

Safety, immunogenicity, and effectiveness of respiratory syncytial virus vaccines for pregnant persons: A living systematic review and meta-analysis

Fernando J Argento, Jamile Ballivian, Ariel Bardach, Daniel Comande, Sami L. Gottlieb, Beate Kampmann, Agustina Mazzoni, Edward P.K. Parker, Federico Rodriguez-Cairolí, Andy Stergachis, Xu Xiong, Sabra Zarea, Agustin Ciapponi, Mabel Berrueta, Pierre M. Buekens

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Citation

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REVIEW TITLE AND BASIC DETAILS

Review title

Safety, immunogenicity, and effectiveness of respiratory syncytial virus vaccines for pregnant persons: A living systematic review and meta-analysis

Review objectives

Primary review questions

How effective are respiratory syncytial virus (RSV) candidate and licensed vaccines in preventing and protecting pregnant persons and infants from severe medically attended respiratory RSV infections?

What is the safety profile of RSV candidate and licensed vaccines administered during pregnancy in terms of adverse maternal/pregnancy, perinatal, neonatal, and postpartum outcomes?

What is the safety profile of RSV candidate and licensed vaccines administered during pregnancy in terms of other nonpregnancy-related adverse maternal outcomes?

What is the immune response associated with RSV candidate and licensed vaccines and how long does it last in vaccinated pregnant persons and newborns?

Is there RSV-specific immune responses with antibody transfer vaccinated pregnant persons to their newborns (placenta and breastmilk)?

Secondary review questions

Are there differential safety, effectiveness, and efficacy effects of various RSV vaccine types (including live attenuated vaccines, subunits, vector-based vaccines, and nanoparticles to RSV fusion protein (F))?

Are there differential safety, effectiveness, and efficacy effects of vaccine by trimester of exposure, maternal risk status, and/or maternal age?

Are there differential safety, effectiveness, and efficacy effects of vaccines by country income level or region?

Are there differential safety, effectiveness, and efficacy effects of vaccine by predominant RSV type in the time window of each study?

What is the cost-effectiveness of RSV vaccines in different countries reported in economic evaluations?

What are the costs (direct, and indirect) attributable to RSV-related disease in pregnant persons and newborns?

Keywords

and webpages safe pregnancy, IECS, medical congresses, Scientific publications, social networks, WHO

SEARCHING AND SCREENING

Searches

We will update the searches of this living systematic review (LSR) at regular intervals to incorporate new relevant reports as they become available.

An experienced librarian will search the Cochrane Library databases, MEDLINE, EMBASE, Latin American and Caribbean Health Sciences Literature (LILACS), Science Citation Index Expanded (SCI-EXPANDED), China Network Knowledge Information (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Science Journal Database (VIP), WHO Database of publications on Sars CoV2, EPPI-Centre map of the current evidence on RSV, RSV-related Congresses, guidelines published by national and international professional societies (e.g., ACOG, RCOG, FIGO), pre-print servers (e.g., ArXiv, BiorXiv, medRxiv, search.bioPreprint), and RSV research websites.

The following sources will also be included:

- IDWEEK (<https://idweek.org/>),
- ISPPD (<https://isppd.kenes.com/>),
- ISRIV (<https://isirv.org/site/>),
- RESVINET (<https://www.resvinet.org/>)
- SLIPE (<https://slipe.org/web/previous-events/>)
- API (<https://www.apiinfectologia.org/>)
- BVSalud (<https://bvsalud.org/es/>)

Ongoing Randomized controlled trials will be tracked in Clinicaltrial.gov and other trial registers (WHO, etc.)

We will search all of the above databases from January 2020 to the present.

No language restrictions will be applied.

We will contact subject matter experts and we will hand-search the reference lists of the identified systematic reviews (SRs) and included studies to identify relevant studies missed by the search strategy.

Additional search strategy information can be found in the attached PDF document (link provided below).

Study design

We will include clinical trials, quasi-experimental, and observational (comparative and non-comparative) study designs, irrespective of publication status, publication year, and language to also incorporate real-world evidence (RWE).

We will consider randomized controlled trials (RCTs), nonrandomized CTs, controlled before-after studies (CBAs), nationwide uncontrolled before-after studies (UBAs), interrupted time series (ITs), controlled-ITs (CITs), and adverse event/safety registries. Phase IV studies, cohort studies, case-control studies, cross-sectional studies, and case series will also be considered, as well economic evaluations, cost studies, and budget impact analyses. We will only consider case reports of previously unknown or unexpected adverse events.

ELIGIBILITY CRITERIA

Condition or domain being studied

RSV A&B (all strains)

Population

Pregnant persons and neonates.

Intervention(s) or exposure(s)

RSV vaccines used in humans, irrespective of the dose and the schedule used.

Comparator(s) or control(s)

Active or inactive comparators without interventions under study, usual care, or placebo.

We will accept non-comparative studies; therefore, a control group will not be mandatory for these outcomes.

Context

Systematic reviews will be included only as a source of primary studies

OUTCOMES TO BE ANALYSED

Main outcomes

1.Safety outcomes concerning obstetric/neonatal outcomes (GAIA definitions of prioritized outcomes based on the standard Brighton Collaboration process).

Obstetric outcomes: Hypertensive disorders of pregnancy, maternal death, non-reassuring fetal status, pathways to preterm birth, postpartum hemorrhage, abortion/miscarriage, antenatal bleeding, gestational diabetes, dysfunctional labor, fetal growth retardation

Neonatal outcomes: Congenital anomalies, death, infections, preterm birth, stillbirth, low birth weight, small for gestational age, encephalopathy, respiratory distress, failure to thrive, and microcephaly.

2.Medically significant RSV low respiratory tract infection (LRTI)/all-cause medically-significant LRTI in infants (≥ 90 days) confirmed by PCR in respiratory secretions; AND ≥ 1 manifestation of LRTI.

3.RSV-LRTI with severe hypoxemia/all-cause LRTI with severe hypoxemia (≥ 90 days)

4.RSV-LRTI hospitalization / all-cause LRTI with hospitalization (≥ 90 days)

Confirmed RSV LRTI, AND hospitalization for a respiratory illness (not for all-cause LRTI with hospitalization).

5.Complications attributed to RSV in neonates, including case fatality rate.

6.Immunogenicity: cellular/humoral immune response and duration and transplacental transfer ratios
-titers of RSV A, B, A/B neutralizing antibodies in maternal serum at delivery and umbilical-cord blood.

7.All-cause mortality (neonatal, post-neonatal infant, and maternal mortality rate)

8. Incident LRTI with hospitalization in neonates
9. Serious adverse events (any and RSV-vaccination-related).

Measures of effect

We will calculate risk ratios (RRs) with a 95% confidence interval (95% CI) for dichotomous outcomes and mean difference (MD) or standardized MD (SMD) for continuous outcomes.

We will also calculate proportions with 95% CI for non-comparative studies.

Additional outcomes

A. Asymptomatic RSV infection: determined by asymptomatic antibody or antigens (indirect immunofluorescence assay [IFA]; ELISA-based test; direct fluorescent antibody assay [DFA]; Lateral flow immunoassay [LFIA]) and/or asymptomatic RSV infection based on real-time PCR based (LNA one-tube nested real-time [OTNRT]-PCR, rapid reverse-transcription recombinase-aided amplification [RT-RAA] assay; reverse transcription strand invasion-based amplification [RT-SIBA]).

B. Mother-to-child transmission: Presence and persistence of RSV (viral load, protective antibodies) in placenta cells, fetal tissues, breast milk, amniotic fluid, cord blood, vaginal fluids, neonatal throat swabs. Measure also time from birth-to- illness.

C. Adverse events:

- Maternal adverse events following immunization (AEFIs) not directly related to the pregnancy outcomes (including reactogenicity).
- Late/delayed adverse event in a child associated with RSV vaccination during pregnancy.

D. Duration of antibody

E. Economic outcomes: Resource use, direct and indirect costs, budget impact, and cost-effectiveness measures.

Measures of effect

Where appropriate, we will calculate risk ratios (RRs) with 95% confidence interval (95% CI) for dichotomous outcomes and mean difference (MD) or standardized MD (SMD) for continuous outcomes.

We will also calculate proportions with 95% CI for non-comparative studies.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

Selection:

Pairs of review authors will independently screen each title and abstract. We will retrieve all potentially relevant full-text study reports/publications and two review authors will independently screen full texts, recording the reasons for the exclusion of the ineligible studies.

Disagreements will be resolved through discussion with the review team. This process will be performed using the web-based software

COVIDENCE.

Data extraction and management:

Study data will be collected and stored using REDCap electronic data capture tools hosted at IECS data servers in Buenos Aires, Argentina. Each REDCap study ID will include a general form where the principal characteristics of the studies will be included, and outcome-specific forms will be generated to extract data to assess independently each endpoint reported in the studies for every outcome. The data extraction will be piloted on a sample of at least ten studies before its formal start-up. Pairs of review authors will independently extract data from included studies in a REDCap form and will resolve disagreements through a discussion with the review team. If needed, we will contact the study authors by e-mail to specify any missing data which may not be reported sufficiently in the publication. Funding source information will be sought for every study included in the LSR.

Data items to consider for extraction from included studies will include identification, items, methods, participants, group allocation, intervention, outcomes, risk of bias, and summary of results.²

Risk of bias (quality) assessment

For RCTs, we will use the Cochrane risk of bias tool - version 2 (RoB 2) as recommended in the Cochrane Handbook for Systematic Reviews of Interventions:

To evaluate the risk of bias in the results of non-randomized studies of interventions (NRSI) that compare the health effects of two or more interventions we will use ROBINS-I tool.⁷

For Controlled Before-After studies (CBAs), we will use the following criteria: baseline measurement; characteristics for studies using the second site as control; blinded assessment of primary outcome(s); reliable primary outcome measure(s); follow-up of professionals (protection against exclusion bias); and follow-up of patients.

For Uncontrolled Before-After studies (UBAs), we used the same criteria as CBAs, except for baseline measurement and characteristics for studies using the second site as control.

For Interrupted Time Series (ITS), we will assess the risk of bias associated with the following seven domains: intervention independent of other changes; shape of intervention effect pre-specified; intervention unlikely to affect data collection; blinding of outcome assessors to intervention allocation; incomplete outcome data; selective outcome reporting; and other sources of bias⁸.

For observational cohort, case-control, cross-sectional and case-series studies we will use the NIH Quality Assessment Tool.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

If data are available and methodologically appropriate, we will undertake the aggregate meta-analyses for each comparison according to the Cochrane Handbook of Systematic Reviews of Interventions and use the random-effects meta-analysis for the primary analysis.

We will also perform proportion meta-analyses to summarize frequencies from one-sample studies.

We will use R statistical software to analyze the data. The main packages selected for data analyses will be Meta, Metafor, and Tidverse.

We will calculate hazard ratios (HRs), risk ratios (RRs), or odds ratios (ORs) with 95% CI for dichotomous outcomes and mean difference (MD) or standardized MD (SMD) for continuous outcomes. We will also calculate proportions with 95% CI for non-comparative studies. To report efficacy/effectiveness outcomes, we will transform other outcome measures into vaccine efficacy/effectiveness (VE) whenever possible by calculating the risk of disease among vaccinated and unvaccinated persons and determining the percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons¹⁰.

We will use adjusted effect measures (e.g., by age, smoking status, parity, body mass index, etc.) over unadjusted estimates. We will investigate heterogeneity through subgroup analyses.

We will present GRADE certainty of evidence¹¹ in 'Summary of findings' tables^{1, 2, 12}

We will provide a frequently updated web repository of the findings.

Analysis of subgroups or subsets

Pre-specified subgroups by pregnancy trimester (first, second or third trimester), country income-level (high or low- and middle-income country), region, maternal age, maternal risk status (low or high), by individual RSV vaccine or by dominant RSV type of the study population.

Additional sensitivity analyses will be undertaken by excluding high-risk of bias studies or by using the fixed-effect model.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

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Funding source

Bill & Melinda Gates Foundation

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TIMELINE OF THE REVIEW

Review timeline

Start date: 01 March 2023. End date: 01 March 2024

Date of first submission to PROSPERO

01 March 2023

Date of registration in PROSPERO

12 March 2023

CURRENT REVIEW STAGE

Publication of review results

The intention is to publish the review once completed. The review will be published in English

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 IP

Risk of bias/quality assessment

Data synthesis

Review status

The review is currently planned or ongoing.

ADDITIONAL INFORMATION

PROSPERO version history

- Version 1.1 published on 12 Mar 2023
- Version 1.0 published on 12 Mar 2023

Review conflict of interest

None known

Country

Argentina

Medical Subject Headings

Humans

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