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Safety, effectiveness, and immunogenicity of mpox vaccines in pregnant persons and their newborns: a living systematic review and meta-analysis.

Mabel Berrueta, Agustin Ciapponi, Jamile Ballivian, Agustina Mazzoni, Ariel Bardach, Juan Sambade, Martin Brizuela, Katharina Stegelman, Daniel Comande, Edward Parker, Andy Stergachis, Xu Xiong, Flor Munoz, Pierre Buekens

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REVIEW TITLE AND BASIC DETAILS

Review title
Safety, effectiveness, and immunogenicity of mpox vaccines in pregnant persons and their newborns: a living systematic review and meta-analysis.

Original language title

English

Review objectives

Primary review questions:

1) What is the safety profile of mpox vaccine candidates and licensed vaccines administered during pregnancy regarding adverse obstetric, maternal neonatal outcomes?

2) What is the safety and tolerability profile of mpox vaccine candidates and licensed vaccines administered during pregnancy concerning nonpregnancy-related adverse maternal outcomes?

3) How effective are mpox vaccine candidates and licensed vaccines in prevention from infection, disease of various degrees of severity, and complications including organ disease (eg. Myocarditis, encephalitis, etc), hospitalization and death?

4) What immune response is associated with mpox vaccine candidates and licensed vaccines, and what is its duration in vaccinated pregnant persons?

5) Are there mpox virus-specific immune responses with antibody transfer from vaccinated pregnant persons to their newborns (via placenta and breastmilk)?

Secondary review questions

1) Is there differential safety, effectiveness, and/or efficacy of mpox vaccine candidates and licensed vaccines in pregnant persons compared to non-pregnant individuals?

2) Is there differential safety, effectiveness, and/or efficacy of mpox vaccines in pregnancy by trimester of exposure, maternal risk status, and maternal age?

3) Is there differential safety, effectiveness, and/or efficacy of vaccines in pregnant persons by country, country income level, or geographic region?

4) What are the long-term safety concerns of mpox vaccination in pregnant persons?

SEARCHING AND SCREENING

Searches

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), EPPI-Centre, WHO Database of publications on mpox virus, mpox-related congresses and laboratory reports, guidelines published by national and international professional societies (e.g., ACOG, RCOG, FIGO), preprint servers (e.g., ArXiv, BiorXiv, medRxiv, search.bioPreprint), and mpox research websites.

We will search all the above databases from January 1970 to the present. No language restrictions will be applied. The searches will be updated every two weeks to incorporate new relevant reports as they become available. In addition, we will hand-search the reference lists of the identified systematic reviews and include studies to identify relevant studies missed by our search strategy. Ongoing

randomized controlled trials will be tracked in Clinicaltrial.gov and other trial registers (WHO, etc.). Our searches will focus on pregnant subjects but will not be limited to them. General adult population data will be included to capture any data related to pregnant individuals.

Study design

Any mpox vaccination schedule will be included in the study, including for pre-exposure or post-exposure prophylaxis. Experimental, quasi-experimental, and observational (comparative and non-comparative) study designs, irrespective of publication status, publication year, and language. We will include randomized controlled trials (all Phases I-IV), non-randomized trials, before-after studies with or without control groups, interrupted time series, controlled-interrupted time series, and adverse events/safety registries, real-world Phase IV studies, cohort studies, case-control studies, cross-sectional studies, and case series. Case reports for previously unknown or unexpected adverse events will be included. Preclinical studies will be included to assess the outcomes of interest in the vaccine candidates.

ELIGIBILITY CRITERIA

Condition or domain being studied

Mpox virus vaccines

Population

Pregnant persons and their newborns; Pregnant animals.

Intervention(s) or exposure(s)

Mpox vaccines in pregnant persons or animals regardless of the dose and schedule.

Comparator(s) or control(s)

Active or inactive comparators without interventions under study, usual care, or placebo. Non-comparative studies will be included; therefore, a control group will not be mandatory.

Context

There is no context limitation.

OUTCOMES TO BE ANALYSED

Main outcomes

1. Safety outcomes

a. Obstetric, maternal and neonatal outcomes:

We will use the standardized case definitions developed by Global Alignment of Immunization Safety Assessment in Pregnancy of prioritized obstetric and neonatal outcomes based on the standard Brighton Collaboration process. The outcomes include (but are not limited to):

• Maternal and Obstetric outcomes: Maternal death, spontaneous abortion/miscarriage, stillbirth, preterm delivery, antenatal, perinatal or post-partum bleeding/hemorrhage, gestational diabetes, hypertensive disorders of pregnancy, dysfunctional labor, non-reassuring fetal status, intrauterine fetal growth retardation

• Neonatal outcomes: Neonatal death, preterm birth, low birth weight, small for gestational age, neonatal infection, neonatal encephalopathy, respiratory distress, congenital anomalies, and microcephaly.

b. Serious adverse events (SAEs) and all-cause mortality related to vaccination (in vaccinated pregnant people and their newborns).

c. Hospitalization due to serious adverse events.

d. Adverse events (AEs) of special interest (AESI) post-vaccination in pregnant persons (not related to pregnancy) and their newborn

The AESIs include (but are not limited to) all events listed in the CEPI-SPEAC AESI list for mpox vaccines available here https://speacsafety.net/tools/aesi-lists/mpox/.

Measures of effect

1. Safety outcomes

a. Obstetric, maternal and neonatal outcomes:

We will use the standardized case definitions developed by Global Alignment of Immunization Safety Assessment in Pregnancy of prioritized obstetric and neonatal outcomes based on the standard Brighton Collaboration process. The outcomes include (but are not limited to):

• Maternal and Obstetric outcomes: Maternal death, spontaneous abortion/miscarriage, stillbirth, preterm delivery, antenatal, perinatal or post-partum bleeding/hemorrhage, gestational diabetes, hypertensive disorders of pregnancy, dysfunctional labor, non-reassuring fetal status, intrauterine fetal growth retardation

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Additional outcomes

2. Efficacy/effectiveness

a. Asymptomatic mpox infection: antibody (four-fold rise) or antigen detection in asymptomatic individuals.

b. Confirmed, probable, and suspected mpox infections

Our target definition (based on the WHO-recommended case definition) for confirmed cases includes persons with laboratory-confirmed MPXV infection by detecting viral DNA by rt-PCR and/or sequencing.

Probable cases:

-A person presenting an unexplained acute skin rash, mucosal lesions, or lymphadenopathy. The skin rash may include single or multiple lesions in the anogenital region or elsewhere. Mucosal lesions may include single or multiple oral, conjunctival, urethral, penile, vaginal, or anorectal lesions. Anorectal lesions can also manifest as proctitis and/or bleeding; and

-One or more of the following: epidemiological link to a probable or confirmed case of mpox 21 days before symptom onset; multiple and/or casual sexual partners 21 days before symptom onset; or positive test for orthopoxviral infection

Suspected cases:

-A contact of a probable or confirmed mpox case in the 21 days before the onset of signs or symptoms and who presents with any of the following: acute onset of fever (>38.5°C), headache, myalgia (muscle pain/body aches), back pain, profound weakness, or fatigue; or

-A person presenting with an unexplained acute skin rash, mucosal lesions, or lymphadenopathy (swollen lymph nodes). The skin rash may include single or multiple lesions in the anogenital region or elsewhere. Mucosal lesions may include single or multiple oral, conjunctival, urethral, penile, vaginal, or anorectal lesions. Anorectal lesions can also manifest as anorectal inflammation (proctitis) and/or bleeding. In addition to the above, the common causes of acute rash or skin lesions should not fully explain the clinical picture.

c. Confirmed mpox case resulting in severe disease (including hospitalization).

3. Immunogenicity:

Immune cellular and humoral responses and duration of immunity (IgM, IgG; neutralizing antibodies in maternal serum at delivery and umbilical cord blood and cellular response markers) transplacental transfer ratios.

Measures of effect

Odds ratios (ORs), Risk ratios (RRs), and Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for dichotomous outcomes, and Mean difference (MD) or Standardized MD (SMD) for continuous outcomes will be estimated. Regarding efficacy/effectiveness, we will report Vaccine efficacy (VE). We will also calculate proportions with 95% CIs for non-comparative studies.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

Selection

A pair of review authors will independently screen each study title and abstract. Any potentially relevant full-text study reports/publications will be retrieved and reviewed independently by two authors, recording the reasons for excluding the ineligible studies. Disagreements will be resolved through discussion with the review team. This process will be performed using the Nested knowledge platform.

Data extraction and management:

Study data will be collected and stored using REDCap electronic data capture tools hosted and maintained by IECS. 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 independently assess 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 that 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.

Risk of bias (quality) assessment

1) Randomized controlled trials: we will use the Cochrane RoB2

2) Non-randomized studies of interventions: we will use the ROBINS-I tool.

3) Controlled before-after studies: we will assess 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.

4) Uncontrolled before-after studies: we will use the same criteria as controlled before-after studies, with the exception of baseline measurement and characteristics for studies using the second site as a control.

5) Interrupted time series: 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 bias.

6) Controlled interrupted time series studies: in addition to the domains considered for interrupted time series studies, we will include three 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 contamination.

We will present GRADE certainty of evidence in the ‘Summary of findings' tables for main outcomes.

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 pre-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 Tidyverse. We will estimate HRs, RRs, ORs, MDs, or SMD with 95% CI. We will also estimate 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 the vaccinated and the comparative group and determining the percentage reduction in disease risk among vaccinated persons relative to the control group. 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 provide a frequently updated online and interactive app to present available data and main findings.

Analysis of subgroups or subsets

Pre-specified subgroups by route (subcutaneous vs intradermal) by pregnancy trimester (first, second, or third trimester), country income level (high or low- and middle-income country), region (based on the Institute for Health Metrics and Evaluation categorization), maternal age, maternal risk status (low or high), by individual mpox vaccine and/or platform, or by immunosuppression status. Additional sensitivity analyses will be undertaken by excluding high-risk bias studies.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

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TIMELINE OF THE REVIEW

Review timeline
Start date: 17 September 2024. End date: 31 December 2024

Date of first submission to PROSPERO
16 September 2024

Date of registration in PROSPERO
30 September 2024

CURRENT REVIEW STAGE

Publication of review results
The intention is not to publish the review once completed.

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 30 Sep 2024
- Version 1.0 published on 30 Sep 2024

Review conflict of interest
None known

Country
Argentina

Medical Subject Headings
Communicable Diseases; Encephalitis; Female; Hospitalization; Humans; Immunity; Immunoglobulins; Infant, Newborn; Maternal Age; Milk, Human; Monkeypox virus; Myocarditis; Placenta; Pregnancy; Smallpox Vaccine; Vaccines

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