

Real-World Incidence of Adverse Events Following COVID-19 Vaccination: A Systematic Review and Meta-Analysis

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Citation

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REVIEW TITLE AND BASIC DETAILS

Review title

Real-World Incidence of Adverse Events Following COVID-19 Vaccination: A Systematic Review and Meta-Analysis

Condition or domain being studied

COVID-19; COVID-19 vaccine; SARS-CoV-2 Virus; Vaccine; Adverse Event; Safety

Using the mnemonic PECOS, the following considerations were made: P: general population vaccinated against COVID-19; E: exposure to COVID-19 vaccination; C: not applicable, considering the descriptive nature of incidence estimation; O: occurrence of adverse events following immunization (AEFI); S: observational studies. Thus, the established question was: What is the real-world incidence of adverse events following immunization (AEFI) associated with COVID-19 vaccines, and how do methodological and epidemiological factors influence reported estimates?

Rationale for the review

The justification for conducting this systematic review lies in the need to evaluate and understand the potential risks associated with COVID-19 vaccination. Although vaccines have demonstrated high effectiveness in preventing severe disease and mortality associated with COVID-19, the early identification and understanding of adverse events are essential to ensure

the continued safety of vaccines and to maintain public confidence in immunization programs. Furthermore, public awareness of events supposedly attributable to vaccination or immunization (ESAVI) contributes to addressing vaccine hesitancy, which was identified by the World Health Organization (WHO) in 2019 as one of the top ten threats to global health.

Review objectives

The objective of this systematic review is to estimate and synthesize real-world incidence measures of adverse events following immunization (AEFI) associated with COVID-19 vaccines in the general population. Specifically, this review aims to: (1) quantify cumulative incidence proportions (individual risk of ≥ 1 event); (2) quantify event-to-exposure ratios (events per individual, per notification, or per administered dose); and (3) examine how methodological characteristics (study design, data source, exposure definition) and epidemiological factors (age group, vaccine platform, number of doses) influence reported incidence estimates.

Keywords

COVID-19; Adverse events; Vaccination; Incidence; Systematic review

Country

Brazil

ELIGIBILITY CRITERIA

Population

Included

Inclusion criteria:

Studies involving the general population who received COVID-19 vaccination will be included. This comprises individuals of any age, sex, or geographic location, provided they belong to the general population and are not restricted to a specific clinical or occupational subgroup. Eligible studies must report events supposedly attributable to vaccination or immunization (ESAVI) following COVID-19 vaccination and provide data allowing the estimation of incidence. Observational study designs, including cohort studies, case-control studies, and analytical or descriptive cross-sectional studies, will be considered, regardless of language or publication date.

Excluded

Exclusion criteria:

Studies conducted exclusively in specific populations, such as pregnant women, healthcare workers, or patients with pre-existing chronic diseases, will be excluded. Studies investigating adverse events related to vaccines other than COVID-19 vaccines, or those evaluating ESAVI resulting from interactions between COVID-19 vaccines and other vaccines or medications, will also be excluded. Additionally, case reports and case series will not be considered.

Intervention(s) or exposure(s)

Included

COVID-19 vaccine; BNT162b2; mRNA-1273; ChAdOx1 nCov-19; Ad26.COV2.S; CoronaVac; BBIBP-CorV

Comparator(s) or control(s)

This review does not have any comparators

Study design

Only nonrandomized study types will be included.

Included

Eligible study designs will include:

Prospective or retrospective cohort studies

Case-control studies

Analytical cross-sectional studies

Descriptive cross-sectional studies

- There will be no restrictions regarding language or publication date.

Excluded

The following study designs will be excluded:

Randomized controlled trials

Other interventional or clinical trials

Case reports

Case series

Systematic reviews and narrative reviews

Study protocols

Editorials, letters, commentaries, opinion articles, and similar documents

Context

Studies conducted in real-world settings involving the general population who received COVID-19 vaccines will be included, regardless of geographic location, healthcare system, or country income level. Eligible studies may use data from national or regional pharmacovigilance systems, electronic health records, vaccination registries, administrative databases, surveillance systems, or population-based cohorts.

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO

25 February 2026

Review timeline

Start date: 1 July 2025. End date: 25 March 2026.

Date of registration in PROSPERO

25 February 2026

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol

A full protocol has been written but is not available because:

This does not apply to the project.

SEARCHING AND SCREENING

Search for unpublished studies

Both published and unpublished studies will be sought.

Main bibliographic databases that will be searched

The main databases to be searched are *CINAHL - Cumulative Index to Nursing and Allied Health Literature*, *Embase - Embase via Ovid*, *Embase.com*, *LILACS - Latin American and Caribbean Health Sciences Literature*, *MEDLINE*, *PubMed* and *Scopus*.

Other important or specialist databases that will be searched

Web of Science (WOS)

Additionally, literature records were obtained through the Google Scholar and ProQuest search engines.

Search language restrictions

There are no language restrictions.

Search date restrictions

There are no search date restrictions.

Other methods of identifying studies

No other methods will be used.

Link to search strategy

A full search strategy has been uploaded to PROSPERO. The PDF may be accessed through this link

<https://www.crd.york.ac.uk/PROSPEROFILES/bdac5a0b59395c7e1ba9b75a39f3983d.pdf>.

Selection process

Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening

None

DATA COLLECTION PROCESS

Data extraction from published articles and reports

Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will not be contacted for further information.

Study risk of bias or quality assessment

Risk of bias will be assessed using:

Risk of bias will be assessed according to study design using the JBI tools and ROBINS-I. The process will be supported by a structured ChatGPT-based agent, with all classifications

reviewed and validated by a human reviewer who retains full responsibility for final judgments. Data will be assessed by one person (or a machine) and checked by at least one other person (or machine).

Additional information will **not** be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment

Risk of bias due to missing results will not be assessed

Certainty assessment

Certainty of findings will not be assessed

OUTCOMES TO BE ANALYSED

Main outcomes

The primary outcomes are real-world incidence measures of AEFI, including cumulative incidence proportions (individual-level risk of ≥ 1 event) and event-to-exposure incidence rates (events per notification, per exposed individual, or per administered dose).

Primary effect measures for data synthesis will include cumulative incidence proportions and event-to-exposure incidence rates, analyzed according to their mathematical structure.

Additional outcomes

There are no additional outcomes.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Data synthesis will be conducted using both qualitative and quantitative approaches, in accordance with PRISMA guidelines. The qualitative synthesis will involve a structured description of the included studies, focusing on the characteristics, types, and severity of events supposedly attributable to vaccination or immunization (ESAVI) following COVID-19 vaccination. This narrative synthesis will allow the identification of patterns, variations, and relevant clinical and methodological characteristics across studies.

For quantitative synthesis, incidence measures will be grouped according to their mathematical structure into:

- (1) event-to-exposure ratios (modeled as incidence rates); and
- (2) cumulative incidence proportions (modeled as incidence proportions).

Random-effects meta-analyses will be conducted. Rate-based measures will be synthesized using log-transformed models, and proportion-based measures using logit transformation. Statistical heterogeneity will be quantified using I^2 , τ^2 , and Cochran's Q statistics. Prespecified subgroup analyses will explore sources of heterogeneity according to study design, information source, vaccine platform, number of doses, life stage, multimorbidity, and severity.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	✓
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status

The review is currently planned or ongoing.

Publication of review results

Results of the review will be published in Portuguese and English.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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Review affiliation

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Funding source

Review has no specific/external funding but is supported by guarantor/review team (non-commercial) institutions.

Peer review

The full review protocol was peer reviewed by independent academic researchers with expertise in epidemiology, vaccine safety, and systematic review methodology. The reviewers evaluated the clarity of the research question, eligibility criteria, data extraction methods, risk of bias assessment, and planned data synthesis. Feedback provided by the reviewers was incorporated to improve the methodological rigor, transparency, and completeness of the protocol prior to registration.

ADDITIONAL INFORMATION

Review conflict of interest

Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings

COVID-19 Vaccines; Drug-Related Side Effects and Adverse Reactions; Observational Studies as Topic; Meta-Analysis as Topic; Pharmacovigilance; Incidence

SIMILAR REVIEWS

Check for similar records already in PROSPERO

PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 20 February 2026). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- A systematic review of adverse events following Covid-19 vaccination in Ghana [published 17 July 2022] [CRD42022346904]. The review was judged **not to be similar**
- Stroke following COVID-19 vaccination: a systematic review and meta-analysis of real-world studies [published 8 January 2023] [CRD42023389925]. The review was judged **not to be similar**
- Incidence of facial palsy following COVID-19 vaccination: A systematic review of cases [published 3 May 2022] [CRD42022328860]. The review was judged **not to be similar**

- Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern in the real-world: a literature review and meta-analysis [published 29 May 2022] [CRD42022334369]. The review was judged **not to be similar**
- Adverse events of COVID-19 vaccination according to the type of vaccine in the world [published 24 January 2023] [CRD42023394192]. The review was judged **not to be similar**
- Uveitis in COVID-19 vaccinated individuals: a systematic review and meta-analysis [published 29 October 2023] [CRD42023477278]. The review was judged **not to be similar**

PROSPERO version history

- [Version 1.0, published 25 Feb 2026](#)

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