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Safety, immunogenicity, and effectiveness of COVID-19 vaccines for pregnant persons: a protocol for a living systematic review and meta-analysis

Agustin Ciapponi, Mabel Berrueta, Ariel Bardach, Agustina Mazzoni, Fernando J Argento, Jamile Ballivian, Daniel Comandé, Erin Goucher, Beate Kampmann, Edward P.K. Parker, Veronica Pingray, Federico Rodriguez Cairoli, Victoria Santa María, Andy Stergachis, Xu Xiong, Sabra Zaraa, Pierre M Buekens

Review methods were amended after registration. Please see the revision notes and previous versions for detail.

Citation 1 change
Agustin Ciapponi, Mabel Berrueta, Ariel Bardach, Agustina Mazzoni, Fernando J Argento, Jamile Ballivian, Daniel Comandé, Erin Goucher, Beate Kampmann, Edward P.K. Parker, Veronica Pingray, Federico Rodriguez Cairoli, Victoria Santa María, Andy Stergachis, Xu Xiong, Sabra Zaraa, Pierre M Buekens. Safety, immunogenicity, and effectiveness of COVID-19 vaccines for pregnant persons: a protocol for a living systematic review and meta-analysis. PROSPERO 2024 Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD42021281290

REVIEW TITLE AND BASIC DETAILS

Review title 1 change
Safety, immunogenicity, and effectiveness of COVID-19 vaccines for pregnant persons: a protocol for a living systematic review and meta-analysis

Review objectives

Primary review questions

Are COVID-19 vaccines administered during pregnancy safe considering maternal/pregnancy, perinatal, neonatal, postpartum outcomes

Are COVID-19 vaccines administered during pregnancy safe with respect to non-pregnancy-related outcomes?

What is the efficacy and/or effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infections, COVID-19 and its complications in pregnant persons?

what is the immune response and how long does it last among vaccinated pregnant persons and their neonates?

Secondary review questions

Are there differential effects of COVID-19 vaccines, vaccine components and vaccine platforms?

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

Are there differential vaccine effects by country income-level or region?

Are there differential vaccine effects by dominant SARS-CoV-2 variant at the time window of each study?

We will follow Cochrane and World Health Organization (WHO) methods1, 2 to conduct the systematic review and PRISMA 2020 for reporting it3, 4.

Keywords

COVID-19, meta-analysis, pregnancy, safety outcomes, systematic review, vaccines

SEARCHING AND SCREENING

Searches

We will update every two weeks the searches of this LSR (living systematic review) 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 COVID-19, guidelines published by national and international professional societies (e.g. ACOG, RCOG, FIGO), pre-print servers (ArXiv, BiorXiv, medRxiv, search.bioPreprint), and COVID-19 research websites (Global research on coronavirus disease (COVID-19) supported by the World Health Organization (WHO), COVID-19 Vaccine Tracker, the LOVE database, and the Covid-19 Living Evidence. Bern: Institute of Social and Preventive Medicine, University of Bern Available from: https://ispmbern.github.io/covid-19/living-review/)

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

No language restrictions will be applied.

We will contact experts in the field relevant to our review question and we will hand search the reference lists of the identified SRs and included studies in order to identify relevant studies misses by the search strategy.
Additional search strategy information can be found in the attached PDF document (link provided below).

Study design

We will include experimental, quasi-experimental and observational (comparative and non-comparative) study designs, irrespective of publication status, publication year, and language to also consider the real word evidence.
We will include randomized controlled trials (RCTs); non-randomized CTs; controlled before-after studies (CBAs); nationwide uncontrolled before-after studies (UBAs); interrupted time series (ITSs); Controlled-ITSs (CITSs); and adverse events/safety registries, including Phase IV studies, cohort studies, case-control, cross-sectional studies, case series, economic evaluations, cost studies and budget impact analysis.
We will only include case-reports for previously unknown or unexpected adverse events.

ELIGIBILITY CRITERIA

Condition or domain being studied

COVID-19, pregnancy.

Population

Pregnant persons and neonates.

Intervention(s) or exposure(s)

COVID-19 vaccines within WHO Emergency Use Listing/Pre-qualification (EUL/PQ), aiming to prevent COVID-19, irrespective of the dose and of 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

No context limitation.

OUTCOMES TO BE ANALYSED

Main outcomes

1.Safety outcomes with respect to obstetric/neonatal outcomes- Primary outcomes:
We will use the 21 standardized case definitions developed by GAIA (Global Alignment of Immunization Safety Assessment in Pregnancy) of prioritized obstetric and neonatal outcomes based on the standard Brighton Collaboration process.5 The outcomes include:
• Obstetric outcomes: Hypertensive disorders of pregnancy, maternal death, non-reassuring fetal status, pathways to preterm birth and postpartum hemorrhaged, abortion/miscarriage, antenatal bleeding, gestational diabetes, dysfunctional labor, fetal growth retardation
• Neonatal outcomes: Congenital anomalies, neonatal death, neonatal infections, preterm birth, stillbirth, low birth weight, small for gestational age, neonatal encephalopathy, respiratory distress, failure to thrive and microcephaly.
2 Prevention of Confirmed and symptomatic mild/moderate/severe COVID-19:
• in pregnant persons with nucleic acid amplification tests (NAAT), such as RT-PCR, confirmed infection
• in pregnant persons with no serological or virological evidence of past SARS-CoV-2 infection
• in pregnant persons with or without serological or virological evidence of past SARS-CoV-2 infection.
3. Prevention of Complications attributed to COVID-19 (including hospital-attended COVID-19 and death).
4. Immunogenicity: immune cellular and humoral responses and duration of immunity
5. All-cause mortality.
6. Serious adverse events (SAEs)
• Any SAEs
• SAEs due to vaccine administration

Measures of effect
We will calculate risk ratios (RRs) with 95% confidence intervals (95% CIs) for dichotomous outcomes and Mean difference (MD) or Standardized MD (SMD) for continuous outcomes.
We will also calculate proportions with 95% CIs for non-comparative studies.

Additional outcomes

A. Asymptomatic SARS-CoV-2 infection: determined by asymptomatic seroconversion of N-binding antibody and/or asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT,), such as RT-PCR
B. Mother-to-child transmission: Presence and persistence of SARS-CoV-2 (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 believed to be linked to COVID-19 vaccination during pregnancy.

D. Time the antibodies last

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

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 and with 95% CI for non-comparative studies.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

Selection:

Pair 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 the full-texts, recording the reasons for exclusion of the ineligible studies.

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

Data extraction and management:

Pairs of review authors will independently extract data from included studies in a predefined form previously piloted with five studies.

Disagreements will be resolved by discussion of the review team. We will contact the study authors by email to specify any missing data, which may not be reported sufficiently or not at all in the publication.

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) that includes five bias domains: randomization process; deviation from intended interventions; missing outcome data; measurement of outcomes; selective reporting of results;

For CBAs: 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 UBAs, we used the same criteria as CBAs, with the exception of baseline measurement and characteristics for studies using the second site as control.

For ITS: 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 bias2.
For CITSs studies we will include three additional domains that assess design-specific threats to validity: imbalance of outcome measures at baseline; comparability of intervention and control group characteristics at baseline; and protection against contamination2.
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 the data are available and methodologically appropriate, we will perform aggregate data meta-analyses using the random-effects meta-analysis for the primary analysis.
A proportion meta-analysis will be used to summarize effects from single-group studies. All results will be presented with 95% confidence intervals (CIs).
We will present GRADE certainty of evidence10 in 'Summary of findings' tables1, 2, 11
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 COVID-19 vaccine, vaccine type (mRNA, vectored, Protein / subunit) components and vaccine platforms or by dominant variant of SARS-CoV-2 of the study population.
Additional sensitivity analyses will be undertaken excluding high-risk of bias studies or by using the fixed-effect model.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

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Funding source
Bill & Melinda Gates Foundation

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TIMELINE OF THE REVIEW

Review timeline
Start date: 01 January 2022. End date: 30 December 2022

Date of first submission to PROSPERO
23 September 2021

Date of registration in PROSPERO
23 September 2021

CURRENT REVIEW STAGE

Publication of review results

The intention is not to publish the review once completed.

Academic Journals, Medical Congress, Social Network, media

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

Additional information

This review is part of a project that covers different research questions about COVID-19 and pregnancy. See our previous publications in this topic:

1. Ciapponi A, Bardach A, Mazzoni A, et al. Safety of components and platforms of COVID-19 vaccines considered for use in pregnancy: A rapid review. Vaccine. Aug 13 2021;doi:10.1016/j.vaccine.2021.08.034

2.Ciapponi A, Bardach A, Comandé D, et al. COVID-19 and pregnancy: An umbrella review of clinical presentation, vertical transmission, and maternal and perinatal outcomes. PLOS ONE. 2021;16(6):e0253974. doi:10.1371/journal.pone.0253974.

3. Berrueta M, Ciapponi A, Bardach A, et al. Maternal and neonatal data collection systems in low- and middle-income countries for maternal vaccines active safety surveillance systems: A scoping review. BMC Pregnancy Childbirth. Mar 17 2021;21(1):217. doi:10.1186/s12884-021-03686-9.

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3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med. Mar 2021;18(3):e1003583. doi:10.1371/journal.pmed.1003583
4. Kahale L, Elkhoury R, El Mikati I, et al. Tailored PRISMA 2020 flow diagrams for living systematic reviews: a methodological survey and a proposal [version 2; peer review: 1 approved, 1 approved with reservations]. F1000Research. 2021;10(192)doi:10.12688/f1000research.51723.2
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9. NIH. Study Quality Assessment Tools Accessed 19 Mar 2020, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
10. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. Jul 2017;87:4-13. doi:10.1016/j.jclinepi.2017.05.006
11. GRADEpro. 3.2.2 for Windows. Updated March 2009. 2009.

PROSPERO version history

- Version 1.3 published on 05 Jan 2023
- Version 1.2 published on 03 Jan 2023
- Version 1.1 published on 11 Mar 2022
- Version 1.0 published on 23 Sep 2021

Review conflict of interest

None known

Country
Argentina, United States of America

Medical Subject Headings
COVID-19; COVID-19 Vaccines; Female; Humans; Pregnancy; SARS-CoV-2; Vaccination; Vaccines

Details of any existing review of the same topic by the same authors
CRD42021243062 about COVID-19 vaccination in pregnant, postnatal and breastfeeding women focused on qualitative outcomes and restricted to studies published in English and Chinese. CRD42021266203 was focused on breastfeeding individuals but no about efficacy. CRD42020196492 was aimed to evaluate the effects of vaccines only trough RCTs. These are the main differences.

Revision note 1 change
Hi we need to change the title to "Safety, reactogenicity, immunogenicity, and effectiveness of COVID-19 vaccines for pregnant persons: A protocol for a living systematic review and living meta-analysis" becase we are publishing the full protocol and the journal demand the inclusion of "....A protocol for a living..." in order to publish it

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