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

Mabel Berrueta, Agustin Ciapponi, Agustin Mazzoni, Jamile Ballivian, Ariel Bardach, Juan Sambade, Martin Brizuela, Katharina Stegelman, 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 Chikungunya vaccines in pregnant persons: a living systematic review and meta-analysis.

Original language title
English

Review objectives

1) What is the safety profile of the vaccine platforms or components of Chikungunya candidates and licensed vaccines (antigen, vehicle, construct, adjuvants, other components) in pregnant persons?
2) What is the safety profile of Chikungunya candidate and licensed vaccines administered during pregnancy regarding adverse maternal/pregnancy, perinatal, neonatal, and postpartum outcomes?
3) What is the safety profile and tolerability of Chikungunya candidate and licensed vaccines administered during pregnancy in terms of other nonpregnancy-related adverse maternaloutcomes?
4) How effective are Chikungunya candidate and licensed vaccines in preventing and protecting pregnant persons from the disease?
5) What is the immune response associated with Chikungunya candidate and licensed vaccines, and how long does it last in vaccinated pregnant persons?
6) Are there Chikungunya virus-specific immune responses with antibody transfer from vaccinated pregnant persons to their newborns (placenta and breastmilk)?
Secondary review questions
1) Are there differential safety effects of various Chikungunya vaccine platforms or components (antigen, vehicle, construct, adjuvants, other components) used by Chikungunya candidate and licensed vaccines in pregnant persons?
2) Are there differential safety, effectiveness, and efficacy effects of Chikungunya vaccine candidates and licensed platforms in pregnant persons?
3) Are there differential safety, effectiveness, and efficacy effects of vaccines by trimester of exposure, maternal risk status, and/or maternal age?
4) Are there differential safety, effectiveness, and efficacy effects of vaccines by country income level or region in pregnant persons?
5) What immune response is associated with Chikungunya candidates and licensed vaccines, and how long does it last pregnant persons?
6) What are the long-term effects of CHIKV vaccination (efficacy, safety) in pregnant persons?

Keywords

Adverse events, Chikungunya, Efficacy, Immunogenicity, Meta-analysis, Safety, Systematic review, Vaccine

SEARCHING AND SCREENING

Searches

We intend to update the searches of this living systematic review (LSR) regularly to incorporate new relevant reports as they are released.
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 map of the current evidence on Chikungunya, WHO Database of publications on Chikungunya virus, Chikungunya-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 Chikungunya research websites.
We will search all the above databases from January 2014 to the present. No language restrictions will be applied. Every two weeks updates of the searches will be performed in order to incorporate new relevant reports as they become available. Besides, we will hand search the reference lists of the identified systematic reviews and included studies in order 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.).
Additional search strategy information can be found in the attached PDF document (link provided below).

Study design

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, controlled before-after studies, nationwide uncontrolled before-after studies, interrupted time series, controlled-interrupted time series, and adverse events/safety registries, real-world Phase IV studies, cohort studies, case-control, cross-sectional studies, and case series.
Case reports for previously unknown or unexpected adverse events will be included.
Preclinical studies will be included.

ELIGIBILITY CRITERIA

Condition or domain being studied

Chikungunya virus vaccines

Population

Pregnant persons and their newborns
Animals

Intervention(s) or exposure(s)

1) Vaccine platforms or components present in Chikungunya candidate and licenses vaccines used in other vaccines in pregnant persons (antigen, vehicle, construct, adjuvants, other components)
2) Chikungunya 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

No context limitation.

OUTCOMES TO BE ANALYSED

Main outcomes

1. Safety outcomes

a. Concerning obstetric/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 not limited to):

• 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, failure to thrive, congenital anomalies and microcephaly.

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

Maternal mortality rate/ratio

Fetal loss – including spontaneous abortion /Miscarriage and stillbirth.

Neonatal mortality rate

Hospitalization for severe myalgia, hypovolemic hyponatremia or atrial fibrillation.

c. Adverse events (AEs) of Special Interest (AESI) post-vaccination in pregnant persons (not related to pregnancy)

The outcomes include (but not limited to): Arthritis/arthralgia, late adverse event in newborns associated with Chikungunya vaccination during pregnancy.

Measures of effect

Odds ratios (ORs), Risk ratios (RRs), 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.

Additional outcomes

Other outcomes: GBS, facial nerve (Bell's) palsy, anaphylaxis, encephalomyelitis, narcolepsy, appendicitis, non-hemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction, myocarditis and pericarditis, deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, immune thrombocytopenia, transverse myelitis, thrombosis with thrombocytopenia, hemorrhage, sensorineural hearing loss2. Efficacy/effectiveness

a. Confirmed, probable and suspected Chikungunya infection (WHO-suggested case definition).

• Case classification:

i) Suspect case: any person with acute onset of fever >38.5°C and severe arthralgia/arthritis not explained by other medical conditions.

ii) Probable case: a patient meeting both the clinical and epidemiological criteria.

iii) Confirmed case: a suspected case with laboratory confirmation.

• Clinical criteria:

iv) Acute onset of fever >38.5°C and severe arthralgia/arthritis not explained by other medical conditions.

v) Epidemiological criteria: Residing or having visited epidemic areas having reported transmission within 15 days before the onset of symptoms.

• Laboratory criteria:

vi) Virus isolation.

vii) Presence of viral RNA by RT-PCR

viii) Presence of virus-specific IgM antibodies in a single serum sample collected in the acute or convalescent stage.

ix) Four-fold increase in IgG values in samples collected at least three weeks apart.

b. Confirmed Chikungunya case resulting in hospitalization.

c. Other complications attributed to Chikungunya vaccination in pregnant persons and their newborns.

3. Immunogenicity:

a. immune cellular and humoral responses and duration of immunity (titers of IgM, IgG, and combined; neutralizing antibodies in maternal serum at delivery and umbilical cord blood and cellular response markers).

b. transplacental transfer ratios.

c. magnitude and duration of antibody response

Additional outcome(s)

a) Viremia from vaccination: magnitude and duration of viremia (based on PCR testing) in mother or baby.

b) Asymptomatic Chikungunya infection: determined by antibody (four-fold rise) or antigen detection in asymptomatic individuals during three months.

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

Measures of effect

Odds ratios (ORs), Risk ratios (RRs), 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 title and abstract. Any potentially relevant full-text study reports/publications will be retrieved and reviewed independently by two authors, 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 COVIDENCE web-based software.

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

Risk of bias (quality) assessment

1) Randomized controlled trials: we will use the Cochrane risk of bias tool - version 2 (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 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: we included 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 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 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 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 vaccinated and the comparative group and determining the percentage reduction in risk of disease 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 an online and interactive app to present available data and main 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 (based on the Institute for Health Metrics and Evaluation categorization), maternal age, maternal risk status (low or high), by individual Chikungunya vaccine and/or platform. Additional sensitivity analyses will be undertaken by excluding high-risk bias studies or using the fixed-effect model.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

- Dr Mabel Berrueta, Instituto de Efectividad Clínica y Sanitaria
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TIMELINE OF THE REVIEW

Review timeline
Start date: 19 February 2024. End date: 03 June 2024

Date of first submission to PROSPERO
22 February 2024

Date of registration in PROSPERO
04 March 2024

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 04 Mar 2024
- Version 1.0 published on 04 Mar 2024

Review conflict of interest
None known

Country
Argentina

Medical Subject Headings

Adjuvants, Immunologic; Chikungunya Fever; Chikungunya virus; Female; Humans; Immunity; Immunoglobulins; Infant, Newborn; Maternal Age; Milk, Human; Placenta; Postpartum Period; Pregnancy; Vaccination; Vaccines

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