (with saturated incidence). v: Vaccination rate (P_1S).	Hybrid: Fractional Calculus (Caputo D^α) + Spatial (PDE, Δ).	Global stability analysis for fractional PDE models. Focus on the impact of spatial diffusion ($\delta_i\Delta$) and fractional order α at R_0.
	El Alami Laaroussi et al. [11]	Multi-Strain SEIR (Spacial). Control $v\ (t,z)$: Vaccination. $w_i(t,z)$: Pengobatan.	Hybrid: Spatial (PDE, Δ) + Optimal Control (PMP).	Finding a spatially optimal control strategy $v\ (t,z)$ (vaccination where and when) with limited resources (integral constraints).

3.2 Trend Analysis and Findings

Table 1 not only maps the research landscape but also uncovers some fundamental trends and paradigm shifts in epidemic modeling.

3.2.1 Paradigm shift: From R_0 Static to Dynamic Estimation $R(t)$

The most significant trend identified according to the initial hypothesis [32] was the shift in focus from static stability analysis to dynamic parameter estimation.

1. Classical Approach (Deterministic): Models in category 1 (Deterministic) [1 - 3] determination of Basic Reproduction Numbers (R_0), usually using the Next Generation Matrix (NGM) method [1]. The goal is to prove that if $R_0 < 1$, the disease will disappear (global stability), and if R_0 >1, the disease will become endemic. R_0 In this model, there is a single scalar value calculated from the model parameters that are assumed to be constant.
2. Real-Time Approach (Data Assimilation): In contrast, models in category 4 [8, 9] overcome the challenge that real-world parameters are not constant. The Ensemble Kalman Filter (EnKF) approach used by Sun et al. [8] does not focus on R_0 Theoretical. Instead, it uses fluctuating daily case data to dynamically correct the state model (e.g., the "true" number of E and I) and estimate the Effective Reproduction Number (R_t), which changes from time to time. These findings validate the initial hypothesis [32] that modern models are shifting from R_0 static to R_t dynamic forecasting for real-time forecasting.

3.2.2 The Challenge of Realism: Overcoming the Limitations of ODE

The classic ODE model (category 1) has been criticized for oversimplifying reality [12]. The 55 articles reviewed show two main mathematical "solutions" to this challenge:

1. **Memory Effects:** The standard ODE model is Markovian, meaning that the rate of change depends solely on the moment. The Fractional Order Model (category 3) [6, 7] replaces the standard derivative $\frac{d}{dt}$ with the Caputo operator, D^{∞}. As Saidi & Radid [6] have shown, the use of fractional orders $a < 1$, allows the model to include a "memory effect", where future dynamics also depend on past statuses, which are believed to be more biologically realistic
2. **Spatial Dynamics:** The ODE model assumes a well-mixed population. Spatial/PDE models (category 5) [10, 11] address this by adding Laplacian operators (triangle symbols). As Bounkaicha & Alali [10] point out, their ”solution formulas” do not only include t (time) but also z (space). This model can predict how diseases diffuse geographically from one region to another, a feature that is not possible in non-spatial ODE models.

3.2.3 Evolution of Goals: From Prediction to Recommendation (Optimal Control)

A major shift is seen in the model's purpose. Category 1 and 3 models aim to *predict* ("what would happen if..."). Instead, the Optimal Control Model (category 2) seeks to *recommend* ("what should we do?")

Articles such as Sigh & Kumari [4] and M.E.H.S. et al. [5] using the maximum principle of Pontryagin (PMP) to find the vaccination rate $u(t)$ optimal. Their "solution formula" (the Hamiltonian system) mathematically balances two conflicting goals: minimizing the number of infections (I) and minimizing the "cost" of intervention (e.g., the cost of vaccine procurement and side effects). These findings refute the initial assumption [32] that optimal control is a "research gap", and instead confirm that this is an established and widely used category of methodology.

3.2.4 Framework Flexibility: Vaccination (Pharmaceutical) vs. Hand Sanitizer (NPI)

The Discussion should interpret the results, exploring their implications, limitations, and how they compare to existing research. Authors should evaluate whether the findings align with theoretical expectations or empirical trends, ensuring that conclusions are well-supported by the data. Furthermore, this section should highlight the novelty and accuracy of the solutions provided, reinforcing their significance in advancing mathematical knowledge.

A comparison between the vaccination model [3] and the NPI model [1] in Category 1(ODE) shows the flexibility of the SEIR framework. Both studies used identical mathematical tools (ODE stability analysis, NGM for R_0).

1. Vaccination Model [3]: Intervention v reduce the number of Susceptible ($S \rightarrow V$). The findings focus on the verge vaccination limit to achieve herd immunity.
2. Model Hand Sanitizer [1]: Intervention u Rute transmission rate (moving individuals to the "conscious" S_2 and I_2 with a contact rate lower). The findings focus on the effectiveness of compliance with health protocols.

This shows that the framework mathematical SEIR is robust, where the "solution formula" (stability analysis) stays the same, despite the interpretation biological and policy from the parameters are very different.

4. CONCLUSION

Systematic literature review of 56 SEIRS modelling articles (and their variants) for COVID-19 vaccination has succeeded in mapping the diverse landscape of research and has evolved rapidly. Research map (Table 1) informs that there is no monolithic single approach; instead, researchers have adopted a five-category methodology mainly for answering the challenge-specific challenges caused by the pandemic.

Key findings from this study are the existence of a paradigm shift, clear methodology, moving away from deterministic (ODE) focused classics on the analysis stability R_0 static [1 - 3] towards a more dynamic and complex approach [12, abstract]. This shift is driven by necessity, insisting on realistic models and relevance policy. Specifically, we identify the following trends.

1. **From R_0 Static to R_t Dinamis:** There is a shift from calculations R_0 theorists (using NGM) [1, 3] to estimate R_t (Effective Reproduction Numbers), in real-time. Data assimilation methods, like Ensemble Kalman Filter (EnKF) [8], have proven to be capable of dynamically correcting parameters that the model uses to obtain observational data daily for more accurate forecasting.
2. **From Prediction to Recommendations:** Modeling objectives have evolved from just predicting the spread to recommending intervention strategies. Category Control Optimal [4, 5, 7,11] using the Pontryagin Maximal Principle (PMP) to mathematically determine the most efficient vaccination, balancing maximization of infection with intervention costs.
3. **Overcoming ODE Simplification:** To overcome the limitations of assumptions "mix-perfect" and "no-memory" roam the classical ODE, two advanced approaches emerged:
   a. Spatial Model (PDE) [10, 11] that models geographic diffusion.
   b. Fractional Order Model [6, 7], which enters "memory effects" (non-Markovian) into the dynamics of transmission.
4. **Framework Flexibility:** The mathematical framework SEIR (stability analysis, NGM) has proven to be very flexible. The same tool is used to analyze the effectiveness of pharmaceutical interventions. (vaccination v) [2] as well as non-pharmaceutical interventions (NPIs, such as hand sanitizer) [3]. Based on the findings and identified gaps, future research is suggested to focus on hybrid models. As shown in Table 1, recent articles that are the most innovative are those that combine the strengths of different categories, like:

a. Spatial (PDE) + Optimal control [11]
b. Fractional Order + Optimal Control [7]
c. Spatial (PDE) + Fractal Order [10]

Development of hybrid models (e.g., Stochastic – Spatial – Optimal Control) that combine real–time forecasting accuracy (Data Assimilation) with policy relevance (Control Optimal) and spatial realism (PDE) is the most promising research direction for defining a resource allocation strategy that is the most efficient in dealing with the pandemic in the future [32].

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