Design and Pilot Testing of a Resource to Assess Risk of Bias in Observational Studies Estimating Vaccine Effectiveness

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i. Abstract

This master's thesis addressed three interrelated research objectives aimed at identifying gaps in the assessment of risk-of-bias (RoB) in observational studies of vaccine effectiveness (VE) and proposing a draft framework for evaluation in the next phases of an ongoing research project. First, I mapped existing RoB tools used in systematic reviews of VE studies (Chapter II). The findings revealed that although RoB assessments are routinely conducted, there is considerable variation in the choice of tools used and their application, many of which were not specifically designed to address VE-related biases. Second, I identified and synthesized key bias concepts relevant to VE estimation and created a framework (Chapter III). I found that most bias concepts fell under three broad categories: confounding bias, selection bias, and information bias, though several cross-cutting biases also emerged. Third, I piloted a consensus-based survey designed to evaluate the framework and its components with the goal to assess its readiness, feasibility and appropriateness for international application (Chapter IV). Collectively, this thesis contributed to the early stages of a larger, ongoing research project focused on developing a new RoB resource for assessing biases in observational studies of VE.

ii. Acknowledgements

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iii. List of Abbreviations

RoB	Risk-of-Bias
VE	Vaccine Effectiveness
RCT	Randomized Controlled Trial
SR/MA	Systematic Review and Meta-Analysis
CIS	Critical Interpretive Synthesis
TND	Test-negative Design
NOS	Newcastle-Ottawa Scale
ROBINS-I	Risk of Bias in Non-randomised Studies of Interventions
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
AHRQ	Agency for Healthcare Research and Quality
QATSDD	Quality Assessment Tool for Studies with Diverse Designs
NIH	National Institutes of Health
NHLBI	National Heart, Lung and Blood Institute
CHERG	Child Health Epidemiology Reference Group
SIGN	Scottish Intercollegiate Guidelines Network
JBI	Joanna Briggs Institute
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PRESS	Peer-Review of Electronic Search Strategies
CAD-AMC	Canadian Drug Agency
PCC	Population-Concept-Context
OR	Odds Ratio
RR	Risk Ratio

HR	Hazard Ratio
IRR	Incidence Rate Ratio
DOR	Diagnostic Odds Ratio
HCP	Healthcare Provider
WHO	World Health Organization

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Chapter I: Introduction

Infectious diseases have long been a major cause of illness and death worldwide, particularly affecting vulnerable populations such as children, pregnant individuals, and older adults (1). The introduction and widespread adoption of routine vaccination have dramatically reduced this burden, transforming public health outcomes across diverse settings (1). The benefits of immunization are evident globally, from reducing childhood mortality and curbing the spread of diseases like measles and pneumococcal infections, to protecting older adults from threats such as respiratory syncytial virus and influenza (2). Over 1974–2024, WHO's Expanded Programme on Immunization is estimated to have averted 154 million deaths from 14 major infectious diseases (3).

Vaccines not only prevent millions of deaths and severe illnesses each year but also alleviate pressure on healthcare systems, reduce economic losses associated with outbreaks, and improve productivity by preventing premature deaths and prolonged illness (1,2). Canada's COVID-19 vaccination program exemplifies this impact, generating an estimated $222 billion in economic gains primarily by preventing premature deaths (4,5).

While vaccines are highly effective, they rarely provide lifelong or complete immunity. Assessing their real-world impact has become increasingly complex due to factors like waning immunity, emerging variants, and diverse population responses. These complexities underscore the need for high quality evidence to guide public health policy, allocate resources, and maintain public trust in immunization programs (6).

Vaccine effectiveness (VE) refers to the proportional reduction in disease outcomes, such as infection, illness, hospitalization, or death among vaccinated individuals compared to unvaccinated individuals under real-world conditions (7). VE can be influenced by a complex interplay of factors (Figure 1-1) related to the recipient, the vaccine, the environment, and the pathogen (5,6). Characteristics of the vaccine recipient, such as age, immune status, history of prior infections, concurrent medications, and social determinants of health, can all impact how well a vaccine works (5). Vaccine-related

factors, including type, dosage, timing and modality of administration, and whether vaccination occurred during an epidemic, also play a role (5). Environmental factors like exposure intensity, herd immunity, along with pathogen-related elements such as strain variation and vaccine-pathogen match, can also influence VE (5). Furthermore, accurately assessing a vaccine's real-world effectiveness depends on reliable methods of infection confirmation, well-defined outcome measures, careful control group selection, and robust strategies to reduce bias (7).

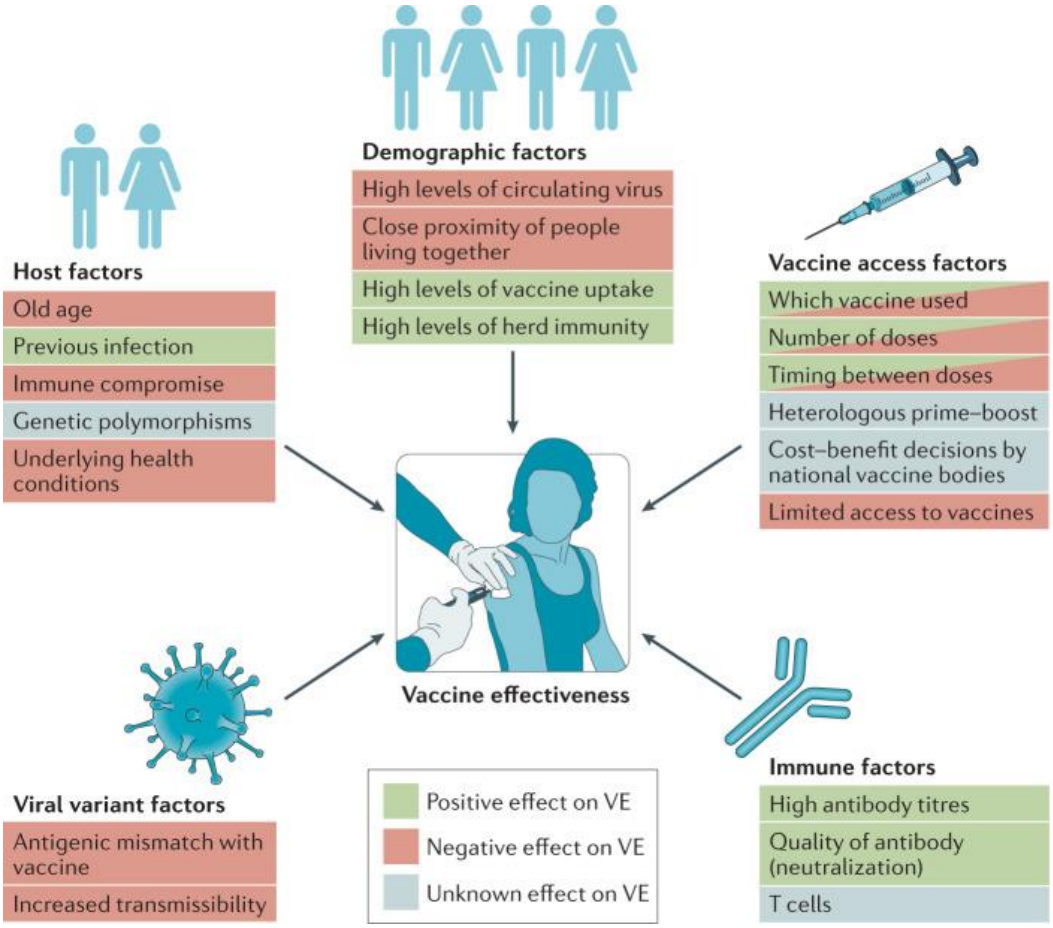

Figure 1-1 Factors affecting vaccine effectiveness (5)

Vaccine efficacy and vaccine effectiveness, while related, are distinct concepts that are sometimes used inconsistently in the literature (Figure 1-2). Vaccine efficacy measures how well a vaccine prevents disease under controlled conditions, typically in clinical trials, while vaccine effectiveness refers to its performance in real-world settings, considering factors like health status and adherence to dosing schedules (8). While clinical trials are

considered the gold standard for evaluating vaccine efficacy, ethical concerns can sometimes limit their use. For example, it would be unethical to withhold a licensed vaccine from individuals who are at high. In such cases, observational studies become essential for assessing VE in real-world settings. These studies allow researchers to evaluate how vaccines perform across diverse populations and settings that may not be fully represented in clinical trials. Factors such as geographic variation, underrepresentation of certain groups (children and pregnant individuals), challenges with vaccine storage and transport (cold-chain issues), incomplete vaccination, incorrect dosing, and the emergence of new variants can all influence real-world vaccine effectiveness, highlighting the importance of observational research in VE (7,8).

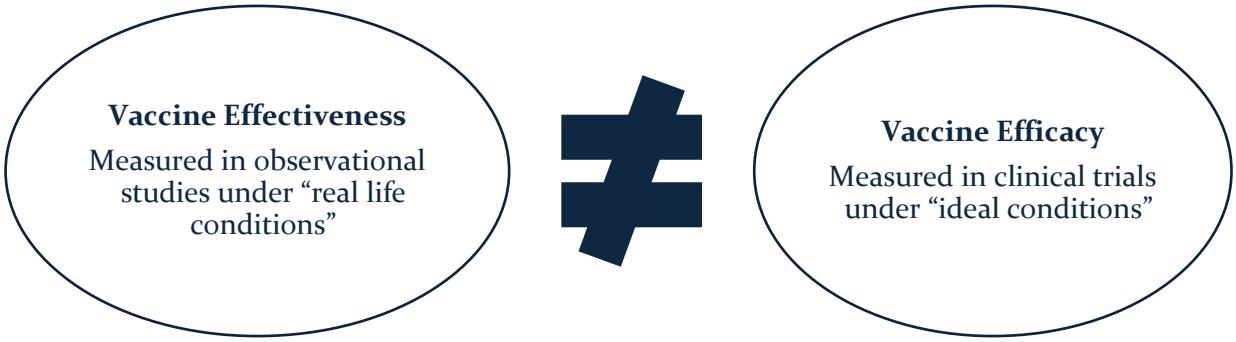

Figure 1-2 Vaccine Effectiveness vs. Vaccine Efficacy

1.1 Observational VE Studies: Key Methodological Challenges

While randomized controlled trials (RCTs) are the gold standard, observational studies offer advantages like larger sample sizes and real-world applicability, making them valuable for evaluating rare and long-term outcomes, and for situations where RCTs are unethical or infeasible. However, observational studies of VE are inherently more susceptible to bias than RCTs due to their lack of randomization and controlled conditions, making it challenging to establish causal relationships. Bias refers to systematic errors in study design, conduct, or analysis that can distort the estimates or results (7). These biases include confounding from known and unknown factors, temporal concerns in determining exposure vs. outcome status, and unique issues like healthy vaccinee bias and healthcare-seeking behavior bias (5,7).

Healthy vaccinee bias and healthcare-seeking behaviour bias are closely related and important sources of selection bias in observational VE studies (9). Healthy vaccinee bias occurs when individuals who choose to be vaccinated are generally healthier, experience fewer comorbidities, have better baseline health, and are more apt to engage in healthcare-seeking behaviors (10). This can lead to an overestimation of VE. These biases are especially difficult to address in older adults where it is difficult to accurately measure and adjust for common characteristics such as frailty, poorer outcomes and lower vaccine uptake (10,11).

Additionally, observational studies employ a range of specific designs, each with distinct methodological strengths and limitations that can influence the accuracy and interpretation of VE estimates (6,7,10). While VE is often assessed using retrospective data, cohort and case-control studies remain the most used designs. Among these, the test-negative design (TND) – a special type of case-control design – has emerged as a prominent and widely adopted approach (12). Table 1-1 summarizes the key strengths and limitations of a select popular study designs for measuring VE in observational studies.

Table 1-1 Summary of Key Strengths and Limitations of Different Study Designs in Observational VE Research (6,7,10)

Study Design	Strengths/Benefits	Limitations/Challenges
Cohort	• Can estimate incidence rates between vaccinated/unvaccinated • Easily interpretable by policymakers due to direct risk comparisons	• Difficulty in accounting for changing vaccination status over time • Healthcare-seeking behaviour bias
Case-control	• Efficient for rare outcomes • Can be conducted retrospectively using existing data	• Recall bias if vaccination self-reported • Challenge in selecting appropriate controls (e.g., healthcare-seeking behaviour bias) • Cannot measure incidence rates between vaccinated/unvaccinated
Cross-sectional	• Cost-effective for large sample sizes • Useful for hypothesis generation (i.e., to establish an association)	• Cannot establish temporal association between vaccination and outcome • Can overestimate VE if study conducted during peak transmission periods • Limitations in studying waning immunity (i.e., duration of protection)
Test-Negative Design	• Useful for real-time surveillance and rapid evaluation • Controls drawn from same care-seeking population as cases	• Sensitive to testing accuracy and practices, and case definitions • Potential for misclassification if vaccination affects symptom severity or testing decision • Reduces bias from healthcare-seeking behaviour
Screening Method	• Cost-effective for large sample sizes	• Dependent on accuracy of population vaccine coverage estimates

Study Design	Strengths/Benefits	Limitations/Challenges
	• Useful for real-time surveillance and rapid evaluation	• Susceptible bias due to misclassification of vaccination status • Limited ability to control for confounding factors

Systematic reviews, rather than individual studies, serve as the cornerstone for public health policy and funding decisions by providing a comprehensive, synthesis of the available evidence. Systematic reviews and meta-analyses of VE studies face additional challenges, as they must synthesize data from multiple studies that may each be subject to different types and degrees of bias (13). Variability in study design, population characteristics, case definitions, and outcome measures can introduce heterogeneity, making it difficult to draw consistent conclusions (13,14). Moreover, biases such as misclassification, selection bias, and confounding present in individual studies can accumulate or even amplify when pooled in meta-analyses, leading to potentially misleading summary estimates (11,13–15). The presence of publication bias, where studies with significant or favorable results are more likely to be published, can further distort the overall picture (7). As a result, systematic reviews and meta-analyses must carefully assess the quality and risk-of-bias (RoB) in included studies, report limitations with transparency, and interpret pooled VE estimates with caution to avoid overconfidence in their findings.

1.2 Research Gaps in Risk-of-Bias Assessment

The research design of a published study is insufficient in isolation to determine its limitations; the specific design and execution elements can vary widely across studies using the same design. As a consequence, a thorough and context-specific evaluation of individual observational studies is essential to determine the credibility of their findings. Recommendations for best practices include clearly defining types of bias to be assessed; using study design–specific criteria; allowing for outcome-specific bias ratings; and avoiding the conflation of poor reporting with bias (16). RoB evaluations should inform sensitivity analyses, interpretation of effect estimates, and grading of the evidence (17). Ultimately, systematic reviews must use transparent and methodologically rigorous

approaches to assess RoB, tailored to the design and context of each study, to ensure credible and actionable conclusions. Standardized tools and independent reviewers help ensure consistency and reliability in RoB evaluations, which is essential for producing accurate and reproducible results.

Current tools for assessing risk-of-bias in individual studies vary in approach. Some approaches focus on reported methods, while others evaluate actual study conduct; but all face challenges due to the lack of standardized protocols and the limitations of reporting-based assessments (6,13). For instance, the Newcastle-Ottawa Scale (NOS) is widely used for non-randomized studies, valued for its simplicity and adaptability across study designs. It provides clear guidance for assessing RoB in domains such as selection, comparability, and outcome assessment (16). However, the NOS has limitations, including a lack of explicit consideration for confounding or selective reporting and the absence of an overall RoB score. Consequently, it is challenging to compare studies directly or to get a sense of the body of the evidence. In contrast, the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool is more comprehensive for non-randomized studies, addressing various domains of bias, including confounding and reporting bias, but it is more complex and time-consuming to apply. It also does not provide a single threshold for assessing missing data, unlike the NOS, which sets a threshold (16). The choice of which tool to use is important in evidence synthesis, as different tools may categorize studies differently, which can impact overall confidence in results (6,13).

There are additional challenges related to the application of existing tools. Tools like NOS assign equal weight to all domains, which may not always be appropriate, as a single flaw can substantially increase the RoB. Additionally, some tools are not applicable to certain observational study designs, such as cross-sectional studies or case series, prompting the development of ad hoc appraisal tools, which may lack the rigor and consistency of the tools (16). Moreover, users of these assessment tools may be less familiar with the specific operationalization of RoB concepts unique to the specific context such as VE studies. Ultimately, the proper selection, operationalization and application of RoB tools are

essential for ensuring that systematic reviews use the best available evidence, leading to reliable conclusions that can inform clinical and policy decisions.

1.3 Thesis Objectives

This thesis is part of a broader, ongoing research project that aims at creating, validating, and disseminating a comprehensive, reliable, and user-friendly RoB assessment tool designed specifically for systematic reviews of VE studies (RoB-VE). While Figure 1-3 outlines the full development process, this thesis represents preliminary work contributing to the early phases of the project. In this manuscript-based thesis, I will address three objectives:

1. Map existing RoB tools that have been used in systematic reviews of VE studies.
2. Identify key bias concepts and concerns that are relevant to VE estimation.
3. Generate a comprehensive list of bias-related items and pilot a consensus-based survey to gather expert feedback.

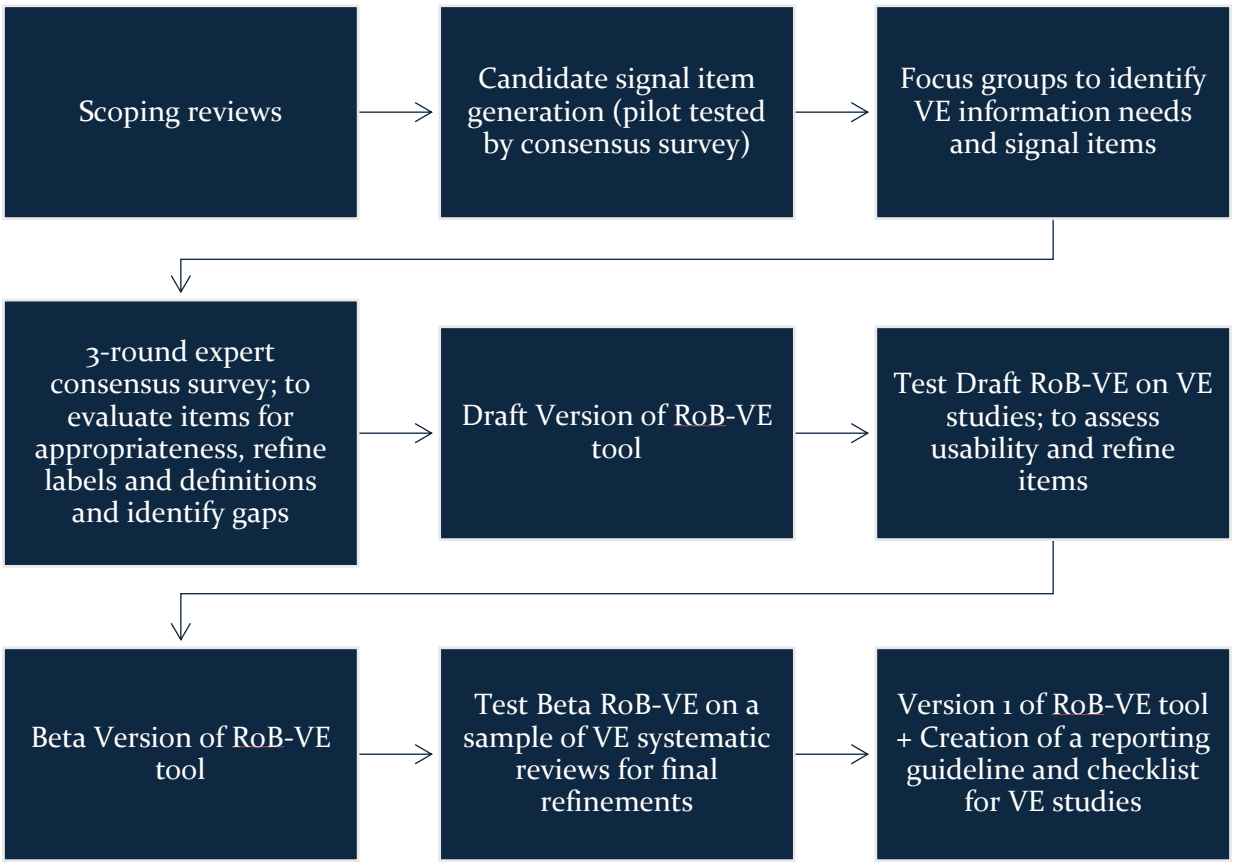

Figure 1-3 Summary of RoB-VE Project Objectives

1.4 Thesis Structure

This thesis is presented in a manuscript-based format and includes three main components:

Chapter II: Risk-of-Bias Tools in Systematic Reviews of Vaccine Effectiveness Studies: A Scoping Review

This chapter presents a scoping review manuscript that maps existing risk-of-bias (RoB) tools applied in systematic reviews of VE studies and assesses their scope, content, and applicability to observational study designs.

Chapter III: Methodological Biases Relevant to Vaccine Effectiveness Estimation: Insights from a Scoping Review

This chapter presents a scoping review manuscript that explores methodological biases that arise in observational studies evaluating VE, with a focus on how these are reported, assessed, and addressed across systematic reviews.

Chapter IV: Pilot Survey on Signal Items

This chapter describes the development and administration of a pilot survey designed to gather feedback on potential "signal items" related to bias in VE studies. Feedback was not used to revise the survey; instead, results will be combined with qualitative input and refined through a participatory-action approach in future phases.

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Chapter II: Risk-of-Bias Tools in Systematic Reviews of Vaccine Effectiveness Studies: A Scoping Review

2.1 Preface

This chapter presents the first manuscript, which provides an overview of how systematic reviews have evaluated the risk-of-bias (RoB) in vaccine effectiveness (VE) studies. It explores the approaches, tools, and methodological challenges involved in assessing the quality of VE evidence, with the aim of clarifying current practices and identifying existing gaps in RoB assessment strategies.

As the first author of this work, I was involved in the implementation of the scoping review from study screening and selection to data synthesis. I worked closely with Dr. Kylie Tingley (CoVaRR-Net*) and Cassandra Laurie (project research coordinator), participating in regular team meetings that helped shape the conceptual direction of the study. I registered the study protocol and contributed to full-text screening data extraction. Subsequently, I worked with my supervisors, Dr. Melissa Brouwers and Dr. Giorgia Sulis, to finalize the data synthesis plan and took the lead in organizing the results into clear, tabular formats. After synthesizing the findings, I drafted the original manuscript, which was revised and finalized in collaboration with my supervisors and the research team and is currently under review in the *Journal of Clinical Epidemiology*.

* CoVaRR-Net: Coronavirus Variants Rapid Response Network

2.2 Title page

Risk-of-Bias Assessment of Vaccine Effectiveness Studies: A Scoping Review of Systematic Reviews

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2.3 Abstract

Background: Observational vaccine effectiveness (VE) studies provide essential information on how vaccines work in real-world settings but are prone to various biases. Assessing methodological quality of VE studies is critical for valid evidence synthesis.

Objectives: We followed the Joanna Briggs Institute guidance to map risk-of-bias (RoB) assessment methods in systematic reviews of observational VE studies.

Design: We searched MEDLINE, Embase and Web of Science from 01 January 2013 to 17 May 2023. We supplemented our search using the CAD-AMC checklist to identify literature from 01 January 2018 to 15 August 2023. We used the PCC framework to include systematic reviews of VE observational across all populations and settings.

Results: We identified 204 systematic reviews. On average, reviews included 51 (±19.78) observational studies; cohort designs were most common (176/204, 86.3%), with COVID-19 (66/204, 32.4%) and seasonal influenza (63/204, 30.9%) most frequently studied.VE was reported descriptively in 29.4% (60/204) of reviews, while 70.6% (144/204) provided meta-analyzed estimates with laboratory-confirmed infection (138/204, 67.7%) and symptomatic disease (129/204, 63.2%) as the most assessed outcomes. RoB assessment was performed in 191/204 (93.6%) reviews using existing tools, most commonly the Newcastle-Ottawa Scale (84/191, 44.0%), GRADE (48/191, 25.1%), and ROBINS-I (43/191, 23.0%) tools. A subset of reviews (31/204, 15.2%) adapted existing tools and 11.8% (24/204) used multiple RoB tools.

Conclusions: Our findings highlight a gap, characterized by insufficient or inconsistent methodological assessment of RoB in observational VE studies, underscoring the need for more rigorous and consistent RoB evaluation to improve research reliability and inform evidence-based vaccination policies.

Registration: https://osf.io/euz9b/

2.4 Introduction

Vaccines are a cornerstone of global public health, playing a crucial role in reducing the burden of infectious diseases worldwide (1). While randomized controlled trials (RCTs) generate evidence of vaccine efficacy under ideal conditions, post-licensure observational studies provide essential real-world evidence on vaccine effectiveness (VE) and public health impact across diverse populations and settings (2). Systematic reviews and meta-analyses (SR/MAs) synthesize findings from these studies to inform clinical practice, public health policies, and vaccination strategies. However, the reliability of SR/MA findings is contingent on the quality of the included studies and their risk-of-bias (RoB) (3).

Generic RoB assessment tools, designed to evaluate a broad spectrum of studies, may be insufficient in the context of VE research. Specifically, observational VE studies are susceptible to some important and often unique challenges compared to observational studies in other clinical areas, such as healthy vaccinee bias, healthcare-seeking behavior bias, temporal bias, and biases related to prior infection or immunization schedules (4). Furthermore, across observational study designs, the types of risk of bias vary. For instance, cohort studies may be affected by differential loss to follow-up and difficulties in accounting for changes in vaccination status, while case-control studies face risks of recall bias, misclassification of vaccination history, and challenges in selecting appropriate control groups (5). The increasingly popular case-control study using a test-negative design (TND) mitigates certain biases (e.g., healthcare-seeking behavior bias) by comparing symptomatic individuals who seek care and test positive for the target pathogen (cases) with those who test negative (controls) (6); however, the TND design introduces its own challenges, including inconsistencies in testing procedures, case definitions, and diagnostic tools (7-8).

SR/MAs of observational VE studies also face challenges due to more pronounced clinical heterogeneity compared to SR/MAs of RCTs, stemming from variations in participant characteristics, interventions, and outcomes, reflecting real-world practices and less stringent inclusion criteria (3). Inconsistencies in exposure and outcome definitions and

measurements across VE studies underscore the need for standardized reporting and rigorous RoB assessment to ensure the validity of pooled evidence from VE research. To gain a more comprehensive understanding of current practices and explore the landscape of RoB assessment in VE research, we conducted a scoping review with the objective to identify tools currently used to assess RoB in VE studies in published systematic reviews with particular attention to the use of current RoB standards, modifications to current standards, and the application of new original strategies employed by the authors.

2.5 Methods

We prospectively registered our scoping review protocol on the Open Science Framework (https://osf.io/euz9b/) (9). We followed the Joanna Briggs Institute (JBI) methodological framework for scoping reviews, initially developed by Arksey and O'Malley (10) and subsequently refined by Levac et al (11). Additionally, this review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (12) and PRISMA 2020 statement (13). A completed PRISMA-ScR checklist is provided in Appendix 2A. While our protocol initially specified an English-only inclusion criterion, we ultimately did not impose language restrictions, allowing the inclusion of studies published in any language.

2.5.1 Search strategy

A professional information specialist (BS), in consultation with the research team, developed the search strategy. The MEDLINE strategy was peer-reviewed by another senior information specialist using the PRESS (Peer-Review of Electronic Search Strategies) Checklist (14) (Appendix 2B). Using the multifile option and deduplication tool on the Ovid platform, we searched Ovid MEDLINE® ALL and Embase Classic+Embase. We also searched the core databases of Web of Science. The search combined controlled vocabulary (e.g., “Vaccine Efficacy”, “Vaccines”, “Systematic Review”) with relevant free text (e.g., “vaccine effectiveness”, “immunization”, “evidence-based review”). We executed all searches on 17 May 2023. There were no language restrictions. To ensure feasibility and budgetary parameters, we limited results to the publication years 2013 to the present. We

downloaded the records to EndNote 9.3.3 (Clarivate Analytics) and deduplicated them prior to uploading them to Covidence (Veritas Health Innovation Ltd). The full search strategy is detailed in Appendix 2C. To identify relevant grey literature and unpublished studies, we utilized the Grey Matters checklist developed by the Canadian Drug Agency (CDA-AMC) (15), to include materials published between 1 January 2018 and 15 August 2023 (Appendix 2D). Our searches were not updated after these dates given the methodological focus of this scoping review and the achievement of saturation.

2.5.2 Selection criteria

Eligibility criteria were defined using the Population-Concept-Context (PCC) framework (9). We included systematic reviews of observational VE studies, with or without meta-analysis, that performed any form of RoB assessment, whether using an established tool or the review authors' own methodology. To maximize the capture of relevant data, we imposed no restrictions on population characteristics, vaccine types, or vaccine-preventable diseases. For the purpose of this review, we defined VE as any measure of the vaccine's protective capacity against various outcomes under real-world conditions, evaluated through post-licensure (phase IV) studies (16). Systematic reviews that solely included RCTs evaluating vaccine efficacy or studies focused solely on immunogenicity outcomes (e.g., antibody titers, markers of cell-mediated responses) were excluded.

2.5.3 Review process

We imported the search results into Covidence (Veritas Health Innovation Ltd) for final deduplication and screening. The study selection process consisted of two stages. First, two independent reviewers (KT and CL) screened all unique records by title and abstract, retaining any record selected by at least one reviewer. In the second stage, three reviewers (KT, CL, ZD) independently conducted full-text screenings of all records selected in the previous stage, resolving any disagreements through team discussions until consensus was reached. To ensure consistency, all reviewers initially screened the same 10 publications at each stage. Results from this pilot phase informed refinements to the screening process.

For non-English publications, we utilized our team's language capabilities and employed ChatGPT (OpenAI) for translation when needed.

2.5.4 Data extraction and synthesis

We developed and piloted a standardized data extraction form in Covidence to systematically collect relevant information from the included systematic reviews. A single reviewer extracted data from the included full-text articles using the form (Appendix 2E), with verification by another reviewer. The following elements were extracted: study design(s) included in the systematic review, number of observational studies included, vaccine(s) assessed, definition(s) of VE, outcomes measured, details about whether and how the review authors conducted risk-of-bias assessment(s) of included studies. For the purposes of our review, we included GRADE as a RoB tool. While technically GRADE is an evidence assessment framework, one of the key domains is risk of bias, which is represented by five key criteria, e.g., "failure to adequately control confounding". Discrepancies during data extraction were resolved through discussion to maintain consistency and accuracy. Descriptive statistics were used to summarize the data.

2.6 Results

2.6.1 Search results

Our searches identified 2,510 unique records from three databases and 54 reports from grey literature sources, all of which underwent title and abstract screening (Figure 2-1). From the databases, 368 records were eligible for full-text assessment, including eight (2.2%) published in languages other than English (Chinese, French, Portuguese, Korean, and Farsi). Of these, 204 systematic reviews (203 in English and one in Portuguese) met inclusion criteria and were included in the data synthesis (Table S2.1, Appendix 2F). A list of excluded studies with reasons for exclusion is provided in Appendix G. Notably, 38 systematic reviews were excluded because no risk-of-bias or quality assessment was reported, thus making them ineligible (Figure 2-1).

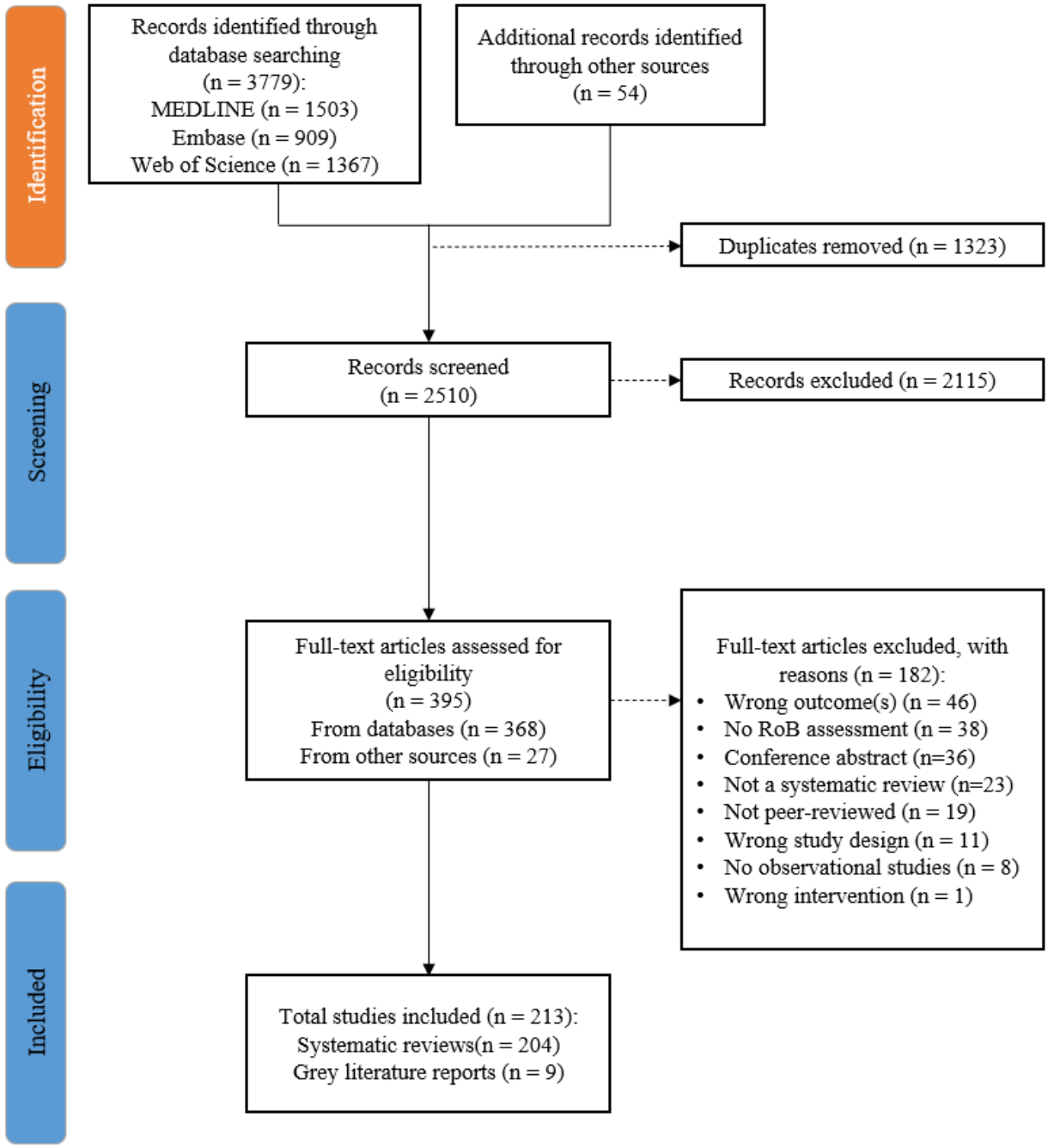

Figure 2-1 The PRISMA flow diagram of study selection (65)

From the 54 records identified through grey literature sources, 27 remained after duplicate removal and were screened, yielding nine eligible reports. Although these were not systematic reviews and thus excluded from the descriptive analysis, we reviewed their RoB assessment approaches. We have summarized these reports in Appendix 2F, Table S2.5, highlighting their valuable methodologies for quality assessment, despite not being discussed further in the main text.

2.6.2 Characteristics of the systematic reviews

Of the 204 systematic reviews included in our analysis, 90 (44.1%) included both RCTs and observational studies (Table 2-1). The systematic reviews included various observational study designs: cohort studies (176/204, 86.4%), case-control studies (132/204, 64.7%), and TND studies (45/204, 22.1%). On average, systematic reviews included 51 observational studies (range 1 to 289); 37.8% of reviews incorporated 10 or fewer primary studies and 19.1% included 30 or more.

Table 2-1 Characteristics of systematic review articles included in the scoping review (N=204)

Characteristic	N	%
RCTs included in the systematic review		
Yes	90	44.1%
No	114	55.9%
Number of observational studies included in the systematic review		
Mean (SD)	51 (±19.78)	
Minimum, maximum	1, 290	
<10	77	37.8%
10-20	62	30.4%
21-30	26	12.8%
>30	39	19.1%
Observational study designs included in reviews [a]		
Cohort	176	86.3%
Case-control	132	64.7%
Test-negative	45	22.1%
Cross-sectional	30	14.7%
Screening method	13	6.4%
Other	9	4.4%
Not reported	6	2.9%
Vaccine-preventable disease under investigation [a]		
COVID-19	66	32.4%

Characteristic	N	%
Seasonal influenza	63	30.9%
Measles, Mumps, Rubella	18	8.8%
Pneumococcal disease	17	8.3%
HPV	15	7.4%
Pandemic influenza	11	5.4%
Varicella, Herpes zoster (shingles)	10	4.9%
Rotavirus disease	8	3.9%
Pertussis	8	3.9%
Other	15	7.4%
Definitions of VE		
Descriptive (VE as reported in primary studies)	60	29.4%
Meta-analyzed (VE based on combined adjusted effect estimates)	144	70.6%
Based on Odds Ratio: (1-OR) ×100 [a]	95	46.6%
Based on Risk Ratio: (1-RR) ×100 [a]	79	38.7%
Based on Hazard Ratio: (1-HR) ×100 [a]	19	9.3%
Based on Incidence Rate Ratio: (1-IRR) ×100 [a]	15	7.4%
Based on Diagnostic Odds Ratio: (1-DOR) ×100 [a]	4	2.0%
Based on alternative VE/effect estimate calculations(s) [a,b]	6	2.9%
Type of effect estimate(s) not specified	16	7.8%
Outcomes assessed [a]		
Laboratory-confirmed infection	138	67.7%
Symptomatic disease	129	63.2%
Hospitalization	88	43.1%
Death	71	34.8%
Contact with HCP [c]	14	6.9%
Disease severity	4	2.0%
Other	5	2.5%
Risk-of-bias assessment performed using an existing RoB tool?		
Yes	191	93.6%
No	13	6.4%

[a] Categories are not mutually exclusive

[b] VE = 1 - [(PCV × (1 - PPV)) / ((1 - PCV) × PPV)], (PCV: proportion of cases vaccinated, PPV: proportion of population vaccinated); VE = 1 - [(c1 / N1) / ((c0 + 1) / (N0 + 1))], where VE = (1 - RR) * 100, RR = (c1 / N1) (risk in the vaccinated group) and the risk in the unvaccinated group is adjusted with a continuity correction (c0 + 1) / (N0 + 1); VE as a dichotomous outcome (e.g., incidence: yes or no), RR = OR / [(1 - P_0) + (P_0 × OR)], (P_0: event incidence in control group, OR: odds ratio); VE(t) = A × e^(-w × t), (A: initial effectiveness, w: waning rate, t: time); VE = 1 - (ARV/ARU) × 100, (ARV, ARU: attack rates in vaccinated and unvaccinated); VE = (pooled HR - 1) / HR or (pooled OR - 1) / OR

[c] Examples include emergency department, urgent care or clinic/office visits

HCP: healthcare professional, HPV: human papillomavirus, SD: standard deviation, RCT: randomized controlled trial, RoB: risk of bias, VE: vaccine effectiveness.

COVID-19 and seasonal influenza vaccines were the most frequently studied across included systematic reviews (66/204 [32.4%] and 63/204 [30.9%], respectively). Others commonly assessed included vaccines against measles, mumps, and rubella (18/204, 8.8%) and pneumococcal disease (17/204, 8.3%). Outcomes evaluated included laboratory-confirmed infections (138/204, 67.7%), symptomatic disease (129/204, 63.2%), and hospitalization (88/204, 43.1%). Details are provided in Table S2.1 (Appendix 2F).

The included systematic reviews revealed diverse approaches to defining and calculating VE. Notably, 144/204 (70.6%) reviews reported meta-analyzed VE estimates based on various adjusted effect measures, while 60/204 (29.4%) reviewed reported VE descriptively as presented in the primary studies, without pooling. Among these 144 reviews, the most used effect measure was the odds ratio (OR), applied in 46.6% (95/204) of the reviews, using the formula VE = (1 - OR) × 100. The risk ratio (RR) was the second most used measure, employed in 38.7% (79/204) of reviews, utilizing the formula VE = (1 - RR) × 100. Less commonly, hazard ratios were used in 19/204 reviews (9.3%), incidence rate ratios in 15/204 reviews (7.4%), and diagnostic odds ratios in 4/204 reviews (2.0%). Further details are provided in Table 2-1.

2.6.3 RoB assessment methods

Most of the systematic reviews (191/204; 93.6%) reported using one (167/204, 81.9%) or multiple (24/204, 11.8%) existing RoB and/or quality of evidence assessment tools or checklists. As shown in Table 2-2, the Newcastle-Ottawa Scale (NOS) (17) was the most employed (84/191, 44.0%), followed by Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) (18) (48/191, 25.1%), and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) (19) (43/191, 23.0%).

Table 2-2 Risk-of-bias or evidence assessment tools/checklists utilized in included systematic reviews (n=191)

RoB tool/checklist*	N	%
Newcastle-Ottawa Scale (NOS)	84	44.0%
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)	48	25.1%
Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I)	43	23.0%
Cochrane risk of bias assessment for non-randomized studies (RoB-2 tool)	9	4.7%
Joanna Briggs Institute (JBI)	9	4.7%
National Institutes of Health (NIH) quality assessment tool	6	3.1%
National Heart, Lung and Blood Institute (NHLBI) Study Quality Assessment Tool	6	3.1%
Checklist recommended by Agency for Healthcare Research and Quality (AHRQ)	5	2.6%
Child Health Epidemiology Reference Group (CHERG)	4	2.1%
Scottish Intercollegiate Guidelines Network (SIGN)	4	2.1%
Other	19	9.9%

*Categories are not mutually exclusive as more than one tool was utilized in some systematic reviews.

Among the 191 systematic reviews that utilized a published RoB assessment tool, 31 (15.2%) reported adapting the tool(s) to better align with the reviews' goals. These adaptations were made to align with characteristics of included primary studies, such as specific study designs, vaccine types, or other relevant features. Detailed descriptions of these modifications and their implications are presented in Tables S2.2-S2.3 (Appendix 2F). Common adjustments included modifications to published scoring systems, refinements to specific assessment criteria, or inclusion/exclusion checklist items. For instance, the authors of some reviews adapted the NOS by converting its star ratings into categorical risk levels (e.g., three or four categories from low to high RoB) (20–23) while others applied scoring cut-offs to interpret the results (24–27). Two systematic reviews customized the

NOS by integrating items from other checklists (27-28). For example, Gupta *et al.* (2022) (28) modified the NOS by incorporating the three domains of selection, comparability and outcome/exposure from the Agency for Healthcare Research and Quality (AHRQ) (30) framework and converting NOS scores to align with AHRQ quality assessment thresholds. Other reviews adapted the assessment criteria of the selected RoB tool by replacing non-relevant criteria with those more appropriate to the specific vaccines, populations, or outcomes under evaluation (31–41). For instance, Petras *et al.* (2022) (42) modified the GRADE (18) framework by including the number of vaccine effectiveness records in their evaluation of strength of evidence. Similarly, Sabu *et al.* (2022) (41) adapted the Quality Assessment Tool for Studies with Diverse Designs (QATSDD) (43) by excluding three criteria deemed irrelevant for assessing the included studies.

Thirteen systematic reviews (6.4%) did not employ a published RoB tool (Table S2.4, Appendix 2F). One review by Kandeil *et al.* (2020) (44) considered the GRADE quality assessment tool but ultimately did not use it, citing the diverse study outcomes and extensive data recalculations required. Instead, the quality of studies was assessed using rubric of the authors' design. Similarly, the remaining 12 reviews employed custom methods to assess biases and study validity. These custom methods often involved creating a checklist, scale or resource that capture RoB and/or quality concepts the authors found relevant. In cases where no applicable tool was available for the study design, the authors provided a narrative description of their quality assessment, commenting on quality characteristics often discussed in the literature (36,45–55). For example, Darvishian *et al* (2014) (47) created a checklist and elicitation scale to evaluate internal and external biases focusing on their potential impact on VE estimates. Similarly, Andani *et al.* (2022) (56) developed an evaluation strategy targeting three key quality features related to case detection, data collection methods, and quantitative methods. This tool classified studies as weak, moderate, strong, or having a fatal error in each domain. Studies receiving a fatal error rating in any domain were excluded from further analysis. Similarly, due to the absence of a validated tool specifically for TND studies, Okoli *et al.* (2021) (57) examined studies on three quality features that could introduce bias: participant enrollment

methods, methods for verifying vaccination status, and statistical adjustments for age and comorbidities.

2.7 Discussion

This scoping review identified 204 systematic reviews of observational VE studies, most of which assessed RoB using a risk-of-bias assessment tool. The systematic application of standardized tools and reporting guidelines is essential to promote research reproducibility and enhance the credibility of scientific findings used to inform clinical and policy decisions. Notwithstanding the widespread usage of RoB tools, our scoping review suggests significant heterogeneity of practices concerning the quality and risk-of-bias assessment of VE studies, reflecting limitations of existing tools when applied to the broad and complex range of VE research. It is noteworthy that in our initial screening 37 systematic reviews were excluded from our review due to the absence of *any* risk-of-bias or quality assessment.

Our findings also show that systematic reviewers often address the lack of tailored assessment tools for VE studies by modifying or adapting an existing tool, or in 13 cases, even developing their own methods. For example, Okoli *et al.* (2021) (57) created their own approach to overcome the lack of a validated assessment tool for TND studies, despite TND being a common design in VE research. TND studies are increasingly employed over traditional case-control studies because they help mitigate confounding from healthcare-seeking behavior by selecting cases and controls among those who seek care at the same facilities and present with similar symptoms and offer greater efficiency than cohort studies (61-62).

Authors employed a diverse array of RoB or quality assessment tools, with NOS (17), ROBINS-I, and GRADE (18) being the most frequently used. Notably, adaptations of these tools, particularly NOS and ROBINS-I (19), along with the Downs and Black checklist (60), were implemented in 31 (15.2%) included reviews and 24 (11.8%) resorted to using multiple RoB tools to evaluate the methodological quality of included studies, reflecting the inadequacies of individual tools in capturing the variability inherent in observational

studies specifically aimed at VE estimation. Each design presents distinct challenges that need to be properly accounted for in risk-of-bias and quality assessment. Cross-sectional studies cannot establish temporal relationships and may overestimate VE when conducted during periods of peak effectiveness. TND studies, while reducing confounding from healthcare-seeking behavior, remain sensitive to differences in testing practices (61). Screening method studies rely heavily on accurate estimates of population vaccination coverage, but they are prone to overestimating VE due to responder bias and limited ability to control for confounding (62). Cohort studies face issues such as differential loss to follow-up, immortal time bias (63), whereas case-control studies are vulnerable to recall bias and require careful selection of controls to ensure valid estimation of VE (64). The complexity of VE estimation and the resulting difficulty of critically appraising VE studies in a standardized manner highlights the urgent need for a comprehensive, reliable, and user-friendly RoB tool tailored specifically to VE research, capable of addressing the unique challenges and biases associated with diverse observational study designs.

Of the 204 systematic reviews, 60 (29.4%) reported VE descriptively without a formal definition, while 16 (7.8%) pooled data without specifying the effect estimates used to define VE, likely to maximize the inclusion of highly diverse primary studies. From a methodological standpoint, the absence of a formal definition can lead to inconsistencies in how studies are designed, executed, and reported. Without a clear and consistent definition, authors may adopt varying interpretations of what constitutes VE, producing heterogeneous results that are difficult to compare or synthesize. This lack of uniformity can undermine the reliability of findings and pose challenges for readers attempting to assess the quality, relevance, and applicability of evidence synthesis results.

Our review has several strengths, including adherence to rigorous scoping review methods, independent duplicate screening and data extraction processes, and a comprehensive literature search that achieved saturation. However, inconsistent and suboptimal reporting practices across studies pose challenges in fully ascertaining risk of bias assessment methodologies and required careful interpretation of data. The quality of our review is

inherently tied to the reporting quality of the included systematic reviews, underscoring once again the need for standardized and transparent reporting practices.

In summary, the identification and evaluation of important sources of bias in observational VE studies is highly dependent on the context and specific characteristics of each study, including its design. Future research should focus on systematically evaluating the main types of bias to be considered, mitigated, and accounted for in VE estimation through various types of VE studies. This would lay the foundation for developing and validating a new RoB tool, or modifying existing ones, to address the unique biases inherent in observational VE studies. Standardized reporting practices are equally critical to ensure that findings are robust, comparable, and capable of informing evidence-based clinical and policy decisions.

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57. Okoli, G. N. *et al.* Decline in Seasonal Influenza Vaccine Effectiveness With Vaccination Program Maturation: A Systematic Review and Meta-analysis. *Open Forum Infect. Dis.* **8**, ofab069 (2021).

58. Mésidor, M. *et al.* Test negative design for vaccine effectiveness estimation in the context of the COVID-19 pandemic: A systematic methodology review. *Vaccine* **42**, 995–1003 (2024).

59. Leis, A. M. *et al.* Evaluation of test-negative design estimates of influenza vaccine effectiveness in the context of multiple, co-circulating, vaccine preventable respiratory viruses. *Vaccine* **42**, 126493 (2024).

60. Downs, S. H. & Black, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J. Epidemiol. Community Health* **52**, 377–384 (1998).

61. Mésidor, M. *et al.* Test negative design for vaccine effectiveness estimation in the context of the COVID-19 pandemic: A systematic methodology review. *Vaccine* **42**, 995–1003 (2024).

62. Teerawattananon, Y. *et al.* A systematic review of methodological approaches for evaluating real-world effectiveness of COVID-19 vaccines: Advising resource-constrained settings. *PLoS One* **17**, e0261930 (2022).

63. Remschmidt, C., Wichmann, O. & Harder, T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. *BMC Infect. Dis.* **15**, 429 (2015).

64. Lu, C. Y. Observational studies: a review of study designs, challenges and strategies to reduce confounding. *Int. J. Clin. Pract.* **63**, 691–697 (2009).

65. Haddaway, N. R., Page, M. J., Pritchard, C. C. & McGuinness, L. A. *PRISMA2020* : An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Syst. Rev.* **18**, e1230 (2022).

2.9 Chapter II: Supplementary Materials

Appendix 2A: PRISMA Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3-4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5-6
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the	6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	6-7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Appendix F, Table S1
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Table 1-2, Appendix F
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	10-11
Limitations	20	Discuss the limitations of the scoping review process.	11
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	12
FUNDING			

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	12

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Appendix 2B: PRESS Checklist

Reference: McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40-6. Available: http://www.jclinepi.com/article/S0895-4356(16)00058-5/pdf.

Search submission: This section to be filled in by the searcher

Searcher: Becky Skidmore

Date submitted: 2023 May 11 Date requested by: 2023 May 13 PM

1. Systematic Review Title

Risk of Bias Tools for Vaccine Effectiveness Studies: A protocol for a scoping review

2. This search strategy is …

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

3. Database (e.g., MEDLINE, CINAHL)

MEDLINE

4. **Interface** (e.g., Ovid, EbscoHost…)

Ovid

5. Research Question (Describe the purpose of the search) *[mandatory]*

KQ1. What are the existing tools used to assess risk of bias in vaccine effectiveness studies?

KQ2. What risk of bias concepts or sources are considered to be of particular concern for vaccine effectiveness studies?

6. PICO Format Outline the PICOs for your question — i.e., Patient, Intervention, Comparison, Outcome, and Study Design — as applicable

P	Vaccine Effectiveness Studies
I / Exposure	
C	
O	
S	Systematic Reviews

7. Inclusion Criteria (List criteria such as age groups, study designs, etc., to be included) *[optional]*

Date limits 2013-present

9. Exclusion Criteria (List criteria such as study designs, date limits, etc., to be excluded)

10. Was a search filter applied? Yes

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question — textbox]*

SR filter derived from CADTH's

11. Notes or comments you feel would be useful for the peer reviewer *[optional]*

Not interested in efficacy. Interest is in RoB considerations/concepts/tools as would be found in context of relevant study designs, e.g., test-negative, Phase IV, real world, observational studies.

Not interested in specific vaccines so language is intentionally generic.

Want to stay away from including concepts of "immunogenicity" - the effectiveness of vaccines in producing an immune response.

This project is being done in multiple parts.

1 – Vaccine effectiveness studies reporting use of an RoB tool/concept (systematic reviews of observational studies)
2 – Methodological papers reporting the development or use of an RoB tool/concept (any study design)
3 – Articles that identify RoB concepts in vaccine effectiveness studies (e.g., guidance for evaluating RoB in vaccine effectiveness studies, articles or reporting guidance that identify sources of bias in vaccine effectiveness studies)

12. Please copy and paste your search strategy here, exactly as run, including the number of hits per line. [mandatory]

Database: Ovid MEDLINE(R) ALL <1946 to May 09, 2023>
Search Strategy:

---

1 Vaccine Efficacy/ [VACCINE EFFECTIVENESS PT 1 - NEW MESH 2022] (732)
2 exp Vaccines/ (275350)
3 exp Vaccination/ (108352)
4 vaccin*.ti,kw,kf. (242408)
5 (immunis* or immuniz*).ti,kw,kf. (48043)
6 (vaccin* or immunis* or immuniz*).ab. /freq=2 (253574)
7 or/2-6 [VACCINES/VACCINATION] (428686)
8 (vaccin* adj5 effective*).tw,kw,kf. (41952)
9 7 and 8 [VACCINE EFFECTIVENESS PT 2] (36759)
10 1 or 9 [VACCINE EFFECTIVENESS PTs 1 or 2] (37039)
11 Systematic Review.pt. (228025)
12 exp Systematic Reviews as Topic/ (10481)
13 Meta Analysis.pt. (180624)
14 exp Meta-Analysis as Topic/ (26934)
15 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf. (276187)
16 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or evidence map* or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf. (365957)
17 exp Technology Assessment, Biomedical/ (12121)
18 (cochrane or health technology assessment or evidence report or systematic reviews).jw. (22499)
19 Network Meta-Analysis/ (4843)
20 (network adj (MA or MAs)).tw,kw,kf. (17)
21 (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf. (9352)
22 indirect* compar*.tw,kw,kf. (2772)
23 (indirect treatment* adj1 compar*).tw,kw,kf. (463)
24 (mixed treatment* adj1 compar*).tw,kw,kf. (524)
25 (multiple treatment* adj1 compar*).tw,kw,kf. (225)
26 (multi-treatment* adj1 compar*).tw,kw,kf. (3)
27 simultaneous* compar*.tw,kw,kf. (1299)
28 mixed comparison?.tw,kw,kf. (44)
29 or/11-28 [SR FILTER] (554924)
30 10 and 29 (1389)
31 limit 30 to yr="2013-current" (1108)

****

Peer review assessment: this section to be filled in by the reviewer

Reviewer: Kaitryn Campbell	Date completed: 13 May 2023

Do you wish to be acknowledged? (If yes, the review team will be advised to add an acknowledgement to any publications related to this work). Yes please.

The suggested acknowledgement is "We thank Kaitryn Campbell, MLIS, MSc for peer review of the Medline search strategy."

1. TRANSLATION

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

2. BOOLEAN AND PROXIMITY OPERATORS

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

3. SUBJECT HEADINGS

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

4. TEXT WORD SEARCHING

A ---No revisions	
B --- Revision(s)suggested	X
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

Line 8, suggest consider adding: efficacies OR efficacious* OR efficacy

5. SPELLING, SYNTAX, AND LINE NUMBERS

A ---No revisions	X
B --- Revision(s)suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

6. LIMITS AND FILTERS

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If “B” or “C,” please provide an explanation or example:

OVERALL EVALUATION (Note: If one or more “revision required” is noted above, the response below must be “revisions required”.)

A ---No revisions	
B --- Revision(s) suggested	X
C --- Revision(s) required	

Additional comments:

Nicely done. No errors or omissions detected. I’ve made a few keyword suggestions.

Appendix 2C: Databases Search Strategy

Embase Classic+Embase <1947 to 2023 May 16>, Ovid MEDLINE(R) ALL <1946 to May 16, 2023>

1 Vaccine Efficacy/ [VACCINE EFFECTIVENESS PT 1 - NEW MESH 2022] (84708)

2 exp Vaccines/ (727189)

3 exp Vaccination/ (368775)

4 vaccin*.ti,kw,kf. (551347)

5 (immunis* or immuniz*).ti,kw,kf. (108023)

6 (vaccin* or immunis* or immuniz*).ab. /freq=2 (583496)

7 or/2-6 [VACCINES/VACCINATION] (1071734)

8 (vaccin* adj5 (effective* or efficacies or efficacious* or efficacy)).tw,kw,kf. (141852)

9 7 and 8 [VACCINE EFFECTIVENESS PT 2] (129315)

10 1 or 9 [VACCINE EFFECTIVENESS PTs 1 or 2] (201211)

11 Systematic Review.pt. (228631)

12 exp Systematic Reviews as Topic/ (42064)

13 Meta Analysis.pt. (181011)

14 exp Meta-Analysis as Topic/ (79750)

15 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf. (643952)

16 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or evidence map* or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf. (826777)

17 exp Technology Assessment, Biomedical/ (29227)

18 (cochrane or health technology assessment or evidence report or systematic reviews).jw. (56589)

19 Network Meta-Analysis/ (12647)

20 (network adj (MA or MAs)).tw,kw,kf. (47)

21 (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf. (24419)

22 indirect* compar*.tw,kw,kf. (8041)

23 (indirect treatment* adj1 compar*).tw,kw,kf. (1645)

24 (mixed treatment* adj1 compar*).tw,kw,kf. (1533)

25 (multiple treatment* adj1 compar*).tw,kw,kf. (524)

26 (multi-treatment* adj1 compar*).tw,kw,kf. (16)

27 simultaneous* compar*.tw,kw,kf. (2923)

28 mixed comparison?.tw,kw,kf. (105)

29 or/11-28 [SR FILTER] (1285272)

30 10 and 29 (5411)

31 limit 30 to yr="2013-current" (4304)

32 31 use medall [MEDLINE RECORDS] (1529)

33 exp vaccine/ (727189)

34 exp vaccination/ (368775)

35 vaccin*.ti,kw,kf. (551347)

36 (immunis* or immuniz*).ti,kw,kf. (108023)

37 (vaccin* or immunis* or immuniz*).ab. /freq=2 (583496)

38 or/33-37 [VACCINES/VACCINATION] (1071734)

39 (vaccin* adj5 (effective* or efficacies or efficacious* or efficacy)).tw,kw,kf. (141852)

40 38 and 39 [VACCINE EFFECTIVENESS PT 2] (129315)

41 "systematic review"/ (663727)

42 "systematic review (topic)"/ (31533)

43 meta analysis/ (473497)

44 "meta analysis (topic)"/ (52790)

45 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf. (643952)

46 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or evidence map* or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf. (826777)

47 biomedical technology assessment/ (28055)

48 (cochrane or health technology assessment or evidence report or systematic reviews).jw. (56589)

49	network meta-analysis/ (12647)
50	(network adj (MA or MAs)).tw,kw,kf. (47)
51	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf. (24419)
52	indirect* compar*.tw,kw,kf. (8041)
53	(indirect treatment* adj1 compar*).tw,kw,kf. (1645)
54	(mixed treatment* adj1 compar*).tw,kw,kf. (1533)
55	(multiple treatment* adj1 compar*).tw,kw,kf. (524)
56	(multi-treatment* adj1 compar*).tw,kw,kf. (16)
57	simultaneous* compar*.tw,kw,kf. (2923)
58	mixed comparison?.tw,kw,kf. (105)
59	or/41-58 [SR FILTER] (1401254)
60	40 and 59 (4938)
61	limit 60 to yr="2013-current" (3913)
62	61 use emczd [EMBASE RECORDS] (2388)
63	32 or 62 [BOTH DATABASES] (3917)
64	remove duplicates from 63 (2412) [TOTAL UNIQUE RECORDS]
65	64 use medall [MEDLINE UNIQUE RECORDS] (1503)
66	64 use emczd [EMBASE UNIQUE RECORDS] (909)

Web of Science

Set #	Search Query	Results
1	TI=(vaccin*) OR AK=(vaccin*)	281551
2	TI=(immunis* or immuniz*) OR AK=(immunis* or immuniz*)	55425
3	#2 OR #1	317969
4	vaccin* NEAR/5 (effective* or efficacies or efficacious* or efficacy) (Title) OR vaccin* NEAR/5 (effective* or efficacies or efficacious* or efficacy) (Abstract) OR vaccin* NEAR/5 (effective* or efficacies or efficacious* or efficacy) (Author Keywords)	64674
5	#3 AND #4	49181
6	"meta-analysis" or "meta-analyses" or "meta-analytic" or "meta-analytical" or metanaly* or metaanaly* or "met analysis" or "met analyses" or "met analytic" or "met analytical" or	324863

	"integrative research" or "integrative review" or "integrative reviews" or "integrative overview" or "integrative overviews" or "research integration" or "research overview" or "research overviews" or "collaborative review" or "collaborative reviews" (Title) OR "meta-analysis" or "meta-analyses" or "meta-analytic" or "meta-analytical" or metanaly* or metaanaly* or "met analysis" or "met analyses" or "met analytic" or "met analytical" or "integrative research" or "integrative review" or "integrative reviews" or "integrative overview" or "integrative overviews" or "research integration" or "research overview" or "research overviews" or "collaborative review" or "collaborative reviews" (Abstract) OR "meta-analysis" or "meta-analyses" or "meta-analytic" or "meta-analytical" or metanaly* or metaanaly* or "met analysis" or "met analyses" or "met analytic" or "met analytical" or "integrative research" or "integrative review" or "integrative reviews" or "integrative overview" or "integrative overviews" or "research integration" or "research overview" or "research overviews" or "collaborative review" or "collaborative reviews" (Author Keywords)	
7	"systematic review" or "systematic reviews" or "systematic overview" or "systematic overviews" or "evidence-based review" or "evidence-based reviews" or "evidence-based overview" or "evidence-based overviews" or (evidence NEAR/3 (review* or overview*)) or "evidence map" or "evidence maps" or "evidence mapping" or "meta-review" or "meta-reviews" or "meta-overview" or "meta-overviews" or "meta-synthesis" or "meta-syntheses" or "mapping review" or "mapping reviews" or "rapid review" or "rapid reviews" or "review of reviews" or "scoping review" or "scoping reviews" or "umbrella review" or "umbrella reviews" or "technology assessment" or "technology assessments" or HTA or HTAs (Title) OR "systematic review" or "systematic reviews" or "systematic overview" or "systematic overviews" or "evidence-based review" or "evidence-based reviews" or "evidence-based overview" or "evidence-based overviews" or (evidence NEAR/3 (review* or overview*)) or "evidence map" or "evidence maps" or "evidence mapping" or "meta-review" or "meta-reviews" or "meta-overview" or "meta-overviews" or "meta-synthesis" or "meta-syntheses" or "mapping review" or "mapping reviews" or "rapid review" or "rapid reviews" or "review of reviews" or "scoping review" or "scoping reviews" or "umbrella review" or "umbrella reviews" or "technology assessment" or "technology assessments" or HTA or HTAs (Abstract) OR "systematic review" or "systematic reviews" or "systematic overview" or "systematic overviews" or "evidence-based review" or "evidence-based reviews" or "evidence-based overview" or "evidence-based overviews" or (evidence NEAR/3 (review* or overview*)) or "evidence map" or "evidence maps" or "evidence mapping" or "meta-review" or "meta-reviews" or "meta-overview" or "meta-overviews" or "meta-synthesis" or "meta-syntheses" or "mapping review" or "mapping reviews" or "rapid review" or "rapid reviews" or "review of reviews" or "scoping review" or "scoping reviews" or "umbrella review" or "umbrella reviews" or "technology assessment" or "technology assessments" or HTA or HTAs (Author Keywords)	434585
8	network NEAR/0 (MA or MAs) (Title) OR network NEAR/0 (MA or MAs) (Abstract) OR network NEAR/0 (MA or MAs) (Author Keywords)	158

9	NMA or NMAs or MTC or MTCs or MAIC or MAICs (Title) OR NMA or NMAs or MTC or MTCs or MAIC or MAICs (Abstract) OR NMA or NMAs or MTC or MTCs or MAIC or MAICs (Author Keywords)	13463
10	indirect* NEAR/0 compar* (Title) OR indirect* NEAR/0 compar* (Abstract) OR indirect* NEAR/0 compar* (Author Keywords)	3533
11	("indirect treatment" or "indirect treatments") NEAR/1 compar* (Title) OR ("indirect treatment" or "indirect treatments") NEAR/1 compar* (Abstract) OR ("indirect treatment" or "indirect treatments") NEAR/1 compar* (Author Keywords)	640
12	("mixed treatment" or "indirect treatments") NEAR/1 compar* (Title) OR ("mixed treatment" or "indirect treatments") NEAR/1 compar* (Abstract) OR ("mixed treatment" or "indirect treatments") NEAR/1 compar* (Author Keywords)	660
13	("multiple treatment" or "indirect treatments") NEAR/1 compar* (Title) OR ("multiple treatment" or "indirect treatments") NEAR/1 compar* (Abstract) OR ("multiple treatment" or "indirect treatments") NEAR/1 compar* (Author Keywords)	199
14	("multi-treatment" or "indirect treatments") NEAR/1 compar* (Title) OR ("multi-treatment" or "indirect treatments") NEAR/1 compar* (Abstract) OR ("multi-treatment" or "indirect treatments") NEAR/1 compar* (Author Keywords)	8
15	simultaneous* NEAR/0 compar* (Title) OR simultaneous* NEAR/0 compar* (Abstract) OR simultaneous* NEAR/0 compar* (Author Keywords)	3181
16	"mixed comparison" or "mixed comparisons" (Title) OR "mixed comparison" or "mixed comparisons" (Abstract) OR "mixed comparison" or "mixed comparisons" (Author Keywords)	52
17	#16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6	619924
18	#17 AND #5	1637
19	#17 AND #5 and 2023 or 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 or 2014 or 2013 (Publication Years)	1367

Appendix 2D: Grey Literature Search Strategy

Suggested search terms: vaccine effectiveness; vaccine effectiveness risk of bias; vaccine risk of bias

Organization	Website Link
Relevant websites suggested by co-authors	
Coalition for Epidemic Preparedness Innovations (CEPI)	https://cepi.net/
NACI	https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html
View Hub	https://view-hub.org/
Vaccine Alliance	https://www.gavi.org/
Selected relevant CADTH sources	
COVID-19 Grey Literature Sources	
Joanna Briggs Institute (JBI) - COVID-19 Special Collection	https://joannabriggs.org/
ECRI-COVID-19 Resource Center	https://www.ecri.org/coronavirus-covid-19-outbreak-preparedness-center/
Centre for Evidence-Based Medicine — Oxford COVID-19 Evidence Service	https://www.cebm.net/oxford-covid-19-evidence-service/
National Institute for Health and Care Excellence - Coronavirus (COVID-19)	https://www.nice.org.uk/guidance/conditions-and-diseases/respiratory-conditions/covid19
Institut national d'excellence en santé et en services sociaux - COVID-19	https://www.inesss.qc.ca/covid-19.html
CADTH - CADTH and COVID-19	https://covid.cadth.ca/
McMaster University — COVID-19 Rapid Evidence Reviews	https://www.nccmt.ca/covid-19/covid-19-evidence-reviews

Health Technology Wales — Coronavirus (COVID-19)	https://www.healthtechnology.wales/covid-19/
Penn Medicine — Penn Medicine COVID-19 Guidance Summaries	http://www.uphs.upenn.edu/cep/COVID/indexCOVID.html
National COVID-19 Clinical Evidence Taskforce — Living Guidelines	https://covid19evidence.net.au/
Public Health Agency of Canada - Coronavirus disease (COVID-19)	https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19.html
Canadian Medical Protective Association - COVID-19 Hub	https://www.cmpa-acpm.ca/en/covid19
Canadian Medical Association - CMA Update: COVID-19	https://www.cma.ca/cma-update-coronavirus
CSA Group-Canadian Standards Association - COVID-19 Response Standards & Handbooks	https://www.csagroup.org/news/covid-19-response-standards-handbooks/
BC Centre for Disease Control - COVID-19 Care	http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care
Shared Health Manitoba - Provincial COVID-19 resources for health-care providers and staff	https://sharedhealthmb.ca/covid19/providers/
Government of Newfoundland and Labrador - COVID-19 Information for Health Professionals	https://www.gov.nl.ca/covid-19/for-health-professionals-2/
Public Health Ontario - Coronavirus Disease 2019 (COVID-19)	https://www.publichealthontario.ca/en/diseases-and-conditions/infectious-diseases/respiratory-diseases/novel-coronavirus
Ontario Ministry of Health and Ministry of Long-Term Care — COVID-19	http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/2019_guidance.aspx

Guidance for the Health Sector	
Medical Society of Prince Edward Island - Health PEI Resources	https://mspei.org/covid/clinical-resources/
Collège des médecins du Québec — Suivez le fil d'actualité du Collège: COVID-19	http://www.cmq.org/page/fr/covid-19-suivez-le-fil-de-l-actualite-du-college.aspx
Saskatchewan Medical Association - COVID-19: Information and resources	https://www.sma.sk.ca/resources/70/covid-19-info-for-physicians.html
Centre d'expertise et de référence en santé publique — Publications	https://www.inspq.qc.ca/publications/notice.asp?E=p&NumPublication=653
Alberta Health Services — Scientific Advisory Group COVID-19 Recommendations	https://www.albertahealthservices.ca/topics/Page17074.aspx
Centers for Disease Control and Prevention — Healthcare Workers: Information on COVID-19	https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html
ISDA–Infection Diseases Society of America — COVID-19 Real-Time Learning Network	https://www.idsociety.org/public-health/COVID-19-Resource-Center/
CIDRAP–Center for Infectious Disease Research and Policy — COVID-19 Resource Center	http://www.cidrap.umn.edu/infectious-disease-topics/covid-19
U.S. Food & Drug Administration — Coronavirus Disease 2019 (COVID-19)	https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19
U.S. Food & Drug Administration — COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders	https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders
APIC–Association for Professionals in Infection	https://apic.org/covid19/

Control and Epidemiology — COVID-19	
United States Department of Labor — Occupational Safety and Health Administration: COVID-19	https://www.osha.gov/SLTC/covid-19/standards.html
Government UK - Coronavirus (COVID-19): guidance	https://www.gov.uk/government/collections/coronavirus-covid-19-list-of-guidance
Public Health England - Finding the evidence: Coronavirus	https://phelibrary.koha-ptfs.co.uk/coronavirusinformation/
NHS England and NHS Improvement — Coronavirus guidance for clinicians and NHS managers	https://www.england.nhs.uk/coronavirus/
MRC Centre for Global Infectious Disease Analysis — COVID-19 reports	https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/
Government of South Australia — Coronavirus Disease 2019 (COVID-19): Information for health professionals	https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs+and+practice+guidelines/infectious+disease+control/coronavirus+disease+2019+information+for+health+professionals/novel+coronavirus+%282019-ncov%29+infection+information+for+health+professionals
Government of Western Australia Department of Health — COVID-19 information for health professionals	https://ww2.health.wa.gov.au/Articles/A_E/Coronavirus/COVID19-information-for-health-professionals
ANZICS–Australian and New Zealand Intensive Care Society — ANZICS COVID-19 Guidelines	https://www.anzics.com.au/coronavirus-guidelines/
Ministry of Health – Manatū Hauora — COVID-19: Information for health professionals	https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-novel-coronavirus-information-specific-audiences/covid-19-novel-coronavirus-resources-health-professionals
NSW–Government — COVID-19 (Coronavirus)	https://www.health.nsw.gov.au/Infectious/diseases/Pages/coronavirus-professionals.aspx
World Health Organization — Country & Technical Guidance - Coronavirus disease (COVID-19)	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

European Centre for Disease Prevention and Control. COVID-19	https://www.ecdc.europa.eu/en/covid-19
Evidence Aid — Coronavirus (COVID-19): Information portal	https://www.evidenceaid.org/coronavirus-resources/
World Health Organization — Coronavirus disease (COVID-2019) situation reports	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
COVID-19 Canada Open Data Working Group — COVID-19 in Canada	https://art-bd.shinyapps.io/covid19canada/
Center for Systems Science and Engineering (CSSE) at Johns Hopkins University — COVID-19 Dashboard for cases globally	https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
Cochrane Library - Coronavirus (COVID-19)	https://www.cochranelibrary.com/covid-19
National Center for Biotechnology Information, U.S. National Library of Medicine — LitCOVID	https://www.ncbi.nlm.nih.gov/research/coronavirus/
U.S. National Library of Medicine – National Institutes of Health — Public Health Emergency COVID-19 Initiative	https://www.ncbi.nlm.nih.gov/pmc/about/covid-19/
Epistemonikos (L-OVE Summary) — COVID-19	https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d
World Health Organization. Global research on coronavirus disease (COVID-19)	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
U.S. Department of Veteran Affairs Evidence Synthesis Program — COVID-19 Evidence Reviews	http://covid19reviews.org/index.cfm
medRxiv — COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv	https://connect.medrxiv.org/relate/content/181

MLA–Medical Library Association — COVID-19 Resources for Medical Librarians & Other Health Information Professionals	https://www.mlanet.org/p/cm/ld/fid=1712
University of British Columbia — Coronavirus Disease 2019 (COVID-19)—for Beginners to Experts	https://wiki.ubc.ca/Coronavirus_Disease_2019_(COVID-19)%E2%80%94For_Beginners_to_Experts
EPPI-Centre — COVID-19: a living systematic map of the evidence	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3765
McMaster University — COVID-End: COVID-19 Evidence Network to support Decision-making	https://www.mcmasterforum.org/networks/covid-end/
Canadian health technology and assessment agencies	
Alberta College of Family Physicians (ACFP)	https://acfp.ca/
Alberta Health and Wellness	http://www.health.alberta.ca/initiatives/AHTDP-reviews.html
CADTH	https://www.cadth.ca/search?keywords
Drug Safety and Effectiveness Network (DSEN)	http://www.cihr-irsc.gc.ca/e/49006.html
Health Quality Council of Alberta (HQCA)	http://hqca.ca/studies-and-reviews/completed-reviews/
Health Quality Ontario (HQO)	http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment
The Hospital for Sick Children (SickKids)	http://lab.research.sickkids.ca/task/reports-theses/
Institut national d'excellence en santé et en services sociaux (INESSS)	http://www.inesss.qc.ca/en/publications/publications.html
Institute of Health Economics (IHE)	http://www.ihe.ca/index.php?/publications
Manitoba Centre for Health Policy (MCHP)	http://mchp-appserv.cpe.umanitoba.ca/deliverablesList.html
McGill University Health Centre (MUHC)	https://muhc.ca/tau/page/tau-reports
NLCAHR : Newfoundland and Labrador Centre for	http://www.nlcahr.mun.ca/CHRSP/CompletedCHRSP.php

Applied Health Research. Contextualized Health Research Synthesis Program (CHRSP)	
Ottawa Hospital Research Institute (OHRI)	http://www.ohri.ca/ksgroup/Publications.aspx
Therapeutics Initiative	http://www.ti.ubc.ca/TherapeuticsLetter
Programs for Assessment of Technology in Health (Canada)	https://www.path-hta.ca/research
UBC Centre for Health Services and Policy Research	https://chspr.ubc.ca/publications/
International health technology and assessment agencies	
INAHTA	https://www.inahta.org/publications/
WHO Health Evidence Network (HEN)	https://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/publications/by-keyword
Australia and New Zealand Horizon Scanning Network (ANZHSN)	http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/technologies-assessed-lp-2
Australian Government Department of Health and Ageing. Medical Services Advisory Committee (MSAC)	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/completed-assessments
Joanna Briggs Institute (JBI)	http://connect.jbiconnectplus.org/Search.aspx
Monash Health. Centre for Clinical Effectiveness (CCE).	http://monashhealth.org/health-professionals/cce/cce-publications/
National Prescribing Service. NPS RADAR	https://www.nps.org.au/radar
COAG Health Council	https://www.coaghealthcouncil.gov.au/AHMAC/Health-Technology-Reference-Group/Reports-and-Briefs
Institute of Technology Assessment (ITA)	http://www.oeaw.ac.at/ita/en/projects
Ludwig Boltzmann Institute of Health Technology Assessment (LBI)	http://eprints.hta.lbg.ac.at/
Belgian Health Care Knowledge Centre (KCE)	https://kce.fgov.be/en/all-reports

CEDIT Recommendations and Reports	http://cedit.aphp.fr/cedit-hta-agency/recommendations-reports/
French National Authority for Health (HAS)	http://www.has-sante.fr/jcms/c_946986/en/english-toutes-nos-publications-ligne-principale?portal=r_1457306
German Institute of Medical Documentation and Information (DIMDI)	https://www.dimdi.de/dynamic/en/homepage/
Health Information and Quality Authority	https://www.hiqa.ie/reports-and-publications/health-technology-assessments
Health Service Executive (Irish Health Repository)	https://www.lenus.ie/hse/
Health Council of the Netherlands	https://www.gezondheidsraad.nl/
National Health Care Institute Netherlands	https://english.zorginstituutnederland.nl/publications
Folkehelseinstituttet. Norwegian Institute of Public Health	https://www.fhi.no/en/publ/
Institute of Health Carlos III	https://publicaciones.isciii.es/
Healthcare Improvement Scotland	http://www.healthcareimprovementscotland.org/
NICE (NHS National Institute for Health and Care Excellence)	https://www.nice.org.uk/
NICE (Advice List)	https://www.nice.org.uk/guidance/published
NIHR	http://www.io.nihr.ac.uk/
NETSCC	https://www.journalslibrary.nihr.ac.uk/programmes/
National Health Service UK (NHS) England	https://www.england.nhs.uk/
AHRQ	https://www.ahrq.gov/cpi/about/index.html
Centers for Medicare and Medicaid Services (CMS)	https://www.cms.gov/About-CMS/About-CMS
Washington State Health Care Authority (HCA)	https://www.hca.wa.gov/about-hca
Clinical Practice Guidelines	
Alberta Medical Association	https://actt.albertadoctors.org/Pages/default.aspx
British Columbia Ministry of Health	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines
Canadian Medical Association (CMA)	https://joulecma.ca/cpg/homepage

Canadian Partnership Against Cancer	https://www.partnershipagainstcancer.ca/tools/cancer-guidelines-database/
Canadian Standards Association (CSA)	https://store.csagroup.org/?cclcl=en_US
The College of Physicians and Surgeons of Ontario (CPSO)	https://www.cpso.on.ca/
Ontario Association of Medical Laboratories (OAML)	https://oaml.com/guidelines/
Public Health Agency of Canada (PHAC)	https://www.canada.ca/en/public-health/services/reports-publications/disease-prevention-control-guidelines.html
Registered Nurses' Association of Ontario (RNAO)	https://rnao.ca/bpg
Winnipeg Regional Health Authority (WRHA)	https://professionals.wrha.mb.ca/old/extranet/eipt/
American Association for Clinical Chemistry (AACC)	https://www.aacc.org/science-and-research/practice-guidelines
Centers for Disease Control and Prevention (CDC)	https://phgkb.cdc.gov/PHGKB/phgHome.action?action=home
The Regulation and Quality Improvement Authority (RQIA)	https://rqia.org.uk/what-we-do/rqia-s-funding-programme/guidelines/
Haute Autorité de santé/ French National Authority for Health (HAS)	https://www.has-sante.fr/jcms/c_6056/en/recherche-avancee?portlet=c_39085&search_antidot=&lang=en&typesf=guidelines
Institute for Clinical Systems Improvement (ICSI)	https://www.icsi.org/guidelines/
National Health and Medical Research Council (NHMRC)	https://www.clinicalguidelines.gov.au/
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/guidance/published
Scottish Intercollegiate Guidelines Network (SIGN)	https://www.sign.ac.uk/
Databases (free)	
Bandolier	http://www.bandolier.org.uk/booth/booths/smoking.html
LILACS	https://lilacs.bvsalud.org/en/
McMaster University, McMaster Health Forum	https://www.healthsystemsevidence.org/
NCBI	https://www.ncbi.nlm.nih.gov/books

TRIP Database	https://www.tripdatabase.com/
University of York (CRD)	https://www.crd.york.ac.uk/CRDWeb/
University of York. PROSPERO	https://www.crd.york.ac.uk/prospero/
US National Library of Medicine (NLM)	http://www.ncbi.nlm.nih.gov/pubmed
US National Library of Medicine & National Institutes of Health (NIH)	http://www.ncbi.nlm.nih.gov/pmc/
Internet Search	
Google (first 5 pages)	http://www.google.com
Google Scholar (first 5 pages)	https://scholar.google.com/
CMA	https://www.cma.ca/about-cma

Appendix 2E: Data Extraction Form

General information

Study ID (Covidence ID)

Title

Lead author last name

Year of publication

Country in which the study conducted

1. United States
2. UK
3. Canada
4. Australia
5. Other

Were there any conflicts of interest declared?

1. Yes
2. No
3. Not reported

If yes, please specify the conflicts of interest:

Was the study funded?

1. Yes
2. No
3. Not reported

If yes, please specify the funding source:

Notes

Additional general information regarding the study

Study methods

Aim of study

Copy and paste authors' description of their study objective/research question

Years included in literature search

Study design(s) included in systematic review

Which study designs were included in the systematic review?

1. ☐ Cohort design
2. ☐ Cross-sectional design
3. ☐ Case-control design
4. ☐ Test-negative design
5. ☐ Not reported
6. ☐ Other

Number of observational studies included

Were RCTs also included in the systematic review?

1. ○ Yes
2. ○ No
3. ○ Unclear

Were there exclusions based on language?

1. ○ Yes
2. ○ No
3. ○ Unclear

If yes, please describe:

List additional exclusions

Study participants

What was the population of interest?

Check all that apply

1. ☐ General population
2. ☐ Pediatric population
3. ☐ Elderly population
4. ☐ People with underlying chronic condition
5. ☐ People with cancer
6. ☐ Pregnant and/or lactating women
7. ☐ Healthcare workers
8. ☐ Occupational group other than HCWs
9. ☐ Unclear
10. ☐ Other

Interventions

Which vaccine(s) were assessed in the systematic review?

Check all that apply

1. ☐ COVID-19
2. ☐ Seasonal influenza
3. ☐ Pandemic influenza
4. ☐ Pneumococcal disease
5. ☐ Meningococcal disease
6. ☐ Pertussis
7. ☐ Rotavirus
8. ☐ HPV
9. ☐ Herpes zoster (Shingles)
10. ☐ Varicella
11. ☐ Measles/mumps/rubella (MMR)
12. ☐ Cholera
13. ☐ Other

Additional details regarding included vaccine(s)

(e.g., tetravalent, live-attenuated, specific SARS-CoV-2 vaccine)

Comparators

Which vaccine(s) was used as the comparator in the systematic review

1. ☐ Unvaccinated
2. ☐ COVID-19
3. ☐ Seasonal influenza
4. ☐ Pandemic influenza
5. ☐ Pneumococcal disease
6. ☐ Meningococcal disease
7. ☐ Pertussis
8. ☐ HPV
9. ☐ Herpes zoster (shingles)
10. ☐ Varicella
11. ☐ Measles/mumps/rubella (MMR)
12. ☐ Cholera
13. ☐ Not reported
14. ☐ Not applicable
15. ☐ Other

Additional details regarding included vaccine(s)

(e.g., tetravalent, live-attenuated, specific SARS-CoV-2 vaccine)

Outcomes

Did the authors formally define vaccine effectiveness?

1. ○ Yes
2. ○ No

Definition of VE from a methodological standpoint

Check all that apply

1. ☐ (1-OR)*100
2. ☐ (1-RR)*100
3. ☐ (1-HR)*100
4. ☐ Not reported
5. ☐ Not applicable
6. ☐ Other

Which outcomes were used to define vaccine effectiveness?

Check all that apply

1. ☐ Laboratory-confirmed infection
2. ☐ Symptomatic disease
3. ☐ Mortality
4. ☐ Hospitalization
5. ☐ Unclear
6. ☐ Not reported
7. ☐ Not applicable
8. ☐ Other

Additional details regarding outcomes (e.g., all-cause mortality)

Were outcomes other than VE considered (e.g., adverse events)?

1. ○ Yes
2. ○ No
3. ○ Unclear

Risk of bias assessment

Did the authors use a previously developed RoB tool?

1. ○ Yes
2. ○ No

If yes, which RoB tool(s) was applied to observational studies in the review?

1. ☐ Newcastle-Ottawa Scale
2. ☐ ROBINS-I
3. ☐ Downs and Black checklist
4. ☐ GRADE
5. ☐ JBI
6. ☐ Not applicable
7. ☐ Other

Did the authors make study-specific modifications to the RoB tool?

1. ○ Yes
2. ○ No
3. ○ Unclear
4. ○ Not applicable

If yes, which modifications were made?

Check all that apply

1. ☐ Dropping items
2. ☐ Adding items
3. ☐ Alternative definitions for some items
4. ☐ Not applicable

5. ☐ Other

Additional details about how the RoB tool was applied

Reference provided for RoB tool

If the authors used a study-specific method to assess RoB, please describe the elements that were included (e.g., types of bias reviewed)

Additional notes

Appendix 2E: Supplementary Tables

Table S2.1 Summary of Characteristics of Included Studies (N=204)

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Feikin (2022), Switzerland [1]	Cohort design; Test-negative case-control, (n=15)	General population; Elderly population	COVID-19 (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Hospitalization	y, ROBINS-I	n
Lindsey (2019), The Gambia [2]	Cohort design; Case-control design, (n=11)	Pediatric population; Elderly population; Other (healthcare workers) Other (Pregnant and/or lactating women)	Seasonal influenza; Pandemic influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Death; Hospitalization; Symptomatic disease; Absenteeism (missed days at work)	y, GRADE	n
Sun (2021), China [3]	Cohort design; Case-control design, (n=64)	Pediatric population	Rotavirus (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Hospitalization	y, NOS	y
Ramsay (2019), Canada [4]	Cohort design; Case-control design; Test-negative case-control; Surveillance; Secondary analysis, (n=20)	General population	Seasonal influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection	y, NOS	y
Wang (2014), China [5]	Cohort design; Case-control design, (n=32)	Pediatric population	Mumps (not reported)	(1-OR)*100; (1-RR)*100	Symptomatic disease	y, NOS	n
Roy (2014), UK [6]	Cohort design, (n=14)	Pediatric population	BCG (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection	y, NOS	n
Pal (2016), New Zealand [7]	Matched case-control design, (n=1)	Pediatric population	Pertussis (unvaccinated)	Narrative description	Laboratory-confirmed infection	y, PRISMA-guided checklist	y
McMillan (2014), Australia [8]	Cohort design; Cross-sectional design; Case-control design, (n=13)	Pediatric population; Other (Pregnant and/or lactating women and infants)	Seasonal influenza; Pandemic influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Hospitalization	y, JBI	n
Alqahtani (2015), Australia [9]	Cohort design; Cross-sectional design; Case-control design, (n=17)	Other (Hajj pilgrims)	Any vaccine that reduces RTIs (influenza, pneumococcal, pertussis, diphtheria,	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, OCEBM tool	unclear

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
			Bacillus Calmette–Guérin (BCG), measles, mumps and rubella vaccine) (unvaccinated)				
Tormen (2022), Italy [10]	Cohort design; Case-control design, (n=14)	Other (Pregnant and/or lactating women)	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Hospitalization	y, ROBINS-I; GRADE	n
Goodman (2022), USA [11]	Not reported, (n=25)	Other (Recurrent respiratory papillomatosis patients, women with HPV-related anogenital disease, MSM, immunocompromised individuals, transgender and non-binary people, sex workers)	HPV (unvaccinated)	Narrative description	Symptomatic disease	y, NOS; GRADE	n
Andersohn (2014), Germany [12]	Cohort design; Case-control design; Prevalence studies; Ecological studies; Self-controlled designs, (n=8)	Pediatric population	Seasonal influenza (unvaccinated)	Narrative description	Symptomatic disease; Death; Hospitalization; Contact with HCP; Quality of Life	y, (IQWiG tool; SIGN tool	unclear
Moberley (2013), Australia [13]	Cohort design; Case-control design, (n=7)	Elderly population; Other (those 18 years and older at higher risk of pneumococcal disease)	Pneumococcal disease (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection	y, RoB-2	unclear
Lukšić (2013), Croatia [14]	Cohort design; Case-control design, (n=11)	Pediatric population	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-RR)*100	Symptomatic disease	y, GRADE	n
Jackson (2013), UK [15]	Cohort design; Case-control design; Screening method studies, (n=30)	General population	Haemophilus influenzae type B (unvaccinated; number of doses received)	(1-OR)*100; Other: VE= 1 - [(PCV* (1 - PPV)) / ((1 - PCV) *PPV)] PCV = Proportion of Cases Vaccinated PPV = Proportion of	Death; Symptomatic disease	n (narrative description/self-developed methods)	n/a

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
				Population Vaccinated			
Breteler (2013), Switzerland [16]	Cohort design; Case-control design, (n=16)	General population	Seasonal influenza; Pandemic influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection; Mortality; Hospitalization; Symptomatic disease (otitis media, ILI, respiratory disease, outpatient visit, respiratory disease, exacerbations of asthma)	y, NOS	unclear
Abubakar (2013), UK [17]	Cohort design; Cross-sectional design; Case-control design; Case population studies, (n=58)	General population	BCG (unvaccinated)	(1-RR)*100; (1-OR)*100	Symptomatic disease; Death	n (narrative description/self-developed methods)	n/a
Eliakim-Raz (2013), Israel [18]	Cohort design; Case-control design, (n=3)	Other (people with cancer)	Seasonal influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	y, NOS; GRADE	y
Davis (2013), USA [19]	Case-control design; pre-post-vaccine introduction time periods, (n=16)	Pediatric population	Pneumococcal disease: Haemophilus influenzae type B (not reported)	(1-RR)*100	Death	y, NOS; CHERG scoring system; GRADE	y
Das (2013), Pakistan [20]	Case-control design, (n=2)	Pediatric population	Cholera; ETEC (unvaccinated)	(1-RR)*100	Symptomatic disease; Death Hospitalization	y, CHERG Rules for Evidence Review	unclear
O'Neill (2014), Canada [21]	Cohort design, (n=5)	Other (Occupational group other than HCWs)	Q fever (unvaccinated)	VE = 1 - [(c1 / N1) / ((co + 1) / (No + 1))], where VE = (1 - RR) * 100, RR = (c1 / N1) (risk in the vaccinated group) and the risk in the unvaccinated group is adjusted with a continuity correction (co + 1) / (No + 1).	Laboratory-confirmed infection; Symptomatic disease	y, ROBANS	unclear

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Chan (2014), China [22]	Cohort design; Case-control design, (n=11)	Elderly population	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Mortality (due to pneumonia or influenza); Hospitalization; Symptomatic disease (clinically defined ILI, clinically defined pneumonia)	y, NOS	y
Darvishian (2014), Netherlands [23]	Cohort design, (n=14)	Elderly population	Seasonal influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	n (narrative description/self-developed methods)	n/a
Remschmidt (2014), Germany [24]	Cohort design, (n=3)	General population; Pediatric population; Other (People with underlying chronic condition); Other (Individuals with HIV infection)	Seasonal influenza (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease; Hospitalization	y, CASP; GRADE	n
Remschmidt (2014), Germany [25]	Cohort design, (n=5)	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	y, CASP; GRADE	n
Machaira (2015), Greece [26]	Cohort design, (n=5)	Pediatric population	Hepatitis B (HBIG recipients)	(1-OR)*100	Laboratory-confirmed infection; Mortality (all-cause)	y, NOS	n
Li (2015), China [27]	Cohort design; Case-control design, (n=18)	General population	Seasonal influenza (not reported)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Hospitalization; Symptomatic disease	y, NOS	n
Remschmidt (2015), Germany [28]	Cohort design; Case-control design, (n=11)	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	y, NOS; GRADE	n
de Oliveira (2015), USA [29]	Case-control design, (n=8)	Pediatric population	Rotavirus (hospitalized controls)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Hospitalization	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Remschmidt (2015), Germany [30]	Cohort design; Case-control (matched) design, (n=23)	General population; Elderly population; Other (People with underlying chronic condition); Other (Pregnant and/or lactating women)	Seasonal influenza (unvaccinated)	(1-OR)*100	Symptomatic disease; Death; Hospitalization	n (narrative description/self-developed methods)	n/a
Hirve (2016), Switzerland [31]	Cohort design; Case-control design, (n=18)	Pediatric population; Elderly population; Other (Pregnant and/or lactating women); Other (high risk individuals, healthy adults)	Seasonal influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	y, NOS	n
Kraicer-Melamed (2016), Canada [32]	Cohort design; Case-control design; Ecological studies; Surveillance methods, (n=29)	Elderly population	Pneumococcal disease (unvaccinated)	Other (Broome method)	Symptomatic disease (community-acquired pneumonia, invasive pneumococcal disease)	y, NACI guidelines for quality assessment	unclear
Fulton (2016), USA [33]	Cohort design; Case-control design; Screening study, (n=23)	Pediatric population	Pertussis (not reported)	Narrative description	Laboratory-confirmed infection; Symptomatic disease	y, CHERG-adapted GRADE process	y
Garland (2016), Australia [34]	Cohort design; Cross-sectional design; Case-control design, (n=29)	General population	HPV (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease (genital warts, cervical lesions)	n (narrative description/self-developed methods)	n/a
Lamberti (2016), USA [35]	Not reported, (n=19)	Pediatric population	Rotavirus (not reported)	(1-OR)*100; (1-HR)*100	Symptomatic disease; Death; Hospitalization	y, CHERG	unclear
Casanova (2016), France [36]	Cohort design; Case-control design, (n=7)	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	Other (Risk reduction)	Death; Hospitalization	y, Gradation of the National Agency of accreditation and health assessment	unclear
Santos (2016), Brazil [37]	Cohort; Cross-sectional; Case-control design; Case series; Surveillance methods, (n=20)	Pediatric population	Rotavirus (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Hospitalization	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Zhang (2016), China [38]	Cohort design; Prospective study, retrospective, (n=5)	Elderly population	Seasonal influenza; Pneumococcal disease (unvaccinated)	(1-RR)*100	Symptomatic disease; Mortality	y, NOS	n
Caspard (2017), USA [39]	Cohort design; Case-control design; Test-negative design, (n=29)	Pediatric population	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection	n (narrative description/self-developed methods)	n/a
Willame (2018), Belgium [40]	Cohort design; Case-control design; Test-negative design, (n=29)	Pediatric population	Rotavirus (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease	y, CoCanCPG	n
Poudel (2019), USA [41]	Cohort design, (n=8)	Other (People with underlying chronic condition); Other (Patients with heart failure)	Seasonal influenza (unvaccinated)	(1-HR)*100	Mortality; Hospitalization	y, NOS	n
Domnich (2017), Italy [42]	Cohort design; Case-control design, (n=11)	General population; Elderly Population (long-term care facilities)	Seasonal influenza (unvaccinated; recipients of other influenza vaccines)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Symptomatic disease; Hospitalization	y, NOS	n
Falkenhorst (2017), Germany [43]	Cohort design; Case-control design; Case-case design, (n=13)	Elderly population; Other (People with underlying chronic condition)	Pneumococcal disease (unvaccinated)	(1-OR)*100	Symptomatic disease	y, NOS; GRADE	unclear
Lansbury (2017), UK [44]	Cohort design; Case-control design; Test-negative design; Screening method studies, (n=36)	General population; Pediatric population	Pandemic influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Hospitalization	y, NOS; AHRQ; RoB-2	unclear
Bekkat-Berkani (2017), USA [45]	Cohort design; Self-controlled case series, (n=9)	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	Narrative description	Death; Hospitalization	y, SIGN checklists	unclear
Tin Tin Htar (2017), Italy [46]	Cohort design; Case-control design; Case-cohort, Self-controlled risk windows, (n=33)	General population	Pneumococcal disease (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Symptomatic disease	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Vasileiou (2017), UK [47]	Cohort design; Case-control design, (n=15)	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Hospitalization	y, EPHPP quality assessment tool; GRADE	n
Bi (2017), USA [48]	Cohort design; Case-control design; Case-cohort, (n=6)	General population	Cholera (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection	y, NOS	n
Hungerford (2017), UK [49]	Cohort design; Case-control design, n=30	General population	Rotavirus (unvaccinated)	(1-OR)*100; (1-RR)*100	Contact with HCP	y, NOS	n
Furuta (2017), Japan [50]	Cohort design; Case-control design, n=13	Other (Pregnant and/or lactating women)	Pertussis (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Pregnancy-related outcomes (preterm deliveries)	y, GRADE; RoB-2	n
Restivo (2018), Italy [51]	Cohort design; Case-control design, n=38	Pediatric population; Elderly population; Other (People with underlying chronic condition); Other (Pregnant and/or lactating women); Other (Healthcare workers)	Seasonal influenza; Pandemic influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Death; Hospitalization	y, NOS; RoB-2	unclear
Zhu (2018), China [52]	Cohort, computer system-based, n=23	Pediatric population	Varicella (not reported)	Narrative description	Symptomatic disease	y, NOS	y
Young (2018), Singapore [53]	Test-negative design, n=14	General population	Seasonal influenza (seasonal influenza)	(1-OR)*100	Laboratory-confirmed infection	y, GRADE	n
Schwerdtle (2018), Australia [54]	Case-control design; Case-cohort design, n=4	General population; Other (areas where cases reached epidemic threshold and cholera epidemic was declared)	Cholera (unvaccinated)	(1-OR)*100	Symptomatic disease	y, JBI	unclear
Yin (2018), China [55]	Cohort design; Case-control design, n=12	Pediatric population	Varicella (varicella)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NOS	n
Bitterman (2018), Israel [56]	Cohort design; Case-control design, n=3	Other (people with cancer)	Seasonal influenza; Pandemic	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Death;	y, NOS; GRADE	unclear

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
			influenza (unvaccinated; placebo)		Hospitalization; Composite outcomes (hospitalizations for fever or acute respiratory infection, pneumonia requiring antibiotics, chemotherapy interruptions due to infection, necessity of antibiotics during hospitalization)		
Dos Santos (2018), Belgium [57]	Cohort design; Case-control design, n=9	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	Narrative description	Symptomatic disease; Death Hospitalization; Contact with HCP	y, SIGN checklist	n
Zimmerman (2018), Australia [58]	Cohort design; Case-control design, n=8	General population; Pediatric population	Other: tuberculosis (BCG) (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, ROBINS-I	n
Lee (2018), Canada [59]	Cohort design, n=4	Elderly population	Seasonal influenza (seasonal influenza)	(1-OR)*100; pooled rVE (to compare HD-IIV_3 versus SD-IIV_3)	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization; Contact with HCP	y, Downs and Black checklist	y
Bartoszko (2018), Canada [60]	Cohort design; Case-control design; Test-negative design, n=34	General population; Pediatric population	Seasonal influenza; Pandemic influenza (seasonal influenza)	(1-OR)*100	Laboratory-confirmed infection	y, NOS; GRADE	n
Markowitz (2018), Canada [61]	Cohort design; Cross-sectional design; Case-control design, n=14	General population	HPV (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease	n (narrative description/self-developed methods)	n
Chit (2018), Canada [62]	Cohort design; Case-control design, n=7	Pediatric population	Pertussis (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, Downs and Black checklist	Unclear
Yin (2018), China [63]	Cohort design; Case-cohort, n=9	Elderly population	Seasonal influenza; Pneumococcal disease (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease (classifications based on (ICD-10-AM,	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
					ICD-9-CM, ICD)); Death; Hospitalization;		
Harder (2018), Germany [64]	Cohort design; Cross-sectional design, n=3	Pediatric population	Pertussis (unvaccinated)	(1-RR)*100	Symptomatic disease (recurrent high grade anal intraepithelial neoplasia (AIN), anal condyloma, persisting oral infection)	y, ROBINS-I; GRADE	n
Campbell (2018), UK [65]	Cohort design; Non-randomized intervention study, n=7	Elderly population	Seasonal influenza; Pneumococcal disease (unvaccinated)	Narrative description	Laboratory-confirmed infection; Hospitalization; Symptomatic disease	y, RoB-2	y
Tricco (2018), Canada [66]	Cohort design; Case-control design; Non-randomized, n=5	Other (Males only (no age restriction))	Herpes zoster (Shingles) (placebo)	(1-OR)*100; (1-RR)*100	Symptomatic disease (herpes zoster ophthalmicus, postherpetic neuralgia)	y, NOS; RoB-2	n
Sings (2019), USA [67]	Case-control design; Indirect cohort, n=8	Pediatric population; Other(infants following immunization in pregnancy)	Pneumococcal disease (unvaccinated)	(1-OR)*100	Symptomatic disease	y, NOS	n
Yakley (2019), USA [68]	Cohort design, n=3	Other (MSM >25 years old, females 9-18 years, females 15-22 with evidence of sexual activity)	HPV (unvaccinated)	Narrative description	Symptomatic disease	n (narrative description/self-developed methods)	n
Ngocho (2019), Tanzania [69]	Laboratory surveillance (before and after vaccine), n=8	Pediatric population	Pneumococcal disease (other: before/after design)	(1-OR)*100; (1-RR)*100	Symptomatic disease	y, NOS; NHLBI Study Quality Assessment Tool	n
Senderovich (2019), Canada [70]	Cohort design; Case-control design, n=7	Elderly population (Long-term care facility residents)	Herpes zoster (Shingles) (unvaccinated)	Narrative description	Laboratory-confirmed infection	y, RoB-2	unclear
Adetokunboh (2019), South Africa [71]	Cohort design; Cross-sectional design; Case-control design, n=9	Pediatric population; Other (HIV-infected in comparison with HIV-exposed or HIV-	Other ('standard' vaccines) (?) (unvaccinated; other)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, GRADE; RoB-2	y

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
		uninfected children aged <18 years)					
Doyon-Plourde (2019), Canada [72]	Cohort design; Case-control design; Case-base, n=22	General population	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100	Laboratory-confirmed infection; Hospitalization; Contact with HCP	y, ROBINS-I; GRADE	y
Vardanjani (2019), Iran [73]	Case-control design; Pre-post studies, n=7	Pediatric population; Other (pediatric population living with and without HIV)	Pneumococcal disease (unvaccinated)	(1-OR)*100; (1-RR)*100	Symptomatic disease	y, NOS	n
Harmala (2019), UK [74]	Cohort design, n=5	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	(1-RR)*100	Death; Hospitalization	y. NOS; GRADE	unclear
NicLochlain (2019), Netherlands [75]	Pre-post (within study comparisons), n=8	Pediatric population; Other (infants <9 months)	Other: first measles-containing vaccine (MCV1) (unvaccinated)	(1-RR)*100	Symptomatic disease	y, GRADE	n
NicLochlain (2019), Netherlands [76]	Not reported, n=2	Pediatric population; Other (infants <9 months)	Other: measles-containing vaccine (unvaccinated)	Narrative description	Symptomatic disease	y, GRADE	n
Friedman (2019), Canada [77]	Cohort design, n=19	General population; Pediatric population; Elderly population	Seasonal influenza (unvaccinated)	(1-OR)*100; (1-RR)*100	Symptomatic disease; Death; Hospitalization; Contact with HCP	y, CASP	y
Drolet (2019), Canada [78]	Time-trend analysis, n=40	General population	HPV (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	n (narrative description/self-developed methods)	n
Lindsey (2019), Gambia [79]	Case-control design; Cohort design, n=11	General population; Pediatric population; Elderly population	Seasonal influenza; Pandemic influenza (not reported)	(1-OR)*100	Laboratory-confirmed infection; Death; Hospitalization	y, GRADE	n
Tadount (2020), Canada [80]	Test-negative design, n=6	Elderly population	Seasonal influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection	y, ROBINS-I; GRADE	y

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Hughes (2020), Canada [81]	Surveillance methods (vaccine registry), n=36	General population	Other: measles-containing vaccine (not reported)	Narrative description	Symptomatic disease	y, ROBINS-I	y
Quach (2020), USA [82]	Cohort design; Case-control design, n=14	Other (Pregnant and/or lactating women)	Seasonal influenza; Pandemic influenza (unvaccinated)	(1-RR)*100; (1-OR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NOS	n
Jarvis (2020), UK [83]	Cohort design; Case-control design; Screening method, n=15	Other (Pregnant and/or lactating women); Pediatric population (infants)	Seasonal influenza; Pandemic influenza (not reported)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Contact with HCP	y, NHLBI tool	n
Vygen-Bonnet (2020), Germany [84]	Cohort design; Case-control design, n=8	Other (Pregnant and/or lactating women); Pediatric population (infants)	Pertussis (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Death; Hospitalization	y, ROBINS-I; GRADE	n
Kalligeros (2020), USA [85]	Test-negative design, n=28	Pediatric population	Seasonal influenza (not reported)	Pooled VE, effect estimate not specified	Hospitalization	y, NOS	n
Berman-Rosa (2020), Canada [86]	Cohort design; Case-control design; Indirect cohort, n=13	Pediatric population	Pneumococcal disease (unvaccinated)	(1-OR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NACI guidelines for quality assessment	y
Di Pietrantonj (2020), Italy [87]	Cohort design; Case-control design; Case-only ecological method studies, n=51	Pediatric population	Varicella; Measles/mumps/ rubella (MMR) (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NOS; GRADE	n
Kandeil (2020), Belgium [88]	Cohort design; Case-control design, n=11	Other (Pregnant and/or lactating women); Pediatric population (infants)	Pertussis (not reported)	(1-OR)*100; (1-RR)*100; (1-HR)*100	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	n (narrative description/self-developed methods)	n
Yitbarek (2020), Ethiopia [89]	Cohort design; Cross-sectional design; Case-control design; Multinational surveillance data analysis, n=6	General population; Pediatric population	BCG (unvaccinated)	Narrative description	Symptomatic disease; Death; Hospitalization	y, JBI	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Mo (2020), China [90]	Cohort design (retrospective), n=5	Other (People with underlying chronic condition)	Pneumococcal disease (unvaccinated; placebo)	(1-RR)*100, where RR = OR / [(1 - Po) + (Po * OR)], where Po is the event incidence in the control group	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization	y, NOS; GRADE	n
Zangiabadian (2020), Iran [91]	Cohort design; Case-control design, n=11	General population	Seasonal influenza (unvaccinated)	Narrative description	Death	y, JBI	n
McMillan (2021), Australia [92]	Cohort design; Cross-sectional design; Case-control design; Interrupted time series, n=22	General population; Pediatric population	Meningococcal disease (unvaccinated; pre- and post-vaccination period)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, ROBINS-I	n
Lee (2021), Canada [93]	Cohort design; Test-negative design, n=12	Elderly population	Seasonal influenza (seasonal influenza)	(1-OR)*100; pooled rVE (to compare HD-IIV3 versus SD-IIV)	Laboratory-confirmed infection; Death; Hospitalization; Contact with HCP	y, Downs and Black checklist	y
van den Boogaard (2021), Netherlands [94]	Not reported, n=1	Pediatric population; Other (Pregnant and/or lactating women)	Other (rubella-containing vaccines) (not reported)	(1-RR)*100	Not reported	y, GRADE	n
Brown (2021), USA [95]	Cohort design; Cross-sectional design, n=33	General population	HPV (unvaccinated; other type of vaccine)	Narrative description	Symptomatic disease (Type-specific anogenital HPV prevalence/incidence in vaccinated versus unvaccinated populations or comparing various dosing schedules, genital warts)	y, ROBINS-I	unclear
Boddington (2021), UK [96]	Case-control design; Test-negative design, n=37	Pediatric population	Seasonal influenza (not reported)	Pooled VE, effect estimate not specified	Hospitalization; Laboratory-confirmed infection	y, ROBINS-I	unclear

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Xu (2021), Canada [97]	Cohort design; Cross-sectional design; Case-control design, n=54	Pediatric population	Measles (MCV1, MCV2) (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, ROBINS-I; GRADE	y
Wall (2021), USA [98]	Cohort design; Test-negative design, n=10	Pediatric population	Seasonal influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Hospitalization	y, NHLBI tool	unclear
Coleman (2021), Canada [99]	Cohort design; Case-control design; Test-negative design, n=20	Elderly population	Seasonal influenza (unvaccinated; non-influenza comparator vaccine)	(1-OR)*100; (1-RR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease (clinically diagnosed influenza)	y, ROBINS-I; GRADE	n
Zhang (2021), China [100]	Cohort design, n=12	Pediatric population	Varicella (not reported)	(1-RR)*100	Symptomatic disease	y. NOS; GRADE	y
Tsentemeidou (2021), Greece [101]	Cross-sectional design, n=4	General population; Pediatric population; Other (Young men who have sex with men)	HPV (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection	y, NIH tool	n
Harder (2021), Germany [102]	Cohort design; Case-control design; Test-negative design, n=28	General population; Other (Healthcare workers)	COVID-19 (unvaccinated)	Narrative description	Laboratory-confirmed infection (asymptomatic SARS-CoV2 infections); Symptomatic disease	y, ROBINS-I	y
Nielsen (2021), Denmark [103]	Cohort design; Cross-sectional design; Case-control design, n=8	General population	HPV (unvaccinated)	Narrative description	Laboratory-confirmed infection	y, NIH tool	n
Harder (2021), Germany [104]	Cohort design; Cross-sectional design; Test-negative design, n=17	General population; Elderly population (Residents of long term care); Other (Healthcare workers)	COVID-19 (unvaccinated)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection; Symptomatic disease (severe disease); Hospitalization; Disease severity	y, ROBINS-I	n
Sharif (2021), Bangladesh [105]	Observational study, n=1	General population	COVID-19 (placebo)	Narrative description	Laboratory-confirmed infection	y, SYRCLE	n
Liu (2021), China [106]	Cohort design; Cross-sectional design; Case-control design, n=32	General population; Elderly population; Other (People with underlying chronic condition); Other (Healthcare workers)	COVID-19 (unvaccinated)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization (ICU admissions)	y, NOS; AHRQ checklist	y

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Chen (2021), China [107]	Cohort design, n=14	Pediatric population	Varicella (unvaccinated)	(1-RR)*100	Symptomatic disease (varicella infection)	y, NOS	y
Kow (2021), UK [108]	Cohort design; Case-control design, n=19	General population; Elderly population; Other (Healthcare workers)	COVID-19 (unvaccinated)	(1-HR); (1-IRR); (1-OR)	Laboratory-confirmed infection	y, NOS	n
Andani (2022) [109]	Not reported, n=28	Pediatric population	Hepatitis A (unvaccinated)	Narrative description	Symptomatic disease (reported Hepatitis A cases)	n (narrative description/self-developed methods)	n
Almasri (2022), Belgium [110]	Cohort design; Case-control design; "Descriptive non-experimental studies or retrospective comparisons of vaccine outcomes"; Survey study (supplementary material), n=32	Other (People with underlying chronic condition)	All vaccines recommended to adults with DM over age 65 (not reported)	Narrative description	Mortality; Hospitalization	y, PRIMA-guided checklist	unclear
Sim (2021), USA [111]	Cohort design; Cross-sectional design, n=4	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, ROBINS-I	n
Fu (2022), Singapore [112]	Cohort design; Cross-sectional design; Case-control design, n=1	Pediatric population; Other (Pregnant and/or lactating women)	COVID-19 (unvaccinated)	Narrative description	Symptomatic disease	y. NIH tool	n
Wang (2021), Canada [113]	Cohort design; Cross-sectional design; Case-control design, n=96	General population; Pediatric population; People with underlying chronic condition	HPV (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease	y, ROBINS-I	y
Sung (2022), Sweden [114]	Retrospective cohort design, n=3	Other (People with underlying chronic condition)	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Mortality	y, NOS	unclear
Kow (2022), UK [115]	Cohort design; Case-control design; Test-negative design, n=7	General population	COVID-19 (unvaccinated)	Other [(pooled HR - 1) / HR or (pooled OR - 1) / OR)]	Laboratory-confirmed infection	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Izurieta (2022), Belgium [116]	Cohort design; Case-control design; Surveillance active prospective, ecological, n=4	Pediatric population	Pneumococcal disease (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease	y, ROBINS-I	n
Puig-Barberà (2022), Spain [117]	Cohort design; Test-negative design, n=12	General population; Elderly population	Seasonal influenza (seasonal influenza)	(1-RR)*100	Laboratory-confirmed infection; Hospitalization; Healthcare utilisation ('outpatient consultation', emergency room visit)	y, ROBINS-I	n
Kow (2022), Malaysia [118]	Cohort design; Case-control design; Test-negative design, n=7	General population	COVID-19 (unvaccinated)	Other [(pooled HR - 1) / HR or (pooled OR - 1) / OR)]	Laboratory-confirmed infection	y, NOS	unclear
Huang (2022), Taiwan [119]	Cohort design, n=1	Other (COVID-19 patients)	COVID-19 (unvaccinated)	(1-RR)*100	Symptomatic disease	y, NOS	n
Bhurwal (2022), USA [120]	Cohort design; Survey-based studies, n=21	Other (People with underlying chronic condition)	COVID-19 (unvaccinated)	(1-OR)*100	Symptomatic disease	y, ROBINS-I;NIH tool	unclear
Gertosio (2022), Italy [121]	Cohort design; Case-control design, n=3	Pediatric population (children with chronic conditions requiring therapy with biologics)	Seasonal influenza; Measles/mumps/ rubella (MMR) (not reported)	Narrative description	Disease exacerbation/deterioration; Relapse of disease	y. STROBE	n
Zheng (2022), China [122]	Cohort design; Case-control design; Test-negative case-control, n=51	General population; Elderly population; Other (Healthcare workers); Other (hospitalized adults, prioritized population, veterans, adolescents)	COVID-19 (not reported)	(1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Laboratory-confirmed infection; Mortality; Hospitalization;	y, Downs and Black checklist	n
Galmiche (2022), France [123]	Cohort design; Test-negative design, n=4	Other (People with underlying chronic condition)	COVID-19 (not reported)	Narrative description	Laboratory-confirmed infection; Hospitalization	y, NIH tool	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Marra (2022), USA [124]	Cohort design, n=33	Other (People with underlying chronic condition)	COVID-19 (unvaccinated; vaccinated control group)	(1-DOR)*100	Symptomatic disease	y, Downs and Black checklist	y
Gärtner (2022), Germany [125]	Retrospective cohort design, n=7	Elderly population	Seasonal influenza (seasonal influenza)	Other (rVE(adjuvanted TIV vs. TIV-HD) = (1 - 1 / (1 - rVE(TIV-HD vs. adjuvanted TIV) / 100)) × 100)	Laboratory-confirmed infection; Symptomatic disease; Death; Hospitalization; Contact with HCP	y, ROBINS-I	n
Ssentongo (2022), USA [126]	Cohort design; Case-control design, n=13	General population	COVID-19 (unvaccinated)	(1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NOS; GRADE	n
Prasad (2022), UK [127]	Cohort design; Case-control design; Test-negative design, n=3	Other (Pregnant and/or lactating women)	COVID-19 (unvaccinated)	(1-HR)*100	Laboratory-confirmed infection; Death; Hospitalization; Symptomatic disease; Pregnancy-related outcomes (delivery and fetal)	y, ROBINS-I	n
Gupta (2022), Canada [128]	Cohort design, n=7	Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	(1-RR)*100	Death; Hospitalization	y, NOS; GRADE	y
Zeng (2022), China [129]	Cohort design; Case-control design; Test-negative design, n=46	General population; Pediatric population; Elderly population (residents of long-term care facilities); Other (Healthcare workers)	COVID-19 (unvaccinated)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection; Symptomatic disease	y, NOS	n
Tsiakos (2022), Greece [130]	Retrospective cohort design, n=5	Other (people with cancer)	Seasonal influenza (unvaccinated)	(1-OR)*100	Mortality; Incidence of disease	y, JBI	n
Piechotta (2022), Germany [131]	Cohort design, n=22	Other (people with cancer)	COVID-19 (not reported)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y; GRADE; RoB-OPS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Marra (2022), Brazil [132]	Cohort design; Case-control design; Before-after (Pre-post), time series, n=48	Pediatric population	Pneumococcal disease (unvaccinated; period prior to pneumococcal vaccination)	(1 - OR)*100; (1 - RR)*100	Symptomatic disease	y, NHLBI tool	unclear
Baradaran (2022), UK [133]	Cohort design, n=8	General population; Healthcare workers	COVID-19 (unvaccinated)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, JBI	n
Domnich (2022), Italy [134]	Retrospective cohort design, n=10	Elderly population	Seasonal influenza (seasonal influenza)	(1 - RR)*100; (1 - HR)*100; (1 - OR)*100 (rVE for aTIV/aQIV versus hdTIV/hdQIV)	Hospitalization; Healthcare utilisation (medical encounters, any cardio-respiratory condition, pneumonia, asthma/COPD/bronchial , coronary artery, myocardial infarction, congestive heart failure, cerebrovascular events, stroke, influenza-related office visits)	y, ROBINS-I; GRACE checklist	n
Zou (2022), USA [135]	Cohort design; Case-control design; Observational study, n=13	Unclear	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection	y, NOS	n
Kechagias (2022), UK [136]	Cohort design; Case-control design, n=12	General population	HPV (unvaccinated)	(1-RR)*100	Symptomatic disease (HPV-related lesion recurrence (e.g., CIN2+, CIN3))	y, ROBINS-I; GRADE	n
Shao (2022), China [137]	Cohort design; Case-control design; Test-negative design, n=113	General population; Elderly population; Healthcare workers; Other: adolescents, close contacts of COVID-19 cases	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization; Healthcare utilisation (emergency department or urgent care visits)	y, NOS	n

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Külper-Schiek (2022), Germany [138]	Cohort design; Case-control design; Test-negative design, n=26	General population; People with underlying chronic condition; Healthcare workers; Other: Veterans	COVID-19 (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, ROBINS-I; GRADE	n
Xia (2022), China [139]	Cohort design, n=19	General population; People with underlying chronic condition	Herpes zoster (Shingles) (unvaccinated)	(1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease	y, RoB-2	n
Petras (2022), Czech Republic [140]	Cohort design; Cross-sectional design; Case-control design, n=290	General population	COVID-19 (unvaccinated)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection; Symptomatic disease	y, NOS; GRADE	y
Markowitz (2022), Canada [141]	Cohort design; Cross-sectional design; Case-control design, n=35	General population	HPV (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease (anogenital warts, cervical abnormalities)	y, ROBINS-I	y
Mbinta (2022), UK [142]	Cohort design; Case-control design, n=22	Elderly population	Herpes zoster (Shingles) (unvaccinated)	(1-HR)*100	Symptomatic disease; Hospitalization; Quality of life	y, JBI; GRADE	n
Au (2022), China [143]	Cohort design; Case-control design, n=47	General population	COVID-19 (unvaccinated)	(1-OR)*100	Symptomatic disease; Mortality; Hospitalization	y, ROBINS-I	unclear
Deng (2022), China [144]	Cohort design; Case-control design, n=11	General population	COVID-19 (COVID-19)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, Downs and Black checklist	n
Gao (2022), China [145]	Cohort design; Cross-sectional design; Case-control design, n=18	General population	COVID-19 (unvaccinated)	(1-RR)*100	Symptomatic disease (long COVID)	y, NOS; AHRQ checklist	n
Rahmani (2022), Netherlands [146]	Cohort design; Case-control design, n=54	General population; Elderly population (Nursing home residents); Other (Healthcare workers)	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100	Laboratory-confirmed infection; Mortality; Hospitalization	y, NOS	n

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Martinez (2022), USA [147]	Cohort design, n=26	General population (infant vaccination on outcomes in young children, adolescents, and adults)	Other: Tuberculosis Bacillus Calmette–Guérin (BCG) (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection	y, NOS	n
Berild (2020), Norway [148]	Cohort design; Case-control design; Test-negative design; Indirect cohort, n=10	Elderly population	Pneumococcal disease (unvaccinated; placebo)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Mortality (all-cause, pneumococcal and/or serotype-specific disease)	y, NOS	y
Bechini (2020), Italy [149]	Cohort design; Case-control design, n=6	Elderly population; Other (People with underlying chronic condition)	Seasonal influenza (unvaccinated)	(1-RR)*100	Mortality; Hospitalization	y, NOS; GRADE	n
Murunga (2020), Kenya [150]	Case-control design, n=13	Pediatric population	Rotavirus (unvaccinated)	(1-OR)*100	Hospitalization	y, NOS; GRADE	n
Yang (2021), China [151]	Case-control design; Test-negative design, n=21	General population	Seasonal influenza (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection	y, NOS; GRADE	n
Okoli (2021), UK [152]	Test-negative design, n=72	General population; Elderly population	Seasonal influenza (not reported)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection	n (narrative description/self-developed methods)	n/a
Iheanacho (2021), Nigeria [153]	Not reported, n=11	General population	COVID-19 (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Mortality	y, NHLBI tool	unclear
Fan (2021), China [154]	Observational study, n=4	General population	COVID-19 (unvaccinated)	(1-RR)*100	Symptomatic disease; Laboratory-confirmed infection (Asymptomatic COVID-19 cases)	y, QUIPS tool	n
Perego (2021), Italy [155]	Cohort design; Cross-sectional design, n=2	Other (US military service members on active duty)	Seasonal influenza (unvaccinated)	(1-OR)*100	Symptomatic disease; Hospitalization	y, NOS; ROBINS-I	n

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Li (2021), China [156]	Cohort design; Case-control design, n=10	Healthcare workers	Seasonal influenza (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease; Absenteeism (incidence of absenteeism, the number of working days lost per person)	y, NOS	unclear
Hayawi (2021), United Arab Emirates [157]	Cohort design; Case-control design; Test-negative design, n=29	General population	COVID-19 (not reported)	Narrative description	Laboratory-confirmed infection	y, GRADE	n
Cheng (2021), Taiwan [158]	Cohort design; Case-control design, n=39	General population; Elderly population (residents of long-term care facility); Other (People with underlying chronic condition); Other (Healthcare workers);	COVID-19 (unvaccinated; number of doses received)	(1-OR)*100; (1-HR)*100; (1 - IRR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization;	y, ROBINS-I	unclear
Pormohammad (2021), Canada [159]	Cohort design; Case-control design, n=35	General population	COVID-19 (unvaccinated)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection; Mortality; Hospitalization; Symptomatic disease	y, JBI	n
Marra (2021), USA [160]	Cohort design; Case-control design, n=16	Other (Healthcare workers)	COVID-19 (unvaccinated)	(1-DOR)*100	Laboratory-confirmed infection	y, Downs and Black checklist	y
Meggiolaro (2022), Italy [161]	Cohort design; Cross-sectional design; Case-control design; Test-negative design, n=31	General population; Elderly population (long-term care facility residents); Other (Healthcare workers)	COVID-19 (unvaccinated; pre- and post-vaccination period)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NOS	y
Ma (2022), China [162]	Cohort design, n=6	Other (Pregnant and/or lactating women)	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, NOS	n
Mahumud (2022), Australia [163]	Cohort design; Case-control design; Case-case design, n=11	Unclear	COVID-19 (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection	y, JBI	n

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Ghazy (2022), Egypt [164]	Cohort design; Case-control design; Observational study, n=14	General population; Elderly population (residents in a long-term care facility, nursing home residents, Veterans, and others); Other (Healthcare workers)	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality	y, NHLBI tool	n
Chang (2022), China [165]	Test-negative design, n=19	General population; Pediatric population (Adolescent patients); Other (Healthcare workers)	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection	y, NOS	n
Wang (2022), China [166]	Cohort design; Case-control design; Test-negative design, n=38	General population; Pediatric population; Elderly population; Other (Healthcare workers)	COVID-19 (unvaccinated; asymptomatic vs symptomatic cases)	y, (1-OR)*100	Laboratory-confirmed infection	y, NOS	n
Cai (2022), China [167]	Cohort design; Case-control design; Case series; Non-randomized, n=28	Other (women with precancerous lesions)	HPV (unvaccinated; not reported)	(1-IRR)*100	Laboratory-confirmed infection (HSIL regression, HPV clearance; would fall under lab-confirmed infection), Symptomatic disease (HSIL recurrence)	y, NOS; ROBINS-I; Recommendations by NICE for case-series	unclear
Jansen (2022), Netherlands [168]	Cohort design, n=8	Pediatric population	Pneumococcal disease; Meningococcal disease; HPV; Varicella; Measles/mumps/ rubella (MMR); Hepatitis A and B (unvaccinated)	Narrative description	Symptomatic disease; Laboratory-confirmed infection	y, OCEBM tool	unclear
Zhu (2022), China [169]	Cohort design; Test-negative case-control, n=7	Unclear	COVID-19 (number of doses received)	(1-OR)*100	Laboratory-confirmed infection	y, NOS	y
Foucambert (2022), USA [170]	Case-control design, n=1	Pediatric population	Dengue (unvaccinated)	Narrative description	Symptomatic disease	y, JBI	y

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Marra (2022), Brazil [171]	Cohort design; Case-control design, n=16	Unclear	COVID-19 (unvaccinated)	(1-DOR)*100	Laboratory-confirmed infection; Hospitalization	y, Downs and Black checklist	y
Liu (2022), China [172]	Cohort design; Case-control design, n=6	Other (People with underlying chronic condition); Other (USA military)	Seasonal influenza (unvaccinated)	(1-OR)*100	Symptomatic disease (atrial fibrillation, ventricular arrythmia, flutter, primary cardiac arrest)	y, NOS	n
Sabu (2022), Australia [173]	Cohort design; Case-control design; Test-negative design, n=13	Pediatric population	COVID-19 (unvaccinated)	(1-OR)*100	Hospitalization (ICU admissions); Symptomatic disease	y, QATSDD tool	y
Wallace (2022), Ethiopia [174]	Cohort design; Test-negative design; Longitudinal household survey, n=26	General population; Other (Pregnant and/or lactating women); Other (Healthcare workers); Other (groups prioritized for vaccination)	COVID-19 (not reported)	(1-OR)*100; (1-RR)*100; (1-HR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, NOS; GRADE	n
Angkasekwinai (2022), Thailand [175]	Cohort design; Case-control design; Test-negative design, n=7	General population; Healthcare workers	COVID-19 (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, NOS	unclear
Ruiz (2023), USA [176]	Cohort design; Cross-sectional design; Case reports, n=3	Other (people with cancer)	COVID-19 (unvaccinated; non-ICI interventions)	(1-RR)*100	Laboratory-confirmed infection	y, NOS	n
Wu (2023), China [177]	Cohort design; Test-negative design; Test-negative case-control, n=4	General population	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Symptomatic disease	y, ROBINS-I	n
Paul (2023), Qatar [178]	Cohort design; Case-control design; Test-negative design, n=51	General population	COVID-19 (unvaccinated)	Narrative description	Laboratory-confirmed infection; Mortality; Hospitalization; Disease severity	y, NOS	unclear
Jones-Gray (2023), Australia [179]	Cohort design; Case-control design; Test-negative design, n=83	General population	Seasonal influenza (unclear)	Pooled VE, effect estimate not specified	Laboratory-confirmed infection	y, ROBINS-I; GRADE	n
Hameed (2023), Pakistan [180]	Cohort design, n=6	Pregnant and/or lactating women	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Hospitalization (ICU admissions)	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
					Pregnancy-related outcomes (delivery and fetal)		
Xu (2023), China [181]	Cohort design; Case-control design; Descriptive studies, n=21	General population	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100	Laboratory-confirmed infection; Symptomatic disease	y, NOS; AHRQ checklist	n
Tan (2023), Singapore [182]	Cross-sectional design; Cohort desing; Non-randomized controlled trial, n=6	Other (People with underlying chronic condition)	COVID-19 (not reported)	Narrative description	Symptomatic disease	y, ROBINS-I	n
Menegale (2023), Italy [183]	Cohort design; Case-control design; Test-negative design, n=40	General population; Pediatric population; Elderly population	COVID-19 (unvaccinated; individuals who received the vaccine not earlier than 14 days)	VE(t) = A * e^(-w * t), VE(t): Represents vaccine effectiveness as a function of time A: A constant representing the initial vaccine effectiveness. e: The base of the natural logarithm. w: A rate constant representing the rate at which vaccine effectiveness wanes over time. t: Time.	Laboratory-confirmed infection; Symptomatic disease	y, NOS	n
Comber (2021), Ireland [184]	Cohort design; Test-negative design, n=9	General population; Elderly population	Seasonal influenza (unvaccinated; placebo; other vaccines of influenza)	(1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Laboratory-confirmed infection; Mortality; Hospitalization	y, ROBINS-I; GRADE	unclear

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Jordan (2023), Ireland [185]	Cohort design; Test-negative design, n=4	General population	Seasonal influenza (unvaccinated; SD-IIV3)	(1-OR)*100	Laboratory-confirmed infection; Hospitalization; Healthcare utilisation (influenza-related hospital encounters, influenza-related office visits); Symptomatic disease (influenza-like illness)	y, ROBINS-I; GRADE	n
O Murchu (2022), Ireland [186]	Cohort design; Case-control design, n=48	General population; Elderly population	Seasonal influenza (unvaccinated; other type of influenza vaccines)	(1-RR)*100; (1-OR)*100	Laboratory-confirmed infection	y, ROBINS-I; GRADE	n
Wu (2023), Canada [187]	Cohort design; Test-negative design, n=65	General population	COVID-19 (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, ROBINS-I	y
Marra (2022), USA [188]	Cohort design; Case-control design, n=10	General population	COVID-19 (unvaccinated)	(1-DOR)*100	Symptomatic disease (post-COVID-19 conditions defined as a wide range of health symptoms that are present 3 or more weeks after having COVID-19)	y, Downs and Black checklist	y
Lopez-Olivo (2022), USA [189]	Cohort design; Case-control design, n=13	Other (people with cancer)	Seasonal influenza (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease (cancer-related outcomes (survival, progression-free survival))	y, NOS	n
van den Berg (2022), Netherlands [190]	Cohort design; Case-control design; Test-negative design; Retrospective record review, n=17	Other (People with underlying chronic condition)	COVID-19 (unvaccinated)	(1-RR)*100; (1-OR)*100	Symptomatic disease (severe disease, breakthrough-infection, pneumonia); Mortality; Hospitalization	y, ROBINS-I	n
Sikjær (2023), Denmark [191]	Cohort design; Case-control design, n=8	Elderly population; Other (People with underlying chronic condition)	Pneumococcal disease (unvaccinated)	Narrative description	Laboratory-confirmed infection	y, NOS	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Mohammed (2023), Australia [192]	Cohort design; Case-control design, n=28	General population; Pediatric population; Elderly population (long-term care residents); Other (People with underlying chronic condition); Other (Healthcare workers)	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization; Disease severity	y, JBI	y
Beran (2023), USA [193]	Cohort design, n=4	Other (People with underlying chronic condition)	COVID-19 (unvaccinated)	(1-RR)*100	Mortality; Hospitalization; Composite outcomes (Need for invasive mechanical ventilation)	y, NOS	unclear
Pratama (2022), Indonesia [194]	Cohort design; Case-control design, n=20	General population	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100	Laboratory-confirmed infection; Symptomatic disease; Hospitalization; Disease severity	y, NOS	n
Gao (2022), China [195]	Cohort design; Cross-sectional design, n=6	Pediatric population	COVID-19 (unvaccinated)	(1-RR)*100	Laboratory-confirmed infection	y, NOS	unclear
Byambasuren (2022), Australia [196]	Cohort design, n=16	General population; Other (Healthcare workers)	COVID-19 (unvaccinated; number of doses received)	Narrative description	Symptomatic disease (Long COVID-19 illness)	y, ROBINS-I	unclear
Macilwraith (2023), Australia [197]	Cohort design; Cross-sectional design, n=3	General population (Men only)	HPV (unvaccinated)	Narrative description	Laboratory-confirmed infection; Symptomatic disease (oropharyngeal cancer)	y, ROBINS-I; NIH tool	n
Dicembrini (2023), Italy [198]	Cohort design; Case-control design, n=13	Other (People with underlying chronic condition)	Seasonal influenza; Pandemic influenza (unvaccinated)	(1-OR)*100	Mortality; Hospitalization	y, NOS	n
Gao (2023), China [199]	Cohort design; Cross-sectional design; Case-control design, n=38	Pediatric population	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100	Laboratory-confirmed infection; Hospitalization	y, NOS; AHRQ checklist	n

Author (year of publication), Country	Observational study designs included, (total n=)	Population of Interest	Vaccine(s) assessed in the SR Comparator)	Definitions of VE	VE-specific outcomes reported	Used a RoB tool (y/n). If yes, name of RoB tool	Modified RoB tool (y/n/unclear/ n/a)
Kontovazainitis (2023), Greece [200]	Cohort design, n=5	Pediatric population (infant outcomes); Other (Pregnant and/or lactating women)	COVID-19 (unvaccinated)	(1-OR)*100	Laboratory-confirmed infection; Mortality; Hospitalization	y, ROBINS-I	n
Guo (2023), China [201]	Cohort design; Case-control design; Test-negative design, n=34	General population	COVID-19 (unvaccinated)	(1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease; Mortality; Hospitalization	y, ROBINS-I	n
Piechotta (2023), Germany [202]	Cohort design; Cross-sectional design; Case-control design; Test-negative design, n=47	Pediatric population	COVID-19 (unvaccinated)	(1- (1-OR)*100; (1-RR)*100; (1-HR)*100; (1-IRR)*100	Laboratory-confirmed infection; Symptomatic disease (Multisystem inflammatory syndrome in children); Mortality; Hospitalization (ICU admission due to COVID-19),	y, ROBINS-I; GRADE	no
Katoto (2023), South Africa [203]	Case-control design, n=9	Pediatric population (adolescents aged 12-17)	COVID-19 (unvaccinated)	[(ARU - ARV) / ARU]*100, where ARU is the attack rate in the unvaccinated group and ARV is the attack rate in the vaccinated group	Laboratory-confirmed infection; Symptomatic disease (Multisystem inflammatory syndrome in children); Hospitalization; Asymptomatic infection; Healthcare utilisation (ED visits); Death	n (narrative description/self-developed methods)	n/a
Luna (2014), Brazil [204]	Cross-sectional, case-control, cohort, ecologic, n=31	General population	influenza (unvaccinated)	Narrative description	mortality, hospitalization, symptomatic disease, lab-confirmed infection	y, ROBINS-I	n

Abbreviations: NOS (Newcastle-Ottawa Scale), GRADE (Grading of Recommendations Assessment, Development and Evaluation), OCEBM (the Oxford Centre for Evidence-Based Medicine), CHERG (Child Health Epidemiology Reference Group), RoB-2 (Risk of Bias 2), ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions), CASP (Critical Appraisal Skills Programme), NACI (National Advisory Committee on Immunization), EPOC (Effective Practice and Organisation of Care), AHRQ (Agency for Healthcare Research and Quality), NICE (National Institute for Health and Care Excellence), GRACE (Good Research for Comparative Effectiveness), VE (Vaccine Effectiveness), JBI (Joanna Briggs Institute), QATSDD (Quality Assessment Tool for Studies with Diverse Designs), NIH (the National Institutes of Health), QUIPS (the Quality in Prognosis Studies), IQWiG (Institute for Quality and Efficiency in Healthcare), ROBANS (Risk Of Bias Assessment Tool for Non-randomized Studies), CoCanCPG (Collaborative Care Clinical Practice Guidelines), EPHPP quality assessment tool (Effective Public Health Practice Project Quality Assessment Tool), SIGN (Scottish Intercollegiate Guidelines Network), SYRCLE (Systematic Review Center for Laboratory animal Experimentation), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), RoB-OPS (Risk of Bias in Non-randomized Studies of Interventions), NHLBI (National Heart, Lung, and Blood Institute; DOR (Diagnostic Odds Ratio)

Table S2.2 Risk of Bias Tools Adapted in Included Studies (N=31)

Adapted RoB tool	N	%
Newcastle Ottawa Scale (NOS)	10	32.26%
Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I)	8	25.81%
Downs and Black checklist	5	16.13%
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)	2	6.45%
Joanna Briggs Institute (JBI)	2	6.45%
Quality Assessment Tool for Studies with Diverse Designs (QATSDD)	1	3.23%
Critical Appraisal Skills Program (CASP)	1	3.23%
National Advisory Committee on Immunization (NACI) Guidelines	1	3.23%
Cochrane risk-of-bias tool for randomized trials (RoB 2)	1	3.23%

Table S2.3 Characteristics of Risk-of-Bias Tool Adaptations (N=31)

Adapted RoB tool	Adapted aspect	Divergence from original tool
Newcastle Ottawa Scale (NOS)	**Scoring system**	This contrasts with the original NOS which employs a 9-star system across three domains (Selection: 4 categories, Comparability: 2 categories, Outcome/Exposure: 3 categories). Items are individually evaluated, with responses earning stars one (in the Selection and Outcome/Exposure domains) and up to two stars (in the Comparability domain).[205]
Sun et al. (2021)[3]	Risk-based scoring system	Low risk: ≤1 inadequate item Medium risk: ≤3 inadequate items High risk: >3 inadequate items Very high risk: No method description
Ramsay et al. (2019)[4]	Risk-based scoring system	Low risk: ≤1 missing item Moderate risk: 2-3 missing items High risk: >3 missing items
Eliakim-Raz et al. (2013)[206]	Risk-based scoring system	Low risk: ≤1 inadequate item Medium risk: ≤3 inadequate items High risk: >3 inadequate items or no method description
Meggiolaro et al. (2022)[161]	Risk-based scoring system	Satisfactory (NOS ≤ 6) Good (NOS > 6)
Zhu et al. (2022)[169]	Quality thresholds	Low Quality: 0–3 stars Moderate Quality: 4–6 stars High Quality: 7 stars or more
Zhang et al. (2021)[100]	Quality thresholds	1–3 points: Low methodological quality 4–6 points: Intermediate methodological quality 7–9 points: High methodological quality
Gupta et al. (2022)[128]	Quality thresholds	Poor quality: defined as 1 star in the selection or outcome/exposure domains, or 0 stars in the comparability domain. Fair quality: defined as 2 stars in the selection domain, 1–2 stars in the comparability domain, and 2–3 stars in the outcome/exposure domain. Good quality: defined as 3–4 stars in the selection domain, 1–2 stars in the comparability domain, and 2–3 stars in the outcome/exposure domain Note: Authors converted the NOS scores to align with Agency for Healthcare Research and Quality (AHRQ) thresholds for overall quality assessment.
Berild et al. (2020)[148]	Quality thresholds	High Quality: 3 or 4 stars in the selection domain

		1 or 2 stars in the comparability domain 2 or 3 stars in the outcome/exposure domain Moderate Quality: 2 stars in the selection domain 1 or 2 stars in the comparability domain 2 or 3 stars in the outcome/exposure domain Low Quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 star in the outcome/exposure domain Note: Authors converted the NOS scores to align with the AHRQ thresholds for overall quality assessment.
Chen et al. (2021)[107]	Quality thresholds; Assessment criteria	The authors included three different domains: 1. Patient selection 2. Comparability of the intervention/control group 3. Outcome assessment. Studies scoring >5 points were considered 'high quality'.
Zhu et al. (2018)[52]	Scoring range; Assessment criteria	The authors streamlined the NOS by excluding unvaccinated control groups, nonexposed cohort selection, and comparability assessments. This modification focused on adapted selection criteria and outcome assessment, reducing the scoring range from 0-9 to 0-6.
Adapted RoB tool	**Adapted aspect**	**Divergence from original tool**
Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I)	**Assessment criteria**	This contrasts with the original ROBINS-I tool encompasses seven domains where bias may be introduced, including confounding, selection of participants, classification of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of reported results. The overall risk of bias can be categorized as Low, Moderate, Serious, or Critical based on responses to the signaling questions and judgments made within each domain.[207]
Doyon-Plourde et al. (2019)[72]	Context-specific assessment criteria	The authors classified bias due to confounding for health status and functional status: Moderate: Requires appropriate control for both health status and functional status. Serious Risk of Bias: Assigned if at least one of the confounding factors (health or functional status) is not adequately controlled. Critical: Given when neither health status nor functional status is properly controlled. Note: Functional status was ascertained if details about a diagnosis of dementia and/or mention of a subject's need for support in activities of daily living were mentioned.
Tadount et al. (2020)[80]	Context-specific assessment criteria	The authors classified bias risk in studies on sex differences in influenza vaccine responses:

		Criteria for serious bias: Studies that failed to adjust for critical confounders, such as age and immune history. (assessed RoB for the outcomes collected, independently of those for which the study was designed) **Low to moderate confounding bias:** Sex-stratified vaccine efficacy estimates were required to account for age, health status, and vaccination history to be considered at low or moderate risk of bias.
Hughes et al. (2020)[81]	Context-specific assessment criteria	The authors classified studies as 'high' risk of bias if they reported issues in the following groups: Cold Chain Issues: Problems related to the storage and transportation of temperature-sensitive vaccines. Width of Age Groups (i.e., age groups spanning 10 years, which may dilute specific age-related effects.) Unclear or Absent Age at First Dose: Lack of clear upper and/or lower age limits for the first vaccine dose.
Xu et al. (2021)[181]	Context-specific assessment criteria; Scoring system	The authors classified bias due to confounding related to the presence of maternal antibodies before vaccination and/or previous measles infection. Low risk: Studies that considered measles antibody levels before vaccination and/or previous measles infection. Moderate risk: Studies that did not control for maternal antibodies but discussed their implications on study results. Critical risk: Studies (especially cross-sectional study designs) that did not control for this confounding or discuss their implications on study results.
Wang et al. (2021)[166]	Context-specific assessment criteria; Scoring system	The authors assessed bias in four domains: 1. Selection Bias 2. Exposure Misclassification 3. Outcome Misclassification 4. Design Limitations. Bias in classification of the intervention was not evaluated. Deviation from intended intervention was also excluded due to the absence of an intervention being assessed.
Markowitz et al. (2022)[141]	Context-specific assessment criteria	The authors examined selection bias by assessing whether participant characteristics or outcomes influenced participant selection. For information bias, they evaluated potential biases in: Measurement of Intervention: This included the validity of data sources for determining dose groups and ensuring adequate intervals between first and second doses for two-dose recipients. Measurement of Outcome: The authors reviewed the validity of algorithms used to identify outcomes and the use of lag time or buffer periods to exclude outcomes arising from pre-existing infections at the time of vaccination. For confounding, the authors investigated differences between dose groups regarding: Prevalence of HPV infection at the first dose Risk of HPV acquisition during follow-up Immunogenicity in studies comparing three, two, and one doses.

Wu et al. (2023)[177]	Context-specific assessment criteria	The authors indicated the tool was adapted to COVID-19, but no additional details were provided.
Harder et al. (2021)[64]	Study-specific assessment criteria	The authors could not apply the ROBINS-I tool to one cohort study with elements of an interrupted time series. Instead, they used the EPOC (Effective Practice and Organisation of Care) framework to assess the risk of bias across relevant domains.

Adapted RoB tool	Adapted aspect	Divergence from original tool
Downs and Black checklist	**Scoring system**	This contrasts with the original Downs and Black checklist which includes 27 items divided into four components: Quality of Reporting (10 questions), External Validity (3 questions), Internal Validity (13 questions), and Statistical Power (1 question). Each item is scored as "yes" (1 point) or "no/unable to determine" (0 points), with one item rated on a 3-point scale (yes=2, partial=1, no=0). Total scores range from 0 to 28, with higher scores indicating better quality.[208]
Marra et al. (2021, 2022, 2022)[124], [160], [188]	Quality thresholds	The authors followed all questions from the scale as original, except for question #27, which was modified from a score of 0 to 5 to a yes or no format. Studies were classified for analysis as: Good quality: 19–23 out of 28 possible points Fair quality: 14–18 out of 28 possible points
Lee et al. (2021)[93]	Quality thresholds	The authors replaced the numerical scoring system with a qualitative rating (poor, fair, good, excellent)
Lee et al. (2018)[59]	Quality thresholds	The authors reduced the number of questions from 27 to 26 (by removing or modifying the statistical power assessment) and replaced the numerical scoring system with a qualitative rating (poor, fair, good, excellent)

Adapted RoB tool	Adapted aspect	Divergence from original tool
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)	**Assessment criteria**	This contrasts with GRADE in which evidence is rated from high to very low quality, with RCTs starting as high-quality and observational studies as low-quality. GRADE uses five downgrading factors (bias, inconsistency, indirectness, imprecision, publication bias) and three upgrading factors (large effect, dose response, plausible confounding).[209]
Davis et al. (2013)[210]	Context-specific assessment criteria	The authors determined that due to meningitis' severity and near-universal hospitalization, studies focusing on hospitalized cases would not be downgraded for generalizability.

Petras et al. (2022)[140]	Context-specific assessment criteria	The authors adopted five criteria to assess the strength of evidence, including number of VE records (added), study limitations, heterogeneity, indirectness based on the difference between vaccinated and unvaccinated participants, and imprecision.
Adapted RoB tool	**Adapted aspect**	**Divergence from original tool**
Joanna Briggs Institute (JBI)	**Checklist**	The JBI Checklist evaluates studies using 10-11 questions, addressing key methodological aspects, including review question clarity, inclusion criteria appropriateness, search strategy, critical appraisal process, data extraction, analysis methods, and publication bias assessment, answered as yes/no/unclear.[211]
Mohammed et al. (2023)[192]	Signaling questions; Response scale	The authors modified the JBI Checklist by creating a combined tool for case-control and cohort studies, featuring 9 tailored items (A-I), compared to the original 10 questions for case-control and 11 for cohort studies.
Foucambert et al. (2022)[170]	Response scale	The authors classified ≥8 "Yes" in a study as 'high' quality.
Adapted RoB tool	**Adapted aspect**	**Divergence from original tool**
Quality Assessment Tool for Studies with Diverse Designs (QATSDD)	**Assessment criteria**	This contrasts with QATSDD, which includes 16 assessments, focusing on key domains such as study design, sampling methods, data collection validity, ethical considerations, analysis appropriateness, and reporting clarity. Each item is rated on a 4-point Likert scale as follows: 0 (not at all), 1 (very slightly), 2 (moderately), and 3 (completely).[212]
Sabu et al. (2022)[173]	Assessment criteria	The authors modified the assessment tool by excluding three criteria deemed irrelevant for evaluating the included studies. Thirteen criteria were scored on a scale of 0 to 3 (similar to the original scale).
Adapted RoB tool	**Adapted aspect**	**Divergence from original tool**
Critical Appraisal Skills Program (CASP)	**Checklist**	This contrasts with the CASP qualitative tool, which includes 10 questions: Was there a clear statement of the aims of the research? Is a qualitative methodology appropriate? Was the research design appropriate to address the aims of the research? Was the recruitment strategy appropriate to the aims of the research? Was data collected in a way that addressed the research issue? Has the relationship between researcher and participants been adequately considered? Have ethical issues been taken into consideration? Was data analysis sufficiently rigorous? Is there a clear statement of findings? How valuable is the research? [213]

Friedman et al. (2019)[77]	Signaling questions	The authors created a framework for evaluating studies using administrative or surveillance data. This checklist centered on three main questions: A) Are the results valid? B) What are the results? C) Will the results help locally? It included criteria such as whether the study addressed an indirect effect, if the cohort was representative, and whether exposure was accurately measured to minimize bias. It also assessed the inclusion of lab-confirmed outcomes, identification and accounting for confounding factors, and whether the study duration was sufficient (minimum of two years).
Adapted RoB tool	**Adapted aspect**	**Divergence from original tool**
National Advisory Committee on Immunization (NACI) Guidelines	**Quality measures**	This contrasts with NACI guidelines, which typically recommend using the JBI Critical Appraisal Checklist for Economic Evaluations. NACI guidelines employ a more comprehensive approach to quality assessment, utilizing categories such as "high quality," "acceptable," or "unacceptable" to evaluate various immunization studies. A key feature of NACI's methodology is the use of the GRADE system to systematically assess the strength and certainty of evidence.[214]
Berman-Rosa et al. (2020)[86]	**Context-specific quality measures**	The authors evaluated the risk of bias using an adapted version of the NACI guidelines for quality assessment, which were based on methods from Harris et al. and the US Preventive Task Force [215]. In this assessment: Studies lacking control for age and/or underlying medical conditions as confounders were classified as 'fair'. Age was identified as a critical confounder due to: Younger children's higher risk for acute otitis media (AOM) and invasive pneumococcal disease (IPD) related to their anatomy and immature immune systems Potential variations in vaccination rates among different age groups based on public health strategies 'Fatal' flaws, determined a priori, included inadequate selection of controls in case-control studies.
Adapted RoB tool	**Adapted aspect**	**Divergence from original tool**
Cochrane risk-of-bias tool for randomized trials (RoB 2)	**Risk categories**	This contrasts with RoB 2, which uses three risk categories (high, some concerns, low), focuses exclusively on randomized controlled trials, employs a structured set of signaling questions for each domain, does not include a "not applicable" option, assesses bias for a single outcome at a time, and does not divide the assessment into separate domains for safety, immunogenicity, and effectiveness.[216]
Campbell et al. (2018)[65]	Risk categories	The authors modified the RoB 2 tool by implementing a four-category system: high risk, intermediate risk, low risk, and not applicable. The 'not applicable' category was introduced for domains irrelevant to certain study designs, particularly observational studies, where aspects like random sequence

	generation, allocation concealment, and participant blinding are often not pertinent. To better assess multifactorial outcomes, they expanded the 'other' category into three separate domains, allowing for a more nuanced evaluation of bias implications across different domains and consideration of additional biases such as confounding in safety, immunogenicity, and effectiveness/efficacy outcomes.

Table S2.4 Characteristics of studies in which authors employed their own risk-of-bias assessment method (N=13)

Reference	Custom Methods	Additional Details
Jackson et al. (2013) [15]	Due to the relatively small number of articles identified, authors report not excluding studies based on their potential for bias but summarizing any methodological concerns in the text.	Control selection and confounding variable were assessed for bias in both case-control and cohort studies.
Abubakar et al. (2013) [217]	The authors developed a criteria to assess bias in observational studies, categorizing risks as high, low, or unclear. Refer to pg. 30 for more details.	To assess RoB in case–control and cross-sectional studies, the authors established a criterion that included: 1) consistency in BCG vaccination definitions between cases and controls 2) blinding of disease status to assessors 3) independent diagnosis from vaccination status, and for matched studies, whether matching was included in the analysis. Cohort studies were evaluated for biases related to: 1) loss to follow-up 2) treatment allocation concealment 3) case ascertainment.
Darvishian et al (2014) [218]	The authors created their own scale and checklist to identify potential internal and external biases. To quantify biases, they created an elicitation scale for additive and proportional biases. See Supplementary materials.	For internal biases, the authors focused on selection, performance, attrition, detection, and other suspected biases. For external bias, they compared study populations to the target population in terms of age, sex, and health status.
Remschmidt et al. (2015) [30]	The authors used a predefined criteria from a methodological framework to assess the risk of healthy vaccinee bias and confounding by indication in the included studies. See Table 1.	'High risk' of healthy vaccinee bias, if vaccinated participants exhibited significantly fewer comorbidities or related indicators, such as medical visits, compared to unvaccinated participants based on baseline characteristics. 'High risk' of confounding by indication if vaccinated participants had significantly more comorbidities than their unvaccinated counterparts.
Garland et al. (2016) [219]	The authors detailed the strengths and limitations of each study included in the formal analysis. See Supplementary Table 2.	Not reported
Caspard et al. (2017) [220]	See Table 1.	The quality of evidence was examined based on the study eligibility criteria and age range. To account for the risk of bias associated with the designs of observational studies, they adjusted for VE estimates using the following formula: 100×(1–consolidated odds ratio or relative risk).
Markowitz et al. (2018) [141]	The authors reported extracting information on how potential biases were addressed in the included studies. Accordingly, no studies were excluded based on methodological quality.	The sources of bias in post-licensure studies examining the impact of HPV vaccination by the number of doses include: (1) differences in characteristics and age at vaccination; (2) the likelihood of prevalent infection at the time of

		vaccination; and (3) the interval between the first and second doses for those receiving two doses.
Yakely et al. (2019) [68]	The authors assessed the quality of effectiveness using their own scale. See Supp 2.	Quality of effectiveness studies were evaluated for: Selection of cohort; Ascertainment of exposure; Control of other factors; Assessment of outcome; Adequacy of follow-up
Drolet et al. (2019) [78]	The authors created their own criteria to assess methodological quality of included studies. See Appendix.	Methodological quality of included studies was assessed for: Risk of selection bias: - By examining changes in the study population characteristics between the pre- and post-vaccination periods. Risk of information bias: - By considering errors in the identification of pre-cancerous cervical lesions during the pre- and post-vaccination periods. Risk of confounding: - By examining whether changes in precancerous lesions between pre- and post-vaccination periods could be diluted or exacerbated by other variables. External validity: - By determining whether results could be generalized to the population at the country or region level.
Andani et al. (2022) [109]	The authors developed an in-house tool to critically appraise the methodological quality of articles reporting real-world studies. See Supplementary Text S2.	The authors developed an in-house quality assessment tool with three sections (a total of 6 questions): A. Case Detection B. Data Collection Methods C. Quantitative Methods The rating system used four categories: Weak, Moderate, Strong, and Fatal Error. If a study received a "Fatal Error" rating, it was excluded from the review.
Okoli et al. (2021) [152]	The authors developed a quality assessment approach for test-negative design (TND) studies in the absence of a validated tool. See Supplementary Table 4.	The authors examined relevant study characteristics that could introduce bias, including: - Patient recruitment into study - Influenza vaccination confirmation methods - Inclusion of age and comorbidity among covariates adjusted in logistic regression analysis for VE These characteristics were synthesized in a tabular form.
Luna et al. (2014) [204]	The authors assessed the quality of included studies based on several criteria.	- Studies with laboratory-confirmed influenza cases were favored. - Representative, randomly selected samples were considered higher quality in vaccination coverage surveys.

		- Methods accounting for seasonal and cyclical variability were preferred in ecological time series studies. - Quality was judged on geographic scope, time period analyzed, and statistical methods that incorporated seasonal disease variability in ecological historical series.
Kandeil et al. (2020) [88]*	The quality of studies reporting population-based outcomes was assessed using an in-house quality assessment tool. See section 3.0 online supplemental file.	Articles with a "fatal error" (a factor undermining the study's main conclusions) were excluded, while all others were included regardless of their overall rating (strong, moderate, or weak). Studies focused on patient follow-up were not evaluated with this tool or existing checklists and were therefore not critically appraised.

***Kandeil et al. (2020)** [88] planned to use the GRADE quality assessment tool for vaccine effectiveness studies but found it unsuitable due to varying study outcomes and the need for data recalculation.

Table S2.5 Summary of quality assessment methods used in other reports identified through grey literature sources (N=9)

Document	Appraisal Method	Description
CoVaRR-Net/ COVID-END: COVID-19 Living Evidence Synthesis (n=4 versions using the same tool) [221]	Adapted version of ROBINS-I	The adapted version of ROBINS-I tailors the tool specifically for vaccine research by incorporating the following study characteristics unique to this field that could potentially introduce bias. 1. Study design 2. Method for confirming vaccination 3. Databases used for retrieval of COVID test results, participant prognostic factors, and clinical outcomes 4. Assignment of infection start date 5. Verification of symptoms 6. Accounting for nonimmune period 7. Inclusion of participants with prior COVID infection 8. Accounting for calendar time 9. Adjustment for prognostic factors 10. Testing frequency Overall "serious" or "critical" judgment given when critical risk in one domain or serious risk in three or more domains. See Appendix 5 for further details.
SPOR/COVID-END: What is the ongoing effectiveness, immunogenicity, and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection? [222]	JBI Checklist	JBI Checklist for Cohort Studies JBI Checklist for Analytical Cross-Sectional Studies Further details about the tool application not available.
SPOR/COVID-END: Transmissibility of COVID-19 among vaccinated individuals [223]	ROBINS-I	RoB was assessed in five non-RCTs. Results shown in Figure 2.
NACI: Repeated Seasonal Influenza Vaccination [224]	AMSTAR-2 for SRs/MAs	The adapted version of AMSTAR 2 differs from its original design in approach to scoring. While the original AMSTAR 2 tool provides an overall qualitative rating based on weaknesses in critical domains without generating a numerical score, the authors converted checklist answers into a numerical scoring system rated out of 16 total points. Results shown in Table 3.
NACI: Updated Recommendations on the Use of Herpes Zoster Vaccines [225]	NOS EPOC	The Newcastle Ottawa Quality Assessment Scale for cohort studies and case-control studies The EPOC Risk of Bias tool for nonrandomized controlled trials. Results shown in Appendix A.

ECDC: Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over [226]	ROBINS-I GRADE	ROBINS-I was adapted to evaluate bias in non-randomized vaccine studies across seven domains, with overall risk determined by the highest domain score. GRADE assessed evidence quality for primary outcomes, considering five factors without automatically downgrading non-randomized studies instead treating as high-certainty evidence, similar to RCTs. The review focused on test-negative design case-control studies for primary effectiveness of laboratory-confirmed influenza and case-control and cohort studies for additional outcomes. Results shown in Table 3.3 and 'summary of findings' table.

Abbreviations: ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions), JBI Checklist (Joanna Briggs Institute Checklist), AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews 2), NOS (Newcastle-Ottawa Scale), EPOC (Effective Practice and Organisation of Care), GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Appendix 2F: List of Excluded Studies

Exclusion reason: Ineligible outcome (n=46)

[1] Ahmad N, Mohammed Nawi A, Jamhari MN, Nurumal SR, Mansor J, Ahmad Zamzuri M 'Ammar I, et al. Post-Exposure Prophylactic Vaccination against Rabies: A Systematic Review. Ijph 2022. https://doi.org/10.18502/ijph.v51i5.9412.

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[9] Cunninghame J, Wen S, Dufficy M, Ullman A, Takashima M, Cann M, et al. Immunogenicity and safety of vaccination in children with paediatric rheumatic diseases: a scoping review. Therapeutic Advances in Vaccines and Immunotherapy 2023;11:25151355231167116. https://doi.org/10.1177/25151355231167116.

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[12] Iheanacho CO, Eze UIH. Immunogenicity and clinical features relating to BNT162b2 messenger RNA COVID-19 vaccine, Ad26.COV2.S and ChAdOx1 adenoviral vector COVID-19 vaccines: a systematic review of non-interventional studies. Futur J Pharm Sci 2022;8:20. https://doi.org/10.1186/s43094-022-00409-5.

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Chapter III: Methodological Biases Relevant to Vaccine Effectiveness Estimation: Insights from A Scoping Review

3.1 Preface

This chapter presents the second manuscript, which offers a comprehensive overview of methodological biases present in vaccine effectiveness (VE) research. By mapping the existing literature, this chapter identifies, categorizes, and summarizes common sources of bias in VE research. Building on the previous scoping review, which examined the tools and strategies used for risk-of-bias assessment, this chapter shifts focus toward understanding the types of methodological biases encountered across VE studies.

The work presented here is the result of a collaborative effort. I was actively involved in this scoping review from its inception, working closely with Dr. Kylie Tingley (CoVaRR-Net*) and Cassandra Laurie (project research coordinator). I participated in regular planning meetings and contributed to the title and abstract screening phase. As the project advanced, I collaborated with Nicole Shaver (KSAU**) in a co-lead role, helping to design the full-text screening form and create a pilot form to guide the screening team. We then developed the data extraction plan together, and I contributed to the extraction process. I led the screening of grey literature sources and helped organize the extracted data into a clearer, structured format to support data synthesis. I continued collaborating with Nicole Shaver (KSAU) and Niyati Vyas (KSAU) to present the results in a meaningful and coherent way. I also contributed to writing the original draft of the manuscript, specifically the introduction, selected sections of the results, and the discussion. The final manuscript was submitted to the *Journal of Clinical Epidemiology* and is currently under review.

* CoVaRR-Net: Coronavirus Variants Rapid Response Network
** KSAU: Knowledge Synthesis and Application Unit

3.2 Title page

Methodological biases relevant to vaccine effectiveness estimation: Insights from a scoping review

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3.3 Abstract

Purpose: Vaccine effectiveness (VE) studies are important to judge real-world vaccine performance but are susceptible to biases. This scoping review aimed to identify risk-of-bias concepts in VE studies and examine their impact on VE estimates.

Methods: We searched electronic databases (Ovid MEDLINE® ALL, Embase Classic+Embase, Web of Science) from 2015 to July 2023 and grey literature from 2019 to 2024. Publications reporting on any risk-of-bias concepts in observational studies of VE were eligible. Titles/abstracts and full texts were screened in duplicate, and data charting and analysis was completed using international methodological standards for scoping reviews and critical interpretive synthesis. We organized risk-of-bias concepts and designed a framework.

Results: 108 studies were eligible. Most bias concepts were related to confounding, selection bias, or information bias, but some cross-cutting biases were identified. VE-specific confounding was noted at individual (e.g., prior immunity), population (e.g., vaccine coverage), and pathogen (e.g., variants of concern) levels. Time-varying confounding was a concern across all levels. Selection biases were categorized by recruitment timing and included biases due to health-seeking behavior, depletion of susceptibles, and ascertainment. Information bias included exposure and outcome misclassification due to recall errors, incomplete records, and challenges in distinguishing vaccination-related symptoms from infection symptoms.

Conclusions: Our findings highlight the complexity of bias in VE research. Risk of bias resources designed to these unique sources of bias may improve the reliability VE estimates for public health decision-making, inform VE study design and reporting, and ultimately lead to more informed public health decision-making.

3.4 Background

Vaccination plays a pivotal role in preventing infectious diseases globally (1). Vaccine effectiveness (VE), which measures how well vaccines protect against outcomes like symptomatic disease, is primarily assessed through observational studies (1). Being conducted in real-life settings, observational studies provide insights that may be more applicable to the general population. However, these studies are inherently more prone to bias due to non-randomization, often exhibiting differences in baseline characteristics between vaccinated and unvaccinated groups that introduce can confounding. This complicates causal inference and makes it challenging to establish the temporal relationship between exposure and outcome (2).

In addition to typical sources of bias inherent in observational study designs, VE studies have unique challenges in accounting for biases that may be unknown, unmeasured, or unreported. Various biases can impact VE estimates, potentially resulting in over- or -underestimation of the true VE. For example, "healthy vaccinee bias" may inflate VE estimates as vaccinated individuals tend to have fewer comorbidities than their unvaccinated counterparts, resulting in vaccines appearing more protective (3). Similarly, "immortal time bias" can lead to overestimated VE by misclassifying individuals as vaccinated from cohort entry, thus artificially extending their follow-up time considered protected (4). Conversely, biases like "differential depletion of susceptibles" can underestimate VE by including previously infected individuals, who are no longer at risk of infection, in the unvaccinated control group (5). Issues with under ascertainment or misclassification of infectious disease outcomes can also bias VE estimates downward (6).

These unique biases are of particular concern in meta-analyses of observational studies due to the pooling of results from studies with varying quality (7). When combining evidence from observational studies, unaccounted for biases can lead to invalid estimates of VE, distorting the true impact of vaccination on health outcomes (2). This creates challenges for decisionmakers and the public health community who depend on high-quality evidence to guide vaccination strategies, allocate resources, and develop effective public health messaging.

While many methodological studies have examined key sources of bias in VE research, gaps remain in fully understanding their cumulative impact and how they interact across diverse study contexts, highlighting the importance of systematically identifying and assessing them. Determining whether these biases inflate, underestimate, or have no effect on VE is crucial for refining estimates and integrating data from multiple studies to support evidence-based public health decision-making. To address this critical gap, we have undertaken the present scoping review (1) to identify key bias concepts or sources of bias considered uniquely important for VE studies and (2) to examine how these biases influence VE estimates.

3.5 Methods

3.5.1 Protocol and registration

We performed a scoping review informed by the methodological frameworks of Arksey and O'Malley, Levac and colleagues, and the Joanna Briggs Institute for scoping reviews (8–10). We adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) statement and checklist in reporting this review (Appendix 3A) (11,12). We followed an a priori protocol made publicly available on Open Science Framework (https://osf.io/euz9b/). We made two protocol deviations due to the substantial volume of literature retrieved: (1) we included records from electronic databases from 2015 onward, rather than from 2008, assuming that earlier literature would not add new concepts as conceptual saturation had been achieved; and (2) we limited the list of study characteristics initially planned for extraction. These modifications enabled us to ensure quality and feasibility while managing costs.

3.5.2 Eligibility criteria

The eligibility criteria are summarized in Table 3-1 (10). We focused on publications discussing risk-of-bias concepts relevant to observational VE studies. Articles solely related to vaccine efficacy were excluded. We considered both quantitative and qualitative studies if they (1) reported on the development or application of one or more risk-of-bias concepts, regardless of the study design, or (2) identified such concepts in VE studies. Systematic

reviews of VE studies reporting a risk-of-bias assessment, without contributing additional conceptual insights, were excluded; these reviews are captured under a separate research question, with findings reported elsewhere.

Table 3-1 Eligibility criteria

Criterion	Inclusion	Exclusion
Population	No restrictions	N/A
Concept	Eligible Criteria for risk-of-bias (RoB)* concept: - RoB tools concepts for vaccine effectiveness studies** - Study designs tool can be applied to: observational studies of vaccine effectiveness - Vaccine types investigated in studies tool can be applied to: Any vaccine aimed at preventing infection/disease caused by any infectious pathogen. - Outcomes tool can be applied to: Clinical outcomes (e.g., overall disease, severity, symptoms, adverse effects), infection transmission. Criteria for Eligible Studies: - Methodological papers reporting the development or use of an RoB concept (any study design) - Articles that identify RoB concepts in vaccine effectiveness studies (e.g., guidance for evaluating RoB in vaccine effectiveness studies, articles or reporting guidance that identify sources of bias in vaccine effectiveness studies) - Vaccine effectiveness studies reporting use of an RoB	Ineligible criteria for RoB tool/concept: - RoB tools or concepts for vaccine efficacy studies, - Tools for RoB assessment in RCTs, ecological study designs. - Tools applied to assess immunogenicity outcomes only (e.g., antibody levels, markers of cell-mediated response) Criteria for ineligible Studies: - Vaccine efficacy studies reporting use of an RoB tool/concept (systematic reviews of RCTs only) - Vaccine effectiveness studies reporting use of an RoB tool (systematic reviews of observational studies) (addressed in KQ1)

	concept (systematic reviews of observational studies)	
Context	Criteria for Eligible Studies: - Any setting - Peer-reviewed studies published between 2015 and 2023 - Grey literature sources published within the last 5 years - Studies in English (2019 and 2024)	N/A

Abbreviations: KQ, Key question; RCT, Randomized Controlled Trial; RoB, Risk of Bias
*Risk of bias was defined as the likelihood of bias, defined by Cochrane as a "systematic error, or deviation from the truth, in results or inferences" (32)
**Vaccine Effectiveness was defined as the measure of how well vaccination protects against various outcomes under "real-world" conditions, measured through post-authorization (phase IV) studies.

3.5.3 Search Strategy and Information Sources

The full search strategy is available in Appendix 3B. An experienced medical information specialist iteratively developed and tested the search strategies with the review team. The MEDLINE search strategy was peer reviewed by another senior information specialist prior to execution using the PRESS Checklist (13) (Appendix 3C). Using the multifile option and deduplication tool available on the Ovid platform, we searched Ovid MEDLINE® ALL and Embase Classic+Embase. We also searched the core databases of Web of Science. All searches were executed on July 27, 2023. Our strategy employed a combination of controlled vocabulary (e.g., "Vaccine Efficacy", "Bias", "Risk Assessment") and keywords (e.g., "vaccine effectiveness", "sampling error", "confounding factor"). Vocabulary and syntax were adjusted across the databases. There were no language restrictions, but results were limited to the publication year 2008 to 2023 (the limitation to 2015 completed post-execution). Search results were downloaded and records deduplicated using EndNote version 9.3.3 (Clarivate Analytics) and uploaded to Covidence (Veritas Health Innovation Ltd.) review software (14). A targeted search of grey literature was also performed to identify relevant non-indexed literature in the past five years (2019 to 2024). We used the Canada's Drug Agency (CDA) Grey Matters checklist as a guide (15) (Appendix 3B).

3.5.4 Selection of evidence

Study selection was completed using Covidence software in two phases: title and abstract screening and full-text screening. Following a pilot exercise at each stage, screening was completed in duplicate, with discrepancies between reviewers resolved by consensus. A PRISMA flowchart (Figure 1) outlines the screening process and reports the final number of included and excluded records.

3.5.5 Data Charting Process, Items and Synthesis

We adopted a Critical Interpretive Synthesis (CIS) approach to guide our data charting, analysis, and synthesis of concepts (16–18). Concepts from included studies were first organized into initial over-arching risk-of-bias themes: (1) selection bias, (2) confounding, (3) information bias, and (4) other. This deductive categorization helped manage the large volume of included studies and facilitated the extraction of recurring themes/concepts by coordinating efforts among our team of reviewers. After a pilot phase to refine our methods, detailed data were extracted from the selected studies and categorized within themes by one reviewer (NS, ZD, NV, NW, AL) and cross-verified by a second reviewer. Extracted data included information on study design, methodologies employed, the biases identified, and their impact on VE findings.

Subsequently, an inductive open-coding technique was applied to the extracted data to identify initial concepts related to risk of bias and a comprehensive list of codes was created to represent various bias concepts. Through an iterative process of reading, coding, and constant comparison among team members, these initial concepts were refined and abstracted into higher-order constructs. These constructs captured broader categories of risk-of-bias concepts relevant to VE studies. Concepts and higher-order themes were recategorized and refined, as appropriate. Finally, the relationships between the developed constructs were synthesized into a final coherent framework. Concepts within the final framework were visually organized into qualitative coding trees, showing the over-arching themes, higher-order constructs, lower-order constructs and synthesized concepts. Consistent with the scoping nature of our review and the goal to synthesize risk-of-bias

concepts rather than critically evaluate the literature, no formal quality appraisal was performed on the included studies.

3.6 Results

A total of 3396 titles and abstracts and 427 full-text articles were reviewed, resulting in 108 included studies (Figure 3-1). A complete list of excluded studies and reasons for their exclusion is available in Appendix 3D.

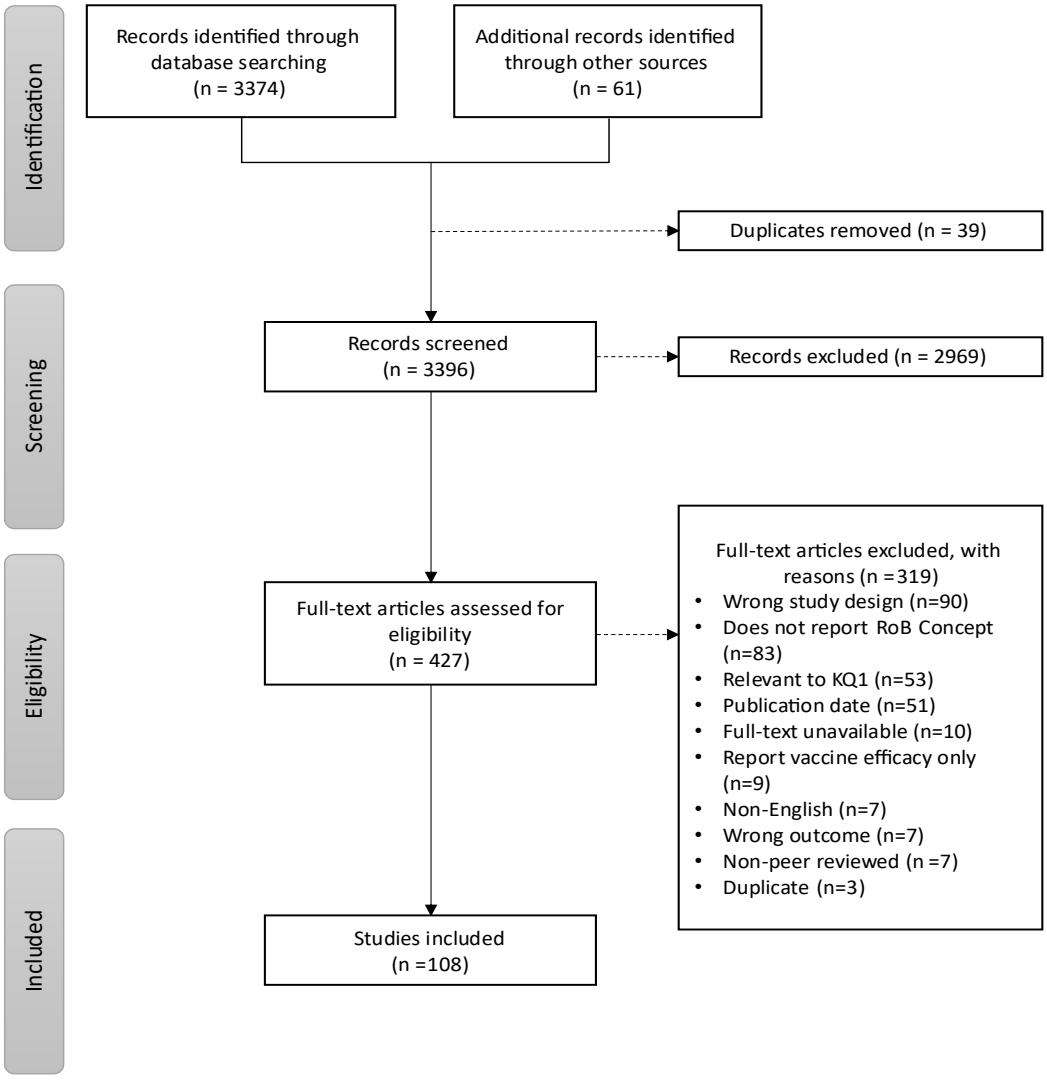

Figure 3-1 PRISMA flow diagram outlining the study selection process

Appendix 3E, Table S3.1 outlines the complete list of included studies, their characteristics and extracted concepts. Studies were published between 2015 and 2024 and predominantly focused on influenza and COVID-19 vaccines. Across the bias categories, influenza vaccines accounted for 38–50% of studies, while COVID-19 vaccines represented 19–31%. Most commonly reported study designs were test-negative designs (14–40%), cohort studies (8–20%), and literature reviews (23–38%).

Figure 3-2 illustrates our overall synthesizing framework with themes and higher-order constructs. The three risk-of-bias themes used for grouping the studies for extraction (selection, information, confounding) were deemed appropriate to group constructs and thus represent the highest categories in the framework. We also created a category for cross-cutting methodological biases that did not fit into these larger themes.

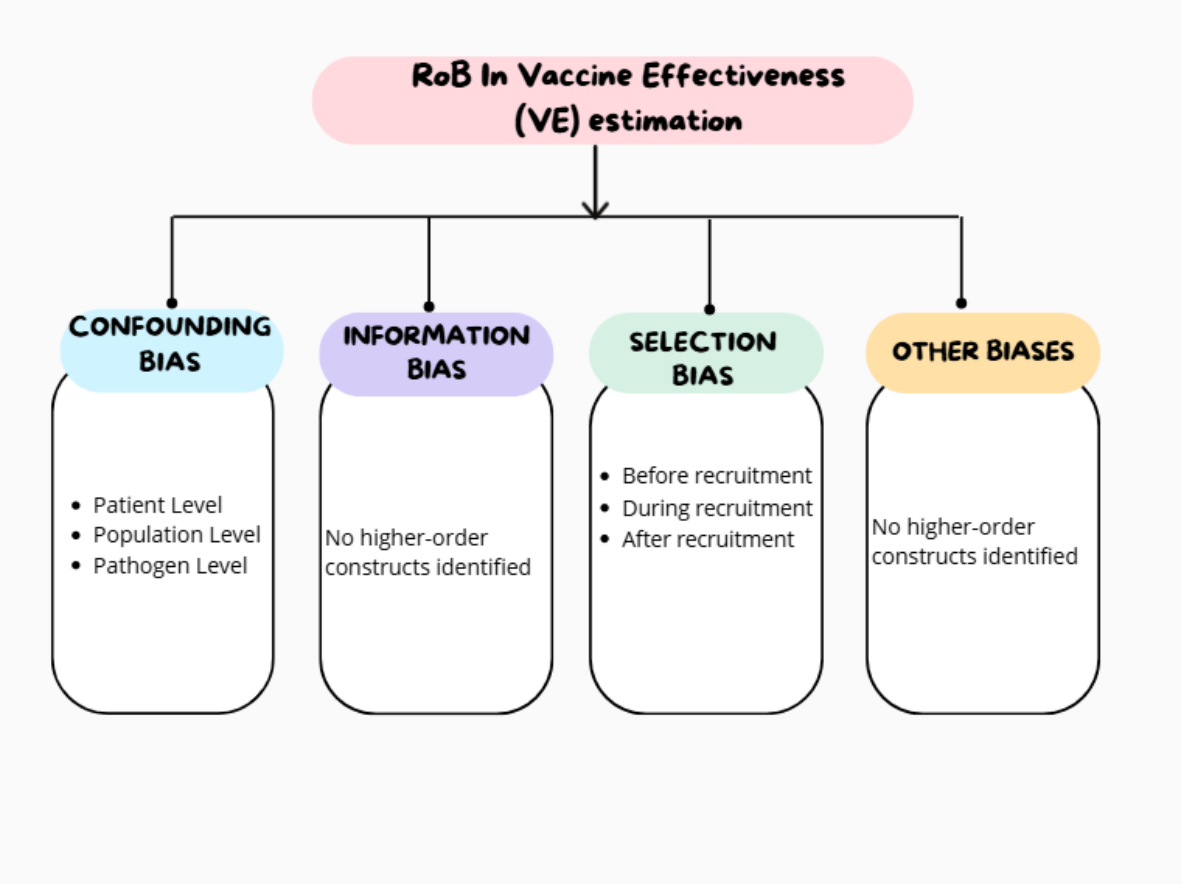

Figure 3-2 Tree diagram of themes and higher-order risk-of-bias (RoB) constructs

Confounding Bias Theme. Figure 3-3 summarizes higher-order constructs related to confounding bias, at patient, population, and pathogen levels (see Appendix 3E, Table S3.2 for extracted concepts). Most constructs pertained to individual-level confounding with demographic characteristics as the most frequently reported confounders. Health-seeking behaviour was also a frequently reported factor influencing both confounding and selection bias. Also identified were vaccination history and differential immunity based on an individual's past infections; these can bias VE estimates if prior immunity impacts susceptibility to infection. Other patient-level confounders included clinical factors (e.g., underlying conditions, comorbidities, medication use). An example of environmental/behavioural factors confounding VE is vaccinated individuals changing their behaviour and having more social interactions (and thus greater opportunities for disease exposure risk) due to relaxed precautions. Additionally, other factors such as improvements in nutrition, healthcare access, or unrelated public health interventions can further complicate VE estimation.

Pathogen-level factors included the likelihood of having a prevalent infection at the time of vaccination, as well as seasonal changes in strain variants. Additionally, exposure to some virus strains may provide cross-protection against antigenically similar strains, impacting VE.

Population-level confounders included high vaccination coverage, resulting in herd immunity and providing partial protection to unvaccinated individuals. Additionally, time-varying confounding was reported in studies due to confounders changing over time to impact VE estimates and may be applicable across all three levels of constructs.

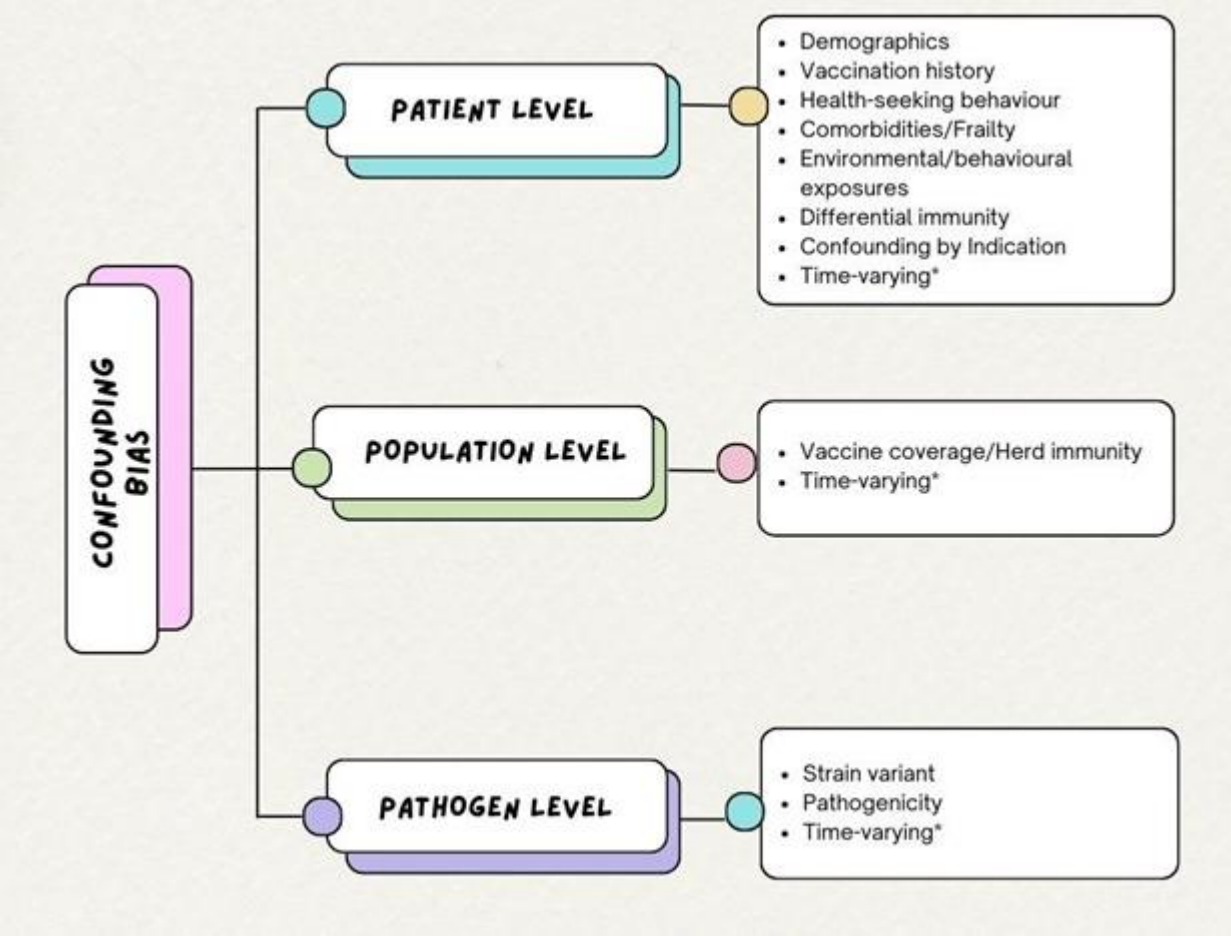

Figure 3-3 Tree diagram of construct for confounding bias
*Time-varying confounding may be relevant to each confounding factor

Selection Bias Theme. Constructs and concepts related to selection bias are summarized in Figure 3-4 and Appendix 3E, Table S3.3, respectively. Biases were often linked to the timing of participant recruitment into the study, leading us to categorize them into three higher-level constructs: selection bias related to design features before, during, or after recruitment. Most constructs were relevant to pre-recruitment phases, but some biases could plausibly affect multiple stages of the recruitment process.

Selection bias due to health-seeking behaviour was the most frequently noted bias associated with pre-recruitment study design. Other biases included healthy vaccinee bias/ frailty bias and timing of patient enrollment, where early versus late vaccination led to time-dependent biases. Selection biases due to unbalanced case and control populations, which arose from differences in vaccination exposure, sampling bias, and

depletion of susceptible bias – manifesting as a reduced risk of infection from early versus late vaccination – were also frequently described in the literature.

The issues of case-counting window bias and ascertainment bias represent specific forms of measurement bias that can affect vaccine effectiveness studies. Case-counting window bias occurs when the periods used to identify cases differ between vaccinated and unvaccinated groups, potentially leading to under- or overestimation of risk. Ascertainment bias arises when testing or case detection is unevenly distributed. Examples of ascertainment bias in VE studies included clinicians' reduced likelihood to suspect or test for vaccine-preventable diseases in vaccinated individuals or a higher testing propensity in unvaccinated populations, perceived as higher risk These biases can impact both pre- and post-recruitment phases, introducing systematic errors that distort outcome measurements. To mitigate these effects, it is essential to standardize follow-up durations, testing protocols, and case definitions across groups, ensuring more accurate and comparable estimates of vaccine effectiveness.

Lastly, biases related to the recruitment and attrition processes, while common to various study types and not specific to VE studies, were identified as constructs given the unique methodological operations specific to recruitment and post-recruitment strategies in VE studies, respectively.

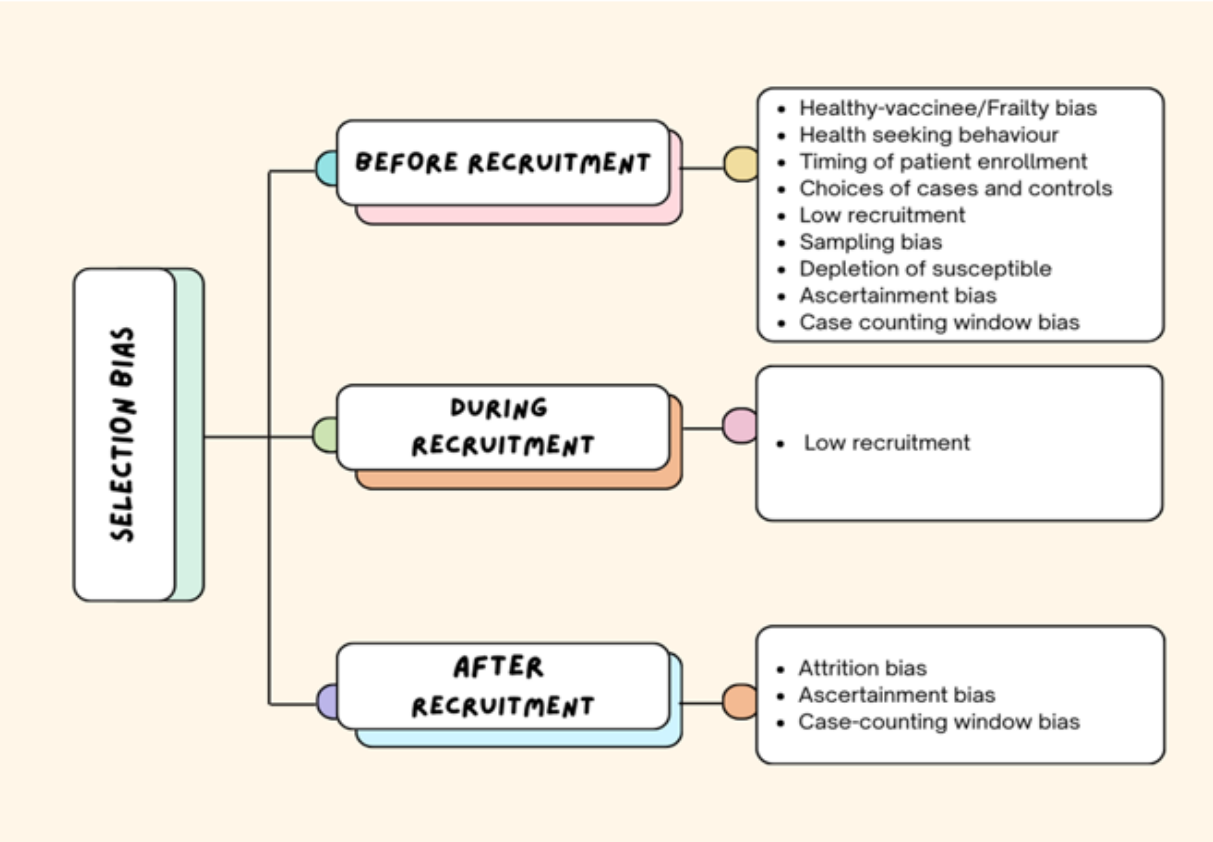

Figure 3-4 Tree diagram of construct for selection bias

Information Bias Theme. We summarized the constructs related to information bias (Figure 3-5, Appendix 3E, Table S3.4), identifying four lower-level constructs: recall bias (or bias due to self-reporting), misclassification of exposure, misclassification of outcome, and missing or incomplete information.

Information bias in VE studies frequently appeared as self-reporting or recall issues, where participants unintentionally misclassified their vaccination status. Misclassification of exposure was primarily reported to stem from inaccurate recall, absence of records, or the categorization of non-consenting participants as unvaccinated. In test-negative design studies, different recruitment methods may create imbalances between cases and controls, and the time lag between infection, symptom onset, and testing further complicates the accurate classification of exposure (i.e., vaccination status). Non-differential misclassification may arise when vaccination status is under-reported equally across all groups, potentially leading to an underestimation of VE. In contrast, differential

misclassification happens when vaccination status is reported differently between individuals with and without exposure or existing infections. For example, high-risk individuals or those with prevalent infections may report their vaccination status more accurately than those without. This type of bias can distort VE estimates in either direction.

Outcome misclassification in VE studies, particularly in test-negative design studies, was attributed to imperfect diagnostic tests, ambiguous clinical outcome definitions, and the challenges of distinguishing between mild or asymptomatic infections and differentiating symptoms related to vaccination from those of the infection. Additionally, information bias was linked to missing or incomplete data, notably from inadequate linkage of vaccination records to health registries. Errors in administrative records also contribute to this bias, leading to further misclassification of both vaccination status and health outcomes, often influenced by participants' health-seeking behavior.

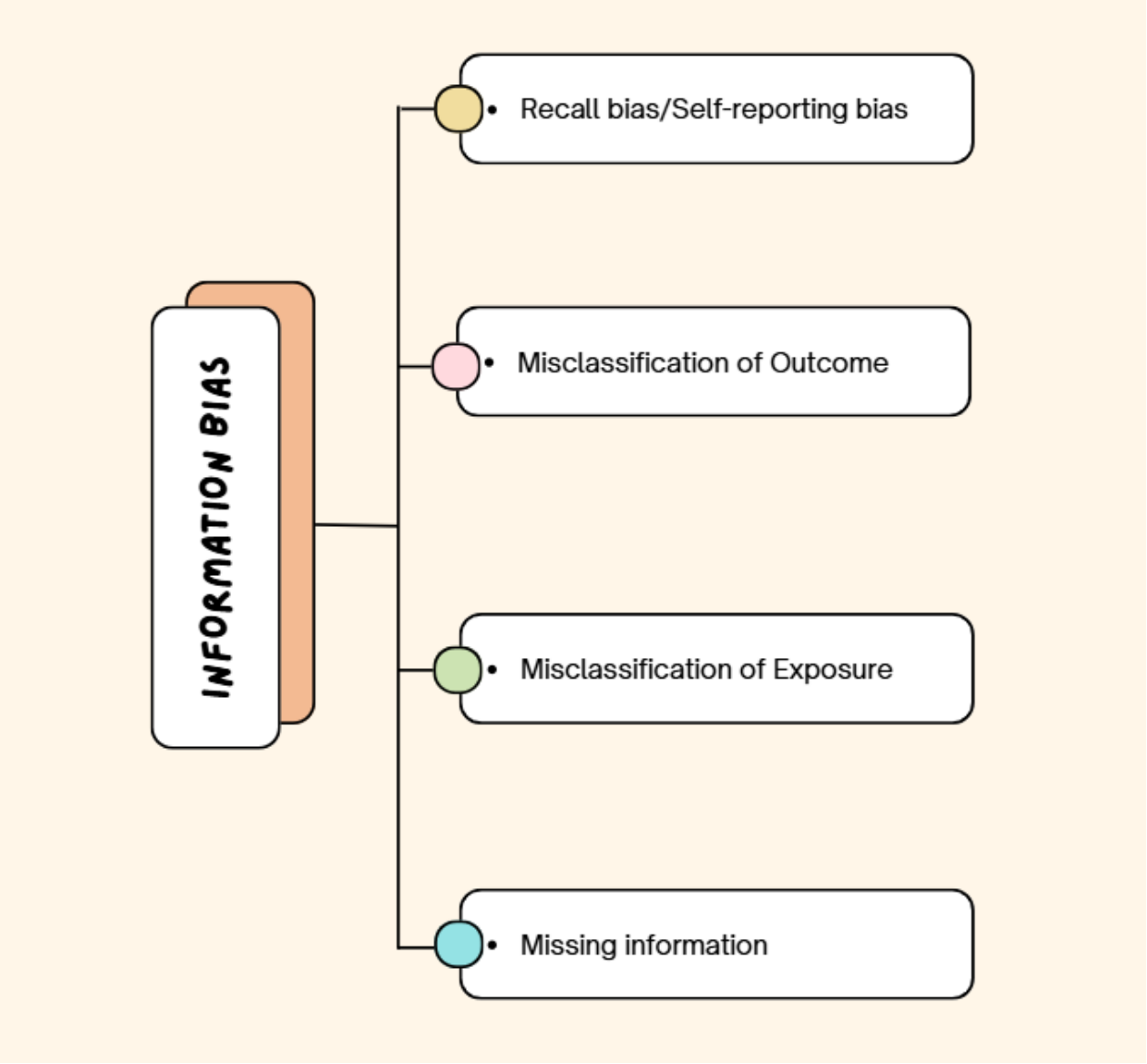

Figure 3-5 Tree diagram of construct for information bias

Cross-Cutting Methodological Biases. Several biases related to VE study design were deemed to be relevant across over-arching themes (Figure 3-6, Appendix 3E, Table S3.5). Collider bias was noted to be a particular concern in test-negative design studies, due to conditioning on testing, which is influenced by both infection status and health-seeking behavior. As with time-varying confounding, the inappropriate consideration of timing in VE study design and analysis may also introduce bias. Waning immunity was a bias reported in studies due to failure to account for changes over time since vaccination. For example, individuals vaccinated earlier may show reduced effectiveness compared to those

vaccinated more recently, not because the vaccine is less effective overall, but due to waning immunity over time. Biases related to "leaky vaccines" – vaccines that prevent the development of severe disease but do not fully prevent infection or transmission – were identified as a challenge to assessing VE. Lastly, publication bias, although not unique to VE studies, was reported as a concern: by favouring the studies with certain types of results, the overall evidence base regarding VE may be distorted.

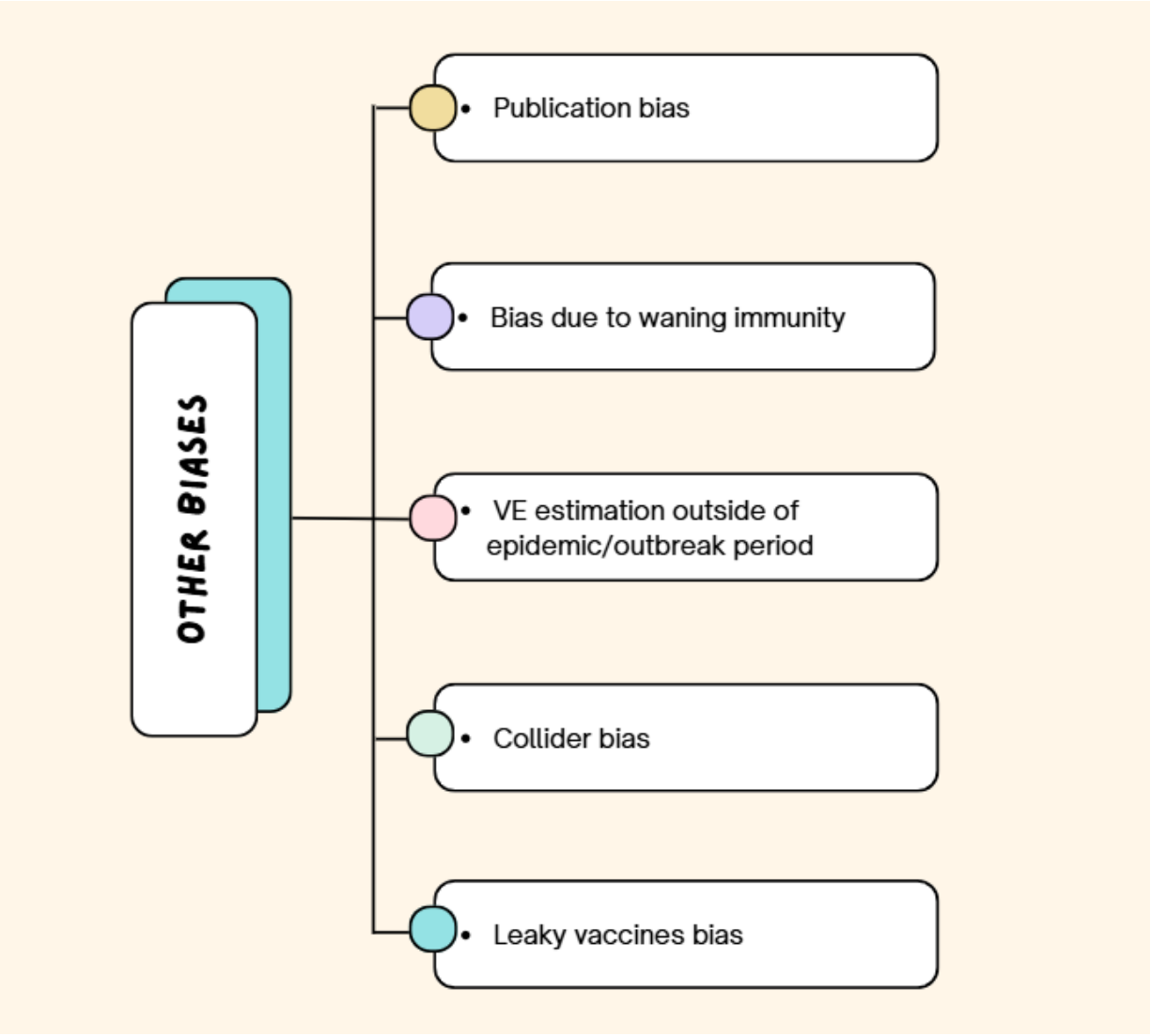

Figure 3-6 Tree diagram of constructs for other cross-cutting biases

3.7 Discussion

The goal of this scoping review was to identify and synthesize unique risk-of-bias concepts reported in the VE literature. Although we found that these concepts were largely related to themes of confounding bias, selection bias or information bias, there were representations unique to the VE context. Moreover, we identified several biases did not fall neatly into any of these larger thematic categories. We identified several VE-specific factors, including confounding related to vaccination history, differential immunity, vaccine coverage, herd immunity, and variants of concern. Selection biases were related to the timing of recruitment, and VE-specific concepts included those related to depletion of susceptible bias or healthcare-seeking behaviour. Examples of VE-specific information biases included outcome misclassification due to mild or asymptomatic infections and difficulties in differentiating vaccination-related symptoms from infection symptoms. Our findings aligned with a 2023 systematic review by Xu et al. and a methodological report by Lipsitch et al, both of which noted challenges related to confounding and other biases in VE studies (19,20).

Accurate and unbiased VE estimates are critical to inform vaccination strategies (19,20). The reliance on biased or inaccurate VE estimates could hinder public health efforts by undermining trust and contributing to vaccine hesitancy (21,22). Existing (general) risk-of-bias assessment resources for observational studies may be insufficient to capture the uniqueness of the VE context. Indeed, both the importance and the complexity of unbiased VE estimation emerged during the COVID-19 pandemic. For example, compared to seasonal epidemics where a proportion of the population is vaccinated prior to the start of the exposure risk window, the COVID-19 vaccines were rolled out gradually and over an extended timeline, creating variability in pathogen exposure across populations and risking overestimations of VE. Furthermore, it may be particularly challenging to interpret VE estimates for groups typically targeted and prioritized for vaccination (e.g., older adults, children, or immunocompromised individuals).

High-quality systematic reviews of VE studies are necessary to inform public health decision-making, but the reliability of the VE estimates within these reviews is linked to

the quality of the risk-of-bias assessment. While several risk-of-bias assessment tools have been developed and validated for observational studies (23–25), our scoping review identified several unique and specific concepts that are not accounted for in these existing tools. Consequently, there is a need to tailor common risk-of-bias concepts specific to VE research. Indeed, developing a risk-of-bias assessment tool tailored to evaluate risk of bias in VE studies may help standardize bias assessment and improve transparency and rigor in VE systematic reviews. Moreover, it can also inform VE study protocol development and reporting guidance for VE studies. The importance of using risk-of-bias tools tailored to specific designs has been increasingly recognized (26–28), and the merit of additional guidance for applying existing risk-of-bias tools to specific content matter has also gained interest. For example, adaptations have been identified as important to address limitations in risk-of-bias assessments of observational studies in nutritional epidemiology sciences (29).

The present scoping review is part of a larger research effort providing the foundation for an international collaboration to develop a risk-of-bias assessment tool and reporting guideline for VE studies. Such a tool could improve the quality and reporting of VE evidence synthesis and promote the translation of high-quality evidence regarding VE into public health action, and may have relevance to policymakers, healthcare practitioners, and vaccine developers. As evidenced by the amount of duplicated effort and research waste produced during the initial stages of the COVID-19 pandemic (30,31), high-quality tools and evaluation standards are important. The development and implementation of such tools prior to outbreak scenarios is necessary to ensure the standardization of evidence synthesis to produce rapid and high-quality evidence.

3.7.1 Strengths and Limitations

Key strengths of our scoping review included adherence to an a priori protocol and PRISMA-ScR reporting guidance. An iterative process of reading, coding, and constant comparison was employed to systematically map the risk-of-bias concepts in VE studies. Additionally, we implemented a comprehensive and peer-reviewed search strategy,

developed and tested by an experienced medical information specialist, ensuring thorough coverage of relevant literature. Our scoping review also had limitations. Despite our comprehensive approach, there remains a possibility that we missed bias concepts that were not well-documented in the published literature. This potential gap could result from biases recognized in practice but not formally reported, or emerging concepts that have not yet been widely discussed in publications. We observed considerable variability in how biases are reported across studies, making it challenging to synthesize findings consistently. Hence, the quality of our results was contingent on how authors described biases, which varied widely. Additionally, we encountered issues with the definitions provided for biases and their labeling, as there was often inconsistency or lack of clarity in terminology used across different studies. These limitations highlight the need for standardized reporting and clearer definitions of biases in VE research. Also, these limitations underscore the need for iterative development and input from all key interest holders in future risk-of-bias tool design. Engaging diverse experts and end-users can address gaps, ensure comprehensive coverage of bias concepts, and improve their practical application in VE studies.

3.7.2 Conclusion

This scoping review provided a comprehensive overview of potential sources of bias in VE studies. By synthesizing these biases, we have laid the groundwork for an international collaborative effort to develop a risk-of-bias assessment tool for VE studies. Such a tool will enhance our ability to evaluate and synthesize VE, ultimately leading to more reliable and actionable public health recommendations. As vaccine research and deployment continues to play a pivotal role in global health strategies, the ability to conduct rigorous, bias-aware analyses is increasingly critical. This work provides a crucial step towards improving the quality and interpretation of VE studies, supporting public health decision-making.

3.8 References

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3.9 Chapter III: Supplemental Materials

Appendix 3A: PRISMA Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4, 5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	5
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5, 6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the	6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	6
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	6, Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	6, Table 1Click here to enter text.
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	6
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	7, 8
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	8, 9
Limitations	20	Discuss the limitations of the scoping review process.	10
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	10
FUNDING			

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	1

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Appendix 3B: Databases Search Strategy

Risk of Bias – Vaccine Effectiveness Studies - Tools
Final Strategies
2023 Jul 27

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2023 July 26>, Ovid MEDLINE(R) ALL <1946 to July 25, 2023>
Search Strategy:
---

1 Vaccine Efficacy/ [VACCINE EFFECTIVENESS PT 1 - NEW MESH 2022] (80631)
2 exp Vaccines/ (728010)
3 exp Vaccination/ (371194)
4 vaccin*.ti,kw,kf. (553548)
5 (immunis* or immuniz*).ti,kw,kf. (108145)
6 (vaccin* or immunis* or immuniz*).ab. /freq=2 (586475)
7 or/2-6 [VACCINES/VACCINATION] (1075497)
8 (vaccin* adj5 (effective* or efficacies or efficacious* or efficacy)).tw,kw,kf. (142125)
9 7 and 8 [VACCINE EFFECTIVENESS PT 2] (129494)
10 1 or 9 [VACCINE EFFECTIVENESS PTs 1 or 2] (198154)
11 exp Bias/ (117355)
12 (bias or biases or "RoB").ti,kw,kf. (85626)
13 (bias or biases or "RoB").ab. /freq=2 (171191)
14 ((selection or sampling) adj3 (bias or biases or error?)).tw,kw,kf. (51248)
15 ((observer* or interobserver* or inter-observer* or intraobserver* or intra-observer* or observation) adj3 (bias or biases or error?)).tw,kw,kf. (6812)
16 *Risk/ (69286)
17 Risk Assessment/ (1040227)
18 ((risk or risks) adj5 (apprais* or assess* or bias* or calculat* or determin* or evaluat* or measur*)).tw,kw,kf. (983680)
19 ((bias or biases) adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)).tw,kw,kf. (117543)
20 (methodolog* adj3 (quality adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))).tw,kw,kf. (33262)
21 ((instrument? or tool?) adj3 (quality adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))).tw,kw,kf. (26899)
22 Confounding Factors, Epidemiologic/ (277169)
23 (confounding adj3 (factor? or variable?)).tw,kw,kf. (115409)
24 or/11-23 [RoB] (2504791)
25 10 and 24 [VACCINE EFFECTIVENESS - RoB] (8986)
26 limit 25 to yr="2008-current" (6748)
27 26 use medall [MEDLINE RECORDS] (1379)
28 exp vaccine/ (728010)
29 exp vaccination/ (371194)
30 vaccin*.ti,kw,kf. (553548)
31 (immunis* or immuniz*).ti,kw,kf. (108145)
32 (vaccin* or immunis* or immuniz*).ab. /freq=2 (586475)
33 or/28-32 [VACCINES/VACCINATION] (1075497)
34 (vaccin* adj5 (effective* or efficacies or efficacious* or efficacy)).tw,kw,kf. (142125)
35 33 and 34 [VACCINE EFFECTIVENESS PT 2] (129494)
36 exp statistical bias/ (117355)

37 (bias or biases or "RoB").ti,kw,kf. (85626)
38 (bias or biases or "RoB").ab. /freq=2 (171191)
39 ((selection or sampling) adj3 (bias or biases or error?)).tw,kw,kf. (51248)
40 ((observer* or interobserver* or inter-observer* or intraobserver* or intra-observer* or observation) adj3 (bias or biases or error?)).tw,kw,kf. (6812)
41 exp *risk/ (467958)
42 exp risk assessment/ (1047392)
43 ((risk or risks) adj5 (apprais* or assess* or bias* or calculat* or determin* or evaluat* or measur*)).tw,kw,kf. (983680)
44 ((bias or biases) adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)).tw,kw,kf. (117543)
45 (methodolog* adj3 (quality adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))).tw,kw,kf. (33262)
46 ((instrument? or tool?) adj3 (quality adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))).tw,kw,kf. (26899)
47 (confounding adj3 (factor? or variable?)).tw,kw,kf. (115409)
48 or/36-47 [RoB] (2456104)
49 35 and 48 [VACCINE EFFECTIVENESS] (5107)
50 limit 49 to yr="2008-current" (4214)
51 50 use emczd [EMBASE RECORDS] (2841)
52 27 or 51 [BOTH DATABASES] (4220)
53 remove duplicates from 52 (3055) [TOTAL UNIQUE RECORDS]
54 53 use medall [MEDLINE UNIQUE RECORDS] (1359)
55 53 use emczd [EMBASE UNIQUE RECORDS] (1696)

****

Web of Science Core Collection

Set #	Search Query	Results
1	TI=(vaccin*) OR AK=(vaccin*)	286517
2	TI=(immunis* or immuniz*) OR AK=(immunis* or immuniz*)	55838
3	#2 OR #1	323063
4	TI=(vaccin* NEAR/5 (effective* or efficacies or efficacious* or efficacy)) OR AB=(vaccin* NEAR/5 (effective* or efficacies or efficacious* or efficacy)) OR AK=(vaccin* NEAR/5 (effective* or efficacies or efficacious* or efficacy))	66106
5	#3 AND #4	50303
6	TI=(bias or biases or "RoB") OR AK=(bias or biases or "RoB")	142853
	TI=((selection or sampling) NEAR/3 (bias or biases or error or errors)) OR AB=((selection or sampling) NEAR/3 (bias or biases or error or errors)) OR AK=((selection or sampling) NEAR/3 (bias or biases or error or errors))	57462
8	TI=((observer* or interobserver* or inter-observer* or intraobserver* or intra-observer* or observation) NEAR/3 (bias or biases or error or errors)) OR AB=((observer* or interobserver* or inter-observer* or intraobserver* or intra-observer* or observation) NEAR/3 (bias or biases or error or errors)) OR AK=((observer* or interobserver* or inter-observer* or intraobserver* or intra-observer* or observation) NEAR/3 (bias or biases or error or errors))	14172

9	TI=((risk or risks) NEAR/5 (apprais* or assess* or bias* or calculat* or determin* or evaluat* or measur*)) OR AB=((risk or risks) NEAR/5 (apprais* or assess* or bias* or calculat* or determin* or evaluat* or measur*)) OR AK=((risk or risks) NEAR/5 (apprais* or assess* or bias* or calculat* or determin* or evaluat* or measur*))	579336
10	TI=((bias or biases) NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)) OR AB=((bias or biases) NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)) OR AK=((bias or biases) NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))	91361
11	TI=(methodolog* NEAR/3 quality NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)) OR AB=(methodolog* NEAR/3 quality NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)) OR AK=(methodolog* NEAR/3 quality NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))	17129
12	TI=((instrument or instruments or tool or tools) NEAR/3 quality NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)) OR AB=((instrument or instruments or tool or tools) NEAR/3 quality NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)) OR AK=((instrument or instruments or tool or tools) NEAR/3 quality NEAR/5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))	13892
13	TI=(confounding NEAR/3 (factor or factors or variable or variables)) OR AB=(confounding NEAR/3 (factor or factors or variable or variables)) OR AK=(confounding NEAR/3 (factor or factors or variable or variables))	52165
14	#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6	888675
15	#14 AND #5	1245

Please note: The grey literature search strategy was shared between Chapters II and III. To avoid redundancy, it is provided only in *Chapter II, Appendix 2D*, and is not duplicated here.

Appendix 3C: PRESS Checklist

PRESS Guideline 2015— Search Submission & Peer Review Assessment

Reference: McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40-6. Available: http://www.jclinepi.com/article/S0895-4356(16)00058-5/pdf.

Search submission: This section to be filled in by the searcher

Searcher: Becky Skidmore

Date submitted: 2023 Jul 25 Date requested by: 2023 Jul 27

13. Systematic Review Title

Risk of Bias Tools for Vaccine Effectiveness Studies: A Scoping Review

14. This search strategy is …

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

15. Database (e.g., MEDLINE, CINAHL)

MEDLINE

16. **Interface** (e.g., Ovid, EbscoHost…)

Ovid

17. Research Question (Describe the purpose of the search) *[mandatory]*

KQ1. What are the existing tools used to assess risk of bias in vaccine effectiveness studies?

KQ2. What risk of bias concepts or sources are considered to be of particular concern for vaccine effectiveness studies?

18. PCC Format Outline the PCC for your question — i.e., Population, Concept, Context — as applicable

Criterion	Inclusion	Exclusion
Population	No restrictions	N/A
Concept	Eligible Criteria for RoB tool/concept: RoB tools or concepts for vaccine effectiveness studies* Study designs tool can be applied to: observational studies of vaccine effectiveness Vaccine types investigated in studies tool can be applied to: Any vaccine aimed at preventing infection/disease caused by any infectious pathogen. Outcomes tool can be applied to: Clinical outcomes (e.g., overall disease, severity, symptoms, adverse effects), infection transmission. Criteria for Eligible Studies: Vaccine effectiveness studies reporting use of an RoB tool/concept (systematic reviews** of observational studies***) Methodological papers reporting the development or use of an RoB tool/concept (any study design) Articles that identify RoB concepts in vaccine effectiveness studies (e.g., guidance for evaluating RoB in vaccine effectiveness studies, articles or reporting guidance that identify sources of bias in vaccine effectiveness studies)	Ineligible criteria for RoB tool/concept: RoB tools or concepts for vaccine efficacy studies, Tools for RoB assessment in RCTs, ecological study designs. Tools applied to assess immunogenicity outcomes only (e.g., antibody levels, markers of cell-mediated response) Criteria for ineligible Studies: Vaccine efficacy studies reporting use of an RoB tool/concept (systematic reviews of RCTs only)
Context	Criteria for Eligible Studies: Any setting	N/A

	Peer-reviewed studies published in the past 15 years (2008 to present) Grey literature sources published within the last 5 years Studies in English	

19. Inclusion Criteria (List criteria such as age groups, study designs, etc., to be included) *[optional]*

2008 – present

21. Exclusion Criteria (List criteria such as study designs, date limits, etc., to be excluded)

22. Was a search filter applied? No

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question — textbox]*

23. Notes or comments you feel would be useful for the peer reviewer *[optional]*

The section on Vaccine Effectiveness has already been PRESSed. The portion on RoB has been tightened to reduce volume.
Not interested in using study designs (e.g., observational) as part of the search.

24. Please copy and paste your search strategy here, exactly as run, including the number of hits per line. [mandatory]

Database: Ovid MEDLINE(R) ALL <1946 to July 21, 2023>
Search Strategy:
---
1 Vaccine Efficacy/ [VACCINE EFFECTIVENESS PT 1 - NEW MESH 2022] (775)
2 exp Vaccines/ (277905)
3 exp Vaccination/ (109775)
4 vaccin*.ti,kw,kf. (246564)
5 (immunis* or immuniz*).ti,kw,kf. (48368)
6 (vaccin* or immunis* or immuniz*).ab. /freq=2 (257816)
7 or/2-6 [VACCINES/VACCINATION] (434063)
8 (vaccin* adj5 (effective* or efficacies or efficacious* or efficacy)).tw,kw,kf. (64473)
9 7 and 8 [VACCINE EFFECTIVENESS PT 2] (57712)
10 1 or 9 [VACCINE EFFECTIVENESS PTs 1 or 2] (57809)
11 exp Bias/ (75685)
12 (bias or biases or "RoB").ti,kw,kf. (38902)
13 (bias or biases or "RoB").ab. /freq=2 (77983)
14 ((selection or sampling) adj3 (bias or biases or error?)).tw,kw,kf. (20864)
15 ((observer* or interobserver* or inter-observer* or intraobserver* or intra-observer* or observation) adj3 (bias or biases or error?)).tw,kw,kf. (2970)
16 *Risk/ (4138)

17 Risk Assessment/ (306566)
18 ((risk or risks) adj5 (apprais* or assess* or bias* or calculat* or determin* or evaluat* or measur*)).tw,kw,kf. (407463)
19 ((bias or biases) adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*)).tw,kw,kf. (52715)
20 (methodolog* adj3 (quality adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))).tw,kw,kf. (15159)
21 ((instrument? or tool?) adj3 (quality adj5 (apprais* or assess* or calculat* or determin* or evaluat* or measur*))).tw,kw,kf. (11713)
22 Confounding Factors, Epidemiologic/ (10599)
23 (confounding adj3 (factor? or variable?)).tw,kw,kf. (48627)
24 or/11-23 [RoB] (870959)
25 10 and 24 [VACCINE EFFECTIVENESS - RoB] (1751)
26 limit 25 to yr="2008-current" (1376)

****

Peer review assessment: this section to be filled in by the reviewer

Reviewer: Kaitryn Campbell	Date completed: 26 Jul 2023

Do you wish to be acknowledged? (If yes, the review team will be advised to add an acknowledgement to any publications related to this work). Yes please.

The suggested acknowledgement is "We thank Kaitryn Campbell, MLIS, MSc for peer review of the Medline search strategy."

1. TRANSLATION

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

2. BOOLEAN AND PROXIMITY OPERATORS

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

3. SUBJECT HEADINGS

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

4. TEXT WORD SEARCHING

A ---No revisions	X
B --- Revision(s)suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

5. SPELLING, SYNTAX, AND LINE NUMBERS

A ---No revisions	X
B --- Revision(s)suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

6. LIMITS AND FILTERS

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

If "B" or "C," please provide an explanation or example:

OVERALL EVALUATION (Note: If one or more "revision required" is noted above, the response below must be "revisions required".)

A ---No revisions	X
B --- Revision(s) suggested	
C --- Revision(s) required	

Additional comments:

No errors or omissions detected no suggestions. Nicely done.

Appendix 3D: List of Excluded Studies (n=319)

Ineligible study design (n=90)

[1] Copland E, Hirst J, Ranger T, Mei W, Dixon S, Coupland C, et al. Analysis of uptake, effectiveness and safety of COVID-19 vaccinations in pregnancy using the QResearch database: research protocol and statistical analysis plan. medRxiv [Internet]. 2022; Available from: https://www.medrxiv.org/http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=empp&NEWS=N&AN=2022075608

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Does not report RoB concept (n=83)

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Appendix 3E: Supplementary Tables

TableS3.1. Included study characteristics with summary concepts and reported VE impact

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Selection bias							
Achtymichuk 2015 [1]	Influenza	Prospective population-based cohort	Healthy-user bias (overestimate)	N/A	N/A	N/A	N/A
Ainslie 2019 [2]	Influenza	Test-negative (TN)	Bias due to differential health-seeking behavior-TND studies (overestimate)	N/A	N/A	N/A	N/A
Atanasov 2023 [3]	Influenza	Passive surveillance cohort (PSC), test-negative (TN), and traditional case control (TCC)	Bias due to differential underlying health status (Not specified)	N/A	N/A	N/A	N/A
Casanova 2016 [4]	Covid-19	Vaccination record	Healthy vaccinee bias (overestimate)	N/A	N/A	N/A	N/A
Ciocanea-Teodorescu 2021 [5]	Cholera	Test-negative (TN)	Bias due differential symptom severity as an intermediate variable between infection and selection into the study TND studies (overestimate)	N/A	N/A	N/A	N/A
Feldstein 2021 [6]	Influenza	Test-negative (TN)	Bias due to preferential control selection	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			and differences in getting tested - TND studies (Either direction)				
Feldstein 2021 [7]	Influenza	Real-time test-negative design (RT-TN)	Patients who undergo clinical influenza testing may differ from those who are not tested regarding influenza status and vaccination status (Influenza) (Either direction)	N/A	N/A	N/A	N/A
Feng 2021 [8]	Influenza	Test-negative (TN)	Bias due to overrepresentation of any age group (Either direction)	N/A	N/A	N/A	N/A
Foppa 2016 [9]	Influenza	Test-negative (TN)	Confounding by indication bias (overestimate)	N/A	N/A	N/A	N/A
Fukushima 2017 [10]	Influenza	Test-negative (TN)	Bias due to study subject limited to those who receive clinician-ordered tests in routine clinical settings which depend on the severity of symptoms or vaccination status (overestimate)	N/A	N/A	N/A	N/A
Fung 2023 [11]	Covid-19	"real-world studies" vs RCTs	Case-counting window bias due to asymmetry in	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			counting cases vs controls. [Cases counted 14 days post-vaccination; controls counted at the beginning of the study.] (COVID-19 vaccines) (Overestimate)				
Glasziou 2022 [12]	Covid-19	National registry	Bias due to differential health-seeking behavior (TND studies) (Not specified)	N/A	N/A	N/A	N/A
Graham 2023 [13]	Covid-19	Questionnaire	Bias due to questionnaire responses (influenced by demographic and clinical differences) (COVID-19 vaccines) (No impact)	N/A	N/A	N/A	N/A
Haber 2015 [14]	Influenza	Test-negative (TN)	Bias due to differential health-seeking behavior (ARI, TND studies) (Overestimate)	N/A	N/A	N/A	N/A
Haber 2018 [15]	Rotavirus	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Bias due to low-income settings and high disease incidence with low test specificity	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			(TND) (Underestimate)				
Haber 2019 [16]	Rotavirus	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Bias due to differences in the propensity of seeking medical care (PSMC)/ HSB between vaccinated and unvaccinated children (Either direction)	N/A	N/A	N/A	N/A
Hitchings 2021 [17]	Covid-19	Test-negative control (TNC)	Bias due to history of natural infection (COVID-19) (Underestimate)	N/A	N/A	N/A	N/A
Hollingsworth 2021 [18]	Influenza	Comparative analysis of experimental, observational, and hybrid methods	Bias due to enrollment of subjects during non-influenza periods (likelihood of exposure reduced in these periods) (Not specified)	N/A	N/A	N/A	N/A
Hosseini-Moghaddam 2022 [19]	Covid-19	Cohort	Healthy vaccinee bias due to differential health seeking behaviour (COVID-19) (Overestimate)	N/A	N/A	N/A	N/A
Jackson 2018 [20]	Influenza	Test-negative (TN)	Bias due to differential health-seeking behavior	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			(ARI, TND studies) (Underestimate)				
Kondo 2017 [21]	Pneumococcal	Case-control	Bias due to the choice of control group (respiratory medicine vs non-respiratory medicine patients) (Either direction)	N/A	N/A	N/A	N/A
Kwong 2019 [22]	Influenza	Cohort using ICES	Bias due to under-representation of vaccinated and over-representation of unvaccinated in the tested populations (Overestimate)	N/A	N/A	N/A	N/A
Lanes 2015 [23]	Rotavirus	A retrospective cohort using the Healthcore Integrated Research Database (HIRD)	Bias due to exclusions based on follow-up times (or incomplete dates) (Not specified)	N/A	N/A	N/A	N/A
Lewnard 2021 [24]	Covid-19	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Bias due to lack of a clear clinical case definition for participant inclusion, particularly due differential health seeking behaviors (TND studies) (Overestimate)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Li 2023 [25]	Multiple	Test-negative (TN)	Collider stratification bias by analyzing only the tested samples (which is influenced by infection status and health-seeking behavior) (TND studies) (Underestimate)	N/A	N/A	N/A	N/A
Lipsitch 2016 [26]	Influenza	Multiple (Observational studies)	Bias by conditioning on testing (collider bias), leading to non-causal associations among those tested between vaccination and infection (TND studies) (Overestimate)	N/A	N/A	N/A	N/A
Lipsitch 2019 [27]	Influenza	Cohort	Bias due susceptible depletion (reduced risk of infection because of early vs late vaccination) (Underestimate)	N/A	N/A	N/A	N/A
Machado 2021 [28]	Influenza	Hospital-based test-negative design (TND)	Bias due to the low recruitment rate of eligible patients (No impact)	N/A	N/A	N/A	N/A
Markowitz 2022 [29]	Human papillomaviru	Multiple (Systematic review of data from	Bias due to incomplete self-	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
	s vaccine (HPV)	national immunization programs)	reporting of vaccination history (Overestimate)				
Mason 2021 [30]	Covid-19	Matched case-control	Healthy vaccinee bias due to differential health seeking behaviour (TND studies) (Overestimate)	bias due to breakthrough infection among HCWs (higher exposure) (COVID-19) (Underestimate)	N/A	N/A	N/A
McGovern 2015 [31]	Multiple	Publicly available data sets from the Demographic and Health Surveys (DHS)	Bias due to under-reporting vaccination status among dead children (Underestimate)	N/A	N/A	N/A	N/A
McGrath 2015 [32]	Influenza	Cohort	Selection bias due to healthy-user bias (Overestimate)	N/A	N/A	N/A	N/A
Murata 2022 [33]	Covid-19	Cohort	Time-dependent bias due to early vs late vaccination (COVID-19 vaccines) (Not Specified)	N/A	N/A	N/A	N/A
Nealon 2019 [34]	Dengue	Test-negative (TN)	Bias due to unbalanced case and control populations (case-control studies, TND) (Underestimate)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Ostropolets 2022 [35]	Covid-19	Cohort	Bias due to baseline characteristics (age, ethnicity, comorbidities and temporal distributions of vaccinations) (COVID-19) (Either direction)	N/A	N/A	N/A	N/A
Patel 2021 [36]	Covid-19	Multiple (summary of post-introduction VE studies)	Bias due to higher infection rates in non-compliance (to nonpharmaceutical interventions e.g., mask wearing) in unvaccinated (overestimation of VE), Selection bias due to breakthrough infection among HCWs (higher exposure) (underestimation of VE) (COVID-19) (Either direction)	N/A	N/A	N/A	N/A
Pearson 2022 [37]	Ebola	Test-negative (TN)	Bias due to self-reporting vs. contact-tracing method of recruitment leading to imbalance between controls vs cases	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			recruits (TND) (Either direction)				
Price 2019 [38]	Influenza	Test-negative (TN)	Bias due differential frequencies of swabbing rate among physicians (Not specified)	N/A	N/A	N/A	N/A
Segaloff 2020 [39]	Influenza	Test-negative (TN)	Selection bias due to time from onset to enrollment (Underestimate)	N/A	N/A	N/A	N/A
Shi 2017 [40]	Influenza	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Healthy vaccinee bias due to differential health seeking behaviour (TND studies) (Overestimate)	N/A	N/A	N/A	N/A
Sullivan 2016 [41]	Influenza	Test-negative (TN)	Confounding by indication bias due to differential test-seeking behavior (because of health-seeking behaviors and the severity of disease) (Overestimate)	N/A	N/A	N/A	N/A
Sullivan 2023 [42]	Influenza	Test-negative (TN)	Bias due to differential health-seeking behavior (TND studies) (Not specified)	N/A	N/A	N/A	N/A
Sullivan 2023 [42]	Influenza	Test-negative (TN)	Sampling bias (restrciting	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			participants who meets case definition) (TND) (Overestimate)				
Talbot 2016 [43]	Influenza	Test-negative (TN)	Selection bias due to age (i.e., frailty) using large administrative databases (Overestimate)	N/A	N/A	N/A	N/A
Turbyfill 2022 [44]	Covid-19	Comparative analysis of test-negative and syndrome-negative controls in the Influenza and Other Viruses in the Acutely Ill (IVY) public health surveillance network	Bias due to differential health-seeking behavior (TND studies) (COVID-19 vaccines) (Not specified)	N/A	N/A	N/A	N/A
Verani 2017 [45]	Multiple	Case-control	Bias due to low enrollment of eligible studies (Not specified, potential underestimate)	N/A	N/A	N/A	N/A
Teerawattananon 2022 [46]	Covid-19	Multiple (systematic review of observational studies)	Selection bias may arise in inpatient studies if patients hospitalized for chronic conditions are more likely to be vaccinated. This could skew the results if the vaccinated group has different	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			underlying health conditions compared to the unvaccinated group (Either direction)				
Confounding							
Ainslie 2019 [2]	Influenza	Test-negative (TN)	Health status (Underestimate)	Health awareness (Underestimate)	Vaccination status (Underestimate)	N/A	N/A
Ainslie 2019 [47]	Influenza	Test-negative (TN)	Vaccination affecting the probability of non-influenza ARI (i.e., in test-negative studies) (Either direction impact on VE)	Health status (Either direction impact on VE)	Health awareness (Either direction impact on VE)	Vaccination modifying care-seeking behaviour (Either direction impact on VE)	N/A
Anderson 2020 [48]	Influenza	Patient surveys and administrative records	Age (people under vs. over age of 65) (Not specified)	Employment status (Not specified)	Pneumococcal vaccination (Not specified)	Comorbidities (Not specified)	N/A
Andrejko 2023 [49]	Covid-19	Patient surveys and administrative records reported to the California Department of Public Health (CDPH)	Age (Underestimate)	Sex (Not specified)	Region and time (Not specified)	Unmeasured confounding (Not specified)	N/A
Balasubramani 2021 [50]	Influenza	Comparative analysis of data from the US Flu VE Network (research database) with a clinical surveillance software system	Frailty among older adults (Not specified)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
		(administrative database)					
Baum 2021 [51]	Influenza	Cohort (simulation study)	Confounding by indication (Underestimate)	Healthy vaccinee bias (Overestimate)	N/A	N/A	N/A
Bermingham 2023 [52]	Covid-19	Using linked vaccination data from the National Immunisation Management System (NIMS) and the Office for National Statistics (ONS) Public Health Data Asset (PHDA) based on the National Health Service (NHS) number	Sociodemographic differences (Not specified)	Health characteristics (Overestimate)	Infection rates (Not specified)	N/A	N/A
Bodner 2023 [53]	Covid-19	Simulation/modelling to compare VE against various contact patterns among vaccinated vs unvaccinated	Vaccinated-contact heterogeneity (Underestimate)	N/A	N/A	N/A	N/A
Bruhn 2017 [54]	Pneumococcal	Nationwide administrative databases in Brazil, Chile, Ecuador, Mexico, and the United States (using synthetic controls)	Confounding factors (Not specified)	N/A	N/A	N/A	N/A
Butler 2019 [55]	Influenza	Medicare data from the United States end-stage renal disease program	Healthy-user bias (Overestimate)	Frailty and health status (Not specified)	Socio-demographic factors (Not specified)	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
		(2009-2013) (Comparative analysis of high vs low dose vaccines)					
Casanova 2016 [4]	Influenza	Systematic review (case-control, cohort)	Confounding by failure to account for pneumococcal vaccination status (in influenza vaccination studies) (Not specified)	N/A	N/A	N/A	N/A
Doll 2022 [56]	Covid-19	Simulation/modelling to quantify bias from inclusion of controls with a non independent exposure in COVID-19 or influenza VE test-negative designs	Confounding through influenza vaccination having an effect on COVID-19 VE (COVID-19 VE test-negative designs with influenza controls) (Not specified)	N/A	N/A	N/A	N/A
Doyon-Plourde 2022 [57]	Influenza	Cohort	Estimating rVE outside of the influenza season, when a vaccine effect should be absent (Not specified)	N/A	N/A	N/A	N/A
Endo 2020 [58]	Multiple	Test-negative (TN)	Age (Underestimate)	N/A	N/A	N/A	N/A
Fell 2022 [59]	Covid-19	Cohort	Maternal characteristics (Not specified)	Demographics (Not specified)	Marginalization measures (Not specified)	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Foppa 2019 [60]	Influenza	Simulation/modelling study to assess vaccination history-associated bias in VE estimates from TND studies	Vaccination history (i.e., vaccine-derived immunity from previous seasons persists, the protective effect of past vaccinations is not separated from the effect of current vaccination) (Either direction impact on VE)	N/A	N/A	N/A	N/A
Franke 2017 [61]	Cholera	Case-control	Health-seeking behaviour (Overestimate)	Recall bias (i.e. overreporting or underreporting of vaccination status) (Overestimate)	Household characteristics (i.e., better access to clean water, hygiene practices, overall health knowledge) (Overestimate)	N/A	N/A
Fukushima 2017 [10]	Influenza	Test-negative (TN)	Health care-seeking behaviour (Affects the true VE but does not specify the direction)	N/A	N/A	N/A	N/A
Fung 2023 [11]	Covid-19	"real-world studies" vs rcts	Age bias (high risk and older ones are prioritized) (Overestimate)	N/A	N/A	N/A	N/A
Graham 2023 [13]	Covid-19	Questionnaire	Household type, household size, clinically extremely vulnerable (CEV)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			status and other variables in the original study (age, gender, ethnicity, geography, index of multiple deprivations, care home status and week of onset) (Not specified)				
Haber 2015 [14]	Influenza	Simulation/modeling study to compare VE estimates from TND and CCD (case-control design) studies	Health-seeking behaviour (Underestimate)	Vaccination having effect on non-influenza (Not specified)	Baseline characteristics (health status, age, exposure, education, socioeconomic status) (Either direction impact on VE depending on other factors)	N/A	N/A
Haber 2019 [16]	Rotavirus	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Health status (Either direction impact on VE)	Seeking medical care (Underestimate)	N/A	N/A	N/A
Hara 2017 [62]	Influenza	Cohort	Baseline characteristics (i.e., age, sex, race, socioeconomic status, residence, comorbid conditions) (Underestimate)	Day care use (Underestimate)	Health-conscious behaviour (Underestimate)	Vaccination history (Underestimate)	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Hellfritzsch 2017 [63]	Influenza	Cross-sectional based on a public health survey conducted in the Central Denmark Region	Socioeconomic status (Not specified)	Health awareness (Not specified)	N/A	N/A	N/A
Hollingsworth 2021 [18]	Influenza	Evaluative Framework	Healthy user bias (Overestimate)	Waning immunity (Not specified)	Vaccination coverage rate, virus transmission (herd immunity for unvaccinated when coverage is high) (Not specified)	Incomplete vaccination history – VE may be influenced by more than one season (TND designs) (Not specified)	N/A
Ioannidis 2022 [64]	Covid-19	Non-randomized studies	Pre-existing immunity (either direction impact on VE)	Exposure differences (either direction impact on VE)	Disease risk factor (Underestimate)	Hospital admission decision and treatment use (Either direction impact on VE)	N/A
Izurieta 2019 [65]	Herpes zoster vaccine (HZV)	Matched cohort using a nationally representative survey of the Medicare population (MCBS)	Impaired mobility (Not specified)	Education levels (Not specified)	Health-seeking behaviour (Not specified)	N/A	N/A
Kahn 2022 [66]	Covid-19	Simulation/modelling study	Heterogeneous risk of infection (Not specified)	N/A	N/A	N/A	N/A
Khan 2023 [67]	Covid-19	Test-negative control (TNC)	Age (Not specified)	Gender (Not specified)	History of SARS-CoV-2 infection (Not specified)	Work area (Not specified)	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Kimiya 2018 [68]	Influenza	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Comorbidities (Underestimate)	Age (i.e., broader age range) (Underestimate)	Participation in group activities (Underestimate)	Vaccination history (Underestimate)	N/A
			Care-seeking behaviour (Overestimate)	Recall bias (Underestimate)	Socioeconomic factors (Not specified)	N/A	N/A
King 2015 [69]	Pneumococcal	Cohort	Confounding factors (Not specified)	N/A	N/A	N/A	N/A
Li 2023 [25]	Multiple	Test-negative (TN)	Healthcare seeking behaviour (Not specified)	Occupation as healthcare worker (Not specified)	Previous infection history (Not specified)	N/A	N/A
Liang 2022 [70]	Influenzas	Population-based case-crossover study	Health status (Not specified)	Comorbidity, frailty, and age (Not specified)	N/A	N/A	N/A
Link-Gelles 2016 [71]	Pneumococcal	Data from the Centers for Disease and Control and Prevention's (CDC) Active Bacterial Core surveillance, an active population- and laboratory-based surveillance matched by SES	Confounding due to SES (No large effect found on VE)	N/A	N/A	N/A	N/A
Loiacono 2022 [72]	Influenza	Review (case-control, cohort)	Estimating rVE outside of the influenza season, when a vaccine effect should be	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			absent (Not specified)				
Markowitz 2018 [73]	Human papillomavirus vaccine (HPV)	Multiple (updated systematic review of data from national immunization programs)	Differences in Characteristics and Age at vaccination (many vs. fewer vaccine doses) (Overestimate)	Likelihood of prevalent infection at vaccination (Overestimate)	Interval between doses (Overestimate)	Socioeconomic status (Overestimate)	Risk behaviours (Overestimate)
Markowitz 2022 [29]	Human papillomavirus vaccine (HPV)	Multiple (Systematic review of data from national immunization programs)	Prevalence of HPV infection (Not specified)	Risk of HPV acquisition (Not specified)	Immunogenicity (Overestimate)	N/A	N/A
McGrath 2015 [32]	Influenza	Cohort	Confounding by unobserved frailty or functional status (Overestimate)	N/A	N/A	N/A	N/A
Murata 2022 [33]	Covid-19	Cohort	Demographic traits (Age, gender, Race and ethnicity, veteran status, smoking history, use of supplemental oxygen) (Not specified)	Comorbidity indices (Not specified)	Predicted Probability of Death scores (Not specified)	Outpatient medication use (Not specified)	Infection variant (Not specified)

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Patel 2021 [36]	Covid-19	Multiple (summary of post-introduction VE studies)	Health-care seeking/access bias (Underestimate)	Confounding by other unspecified factors (Occurs when there are common causes of receipt (or lack of receipt) of vaccine and risk of SARSCoV-2 exposure) (Not specified)	Health-seeking behaviour (Either direction)	N/A	N/A
Ray 2020 [74]	Influenza	Comparative analysis of two hypothetical rcts	Depletion of susceptible bias (Not specified)	N/A	N/A	N/A	N/A
Remschmidt 2015 [75]	Influenza	Systematic review (cohort, case-control)	Confounding by indication (Underestimate VE)	N/A	N/A	N/A	N/A
Remschmidt 2015 [76]	Influenza	Systematic review (cohort, case-control)	Confounding by indication (Underestimate)	Healthy vaccinee bias (Overestimate)	N/A	N/A	N/A
Robison 2018 [77]	Influenza	Linked data from Immunization Information Systems (IIS) and hospital data across a metropolitan area to assess HD VE in the 2016–17 influenza season	Healthy Vaccinee Bias (i.e., individuals who receive vaccinations are generally healthier) (Overestimate)	Unhealthy Vaccinee Bias/At-Risk Vaccinee Bias (i.e., individuals with a high risk of suffering from consequences irrespective of getting vaccinated) (Underestimate)	Relevant strata (Exact age, local residence areas and provider biases) (Affects the true VE but direction not specified)	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Shi 2017 [40]	Influenza	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Covariates such as health status, age, exposure, education and socioeconomic status may be associated with both the likelihood of being vaccinated and the likelihood of developing influenza and non-influenza ARIs (Not specified)	N/A	N/A	N/A	N/A
Streeter 2022 [78]	Pneumococcal	Cohort study using the UK Clinical Practice Research Datalink	Age (Not specified)	Baseline characteristics (i.e., with comorbidities) (Not specified)	Prior events (Not specified)	Mortality rates (Not specified)	Sex (Not specified)
Suah 2022 [79]	Multiple	Simulation/modeling study VE bias with time-varying vaccine coverage, and heterogeneous testing and baseline attack rates (cohort and TND)	Time-varying vaccine overage (Not specified)	N/A	N/A	N/A	N/A
Sullivan 2016 [41]	Influenza	Test-negative (TN)	Confounding by prior infection status and pior vaccination status (Not specified)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Ulyte 2020 [80]	Influenza	Cohort from the Swiss Federal Office of Public Health(FOPH)	Age (Not specified)	Sex (Not specified)	Chronic diseases (Not specified)	Healthcare use (Not specified)	Healthcare expenditure (Not specified)
Wei 2023 [81]	Covid-19	Simulation/modeling study using IQVIA Medical Research Database (IMRD)	Sociodemographic factors (i.e., age, sex, Townsend Deprivation Index, geographic location, race) (Not specified)	Clinical factors (i.e., BMI, alcohol use, smoking status, influenza vaccination history, comorbidities prior to the index date [i.e., hypertesnion, diabetes, chronic kidney disease, influenza, cancer, atrial fibrillation, venous thrombosis, ischemic heart disease, congestive heart failure, stroke, trauma, fracture, liver disease, fall, dementia, and depression) (Not specified)	Medication use (i.e., antidiabetic, antihypertensive, statin, diuretics, glucocorticoids, nonsteroidal anti-infammatory drugs, opioids, proton-pump inhibitors, biologic disease modifying antirheumatic drugs) (Not specified)	Healthcare utilization during the past one year (Not specified)	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Young-Xu 2019 [82]	Influenza	Cohort	Demographics (age, sex, race, healthcare utilization) in terms of higher baseline risks (Underestimate)	Co-morbidities (Underestimate)	Confounding by indication (High vaccine dose [HD] vs. Standard dose [SD]) (Either direction impact on VE)	N/A	N/A
Information bias							
Ainslie 2017 [83]	Influenza	Test-negative (TN)	Bias due to health seeking behavior-vaccinated less likely seek care (symptomatic influenza) (Overestimate)	N/A	N/A	N/A	N/A
Ainslie 2019 [47]	Influenza	Test-negative (TN)	Exposure misclassification-infection status-due to imperfect test (Underestimate)	Misclassification of vaccination status-recall bias (Overestimate)	N/A	N/A	N/A
Ainslie 2019 [47]	Influenza	Test-negative (TN)	Misclassification due to delay in vaccination -prior infection (Overestimate)	Misclassification due to timing of vaccination (eg during outbreak) (Downward)	N/A	N/A	N/A
Amin 2022 [84]	Rotavirus	Administrative data from US surveillance network	Misclassification due to imperfect diagnostic test (TND) (Not specified)	N/A	N/A	N/A	N/A
Andrejko 2023 [49]	Covid-19	Patient surveys and administrative	Misclassification based on	End-point misclassification	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
		records reported to the California Department of Public Health (CDPH)	vaccination status due to absence of record (limited impact)	-errors in identifying the symptoms related to vaccination (Not specified)			
Balasubramani 2021 [50]	Influenza	Comparative analysis of data from the US Flu VE Network (research database) with a clinical surveillance software system (administrative database)	Misclassification due to imperfect test (Underestimate)	Limited/missing information in the database (Not specified)	N/A	N/A	N/A
Baum 2021 [85]	Influenza	Population Information System and the Finnish Vaccination Register	Outcome misclassification due to error in identifying presence or absence of infection (Underestimate)	N/A	N/A	N/A	N/A
Baum 2021 [86]	Multiple	Simulation/modeling study	Exposure misclassification - measurement error (both direction)	N/A	N/A	N/A	N/A
Brookmeyer 2022 [87]	Multiple	Linked data from Population-Based Health Registries	Non differential misclassification of exposure-underreporting of vaccinated persons (Underestimate)	Misclassification of disease due to incomplete linkage of vaccination data to registries (Either direction)	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Chambers 2023 [88]	HPV	Cohort	Misclassification due to self-reporting of vaccination status (Underestimate)	N/A	N/A	N/A	N/A
DeSmedt 2018 [89]	Multiple	Simulation/modeling study	Non-differential exposure misclassification-vaccine status (Underestimate)	Differential exposure misclassification (Either direction)	Differential disease misclassification (Either direction)	N/A	N/A
Doyon-Plourde 2022 [57]	Influenza	Cohort	Misclassification due to errors in administrative healthcare records (Inaccurately classified regarding their vaccination status or health outcomes based on their health seeking behaviour) (Underestimate)	N/A	N/A	N/A	N/A
Endo 2020 [58]	Multiple	Test-negative (TN)	Misclassification of outcome based on imperfect diagnostic test (Underestimate)	N/A	N/A	N/A	N/A
Eusebi 2023 [90]	Covid-19	Simulation/modemed study to evaluate the ability of the Bayesian models to address different magnitudes of misclassification bias	Misclassification due to imperfect diagnostic test (TND) (Underestimate)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Foppa 2019 [60]	Influenza	Simulation/modelling study to assess vaccination history-associated bias in VE estimates from TND studies	Misclassification of vaccination status (Underestimate)	N/A	N/A	N/A	N/A
Goldman 2022 [91]	Multiple	Review of 7 vaccine studies	Outcome-reporting bias due to selective reporting (Not specified)	N/A	N/A	N/A	N/A
Goldstein 2016 [92]	Pertussis	Cohort (KIDS Plus IIS)	Misclassification of outcome-change in case definitions (Underestimate)	N/A	N/A	N/A	N/A
Graham 2023 [13]	Covid-19	Questionnaire	Recall bias related to self-reporting of vaccination date (COVID-19 vaccines) (Underestimate)	Recall bias related to self-reporting of onset date (COVID-19 vaccines (Underestimate)	N/A	N/A	N/A
Haber 2015 [14]	Influenza	Simulation/modeling study to compare VE estimates from TND and CCD (case-control design) studies	Misclassification due to imperfect test (Not specified)	N/A	N/A	N/A	N/A
Haber 2018 [15]	Rotavirus	Comparative analysis of TNC (Test-negative control studies) and TCC studies	Misclassification due to imperfect test (Underestimate)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
		(Traditional case-control studies)					
Hara 2017 [62]	Influenza	Cohort	Differential misclassification of outcome-vaccination status (Either direction)	N/A	N/A	N/A	N/A
Hitchings 2021 [17]	Covid-19	Test-negative control (TNC)	Bias due to prior infection status (Downward)	Misclassification of outcome (Underestimate)	N/A	N/A	N/A
Hungerford 2018 [93]	Rotavirus	Simulation/modeling study using comparator populations with various vaccine uptake	Misclassification of disease due to different GP practices (Not specified)	N/A	N/A	N/A	N/A
Ioannidis 2022 [64]	Covid-19	Non-randomized studies	Non differential misclassification (Underestimate)	Differential misclassification -recall bias due to self-reporting of vaccination (Not specified)	Misclassification of outcome due to testing interpretation (Not specified)	Misclassification of outcome due to judgement based on test results and patient symptoms (Not specified)	N/A
Ioannidis 2022 [64]	Covid-19	Non-randomized studies	Bias due to death attribution (Either direction)	N/A	N/A	N/A	N/A
Jackson 2015 [94]	Influenza	Test-negative (TN)	Misclassification due to imperfect test (Underestimate)	N/A	N/A	N/A	N/A
Jackson 2019 [95]	Influenza	Test-negative (TN)	Misclassification of outcome-due to	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
			self-reported vaccination history (Underestimate)				
Kimiya 2018 [68]	Influenza	Comparative analysis of TNC (Test-negative control studies) and TCC studies (Traditional case-control studies)	Differential misclassification-health seeking behavior (TCCs) (Underestimate)	Non-differential misclassification of outcome (based on clinical rather than test based) (TCCs) (Underestimate)	Recall Bias (Underestimate)	N/A	N/A
King 2015 [69]	Pneumococcal	Cohort	Misclassification due to partial vaccination (Underestimate)	N/A	N/A	N/A	N/A
King 2015 [69]	Pneumococcal	Cohort	Misclassification due to missing vaccination record (Underestimate)	misclassification due to death (Overestimate)	N/A	N/A	N/A
Kwong 2019 [22]	Influenza	Cohort using ICES	Bias due to false negative results (interval between illness onset and specimen collection is too long) (Underestimate)	N/A	N/A	N/A	N/A
Lewnard 2020 [96]	Multiple	Case–control	Misclassification of outcome-symptomatic and tested vs asymptomatic and tested (Both direction)	N/A	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Markowitz 2018 [73]	Human papillomavirus vaccine (HPV)	Multiple (updated systematic review of data from national immunization programs)	Differential exposure misclassification - sexual exposure, prevalent infection at the time of vaccination (Underestimate)	N/A	N/A	N/A	N/A
Markowitz 2022 [29]	Human papillomavirus vaccine (HPV)	Multiple (Systematic review of data from national immunization programs)	Measurement bias in intervention (interval between doses and validity of data source) (Underestimate)	Measurement bias in outcome (validity of algorithms used for outcome classification and time interval after vaccination before counting outcomes to ensure that only cases that occur after the vaccine is expected to be effective are considered) (Underestimate)	N/A	N/A	N/A
Nikas 2023 [97]	Multiple	Simulation/modeling study on an agent-based model of acute viral infection with a constant background force of infection	Bias due to not accounting heterogeneity in the vaccine response (Underestimate)	N/A	N/A	N/A	N/A
Patel 2021 [36]	Covid-19	Multiple (summary of post-introduction VE studies)	Misclassification bias due to imperfect test (Decrease)	Exposure misclassification - delay between the date of infection and	N/A	N/A	N/A

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
				development of symptoms and presentation for testing (Decrease)			
Sullivan 2016 [41]	Influenza	Test-negative (TN)	Misclassification of outcome- due to testing limitation (cohort-case control study) (Not Specified)	N/A	N/A	N/A	N/A
Tormen 2023 [98]	Covid-19	Systematic review (case-control, cohort)	Publication bias (Not specified)	N/A	N/A	N/A	N/A
VanWerkhoven 2024 [99]	Covid-19	Linked data from Population-Based Health Registries	Non-Consented participants classified as unvaccinated due to absence of record (COVID-19 vaccination) (Downward)	Misclassification of outcome (COVID hospitalizations where primary covid-19 reasons not) (Lower)	N/A	N/A	N/A
Verani 2017 [45]	Multiple	Case-control	Differential misclassification of outcome- vaccination status (Either direction)	Non-differential misclassificationod outcome - vaccination status (Underestimate)	N/A	N/A	N/A
Wei 2023 [81]	Covid-19	Simulation/modeling cohort study using IQVIA Medical Research Database (IMRD)	Misclassification based on underreporting of test (Not specified)	N/A	N/A	N/A	N/A
Cross-cutting biases							

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Brookmeyer 2022 [87]	Multiple	Linked data from Population-Based Health Registries	Underestimation of population size (Upwards VE)	Overestimation of population size (Downwards VE)	N/A	N/A	N/A
Bruhn 2017 [54]	Pneumococcal	Nationwide administrative databases in Brazil, Chile, Ecuador, Mexico, and the United States (using synthetic controls)	Time-frame bias – to include pandemic data (Overestimate)	N/A	N/A	N/A	N/A
Casanova 2016 [4]	Influenza	Systematic review (case-control, cohort)	Rating bias – representing indirect outcomes (Decrease VE)	N/A	N/A	N/A	N/A
Ferdinands 2017 [100]	Influenza	Administrative data from the US Influenza Vaccine Effectiveness Network, 2011-12 through 2014-15	Bias due to the heterogeneity of the at-risk population (Overestimate)	N/A	N/A	N/A	N/A
Fung 2023 [11]	Covid-19	"real-world studies" vs rcts	Case-counting window bias – asymmetry among vaccinated and unvaccinated (Overestimate)	Bias – background infection (Overestimate)	N/A	N/A	N/A
Hitchings 2022 [101]	Covid-19	Test-negative (TN)	Time variant + time varying bias (Either direction)	N/A	N/A	N/A	N/A
Lau 2013 [102]	Influenza	Cohort	Healthy vaccine bias (Overestimate)	N/A	N/A	N/A	

Author (year)	Vaccine(s) Assessed	Study Design(s) Reported/Used	Concept 1 (VE impact)	Concept 2 (VE impact)	Concept 3 (VE impact)	Concept 4 (VE impact)	Concept 5 (VE impact)
Li 2023 [25]	Multiple	Test-negative (TN)	Collider bias – due to HSB, infection status and risk factors (Not specified)	N/A	N/A	N/A	N/A
Lund 2023 [103]	Covid-19	Simulation/modeling study	Temporal bias – time under observation vs. calendar time scale (Overestimate)	N/A	N/A	N/A	N/A
Patel 2021 [36]	Covid-19	Multiple (summary of post-introduction VE studies)	Diagnostic bias – testing unvaccinated (Increase VE)	Bias due to non-specific vaccine effect (Either direction)	Bias due to prior infection (Decrease VE	Bias – spurious waning (Decrease VE)	Survivorship bias (Decrease VE)
Ray 2020 [74]	Influenza	Comparative analysis of two hypothetical rcts	Depletion of susceptible bias (Underestimate)	N/A	N/A	N/A	N/A
Remschmidt 2015 [75]	Influenza	Systematic review (cohort, case-control)	Healthy vaccinee bias (Overestimate)	N/A	N/A	N/A	

Table S3.2 Construct Maps of concepts related to Confounding Bias

Higher Order Constructs	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Population-level confounders	Individual-level confounders	Pathogen-level confounders	Pathogen-level confounders
Lower Order Constructs	Demographics	Vaccination history	Differential immunity	Health seeking behaviour	Comorbidities & Frailty Bias	Healthy vaccine bias	Confounding by indication	Vaccine coverage/Herd Immunity	Behavioral and environmental exposures	Infection Variant	Infection Prevalence
Unique concepts	Age, Sex/Gender, SES-related factors (employment status, education, household characteristics), Race	Confounding by prior infection status and prior vaccination status	Interval between doses, history of infection, pre-existing immunity		Fragility and health status, medication use, health status	Healthy user bias, health awareness	Confounding by indication (High vaccine dose [HD] vs. standard dose [SD])	Vaccination coverage rate, virus transmission (herd immunity for unvaccinated when coverage is high)	Participation in group activities, day case use, work area, risk behaviours	Infection Variant, Infection Rates (Prevalence of Disease Over Time)	Infection rates (prevalence of disease over time)
		Vaccination history ((i.e, vaccine-derived immunity from previous seasons persists, the protectiv	Vaccination affecting the probability of non-influenza ARI (i.e., in test-negative				Confounding by indication bias (individuals with chronic conditions are more likely to be hospitalized and vaccinated	Confounding by other unspecified factors (Occurs when there are common causes of receipt (or lack of receipt) of vaccine and risk of	Vaccinated contact heterogeneity		bias-background infection rate

Higher Order Constructs	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Individual-level confounders	Population-level confounders	Individual-level confounders	Pathogen-level confounders	Pathogen-level confounders
Lower Order Constructs	Demographics	Vaccination history	Differential immunity	Health seeking behaviour	Comorbidities & Frailty Bias	Healthy vaccine bias	Confounding by indication	Vaccine coverage/Herd Immunity	Behavioral and environmental exposures	Infection Variant	Infection Prevalence
		e effect of past vaccinations is not separated from the effect of current vaccination)	(TN) studies)				, leading to higher vaccination rates in the control group (influenza-negative patients)) (Influenza vaccines)	SARSCoV-2 exposure)			

Table S3.3 Construct Map of concepts related to selection bias

Higher Order Construct: At what point during selection process would these occur?	Before/after recruitment	Before Recruitment	Before Recruitment	Before Recruitment	Before Recruitment	Before Recruitment	Before/ during recruitment	Before/after recruitment	After recruitment
Lower Order Constructs	Case Counting Window Bias	Healthy Vaccinee Bias/Frailty Bias	Health Seeking Behaviour	Timing Of Patient Enrollment	Sampling Bias	Choice of cases and controls	Low recruitment	Differential Testing/Ascertainment Bias	Attrition Bias
Unique concepts	Case-counting window bias due to asymmetry in counting cases vs controls. [Cases counted 14 days post-vaccination; controls counted at the beginning of the study.] (COVID-19 vaccines)	Healthy user bias	Healthy vaccinee bias due to differential health seeking behaviour	Time-dependent bias due to early vs late vaccination (COVID-19 vaccines)	Sampling bias (restricting participants who meets case definition) (TND)	Selection bias due to the choice of control group (respiratory medicine vs non-respiratory medicine patients)	Selection bias due to the low recruitment rate of eligible patients	Selection bias due differential frequencies of swabbing rate among physicians	Selection bias due to exclusions based on follow-up times (or incomplete dates)
		Confounding by unobserved frailty or functional status	Selection biases due to differences in the propensity of seeking medical care (PSMC)/ HSB between	Time-dependent bias due to early vs late vaccination (COVID-19 vaccines)	Selection bias due to overrepresentation of any age group	Selection bias due to lack of a clear clinical case definition for participant inclusion, particularly due differential health seeking		Selection bias can occur if study subjects are limited to those who receive clinician-ordered tests in routine	

Higher Order Construct: At what point during selection process would these occur?	Before/after recruitment	Before Recruitment	Before Recruitment	Before Recruitment	Before Recruitment	Before Recruitment	Before/ during recruitment	Before/after recruitment	After recruitment
Lower Order Constructs	Case Counting Window Bias	Healthy Vaccinee Bias/Frailty Bias	Health Seeking Behaviour	Timing Of Patient Enrollment	Sampling Bias	Choice of cases and controls	Low recruitment	Differential Testing/Ascertainment Bias	Attrition Bias
			vaccinated and unvaccinated children			behaviors (TND studies)		clinical settings which depend on the severity of symptoms or vaccination status	
		Selection bias due to age (i.e., frailty) using large administrative databases Selection bias due to differential underlying health status (COVID-19 vaccines)	Selection bias due to higher infection rates in non-compliance (to nonpharmaceutical interventions e.g., mask wearing) in unvaccinated (overestimation of VE)	Selection bias due to time from onset to enrollment					

Table S3.4 Construct map of extracted concepts related to information bias

Constructs	Recall bias / bias due to self-reporting	Misclassification of exposure	Misclassification of outcome	Missing/lack of information
Unique concepts	Misclassification of outcome due to self-reported vaccination history	Misclassification based on vaccination status due to absence of record	Misclassification of outcome due to judgement based on test results and patient symptoms	Limited/missing information in the database
	Recall bias (i.e., overreporting or underreporting of vaccination status	Non-Consented participants classified as unvaccinated due to absence of record (COVID-19 vaccination)	Misclassification of outcome-change in case definitions	Misclassification of disease due to incomplete linkage of vaccination data to registries
	Selection bias due to incomplete self-reporting of vaccination history	Differential exposure misclassification -sexual exposure, prevalent infection at the time of vaccination	Outcome misclassification due to error in identifying presence or absence of infection	Misclassification due to errors in administrative healthcare records (Inaccurately classified regarding their vaccination status or health outcomes based on their health seeking behaviour)
	Bias due to questionnaire responses (influenced by demographic and clinical differences) (COVID-19 vaccines	Exposure misclassification-Delay between the date of infection and development of symptoms and presentation for testing	Misclassification of outcome based on imperfect diagnostic test	
	Bias due to self-reporting vs. contact-tracing method of recruitment leading to imbalance between controls vs cases recruits (TND)	Misclassification based on vaccination status due to absence of record	Non-differential misclassification of outcome (based on clinical rather than test-based) (TCCs)	

Constructs	Recall bias / bias due to self-reporting	Misclassification of exposure	Misclassification of outcome	Missing/lack of information
	Recall bias related to self-reporting of onset date (COVID-19 vaccines)	Misclassification due to partial vaccination	End-point misclassification-errors in identifying the symptoms related to vaccination	
		Misclassification due to delay in vaccination -prior infection		
		Non differential misclassification of exposure-underreporting of vaccinated persons		

Table S3.5 Construct map of other methodological considerations related to observational studies of vaccine effectiveness

Constructs	Collider Bias	Publication Bias	Waning Immunity	Leaky Vaccines	Estimating VE outside epidemic setting
Examples of extracted concepts	Collider stratification bias by analyzing only the tested samples (which is influenced by infection status and health-seeking behavior) (TND studies)	Publication bias	Spurious waning	Bias due to not considering suitable model of vaccine failure (e.g., leaky vaccines)	Estimating rVE outside of the influenza season, when a vaccine effect should be absent (can be used to test for residual confounding)
	Selection bias by conditioning on testing (collider bias), leading to non-causal associations among those tested between vaccination and infection (TND studies)	N/A	N/A	N/A	Enrollment of subjects during non-influenza periods (likelihood of exposure reduced in these periods)

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Chapter IV: Refining Signal Items for Risk of Bias Assessment Tool in Vaccine Effectiveness Studies: A Pilot Survey

4.1 Preface

For this chapter, I designed a survey questionnaire using SurveyMonkey (SurveyMonkey Inc., San Mateo, CA) and refined it based on iterative feedback from my supervisors (Dr. Melissa Brouwers and Dr. Giorgia Sulis). With the help of Dr. Melissa Brouwers and Dr. Giorgia Sulis, I identified potential participants and created an email and participant list, which Cassandra Laurie, the project's coordinator, used to distribute the invitation to participate.

I finalized the analysis plan in collaboration with Dr. Melissa Brouwers and Dr. Giorgia Sulis. After collecting the data, I exported it into Microsoft Excel for organization and conducted quantitative analysis using SAS software (SAS Institute Inc. SAS/STAT® software, Version 9.4). I also performed thematic analysis in Microsoft Word by highlighting key themes in the responses. The findings were then communicated to the research team, which allowed for further refinement of the survey to prepare it for full-scale implementation.

4.2 Abstract

Introduction: A draft conceptual framework was developed to identify and categorize sources of bias in vaccine effectiveness (VE) studies (the materials). This pilot study aimed to evaluate materials and its assessment strategy for clarity, relevance, and feasibility through stakeholder feedback.

Objectives: The primary objective was to assess the clarity, appropriateness, and feasibility of the survey instrument before its international implementation. Additionally, the study sought to gather preliminary feedback on the clarity, relevance, and usability of the framework itself.

Methods: A 21-page, 66-question pilot survey was administered via SurveyMonkey to 15 invited experts in VE, evidence synthesis, and related fields.

Results: 14 responses (93%) were received. Participants rated domains and concepts using Likert scales and provided open-text feedback. Most participants (57%) completed the survey within 10–20 minutes, indicating that the length and structure were appropriate. The consensus was that the survey demonstrated clear and sound structure, supporting its potential for assessing the usability and comprehensiveness of the framework. However, responses also highlighted specific areas for refinement prior to broader implementation. These include enhancing the readability of the survey, incorporating more illustrative and user-friendly examples, ensuring consistency in definitions and terminology, and refining the organization and language of certain bias categories.

Conclusion: The survey was generally well-received, with participants affirming its clarity and structure as suitable for evaluating the framework's usability.

4.3 Introduction

Assessing the risk-of-bias (RoB) in vaccine effectiveness (VE) studies is essential to ensure the credibility of observational research findings. However, existing RoB assessment tools often fail to adequately account for the unique methodological complexities inherent to VE studies. To address this gap, a dedicated program of research is underway, with the ultimate goal of developing a tailored RoB assessment resource and an associated reporting guideline for VE studies through a multi-step process. Thus far, two scoping reviews have been completed to examine how RoB has been assessed in VE studies and to identify RoB concepts specific to this type of research (see Chapters 2 and 3). These efforts have yielded a preliminary RoB-VE framework and a set of candidate concepts for potential inclusion in the future tool. The next phase involves conducting a multi-round international Delphi consensus process with experts in vaccinology and and/or research methods to refine and validate the framework and proposed candidate concepts.

Given the complexity of the framework and its components, we conducted a pilot study to pretest the survey and associated materials. Serving as a "dress rehearsal"(1), the pilot was designed to identify ambiguities in language, logistical issues, and opportunities to improve participant engagement, thereby ensuring the final survey's methodological soundness, clarity and alignment with the project's objectives. The pilot survey addressed three main objectives as outlined in Figure 4-1.

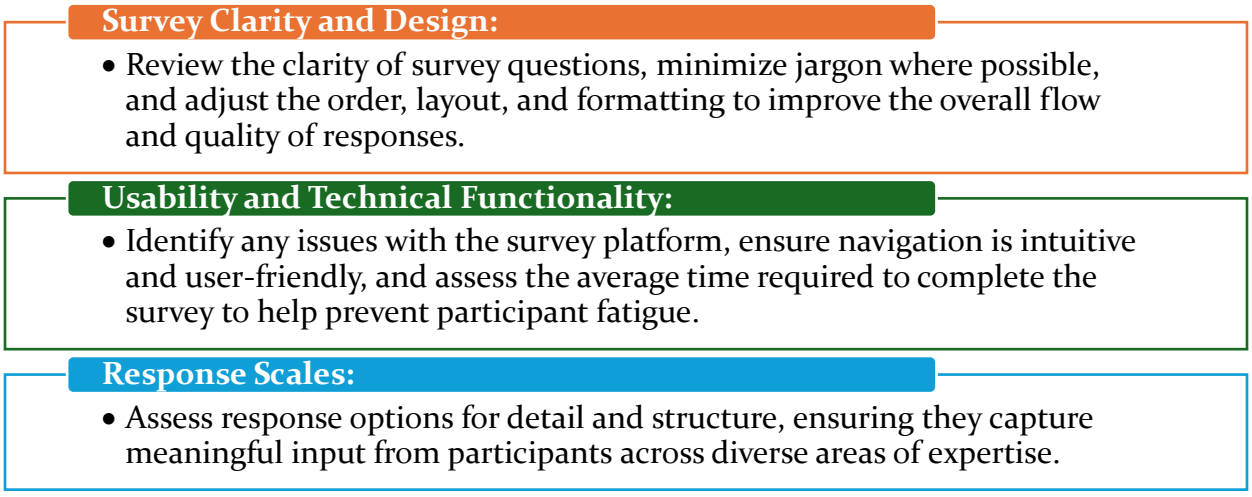

Figure 4-1 Pilot Survey Objectives

4.4 Methods

The RoB-VE Survey was implemented as a pilot study specifically designed to evaluate the survey's design, presentation, and usability. Participants were asked to review the survey and provide comprehensive feedback to help improve its structure, functionality, and user experience, with the primary goal being to refine the survey instrument itself rather than to assess the validity of the risk-of-bias (RoB) concepts it contained.

4.4.1 Participants

The pilot survey was distributed to 15 participants, comprising research associates from the University of Ottawa's School of Epidemiology and Public Health, as well as members of our international team, including methodologists, vaccine scientists, and knowledge users.

4.4.2 Procedures

Invitations containing the survey link were distributed by email on March 4, 2025, with a completion deadline set for March 18, 2025. A reminder email was sent on March 12, 2025, to encourage participation The RoB-VE Pilot Survey was securely hosted on SurveyMonkey (SurveyMonkey Inc., San Mateo, CA) (2). All responses were automatically recorded on the platform and later exported to Microsoft Excel for analysis.

4.4.2 Materials

The pilot survey included a set of candidate RoB concepts presented in 66 questions across 21 screens. Questions varied in format, including 5-point Likert scale items, checklist-style responses, and open-ended comment fields (Appendix 4A). The content was organized around four core risk of bias domains relevant to vaccine effectiveness (VE) studies: confounding bias, information bias, selection bias, and other sources of bias. After reviewing the materials, participants provided feedback in the form of both quantitative ratings and written comments. Although the survey content was not revised based on participant input during this stage, the feedback provided important insights to guide future refinement.

Within each domain, participants reviewed draft signal items comprising labels, definitions, and examples, and provided quantitative feedback on each concept using a 5-point Likert scale. After completing each screen, participants were asked to provide written comments about the presentation and framing of that specific section, ensuring detailed feedback on every component of the survey interface.

Beyond evaluating individual screens, participants also assessed their overall experience with the pilot survey. They provided feedback on the introduction and instructions, question wording and layout, the usefulness and clarity of response scales, and any technical or navigation issues encountered during the pilot testing process. The survey also tracked time to completion to assess user burden and minimize fatigue in future iterations.

At the conclusion of the pilot, participants were encouraged to share comprehensive suggestions for improving both the survey interface and the presentation methodology, reinforcing that this pilot's primary purpose was to refine the survey design before any content validation would be underataken in subsequent phases.

4.4.3 Data analysis

We used a mixed-methods approach to analyze pilot survey responses, focusing on evaluating the survey design rather than interpreting feedback on the candidate RoB concepts. Open-ended responses were analyzed thematically to identify issues related to question clarity, structural organization, and overall presentation of the survey. Quantitative data from the Likert-scale questions were analyzed using SAS software (SAS Institute Inc. SAS/STAT® software, Version 9.4) (3). Responses were numerically coded (1 = "Strongly Disagree" to 5 = "Strongly Agree"), and descriptive statistics (means and standard deviations) were calculated for each item. This analysis was conducted solely to test the functionality of the survey, assess the performance of response scales, and detect any issues with question design. The results were not used to interpret participant views or revise content at this stage but instead served as a diagnostic tool to inform refinements to the survey before broader implementation.

4.5 Results

A total of 14 out of 15 invited participants responded to the survey (93% response rate). Most participants (57%) completed the survey within 10–20 minutes, indicating that the survey was generally efficient and user-friendly (Figure 4-2).

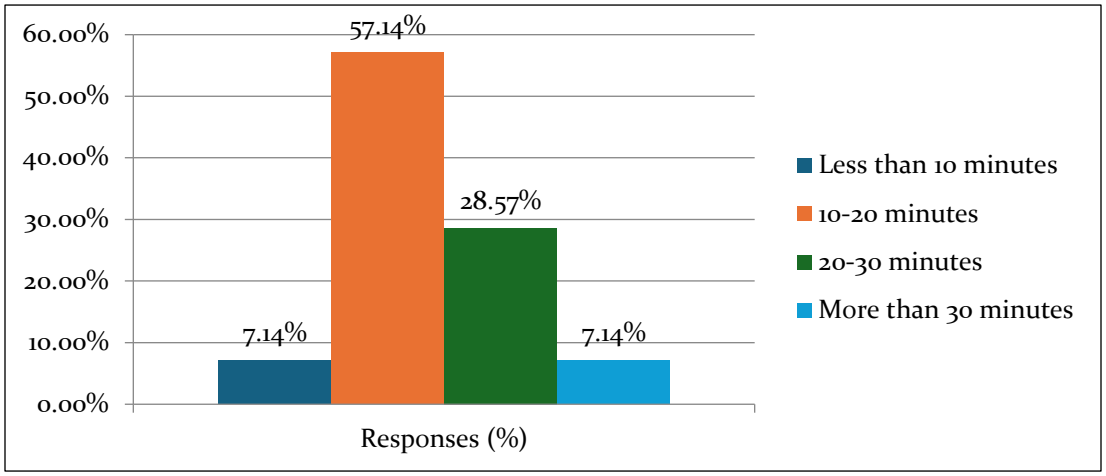

Figure 4-2 Participants' Survey Completion Time (n=14)

The pilot survey successfully captured a broad range of relevant expertise among participants (Figure 4-3). Most respondents identified as risk-of-bias or evidence synthesis methodologists. Several identified with backgrounds in scientific research, coordination, management, and vaccine evaluation. A smaller subset identified with additional roles, such as public sector professionals and primary effectiveness researchers. These categories were not mutually exclusive, with many participants bringing overlapping expertise and perspectives.

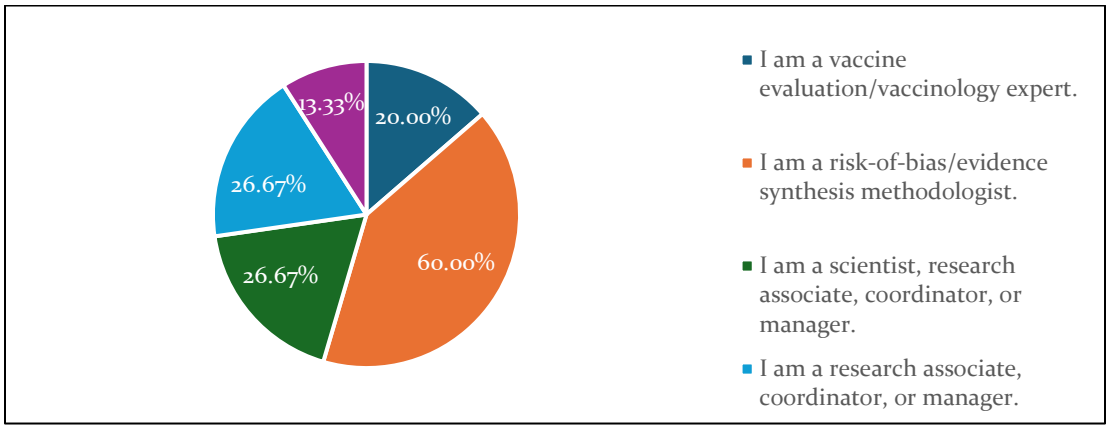

Figure 4-3 Participants' Areas of Expertise (n=14)*

*Other: Researcher designing and leading primary studies of effectiveness, both trials and non-randomized studies; A federal government employee and anticipated knowledge user.

Participants provided valuable feedback on their experience with the survey, highlighting areas for improvement and suggesting enhancements to the user experience. Several respondents recommended adding a preamble to outline key survey logistics, such as the estimated completion time and the ability to save progress or skip questions that fell outside their area of expertise. Additionally, one participant suggested including a self-rated expertise question (using a Likert scale from 1–5) to allow for future weighting of responses based on expertise level. A progress tracker was suggested to improve user experience by showing survey progress and increasing engagement.

The quantitative scores reported in Table 4-1 support the qualitative feedback, suggesting that while the survey was generally well-received (mean scores around 3.8–3.9), the framework itself needs clearer presentation. Participant feedback on the survey experience highlighted several key themes related to clarity, usability, and accessibility. Overall, respondents found the project introduction and survey instructions to be clear and easy to follow, with mean scores approaching "agree" on the Likert scale. Many participants appreciated the structure of the survey but suggested that the readability could be further improved, particularly if the survey is intended for a broader audience, including patient partners. Comments emphasized the value of including more concrete and user-friendly examples to clarify complex concepts and reduce ambiguity. Some respondents noted areas where definitions and terminology could be more consistent with established frameworks or better aligned with other risk-of-bias tools. There was also feedback suggesting that separating or clarifying certain bias categories would enhance understanding, and that the survey's language could be refined to improve precision and accessibility.

Table 4-1 Analysis of Participants' Feedback on the Survey Experience (n = 14)

Statement	Responses
The introduction of the project is clear.	3.9 (1.1)
The survey instructions are clear and easy to follow.	3.9 (1.1)
The draft RoB-VE framework (e.g., domains, concepts, examples) is well-described and presented in a clear, easy-to-understand manner.	3.6 (0.9)
The survey questions are clear, precise, and free of ambiguity.	3.9 (1.0)
The survey responses will provide clear guidance on refining the framework and advancing to the next stages of the program of research.	3.8 (1.2)

Note: Mean scores were calculated by converting Likert-scale responses to numerical values as follows: Strongly Disagree = 1, Disagree = 2, Neither Disagree nor Agree = 3, Agree = 4, and Strongly Agree = 5.
Each cell presents the mean (SD) for the corresponding item.

We also collected quantitative feedback on the scales used for each bias domain, as presented in Appendix 4B (Tables S4.1 and S4.2), to illustrate how the results might appear in future surveys.

4.6 Discussion

Overall, the feedback underscores the importance of clear instructions, illustrative examples, and accessible language to ensure the survey is both user-friendly and effective in gathering meaningful input for refining the RoB-VE framework.

A limitation of the survey was the way participants' areas of expertise were captured. The categories provided were overlapping, which may have led to confusion. In future iterations, it would be beneficial to define each area of expertise more clearly and ensure the categories are mutually exclusive. One participant even suggested including a scale to better represent their specific area of expertise.

Additionally, although the pilot survey was intended to gather feedback on the design and presentation of the survey, only, most participants also focused their comments on the content itself. This suggests that the survey's objectives may not have been clearly communicated at the outset, underscoring the need for a more explicit introduction and

framing. Nonetheless, a key strength was the overall feasibility of the survey in terms of time commitment, with no major concerns raised about its length. With minor adjustments to the clarity of instructions, definitions, and framing, the survey tool shows promise for effective use in subsequent stages of research project.

4.7 References

1. Statistics Canada. Survey Methods and Practices. Ottawa: Minister of Industry; 2003. ISBN: 978-1-100-16410-6.
2. SurveyMonkey Inc. [Internet]. San Mateo, California: SurveyMonkey Inc.; [cited 2025 Apr 14]. Available from: https://www.surveymonkey.com/.
3. SAS Institute Inc. SAS System for Windows, Version 9.4. Cary, NC: SAS Institute Inc.; 2016.

4.8 Chapter IV: Supplementary Materials

Appendix 4A: Pilot Survey Questionnaire

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Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Dear RoB-VE Project Colleagues,

As part of our foundational work for the RoB-VE research project, we conducted a scoping review of the published literature to identify risk of bias (RoB) concepts unique to vaccine effectiveness (VE) studies. Using critical interpretive synthesis methods, we have summarized our findings in Figure 1 (see next page).

This draft framework identifies four core domains: confounding bias, information bias, selection bias, and other biases. Within each domain, you will find a list of concepts (the bulleted items) that could serve as candidate items for our future RoB-VE tool. We plan to seek input from both VE and RoB experts to refine this framework and its components.

At this stage, we are conducting a **pilot study** with team members. We kindly ask you to complete the survey as a participant and share your feedback on its content, usability, and overall structure. Your participation will help inform the design and content of the RoB-VE tool. The findings from this pilot will be presented at the first team meeting, which is currently being scheduled.

Your participation and collaboration are greatly appreciated.

Sincerely,
Giorgia Sulis and Melissa Brouwers

Université d'Ottawa | University of Ottawa

Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Dear Participant,

We are seeking input from vaccine experts and methodological experts, such as you, to get feedback on this work. By continuing with this survey, you consent to participate and acknowledge that your responses will be used for research purposes only. Your data, including your name, will be handled confidentially and will only be used to contact you regarding this survey if necessary.

Sincerely,
Giorgia Sulis and Melissa Brouwers

*** Please state your full name:**

First name

Last name

*** Please select all that apply:**

- ☐ I am a vaccine evaluation/vaccinology expert.
- ☐ I am a risk-of-bias/evidence synthesis methodologist.
- ☐ I am a scientist.
- ☐ I am a research associate, coordinator, or manager.
- ☐ Other (please specify)

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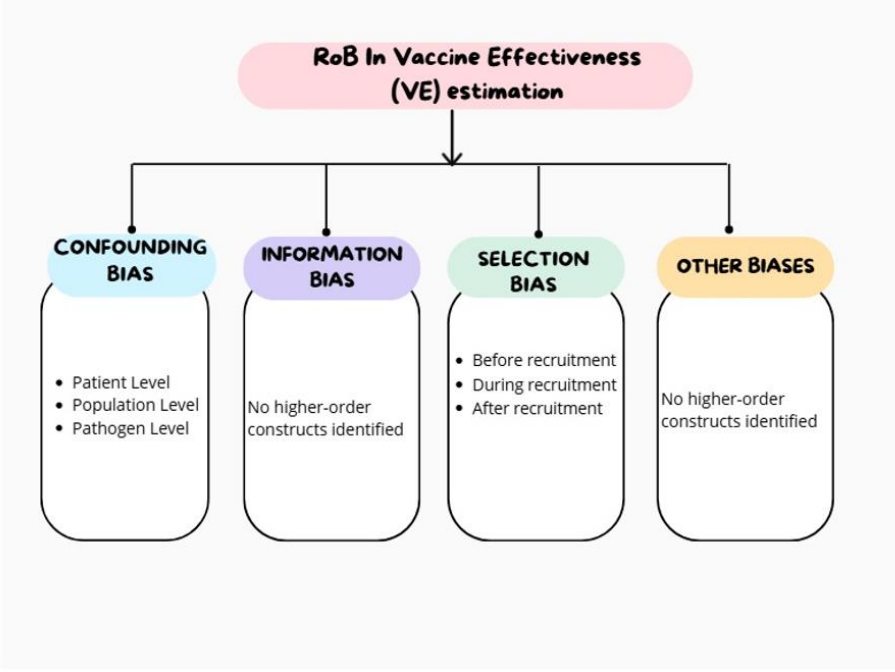
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Overview

Vaccine effectiveness (VE) studies, often based on observational designs, provide crucial insights into how vaccines perform in real-world settings. Assessing the methodological quality of these studies is essential when compiling and synthesizing evidence. However, existing risk of bias (RoB) assessment tools for observational studies do not adequately address biases unique to vaccine evaluation. To address this gap, the RoB-VE Project team, an international group, aims to develop a resource supporting RoB assessments of VE studies. As part of our foundational work, we conducted a scoping review of the literature to identify RoB concepts specific to VE studies. Using critical interpretive synthesis methods, we summarized our findings in a draft framework that outlines four core domains: confounding bias, information bias, selection bias, and other biases. Each domain includes concepts that could serve as potential candidate items in future RoB assessment tools. Figure 1 summarizes our findings. In the following pages, we will ask for your feedback on each bias domain and their roles in becoming a component of a RoB-VE tool.

Figure 1.



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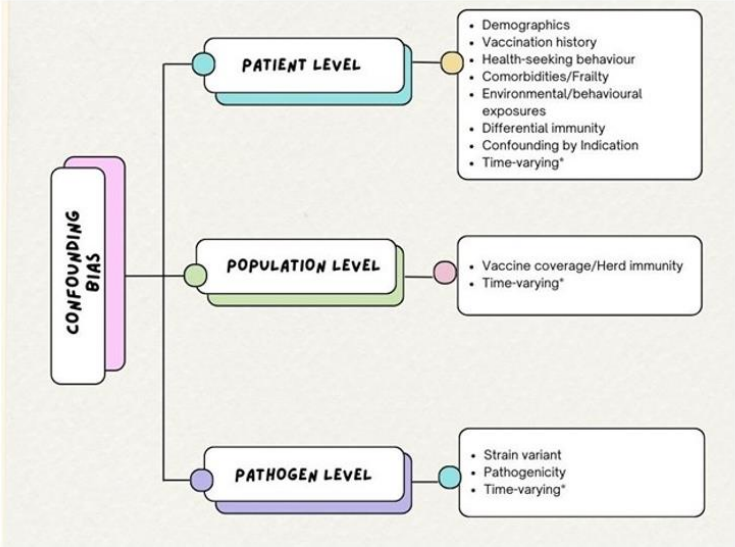
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 1. Confounding Bias - Overview

Figure 2 shows a preliminary categorization of the Confounding Bias domain into three concepts represented as three unique levels that affect vaccine effectiveness estimation: Patient Level, Population Level and Pathogen level. Each concept is defined by specific examples.

Please take a moment to review Figure 2 and answer the questions on the following pages about the label, definition, and associated examples for each concept.

Figure 2.



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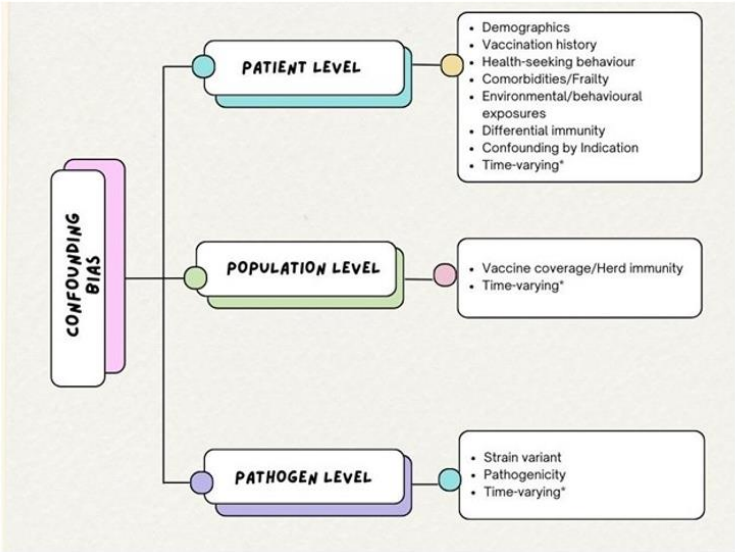
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 1. Confounding Bias - Patient Level Concept

Concept Label: 'Patient Level' Confounding Bias
Concept Definition: Bias occurs when differences in underlying patient/participant characteristics affect the relationship between vaccination status and one or more outcome(s), resulting in a distorted assessment of the vaccine's true effectiveness.
Concept Examples:

- **Demographics**
  Demographic factors such as age, sex, and socioeconomic status can confound VE estimates.
- **Vaccination History**
  Individuals who regularly receive vaccines may have different health behaviors or risk profiles compared to those who do not.
- **Healthcare-seeking Behaviour**
  Vaccinated individuals may be more likely to seek medical care or get tested for the disease of interest than unvaccinated individuals.
- **Comorbidities/Frailty**
  Individuals with underlying health conditions may be more likely to get vaccinated but also at higher risk for adverse outcomes.
- **Environmental/Behavioral Exposures**
  Environmental and behavioral factors, such as mask-wearing or physical distancing, can confound VE estimates.
- **Differential Immunity**
  Variations in immune response among individuals can confound VE estimates. For example, individuals with stronger immune systems may be more likely to respond well to vaccines and also have better outcomes.
- **Confounding by Indication**
  This occurs when the reason for vaccination is related to the person's health status or risk of the outcome being studied.
- **Time-varying Factors**
  Changes in vaccination status, disease prevalence, or other factors over time can introduce bias in VE studies.

Figure 2.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	○	○	○	○	○
The concept definition is clearly stated, precise, and easily understandable.	○	○	○	○	○
The concept examples accurately define the concept.	○	○	○	○	○
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	○	○	○	○	○

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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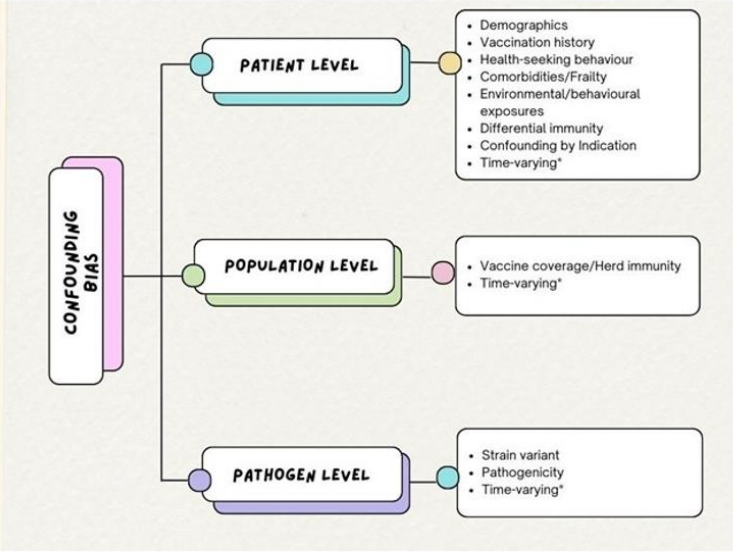
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 1. Confounding Bias - Population Level Concept

Concept Label: 'Population Level' Confounding Bias
Concept Definition: Bias occurs when differences in underlying population characteristics affect the relationship between vaccination status and outcomes, resulting in a distorted assessment of the vaccine's true effectiveness.
Concept Examples:

- **Vaccine Coverage/Herd Immunity**
  Vaccine coverage and herd immunity can introduce confounding bias in population-level VE studies. For example, high vaccine coverage can create herd immunity effects, indirectly protecting unvaccinated individuals and potentially underestimating the true VE.
- **Time-varying Factors**
  Changes in vaccination status, disease prevalence, or other factors in a population over time can introduce bias in VE studies.

Figure 2.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	◯	◯	◯	◯	◯
The concept definition is clearly stated, precise, and easily understandable.	◯	◯	◯	◯	◯
The concept examples accurately define the concept.	◯	◯	◯	◯	◯
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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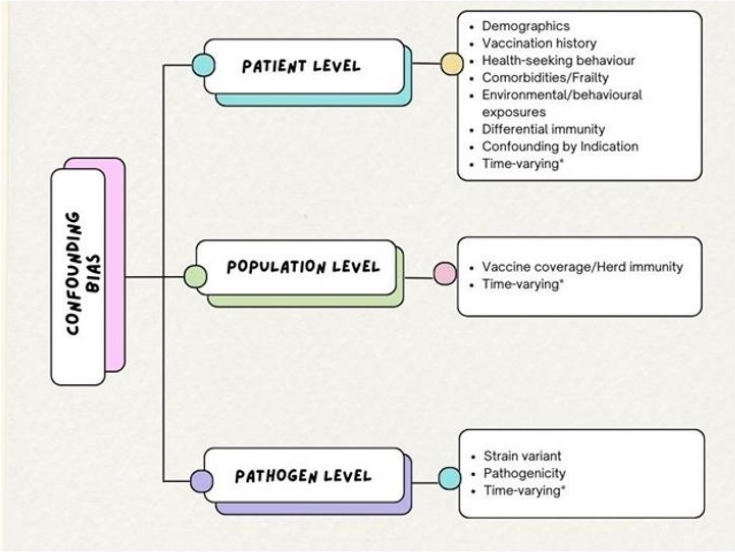
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 1. Confounding Bias - Pathogen Level Concept

Concept Label: 'Pathogen Level' Confounding Bias
Concept Definition: Bias occurs when a characteristic of the pathogen (e.g., strain/serotype) influences exposure (vaccination status) and outcome (e.g., symptomatic disease), resulting in a distorted estimation of vaccine effectiveness.
Concept Examples:

- **Strain Variant**
  Genetic changes in pathogens over time can lead to varying vaccine effectiveness, potentially confounding VE estimates.
- **Pathogenicity**
  Differences in the capacity of a pathogen to cause disease in a host among pathogen strains can confound VE measurements.
- **Time-varying**
  Dynamic changes in pathogen characteristics over time can confound VE estimates.

Figure 2.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

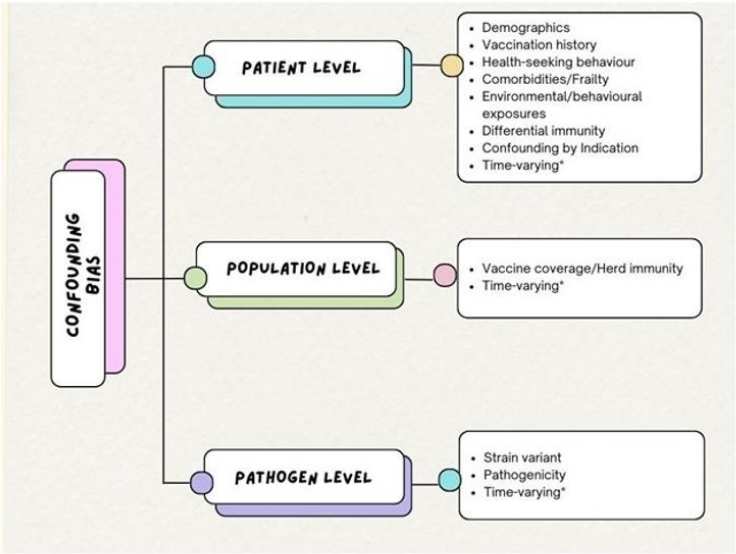
	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	◯	◯	◯	◯	◯
The concept definition is clearly stated, precise, and easily understandable.	◯	◯	◯	◯	◯
The concept examples accurately define the concept.	◯	◯	◯	◯	◯
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 1. Confounding Bias - Reflections

Figure 2.



*** Considering the Confounding Bias domain as a whole, please rate your agreement with each statement from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The structure of this domain (examples nested within concepts, nested within the domain) is conceptually and methodologically sound.	◯	◯	◯	◯	◯
The structure of this domain is comprehensive.	◯	◯	◯	◯	◯
The structure of this domain is complete.	◯	◯	◯	◯	◯
The structure of this domain is clear.	◯	◯	◯	◯	◯
This domain reflects constructs unique to VE studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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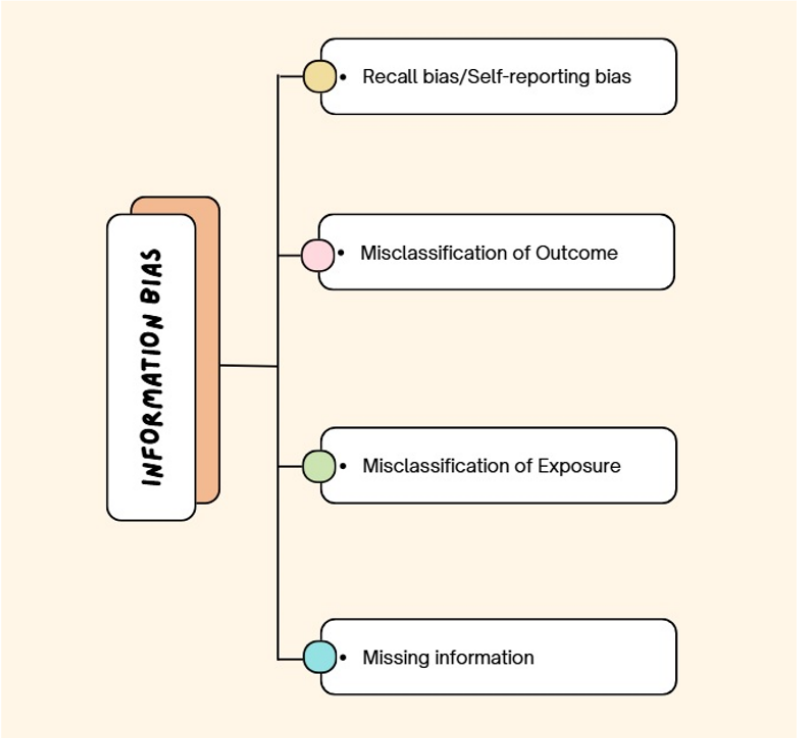
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 2. Information Bias - Overview

Figure 3 illustrates the preliminary categorization of the Information Bias domain into four concepts that affect vaccine effectiveness estimation: Recall Bias, Misclassification of Outcome, Misclassification of Exposure, and Missing Information. Please note that we did not develop higher-order constructs for Information Bias. As a result, the lower-order concepts are listed individually in Figure 3.

Please review Figure 3, then answer the questions on the following pages regarding the label, definition, and associated concepts.

Figure 3.



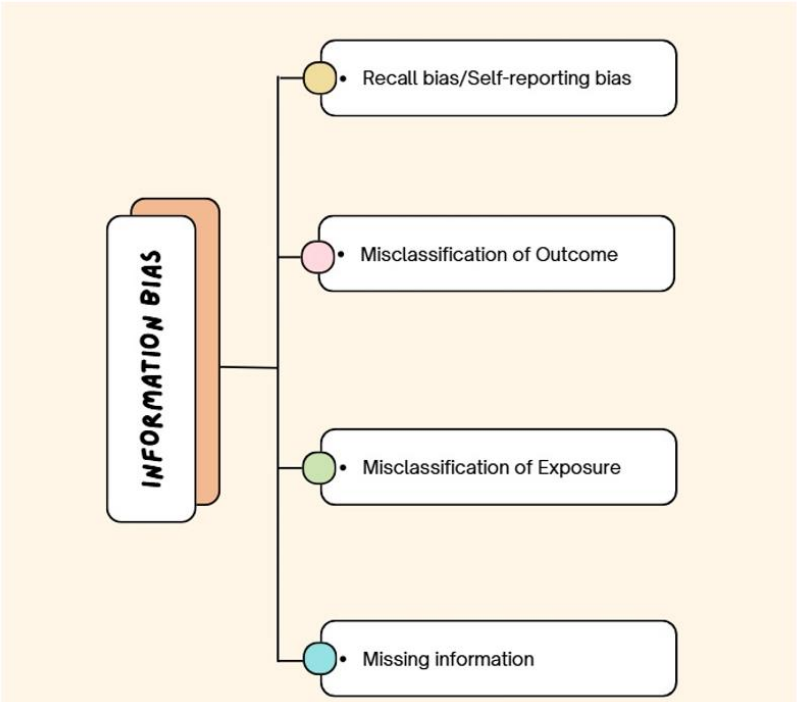
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 2. Information Bias - Concept

Concept Label: Information Bias
Concept Definition: Bias occurs when there are inaccuracies or inconsistencies in how data on vaccination or outcome status is collected, recorded, or interpreted, which can distort the true association between vaccination status and outcomes.
Concept Examples:

- **Recall Bias or Poor Recall**
  Systematic error occurring when participants inaccurately remember their vaccination history.
- **Misclassification of Outcome**
  Errors in identifying or classifying disease cases, due to variations in disease testing or diagnosis procedures between vaccinated and unvaccinated groups.
- **Misclassification of Exposure**
  Inaccuracies in determining an individual's true vaccination status, arising from sources such as inaccurate self-reporting, or errors in medical records or registries.
- **Missing Information**
  Incomplete data on vaccination status or disease outcomes, often due to non-response or inability to provide or collect information.

Figure 3.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	○	○	○	○	○
The concept definition is clearly stated, precise, and easily understandable.	○	○	○	○	○
The concept examples accurately define the concept.	○	○	○	○	○
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	○	○	○	○	○

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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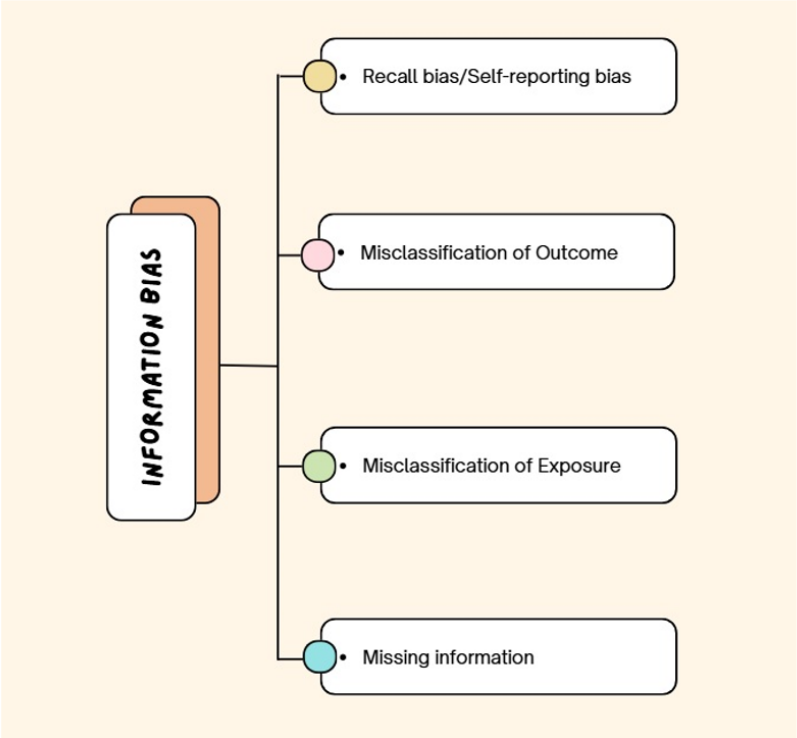
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 2. Information Bias - Reflections

Figure 3.



*** Considering the Information Bias domain as a whole, please rate your agreement with each statement from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The structure of this domain (examples nested within the domain) is conceptually and methodologically sound.	◯	◯	◯	◯	◯
The structure of this domain is comprehensive.	◯	◯	◯	◯	◯
The structure of this domain is complete.	◯	◯	◯	◯	◯
The structure of this domain is clear.	◯	◯	◯	◯	◯
This domain reflects constructs unique to VE studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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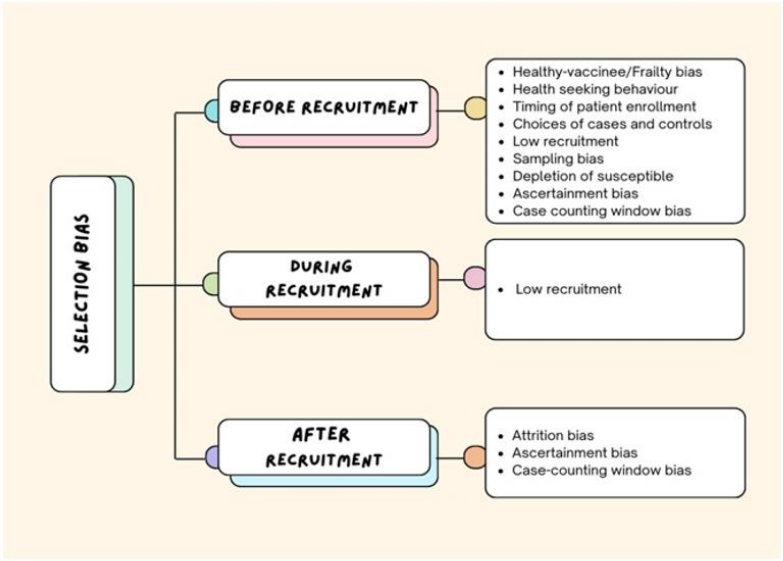
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 3. Selection Bias - Overview

Figure 4 shows preliminary categorization of the Selection Bias domain into three concepts represented as three unique levels that affect vaccine effectiveness estimation: Before Recruitment, During Recruitment, and After Recruitment. Each concept is defined by specific examples.

Please take a moment to review Figure 4 and answer the questions on the following pages about the label, definition, and associated examples for each concept.

Figure 4.



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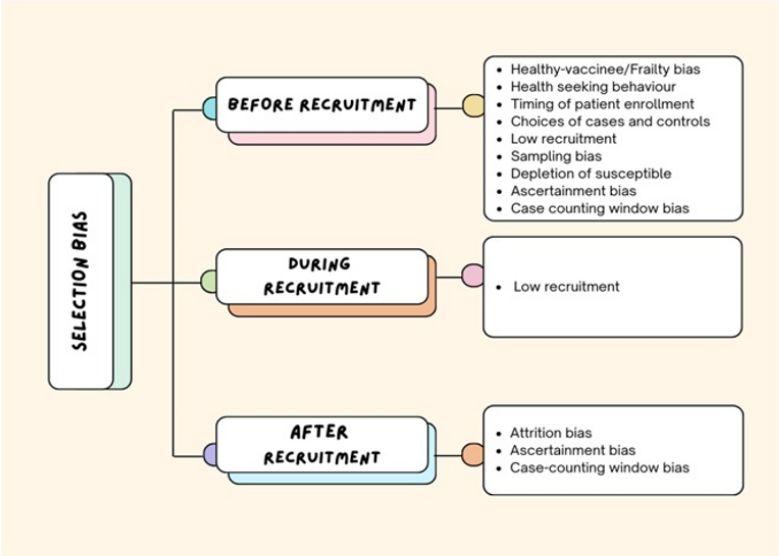
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 3. Selection Bias - Before Recruitment Concept

Concept Label: 'Before Recruitment' Selection bias
Concept Definition: Any systematic error in identifying and selecting study participants, leading to a non-representative sample of the target population, distorting the true relationship between vaccination status and outcomes.
Concept Examples:

- **Healthy-vaccinee/Frailty bias**
  Systematic differences in health status between vaccinated and unvaccinated individuals, where healthier or more health-conscious people are more likely to be vaccinated.
- **Healthcare-seeking behaviour**
  Tendency of vaccinated individuals to seek medical care or testing more readily than unvaccinated ones.
- **Timing of patient enrollment**
  Variation in vaccine effectiveness estimates based on when participants are enrolled in the study, particularly in relation to vaccination campaigns and disease prevalence.
- **Choices of cases and controls**
  Selection of study participants that may not accurately represent the target population, potentially introducing bias if vaccination status influences inclusion criteria.
- **Low recruitment**
  Insufficient sample size due to low participation rates stemming from participant characteristics that influence vaccine uptake, potentially resulting in underpowered studies and biased vaccine effectiveness estimates.
- **Sampling bias**
  The non-random selection of participants, leading to a study population that is not representative of the target population, which may bias vaccine effectiveness estimates.
- **Depletion of susceptible**
  Gradual removal of highly susceptible individuals from the unvaccinated group over time, which may lead to an underestimation of vaccine effectiveness as the remaining unvaccinated individuals are less susceptible to infection.
- **Ascertainment bias**
  Differential identification of cases between vaccinated and unvaccinated groups, potentially due to varying testing practices or healthcare access, leading to biased vaccine effectiveness estimates.
- **Case counting window bias**
  Inconsistent or inappropriate definition of the time window for counting cases after vaccination, potentially leading to inaccurate estimates of vaccine effectiveness.

Figure 4.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	○	○	○	○	○
The concept definition is clearly stated, precise, and easily understandable.	○	○	○	○	○
The concept examples accurately define the concept.	○	○	○	○	○
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	○	○	○	○	○

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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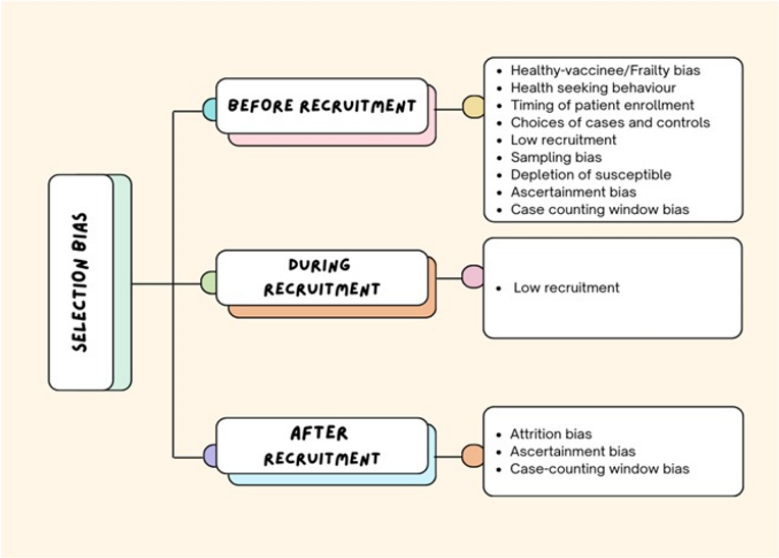
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 3. Selection Bias - During Recruitment Concept

Concept Label: 'During recruitment' Selection bias
Concept Definition: Bias during recruitment happens when certain groups are more likely to participate in a study than others, skewing the sample composition, and leading to distortions in the estimation of true vaccine effectiveness.
Concept Examples:

- **Low recruitment**
  Low recruitment in vaccine effectiveness studies can result in insufficient sample sizes due to participation biases. Key factors influencing recruitment may include socioeconomic status, healthcare access, language proficiency, time constraints, geographic location, and education level.

Figure 4.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	◯	◯	◯	◯	◯
The concept definition is clearly stated, precise, and easily understandable.	◯	◯	◯	◯	◯
The concept examples accurately define the concept.	◯	◯	◯	◯	◯
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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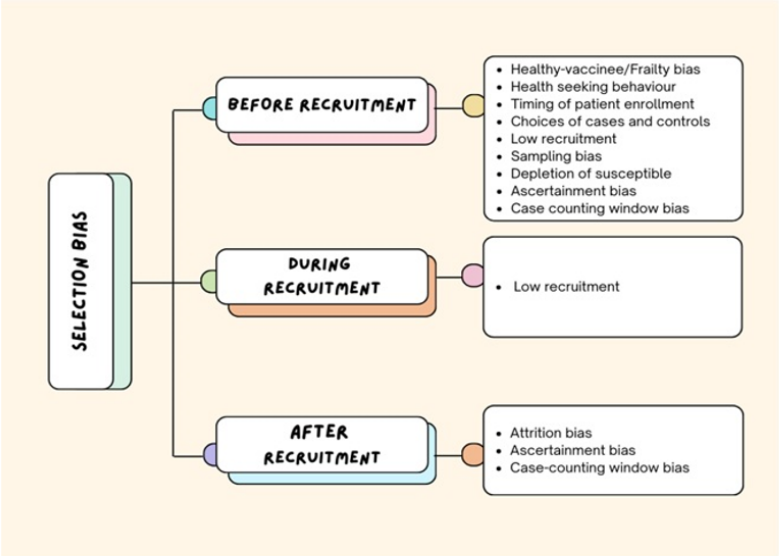
Domain 3. Selection Bias - After Recruitment Concept

Concept Label: 'After Recruitment' Selection Bias
Concept Definition: Bias occurs when systematic differences in participant retention, follow-up, or data collection emerge between study groups, leading to distortions in the estimation of vaccine effectiveness.
Concept Examples:

- **Attrition Bias**
  Systematic differences between participants who remain in the study and those who drop out over time. For example, individuals from lower socioeconomic backgrounds may be more likely to leave the study or not visit health facilities for diagnosis, potentially leading to an overestimation of vaccine effectiveness if these higher-risk individuals are disproportionately lost from the study population.
- **Ascertainment Bias**
  Differential identification of cases between vaccinated and unvaccinated groups, often due to varying testing practices or healthcare access. For instance, vaccinated individuals may be more likely to seek medical care or testing for mild symptoms, potentially leading to an underestimation of vaccine effectiveness due to increased case detection in the vaccinated group.
- **Case-counting Window Bias**
  Inconsistent or inappropriate definition of the time window for counting cases after vaccination. This occurs when cases are counted from the start of follow-up for the unvaccinated group but only after a specified period (e.g., 14 days) post-vaccination for the vaccinated group. This asymmetry can lead to biased estimates of vaccine effectiveness, as it excludes early post-vaccination cases in the vaccinated group while including all cases in the unvaccinated group.

Figure 4.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

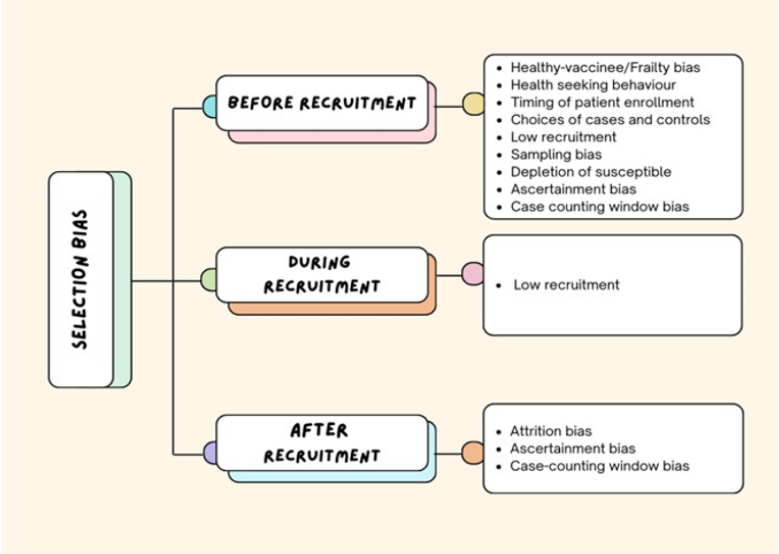
	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	○	○	○	○	○
The concept definition is clearly stated, precise, and easily understandable.	○	○	○	○	○
The concept examples accurately define the concept.	○	○	○	○	○
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	○	○	○	○	○

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 3. Selection Bias - Reflections

Figure 4.



*** Considering the Selection Bias domain as a whole, please rate your agreement with each statement from "Strongly Disagree" to "Strongly Agree".**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The structure of this domain (examples nested within concepts, nested within the domain) is conceptually and methodologically sound.	◯	◯	◯	◯	◯
The structure of this domain is comprehensive.	◯	◯	◯	◯	◯
The structure of this domain is complete.	◯	◯	◯	◯	◯
The structure of this domain is clear.	◯	◯	◯	◯	◯
This domain reflects constructs unique to VE studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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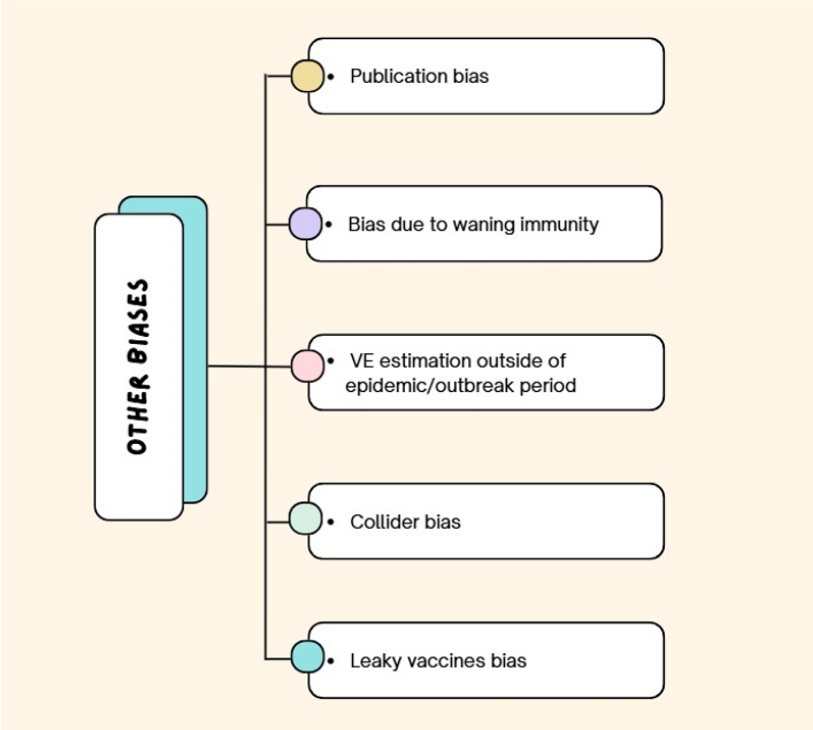
Domain 4. Other Biases - Overview

Figure 5 illustrates our categorization of the Other Biases domain in our draft framework into five concepts that affect vaccine effectiveness estimation: Publication Bias, Biases due to Waning Immunity, Biases due to VE Estimation Outside of Epidemic/Outbreak Period, Collider Bias, and Leaky Vaccines. Please note that we did not develop higher-order constructs for Other Bias. As a result, the lower-order concepts are listed individually in Figure 5. The Other Biases domain includes biases that did not fit neatly into existing categories in our framework. This approach allows us to capture important potential sources of bias that might otherwise be overlooked.

Please review Figure 5 and answer the questions on the following pages regarding the label, definition, and associated concepts.

Figure 5.



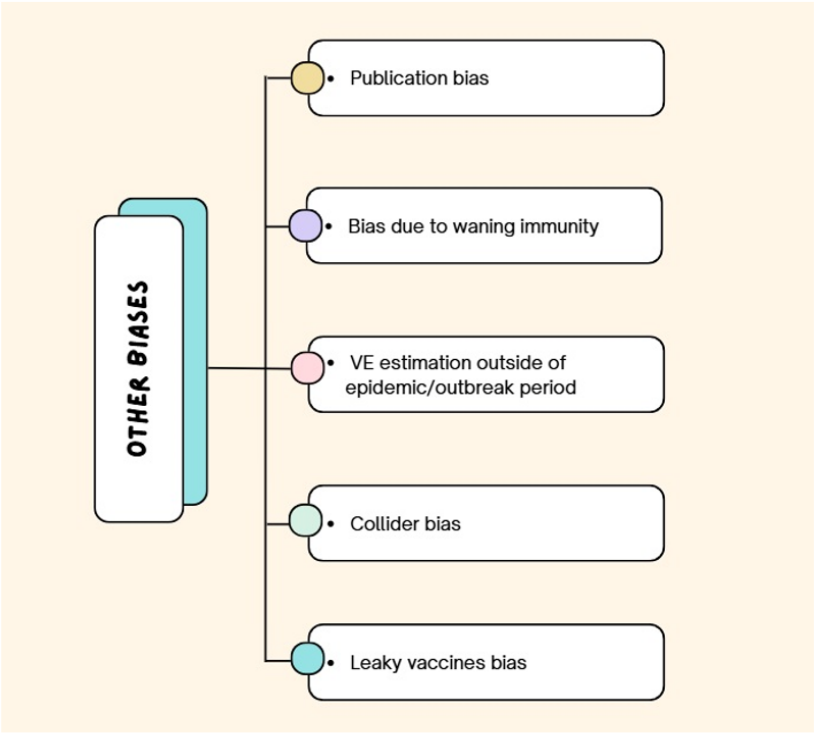
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 4. Other Biases - Concept

Concept Label: Other Biases
Concept Definition: Systematic errors in study design or methodology that do not clearly fall into selection bias, information bias, or confounding domains, but may overlap with other biases. These errors can distort data collection, analysis, or interpretation, affecting vaccine effectiveness estimates.
Concept Examples:

- **Publication Bias**
  Selective publication of research studies based on their results, with positive or statistically significant findings more likely to be published than negative or non-statistically significant ones.
- **Waning Immunity**
  The decrease of vaccine-induced immune protection over time. This is evidenced by declining antibody titers and potentially reduced cellular responses, which may lower estimates of vaccine effectiveness against infection and severe outcomes over time.
- **Estimating VE Outside an Epidemic Setting**
  The process of determining vaccine effectiveness in non-epidemic conditions, which can be challenging due to lower infection rates. This may require longer observation periods or larger sample sizes to detect significant effects, and results may not be directly comparable to estimates obtained during epidemic peaks.
- **Collider Bias**
  Conditioning on a common effect of both the exposure and the outcome can potentially create spurious associations. In vaccine effectiveness studies, this may arise when analyzing only symptomatic cases, as both vaccination status and infection can influence symptom development
- **Leaky Vaccines**
  Vaccines that reduce the probability of infection or transmission but do not completely prevent it. This concept is relevant when estimating vaccine effectiveness against transmission, as it affects how the vaccine's impact on viral load and infectiousness is interpreted.

Figure 5.



*** Please rate your agreement with each statement on a scale from "Strongly Disagree" to "Strongly Agree."**

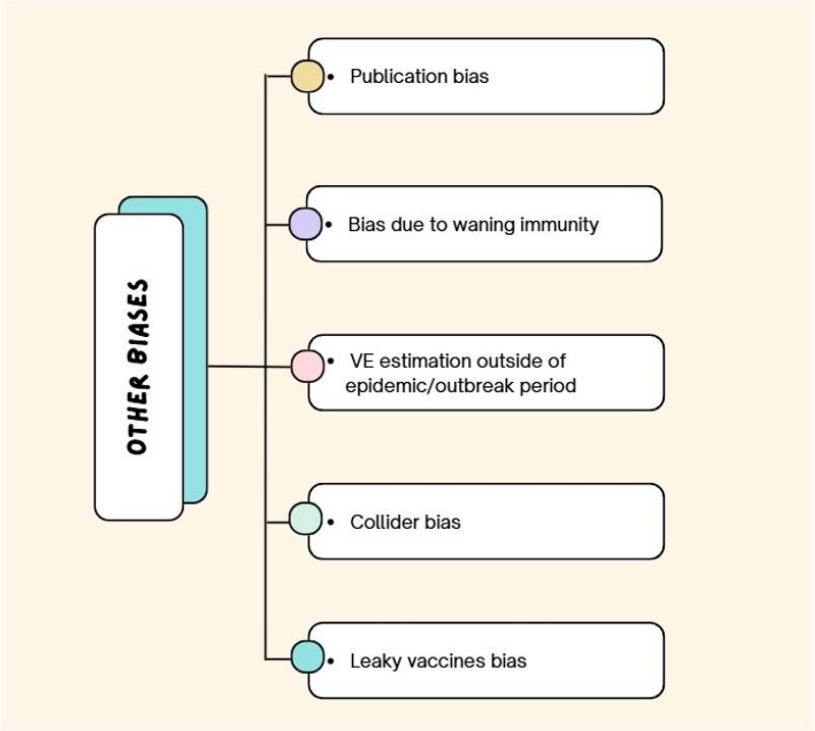
	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The concept label is appropriate.	○	○	○	○	○
The concept definition is clearly stated, precise, and easily understandable.	○	○	○	○	○
The concept examples accurately define the concept.	○	○	○	○	○
This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	○	○	○	○	○

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Domain 4. Other Biases - Reflections

Figure 5.



*** Considering the Other Biases domain as a whole, please rate your agreement with each statement from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The structure of this domain (examples nested within the domain) is conceptually and methodologically sound.	◯	◯	◯	◯	◯
The structure of this domain is comprehensive.	◯	◯	◯	◯	◯
The structure of this domain is complete.	◯	◯	◯	◯	◯
The structure of this domain is clear.	◯	◯	◯	◯	◯
This domain reflects constructs unique to VE studies.	◯	◯	◯	◯	◯

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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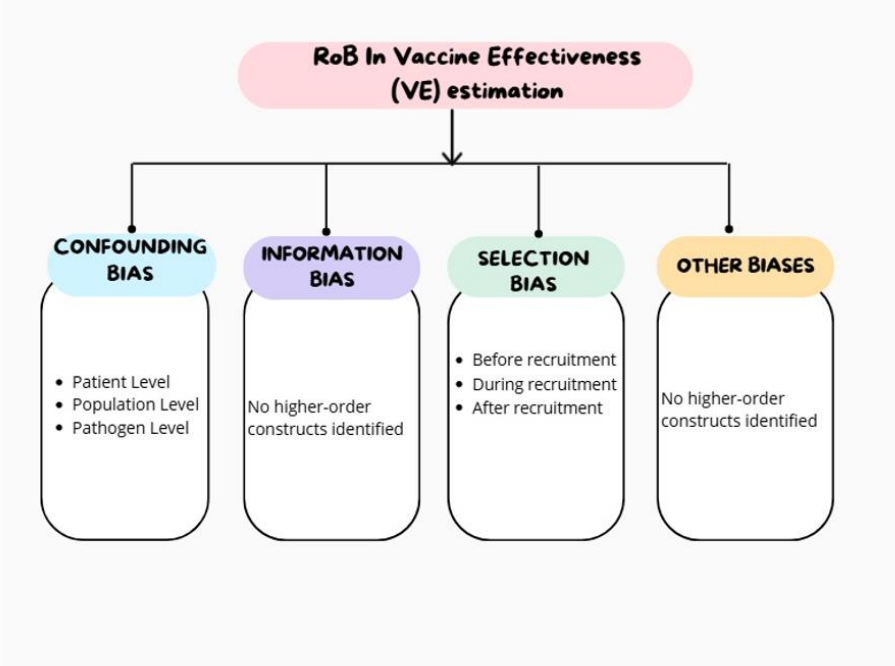
Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Final Reflections

Figure 1.



*** Considering the high-order RoB-VE framework as a whole, please rate your agreement with each statement from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree
The structure of this framework is conceptually and methodologically sound.	○	○	○	○	○
The structure of this framework is comprehensive.	○	○	○	○	○
The structure of this framework is complete.	○	○	○	○	○
The structure of this framework is clear.	○	○	○	○	○
This framework reflects RoB constructs unique to VE studies.	○	○	○	○	○

If relevant, please suggest any changes to this section of the survey to improve clarity of framing.

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Pilot Survey (1): Risk of Bias Vaccine Effectiveness (RoB-VE) Project

Survey Experience Feedback

Thank you for taking the time to complete the survey. We now invite you to answer a few questions about your experience. Your feedback will help us improve subsequent surveys.

*** Please rate your agreement with the following statements from "Strongly Disagree" to "Strongly Agree."**

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
The introduction of the project is clear.	◯	◯	◯	◯	◯
The survey instructions are clear and easy to follow.	◯	◯	◯	◯	◯
The draft RoB-VE framework (e.g., domains, concepts, examples) is well-described and presented in a clear, easy-to-understand manner.	◯	◯	◯	◯	◯
The survey questions are clear, precise, and free of ambiguity.	◯	◯	◯	◯	◯
The survey responses will provide clear guidance on refining the framework and advancing to the next stages of the program of research.	◯	◯	◯	◯	◯

Comments:

*** How long did it take you to complete this survey?**

- ◯ Less than 10 minutes
- ◯ 10-20 minutes
- ◯ 20-30 minutes
- ◯ More than 30 minutes

*** Did you encounter any technical issues while completing the survey?**

◯ Yes

◯ No

If yes, please describe:

Do you have any suggestions for improving the usability or functionality of this survey? Are there any items that should be added, removed, or revised?

Appendix 4B: Supplementary Tables

Table S4.1 Analysis of Bias Domain/Framework Structure Using Likert-Scale Survey Responses (n = 14)

	Likert-scale rated from "Strongly Disagree" to "Strongly Agree"				
Bias domain/framework	The structure of this domain/ framework is conceptually and methodologically sound.	The structure of this domain/ framework is comprehensive.	The structure of this domain/ framework is complete.	The structure of this domain/ framework is clear.	This domain/ framework reflects constructs unique to VE studies.
Framework as a "whole"	3.7 (1.1)	3.9 (0.8)	3.7 (0.9)	3.7 (0.9)	3.2 (1.2)
Confounding bias	4.2 (0.6)	3.9 (0.6)	3.8 (0.8)	3.9 (0.8)	3.4 (13)
Information bias	3.7 (1.3)	3.9 (1.0)	3.9 (1.0)	3.8 (1.0)	3.0 (1.3)
Selection bias	3.7 (1.3)	3.9 (1.0)	3.9 (1.0)	3.8 (1.0)	3.1 (1.5)
Other biases	3.7 (1.3)	3.9 (0.8)	3.8 (0.8)	3.9 (0.8)	3.1 (1.4)

Note: Mean scores were calculated by converting Likert-scale responses to numerical values as follows: Strongly Disagree = 1, Disagree = 2, Neither Disagree nor Agree = 3, Agree = 4, and Strongly Agree = 5.
Each cell presents the mean (SD) for the corresponding item.

Table S4.2 Analysis of Bias Concepts Through Survey Responses on a Likert Scale (n = 14)

		Likert-scale rated from "Strongly Disagree" to "Strongly Agree"				
Bias concept	Higher-order constructs	The concept label is appropriate.	The concept definition is clearly stated, precise, and easily understandable.	The concept examples accurately define the concept.	This component of the draft framework accurately reflects a distinct quality construct unique to vaccine effectiveness studies.	Overall
Confounding bias	Patient level	4.1 (0.5)	4.1 (0.7)	3.8 (1.2)	3.7 (1.1)	3.9 (0.9)
	Population level	3.8 (1.1)	4.1 (0.7)	4.0 (0.8)	3.6 (1.2)	3.9 (1.0)
	Pathogen level	3.9 (1.2)	4.0 (0.8)	3.8 (1.0)	3.9 (0.8)	3.9 (0.9)
Information bias	N/A	3.8 (1.3)	3.9 (1.0)	3.9 (1.0)	3.2 (1.2)	3.7 (1.1)
Selection bias	Before recruitment	3.7 (1.3)	3.9 (1.0)	3.6 (1.1)	3.1 (1.2)	3.6 (1.2)
	During recruitment	3.5 (1.2)	3.7 (1.0)	3.7 (1.2)	2.8 (1.3)	3.4 (1.2)
	After recruitment	4.0 (0.9)	3.9 (0.8)	3.9 (0.8)	3.2 (1.4)	3.8 (1.0)
Other biases	N/A	3.8 (1.2)	3.9 (1.0)	3.6 (1.1)	3.1 (1.3)	3.6 (1.2)

Note: Mean scores were calculated by converting Likert-scale responses to numerical values as follows: Strongly Disagree = 1, Disagree = 2, Neither Disagree nor Agree = 3, Agree = 4, and Strongly Agree = 5.
Each cell presents the mean (SD) for the corresponding item.

Chapter V: Summary and Conclusions

5.1 Summary of results

The first scoping review(Chapter II) showed that most systematic reviews of observational VE studies published between 2013 and 2023 (191/204 [93.6%]) employed existing risk of bias assessment tool. However, the choice of RoB tool varied widely, and a subset of the reviews applied more than one tool (24/204 [11.8%]) or adapted (31/204, [15.2%]) the existing tool(s). Furthermore, a subset of reviews (13/204, [6.4%]) noted that existing tools fell short in capturing biases relevant to specific study designs, such as the TND or to studies with diverse outcomes that could not be easily synthesized. As a result, these reviews developed their own checklists, scales, or resources tailored to the unique bias considerations of their study characteristics. Additionally, as detailed in the scoping review (Chapter II), 144 out of 204 reviews (70.6%) reported pooled VE estimates based on various adjusted effect measures. In contrast, 60 reviews (29.4%) presented VE findings descriptively, as reported in the primary studies, without conducting any pooling. However, the rationale for pooling decisions was often not clearly reported, and it was frequently unclear which outcomes were used to define VE in the meta-analyses. Overall, this lack of reporting and transparency emerged as a notable issue across the reviews.

The second scoping review (Chapter III) applied a critical interpretive synthesis approach to identify recurring bias themes in observational VE studies. We organized the findings into four main domains of bias commonly observed in the literature: confounding bias, selection bias, information bias, and cross-cutting biases. These domains were further categorized into higher-order and lower-order constructs. For example, higher-order constructs related to confounding bias were observed at the patient, population, and pathogen levels, while selection bias was often tied to the timing of participant recruitment into the study. We did not identify broader categories within information bias that warranted grouping into higher-order constructs. Although we included 108 studies that discussed or assessed risk-of-bias concepts relevant to VE research, there was a notable lack of literature exploring the complexity of these biases in depth. Moreover, nearly half of the studies focused on COVID-19, meaning their findings and bias

considerations may not be directly applicable to other vaccine-preventable diseases. Together, these studies provide a strong foundation to create a RoB resource tailored to VE studies. Specifically, the data demonstrate there is not a common "gold" standard practice to assess VE studies and there are unique operational aspects that may lead to bias in VE studies that is not adequately accounted. This led to the development of our RoB-VE framework.

Finally, the pilot survey (Chapter IV) gathered feedback from 14 experts in vaccinology, evidence synthesis methods, or related fields. The survey primarily evaluated the clarity of content and design, usability, technical functionality, and response scales we intend to assess the RoB-VE framework not the content of the RoB-VE framework that resulted from the work described in Chapter III. Most participants completed the survey within 10 to 20 minutes. Overall, the results indicated generally positive feedback on the clarity and usefulness of the materials presented. Participants agreed that the project introduction, survey instructions, and questions were clear and easy to follow. While the draft RoB-VE framework received slightly lower ratings for clarity compared to other components, the feedback was still positive. The responses highlighted several areas for improvement, including simplifying language to enhance accessibility, offering more information upfront about the survey's objectives, adding progress trackers and estimated completion times, enabling respondents to save their progress, and allowing the option to skip questions that fall outside their area of expertise. The results of this study will allow full-scale implementation of the next step in the research project in Fall 2025.

5.2 Strengths, limitations and Implications for Future

The scoping review (chapter II) is the first to comprehensively map risk-of-bias assessment practices in systematic reviews of VE studies. International methodological standards were used in the design and conduct of this scoping review. While previous work by Jiu *et al.* (2024) (1), evaluated tools for assessing study quality in the context of real-world data, it did not focus specifically on VE. Ainslie and colleagues (2019) (2) examined the challenges in VE estimation but were limited to specific infectious diseases (e.g., influenza). In contrast, this review uniquely synthesizes the available evidence on risk-of-bias assessment

in VE studies, without restrictions on setting, vaccine type, population, or quality assessment method. Additionally, a key strength of my scoping review (chapter II) is that it was the first to systematically map both the clinical and methodological definitions of vaccine effectiveness, highlighting important gaps in the existing literature and setting the stage for greater clarity and consistency in future research. Current evidence base primarily relies on data from RCTs, although considered the gold standard for assessing vaccine efficacy, do not fully reflect real-world conditions. Among studies that did examine real-world data, there was a notable lack of standardized definitions for vaccine effectiveness. For example, some reviews presented a mix of adjusted and unadjusted estimates due to heterogeneity in the results. Bitterman *et al.* (2018) (3), for instance, reported that adjusted analyses were available in only two studies, and only for the outcome of mortality.

However, this review (Chapter II) also faced limitations. One challenge was the generally poor reporting quality in the included studies, which made it difficult to provide a comprehensive discussion on how risk-of-bias tools were actually used. Although the goal was to map the tools reported by authors in their systematic reviews, the review did not include an explicit discussion of each tool due to these reporting gaps. Additionally, the extraction process was conducted in Covidence (Veritas Health Innovation Ltd), which does not blind the second extractor to the first's entries, potentially introducing bias. Overall, the absence of clear, formal definitions for extracted data limited the depth of analysis beyond what was reported in the included reviews. In the future, planning a more detailed preliminary analysis at the outset of scoping reviews could help clarify which types of information should be extracted, ensuring that the data collected aligns more closely with the review's objectives. This approach would support more targeted and meaningful interpretations and enhance the clarity and utility of the findings.

The second scoping review (Chapter III) holds significant value as the first systematic effort to compile a comprehensive list of candidate risk-of-bias concepts relevant to observational vaccine effectiveness studies. By synthesizing these concepts, this chapter established a foundational framework for assessing methodological quality in VE research, laying the groundwork for the broader CIHR-funded project led by my supervisors. While the review

aimed to ensure that all pertinent biases were identified and categorized, the inductive coding approach inherent to qualitative synthesis introduced potential limitations. Some concepts may not have been fully captured or optimally categorized into domains, and certain biases identified may not be unique to VE research. Additionally, due to time and resource limitations, the search was restricted to studies published from 2015 onward, which may have excluded earlier definitions or methodological discussions. Furthermore, the application of critical interpretive synthesis required iterative refinement of the analytical approach during the review process. This lack of standardization introduced challenges for later stages of the research, particularly when revisiting concepts for validation. Despite these limitations, our scoping review (Chapter III) provided a critical foundation for identifying key biases to evaluate through expert feedback and engagement of key interest holders, ensuring that subsequent phases of the project are informed by these concepts.

The pilot survey (Chapter IV) was conducted as a preliminary step to evaluate the functionality and user experience of the survey instrument prior to its implementation on a large scale. The survey instrument stemmed directly from the work described in Chapter III. The pilot survey offered valuable insights into the feasibility and logistics of administering the questionnaire, including the time required for completion and layout considerations to enhance participant engagement. It helped identify issues related to question clarity, comprehension, and overall design, allowing for necessary revisions before broader implementation. By providing early feedback on both methodological and practical aspects, the pilot survey improved the likelihood of obtaining high-quality, actionable feedback in the larger-scale survey. A notable limitation is the small sample size: only 15 individuals were invited to participate, all of whom were members of the RoB-VE project team. While this limited the diversity of perspectives and may introduce bias, it was a deliberate choice for the pilot phase to facilitate rapid feedback and iterative refinement of the questionnaire. Importantly, the pilot participants represented a range of expertise levels which broadly reflects the multidisciplinary audience targeted for the future large-scale survey.

5.3 Conclusion

In summary, this thesis addresses key knowledge gaps in risk-of-bias assessment of observational vaccine effectiveness studies, with a particular focus on providing a comprehensive overview of current practices and knowledge gaps. By systematically mapping application of existing tools, identifying recurring bias concepts, and piloting a survey on draft RoB-VE framework, it lays the groundwork for more transparent and rigorous evaluations of VE evidence. This research project has the potential to inform both methodological standards and policy decisions, with future international and multi-disciplinarily collaboration playing a key role in advancing the broader research agenda of developing a new risk-of-bias tool tailored to observational VE studies along with accompanying guidelines.

5.4 References

1. Jiu L, Hartog M, Wang J, Vreman RA, Klungel OH, Mantel-Teeuwisse AK, et al. Tools for assessing quality of studies investigating health interventions using real-world data: a literature review and content analysis. BMJ Open [Internet]. 2024 Feb [cited 2025 May 6];14(2):e075173. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2023-075173

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