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Post-licensure Safety of the Live-Attenuated Chikungunya Vaccine in Older Adults: An Integrative Review With Implications for Brazil

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Abstract

Post-licensure reports of serious adverse events in older adults have raised concern about the live-attenuated chikungunya vaccine, which is being used in a pilot program in Brazil. This integrative review synthesizes the post-licensure safety evidence for this vaccine in older adults and discusses what it means for Brazilian policy.

A single database, PubMed, was searched on 8 October 2026 for records published from 2023 onward (70 records identified and 30 included). Regulatory documents and press reports were consulted separately as supplementary sources and are not counted among the 30 records. Screening was performed by a single reviewer with artificial intelligence assistance and without independent duplicate screening, but all screening decisions and extracted data were verified by two reviewers. The evidence was synthesized by theme without a formal risk-of-bias tool.

In this review, serious events reported after vaccination clustered in adults aged 65 years and older. An exploratory calculation from passive surveillance data suggested a crude reporting rate in older adults roughly seven times that in younger recipients (ratio of reporting rates about 6.9; exact 95% confidence interval 3.0 to 17.5; a reporting ratio, not a relative risk). A second exploratory calculation indicated that the pivotal trial had roughly a 25% to 40% chance of recording even one such event among its older participants, so the pre-licensure data could not have excluded a rare, age-specific signal. Age restriction appears to be the most direct safeguard currently available, although older adults remain at increased risk of severe chikungunya and no comparative data show that an age limit prevents events.

Passive surveillance, a single database, manufacturer-affiliated sources, and single-screener, artificial intelligence-assisted screening limit these findings. Age-restricted use, active pharmacovigilance within the Brazilian pilot, and evaluation of the virus-like particle vaccine for older adults deserve priority.

Categories: Geriatrics, Epidemiology/Public Health, Infectious Disease
Keywords: brazil, chikungunya vaccine, ixchiq, live-attenuated vaccine, older adults, pharmacovigilance, vaccine safety, virus-like particle vaccine

Introduction And Background

Chikungunya is a mosquito-borne viral disease in which the acute illness typically comes with severe pain in several joints [1]. A spatial modeling study estimated 14.4 million infections and 0.96 million disability-adjusted life years worldwide in 2020 under the observed-burden scenario. The chronic phase accounted for 54% of that burden, and mortality fell disproportionately on children younger than 10 years and adults older than 80 years [2].

Brazil carries a large share of this burden. An estimated 3.2 million cases and US$9.8 billion in costs were recorded in the country between 2011 and 2020 [3]. Notified cases follow a cyclic pattern, have expanded toward the Southeast and South, and are concentrated in socioeconomically disadvantaged municipalities, particularly in the Northeast [1].

Two single-dose vaccines are now licensed in several countries: a live-attenuated vaccine (Ixchiq, VLA1553, Valneva) and a virus-like particle vaccine (Vimkunya, PXVX0317, Bavarian Nordic) [4]. The live-attenuated

vaccine contains a weakened virus that replicates briefly in the vaccinated person, whereas the virus-like particle vaccine contains non-infectious viral protein particles that cannot replicate. No head-to-head study exists. Efficacy against clinical chikungunya disease has not been demonstrated in field trials for either product, so licensure rested on neutralizing antibody titers accepted as surrogate markers of protection [4,5]. In April 2025, Brazil became the first endemic country to license the live-attenuated vaccine [6].

The safety data available at licensure were reassuring. In a pooled analysis of three United States trials, serious adverse events (events that are fatal, life-threatening, or lead to hospitalization or disability) were reported in 1.5% of 3,520 vaccine recipients and 0.8% of 1,033 placebo recipients, and the authors of that analysis reported a comparable safety profile in participants aged 18 to 64 years and in those aged 65 years and older [7], although few older participants were enrolled and such a comparison cannot exclude rare events. Once the vaccine reached routine use, the picture changed. Passive surveillance in the United States, which relies on voluntary reports and can generate signals but cannot measure incidence, and an outbreak-response campaign on Réunion Island identified serious neurological and cardiac events, including deaths, reported mainly in older adults [8-10]. These reports describe events that followed vaccination. Causality could not be established for individual reports, although vaccine-strain virus was identified in the fatal Réunion case [8,10]. Regulatory responses varied: restrictions on use in older adults were imposed, lifted, or modified in Europe and the United States, and the United States license was suspended in August 2025 [8,11,12].

Several reviews have covered the two vaccines. A systematic review by a German working group noted a higher risk of serious events in elderly recipients of the live-attenuated vaccine in post-marketing data [5], a scoping review mapped 77 sources of evidence up to June 2026 [13], and a travel-medicine review described the divergent regulatory decisions [14]. These reviews summarize or map the published evidence. What we could not find was an analysis that places the age-specific post-marketing signal in quantitative perspective against the age composition of the pivotal trial, sets the regulatory divergence beside the proposed immunological mechanism, and reads both against the Brazilian situation, where the vaccine is licensed [6], is being produced locally, and is used in a pilot program [15]. The contribution of this review is therefore integrative and exploratory: it adds derived age-stratified reporting rates and a detectability analysis of the pivotal trial, links them to the regulatory record and to the Brazilian setting, and does not provide pooled estimates of risk. Brazil is a relevant setting because the vaccine is delivered there through a pilot program in selected municipalities rather than routine immunization [15], under a national regulator with its own labeling and pharmacovigilance decisions.

Why age might modify the safety of a replicating vaccine is not established. Possible explanations include age-related changes in the immune control of the vaccine virus, a greater burden of chronic disease, and frailty; these are hypotheses rather than established mechanisms and are examined in the Discussion. The primary objective of this review was to evaluate the post-licensure safety evidence for the live-attenuated chikungunya vaccine in older adults, defined here as adults aged 65 years and older unless stated otherwise, because regulators and studies use thresholds between 60 and 65 years. The secondary objectives were to describe, as crude reporting rates that do not represent incidence or causal risk, the age gradient in the published pharmacovigilance data and the capacity of the pivotal trial to detect it; to summarize the proposed mechanism and the regulatory responses; and to consider what these findings imply for vaccine policy in Brazil.

Review

Methods

Study Design and Reporting

This is an integrative review, which brings together evidence from different designs (clinical trials, surveillance reports, case reports, modeling studies, and regulatory documents), with a structured and reproducible literature search. It was not registered in a prospective registry, and it is not a formal systematic review. The flow of records is shown in the style of a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to make the selection transparent (Figure *1*). Elements of the PRISMA 2020 statement were used for transparency where applicable, and full compliance with PRISMA is not claimed. Because the evidence comes from different designs, each source was interpreted according to its design: randomized trials, passive surveillance, case reports and series, reviews, and models.

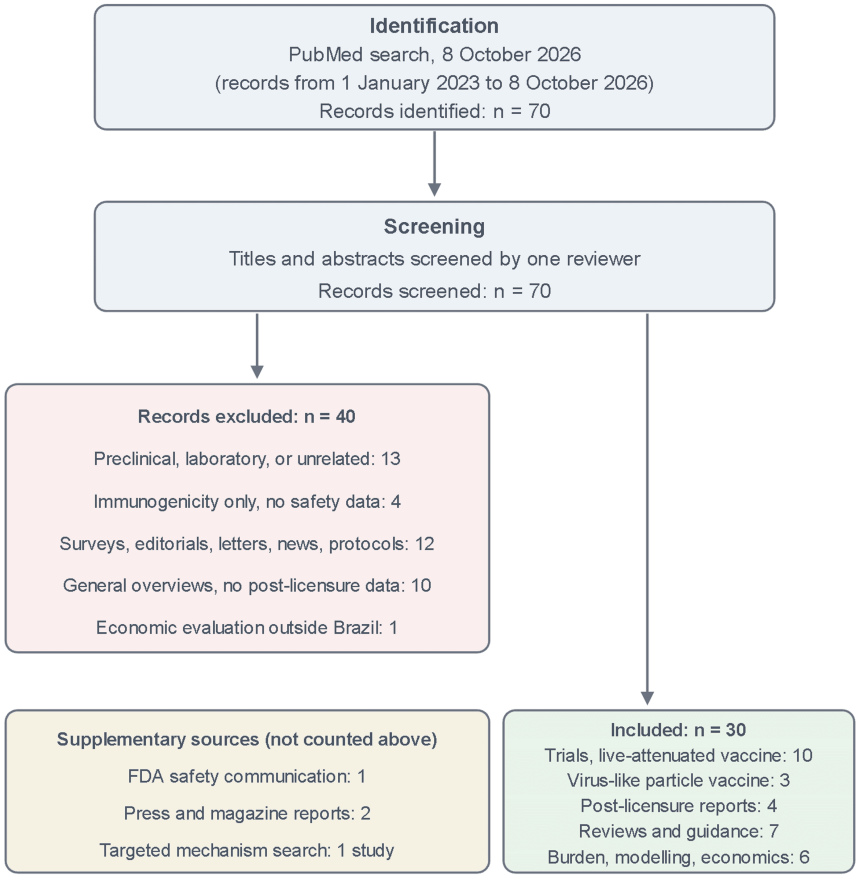


FIGURE 1: Flow of records through the search and selection process

PubMed was searched on 8 October 2026 for records published from 1 January 2023. Supplementary sources were consulted separately and are not counted among the 70 records.

Search Strategy

PubMed was searched on 8 October 2026 for records published between 1 January 2023 and 8 October 2026, with no language restriction. The query combined vaccine terms (the PubMed supplementary concept for chikungunya vaccine, "chikungunya vaccine", "chikungunya vaccines", Ixchiq, VLA1553, Vimkunya, and PXVX0317) with outcome and population terms (safety, "adverse event", "adverse events", tolerability, pharmacovigilance, "serious adverse", postmarketing, post-marketing, "older adults", elderly, aged, and Brazil). The search returned 70 records (Figure *1*). The start date was set to include the publication of the pivotal phase 3 trial of the live-attenuated vaccine in 2023 [16], the first licensure in November 2023 [8], and all post-licensure reports; earlier phase 1 and 2 studies were not searched. Only PubMed was searched. Embase, Scopus, and Web of Science were not, which is a limitation (see Limitations), and the review does not claim exhaustive coverage. The complete search string, with Boolean operators and field tags, is given in Appendix 1. Terms for both the live-attenuated and the virus-like particle vaccine were included because the virus-like particle vaccine is the main alternative for older adults considered in the Discussion.

Supplementary Sources

Regulatory decisions and Brazilian policy are documented mainly outside the indexed literature. We therefore also consulted the safety communication published by the United States Food and Drug Administration (FDA) on the license suspension, a press report on the Brazilian regulatory and production status published on 17 August 2026, and a science magazine report on the Brazilian registration. Two targeted PubMed searches supported the discussion of mechanism: one on the prevalence of neutralizing autoantibodies against type I interferons by age, which identified one population-based study, and one on age and serious adverse events after yellow fever vaccination, which returned no eligible records. During revision, we retrieved and read the pharmacovigilance alert 03/2026 of the Brazilian regulator (Anvisa), which had initially been cited by its title only, and three further official Brazilian documents: the Anvisa registration record of the vaccine, the professional label of the vaccine, and the Anvisa record of Butantan-

CHIK. Eight supplementary sources are therefore cited. Four were identified at the time of the search and are counted separately in Figure *1* (the FDA safety communication, two press or magazine reports, and one study identified by the targeted mechanism search), and four were added during revision; none of these is part of the 70 records or of the 30 included records, so the 38 references cited are the 30 included records plus the eight supplementary sources.

Eligibility Criteria

Records were eligible if they reported human or modeling data on licensed chikungunya vaccines and addressed safety or tolerability, pharmacovigilance or regulatory action, age-related immunogenicity relevant to the benefit-risk balance, the mechanism of vaccine-strain disease, or the Brazilian burden, policy, or economic context. We excluded preclinical and laboratory studies and records on unrelated topics (13 records); reports of immunogenicity without safety data or age-stratified results (four records); acceptability surveys, editorials, letters, news items, study protocols, and a bibliometric analysis (12 records); general overviews that did not address post-licensure safety or age (10 records); and an economic evaluation set outside Brazil (one record). In total, 30 records from the PubMed search were included. The supplementary sources described above are not counted in this total. The list of excluded records with the reason for each is available from the authors on request. Eligibility was assessed at the publication level: when several publications reported on the same trial program, each was retained if it contributed distinct data (for example, different follow-up periods or populations), and the overlap is noted where relevant. Records on pediatric trials, modeling, and economic evaluations, including those set outside Brazil, were retained only as context for the benefit-risk balance and carry little weight in the conclusions. One record from 2021, outside the search period, was identified by the targeted mechanism search and is cited for the age-specific prevalence of interferon autoantibodies.

Data Extraction and Synthesis

One reviewer screened titles and abstracts and extracted study design, population, exposure, events, and main findings. Open-access full texts were read for the United States surveillance report, the Brazilian epidemiological analysis, the Brazilian cost-effectiveness analysis, and the Réunion case series. For the remaining records, the abstract was the main source, and numbers were transcribed as published and rechecked against the text available to us (the full text for those four records and the abstract for the others), so that findings drawn only from abstracts are limited to what the abstracts state. Screening, data extraction, and calculations were assisted by an artificial intelligence tool (Claude, Anthropic), which was also used to format the tables and Figure *1* from the extracted data. The tool was used to propose screening decisions and to extract and format data, and its output was treated as a draft. All screening decisions, every extracted figure, all calculations, and the content of the tables and figure were then checked against the source text by two reviewers, and any discrepancy was resolved in favor of the source text. This verification was not independent duplicate screening: it was applied to decisions that had already been made, so it could detect errors of inclusion and transcription more readily than missed records. No separate log of AI-assisted decisions is provided with this manuscript. Single-reviewer screening is a recognized shortcut in rapid and integrative reviews that increases the risk of selection bias, and we address this in the Limitations. The manuscript was reviewed by a second author. No formal risk-of-bias instrument was applied because the evidence consisted mostly of surveillance reports, case reports, narrative reviews, and models for which no single instrument is appropriate. Instead, each source was classified by design, and its limitations were weighed qualitatively according to that design; the classes are distinguished in the table below in the Results section and in the text. The implications for Brazil were derived by comparing the evidence with the Brazilian regulatory status, the target population, the pilot program, and the Brazilian burden and modeling studies; they are interpretive, are presented separately from the empirical findings, and are qualified where they rest on secondary sources. The evidence was synthesized by theme.

Derived Calculations

Two calculations went beyond what the source documents reported. First, age-stratified crude reporting rates of serious adverse events were derived from the worldwide pharmacovigilance summary, which gave total doses (about 55,900), total events (35), the share of doses given to adults aged 65 years and older (33%), and their share of events (77%). We converted the percentages to counts (18,447 doses and 27 events at 65 years and older; 37,453 doses and eight events below 65 years), computed rates per 10,000 doses and their ratio, and calculated an exact binomial 95% confidence interval for the ratio conditional on the total number of events (a Clopper-Pearson interval for the proportion of events at 65 years and older, transformed to the rate-ratio scale; formulas, inputs, and code are in Appendix 1). The dose shares were treated as fixed, and reporting was assumed to be equal across ages for the purpose of the calculation, an assumption that is unlikely to hold (see Limitations). These are reporting rates and a ratio of reporting rates, not incidence rates or relative risks. Because the inputs are rounded percentages, we also report the range of the ratio under the rounding limits of the dose share (32.5% to 33.5%), with the event count fixed at 27 because events are whole numbers.

Second, we estimated the probability that the pivotal trial would have observed at least one serious event

among its older participants as $1-(1-r)^n$, where r is the event rate per dose estimated in the United States (primary analysis), or the age-specific worldwide rate derived above (sensitivity analysis), and n is the number of older participants. The number of participants needed for a given probability P was $\frac{\ln(1-P)}{\ln(1-r)}$. The calculations were run in Python and independently checked with Wolfram Alpha. Both are exploratory and descriptive and do not replace formal signal detection. The detectability calculation is a hypothetical sensitivity analysis that illustrates how difficult it is to detect a rare event in a small group; it applies a passive post-marketing reporting rate to an actively monitored trial population and does not estimate the probability that the trial would actually have detected vaccine-related events.

Results

Study Selection and Evidence Base

The search identified 70 records. After applying the criteria, 40 were excluded and 30 were included (Figure *1*). The supplementary sources are not counted in these totals. Figure *1* shows the four supplementary sources identified at the time of the search (30 included records plus four supplementary sources, 34 sources in all); the four official Brazilian documents added during revision bring the total to 38 references cited, that is, the 30 included records plus eight supplementary sources (Appendix 1). The included records comprised 10 reports from clinical trials of the live-attenuated vaccine, three reports on the virus-like particle vaccine, four post-licensure safety reports or case reports, seven reviews or guidance documents, and six studies on burden, transmission modeling, or economics, four of them set in Brazil.

Pre-licensure Safety and Immunogenicity

The pivotal phase 3 trial randomized 4,128 adults aged 18 years and older in the United States (3,093 to the vaccine and 1,035 to placebo). Seroprotective neutralizing antibody levels were reached by 263 of 266 vaccinees (98.9%) in the per-protocol population 28 days after vaccination, independent of age. Serious adverse events were reported in 46 of 3,082 vaccine recipients (1.5%) and eight of 1,033 placebo recipients (0.8%), and two were judged related to the vaccine [16]. The related events were a hospitalization for severe myalgia in a 58-year-old woman and one for atrial fibrillation with severe hyponatremia in a 66-year-old man [8]. In a lot-to-lot consistency trial of 408 adults aged 18 to 45 years, none of the six serious events was related to vaccination [17].

Pooling the pivotal, lot-to-lot consistency, and dose-finding trials gave 3,520 vaccine recipients and 1,033 placebo recipients. Medically attended events, adverse events of special interest, and serious events occurred in 12.4%, 0.3%, and 1.5% of vaccinees and in 11.3%, 0.1%, and 0.8% of placebo recipients, respectively, with no clinically important differences by age or medical history [7]. A post hoc broad definition of adverse events of special interest (fever plus at least one additional symptom within 30 days) identified events in 11.7% of vaccinees (361 of 3,082) and 0.6% of placebo recipients (6 of 1,033), most of them solicited symptoms [18].

Immunogenicity in older adults mirrored that in younger adults. In a combined analysis of two phase 3 trials, the seroresponse did not differ between participants aged 18 to 64 years and those aged 65 years and older [19]. Seroprotection persisted at 98.0% (50 of 51) among adults aged 65 years and older at two years [20], and the overall seroresponse was 94.5% (240 of 254) at four years [21]. In 754 Brazilian adolescents, related adverse events were more frequent with the vaccine than with placebo (70% versus 48%), one serious event (a high-grade fever) was possibly related, and seroprotection reached 98.8% at 28 days and 98.3% at 12 months among baseline seronegative participants [22,23]. A phase 2 trial in 304 children aged 1 to 11 years found no significant difference in solicited events between vaccine and control groups [24]. A meta-analysis of 14 datasets and more than 4,000 participants, published before the post-licensure reports, found no significant increase in serious adverse events among vaccinated participants across candidate chikungunya vaccines [25].

Post-licensure Safety Reports

Spontaneous reports describe events that followed vaccination without establishing causality, whereas trial events are collected prospectively and individually investigated cases can have laboratory evidence; we distinguish these categories below. In the United States, passive surveillance through the Vaccine Adverse Event Reporting System recorded 28 reports for vaccinations given in 2024: 22 non-serious and six serious. All six serious events occurred in men aged 65 years and older, with onset three to five days after vaccination. Three were encephalopathies, one was aseptic meningitis, one was atrial flutter with a suspected small myocardial infarction, and one was prolonged hypotension. Chikungunya virus RNA was detected in serum on day 13 in one patient, and chikungunya antibodies were found in cerebrospinal fluid in another. Expert reviewers considered an association with the vaccine plausible for each report [8]. Based on 13,891 doses sold in 2024, 52.7% of which were administered to persons aged 65 years and older, the estimated rate among older adults was 82 per 100,000 doses for serious events (95% confidence interval 30

to 180) and 68 per 100,000 for hospitalization (20 to 160). The denominator was not adjusted for incomplete capture of sales, and the age split came from retail pharmacy data only [8].

By 31 August 2025, about 55,900 doses had been given worldwide and 35 serious adverse events had been reported, or 6.3 per 10,000 doses. Adults aged 65 years and older received 33% of doses and accounted for 77% of events. The median age of those with events was 73 years and 91% had comorbidities. Most events began within seven days and consisted of chikungunya-like systemic reactions (15 events), neurological events (13 events), cardiac events (three events), and renal events (three events). Three deaths occurred in older men with multimorbidity, and one case of vaccine-strain encephalitis was considered probably related to vaccination [9]. This report was written by authors affiliated with the manufacturer, who noted that regulatory reviews judged the benefit-risk balance to remain favorable within authorized and nationally recommended populations.

On Réunion Island, an outbreak-response campaign in 2025 vaccinated 6,418 adults, about 4,500 of them aged 65 years and older [26], in an older and multimorbid population [9]. One 84-year-old man developed fever, polyarthralgia, confusion, acute kidney injury, and hemodynamic instability after vaccination and died 14 days after symptom onset. Vaccine-strain virus was identified by sequencing in serum and cerebrospinal fluid, and French authorities recognized the event as plausibly related to the vaccine [10]. The principal post-licensure reports are summarized in Table *1*.

Source	Setting and period	Exposure and events	Main finding
Pivotal and pooled trials [7,16]	United States, 2020 to 2021 (pre-licensure)	3,082 vaccine and 1,033 placebo recipients in the pivotal safety population; 3,520 vaccine recipients pooled	Serious events 1.5% versus 0.8%; two related to the vaccine; no clinically important differences by age
Passive surveillance [8]	United States, 2024	13,891 doses sold; 52.7% to persons aged 65 years and older; six serious events	All six serious events in men aged 65 years and older; estimated rate 82 per 100,000 doses at 65 years and older
Global pharmacovigilance [9]	Worldwide, 9 November 2023 to 31 August 2025	About 55,900 doses; 35 serious events (6.3 per 10,000 doses)	33% of doses and 77% of events at 65 years and older; three deaths; one probable vaccine-strain encephalitis
Fatal case report [10]	Réunion Island, 2025	One man aged 84 years	Febrile encephalopathy with death; vaccine strain in serum and cerebrospinal fluid
Case series [26]	Réunion Island, 2025	Five adults aged 82 to 88 years among 6,418 vaccinated adults; two deaths	Autoantibodies against type I interferons in all three encephalitis cases
Virus-like particle vaccine [27]	United States and Germany, to 31 August 2025	More than 12,500 doses	No serious events reported at 65 years and older

TABLE 1: Principal post-licensure safety reports for chikungunya vaccines

The Réunion case report and case series probably include the same fatal patient, and the United States cases are also part of the global total.

Age-Stratified Crude Reporting Rates

The derived calculation implies about 27 events in 18,447 doses given at 65 years and older (14.6 per 10,000 doses) and about eight events in 37,453 doses given below 65 years (2.1 per 10,000). The rate ratio was about 6.9 (conditional exact 95% confidence interval 3.0 to 17.5; 6.7 to 7.0 under the rounding limits of the reported dose share). These are crude reporting rates and a ratio of reporting rates, not incidence rates or a relative risk. The ratio derives from rounded percentages, does not adjust for comorbidity, frailty, or reporting behavior, and rests on passive reports.

Detectability of an Age-Specific Signal in the Pivotal Trial

The vaccine arm of the pivotal trial included 287 participants aged 65 to 74 years and 59 aged 75 years and older, 346 older participants in total [8]. If serious events occurred at the rate estimated for the United States (82 per 100,000 doses), the probability that these 346 participants would have produced at least one event was 24.7% (9.9% to 46.4% across the confidence interval). For the 59 participants aged 75 years and older, the probability was 4.7%. A trial would have needed about 1,960 older participants for an 80% chance of

observing one such event and about 3,650 for a 95% chance. With the higher age-specific worldwide rate derived above (14.6 per 10,000 doses) as a sensitivity analysis, the probabilities were 39.8% and 8.3%, and about 1,100 and 2,050 older participants would have been needed for an 80% and a 95% chance. Among the 346 older participants, the trial did record one vaccine-related serious event, atrial fibrillation with hyponatremia in a 66-year-old man described above [8]. The trial data are therefore compatible with the later signal, but a single case could not have identified it. These figures rest on an imprecise rate based on few events, so they indicate scale rather than a firm estimate. They are hypothetical sensitivity analyses that show how difficult it is to detect a rare event in a small group, not estimates of the probability that the trial would actually have detected vaccine-related events, because they apply a passive post-marketing reporting rate to an actively monitored trial population.

Proposed Mechanism

Gervais et al. studied five unrelated adults aged 82 to 88 years who developed severe reactions after vaccination on Réunion Island in 2025; two died. This is a very small case series, and the association between interferon autoantibodies and encephalitis rests on only three encephalitis cases. The three patients with encephalitis (aged 84 to 85 years, one fatal) all carried immunoglobulin G autoantibodies that neutralized high concentrations of interferon alpha and omega on admission. The two patients without encephalitis, one with rhabdomyolysis and one who died during hospitalization for chikungunya after late vaccination, lacked these autoantibodies [26]. In a sample of 34,159 uninfected people from the general population, comparable autoantibodies were present in 0.18% of those aged 18 to 69 years, 1.1% of those aged 70 to 79 years, and 3.4% of those aged 80 years and older [28]. Relative to the prevalence in the general population, the authors estimated odds ratios for carriers of 110.6 (95% CI 20.2 to 704.0) for serious events and 553 (95% CI 50.8 to 75,503.7) for encephalitis, and they recommended screening people older than 65 years before vaccination, noting that a whole-blood assay has been developed [26]. The United States investigators proposed immunosenescence, as described for yellow fever vaccine, as a possible reason for inadequate control of replicating vaccine virus [8], and a recent review notes that advancing age is associated with a greater risk of serious adverse events after yellow fever vaccination [29].

Regulatory Responses

Regulatory responses diverged over a few months in 2025 (Table *2*). After the United States Advisory Committee introduced a precaution for adults aged 65 years and older in April, French authorities removed the recommendation for that age group on Réunion. The European Medicines Agency reported 17 serious events worldwide, including two deaths, and recommended a pause for persons aged 65 years and older on 7 May, and the United States agencies recommended a pause for those aged 60 years and older on 9 May [8]. The European pause was lifted in July with strengthened warnings, and the United States pause was lifted on 6 August with a labeling update stating that the vaccine is indicated only for people at high risk of exposure [8]. On 22 August 2025, the FDA suspended the license, citing more than 20 serious adverse events, 21 hospitalizations, and three deaths [12].

Date	Authority	Action
November 2023	FDA	Licensed for adults aged 18 years and older[8]
April 2025	Anvisa	Registered the vaccine [6]; one report gives an indication of up to 65 years[30]
April 2025	ACIP	Voted to introduce a precaution for age 65 years and older[8]
26 April 2025	French authorities	Removed the recommendation for persons aged 65 years and older on Réunion[8]
7 May 2025	EMA	Reported 17 serious events including two deaths (ages 62 to 89 years) and recommended a pause at 65 years and older [8]
9 May 2025	FDA and CDC	Recommended a pause at 60 years and older[8]
July 2025	EMA	Lifted the pause; use only when chikungunya risk is significant, after benefit-risk assessment[8]
6 August 2025	FDA	Lifted the pause and required a labeling update[8]
22 August 2025	FDA	Suspended the biologics license, citing more than 20 serious events, 21 hospitalizations, and three deaths [12]
2026	Anvisa	Pharmacovigilance alert 03/2026 on update of indication and safety information (content not retrieved) [31]
May 2026	Anvisa	Authorized Butantan to produce Butantan-CHIK for adults aged 18 to 59 years at increased risk of exposure [15]
June 2026	Anvisa	Received a submission for a virus-like particle vaccine [15]

TABLE 2: Regulatory timeline for the live-attenuated chikungunya vaccine

ACIP: Advisory Committee on Immunization Practices (United States); Anvisa: Brazilian Health Regulatory Agency; CDC: Centers for Disease Control and Prevention; EMA: European Medicines Agency; FDA: United States Food and Drug Administration

Virus-Like Particle Vaccine

In a phase 3 trial of 3,258 participants aged 12 to 64 years, 97.8% of 2,559 evaluable vaccine recipients had a seroresponse at day 22 compared with 1.2% of 424 placebo recipients. Most adverse events were grade 1 or 2, and injection site pain (23.7%) and fatigue (19.9%) were the most common [32]. In a separate trial of 413 adults aged 65 years and older, the seroresponse was 87% (165 of 189) at day 22 and 76% (139 of 184) at day 183, and no vaccine-related serious adverse events or deaths occurred [33]. Up to 31 August 2025, more than 12,500 doses had been administered in the United States and Germany, and no serious adverse events were reported in persons aged 65 years and older, although the abstract does not state how many older persons were vaccinated. The report was written by employees of the manufacturer [27].

Brazilian Context

The Brazilian regulator registered the live-attenuated vaccine in April 2025 [6]. A science magazine reported the registration as being for people up to 65 years [30], and a 2026 press report describes the current authorization as ending at 59 years, with the vaccine contraindicated in pregnancy and in immunodeficient or immunosuppressed people [15]. The Anvisa pharmacovigilance alert 03/2026, which we retrieved and read in full during revision, resolves the difference: it restricted the indication to adults aged 18 to 59 years at increased risk of exposure, added contraindications for immunosuppression, poorly controlled or multiple chronic medical conditions, and pregnancy, and added warnings and adverse reactions identified after marketing in other countries, citing safety signals mainly in people aged 60 years and older and in people with chronic disease [31]. In May 2026, the regulator authorized the Butantan Institute to produce Butantan-CHIK for adults aged 18 to 59 years at increased risk of exposure, which, according to the press report, shares the active ingredient, composition, and manufacturing process of Ixchiq [15]. The Ministry of Health said that vaccination takes place only in a pilot run by Butantan in municipalities of six states (Alagoas, Goiás, Minas Gerais, Mato Grosso do Sul, Sergipe, and São Paulo), with about 48,000 doses administered, and that incorporation into the public health system requires a favorable opinion from the national commission for technology incorporation (Conitec) [15]. A virus-like particle vaccine was submitted to Anvisa for review by a Brazilian company in June 2026 [15].

Modeling work points to working-age adults as the group with the largest absolute benefit in Brazil. In an age-structured model across 11 states, vaccinating adults aged 18 to 59 years averted the largest absolute number of symptomatic cases (62.5% with the virus-like particle vaccine and 66.2% with the live-attenuated vaccine under disease- and infection-blocking assumptions), whereas vaccinating children aged 1 to 11 years gave the lowest number needed to vaccinate [6]. A cost-effectiveness analysis for adults aged 18 years and older found the live-attenuated vaccine dominant over both the recombinant vaccine and no vaccination from the health-sector and societal perspectives. It assumed a serious adverse event proportion of 0.1% for the live-attenuated vaccine and left older adults and immunocompromised persons outside its scope [3]. A compartmental model suggested that uniform countrywide vaccination has a limited effect on disease costs and that vaccinating about 10% of the population early was the most efficient scenario [34]. A model of an epidemic in Paraguay estimated that a 75%-efficacious vaccine given to 40% of persons aged 12 years and older over three months would have prevented 23% of cases [35].

Discussion

Serious events after vaccination with the live-attenuated chikungunya vaccine cluster in adults aged 65 years and older, with a crude rate roughly seven times that of younger recipients, although the interval around that ratio is wide. The pivotal trial enrolled too few older participants to have detected an event of that frequency reliably [8,16]. A host mechanism, neutralizing autoantibodies against type I interferons, was found in all three encephalitis cases studied, which offers a biologically coherent explanation that becomes more common with age. This review reads that evidence against the Brazilian situation.

Strength of the Signal

The signal comes from several sources, although they are not fully independent. The United States cases are also part of the global total, and the Réunion case report and case series probably describe the same fatal patient [8-10,26]. Detection of vaccine-strain virus in blood and cerebrospinal fluid in the fatal Réunion case supports a causal role in that patient [10]. In the United States series, chikungunya antibodies in cerebrospinal fluid in one patient and viral RNA at an unusually long interval in another were considered supportive of an association, but causality could not be established for individual reports, and passive systems cannot provide incidence [8]. The age-specific rates derived here inherit those weaknesses. The numerator comes from spontaneous reports, whose completeness may differ by age, and the denominator is estimated from sales or administered doses. In Réunion, the vaccinated population was also selected for age and comorbidity [9], so more events in older people reflect the exposure of a frail group as well as susceptibility. Age is also confounded with comorbidity and frailty, so it is better read as a marker of risk than as a definitive predictor: the median age of those with events was 73 years and 91% had comorbidities [9], and Anvisa likewise described the signals as occurring mainly in people aged 60 years and older and in people with chronic disease [31]. The ratio indicates the direction of the effect, not its size.

Why the Trials Could Not Exclude It

Before licensure, a pooled analysis reported comparable safety below and above 65 years [7], and a meta-analysis found no excess of serious events [25]. Those conclusions were correct for the populations studied. Our calculation shows why they could not exclude a rare, age-specific event. With 346 participants aged 65 years and older and 59 aged 75 years and older, the chance of seeing a single event at the United States post-marketing rate was about one in four and about one in 20, and about 40% and 8% at the higher worldwide rate. The trial did record one related cardiac event in a 66-year-old man [8], which fits the later signal but was a single case. The Anvisa assessment of the registration dossier also records that, among about 360 trial participants aged 65 years and older, serious adverse events and medically attended events associated with the vaccine were more frequent than in younger participants [36], so the statement that safety was comparable across age groups [7] should be read with caution. Trial volunteers were healthy by design [16], whereas among people with serious events after licensure the median age was 73 years and 91% had comorbidities [9]. The German systematic review drew a similar contrast between acceptable pivotal safety and a higher post-marketing risk in elderly patients [5], and the authors of the meta-analysis had already called for studies in frail populations [25]. Small cohorts of healthy older volunteers provide limited information on frail older adults.

Mechanism and Its Limits

The autoantibody finding offers a biologically coherent explanation and parallels the yellow fever vaccine experience [26,29]. Population data show that such autoantibodies are uncommon below 70 years and become more frequent afterward [28], which fits the age gradient. The evidence is thin, however: it comes from a case series of five patients. Only three encephalitis cases were studied; the odds ratios rest on a handful of patients and have very wide intervals, and the two other severe reactions in that series were not explained by autoantibodies [26]. The mechanism therefore cannot account for every serious event, such as the cardiac and renal events in the global series [9]. The authors recommend screening older adults before vaccination [26], but we found no evidence that such a program has been validated or implemented, so age remains the practical proxy for now.

Regulatory Divergence

Regulators looked at similar data and reached different decisions. Europe kept the vaccine with strengthened warnings and a requirement of significant chikungunya risk, the United States paused and then suspended it, and several other countries restricted use in older adults [8,11,12]. Much of the divergence can be explained by the setting. The United States label itself concluded that vaccination is not advisable for most United States travelers because their risk of chikungunya is low [8]. For residents of an outbreak area, the same vaccine risk is weighed against a real risk of severe disease, which is higher in older adults [8,27,33]. The FDA statement that clinical benefit had not been verified in confirmatory studies [12] is also a reminder that licensure rested on surrogate antibody levels [5].

Implications for Brazil

The official records resolve the discrepancy in the reported age ceiling. Anvisa registered the vaccine in April 2025 for adults aged 18 years and older at increased risk of exposure, with no upper age limit [36], so the ceiling of 65 years reported by a magazine [30] is not supported by the registration record. The ceiling of 59 years was introduced by Anvisa alert 03/2026 [31] and appears in the professional label of the vaccine [37]. It keeps the vaccine away from the group in which events clustered. In the evidence reviewed, age is the most direct safeguard available while individual susceptibility cannot be tested routinely, although no comparative data show that an age limit prevents events and age is confounded with comorbidity and frailty; the contraindications added by Anvisa for poorly controlled or multiple chronic conditions address comorbidity directly [31]. The ceiling of 59 years leaves adults aged 60 to 64 years outside the indication, a group on which the data reviewed say little. Modeling points to working-age adults as the group with the largest absolute benefit [6], which fits the label. Yet older adults are at increased risk of severe chikungunya [8,27,33], and mortality is concentrated in children and in adults older than 80 years [2], so the people at highest risk of dying from the disease are those for whom the live vaccine is least suitable. A label restriction also does not guarantee practice. In a program that has already delivered about 48,000 doses through public services [15], preventing off-label vaccination of older people and of immunosuppressed persons requires explicit screening at the point of care.

The pilot also offers an opportunity that the early international experience lacked. Age-stratified, denominator-based active surveillance with standardized case definitions for predefined events, such as encephalitis, aseptic meningitis, cardiac events, and hospitalization after vaccination, with early collection of serum and cerebrospinal fluid for molecular testing and sequencing to separate vaccine strain from wild-type virus, would produce the incidence figures that passive systems cannot. The Réunion case shows that sequencing can settle the question [10]. Anvisa considers the Butantan product equivalent to Ixchiq, with the same active ingredient and equivalent composition, formulation, and manufacturing process, and it considers the clinical and safety data obtained for Ixchiq applicable to it [38]; the international safety record is therefore relevant to the Brazilian product.

For the national commission and the immunization program, the cost-effectiveness analysis that found the live-attenuated vaccine dominant explicitly left older adults and immunocompromised persons outside its scope, and its authors advise that policy weigh emerging safety data [3]. It should be updated if the vaccine is considered for any group beyond working age. The virus-like particle vaccine, now under review by the regulator [15], has so far shown no serious events in adults aged 65 years and older in a short, manufacturer-authored post-authorization report [27], together with a good immune response in the older-adult trial [33]. It is therefore a candidate for the older groups; although its post-authorization experience is brief, the number of older recipients is unknown, and no head-to-head comparison exists [4]. The strategy suggested for Brazil, starting in high-incidence Northeast municipalities and extending to Southeast urban centers [1], can be combined with age-restricted use of the live vaccine and evaluation of the non-replicating alternative for older adults.

Limitations

The search covered one database for records from 2023 onward, and screening was done by one reviewer with artificial intelligence assistance and without independent duplicate screening (although the screening decisions were verified by two reviewers), so relevant reports such as conference abstracts, regulatory assessments, and literature indexed only elsewhere may have been missed. Embase, Scopus, and Web of Science were not searched; the start date of 2023 excluded earlier phase 1 and 2 studies, and the eligibility criteria were broad, spanning safety, immunogenicity, mechanism, modeling, and policy evidence, which leaves room for subjective selection decisions; the list of excluded records is available on request rather than published. For most records, only the abstract was available, and details could differ from the full text; this includes the worldwide pharmacovigilance summary from which the age-stratified rates were derived, which was read as an abstract. No formal critical appraisal tool was applied, so the weight given to each source rests on a qualitative judgment. Brazilian regulatory information was verified against official Anvisa and Butantan documents retrieved during revision, but the actions of other agencies (the European Medicines Agency and the United States Advisory Committee) are reported through a peer-reviewed surveillance report and FDA communication rather than through the documents of those agencies themselves, and part of the information on the Brazilian pilot comes from a press report. Key post-marketing figures originate from

passive surveillance and from a report by manufacturer-affiliated investigators. The pivotal trials of the live-attenuated vaccine were sponsored by its manufacturer, and the virus-like particle trials and the early post-authorization report on that vaccine were sponsored or written by its manufacturer, so reporting and sponsorship bias cannot be excluded. The derived rates and detectability estimates rest on rounded percentages, an estimated denominator, and few events, and they assume equal reporting across age groups, so they are exploratory. The integrative design does not permit pooled estimates, and the observations on the virus-like particle vaccine rely on short follow-up. The implications for Brazil are interpretive: no structured framework for transferring international evidence to the Brazilian setting was applied, and they are presented separately from the empirical findings.

Research priorities

The most useful next steps are prospective, age-stratified active surveillance in the Brazilian pilot, studies of interferon autoantibody prevalence in older Brazilians and of whether pre-vaccination testing predicts reactions, and direct comparison of the two vaccines in older adults.

Conclusions

Serious adverse events reported after the live-attenuated chikungunya vaccine concentrate in adults aged 65 years and older, and the available passive-surveillance data suggest a reporting rate several times higher than in younger recipients, although age is confounded with comorbidity and frailty. The pivotal trial included too few older participants to detect events of this size, and a mechanism involving autoantibodies against type I interferons has now been described in a small case series. Regulators responded in different ways, and the evidence still rests largely on passive reports.

For Brazil, the live-attenuated vaccine should stay out of use in older adults. The current Brazilian indication ends at 59 years, according to the regulator's 2026 alert and the product label. Adding active pharmacovigilance to the pilot and assessing the virus-like particle vaccine for older adults are advisable next steps. Older adults remain at increased risk of severe chikungunya and should not be left without options, and policy should be updated as active surveillance data become available.

Appendices

Appendix 1

Post-licensure safety of the live-attenuated chikungunya vaccine in older adults: an integrative review with implications for Brazil (article ID 548279)

A. PubMed search string

Database: PubMed. Date of search: 8 October 2026. Publication date limits: 1 January 2023 to 8 October 2026. No language restriction. Records returned: 70.

("Chikungunya Vaccine"[Supplementary Concept] OR "chikungunya vaccine" OR "chikungunya vaccines" OR Ixchiq OR VLA1553 OR Vimkunya OR PXVX0317) AND (safety OR "adverse event" OR "adverse events" OR tolerability OR pharmacovigilance OR "serious adverse" OR postmarketing OR post-marketing OR "older adults" OR elderly OR aged OR Brazil) AND 2023/01/01:2026/10/08[Date - Publication]

B. Derived calculations

Calculation 1. Age-stratified crude reporting rates of serious adverse events (worldwide pharmacovigilance summary, to 31 August 2025).

· Inputs: total doses N = 55,900; total serious events E = 35; share of doses at 65 years and older = 33%; share of events at 65 years and older = 77%.

· Doses at 65 years and older = 0.33 x 55,900 = 18,447; doses below 65 = 55,900 - 18,447 = 37,453.

· Events at 65 years and older = 0.77 x 35 = 26.95, rounded to 27; events below 65 = 35 - 27 = 8.

· Rates per 10,000 doses: 27/18,447 x 10,000 = 14.6 (65 and older); 8/37,453 x 10,000 = 2.1 (below 65).

· Rate ratio = (27/18,447) / (8/37,453) = 6.85, reported as about 6.9.

· Exact 95% confidence interval, conditional on the total of 35 events: Clopper-Pearson interval (L, U) for the proportion p = 27/35, transformed to the rate-ratio scale as RR = [p/(1 - p)] x (37,453/18,447). Result: 3.0 to 17.5.

· Rounding sensitivity: with the dose share at 32.5% and 33.5%, the rate ratio is 7.0 and 6.7.

· Assumptions: dose shares fixed; equal reporting across ages. These are crude reporting rates, not incidence rates.

Calculation 2. Detectability of an age-specific signal in the pivotal trial.

· Probability of at least one event among n older participants: P = 1 - (1 - r)^n, where r is the event rate per dose.

· Participants needed for a probability P: n = ln(1 - P) / ln(1 - r).

· Inputs: n = 346 participants aged 65 years and older (287 aged 65 to 74 and 59 aged 75 and older); primary r = 82 per 100,000 doses (United States; 95% CI 30 to 180); sensitivity r = 14.6 per 10,000 doses (worldwide, Calculation 1).

· Results, r = 82 per 100,000: P = 24.7% for n = 346 (9.9% to 46.4% across the confidence interval); 4.7% for n = 59; about 1,960 participants for P = 80% and about 3,650 for P = 95%.

· Results, r = 14.6 per 10,000: P = 39.8% for n = 346 and 8.3% for n = 59; about 1,100 and 2,050 participants for P = 80% and 95%.

· This is a hypothetical sensitivity analysis. It applies a passive post-marketing reporting rate to an actively monitored trial population.

Code (Python 3, SciPy):

```
from scipy.stats import beta
import math
N, E = 55900, 35
d65 = round(N*0.33); e65 = round(E*0.77)
dlo = N - d65; elo = E - e65
rate65 = e65/d65*1e4; ratelo = elo/dlo*1e4
rr = (e65/d65)/(elo/dlo)
lo = beta.ppf(0.025, e65, E-e65+1)
hi = beta.ppf(0.975, e65+1, E-e65)
to_rr = lambda p: p/(1-p)*(dlo/d65)
ci = (to_rr(lo), to_rr(hi))
def p_atleast1(r, n): return 1-(1-r)**n
def n_needed(r, P): return math.log(1-P)/math.log(1-r)
```

Results were independently checked with Wolfram Alpha.

C. Supplementary (non-PubMed) sources

These sources were consulted separately and are not counted among the 70 PubMed records. The reference numbers are those of the reference list.

1. U.S. Food and Drug Administration. FDA update on the safety of Ixchiq (chikungunya vaccine, live): FDA suspends biologics license (2025). Accessed 8 October 2026.

2. Tribuna de Minas. Chikungunya vaccine: Anvisa evaluates new immunizing agent and Butantan begins production (2026). Accessed 8 October 2026.

3. Revista Pesquisa FAPESP. FDA suspends chikungunya vaccine approved in Brazil (2025). Accessed 8 October 2026.

4. Anvisa. Alert 03/2026 (pharmacovigilance): update to the indication and safety information for the chikungunya vaccine (live-attenuated recombinant) Ixchiq (2026). Accessed 11 November 2026.

5. Anvisa. IXCHIQ (chikungunya vaccine): new registration (2025). Accessed 11 November 2026.

6. Butantan Institute. IXCHIQ (chikungunya vaccine, recombinant and live-attenuated): healthcare professional package insert (2026). Accessed 11 November 2026.

7. Anvisa. Butantan-CHIK (2026). Accessed 11 November 2026

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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