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REVIEW

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Umbrella review of the safety of Chikungunya vaccine platforms used in other vaccines

Ariel Bardach[a], Martin Brizuela[b], Mabel Berrueta[c], Agustín Ciapponi[d], Juan M. Sambade[b], Jamile Ballivian[b], Vanesa Ortega[c], Noelia Castellana[b], Daniel Comandé[b], Edward P. K. Parker[e], Beate Kampmann[f,g], Katharina Stegelmann[b], Xu Xiong[h], Andy Stergachis[i], Flor M. Munoz[j], Pierre Buekens[h], and Agustina Mazzoni[b]

[a]Center for Research in Epidemiology and Public Health (CIESP-IECS), CONICET, Buenos Aires, Argentina; [b]Department of Health Technology Assessment and Economic Evaluations, Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina; [c]Department of Mother and Child Health, Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina; [d]Argentine Cochrane Center, Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina; [e]The Vaccine Centre, London School of Hygiene & Tropical Medicine, Keppel Street, London, UK; [f]Health Protection Research Unit in Immunisation, London School of Hygiene & Tropical Medicine, London, UK; [g]Charite Centre for Global Health, Charité, Universitätsmedizin, Vaccine Centre, Berlin, Germany; [h]School of Public Health and Tropical Medicine, Tulane University, New Orleans, USA; [i]Schools of Pharmacy and Public Health, University of Washington, Seattle, USA; [j]Departments of Pediatrics and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, USA

ABSTRACT

Chikungunya virus (CHIKV), transmitted through *Aedes* mosquitoes, is a significant global health concern. Various vaccine platforms have been explored to combat CHIKV, including formalin inactivation, live-attenuated strains, virus-like particles (VLPs), viral vectors, and mRNA technologies. This umbrella review synthesizes evidence on the safety profiles of vaccine platforms used in Chikungunya vaccines that have been applied in other vaccines, focusing on adverse events of special interest (AESI) in pregnant persons, children, and adolescents. A comprehensive overview of systematic reviews (SRs) was conducted. Results: Seven systematic reviews were included and complemented with primary studies. Vaccines like influenza, human papillomavirus (HPV), and COVID-19, which share platforms with Chikungunya vaccines, showed no significant increase in AESI. Moderate-to high-quality SRs supported favorable safety profiles. Vaccines sharing platforms with Chikungunya vaccines generally exhibit acceptable safety profiles in pregnant persons, children, and adolescents.

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Chikungunya; vaccine safety; adverse events; pregnant persons; children and adolescents; vaccine platforms

Background

Chikungunya virus (CHIKV), first identified in Tanzania in 1952, has become a significant global health concern. Its geographical distribution is closely aligned with its primary vector, *Aedes albopictus*, and transmission occurs through *Aedes* mosquito saliva.[1] While maternal-fetal transmission has been documented, it has not shown significant impacts on pregnancy and birth outcomes.[2,3]

Various vaccine platforms have been explored to combat CHIKV, including formalin inactivation, live-attenuated strains, virus-like particles (VLPs), viral vectors, and mRNA technologies.

Early efforts in the 1960s and 1970s focused on formalin and UV-inactivated vaccines, but these did not progress beyond the initial stages of clinical development.[4] A phase I clinical trial evaluated the inactivated chikungunya vaccine BBV87 in healthy adults in India, with a good safety profile.[5] Other phase II and III clinical trials are ongoing in Colombia, Panama, Thailand, Guatemala and Costa Rica, including participants between 12 and 65 years old.[6–8]

The first live-attenuated candidate, 181/clone25, developed by the U.S. military in 1985, has not been tested in clinical studies since 2005.[9] Recent phase 2 and 3 clinical trials, including healthy adults between 18 and 60, have shown promising results for several vaccine candidates.[10,11]

The live-attenuated vaccine VLA1553 is the only vaccine approved by the Food and Drugs Administration (FDA) from the United States and the European Medicines Agency (EMA). Phase 2 and 3 clinical trials where it was studied have not shown serious adverse events among adults[12,13] and adolescents.[14,15]

Virus-like particles (CHIKV VLPs) have been studied in a phase I clinical trial.[16] A recent phase III trial, which included participants between 12 and 64 years old, showed favorable safety and immunological profiles.[17]

Viral-vectored vaccines include MV-CHIK, based on the Schwarz strain of the measles vaccine, which showed good safety and tolerability profiles with no serious adverse events in phase 2 clinical trials[10,18] and the ChAdOx1, which used an adenoviral vector in a phase 1 clinical trial.[6,18]

Vesicular stomatitis virus-vectored vaccine (VSVΔG-CHIKV) safety data indicated no serious adverse reactions at any tested dose. Modified Vaccinia virus Ankara-vectored vaccine (MVA-CHIK) is a highly attenuated poxvirus-based candidate that has not yet entered clinical trials.[19]

CONTACT Ariel Bardach abardach@iecs.org.ar Center for Research in Epidemiology and Public Health (CIESP-IECS), CONICET, Emilio Ravignani 2024, Buenos Aires C1414CPV, Argentina.

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Finally, an mRNA vaccine (mRNA-1388 or VAL-181388) is a single mRNA construct encoding the complete native structural polyprotein of CHIKV that requires further evaluation. A phase 1 clinical trial has evaluated safety and immunogenicity in healthy adults.[20,21] In a recent systematic review and meta-analysis, Rosso et al. detailed that the vaccines against CHIKV in development have shown an acceptable overall safety profile.[22]

Ongoing research focuses on developing vaccines and antivirals, particularly virus-encoded replication proteins, as potential therapeutic targets. CHIKV vaccines are in different stages of clinical development, but evidence is currently lacking on safety in key populations, including pregnant persons, children, and adolescents. On the other hand, these vaccines use platforms that have been implemented more widely, offering preliminary insights into the potential safety profile of CHIK vaccine candidates that may progress to widespread implementation. This correlation of platforms allows researchers to draw on safety and efficacy data from similar vaccine technologies, potentially streamlining the development and approval process for Chikungunya vaccines.

Objective

The primary objective of this overview is to identify and synthesize evidence on the platforms used in Chikungunya vaccines that have been applied in other vaccines, with particular attention to their safety profiles. The outcomes of interest were adverse events of special interest (AESI)[23] associated with these vaccines in specific populations, namely pregnant persons, children, and adolescents under 18.

Methods

Study design

We conducted an overview of systematic reviews, adhering to the PRISMA guidelines[24] and following the Cochrane methodology.[25]

Studies eligibility criteria

We included meta-analyses complemented by systematic reviews (SRs)[26] without meta-analysis (if a meta-analysis was unavailable for a specific vaccine). To be included, SRs had to meet the following criteria regarding population, exposure, comparators, and outcomes.

The included population were pregnant persons, children up to 12 years old, and adolescents between 12 and 18 years old.

Exposures of interest were defined as the platforms of Chikungunya vaccines. The development of Chikungunya vaccines has provided safety and efficacy data through different phase 1, 2, and 3 clinical studies. The platforms underlying specific Chikungunya vaccine candidates have been more widely implemented in the context of vaccines targeting other diseases. The selection of relevant vaccine platforms was based on similarities in technology and design with Chikungunya vaccines in development. Due to their comparable technology, Chikungunya mRNA vaccines were correlated with COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2). Viral vector vaccines using measles virus vectors were correlated with measles, MMR (measles, mumps, rubella), or MMRV (measles, mumps, rubella, varicella) vaccines. Viral vector vaccines using ChAdOx1 adenovirus vector were correlated with the ChAdOx COVID-19 vaccine (Oxford-AstraZeneca). In the case of the live-attenuated vaccine VL1553, no direct safety proxy was found, as the safety profile is dependent on the characteristics of the attenuated Chikungunya virus. Virus-like particles (VLP), considered a protein subunit platform, were correlated with similar vaccines for Hepatitis B, HPV, and Hepatitis E. The inactivated vaccine platform was correlated with other inactivated virus vaccines, including Influenza A H1N1 monovalent, combined Hepatitis A and B vaccine, and inactivated COVID-19 vaccines (Sinopharm, Covaxin, and Coronavac). Finally, the vesicular stomatitis virus-based vaccine was correlated with the Ebola vaccine platform, which uses a similar approach. The evaluated vaccines were chosen based on the clinical judgment of the study team and validated by the steering committee research committee's criteria.

For pregnant persons, vaccines of interest were Hepatitis B vaccine (recombinant), HEV 239 (Hepatitis E), Influenza A (H1N1) 2009 Monovalent, COVID-19, Hepatitis A virus (HAV), HPV, and Flublok Quadrivalent. For children and adolescents under 18 years old, vaccines of interest included HPV, Hepatitis B vaccine (recombinant), HAV, Influenza A (H1N1) 2009 Monovalent, Sinopharm (COVID-19), Coronavac (COVID-19), Covaxin (COVID-19), Oxford-AstraZeneca COVID-19 vaccine, BNT162b2 (COVID-19) mRNA-1273 (COVID-19), M (measles), MMR (measles, mumps, rubella), MMRV (measles, mumps, rubella, varicella), Ervebo, V920 (Ebola vaccine).

We included SRs with comparative and non-comparative studies. Comparators were active or inactive without the interventions under study, usual care, or placebo. The outcomes of interest were the following selected subgroup of AESIs: generalized convulsion, Guillain-Barré Syndrome (GBS), acute disseminated encephalomyelitis (ADEM), thrombosis with thrombocytopenia syndrome, anaphylaxis, vasculitides, aseptic meningitis, encephalitis, encephalomyelitis, acute aseptic arthritis, myocarditis, abortion, stillbirth, maternal death, neonatal encephalopathy, and neonatal death. These AESIs were selected from the list published by the Safety Platform for Emergency Vaccines (SPEAC) group based on three criteria: known association with immunization or a specific vaccine platform, occurrence during wild-type disease as a result of viral replication and/or immunopathogenesis, and a theoretical association based on animal models. The final list of outcomes was selected from the SPEAC list by our Scientific and Technical Advisory Group, considering those outcomes reported from vaccines that share the same platforms as the Chikungunya vaccines. The selection aimed to identify potential safety signals that warrant close monitoring during clinical development and post-authorization surveillance of Chikungunya vaccines.

Search strategy

An experienced librarian searched PubMed, Embase, LiLACS, Cochrane Library, and Web of Science databases. The search focused on systematic reviews with meta-analysis, without a publication time limit, encompassing the development of

vaccines for Chikungunya and other related viral diseases. The search strategy included terms related to Chikungunya, vaccines, AESI, and the target populations.

Study selection, data extraction, and quality appraisal

Pairs of reviewers independently screened titles and abstracts. We retrieved all potentially relevant full-text studies, and two reviewers independently evaluated the full texts, recording the reasons for excluding the ineligible studies. Disagreements were resolved through discussion with the review team. This process was performed using the web-based software COVIDENCE.[27] Also, pairs of reviewers independently performed the first data extraction through an online form previously piloted in five studies. We recorded the publication date, study design, number of included studies, quality items, population, vaccines, comparisons, and outcomes. Pairs of reviewers (VO, MB) independently assessed the quality of SRs through the AMSTAR-2 tool.[28] The instrument has 16 items, and it is not intended to generate an overall score. Nonetheless, it provides a categorical rating based on critical domains: protocol register, adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies being included, appropriateness of meta-analytical methods, consideration of the risk of bias when interpreting the results, assessment of publication bias. The overall quality or confidence in the results of the review can be rated as "high" (no or one non-critical weakness), "moderate" (more than one non-critical weakness), "low" (one critical flaw with or without non-critical weaknesses), and "critically low" (more than one critical flaw with or without non-critical weaknesses). Two reviewers (VO, MB) independently extracted data on selected SRs using a predefined extraction form, including the pooled measure, its confidence interval, and whether safety concerns were identified. Discrepancies were resolved by consensus.

When multiple meta-analyses were identified for a particular vaccine, the most appropriate one was selected based on the following sequential criteria: (1) inclusion of the largest number of relevant outcomes, (2) inclusion of the largest number of studies, (3) quality of the systematic review as assessed by AMSTAR 2, and (4) the most recent publication date. All were included in cases where more than one high-quality systematic review addressed different outcomes for the same vaccine. If a systematic review was excluded for reporting fewer outcomes, but those outcomes were considered important, they were incorporated into the discussion. We included the effect measure expressed by OR or RR (adjusted when available) for comparative studies. For non-comparative studies, where information provided was expressed by incidence rates, we used background rates of those outcomes reported in the literature.

Ethical considerations

This overview does not involve primary data collection with human subjects and, therefore, does not require ethical approval.

Results

The search strategy is shown in Supplementary Table S1. The search retrieval was 954 articles. After removing duplicates, 890 articles were assessed by title and abstract. One hundred forty full-text articles were evaluated for eligibility, and seven SRs were finally included (Figure 1. PRISMA).

The included studies and the list of excluded studies with their exclusion reasons are shown in Table 1, and Supplementary Table S2, respectively. This overview summarizes the characteristics of systematic reviews focusing on vaccine safety. The analysis encompasses various aspects of the included reviews, providing insights into their methodological quality, vaccine types, target populations, and assessed outcomes. The overview includes systematic reviews with meta-analyses, including one Cochrane review. The methodological quality of the selected systematic reviews, as evaluated by the AMSTAR 2 tool (Supplementary Table S3), varied across the spectrum from high to critically low, indicating a range in the rigor of the review processes. The reviews covered various vaccines, including hepatitis B, HPV, influenza, COVID-19, measles, mumps, rubella, and varicella (MMRV). Notably, some vaccines, such as hepatitis E, standalone measles, and MMR, were not represented in the included reviews. We included five reviews for pregnant persons and three with children and adolescents. Key outcomes included neurological (generalized convulsion, Guillain-Barré Syndrome, acute disseminated encephalomyelitis, aseptic meningitis, encephalitis), cardiovascular (myocarditis), immunological (anaphylaxis), hematological (thrombosis with thrombocytopenia syndrome), pregnancy-related (abortion, stillbirth, maternal death, neonatal encephalopathy, and neonatal death), and musculoskeletal (acute aseptic arthritis). It is worth noting that some potential adverse events, such as vasculitides, and encephalomyelitis, were not explicitly addressed in the included reviews.

After applying the inclusion criteria described in Methods, we chose the most appropriate one for each condition (Table 2 and 3). Five SRs were selected for the pregnant population and three for children and adolescents. Supplementary Table S4 shows outcomes of interest and their respective background rates from the literature.

Table 2 summarizes meta-analyses on outcomes in pregnant persons receiving various vaccines sharing components with those of Chikungunya vaccines, highlighting studies on Influenza A H1N1, Influenza Quadrivalent, HPV, and COVID-19 vaccines.

For the Influenza A H1N1 vaccine, Zhang[29] analyzed data from 19 studies involving three comparative cohort studies on abortion and 11 on stillbirth, involving 8,025 and 171,906 pregnant persons, respectively, with an inactivated virus platform. The results showed an adjusted risk ratio (aRR) of 1.04 (95% CI: 0.72–1.52) for abortion and an adjusted hazard ratio (aHR) of 0.80 (95% CI: 0.69–0.92) for stillbirth, both with critically low AMSTAR-2 quality ratings and no reported safety concerns. Similarly, Gidengil investigated the Influenza Quadrivalent vaccine through a single RCT, reporting non-significant risk ratios for both abortion (RR 0.67; 95% CI: 0.02–19.79) and stillbirth (RR 1; 95% CI: 0.06-16-04), also

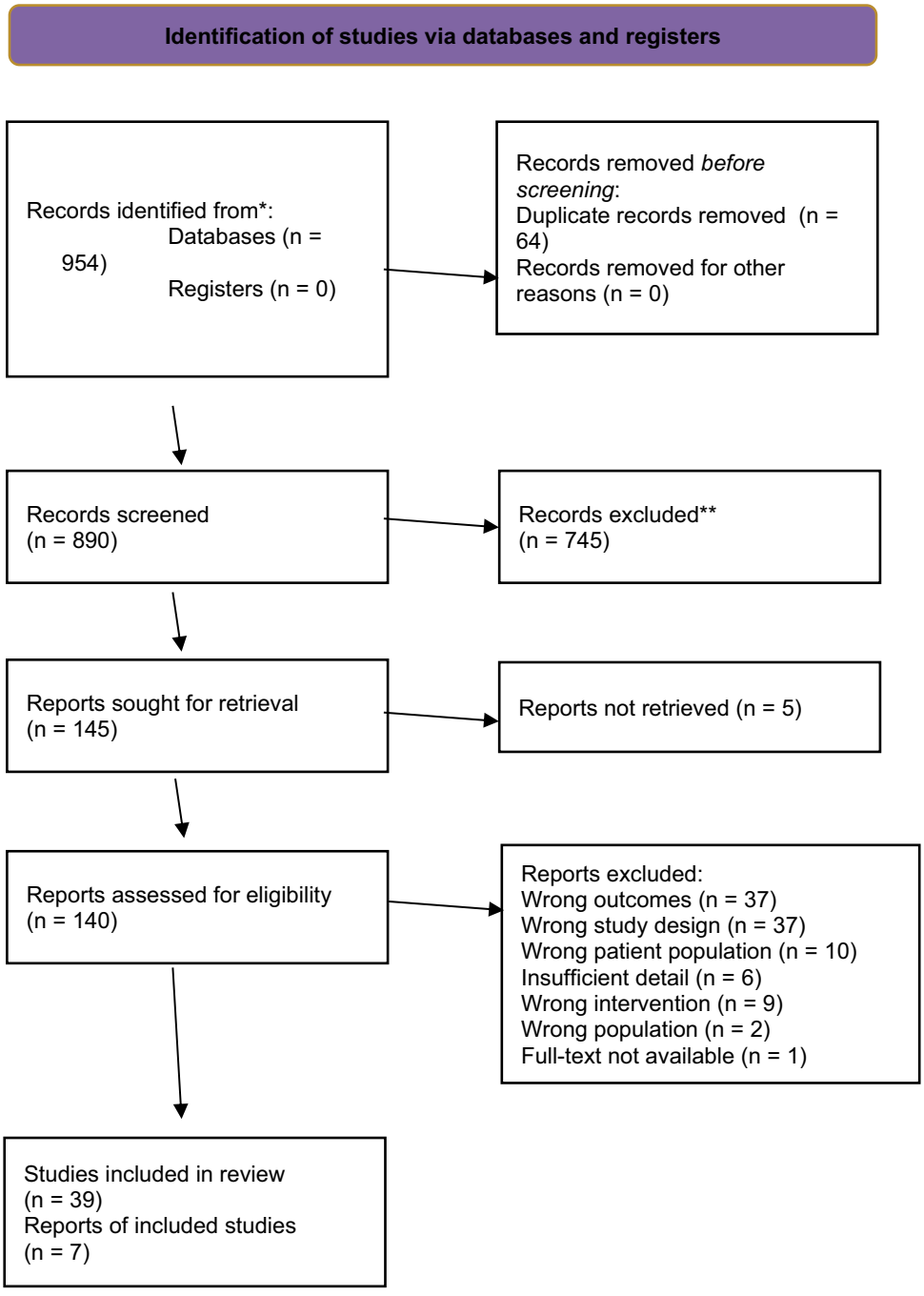

Figure 1. PRISMA 2020 study flow diagram.

with no safety concerns.[34] For the outcome of maternal death, we found a Cochrane systematic review with a high AMSTAR 2 quality. Salam et al., another SR, included a single trial on viral influenza vaccine placebo-controlled. They report no clear difference between the viral influenza and placebo control group for maternal death (RR 4.96; 95% CI: 0.24 to 103.24), with moderate quality evidence.[36]

Regarding the HPV vaccine, Yan included 12 studies with protein/subunit platform, with abortion data from 11 comparative cohort studies and RCTs involving 56,384 pregnant persons and stillbirth data from 7 studies involving 9,872 women. The results showed RRs around unity for both abortion and stillbirth across different study types, rated low in quality by AMSTAR-2, with no specific safety concerns mentioned.[36]

Ciapponi et al. extensively reviewed the COVID-19 vaccines, compiling data from 177 observational studies, mainly mRNA vaccines (154 studies), viral vectors (51 studies), and inactivated virus vaccines (17 studies). Key outcomes included non-significant association with abortion (OR 0.91; 95% CI: 0.70–1.20) and stillbirth (OR 0.49; 95%CI: 0.2–1.19). There was no significant increase in the occurrence of critical neonatal outcomes such as neonatal death, measured at 0 (95% CI, 0–15) per 1,000, or neonatal encephalopathy, at 0 (95% CI, 0–0.15) per 1,000, when compared to global background rates of 17.55 (95% CI,16.56–19.46) per 1,000 and 3 (95% CI, 2.7 to

Table 1. Characteristics of included systematic reviews ($N = 7$).

	Number of studies	References
Review type		
SR + MA	6	29,30,32–35
Cochrane Review	1	31
Platform		
mRNA		
COVID-19: mRNA-1273 and BNT162b	2	32,33
Viral vector (measles)		
Measles	0	31
MMR*	0	
MMRV**	1	
Viral vector (adenovirus)		
COVID-19 ChAdOx	3	30,32,33
Virus-like particles (VLP)		
HBV	1	34
HPV	2	34,35
HEV	0	
Inactivated		
Influenza A H1N1 monovalent	2	29,34
HAV/HBV	1	34
COVID-19 (Sinopharm, Covaxin, Coronavac)	2	32,33
Vesicular stomatitis virus		
Ebola	0	
Population		
Pregnant persons	5	29,30,33–35
Children and adolescents	3	31,32,34
Outcomes assessed #		
Generalized convulsion	1	33
Guillain Barre Syndrome (GBS)	1	32
Acute disseminated encephalomyelitis (ADEM)	2	32
Thrombosis with thrombocytopenia syndrome	3	30–32
Anaphylaxis		
Vasculitides	3	31,33,34
Aseptic meningitis	0	
Encephalitis	1	31
Encephalomyelitis	1	31
Acute aseptic Arthritis	0	
Myocarditis	1	32
Abortion	2	32,33
Stillbirth	4	29,33–35
Maternal Death	4	29,33–35
Neonatal Encephalopathy	1	33
Neonatal death	1	33
	1	33

As defined by SPEAC.
MMR: measles, mumps, rubella.
MMRV: measles, mumps, rubella, varicella.

3.3) per 1,000, respectively. For maternal outcomes, the incidences were as follows: generalized convulsion occurred at a rate of 0.05 (95% CI, 0–0.26) per 100, anaphylaxis at 2 (95% CI, 0–92) per 100,000, and myocarditis at 0 (95% CI, 0–1.19) per 100, none of which showed an association with the vaccine. (33) The quality rating was low, with no significant safety issues reported. The background rate for anaphylaxis is 2 (95% CI, 1.5–3.8) per 100,000 pregnancies.[37] Ma et al, in their systematic review of COVID-19 vaccination in pregnant persons, found an OR 2.44 (0.12–51.05) for thromboembolism, denoting a non-significative association with vaccination.[30] The quality rating was high, with no significant safety issues reported.

Table 3 provides an overview of the main characteristics, outcomes, and findings of meta-analyses on vaccine-related health outcomes in children and adolescents for various vaccines that share components with those of Chikungunya, including COVID-19, MMRV, Hepatitis B, HPV, and Hepatitis A.

The meta-analysis by Katoto investigated the BNT162b2 mRNA COVID-19 vaccine, encompassing ten studies involving two RCTs and eight cohort studies, with a large sample size ranging from 257,805 to 754,303 children and adolescents. The health outcomes examined included Guillain-Barré Syndrome (GBS) at 0.01 (95% CI, 0–1.32) cases per 100,000 individuals, anaphylaxis at 0.64 (95% CI, 0.37–0.99) per 1,000, myocarditis at 5.95 (95% CI, 0–25.5) per 1,000 individuals, thromboembolic disorder at 0.08 (95% CI, 0.01–0.22) per 1,000 persons, and no cases of acute aseptic arthritis. The background rates for these conditions were: GBS at 0.64 (95% CI, 0.45–0.89) per 100,000 people, anaphylaxis at 0.8 (95% CI, 0.5–1.12) per 1,000, and myocarditis at 0.23 (95% CI, 0.21–0.24) per 100,000, and 0.016–1.50 per 1,000 persons for thromboembolic disorders. It's important to highlight the increased risk of myocarditis associated with mRNA vaccines. The AMSTAR-2 quality rating for these studies was moderate, and no significant safety concerns were reported.[32]

Table 2. Main characteristics, outcomes, and findings of the included meta-analysis in pregnant persons.

Author and year (Total N of studies) by vaccine	Platform	N Studies	Types of studies included in the SR	N pregnant persons (exposed)	Included outcomes	Effect measure (95% CI)	AMSTAR-2	Reported Safety Concerns Yes/No
Influenza A H1N1								
Zhang 2018 (*N* = 19)	Inactivated	3	Comparative cohort studies	8025	Abortion	aRR 1.04 (0.72–1.52)	Critically low	No
	Inactivated	11	Comparative cohort studies	171906	Stillbirth	aHR 0.80 (0.69–0.92)	Critically low	No
Influenza Quadrivalent (influenza A and B)								
Gidengil 2021 (*N* = 338)	Inactivated	1	RCT	4328	Abortion	RR 0.67 (0.02–19.79)	High	No
	Inactivated	1	RCT	4328	Stillbirth	RR 1 (0.06–16.04)	High	No
HPV								
Yan 2023 (*N* = 12)	Protein/ Subunit	11	Comparative cohort studies and RCTs	56384	Abortion	RR 1.06 (0.84–1.33) Cohort studies HPV2; RR 0.95 (0.84–1.07) RCT HPV4; RR 0.97 (0.79–1.18) Cohort studies HPV4 *	High	No
Yan 2023 (*N* = 12)	Protein/ Subunit	7	Comparative cohort studies and RCTs	9872	Stillbirth	RR 1.26 (0.65–2.42) RCT HPV4; RR 0.99 (0.61–1.62) Cohort studies HPV4	High	No
COVID-19								
Ciapponi 2024 (*N* = 177)	mRNA	2	Comparative cohort	22194	Abortion	OR 0,91 (0,70–1,20)	Low	No
	mRNA	3	Comparative cohort	62769	Stillbirth	OR 0.49 (0,20–1,19)	Low	No
	mRNA	1	Comparative cohort	Not reported	Maternal death	OR 0 (0–26)	Low	No
	mRNA	1	Non-comparative cohort		Neonatal death	0 (0–15)/1000	Low	No
	mRNA	1	Non-comparative cohort		Neonatal Encephalopathy	0 (0–0.5)/100	Low	No
	mRNA	1	Non-comparative cohort		Generalized convulsion	0.05 (0–0.26)/100	Low	No
	mRNA	4	Non-comparative cohort		Anaphylaxis	2 (0–92)/100000	Low	No
	mRNA	1	Non-comparative cohort		Myocarditis	0 (0–1.19)/100	Low	No
Ma 2022(*N* = 6)	mRNA	2	Comparative cohort		Thromboembolism	OR 2.44 (0.12–51.05)	Low	No

*The number after HPV means the number of genotypes included in the vaccine. For example, HPV4: 4 genotypes are included in the vaccine.

Table 3. Main characteristics, outcomes, and findings of the included meta-analysis in children and adolescents.

Author and year (Total N of studies), by vaccine	Platform	N Studies	Type of studies	N children and adolescents	Included outcomes	Effect measure (95% CI)	AMSTAR-2	Safety concerns Yes/No
COVID-19								
Katoto 2022 ($N = 10$) BNT162b2	mRNA	2	RCTs	258719	Guillain Barré Syndrome	0.01 (0–1.32)/100,000	Low	No
	mRNA	2	RCTs	258719	Anaphylaxis	0.64 (0.37–0.99)/1000	Low	No
	mRNA	1	RCTs	257805	Acute aseptic arthritis	0 (0–0)/100	Low	No
	mRNA	4	RCTs	754303	Myocarditis	5.95 (0–25.47)/1000	Low	No
	mRNA	1	Cohort	138141	Thromboembolic disorder	0.08 (0.01–0.22)/1,000	Low	No
MMRV								
Pietrantonj 2021 ($N = 87$)	Live attenuated	1	Comparative cohort		Acute disseminated encephalomyelitis	OR 1.03 (0.44–2.42)	High	No
Pietrantonj 2021 ($N = 87$)	Live attenuated	1	Comparative cohort		Generalized convulsions	Within 1 week: RR 2.45 (2.21–2.71) 1–2 weeks after vaccination RR 3.16 (2.89–3.46) >2 weeks after vaccination RR 0.97 (0.49–1.94)	High	
Pietrantonj 2021 ($N = 87$)	Live attenuated	1	Comparative cohort		Thrombocytopenia	OR 2.8 (1.5–5.23)	High	No
Pietrantonj 2021 ($N = 87$)	Live attenuated	1	Comparative cohort		Aseptic meningitis	Jeryl Lynn 0 to 30 days OR 0.85 (0.21–3.41)- Urabe or Hoshino OR 4.00 (2.23 to 7.20) Jeryl Lynn or Rubini OR 0.60 (0.18–1.99)	High	No
Hepatitis B								
Gidengil 2021 ($N = 338$)	Recombinant	1	Observational study		Acute disseminated encephalomyelitis	aOR 0 (0–128.7)	High	No
HPV								
Gidengil 2021 ($N = 338$)	Protein/ subunit	1	Observational study	7071	Anaphylaxis	RR 2 (0.07–59.66)	High	No
Hepatitis A								
Gidengil 2021 ($N = 338$)	Inactivated	1	Observational study		Acute disseminated encephalomyelitis	aOR 1.9 (0.1–13)	High	No

Pietrantonj's meta-analysis, rated high in quality by AMSTAR-2, examined the MMRV (measles, mumps, rubella, and varicella) vaccine based on 87 observational studies, with outcomes including ADEM, aseptic meningitis, and encephalitis, showing non-significant odds ratios (ORs) ranging from 0.60 to 1.03. Regarding generalized convulsions, they described an increased risk of seizures post-vaccination, which varies according to the time elapsed. The differences were statistically significant after vaccination in the first week (RR 2.45; 95% CI: 2.21–2.71) and between 1 to 2 weeks (RR 3.16; 95% CI: 2.89–3.46). However, the risk was decreasing since the second week after vaccination, with no significant association (RR 0.97; 95% CI: 0.49–1.94). Regarding MMR-associated aseptic meningitis, the risk varied according to the vaccine strain used, Jeryl Lynn (OR 0.85; 95% CI: 0.21–3.41) or Rubini strains (OR 0.60; 95% CI: 0.18–1.99), Urabe and Hoshino strains (OR 4; 95% CI: 2.23–7.20), in all the cases with no significant association.[31]

Gidengil's 2021 analysis covered 338 studies on Hepatitis B, HPV, and Hepatitis A vaccines. The Hepatitis B vaccine analysis reported an adjusted odds ratio (aOR) of 0 (95% CI: 0–128) for ADEM, indicating no cases. The HPV vaccine analysis observed a non-significant relative risk (RR) of 2 (95% CI: 0.07–59.66) for anaphylaxis, while the Hepatitis A vaccine analysis showed a non-significant aOR of 1.9 (95% CI: 0.1–13) for ADEM. The AMSTAR-2 quality ratings for these analyses ranged from high for the MMRV study to moderate for the Hepatitis B, HPV, and Hepatitis A studies, with no notable safety concerns reported across these vaccines.[34]

Discussion

This umbrella review synthesized evidence from meta-analyses on the safety profiles of vaccine platforms used in Chikungunya vaccines, focusing on AESI in pregnant persons, children, and adolescents under 18. Our findings indicate that vaccines sharing platforms with Chikungunya vaccines generally have acceptable safety profiles in these sensitive populations, with no significant increase in the risk of the evaluated AESI.

For pregnant persons, vaccines using similar platforms (including Influenza A H1N1, Quadrivalent Influenza, HPV, and COVID-19 vaccines) showed no significant increase in adverse pregnancy outcomes. Specifically, there was no elevated risk of abortion or stillbirth across multiple studies. The mRNA platform vaccines demonstrated initial reassuring safety data in pregnancy.[29,34,35] Zhang and colleagues identified higher spontaneous abortion risks when HPV types 2 and 9 vaccines were given 45–90 days before the last menstrual period. However, they stress that these findings need more research before drawing definitive conclusions.[38] Regarding other relevant outcomes not included in this OV, Juvet et al. reviewed five systematic reviews examining H1N1 pandemic vaccine safety during pregnancy. Of these reviews, only one showed a minor increase in congenital malformations.[39] Their overall conclusion supports H1N1 vaccine safety during pregnancy, noting that vaccination offers significant advantages compared to infection. Separately, Marchand's research noted higher cesarean section rates among pregnant individuals who received the COVID-19 vaccine. However, they did not find an explanation for this outcome.[40]

In children and adolescents, vaccines such as the BNT162b2 mRNA COVID-19, MMRV (measles, mumps, rubella, varicella), Hepatitis B, HPV, and Hepatitis A showed acceptable safety profiles. Serious adverse events were rare, with very low incidence rates of conditions like Guillain-Barré Syndrome and anaphylaxis and no significant increase in ADEM risk with MMR vaccination, except for myocarditis.

A comprehensive overview by Gee et al.[41] examines safety data of COVID-19 vaccines in the general population, including pregnant persons, derived from both active and passive surveillance sources in the United States. This study meticulously analyzes information sources and associated safety outcomes. Post-marketing surveillance and monitoring systems have proven robust and reliable for detecting rare adverse events. The study specifically highlights the detection of myocarditis cases associated with mRNA platform vaccines in adolescents. These cases were initially identified through notification in surveillance systems, enabling informed decision-making regarding the continued use of these vaccines. This underscores the critical role of real-world surveillance systems in providing safety data for vaccines and platforms under development, particularly for special populations such as pregnant persons and children/adolescents, who are often underrepresented in clinical trials.[41] Another systematic review conducted by Ciapponi et al. offers insights into the safety of components and platforms used in COVID-19 vaccine development. This systematic review concluded that the employed platforms and components were safe for administration in pregnant persons, based on data from other vaccines studied and used in real-world settings.[42] These findings emphasize the importance of comprehensive post-marketing surveillance in complementing clinical trial data, especially for vulnerable populations. Such robust monitoring systems are crucial for continuously evaluating vaccine safety profiles and informing public health decisions in real-time.[43]

Jiesisibieke et al., in their overview of COVID-19 vaccines, demonstrated that different vaccine platforms have shown varying adverse event profiles. mRNA vaccines were associated with a higher incidence of adverse events than other available platforms. While COVID-19 infection itself can affect multiple organ systems, vaccinations were not found to increase the risk of severe complications such as arrhythmia, acute kidney injury, pulmonary embolism, deep-vein thrombosis, myocardial infarction, pericarditis, or intracranial hemorrhage.[44] Gao et al., in their SR and MA of different platforms of COVID-19 in children and adolescents between 2 and 18 years old, described an increase in the incidence rate of thrombosis.[45] Etti et al., in their narrative review of current maternal vaccination, have indicated that hepatitis B and hepatitis A vaccines administered during pregnancy have not been associated with increased adverse pregnancy outcomes.[46] On the other hand, among patients under 18 years old, Gidengil et al. reported an increased risk for several adverse events, such as idiopathic thrombocytopenic purpura in association with Hepatitis A and MMR vaccines, anaphylaxis in patients with allergic history and febrile seizures with MMR vaccine. Juvet et al. reported an

increased frequency of narcolepsy among children and adolescents who received the pandemic vaccine in comparison with the unvaccinated population.[39]

Our review also highlighted gaps in the literature. For some vaccines, such as the Hepatitis E vaccine (HEV 239), evidence is limited, particularly concerning its safety in pregnant persons and children.[31,47] While some studies suggest potential benefits, including protection against maternal and neonatal deaths due to Hepatitis E virus infection,[48] safety data remain insufficient to make definitive conclusions.[49,50] The Global Advisory Committee on Vaccine Safety (GACVS) noted a safety signal related to spontaneous abortions in a trial in Bangladesh, indicating the need for further investigation.[50]

In the overview by Vichnin et al., no increased incidence was found compared to background rates of adverse pregnancy outcomes, autoimmune diseases (including Guillain-Barre Syndrome), and anaphylaxis, suggesting a favorable safety profile for the HPV4 vaccine.[51] Ropero Álvarez et al., with data from Latin America and the Caribbean about influenza H1N1 vaccination, showed the most frequently reported serious adverse events were febrile seizures, Guillain-Barré Syndrome (GBS), anaphylaxis, and seizures, among others. For pregnant persons specifically, the most commonly reported events were miscarriage or spontaneous abortions and preterm labor and delivery.[52] Macias Saint-Gerons et al. reported several important findings in their comprehensive review of adverse events associated with vaccines recommended during pregnancy. The Hepatitis B vaccination during pregnancy did not show any significant effect on the risk of miscarriage or stillbirth, suggesting that the vaccine maintains a favorable safety profile for pregnant persons. H1N1pdm09 influenza vaccination was not associated with an increased risk of miscarriage or stillbirth, and interestingly, it might potentially reduce the frequency of neonatal death, or at the very least, it does not increase this risk. In general, the evidence indicates that pandemic Influenza vaccination likely does not increase the risk of fetal death. These results collectively support the safety of these vaccinations during pregnancy, particularly concerning fetal and neonatal outcomes.[53] Legardi-Williams et al.[54] investigated vaccine safety in 84 pregnant persons who received the Ervebo vaccine (rVSVΔ-ZEBOV-GP) for Ebola. Comparing their outcomes with 31 pregnant women who weren't vaccinated from Sierra Leone showed a notable rate of pregnancy losses among participants. The researchers concluded that these adverse events were not linked to the vaccination.

A key strength of this umbrella review is its comprehensive and systematic approach, which adheres to PRISMA guidelines[24] and employs rigorous selection criteria. Also, most platforms are those included in other emerging vaccines, like Lassa fever or Monkeypox.

However, several limitations should be acknowledged. First, the quality of the included systematic reviews varied, with some rated as "critically low" or "low" according to the AMSTAR-2 tool 28. This variability may impact the reliability of the findings. Second, heterogeneity in study designs, populations, and outcome definitions among the included reviews may limit the comparability of results. Third, some AESI, such as vasculitides and encephalomyelitis, were not explicitly addressed in the included reviews, indicating gaps in the available evidence. Additionally, the reliance on published systematic reviews may have led to the exclusion of recent studies not yet included in reviews, potentially affecting the comprehensiveness of our findings. The inclusion of only English-language publications may also introduce language bias. Moreover, the overall safety profile of any biologic is determined by the intrinsic characteristics of the vaccine platform, the inherent risks associated with its production, and the antigens expressed within an immunogenic formulation. Therefore, the common practice of limiting data analysis to primarily licensed vaccines overlooks the possibility that a platform technology, which may appear safe, could result in candidate vaccines with higher risks when combined with certain viral antigens. Finally, due to the selection of a small number of AESIs that were considered of greater relevance, it is possible that other frequent adverse events were left out of the analysis. However, outcomes of some notoriety have been commented on in the discussion.

The findings of this umbrella review have important implications for public health practice and vaccine policy. The generally favorable safety profiles of vaccines sharing platforms with Chikungunya vaccines in sensitive populations support the consideration of these platforms for Chikungunya vaccine development and deployment.

Future research should focus on filling the identified gaps, particularly regarding the safety of certain vaccines like Hepatitis E in pregnant persons and children. Ongoing surveillance and post-marketing studies are essential to monitor the safety of newly approved Chikungunya vaccines, such as the live-attenuated VLA1553 vaccine recently approved by the FDA and EMA.[15,54] Further studies are needed to assess Chikungunya vaccines' long-term safety and efficacy in diverse populations, including those with comorbidities and in different geographic regions. Investigations into AESI that are not extensively covered in current literature, such as thrombocytopenia and vasculitides, are also warranted.

Conclusion

This umbrella review indicates that vaccine platforms used in Chikungunya vaccines, when applied in other vaccines, generally exhibit acceptable safety profiles in pregnant persons, children, and adolescents under 18. These findings support the continued development and implementation of Chikungunya vaccines using these platforms, although ongoing monitoring and further research are warranted to address the remaining uncertainties. Some associations between vaccination and specific outcomes, should be interpreted within the context of overall vaccine benefits and the risks of vaccine-preventable diseases during pregnancy and childhood. The identified risks are generally small in magnitude, and many studies emphasize the need for continued surveillance and research to better understand these associations.

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Notes on contributors

Ariel Bardach is a physician specializing in public health, epidemiology, and evidence synthesis. He graduated from the National University of La Plata in 1996, earned a Master's in Epidemiology from the London School of Hygiene and Tropical Medicine, and holds a PhD in Public Health from the University of Buenos Aires. A Bernard Lown Scholar at Harvard, he focuses on cardiovascular disease epidemiology. He directs the Center for Research in Epidemiology and Public Health at Argentina's CONICET, within the Institute for Clinical Effectiveness and Health Policy (IECS), where he also contributes to the Cochrane Center and Health Technology Assessment Department. At IECS, he advances health systems' efficiency, equity, and quality through research and education.

Bardach has consulted for Argentina's Ministry of Health, focusing on communicable and non-communicable diseases. He has also been a GP for over 20 years, emphasizing primary care and preventive medicine. With over 150 peer-reviewed publications, his research spans infectious disease epidemiology, cardiovascular epidemiology, tobacco control, and health economics. His recent work addresses cost-effectiveness in public health interventions and the impact of policies on chronic diseases, contributing to global health improvements.

ORCID

Ariel Bardach http://orcid.org/0000-0003-4437-0073

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