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

Mabel Berrueta, Agustin Ciapponi, Jamile Ballivian, Agustin Mazzoni, 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, immunogenicity, and effectiveness of Lassa 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 are the safety profiles of the vaccine platforms or components (antigen, vehicle, construct, adjuvants, other components) in Lassa candidates and licensed vaccines in children?

2) What is the safety profile of Lassa candidates and licensed vaccines administered during childhood regarding adverse events and children's outcomes?

3) What is the safety profile and tolerability of Lassa candidates and licensed vaccines administered to children?

4) How effective are Lassa candidates and licensed vaccines in preventing and protecting children from the disease?

5) What immune response is associated with Lassa candidates and licensed vaccines, and how long does it last in children?

6) What are the long-term effects of Lassa vaccination (efficacy, safety) in children?

Secondary review questions

1) Are there differential safety effects of various Lassa vaccine platforms or components (antigen, vehicle, construct, adjuvants, other components) used by Lassa candidate vaccines in children?

2) Are there differential safety, effectiveness, and efficacy effects of Lassa 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, Efficacy, Immunogenicity, Lassa virus, 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 Lassa, WHO Database of publications on Lassa virus, Lassa-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 Lassa research websites.

We will search all the above databases from January 2014 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. Besides, 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.).
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

Lassa virus

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 Lassa candidate and licenses vaccines used in other vaccines in children (antigen, vehicle, construct, adjuvants, other components).
2) Lassa 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. Non-comparative studies will be included; therefore, a control group will not be mandatory.

OUTCOMES TO BE ANALYSED

Main outcomes

1.Safety outcomesa. Serious adverse events (SAEs) and all-cause mortality related to LASV vaccination in children.
b. Adverse Events (AEs) of Special Interest (AESI) post-vaccination in children: Hemorrhagic disease (bleeding from mucosa / skin), Vaccine-associated Immune Thrombotic Thrombocytopenia (VITT), Thrombocytopenia, Anaphylaxis

Single Organ Cutaneous Vasculitis, Severe Lassa Fever infection (ARDS; AKI with KDIGO ≥2; NEWS2≥7; LFTs≥3X upper limit of normal; shock; multiorgan failure; death), Acute aseptic arthritis, Aseptic meningitis, Acute Encephalitis, Myelitis, Generalized convulsion, Guillain-Barré Syndrome, Sensorineural Hearing Loss, Acute Kidney Injury, Acute Respiratory Distress Syndrome (ARDS)
2. Efficacy/effectiveness: We will use WHO-suggested outbreak case definition
3. Immunogenicity
a. Immune cellular and humoral responses and duration of immunity -titers of IgM, IgG, and combined, neutralizing antibodies in children's serum after a primary/booster scheme.
b. Magnitude and duration of antibody response

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
a. Viremia from vaccination: magnitude and duration, in infants, children, and/ or adolescents, presence of viremia, and duration as well – prolonged viremia might be an issue.
b. Asymptomatic LASV infection: determined by antibody or antigen detection in asymptomatic individuals.

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 excluding the ineligible studies.
Disagreements will be resolved through discussion with the review team. This process will be performed using the web-based software Nested Knowledge.
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 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 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 (e.g. 0-<1 yr, 0-4 years, 5 to 11 years, 12-17 years), by individual LASSA vaccine and/or platform, or by dominant Lassa 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

Review team members

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TIMELINE OF THE REVIEW

Review timeline
Start date: 04 June 2024. End date: 30 September 2024

Date of first submission to PROSPERO
11 June 2024

Date of registration in PROSPERO
21 June 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		

Review stage	Started	Completed
Screening search results against inclusion criteria		
Data extraction or receipt of IP		
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 21 Jun 2024
- Version 1.0 published on 21 Jun 2024

Review conflict of interest
None known

Country
Argentina

Medical Subject Headings
Adjuvants, Immunologic; Adjuvants, Pharmaceutic; Adolescent; Child; Humans; Immunity; Infant; Infant, Newborn; Vaccination; Vaccines

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