Reproductive Health

STUDY PROTOCOL

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Safety, immunogenicity, and effectiveness of chikungunya vaccines in pregnant persons, children, and adolescents: a protocol for a living systematic review and meta-analysis

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Abstract

Background Chikungunya virus significantly impacts public health, primarily affecting regions in Africa and the Americas (predominantly Latin America and the Caribbean). Despite the global spread of the virus and its clinical manifestations and complications in vulnerable populations such as children and pregnant persons, no widely available vaccine is currently available. With recent advancements in vaccine development, there is a need to systematically evaluate the emerging evidence on the safety, immunogenicity, and efficacy of chikungunya vaccine candidates. This protocol outlines a living systematic review designed to continuously assess the growing research on chikungunya vaccines, focusing on diverse populations, including children and pregnant persons. We aim to provide up-to-date evidence to inform public health decisions and vaccine recommendations as new data is available.

Methods Our objective is to carry out a living systematic review and meta-analysis through biweekly searches in medical databases and clinical trial registries, aiming to identify relevant chikungunya vaccines studies on pregnant individuals, children, and adolescents. Pairs of reviewers will independently screen studies, extract data, and assess the risk of bias. Clinical trials, quasi-experimental studies, and observational studies, including case reports, will be considered for inclusion. Main outcomes will include the safety, efficacy, and effectiveness of chikungunya vaccines in pregnant individuals (including neonatal outcomes), as well as in children and adolescents. Reactogenicity and immunogenicity will be considered as secondary outcomes. Paired meta-analyses, incorporating predefined subgroup and sensitivity analyses, will be performed. Evidence certainty will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Discussion This living systematic review and meta-analysis will continuously assess the safety, immunogenicity, and effectiveness of chikungunya vaccines in pregnant persons, children, and adolescents. Given the significant disease burden and potential complications in these populations, synthesizing emerging evidence is crucial for guiding immunization policies and clinical recommendations. By maintaining an updated analysis, this review will provide timely insights for public health agencies, researchers, and clinicians involved in vaccine implementation and maternal-child health.

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Study registration Two protocols were registered in the International Prospective Register of Systematic Reviews database, CRD42024514513 and CRD42024516754.

Keywords Chikungunya, Vaccine, Pregnancy, Children, Protocol, Systematic review, Meta-analyses

Introduction

The burden of disease caused by Chikungunya virus

Chikungunya virus (CHIKV) is a single-stranded RNA virus of the *Alphavirus* genus and *Togaviridae* family. It was first identified in Tanzania in the early 1950s [1] and is transmitted to humans by *Aedes aegypti* and *Aedes albopictus* mosquitoes [2].

Chikungunya virus has a significant global impact on public health, primarily affecting regions in Africa and the Americas (predominantly Latin America and the Caribbean) [1–3]. A recent systematic review (SR) and meta-analysis (MA) of seroprevalence studies indicates significant variation in seroprevalence rates across different World Health Organization (WHO) regions. Specifically, Africa presents the highest seroprevalence at 31% (95% CI 21–41%), followed closely by the Americas at 29% (95% CI 19–39%).(4) Additionally, this study highlights considerable heterogeneity in seropositivity within the Americas, ranging from 13.1 to 57.9% [3, 4]. In the same study, among those surveys that included only children, the pooled seroprevalence was 7%, varying from 0.2 to 53.3%.

In endemic African regions, CHIKV transmission follows a cyclical pattern involving humans, *Aedes* mosquitoes, other mosquito species, and animals, including primates. Outside Africa, major outbreaks primarily involve mosquito–human transmission [5, 6]. These outbreaks are primarily observed during tropical rainy seasons and diminish during the dry seasons. CHIKV is notorious for causing extensive outbreaks, with attack rates ranging from one-third to three-quarters of the population in the affected areas [7–9]. The presence of vectors and infected travelers often introduces the virus into new regions [10–12].

Since its reemergence in coastal Kenya in 2004, the virus has rapidly spread, causing large epidemics and affecting millions of people worldwide [5, 13]. In 2013, the Americas experienced their first cases of locally acquired chikungunya, originating from the Caribbean islands and spreading substantially across the Americas [5–7]. From 2014 to 2016, the United States reported close to 4000 cases, predominantly among travelers from the Americas, specifically the Dominican Republic, Puerto Rico, and Haiti [8]. Notably, the co-circulation of dengue and Zika viruses, which share the same mosquito vectors as CHIKV, has been reported in various regions [9, 10].

CHIKV infection in pregnant persons can result in maternal–fetal transmission [11, 12]. However, the highest risk of transmission to the fetus is noted when maternal symptoms occur close to the time of delivery, with approximately half of such cases resulting in vertical transmission [11]. CHIKV has not been detected in breast milk, and no transmission through breastfeeding has been reported. Therefore, continued breastfeeding is encouraged even in regions affected by the virus [14, 15]. Perinatal transmissions from an infected mother to a child causes fever, apnea, poor feeding, cyanosis, irritability, and other manifestations in the newborn [16, 17]. Neonatal infections present with symptoms such as fever, poor feeding, rash, peripheral edema, and severe complications, including neurological and myocardial manifestations and poor neurocognitive outcomes in some infants. In children, almost 40% of cases are asymptomatic. The most common symptoms are fever, maculopapular rash, headache, vomiting, and joint pain [11, 18]. Cardiac involvement has been described, including myocardial hypertrophy, ventricular dysfunction, pericarditis, and coronary artery dilatation [19].

Among children, it is estimated that 35% of patients fully recover by day 11 of the disease [20]. Long-term sequelae can include neurological involvement with neurocognitive delay, cerebral palsy, blindness, behavioral or postural deficiencies, language delay, deafness, persistent seizures, osteoarticular or muscular-like tenosynovitis with flexion deformity of the thumb, tone abnormalities, arthralgia, progressive sclerosis of digital skin with limited range of motion, and tapering of distal fingertips, among others [20]. Children aged less than five years have the highest risk of CHIKV morbidity. The case fatality rate is approximately 1% and is associated with the development of respiratory distress, cardiac arrest, intraventricular, gastrointestinal or cerebral bleeding, renal failure, cerebral edema, pleural or pericardial effusion, enterocolitis, coma, and collapse of the circulatory system. Death is most frequent among children < 5 years old and those with comorbidities [21]. In the general population, the estimates of deaths exhibit variability, with a case-fatality rate of 0.07% (0.012–1.8%) [22–24].

According to the available data, CHIKV resulted in an annual average loss of more than 106,000 disability-adjusted life years (DALYs) worldwide between 2010 and 2019. The burden was notably higher in the Americas

than in any other World Health Organization (WHO) region (Americas region DALYs 94,995, African region DALYs 888) [24].

Chikungunya vaccine development

Efforts to develop vaccines are currently ongoing, with multiple candidates progressing through various stages of development [25–30]. When writing this protocol, we identified the vaccine candidates using the following vaccine platforms: live attenuated virus, protein subunit, inactivated virus, viral vector, and nucleic acid (see Table 1). Regarding participant demographics, most of the studies include adult healthy participants. Per our revision of the literature available, few studies incorporate participants under 18 years old [31, 32], and no study inclusion criteria allowed pregnant participants [26, 28–30, 33–37]. There is increasing data regarding the safety, immunogenicity, and efficacy of CHIKV vaccines. Live-attenuated vaccine VLA1553 has been shown to provide seroprotective neutralizing antibodies in 99% of participants by 28 days post-vaccination, which persisted in 96% of participants at 180 days [33, 34]. MV-CHIK (a measles-vectored vaccine) induced neutralizing antibodies in 50–100% after one or two doses in non-endemic regions, with immunity persisting for 6 months. VRC-CHKVLP059-00-VP (a virus-like particle CHIKV vaccine) resulted in 88% seroconversion in seronegative adults in endemic regions with immunity lasting for 72 weeks [38]. Phase 3 trials of PXVX0317, an adjuvanted vaccine, are underway [35]. Nucleic acid vaccines, such as VLA-181388, an mRNA vaccine, are in phase 1 trials [37, 39]. Finally, an Inactivated whole virion CHIKV vaccine is also in phase 2b of development (NCT04566484) [40].

Recently, the FDA approved Valneva's IXCHIQ® single-dose, a live-attenuated vaccine for chikungunya prevention in high-risk adults ≥ 18 years based on antibody response, requiring confirmatory studies for continued approval [41].

Further research should focus on examining vaccine efficacy, cross-protection, duration of immunity, safety, and efficacy in diverse populations. Considering the potential for mother-to-child transmission and severe neonatal illness, developing maternal immunization strategies against CHIKV is essential [42]. The Advisory Committee on Immunization Practices (ACIP) recommends the chikungunya vaccine for persons aged ≥ 18 years traveling to a country or territory with a chikungunya outbreak. However, the ACIP noted that Chikungunya vaccination should be deferred until after delivery but may be considered for individuals at increased risk for exposure [43]. As vaccine safety and efficacy data emerge, universal versus risk-based vaccines will become clearer. The safety profiles of various vaccine platforms used for maternal and infant immunization require thorough evaluation to inform future public health strategies.

The main objectives of our study are to assess the safety, efficacy/effectiveness, and immunogenicity of chikungunya vaccine candidates in pregnant persons, children, and adolescents.

Methods

We will develop a living systematic review (LSR) and meta-analysis (MA) of chikungunya vaccine candidates in pregnant persons, children, and adolescents, following the Cochrane and World Health Organization (WHO) methods [44–46] and the PRISMA statement/extension for developing and implementing a living systematic review (LSR) of chikungunya vaccines in pregnant persons, children, and adolescents [47, 48]. Two protocols were registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. One for

Table 1 Chikungunya vaccine candidates

Platform	Developer/manufacturer	Vaccine candidates
Live attenuated	Valneva Austria/Butantan Institute	VLA 1553 / IXCHIQ
	181/clone 25 US Army Medical Research Institute of Infectious Disease, University of Maryland	TSI-GSD-218 (181/clone25)
Protein/subunit	Bavarian Nordic/NIH- PaxVax	PXVX0317
	Emergent biosolutions	CHIKV VLP
	National Institutes of Health Clinical Center (Bethesda, MD, USA)	VRC-CHKVLP059-00-VP
Inactivated	Bharat biotech/BBV87	BBV87/IVICHIK001
Vectored	Themis Bioscience GmbH	MV CHIK 202/206
	National Institute of Allergy and Infectious Diseases (NIAID)/NIH	MV-CHIK
	Oxford University	ChAdOx1 Chik (CHIK001)
Nucleic acid/mRNA	Moderna TX Inc	VAL-181388-P101
	Others	mRNA-1944

pregnant persons (CRD42024514513) and the other for children and adolescents (CRD42024516754). Furthermore, to assess the safety of chikungunya vaccine components, we will also conduct an overview of systematic reviews adhering to the PRISMA guidelines and following the Cochrane methodology.

Literature search strategy

We will conduct searches for the LSR regularly (every 2 weeks) to incorporate new relevant reports as they are released. An experienced librarian will search MEDLINE, the databases of the Cochrane Library, EMBASE, Latin American and Caribbean Health Sciences Literature (LILACS), and 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, FIGO, RCOG), preprint servers (e.g., ArXiv, BiorXiv, medRxiv, search.bioPreprint), regulatory agencies and chikungunya research websites. We will search the databases mentioned above from January 2014 until the end of the project. No language restrictions will be applied. Additionally, we will manually search the reference lists of identified systematic reviews and included studies to locate any relevant studies which were not captured by our search strategy. Ongoing randomized controlled trials will be monitored through Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

Search strategy

Below, we briefly describe the search terms to be used in Medline.

CHIKV vaccines (animals and humans)

(Chikungunya Fever[Mesh] OR Chikungunya[tiab] OR Chikungunya Virus[Mesh] OR CHIKV[tiab] OR VLA-1553[tiab] OR Ixchiq[tiab] OR PXVX0317[tiab] OR BBV87[tiab] OR MV-CHIK 202[tiab] OR MV-CHIK 206[tiab] OR CHIKV VLP[tiab] OR ChAdOx1 Chik[tiab] OR VAL-181388*[tiab] OR VRC-CHKVLP059*[tiab] OR TSI-GSD-218[tiab]) **AND** (Immunization[Mesh] OR Vaccin*[tiab] OR Immunogenicity, Vaccine[Mesh] OR Immun*[tiab]).

CHIKV vaccine for infant, children, and adolescents

(Virus-Like Particle*[tiab] OR VLP[tiab] OR Measles[tiab] OR mRNA[tiab] OR Adenoviral Vector[tiab] OR Inactivated[tiab] OR **Vaccines, Attenuated[Mesh]** OR Recombinant Live-Attenuated[tiab] OR Chimpanzee Adenoviral[tiab] OR Trans-Amplifying RNA[tiab] OR taRNA[tiab] OR Havrix[tiab] OR Engerix-B[tiab] OR Twinrix[tiab] OR Hepatitis A Vaccines[Mesh] OR Hepatitis A Vaccin*[tiab] OR Recombivax[tiab] OR Vaqta[tiab] OR Comvax[tiab] OR Pediarix[tiab] OR Alhydrogel[tiab] OR Aluminum*[tiab] OR Influenza Vaccines[Mesh] OR Influenza Vaccine*[tiab] OR Flu Vaccine*[tiab] OR Dynavax[tiab] OR Hepatitis B Vaccines[Mesh] OR Hepatitis B Vaccin*[tiab] OR HEPLISAV-B[tiab]) **OR** (Immunization[Mesh] OR Immunization*[tiab] OR Immunisation*[tiab] OR Vaccin*[tiab] OR Immunogenicity, Vaccine[Mesh]) **AND Vaccines, Attenuated[Mesh]** OR Recombinant Live-Attenuated[tiab]) **AND** (Immunization[Mesh] OR Immunization*[tiab] OR Immunisation*[tiab] OR Vaccin*[tiab] OR Immunogenicity, Vaccine[Mesh]) **AND** (**Infant[Mesh]** OR Infant*[tiab] OR **Stillbirth[Mesh]** OR Stillbirth*[tiab] OR Neonat*[tiab] OR Newborn*[tiab] OR Pediatric*[tiab] OR Paediatric*[tiab] OR Child*[tiab] OR Toddler*[tiab] OR Babies[tiab] OR Preschool[tiab] OR **Adolescent[Mesh]** OR Adolescen*[tiab] OR Teenage*[tiab] OR Teens[tiab] OR Youth*[tiab]) **= > 2014.**

CHIKV vaccine components for mothers

((Virus-Like Particle*[tiab] OR VLP[tiab] OR Measles[tiab] OR mRNA[tiab] OR Adenoviral Vector[tiab] OR Inactivated[tiab] OR Vaccines, Attenuated[Mesh] OR Recombinant Live-Attenuated[tiab] OR Chimpanzee Adenoviral[tiab] OR Trans-Amplifying RNA[tiab] OR taRNA[tiab] OR Havrix[tiab] OR Engerix-B[tiab] OR Twinrix[tiab] OR Hepatitis A Vaccines[Mesh] OR Hepatitis A Vaccin*[tiab] OR Recombivax[tiab] OR Vaqta[tiab] OR Comvax[tiab] OR Pediarix[tiab] OR Alhydrogel[tiab] OR Aluminum*[tiab] OR Influenza Vaccines[Mesh] OR Influenza Vaccine*[tiab] OR Flu Vaccine*[tiab] OR Dynavax[tiab] OR Hepatitis B Vaccines[Mesh] OR Hepatitis B Vaccin*[tiab] OR HEPLISAV-B[tiab]) **AND** (Immunization[Mesh] OR Immunization*[tiab] OR Immunisation*[tiab] OR Vaccin*[tiab] OR Immunogenicity, Vaccine[Mesh]) **AND** (Pregnancy[Mesh] OR Pregnan*[tiab] OR Pregnancy Complications[Mesh] OR Abortion, Spontaneous[Mesh] OR Abortion*[tiab] OR Miscarriage*[tiab] OR Gestational[tiab] OR Parturition[Mesh] OR Childbirth*[tiab] OR Parturition*[tiab] OR Partum[tiab] OR Fetus[Mesh] OR Fetal[tiab] OR Fetus[tiab] OR Maternofetal[tiab] OR Materno Fetal[tiab] OR Fetomaternal[tiab] OR Feto Maternal[tiab] OR DART[tiab])) **AND** (Pregnancy[Mesh] OR Pregnan*[tiab] OR Pregnancy Complications[Mesh] OR Abortio **AND** (Vaccines, Attenuated[Mesh] OR Recombinant Live-Attenuated[tiab])).

Study designs

We will include clinical trials, quasi-experimental, and observational (comparative and non-comparative) study designs, irrespective of publication status, publication year, and language to incorporate real-world evidence (RWE). We will consider randomized controlled trials (RCTs) (all phase I, II, or III trials involving human subjects), 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. Phase IV studies, cohort studies, case–control studies, cross-sectional studies, and case series will also be considered. We will only consider case reports of previously unknown or unexpected adverse events. Preclinical studies assessing outcomes of interest in animals will also be included.

Types of participants

Study participants will be newborns, infants, children, adolescents, and pregnant persons and their fetuses, irrespective of prior exposure to CHIKV, immune status, comorbidities, and risk group. Observational studies reporting safety and efficacy or effectiveness outcomes with at least 50 subjects and immunogenicity studies with samples of at least ten subjects will be included. We will include case reports of infrequent adverse events. Animal studies will be included as indirect evidence of populations under study. General adult population data will be included to capture any data related to pregnant individuals.

Types of interventions

Chikungunya candidate and licensed vaccines, vaccine platforms, or adjuvants present in chikungunya candidate and licensed vaccines and used in other human vaccines (antigen, vehicle, construct, adjuvants, other components) regardless of the dose and schedule.

Types of comparisons

Any comparison group will be considered, whether it involves standard care, lack of intervention, a different chikungunya vaccine, or any other comparator, irrespective of co-interventions. Additionally, non-comparative studies assessing safety outcomes will be included; for these outcomes, a comparison group will not be obligatory.

Measures of effect

Odds ratios (ORs), Risk ratios (RRs), and Hazard ratios (HRs) with 95% confidence intervals (95% CIs) will be extracted for dichotomous outcomes, and Mean Difference (MD) or Standardized MD (SMD) will be extracted for continuous outcomes. We will report Vaccine efficacy/effectiveness (VE) for relevant clinical trials (of efficacy) and post-implementation observational studies (of effectiveness). We will also calculate proportions with 95% CIs for non-comparative studies.

Primary outcomes

Following immunization of pregnant persons

Safety outcomes

(a) Obstetric/neonatal outcomes after maternal vaccination.

We will use the standardized case definitions developed by the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project of prioritized obstetric and neonatal outcomes based on the standard Brighton Collaboration process and the Safety Platform for Emergency vACcines (SPEAC) guidance (https://brightoncollaboration.org/speac/). The outcomes include, but not limited to, are listed elsewhere [49].

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

Regarding SAEs, we will focus on outcomes related to fetal loss—including SAB/miscarriage and stillbirth, neonatal mortality rate, infant mortality rate, maternal mortality rate and hospitalization for severe myalgia, hypovolemic hyponatremia, or atrial fibrillation.

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

The outcomes are informed by SPEAC guidance and include (but are not limited to): Arthritis/arthralgia, late/delayed adverse event in newborns associated with chikungunya vaccination during pregnancy.

Others: GBS, facial nerve (Bell's) palsy, anaphylaxis, encephalomyelitis, narcolepsy, appendicitis, non-hemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction (AMI), myocarditis and pericarditis, deep vein thrombosis (DVT), thrombosis, pulmonary embolism, disseminated intravascular coagulation (DIC), immune thrombocytopenia (ITP), transverse myelitis, thrombosis with thrombocytopenia (TWT), hemorrhage, sensorineural hearing loss (SNHL), puerperal sepsis, hepatitis, anemia, acute kidney injury.

Efficacy/effectiveness in the prevention of chikungunya infection according to the WHO-suggested case definition

(a) Confirmed, probable, or suspected.

Chikungunya infection can be classified as confirmed, probable, or suspected based on the WHO case definition (Table 2) [50]. The evaluation of vaccine efficacy or effectiveness includes its impact on maternal and neonatal infection, severe disease, and mortality due to chikungunya.

(b) Confirmed chikungunya hospitalization.
(c) Other complications attributed to chikungunya.

Immunogenicity

(a) Cellular and humoral immune 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.

A) Cellular and humoral immune 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).

Others Case fatality rate (CFR) in mothers.

Following immunization of infants, children and adolescents

Safety outcomes We will use the standardized case definitions developed by the GAIA project of prioritized outcomes based on the standard Brighton Collaboration process and SPEAC guidance (https://brightoncollaboration.org/speac/). The outcomes include (but are not limited to):

(a) **Serious adverse events (SAEs) and all-cause mortality related to vaccination.** SAEs such as infant, children, and adolescent mortality rate and hospitalization for severe myalgia, hypovolemic hyponatremia, or atrial fibrillation.
(b) **Adverse events (AEs) of Special Interest (AESI) post-vaccination in children.** Adverse events of special interest (AESI) post-vaccination: arthritis/ arthralgia, GBS, facial nerve (Bell's) palsy, anaphylaxis, encephalomyelitis, narcolepsy, appendicitis, non-hemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction (AMI), myocarditis and pericarditis, deep vein thrombosis (DVT), pulmonary embolism, disseminated intravascular coagulation(DIC), immune thrombocytopenia(ITP), transverse myelitis, and the occurrence of thrombosis with thrombocytopenia(TWT), psychiatric disorder, syndrome of inappropriate antidiuretic hormone secretion [SIADH], laboratory tests [including blood cells counts (white cells, red and platelets) and transaminases].

Efficacy/effectiveness in the prevention of chikungunya infection according to the WHO-suggested case definition

(a) Confirmed, Probable or Suspected (WHO case definition) see Table 2.
(b) Confirmed chikungunya hospitalization.
(c) Other complications attributed to chikungunya vaccination in children.

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 serum after primary and/or booster scheme.

Table 2 Chikungunya case definition

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 prior to the onset of symptoms
Laboratory criteria	Virus isolation Presence of viral RNA by RT-PCR Presence of virus-specific IgM antibodies in single serum sample collected in acute or convalescent stage Four-fold increase in IgG values in samples collected at least 3 weeks apart
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

Others Case fatality rate (CFR) in children.

Secondary outcomes

(a) Viremia after vaccination: presence, magnitude, and duration of viremia in mother, newborn, infant, child, and adolescent.
(b) Asymptomatic chikungunya infection after vaccination: determined by antibody or antigen detection in asymptomatic individuals.
(c) Mother-to-child transmission: Presence and persistence of CHIKV (viral load, protective antibodies) in the placenta, fetal tissues, amniotic fluid, cord blood, vaginal fluids, breast milk, or neonatal throat swabs.

Data extraction and management

Selection

Pairs of reviewers will independently screen each title and abstract and any potentially relevant full-text studies and reports will be **retrieved**. These will be independently selected, and any exclusion criteria will be documented for ineligible studies. Any disagreements will be resolved through review team discussions. This process will be performed using the web-based software Nested Knowledge (https://nested-knowledge.com/).

Data collection

Data collection and storage will be managed using REDCap electronic data capture tools [51], hosted on the servers of the Institute for Clinical Effectiveness and Health Policy in Buenos Aires, Argentina. A preliminary data extraction will be conducted on a sample of at least ten studies before the formal process begins. Two review authors will independently extract data from the studies included in the review using a REDCap form, and any disagreements will be addressed through discussion with the review team. We will reach out to the study corresponding authors via e-mail to clarify any missing data or clarification. Information on funding sources will be collected for each study included.

Risk of bias assessment

Each study will be assessed based on its design and relevant bias domains. For randomized controlled trials, we will use the Cochrane risk of bias tool—version 2 (RoB2), which includes five domains: randomization process, deviation from intended interventions, missing outcome data, measurement of outcomes, selective reporting of results, and overall assessment of the risk of bias [51]. For non-randomized studies of interventions, we will use the ROBINS-I tool [52]. For controlled before-after studies, we will evaluate baseline measurements, participant characteristics (for studies using a second site as a control), blinding of primary outcome assessment, reliability of primary outcome measures, follow-up of professionals (to mitigate exclusion bias), and follow-up of patients. We will apply the same criteria for uncontrolled before-after studies, except for baseline measurements and participant characteristics related to a second-site control. IFor interrupted time series, we will evaluate the risk of bias in seven areas: intervention being independent of other changes, predetermined shape of the intervention effect, intervention´s limited impact **on** data collection, blinding of outcome assessors, incomplete outcome data, selective reporting of outcomes, and other potential sources of bias. For controlled interrupted time series 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 contamination. For non-comparative studies, we will use the NIH Quality Assessment Tool [53]. After answering to the various signaling questions—*yes, no, cannot determined, not applicable, or not reported*—the reviewers will categorize the study quality as good, fair, or poor. We will use the classifications low, high, or unclear risk of bias for consistency with the other designs. We will present GRADE certainty of evidence in the 'Summary of findings' tables.

Data synthesis plan

Provided that data are available and methodologically suitable, we will perform aggregate meta-analyses for each comparison in accordance with the Cochrane Handbook of Systematic Reviews of Interventions, employing random-effects meta-analysis for the primary analysis. Proportional meta-analyses will be performed to summarize frequencies from 1-sample studies. R statistical software [54] will be used to analyze the data. Meta, Metafor [50] and Tidyverse are the main packages selected for data analyses [55]. Hazard ratios, risk ratios, or odds ratios along with their corresponding 95% confidence intervals (95% CI) will be computed for dichotomous outcomes, whereas mean differences or standardized mean differences will be determined for continuous outcomes. Additionally, we will determine proportions with 95% CI for non-comparative studies. For reporting efficacy/effectiveness outcomes, we will convert other measures into vaccine efficacy whenever feasible. We will prioritize adjusted effect measures (e.g., by age, region,

etc.) over unadjusted estimates. Heterogeneity will be explored through subgroup analyses.

Subgroup analysis

We will perform the following prespecified subgroup analyses when analyzing the primary outcomes:

- Country income level (high or low and middle-income country).
- Region (based on the Institute for Health Metrics and Evaluation categorization).
- Pre-specified subgroups by pregnancy trimester (first, second, or third trimester).
- Age range of pediatric participants (0–27 days, 28 days–1 year, 0–4 years, 5–11 years, 12–17 years).
- Chikungunya vaccine administered.
- Vaccine platform.
- Dominant Chikungunya virus variants.
- Study design.

Sensitivity analysis

Additional sensitivity analyses will be undertaken by excluding high-risk bias studies.

Data visualization

We will use an online interactive dashboard for data visualization using Microsoft Power BI. The most relevant variables will be selected among pregnant individuals, infants, and children, and safety and effectiveness outcomes will be presented in figures and tables. Data visualization will be delivered by primary series (complete and incomplete)/booster vaccine. Since this project is an LSR, the living meta-analysis section will be accessible to users as an interactive tool created as a Shiny application using R Studio [56]. The application will allow the users to display meta-analyses of interest by selecting filters (age, region, vaccine platform and doses, among others). Subgroup analyses will be available. The research team will develop an algorithm to select the endpoints for each study included in the living meta-analysis. A validation process will be carried out by the researchers to ensure the accuracy of the endpoint selection algorithm.

Discussion

This living systematic review is designed to continuously incorporate new evidence on chikungunya vaccines, ensuring that emerging data are promptly evaluated and integrated into the analysis. Given the rapidly evolving landscape of vaccine development, maintaining an updated synthesis of evidence is crucial for informing public health policies and clinical recommendations. The living systematic review framework allows for real-time modifications and timely dissemination of findings as additional studies become available. Unlike traditional systematic reviews, which provide static assessments, the living systematic review framework enables real-time updates and rapid dissemination of findings as new studies emerge, ensuring continuous relevance and applicability.

A comprehensive search strategy spanning multiple databases strengthens the robustness of this review. By systematically biweekly identifying and including relevant studies across diverse sources, the risk of missing critical data is minimized, thereby enhancing the completeness and reliability of the analysis. The inclusion of randomized controlled trials, observational studies, and case reports will facilitate a thorough examination of vaccine safety, efficacy, effectiveness in real world and immunogenicity in our population.

This protocol adheres to rigorous methodological standards, following PRISMA guidelines and incorporating validated tools for risk of bias assessment. Ensuring methodological transparency and consistency enhances the credibility of the findings and allows for reproducibility. Additionally, the use of sensitivity analyses will help address potential biases and methodological heterogeneity among included studies, thereby improving the accuracy of pooled estimates.

A key strength of this review is its inclusion of diverse populations, including children and pregnant persons. Given the heightened risk of severe chikungunya disease in these populations, evaluating vaccine safety, efficacy and effectiveness within these subgroups is essential. The findings will provide valuable insights into the differential immunogenicity, adverse event profiles, and potential vertical transmission risks associated with chikungunya vaccination.

Despite its strengths, this review faces potential challenges, primarily due to variability in study quality and heterogeneity across vaccine platforms. Differences in study design, vaccine formulations, dosing regimens, and population characteristics may complicate the synthesis of findings. However, pre-specified subgroup analyses and sensitivity assessments will be conducted to address these variations and ensure the robustness of conclusions drawn from the data by an expert team.

In conclusion, this living systematic review will be a critical resource for stakeholders involved in vaccine policy, maternal-child health, and global infectious disease prevention. By continuously updating the evidence base, this review aims to support informed decision-making

regarding chikungunya vaccine deployment, particularly in populations at most significant risk.

Abbreviations

CHIKV	Chikungunya Virus
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
SAE	Serious adverse events
AESI	Adverse events of special interest
LSR	Living systematic review
RCT	Randomized controlled trial
WHO	World Health Organization
DALYs	Disability-adjusted life years
ACIP	Advisory Committee on Immunization Practices
GRADE	Grading of recommendations, assessment, development, and evaluation
GAIA	Global Alignment of Immunization Safety Assessment in Pregnancy
SPEAC	Safety platform for emergency vaccines
PROSPERO	International Prospective Register of Systematic Reviews
ICTRP	International Clinical Trials Registry Platform
CI	Confidence interval
HR	Hazard ratio
RR	Risk ratio
OR	Odds ratio
GMT	Geometric mean titer
VE	Vaccine efficacy/effectiveness
NIH	National Institutes of Health
CDC	Centers for Disease Control and Prevention
EMA	European Medicines Agency
FDA	Food and Drug Administration
ITS	Interrupted time series
CITS	Controlled interrupted time series
DIC	Disseminated intravascular coagulation
ITP	Immune thrombocytopenia
TWT	Thrombosis with thrombocytopenia
CFR	Case fatality rate

Author contributions

All authors contributed to the conception and design of this study.MB, AC, AM, JB, AB, JMS, MB, KS, DC, EPKP, AS, XX, FMM, and PMB contributed equally to the conception and design of this study. MB, AC and JB wrote the main manuscript text. All authors reviewed the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics and dissemination

Ethical approval is not required for this study, given that this is a protocol for a systematic review and meta-analysis using published data. The systematic review and living meta-analysis results will be widely disseminated via the online dashboards described above. One or more summary papers will be submitted to a leading peer-reviewed journal in this field, adhering to the PRISMA statement/extension for reporting LSR. (56).

Consent for publication

Not applicable. This study does not involve individual patient data or identifiable personal information requiring consent for publication.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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