International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Methods Used to Estimate Relative Vaccine Effectiveness for Seasonal Respiratory Viruses: A Scoping Review Protocol

INPLASY202670092
doi: 10.37766/inplasy2026.7.0092
Received: 24 July 2026
Published: 24 July 2026

Roser, M; Martin, B; Smoll, N; Lau, C.

Corresponding author:
Madisen Roser

madisen.roser@uq.edu.au

Author Affiliation:
Frazer Institute, University of Queensland; Sunshine Coast Public Health Unit, Queensland Health.

ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - Nicolas Smoll has received research and educational grants from Pfizer and Moderna. He has not received travel or speaker fees from these companies.

INPLASY registration number: INPLASY202670092

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 July 2026 and was last updated on 24 July 2026.

INTRODUCTION

Review question / Objective This scoping review aims to identify the strengths and limitations of current relative vaccine effectiveness (rVE) estimation methods for COVID-19, influenza, and respiratory syncytial virus (RSV). The key elements of this review are defined according to the population, concept, and context framework. The population comprises individuals receiving vaccines against specified respiratory viruses. The concept encompasses the methods used to estimate rVE against severe disease, including study design, statistical approaches, adjustment methods, and comparator definitions (e.g., comparison between different vaccine formulations). The context is limited to real-world observational studies published within the past decade. The objectives of this review are to (1) identify and evaluate the rVE estimation methods used, (2) identify and evaluate how antigenic distance is incorporated in current rVE estimation methods, (3) identify key factors that impact the validity and comparability of rVE estimates and, (4) identify opportunities for future methodological improvements in rVE estimation.

Background Seasonal respiratory infections, such as influenza, COVID-19 and respiratory syncytial virus (RSV), are unique from other vaccine preventable diseases due to ongoing viral mutation and waves of exposure in the population, unlike relatively antigenically stable pathogens such as hepatitis A. This rapid viral evolution makes common respiratory infections vulnerable to greater antigenic distance (AD). AD refers to the degree of alignment between the vaccine and the circulating variant or strain of a pathogen. Higher AD can result in suboptimal vaccine-derived protection due to poor immune recognition upon infection. In the context of rapid viral evolution and dynamic population immunity, AD is a highly relevant consideration for vaccine evaluation.

Rationale The population experiences dynamic immunity against seasonal respiratory viruses

through vaccination and/or infection. The rVE framework allows for such comparisons, accepting the varying immunological experience of the host. Specifically, rVE estimates the incremental protection associated with one vaccine exposure, formulation, or immunological state relative to another. rVE can be estimated using a range of methods, each with different assumptions, strengths, and limitations. A scoping review of rVE estimation methods is therefore warranted to characterise how these analytical approaches have been defined, implemented, and interpreted within existing respiratory virus literature.

METHODS

Strategy of data synthesis The databases that will be searched are PubMed, Embase, Scopus and Web of Science. Each of the search terms will be restricted to a title/abstract search. Example search terms (PubMed):
("Respiratory Syncytial Virus,Human"[Mesh] OR RSV[tiab] OR "Respiratory syncytial virus"[tiab]
OR
COVID19[tiab] OR COVID-19[tiab] OR COVID-19[Mesh] OR "COVID-19 Vaccines"[Mesh] OR SARS-CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR SARS-CoV2[tiab] OR sars-cov-2[Mesh] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[tiab] OR "2019 NCOV"[tiab]
OR
"Influenza, Human"[Mesh] OR influenza*[tiab] OR flu[tiab] OR h1n1[tiab] OR h3n2[tiab])
AND
((vaccine*[tiab] OR vaccinat*[tiab])
AND
("relative effectiveness"[tiab] OR "relative vaccine effectiveness"[tiab] OR "relative VE"[tiab] OR rVE[tiab] OR "relative protection"[tiab] OR "comparative vaccine effectiveness"[tiab] OR "comparative effectiveness"[tiab] OR "marginal vaccine effectiveness"[tiab] OR "marginal effectiveness"[tiab] OR "incremental vaccine effectiveness"[tiab] OR "incremental effectiveness"[tiab] OR "incremental protection"[tiab] OR "incremental benefit"[tiab] OR "additional effectiveness"[tiab] OR "additional vaccine effectiveness"[tiab:~1] OR "additional protection"[tiab] OR "additional benefit"[tiab] OR "booster effectiveness"[tiab])).

Eligibility criteria Studies will be eligible for inclusion if they report estimates of rVE. Studies reporting both vaccine effectiveness (VE) and rVE will be included where the rVE component can be identified and extracted. Cost-effectiveness or economic evaluation studies will also be eligible if they include an rVE estimate. Eligible studies will be published between 2016 and 2026, focus on influenza, COVID-19, or RSV, and be available as full-text articles. Only primary, observational research conducted in human populations of any age and from any geographic region will be included. Studies will be required to examine disease severity outcomes, including hospitalisation, intensive care unit (ICU) admission, and/or mortality, and to employ generalised linear modelling methods for rVE estimation. Studies will be excluded if they report immunogenicity, serological or other biological response outcomes without estimating rVE. Additionally, conference abstracts, any publication that is not primary research, studies which are not observational, and studies using methods other than generalised linear modelling for rVE estimation will be excluded. Only English publications will be considered.

Source of evidence screening and selection Two reviewers will independently screen the title and abstract according to the exclusion criteria. Key criteria considered at this stage include disease/outcome, study design and publication type. Studies for which eligibility is unclear at initial screening will progress to full-text review. The full-text review will confirm if the article meets the inclusion criteria and has relevance to the research question. Any disagreements regarding study eligibility will be resolved through discussion and consensus. If consensus cannot be reached, an additional reviewer will be consulted to determine the final decision. Reasons for exclusion following full-text review will be documented.

Data management All articles will be stored in Zotero (for reference management) and Covidence (for de-duplication, screening and data extraction). Data will be extracted into an Excel spreadsheet. The Excel spreadsheet will be developed with input and agreeance from both reviewers. Extracted data will be stored securely on password-protected institutional servers in accordance with relevant data management and security requirements. No sensitive or personal data will be handled in the conduct of this scoping review.

Reporting results / Analysis of the evidence A descriptive analysis will identify common study characteristics and analytical rVE estimation approaches. Methodological appraisal will be guided by numerous sources, including the strengthening the reporting of observational studies in epidemiology (STROBE) checklist (for reporting quality), the target trial emulation

framework (for causal study design), and WHO guidance for real-world vaccine effectiveness studies (for methodological best practice). The strengths, limitations, and knowledge gaps in the existing literature will be identified and discussed.

Presentation of the results Descriptive results will be summarised using counts and percentages. Findings will be presented using summary tables and visualisations where appropriate, including bar charts, Sankey diagrams, and temporal trend plots.

Language restriction English only.

Country(ies) involved Australia.

Keywords relative vaccine effectiveness; influenza; COVID-19; respiratory syncytial virus; RSV; antigenic distance; methods.

Contributions of each author

Author 1 - Madisen Roser - Contributed to research question development, protocol design, methodology development, analysis plan development, manuscript draft preparation, manuscript review and editing, and protocol registration.
Email: madisen.roser@uq.edu.au
Author 2 - Beatris Martin - Contributed to protocol design and refinement, analysis plan development, and manuscript review and editing.
Email: beatris.martin@uq.edu.au
Author 3 - Nicolas Smoll - Contributed to research question development, protocol refinement, manuscript review and editing, and supervision.
Email: nicolas.smoll@health.qld.gov.au
Author 4 - Colleen Lau - Contributed to research question development, protocol refinement, manuscript review and editing, and supervision.
Email: colleen.lau@uq.edu.au