

Meta-Analysis

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Safety of chikungunya vaccines for adolescents and adults: A meta-analysis

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ABSTRACT

Objective: To systematically review the safety of different types of chikungunya vaccines in human populations.

Methods: This study retrieved randomized controlled trials (RCTs) reporting on the safety of chikungunya vaccines in human populations through electronic searches of the Web of Science, PubMed, EMbase, and Cochrane Library databases. Two reviewers independently performed literature screening, data extraction, and risk of bias assessment for the included studies. Meta-analysis was conducted using STATA 18.0 software.

Results: A total of eight RCTs involving 9 336 subjects were included in this study. Meta-analysis showed that three out of the five chikungunya vaccines (VLA1553, mRNA-1388, and PXVX0317) exhibited favorable safety profiles, with no significant increase in the incidence of serious adverse events. The vaccine group had a higher incidence of any adverse events [risk ratio (*RR*)=1.26, *P*<0.001] and any systemic adverse events (*RR*=1.18, *P*=0.010) compared to the placebo group. The incidence of local adverse events was also higher in the vaccine group (*RR*=2.09, *P*<0.001). However, there were no significant differences between the two groups in the incidences of erythema (*RR*=1.41, *P*=0.402), headache (*RR*=1.14, *P*=0.457), or arthralgia (*RR*=1.45, *P*=0.660).

Conclusions: Current evidence supports that chikungunya vaccines have a favorable safety profile. However, due to limitations in the number and quality of included studies, further high-quality research is needed to validate these conclusions.

KEYWORDS: Chikungunya vaccine; Safety; Meta-analysis; Systematic review; Randomized controlled trials

1. Introduction

Chikungunya fever (CHIK) is an arboviral disease caused by chikungunya virus (CHIKV), transmitted primarily through bites of *Aedes* mosquitos. It is characterized by acute febrile polyarthralgia, arthritis, and rash as cardinal clinical manifestations[1-3]. While most patients achieve complete resolution of acute infection with subsequent life-long immunity, a clinically significant subset develops persistent arthralgia lasting months to years beyond disease onset[4,5]. Chikungunya virus imposes a substantial health burden worldwide, with the highest disease incidence observed across Africa and the Americas—particularly throughout Latin America

Summary

Question: What is the safety profile of different chikungunya virus vaccines in human populations?

Findings: This meta-analysis of 8 randomized controlled trials (*n*=9 336) found that three vaccines (VLA1553, mRNA-1388, PXVX0317) demonstrated favorable safety profiles with no significant increase in serious adverse events. Vaccinated groups showed significantly higher rates of any adverse events (*RR*=1.26) and local adverse events (*RR*=2.09) compared to placebo group.

Meaning: Current evidence supports the acceptable safety of chikungunya vaccines, though further high-quality studies are needed to confirm these findings.

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and the Caribbean[1,6]. As of 2025, autochthonous transmission has been documented in 119 countries/territories, with multiple Chinese provinces reporting local outbreaks triggered by imported cases[7]. At present, there is no specific antiviral therapy for chikungunya fever[8]. In the absence of specific antiviral drugs, the development and monitoring of vaccines are of vital importance for controlling the spread of vector-borne viruses[4,9]. In November 2023, the US FDA approved VLA1553 (IXCHIQ®), a live-attenuated vaccine, for adult immunization[10]. Although multiple candidates (*e.g.*, mRNA-1388, PXVX0317, MV-CHIK) are in clinical trials, their safety profiles and long-term immunogenicity require further large-scale validation[11-14]. Thus, systematic reviews and meta-analyses synthesizing vaccine safety evidence are critically important for guiding clinical practice, optimizing immunization policies, and advancing vaccine development. This systematic review was not prospectively registered in a dedicated registry.

2. Methods

2.1. Inclusion criteria and exclusion criteria

The study retrieved randomized controlled trials (RCTs). Inclusion criteria were as follows: (1) participants were healthy adolescents or adults aged 12 and above with no prior history of CHIKV infection; (2) interventions involve the experimental group receiving chikungunya vaccine injections and the control group receiving placebo injections; (3) outcome measures include safety indicators such as serious adverse events, any adverse events, any local adverse events (including pain, erythema, and swelling), and any systemic adverse events (including fever, headache, fatigue, myalgia, and arthralgia).

Exclusion criteria encompass non-English literature, non-phase Ⅰ, Ⅱ, or Ⅲ clinical trials, coadministration with other vaccines, unavailable full texts, lack of outcome indicators or inability to extract essential data, as well as animal studies, cell studies, reviews, meta-analyses, duplicates, case reports, and letters to the editor.

2.2. Systematic review search strategy

Database Sources: Computerized searches were performed across Web of Science Core Collection, PubMed, EMbase (Excerpta Medica Database), and the Cochrane Central Register of Controlled Trials (CENTRAL). Timeframe: From database inception to July 25, 2025. Search methodology: Combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators. Key search terms included: Disease terminology: chikungunya, chikungunya virus, CHIKV. Intervention: vaccine, vaccination, immunization. Outcomes: safety, adverse events, adverse reactions, side effects.

2.3. Literature screening and data extraction

All retrieved literature underwent duplicate removal, followed by initial screening of titles and abstracts based on the PICOS (P-Population, I-Intervention, C-Comparison, O-Outcome, S-Study Design) criteria using EndNote. Articles passing initial screening were subjected to full-text review and qualitative assessment. Data were extracted according to study design, patient baseline characteristics, and outcome indicators. The literature screening process was conducted independently by two reviewers (DMC, YW). Disagreements were resolved through discussion or third-party arbitration. A comprehensive feasibility assessment was performed to ensure clear inclusion criteria and comparable reporting methods, thereby reducing heterogeneity and potential outlier effects. This meta-analysis was not registered in a prospective registry (*e.g.*, PROSPERO) as it was initially undertaken as an educational exercise. Our attention was drawn to the importance of prospective registration after the data extraction stage was completed, at which point registration was no longer permitted per PROSPERO policy.

2.4. Risk of bias assessment for included studies

Evaluation process: Risk of bias assessments were conducted independently by two investigators using Review Manager 5.4 in accordance with the criteria established in the Cochrane Handbook v5.1.0. Cross-verification of the results was performed through a consensus-based reconciliation protocol.

2.5. Data analysis

Statistical analyses were performed using STATA 18.0 (StataCorp LP). Dichotomous variables were expressed as risk ratios (*RR*) with 95% confidence intervals. Heterogeneity among included studies was assessed using the *Chi*-square test (significance level set at α=0.10), and the magnitude of heterogeneity was quantified by the I^2 statistic. A fixed-effect model was applied in the absence of significant statistical heterogeneity; otherwise, a random-effects model was used after exploring potential sources of heterogeneity and excluding overt clinical heterogeneity. The significance level for meta-analysis was set at α=0.05. Substantial clinical heterogeneity was addressed through subgroup analysis, sensitivity analysis, or descriptive synthesis.

3. Results

3.1. Literature screening process and results

A total of 372 potentially relevant articles were identified through the initial search. After a tiered screening process, eight randomized controlled trials (RCTs)[11-18] involving 9 336 subjects were ultimately included. The literature screening process and results were presented in Figure 1.

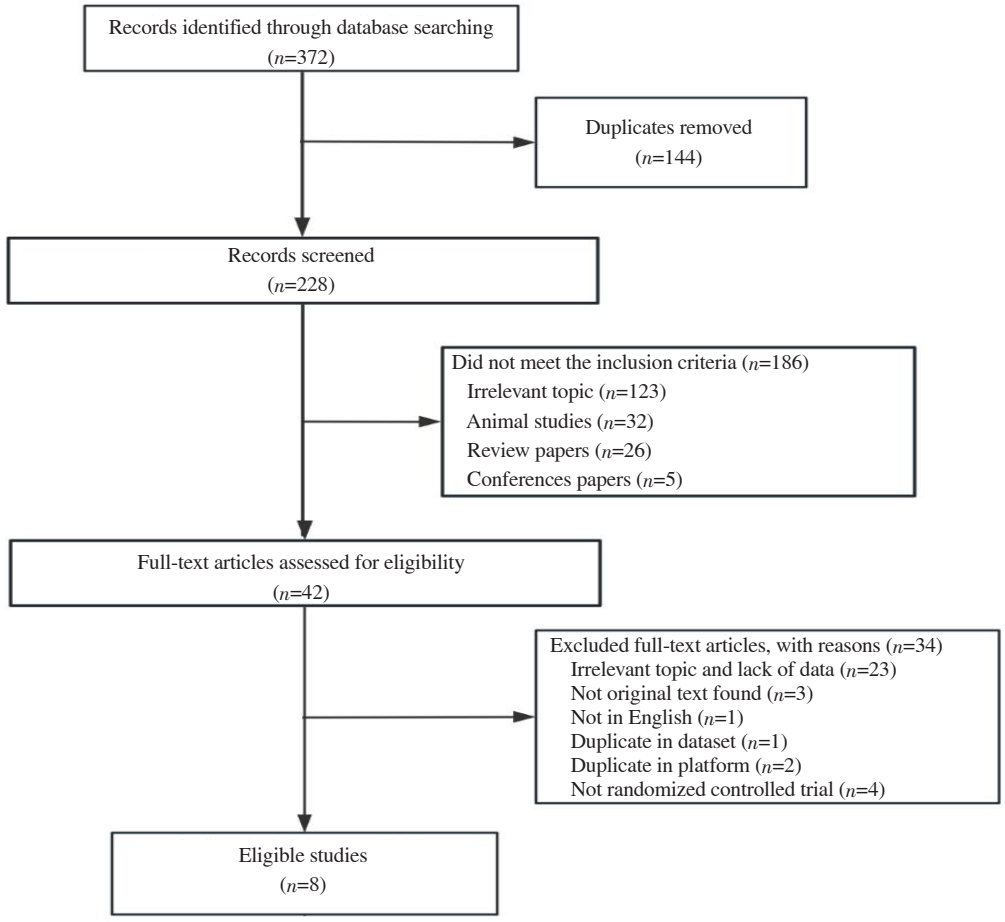

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of the included studies.

Author/Year	Country	Phase	Case (T/C)	Age (Y)	Sex (M/F, cases)		Vaccine		Outcomes: safety indicators
					Test	Control	Vaccine type	Dose	
Tindale *et al*, 2025[14]	USA	3	206/207	65	81/125	90/117	PXVX0317	1	1,2,3,4,5,6,7,8,9,10,11,12
Richardson *et al*, 2025[12]	USA	3	2794/464	12-64	1358/1436	233/231	PXVX0317	1	1,2,3,4,5,6,7,8,9,10,11,12
Buerger *et al*, 2025[15]	Brazil	3	502/252	12-18	233/269	115/137	VLA1553	1	1,2,4,8,9,10,11,12
Schneider *et al*, 2023[16]	USA	3	3082/1033	18-94	1400/1682	464/569	VLA1553	1	1,2,4,8,9,10,11,12
Shaw *et al*, 2023[13]	USA	1	45/15	18-49	19/26	7/8	mRNA-1388	2, 28 days apart	1,2,3,4,5,6,7,8,9,10,11,12
Chen *et al*, 2020[17]	Several	2	201/199	18-60	105/96	96/103	PXVX0317	2, 28 days apart	1,3,4,5,6,7,8,9,11,12
Reisinger *et al*, 2018[11]	Austria/ Germany	2	229/34	18-55	123/106	17/17	MV-CHIK	2, 28 days apart	2,4,5,6,8,9,10,11,12
Edelman *et al*, 2000[18]	USA	2	59/14	18-40	35/24	12/2	TSI-GSD-218	1	3,7,12

T: test; C: control; Y: years, M: males; F: Females; PXVX0317 vaccine is also defined as VRC-CHKVLP059-00-VP; mRNA-1388 vaccine is also defined VAL-181388; 1: serious adverse events; 2: any adverse event; 3: any local adverse event; 4: pain; 5: erythema; 6: swelling; 7: any systemic adverse event; 8: fever; 9: headache; 10: fatigue; 11: myalgia; 12: arthralgia.

3.2. Basic characteristics of included studies and bias risk assessment

The basic characteristics of the included studies were presented in Table 1, and the bias risk assessment results were shown in Figure 2.

3.3. Meta-analysis results

3.3.1. Incidence of serious adverse events

Serious adverse events (SAEs) were reported in six of the eight included randomised controlled trials (RCTs)[12–17]. The remaining two studies did not report SAE data or presented them in a format

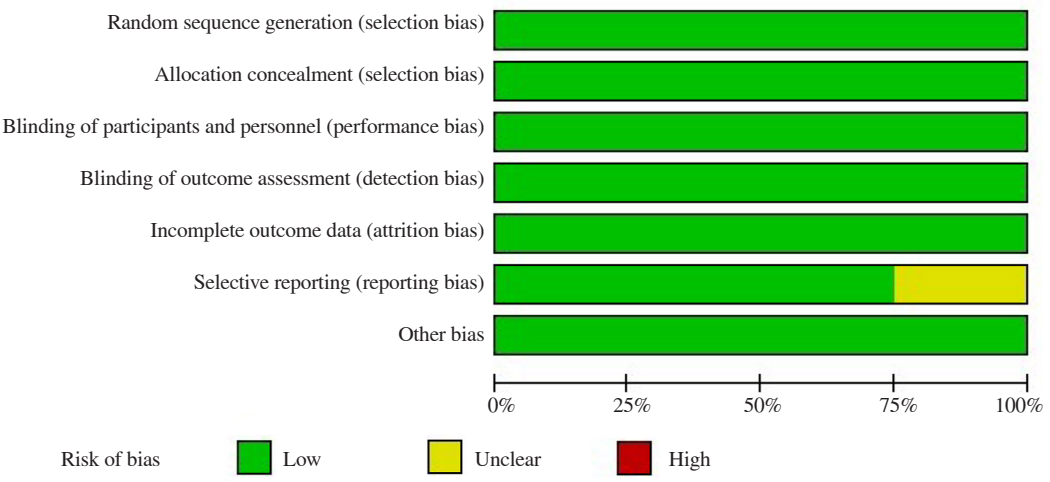

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 2. Meta-analysis results: safety of chikungunya virus vaccines.

Outcome	Included studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
SAEs[12–17]	6	0.962	0.00%	fixed	1.84 (0.75, 4.50)	0.185
Any AEs[11–16]	6	0.022	62.00%	random	1.26 (1.13, 1.41)	<0.001
Any local AEs[12–14,17,18]	5	0.426	0.00%	fixed	2.09 (1.70, 2.57)	<0.001
Pain[11–17]	7	0.046	53.50%	random	1.69 (1.36, 2.10)	<0.001
Erythema[11–14,17]	5	0.818	0.00%	fixed	1.41 (0.63, 3.15)	0.402
Swelling[11–14,17]	5	0.876	0.00%	fixed	3.74 (1.00, 13.91)	0.049
Any systemic AEs[12–14,17,18]	5	0.154	40.20%	fixed	1.18 (1.04, 1.34)	0.010
Fever[11–17]	7	<0.001	76.00%	random	2.49 (1.01, 6.15)	0.048
Headache[11–17]	7	<0.001	88.80%	random	1.14 (0.81, 1.59)	0.457
Fatigue[11–16]	6	<0.001	81.20%	random	1.47 (1.02, 2.13)	0.039
Myalgia[11–17]	7	<0.001	79.20%	random	1.66 (1.16, 2.37)	0.006
Arthralgia[11–18]	8	<0.001	77.20%	random	1.45 (0.90, 2.33)	0.125

SAEs: serious adverse events; AEs: adverse events; AR: adverse events; *RR*: risk ratio.

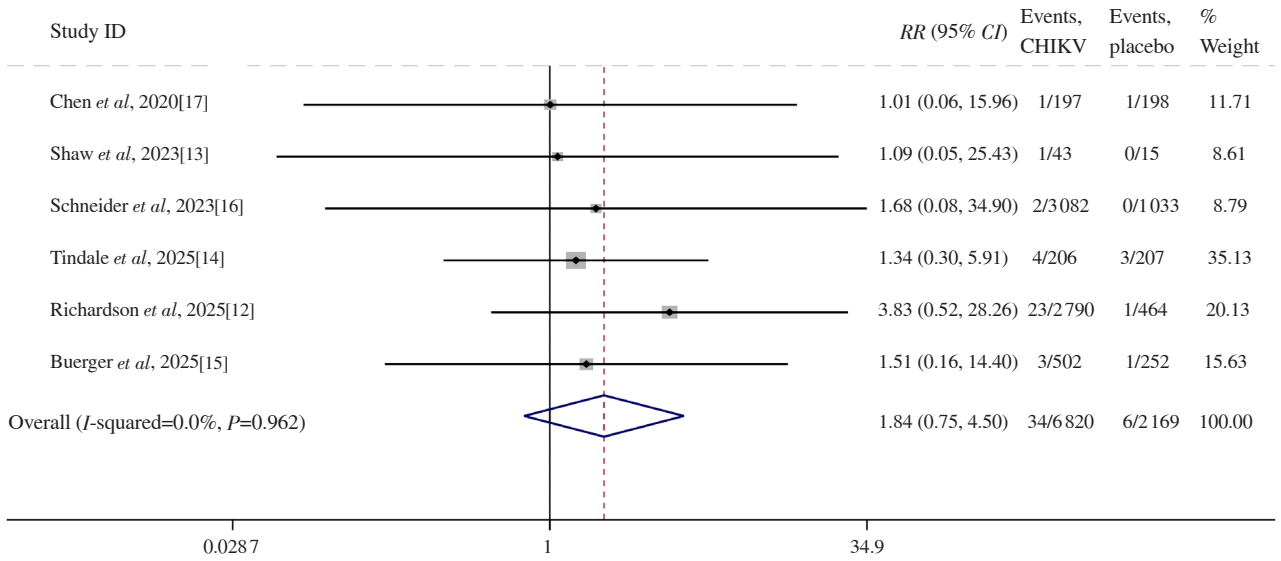

Figure 3. Pooled incidence of serious adverse events (SAE) after chikungunya vaccination.

unsuitable for quantitative extraction. Therefore, the meta-analysis of SAEs was performed based on the six trials with available data. Meta-analysis using a fixed-effect model showed no statistically significant difference between the vaccine group and the placebo group (*RR*=1.84, 95% *CI* 0.75-4.50, *P*=0.185) (Table 2 and Figure 3).

3.3.2. Incidence of any adverse reactions

A total of six RCTs[11–16] reported data on the incidence of any adverse events. Meta-analysis with a random-effects model indicated a higher incidence of any adverse events in the vaccine group compared to the placebo group (*RR*=1.26, 95% *CI* 1.13-1.41,

Table 3. Subgroup analysis of any adverse events.

Subgroup	Included studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	6	0.022	62.00%	random	1.26 (1.13, 1.41)	<0.001
Phase 1	1	/	/	/	2.03 (1.08, 3.84)	0.029
Phase 2	1	/	/	/	1.04 (0.83, 1.31)	0.743
Phase 3	4	0.069	57.70%	random	1.29 (1.17, 1.43)	<0.001
USA	4	0.051	61.50%	random	1.31 (1.12, 1.52)	0.001
Austria/Germany	1	/	/	/	1.04 (0.83, 1.31)	0.743
Brazil	1	/	/	/	1.27 (1.14, 1.42)	<0.001
mRNA-1388	1	/	/	/	2.03 (1.08, 3.84)	0.029
MV-CHIK	1	/	/	/	1.04 (0.83, 1.31)	0.743
PXVX0317	2	0.057	72.40%	random	1.13 (0.80, 1.59)	0.495
VLA1553	2	0.162	48.80%	random	1.34 (1.23, 1.47)	<0.001
Dose 1	4	0.069	57.70%	random	1.29 (1.17, 1.43)	<0.001
Dose 2	2	0.039	76.60%	random	1.37 (0.69, 2.73)	0.371

For some subgroups, heterogeneity could not be calculated as only one study was included; thus, the result of the heterogeneity test is reported as "/".

P<0.001) (Table 2). Subgroup analysis revealed a significantly higher incidence in Phase Ⅰ (*RR*=2.03, 95% *CI* 1.08-3.84, *P*=0.029) and Phase Ⅲ (*RR*=1.29, 95% *CI* 1.17-1.43, *P*<0.001) clinical trials, with no significant difference observed in Phase Ⅱ trials (*P*>0.05) (Table 3). Stratified by country, significantly increased risks were observed in studies conducted in the United States (*P*=0.001) and Brazil (*P*<0.001), while no significant difference was found in the study from Austria/Germany. In vaccine-specific subgroup analyses, mRNA-1388 and VLA1553 vaccines showed significantly higher risks of adverse events (both *P*<0.05), whereas no significant differences were found for MV-CHIK or PXVX0317. In the dosing subgroup, a significantly increased risk was only observed after dose 1 (*RR*=1.29, 95% *CI* 1.17-1.43, *P*<0.001) (Table 3).

3.3.3. Incidence of local adverse reactions

A total of five RCTs[12–14,17,18] reported the incidence of local adverse events. Fixed-effect meta-analysis showed a significantly higher incidence in the vaccine group compared to the placebo group (*RR*=2.09, 95% *CI* 1.70-2.57, *P*<0.001) (Table 2). Subgroup analyses indicated significantly increased risks in Phase Ⅰ, Ⅱ, and Ⅲ clinical trials (all *P*<0.05). Studies conducted in the United States and multicountry sites also showed elevated risks (both *P*<0.01). In vaccine-specific subgroups, mRNA-1388 and PXVX0317 were associated with higher risks (both *P*<0.05), while no significant difference was observed for TSI-GSD-218. Both dose 1 and dose 2 resulted in significantly higher risks (*RR*=2.19 and *RR*=1.88, respectively; both *P*<0.001) (Table 4).

Table 4. Subgroup analysis of any local adverse events.

Subgroup	Included studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	5	0.426	0.00%	fixed	2.09 (1.70, 2.57)	<0.001
Phase 1	1	/	/	/	2.79 (1.18, 6.58)	0.019
Phase 2	2	0.314	1.50%	fixed	1.65 (1.18, 2.30)	0.004
Phase 3	2	0.72	0.00%	fixed	2.26 (1.73, 2.94)	<0.001
USA	4	0.454	0.00%	fixed	2.23 (1.74, 2.85)	<0.001
Multicountry sites	1	/	/	/	1.74 (1.22, 2.48)	0.002
mRNA-1388	1	/	/	/	2.79 (1.18, 6.58)	0.019
TSI-GSD-218	1	/	/	/	0.95 (0.31, 2.92)	0.927
PXVX0317	3	0.465	0.00%	fixed	2.10 (1.70, 2.61)	<0.001
Dose 1	3	0.314	13.60%	fixed	2.19 (1.69, 2.84)	<0.001
Dose 2	2	0.316	0.50%	fixed	1.88 (1.36, 2.61)	<0.001

Table 5. Subgroup analysis of any systemic adverse events.

Subgroup	Included studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	5	0.154	40.20%	fixed	1.18 (1.04, 1.34)	0.010
Phase 1	1	/	/	/	1.79 (0.60, 5.31)	0.297
Phase 2	2	0.585	0.00%	random	1.00 (0.82, 1.22)	0.995
Phase 3	2	0.099	63.20%	random	1.11(0.72,1.72)	0.642
USA	4	0.161	41.80%	random	1.11 (0.83, 1.47)	0.479
Multicountry sites	1	/	/	/	1.03 (0.82, 1.29)	0.805
mRNA-1388	1	/	/	/	1.79 (0.60, 5.31)	0.297
TSI-GSD-218	1	/	/	/	0.90 (0.57, 1.40)	0.632
PXVX0317	3	0.096	57.40%	random	1.11 (0.88, 1.40)	0.373
Dose 1	3	0.097	57.10%	random	1.05 (0.84, 1.31)	0.651
Dose 2	2	0.328	0.00%	random	1.06 (0.77, 1.46)	0.727

3.3.3.1. Incidence of pain

The incidence of pain was reported in seven RCTs[11–17]. Random-effects meta-analysis showed a higher incidence in the vaccine group (*RR*=1.69, 95% *CI* 1.36-2.10, *P*<0.001) (Table 2). Subgroup analyses revealed significantly higher risks in Phase Ⅰ and Ⅲ trials (both *P*<0.05), but not in Phase Ⅱ. Elevated risks were also observed in studies conducted in the United States, Brazil, and multicountry sites (all *P*<0.01). Among vaccine subtypes, mRNA 1388 (*RR*=3.26, 95% *CI* 1.16-9.17), PXVX0317(*RR*=2.02, 95% *CI* 1.55-2.65), and VLA1553 (*RR*=1.37, 95% *CI* 1.16-1.61) showed higher risks (all *P*<0.05), while no significant difference was found for MV-CHIK. Both dose 1 (*RR*=1.67, *P*=0.001) and dose 2 (*RR*=1.74, *P*<0.001) were associated with increased risk of pain (Supplementary Table 1).

3.3.3.2. Incidence of erythema

The incidence of erythema was reported in five RCTs[11–14,17]. Fixed-effect meta-analysis showed no significant difference between groups (*RR*=1.41, 95% *CI* 0.63-3.15, *P*=0.402) (Table 2).

3.3.3.3. Incidence of swelling

Swelling was reported in five RCTs[11–14,17]. Fixed-effect meta-analysis indicated a higher incidence in the vaccine group (*RR*=3.74, 95% *CI* 1.00-13.91, *P*=0.049) (Table 2). No other results showing significance were observed in subgroup analyses (Supplementary Table 2).

3.3.4. Incidence of systemic adverse reactions

A total of five RCTs[12–14,17,18] reported the incidence of systemic adverse events. Fixed-effect meta-analysis indicated a higher incidence in the vaccine group compared to the placebo group (*RR*=1.18, 95% *CI* 1.04-1.34, *P*=0.010) (Table 2). No significant differences were identified in subgroup analyses stratified by trial phase, country, vaccine type, or number of doses (Table 5).

3.3.4.1. Incidence of fever

The incidence of fever was reported in seven RCTs[11–17]. Random-effects meta-analysis showed a higher incidence in the vaccine group (*RR*=2.49, 95% *CI* 1.01-6.15, *P*=0.048) (Table 2). Subgroup analyses revealed significantly increased risks only in Phase Ⅲ trials (*RR*=4.77, *P*=0.001), with the VLA1553 vaccine (*RR*=6.83, *P*<0.001), and after dose 1 (*RR*=4.77, *P*=0.001). A significantly reduced risk was observed in studies conducted in Brazil (*RR*=0.59, *P*<0.001) (Supplementary Table 3).

3.3.4.2. Incidence of headache

The incidence of headache was reported in seven RCTs[11–17]. Random-effects meta-analysis showed no statistically significant difference between the groups (*RR*=1.14, 95% *CI* 0.81-1.59, *P*=0.457) (Table 2).

3.3.4.3. Incidence of fatigue

The incidence of fatigue was reported in six RCTs[11–16]. Random-effects meta-analysis indicated a higher incidence in the vaccine group (*RR*=1.47, 95% *CI* 1.02-2.13, *P*=0.039) (Table 2). Significantly increased risks were observed only in Phase Ⅲ trials (*RR*=1.65, *P*=0.016), in studies conducted in Brazil (*RR*=2.27, *P*<0.001), with the VLA1553 vaccine (*RR*=2.18, *P*<0.001), and after dose 1 (*RR*=1.65, *P*=0.016) (Supplementary Table 4).

3.3.4.4. Incidence of myalgia

The incidence of myalgia was reported in seven RCTs[11–17]. Random-effects meta-analysis showed a higher incidence in the vaccine group (*RR*=1.66, 95% *CI* 1.16-2.37, *P*=0.006) (Table 2). Subgroup analyses indicated significantly increased risks in Phase Ⅲ trials (*RR*=2.07, *P*<0.001), in studies conducted in the United States (*RR*=1.87, *P*=0.012) and Brazil (*RR*=2.14, *P*<0.001), with the VLA1553 (*RR*=2.63, *P*<0.001) and PXVX0317 vaccines (*RR*=1.47, *P*=0.026), and after dose 1 (*RR*=2.07, *P*<0.001) (Supplementary Table 5).

3.3.4.5. Incidence of arthralgia

Arthralgia was reported in eight RCTs[11–18]. Random-effects meta-analysis showed no statistically significant difference between the groups (*RR*=1.45, 95% *CI* 0.90-2.33, *P*=0.125) (Table 2).

4. Discussion

This study systematically evaluated the safety of CHIKV vaccines by analyzing data from eight RCTs. The results indicated that there was no significant difference for incidence of serious adverse events (SAEs) between vaccine and placebo group (*RR*=1.84, *P*=0.185), revealing good safety overall and supporting broader population use. Notably, significant differences were observed for overall adverse events (AEs) (*RR*=1.26, *P*<0.001), local reactions (*RR*=2.09, *P*<0.001), and specific systemic reactions including fever, fatigue, and myalgia. These findings align with previous researches on vaccine-related adverse events. The increased risk observed for overall AEs may stem from variations in AE reporting methodologies and differences in study populations, which was not adequately controlled in earlier studies[5,19], underscoring the necessity for standardized reporting practices to ensure consistency across trials[19,20].

Subgroup analysis of local AEs demonstrated increased risk across various clinical trial phases, countries, vaccine types, and dosing schedules. Pain at the injection site was significantly more frequent (*RR*=1.69, *P*<0.001), regardless of vaccine type or dosing, and was considered as an intrinsic, inflammation-specific reaction. Swelling

also showed an elevated trendency (*RR*=3.74), but with a wide 95% *CI* (1.00-13.91). After vaccination, an inflammatory response was triggered, causing the subjects to experience symptoms such as erythema, swelling, and pain. This is consistent with results of Caroline Hervé's study[21] and Ren *et al*'s study[22]. Consequently, injection site pain should be clearly communicated to vaccinees pre-administration[20].

Among systemic reactions, significant risk increase was confirmed for fever (*RR*=2.49, *P*=0.048), fatigue (*RR*=1.47, *P*=0.039), and myalgia (*RR*=1.66, *P*=0.006). Stratified analysis showed results were mainly attributed to different trials, vaccines, single doses, and areas (except for fever). VLA1553, as a live attenuated vaccine, is more likely to trigger an inflammatory response in the body[15]. The inflammatory mediators act on the central nervous system through the body fluids or neural pathways (such as the vagus nerve), causing "flu-like symptoms" such as fever and headache[23]. It is worth noting that in Brazil, the risk of fever among those who received the vaccine was lower than that among those who received the placebo. This is contrary to the conclusion made by Yousfi *et al*[24], who reported an increasing rate of adverse events after vaccination during childhood and adolescence, while the rate decreased in adulthood. This observation might be attributed to the study's location in Brazil, a region with a high prevalence of chikungunya fever, and the placebo group had a higher background fever rate due to exposure to the mosquito-borne chikungunya virus. Antigen testing helps to distinguish vaccine responses from natural infections. Arthralgia showed no statistically significant increase (*RR*=1.45, *P*=0.125)–a crucial finding given that joint symptoms are a hallmark of CHIKV infection and a major vaccine hesitancy factor[19].

VLA1553 is derived from the chikungunya virus strain LR2006-OPY. Its development strategy involves the targeted deletion of most coding regions for non-structural protein 3 (nsP3) within the viral genome to achieve stable attenuation. This protein is critical for viral replication capability[25–28]. Firstly, regarding the incidence of serious adverse events (SAEs), the risk demonstrated no statistically significant difference compared to the placebo group (*RR*=1.84, *P*=0.185), which supports the favorable benefit-risk profile and facilitates the widespread adoption of the VLA1553 live-attenuated vaccine. This conclusion is supported by the study of Maurer *et al*[29]. Secondly, in terms of local reactions, the vaccine was primarily associated with manageable pain (*RR*=1.37, 95% *CI* 1.16-1.61), a rate significantly lower than that of the mRNA platform (*RR*=3.26, 95% *CI* 1.16-9.17), and VLP platform (PXVX0317: *RR*=2.02, 95% *CI* 1.55-2.65). Thirdly, regarding systemic reactions, although the risks of fever (*RR*=2.49, 95% *CI* 1.01-6.15), fatigue (*RR*=1.47, 95% *CI* 1.02-2.13), and myalgia (*RR*=1.66, 95% *CI* 1.16-2.37) were elevated compared to the placebo group, these reactions were clearly self-limiting, and most resolved spontaneously without requiring medical intervention. Fourthly, in terms of joint-related safety, the risk of arthralgia was not significantly increased (*RR*=1.45, 95% *CI* 0.90-2.33, *P*=0.125), and no vaccine-associated arthritis was reported. These findings are consistent with the results reported by Maurer *et al*[30]. However, in current trials, the sample size of adolescent participants aged 12-18 years is insufficient, necessitating expanded monitoring in younger cohorts to further supplement our findings[15]. Additionally, travelers are often co-exposed to arboviruses such as dengue fever, thus requiring further evaluation of the impact of cross-immunity on safety[31].

In 2010, the Virus-like Particle (VLP) vaccine VRC-CHIKVLP059-00-VP (also named PXVX0317/CHIKV VLP) was developed by the Vaccine Research Center (VRC) located in Maryland, USA[32]. This class of virus-like particles exhibits high immunogenicity and a favorable safety profile, as it mimics conformational epitopes of the virus without requiring the use of the full viral genome[33,34]. VLP vaccines offer significant advantages over traditional vaccines, such as live-attenuated and inactivated vaccines. First, VLPs are non-replicating, resulting in an enhanced safety profile that makes them suitable for broader populations, including pregnant women and immunocompromised individuals. Second, they eliminate the risk of genetic reassortment associated with live-attenuated vaccines[35]. Third, VLPs closely mimic the native virus structure and can elicit potent immune responses even at low doses[36–38]. In this meta-analysis, PXVX0317 demonstrates favorable potential. The vaccine exhibited a satisfactory safety profile in individuals aged 12 and above following a single dose, particularly with respect to systemic adverse reactions. For instance, it showed the lowest risk of fever (*RR*=1.68, 95% *CI* 0.51-5.52). Moreover, in terms of myalgia, PXVX0317 (*RR*=1.47, 95% *CI* 1.05-2.06) demonstrated a lower risk compared to VLA1553 (*RR*=2.63, 95% *CI* 1.86-3.73). These results support its promise as a novel VLP vaccine poised for FDA approval.

In summary, the safety data accumulated in this study provide a foundation for developing public health strategies regarding large-scale vaccination against chikungunya, with an emphasis on implementing informed consent and proactively managing expected adverse reactions. It is noteworthy that significant heterogeneity was observed in certain outcome measures in this study—such as headache (I^2=88.80%) and fever (I^2=76.00%). Potential reasons for this include: firstly, differences in adjuvants and immunogenicity among vaccine platforms (live-attenuated/VLP/mRNA)[39]; secondly, variations in baseline symptom reporting rates between populations in endemic and non-endemic areas[40]; and thirdly, insufficient diagnostic capacity in some endemic regions, where the lack of rapid and specific testing tools may lead to misattribution of symptoms caused by natural infection to vaccination[19].

This meta-analysis has several limitations that should be considered when interpreting the results. Firstly, only eight RCTs were included,

therefore, no assessment of publication bias was conducted. Secondly, the evidence regarding safety in adolescent populations remains insufficient: although the analysis encompassed multiple populations, data in this subgroup are limited—only two trials partially included adolescent participants, precluding stratified safety analyses by age group.

In conclusion, this meta-analysis confirms that the chikungunya vaccine does not increase the risk of serious adverse events in adolescents and adults, supporting its favorable overall safety profile. However, it may lead to a higher incidence of local reactions (such as pain and swelling) and some systemic reactions (including fever, fatigue, and myalgia). These reactions are mostly transient and clinically manageable, and the absence of a significant increase in arthralgia risk further reinforces its positive benefit-risk profile. Moving forward, it is essential to establish a standardized active surveillance system, promote platform-specific vaccine evaluations, and address the data gap in adolescent populations to inform more precise global immunization strategies.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

DMC and YW conceived and designed the work, data collection, data analysis, interpretation and critical revision of the article and approved the final draft. HYL, LPY, NYW and PW analyzed the data, figures and tables, drafting the article. Both DMC and PW contributed to the final version of the manuscript.

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Supplementary Table 1. Subgroup analysis of pain.

Subgroup	Include studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	7	0.046	53.50%	random	1.69 (1.36, 2.10)	<0.001
Phase 1	1	/	/	/	3.26 (1.16, 9.17)	0.018
Phase 2	2	0.917	0.00%	random	1.64 (1.20, 2.26)	0.927
Phase 3	4	0.012	72.60%	random	1.67 (1.22, 2.27)	<0.001
USA	4	0.012	72.60%	random	2.01 (1.31, 3.08)	0.001
Austria/Germany	1	/	/	/	1.59 (0.80, 3.16)	0.185
Brazil	1	/	/	/	1.36 (1.04, 1.78)	0.025
Multicountry sites	1	/	/	/	1.66 (1.16, 2.37)	0.006
mRNA-1388	1	/	/	/	3.26 (1.16, 9.17)	0.025
MV-CHIK	1	/	/	/	1.59 (0.80, 3.16)	0.185
PXVX0317	3	0.274	22.80%	random	2.02 (1.55, 2.65)	<0.001
VLA1553	2	0.964	0.00%	random	1.37 (1.16, 1.61)	<0.001
Dose 1	4	0.012	72.60%	random	1.67 (1.22, 2.27)	0.001
Dose 2	3	0.459	0.00%	random	1.74 (1.29, 2.36)	<0.001

Supplementary Table 2. Subgroup analysis of swelling.

Subgroup	Include studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	5	0.876	0.00%	fixed	3.74 (1.00, 13.91)	0.049
Phase 1	1	/	/	/	1.09 (0.05, 25.43)	0.957
Phase 2	2	0.971	0.00%	/	4.72 (0.29, 77.08)	0.072
Phase 3	2	/	/	/	3.51 (0.21, 59.78)	0.386
USA	3	0.578	0.00%	fixed	2.39 (0.30, 19.42)	0.414
Austria/Germany	1	/	/	/	4.72 (0.29, 77.08)	0.276
Multicountry sites	1	/	/	/	5.03 (0.59, 42.63)	0.139
mRNA-1388	1	/	/	/	1.09 (0.05, 25.43)	0.975
MV-CHIK	1	0.971	0.00%	fixed	4.72 (0.29, 77.08)	0.276
PXVX0317	3	0.842	0.00%	fixed	4.32 (0.78, 23.95)	0.094
Dose 1	2	/	/	/	3.51 (0.21, 59.78)	0.386
Dose 2	3	0.707	0.00%	fixed	3.81 (0.87, 16.75)	0.076

Supplementary Table 3. Subgroup analysis of fever.

Subgroup	Include studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	7	0.000	76.00%	random	2.49 (1.01, 6.15)	0.048
Phase 1	1	/	/	/	0.35 (0.02, 5.24)	0.446
Phase 2	2	0.365	0.00%	random	1.45 (0.55, 3.80)	0.449
Phase 3	4	0.008	74.70%	random	4.77 (1.83, 12.41)	0.001
USA	4	0.006	76.30%	random	1.94 (0.28, 13.54)	0.502
Austria/Germany	1	/	/	/	0.59 (0.07, 5.16)	0.637
Brazil	1	/	/	/	0.59 (0.07, 5.16)	<0.001
Multicountry sites	1	/	/	/	4.30 (2.62, 7.05)	0.280
mRNA-1388	1	/	/	/	0.35 (0.02, 5.24)	0.446
MV-CHIK	1	/	/	/	0.59 (0.07, 5.16)	0.637
PXVX0317	3	0.262	25.40%	random	1.68 (0.51, 5.52)	0.393
VLA1553	2	0.009	85.20%	random	6.83 (2.62, 17.81)	<0.001
Dose 1	4	0.008	74.70%	random	4.77 (1.83, 12.41)	0.001
Dose 2	3	0.413	0.00%	random	1.24 (0.50, 3.06)	0.647

Supplementary Table 4. Subgroup analysis of fatigue.

Subgroup	Include studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	6	0.000	81.20%	random	1.47 (1.02, 2.13)	0.039
Phase 1	1	/	/	/	0.73 (0.15, 3.59)	0.700
Phase 2	1	/	/	/	0.97 (0.50, 1.85)	0.915
Phase 3	4	0.000	86.50%	random	1.65 (1.10, 2.48)	0.016
USA	4	0.000	86.20%	random	1.40 (0.86, 2.28)	0.174
Austria/Germany	1	/	/	/	0.97 (0.50, 1.85)	0.915
Brazil	1	/	/	/	2.27 (1.51, 3.40)	<0.001
mRNA-1388	1	/	/	/	0.73 (0.15, 3.59)	0.700
MV-CHIK	1	/	/	/	0.97 (0.50, 1.85)	0.915
PXVX0317	2	0.836	0.00%	random	1.18 (0.96, 1.45)	0.126
VLA1553	2	0.838	0.00%	random	2.18 (1.87, 2.54)	<0.001
Dose 1	4	0.000	86.50%	random	1.65 (1.10, 2.48)	0.016
Dose 2	2	0.752	0.00%	random	0.93 (0.51, 1.69)	0.807

Supplementary Table 5. Subgroup analysis of myalgia.

Subgroup	Include studies	Heterogeneity test		Effect models	Meta analysis	
		P	I^2		*RR* (95% *CI*)	*P*
Total	7	0.000	79.20%	random	1.66 (1.16, 2.37)	0.006
Phase 1	1	/	/	/	1.07 (0.24, 4.74)	0.928
Phase 2	2	0.346	0.00%	random	1.18 (0.83, 1.68)	0.347
Phase 3	4	0.004	77.90%	random	2.07 (1.43, 2.97)	<0.001
USA	4	0.002	79.10%	random	1.87 (1.15, 3.06)	0.012
Austria/Germany	1	/	/	/	0.84 (0.38, 1.85)	0.668
Brazil	1	/	/	/	2.14 (1.52, 3.04)	<0.001
Multicountry sites	1	/	/	/	1.28 (0.87, 1.89)	0.207
mRNA-1388	1	/	/	/	1.07 (0.24, 4.74)	0.928
MV-CHIK	2	/	/	/	0.84 (0.38, 1.85)	0.668
PXVX0317	3	0.154	46.50%	random	1.47 (1.05, 2.06)	0.026
VLA1553	2	0.086	66.20%	random	2.63 (1.86, 3.73)	<0.001
Dose 1	4	0.004	77.90%	random	2.07 (1.43, 2.97)	<0.001
Dose 2	3	0.637	0.00%	random	1.18 (0.84, 1.65)	0.349