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Safety, immunogenicity, and effectiveness of Chikungunya vaccines in newborns, infants, children, and adolescents: a living systematic review and meta-analysis

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REVIEW TITLE AND BASIC DETAILS

Review title
Safety, immunogenicity, and effectiveness of Chikungunya vaccines in newborns, infants, children, and adolescents: a living systematic review and meta-analysis

Original language title
English

Review objectives
Primary review questions
1) What is the safety profile of the vaccine platforms or components (antigen, vehicle, construct, adjuvants, other components) in Chikungunya candidates and licensed vaccines in children?
2) What is the safety profile of Chikungunya candidates and licensed vaccines administered during childhood in terms of adverse events and children's outcomes?
3) What is the safety profile and tolerability of Chikungunya candidates and licensed vaccines administered to children?
4) How effective are Chikungunya candidates and licensed vaccines in preventing and protecting children from the disease?
5) What immune response is associated with Chikungunya candidates and licensed vaccines, and how long does it last in children?
6) What are the long-term effects of CHIKV vaccination (efficacy, safety) in children?
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 vaccines in children?
2) Are there differential safety, effectiveness, and efficacy effects of Chikungunya vaccine candidates and licensed platforms?
3) Are there differential safety, effectiveness, and efficacy effects of vaccines by country income level or region in children?

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

SEARCHING AND SCREENING

Searches
We will update the searches of this living systematic review (LSR) regularly 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), EPPI-Centre map of the current evidence on Chikungunya, WHO Database of publications on Chikungunya virus, Chikungunya-related Congresses, 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 of 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

We will include clinical trials, quasi-experimental, and observational (comparative and non-comparative) study designs, irrespective of publication status, publication year, and language also to incorporate real-world evidence (RWE).
We will consider randomized controlled trials (RCTs) (all Phases I-IV), non-randomized CTs, controlled before-after studies (CBAs), nationwide uncontrolled before-after studies (UBAs), interrupted time series (ITSs), controlled-ITSs (CITSs), and adverse event/safety registries. Real-world phase IV studies, cohort studies, case-control studies, cross-sectional studies, and case series will also be considered. We will also consider case reports of previously unknown or unexpected adverse events.

ELIGIBILITY CRITERIA

Condition or domain being studied

Chikungunya

Population

Children up to 18 years of age (0 to < 18 years old).

Intervention(s) or exposure(s)

1) Vaccine platforms or components present in Chikungunya candidate and licenses vaccines used in other vaccines in children (antigen, vehicle, construct, adjuvants, other components).
2) Chikungunya vaccines used in children, regardless of the dose and schedule.

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:

a. Serious adverse events and all-cause mortality related to vaccination in children.

b. Adverse events of Special Interest post-vaccination in children: Arthritis/arthralgia, 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, and the occurrence of thrombosis with thrombocytopenia, psychiatric disorder, syndrome of inappropriate antidiuretic hormone secretion, laboratory tests [including blood cells counts and transaminases].

2. Efficacy/effectiveness: We will use WHO-suggested outbreak case definition

a. Clinical Chikungunya

i) Clinical criteria:

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

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

ii) Laboratory criteria:

Virus isolation.

Presence of viral RNA by RT-PCR

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

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

iii) Case classification:

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

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

Confirmed case: a suspected case with laboratory confirmation.

Measures of effect

Where appropriate, 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. Regarding efficacy/effectiveness, we will report Vaccine efficacy (VE).

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

Additional outcomes

3. Efficacy/effectiveness in the prevention of confirmed Chikungunya hospitalization

4. Other complications attributed to Chikungunya vaccination in children

5. Immunogenicity:

a) Humoral response including duration of antibody response (number of participants with four-fold seroconversion), cellular response, titers of neutralizing antibodies, geometric mean titers (GMT)] in children's serum after primary and/or booster scheme.
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.
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. Regarding efficacy/effectiveness, we will report Vaccine efficacy (VE).
We will also calculate proportions with 95% CI for non-comparative studies.
Additional outcomes
1) Viremia from vaccination: presence of viremia (as determined by PCR) and duration
2) Asymptomatic Chikungunya infection: determined by antibody or antigen detection in asymptomatic individuals.

Measures of effect
Where appropriate, 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. Regarding efficacy/effectiveness, we will report Vaccine efficacy (VE).
We will also calculate proportions with 95% CI for non-comparative studies.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

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 excluding 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 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

For RCTs, we will use the RoB 2
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.
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, 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, we will assess the risk of bias associated with: 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. As for CBAs, for Controlled ITSs 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.

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 analyze the data using R statistical software. The main packages selected for data analyses will be Meta, Metafor, and

Tidyverse.
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 the 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, sex, country or region 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 region, infant risk status (low or high), age (eg. 0-<1 yr, 0-4 years, 5 to 11 years, 12-17 years), by individual Chikungunya vaccine and/or platform, or by dominant Chikungunya type of the study population.
Additional sensitivity analyses will be undertaken by excluding high-risk bias studies or using the fixed-effect model.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

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Funding source
https:\/\/iecs.org.ar\/

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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		

Review stage	Started	Completed
Risk of bias/quality assessment		
Data synthesis		

No other relevant information

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; Adjuvants, Pharmaceutic; Adolescent; Chikungunya Fever; Child; Humans; Immunity; Infant; Infant, Newborn; Vaccination; Vaccines

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