

Global epidemiology and molecular virology of chikungunya virus: Two decades of resurgence, spread, and emerging control strategies (2004-2026)

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Chikungunya virus (CHIKV) is an Aedes-borne alphavirus of the family Togaviridae that has undergone one of the most dramatic geographic expansions of any arbovirus over the past two decades. Once regarded as a geographically confined, self-limiting febrile illness of East Africa and South Asia, CHIKV has, since 2004, established autochthonous transmission in at least 119 countries and territories across all six WHO regions, with modelled global incidence of autochthonous cases rising from an estimated 0.28 to 11.13 per 100,000 population between 2004 and 2024¹. This review synthesises two decades of peer-reviewed molecular-virological, phylogenetic and epidemiological literature, together with contemporary WHO, PAHO, ECDC and Africa CDC surveillance data, with two aims: first, to consolidate current understanding of CHIKV genome organisation, replication, receptor usage, genotype evolution and the molecular determinants of vector adaptation and pathogenicity; and second, to trace the virus's regional epidemiological trajectories - the founding 2004-2006 East African and Indian Ocean epidemic and the E1-A226V substitution that adapted the virus to *Aedes albopictus*; explosive re-emergence and endemic settling across the Indian subcontinent and South/Southeast Asia; introduction into the Americas via the Caribbean in December 2013 and subsequent hemispheric spread; recurrent outbreaks across sub-Saharan and East Africa; progressively frequent autochthonous transmission in Europe since 2007, culminating in an unprecedented 2025 outbreak in mainland France linked to a major epidemic on Réunion Island; and the first large mainland Chinese outbreak (Guangdong, 2025). We further examine the environmental and socioeconomic factors associated with this resurgence - without inferring causation from ecological correlations - and critically appraise the rapid but troubled rollout of the first licensed chikungunya vaccines, IXCHIQ and VIMKUNYA, including the 2025 safety-related suspension of IXCHIQ's US biologics licence. Persistent gaps in molecular surveillance, case confirmation and burden estimation continue to obscure the true scale of CHIKV disease, particularly in low-resource settings. We conclude by identifying the principal microbiological knowledge gaps - including incomplete understanding of the determinants of chronic arthralgia, the correlates of vaccine-induced protection, and the real-time genomic surveillance capacity needed to track further vector-adaptive evolution - that should guide the next phase of CHIKV research.

Keywords: Chikungunya virus, Molecular virology, Genotype evolution, Mxra8 receptor, Global epidemiology, Arbovirus, *Aedes albopictus*, *Aedes aegypti*, E1-A226V, Vaccine safety

INTRODUCTION

Chikungunya virus (CHIKV) belongs to the genus Alphavirus within the family Togaviridae and is transmitted principally by *Aedes aegypti* and *Ae. albopictus* mosquitoes.

Following inoculation, the virus replicates in multiple peripheral cell types, producing detectable viraemia within 2-12 days¹. Human infection is characterised by acute fever, polyarthralgia and rash; approximately half of patients

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develop chronic polyarthralgia that may persist for months to years, and unusual complications including hepatitis, myocarditis, encephalopathy and, in neonates, mother-to-child transmission have been documented^{2,3}. Classical estimates placed CHIKV mortality at roughly 1 per 1,000 infections, but recent large epidemics have shown markedly higher case-fatality among elderly and comorbid patients.

CHIKV was first isolated during an outbreak in the Southern Province of Tanganyika (present-day Tanzania) in 1952-1953^{4,5}, after which the virus circulated sporadically and regionally across Africa and Asia for five decades. Since 2004, however, CHIKV has undergone an unprecedented and still-accelerating geographic expansion: autochthonous transmission has now been documented in at least 119 countries and territories across Africa, Asia, Europe, the Americas and the Western Pacific⁶, and the disease has repeatedly demonstrated the capacity to establish itself in regions with no prior history of transmission.

Most existing narrative reviews of this resurgence are epidemiologically oriented. The present review instead gives equal weight to the underlying molecular virology - genome organisation and replication, receptor usage, genotype evolution, and the specific viral determinants of vector adaptation and disease pathogenesis - before using that mechanistic foundation to interpret two decades (2004-2026) of regional epidemiological data and the current state of chikungunya vaccination.

Molecular virology: Genome, replication, genotype evolution and pathogenesis

Genome organisation and virion structure

CHIKV is an enveloped virus with an 11,805-nucleotide, positive-sense, single-stranded RNA genome that encodes two polyproteins: a non-structural polyprotein (nsP1-nsP4) required for RNA replication, and a structural polyprotein (C, E3, E2, 6K, E1) that is proteolytically processed into the mature virion proteins after translation (Fig. 1 and 2). Fig. 1 shows the genome organisation and translation products at the RNA and protein level; Fig. 2 shows the structural organisation of the CHIKV virion.

Replication cycle and receptor usage

CHIKV entry begins with attachment of the E2 glycoprotein to the cell-adhesion molecule Mxra8, identified through a genome-wide CRISPR/Cas9 screen as a shared entry receptor for several arthritogenic alphaviruses, including CHIKV, Ross River, Mayaro and o'nyong-nyong viruses⁷. Cryo-electron microscopy shows that Mxra8 wedges into a cleft formed between adjacent E2-E1 heterodimers within a trimeric spike, and that Mxra8 occupancy is reduced on virions retaining the E3 protein, linking receptor engagement to virion maturation state⁸. Mxra8 is expressed on synovial fibroblasts, osteoblasts, chondrocytes and skeletal muscle cells, and antibody blockade of Mxra8 reduces both CHIKV

infection and virus-associated joint swelling in mice⁷ - a finding directly relevant to the joint tropism discussed in the next section. Following receptor-mediated endocytosis and low-pH-triggered membrane fusion, the viral genome is released into the cytoplasm, where the non-structural polyprotein is translated and cleaved by the nsP2 protease to assemble a membrane-associated replication complex; this complex first synthesises a full-length negative-sense RNA template and subsequently the genomic and subgenomic (structural-protein-encoding) positive-sense RNAs². Structural proteins are translated from the subgenomic RNA, and progeny virions bud from the plasma membrane after nucleocapsid assembly and glycoprotein maturation.

Genotype evolution and the molecular basis of vector adaptation

E1-gene-based phylogenetic analysis distinguishes three CHIKV genotypes: West African, Asian, and East/Central/South African (ECSA)⁹. The Indian Ocean Lineage (IOL) that drove the 2005-2006 epidemic and its downstream spread across the Indian subcontinent is a sublineage nested within the ECSA genotype, distinguished by the E1-A226V substitution described below. Genetic variation in the structural glycoproteins can materially alter vector competence and virulence. During the 2005-2006 Indian Ocean epidemic, the initially circulating ECSA strains, which carried alanine at E1 position 226, were progressively replaced by variants carrying a valine substitution at this position (E1-A226V), which came to predominate in over 90% of sequenced isolates from later in the outbreak^{10,11}. This substitution followed an intensive anti-*Ae. aegypti* campaign on Réunion Island; under the resulting selective pressure, the mutated virus adapted more efficiently to the island's secondary vector, *Ae. albopictus*^{12,13}, a shift subsequently confirmed by reverse-genetics experiments showing that the single E1-A226V substitution measurably increases CHIKV infectivity for *Ae. albopictus* relative to *Ae. aegypti*¹⁴. Comparative full-genome analysis of the 2007 Indian outbreak strains independently confirmed the same E1-A226V shift outside the Indian Ocean islands¹⁵, and subsequent Indian isolates carrying this substitution were linked to the 2007 Kerala outbreak¹⁶. Because this single substitution is the central, recurring molecular explanation for CHIKV's altered vector range across multiple, independent regional epidemics discussed in separate sections, it is described here once in mechanistic detail and cross-referenced rather than re-derived in each regional subsection. Later compensatory mutations in the E2 and capsid genes, identified in genomic surveillance of India's 2016-2017 resurgence relative to strains circulating in 2010-2016, illustrate that vector-adaptive evolution has continued well beyond the original A226V event, although the phenotypic consequences of these later substitutions are less thoroughly characterised experimentally than A226V itself.

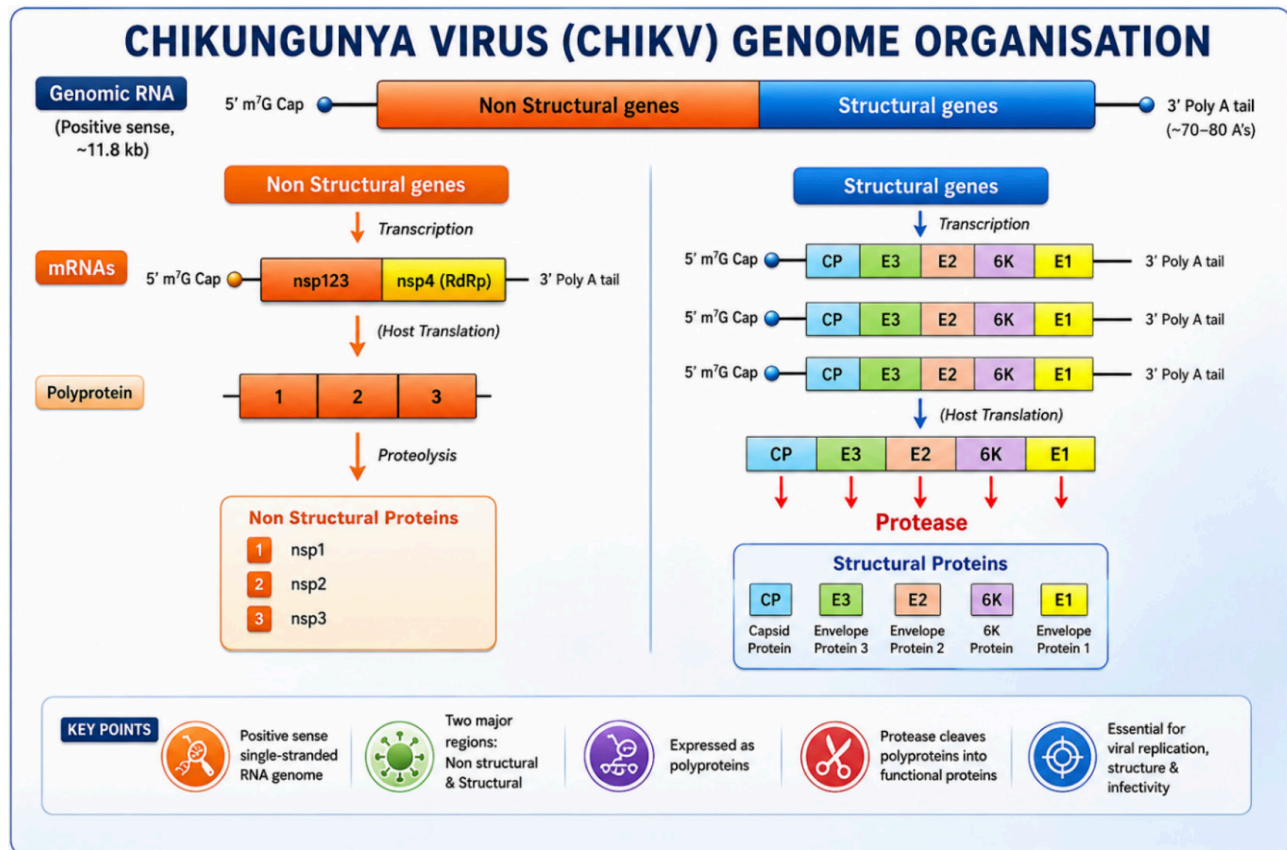


Figure 1. Genome organisation of CHIKV. The genome contains two expression units - non-structural and structural - transcribed as two separate polycistronic RNA molecules and subsequently translated and proteolytically processed

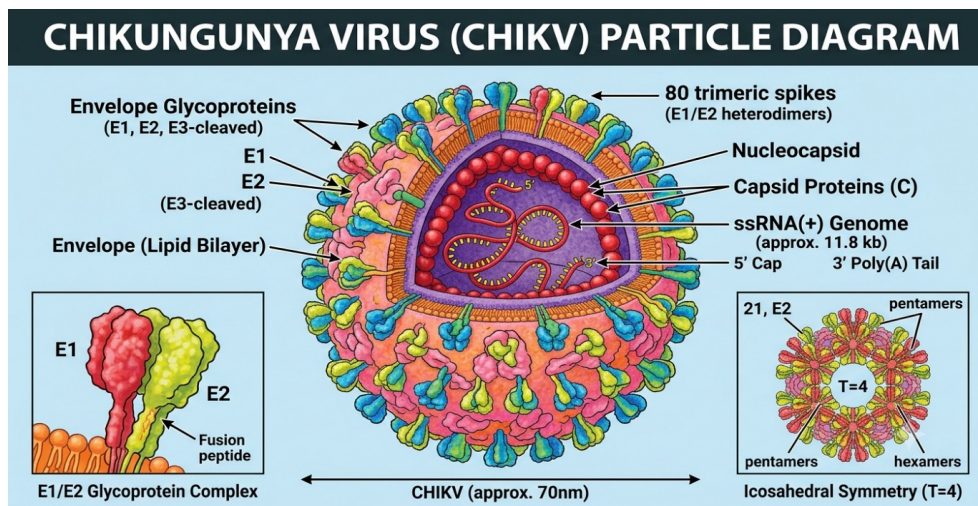


Figure 2. Structure and organisation of the CHIKV virion

Host-virus interactions and innate immune evasion

CHIKV replication triggers a general host translational shutoff and additionally suppresses the type I/II interferon (IFN) response through a mechanism independent of that shutoff. Expression of the non-structural protein nsP2 alone is sufficient to block IFN-induced Janus kinase-

signal transducer and activator of transcription (JAK-STAT) signalling, preventing STAT1 phosphorylation and nuclear translocation in response to either type I or type II IFN¹⁷. The C-terminal, nuclear-localising domain of nsP2 is required for this JAK-STAT antagonism and acts independently of nsP2's roles in RNA replication

and cytopathicity¹⁸, and more recent work has shown that the nsP2 methyltransferase-like domain promotes nuclear export of STAT1 as a distinct mechanism of IFN antagonism¹⁹. This capacity to blunt innate antiviral signalling early in infection is thought to permit the high peak viraemia that underlies CHIKV's efficient mosquito-to-human and human-to-mosquito transmission, and helps explain why exogenous IFN administration has shown limited clinical benefit once infection is established.

Mechanisms of pathogenicity and chronic arthralgia

CHIKV shows marked tropism for joint and musculoskeletal tissue, replicating efficiently in synovial fibroblasts, macrophages, osteoblasts, chondrocytes and skeletal muscle cells - a tropism that follows directly from the tissue distribution of the Mxra8 receptor described previously⁷. Acute disease reflects high-titre local viral replication and an associated pro-inflammatory cytokine response in synovial tissue, while the chronic, sometimes debilitating polyarthralgia that affects roughly half of patients is attributed to a combination of prolonged low-level viral or viral-antigen persistence in joint macrophages and synovial tissue and a sustained, partly immune-mediated inflammatory process rather than ongoing high-titre replication; the relative contribution of true viral persistence versus immunopathology to chronic disease remains incompletely resolved and is identified in the last section as a priority for future mechanistic research. Rare severe manifestations - hepatitis, myocarditis, and encephalopathy, including mother-to-child transmission with neonatal encephalopathy - likely reflect atypical extra-articular spread in the context of high viraemia, particularly in neonates and older, comorbid adults^{3,4}.

Clinical features

The incubation period of CHIKV is 2-12 days, with first symptoms typically appearing within 48 hours of the infective bite. The classical triad of high fever, incapacitating polyarthralgia and maculopapular rash reflects the acute viraemic and synovial inflammatory process described in a separate section, and is accompanied in a subset of patients by myalgia, hepatitis, mild haemorrhage, pre-renal failure, cardiac manifestations and neurological disease^{3,20-22}. At least 260 CHIKV-associated deaths were documented on Réunion Island during the 2005-2006 epidemic²³, and severe neonatal CHIKV infection with encephalopathy, consistent with mother-to-child transmission, has also been reported⁴. The 2025 Réunion epidemic reinforced that case-fatality is strongly age-dependent, reaching an estimated 2.4% among adults aged 65 years and older²⁴.

Search strategy and study selection

This narrative review draws on peer-reviewed literature indexed in PubMed, Scopus and Web of Science (search

terms: “chikungunya” combined with “epidemiology”, “outbreak”, “genotype”, “vector adaptation”, “vaccine”, and individual region and country names), supplemented by situation reports and surveillance bulletins from the World Health Organization, the Pan American Health Organization, the European Centre for Disease Prevention and Control, the Africa Centres for Disease Control and Prevention, and national vector-borne disease control programmes. Given the inherent lag in peer-reviewed publication, agency situation reports were prioritised for the most recent period (2023-2026) to capture the still-evolving 2025-2026 global resurgence. The search covered January 2004 to July 2026 and was restricted to English-language sources; the review title and scope have accordingly been revised from “2004-2025” to “2004-2026” to match the actual search window.

Records were screened in three stages consistent with a PRISMA-style narrative-review workflow: (i) title/abstract screening for relevance to CHIKV molecular virology, vector biology, epidemiology or vaccination; (ii) full-text screening against pre-specified exclusion criteria (non-English language; case reports of a single imported infection with no epidemiological or virological data beyond the index case; conference abstracts without a corresponding peer-reviewed or preprint manuscript); and (iii) reference-list (snowball) screening of included articles and relevant agency reports for additional eligible sources.

Global burden and temporal trends, 2004-2026

A worldwide observational analysis compiling country-year-level autochthonous case data across all six WHO regions estimated that global CHIKV incidence rose from 0.28 to 11.13 per 100,000 population between 2004 and 2024, with local transmission recorded in 119 countries by the end of 2024¹. In 2024, the Americas bore the heaviest regional burden (43.9 per 100,000; 431,305 cases), followed by South-East Asia (14.3 per 100,000; 258,854 cases), while Africa, Europe and the Western Pacific reported comparatively few cases that year⁶. Using a generalised additive model, the same analysis identified a sharp, non-linear rise in modelled incidence above a mean temperature of approximately 17°C, a complex non-linear association with the proportion of the population that is urban, and an inverse association between incidence and GDP per capita at low-to-moderate income levels⁶. These are ecological associations derived from a generalised additive model and should not be read as demonstrating that temperature, urbanisation or GDP directly cause CHIKV transmission; they are, however, consistent with CHIKV's known dependence on peri-domestic *Aedes* breeding habitats concentrated in warm, rapidly urbanising, resource-limited settings, and with the vector biology described in the earlier section.

This upward trend accelerated sharply in 2025. Between

1 January and 30 September 2025, WHO recorded 445,271 suspected and confirmed CHIKV cases and 155 deaths across 40 countries - a heterogeneous resurgence driven overwhelmingly by outbreaks in the Indian Ocean region and its downstream seeding of cases into mainland Europe and, for the first time at scale, mainland China²⁵. Reported case counts everywhere are understood to substantially underestimate the true burden: in Brazil, for example, the proportion of suspected cases that are laboratory-confirmed has repeatedly been below 70%, reflecting misdiagnosis (particularly against co-circulating dengue and Zika) and limited diagnostic coverage²⁶. Fig. 3 summarises global CHIKV outbreak activity between 2004 and 2025; Table 1 provides the corresponding country-level detail.

Regional epidemiology

Sub-Saharan and East Africa

Africa is both the ancestral home of CHIKV and a continuing, under-recognised source of transmission. Following the original 1952-1953 Tanganyika outbreak, a large epidemic struck Kenya's coastal region - including Lamu and Mombasa - in 2004, affecting more than 13,500 people; phylogenetic work subsequently linked this outbreak to the ECSA strain that seeded the 2005-2006 Indian Ocean

epidemic²⁷. Recurrent, often under-reported outbreaks have continued across the continent in the last decade: Sudan recorded a major epidemic in 2018-2019 affecting seven states, with case counts variously reported between roughly 14,000 and 49,000 depending on source and case definition; the Republic of Congo and the Democratic Republic of the Congo each reported large outbreaks centred on Brazzaville and Kinshasa in 2019; Chad experienced substantial transmission in 2020; and Ethiopia reported over 40,000 suspected cases in 2019 and several hundred confirmed cases in 2022. Kenya reported far smaller counts in 2022 (fewer than 100 cases), yet pooled seroprevalence estimates for East Africa of around 20.6% - reaching 63% in parts of Rwanda and 50.4% in Djibouti - indicate substantial silent, endemic circulation well beyond what passive case surveillance captures³³. More recently, Somalia confirmed an outbreak in the Sool region in 2025 (488 suspected cases, most laboratory-confirmed), Senegal reported cases in the Kaffrine region in early 2025, and travel-associated West African-lineage infections were repeatedly documented among French travellers returning from Côte d'Ivoire in 2023-2024, underscoring ongoing low-level circulation of the historically less epidemic West African genotype alongside the more explosive ECSA lineage.

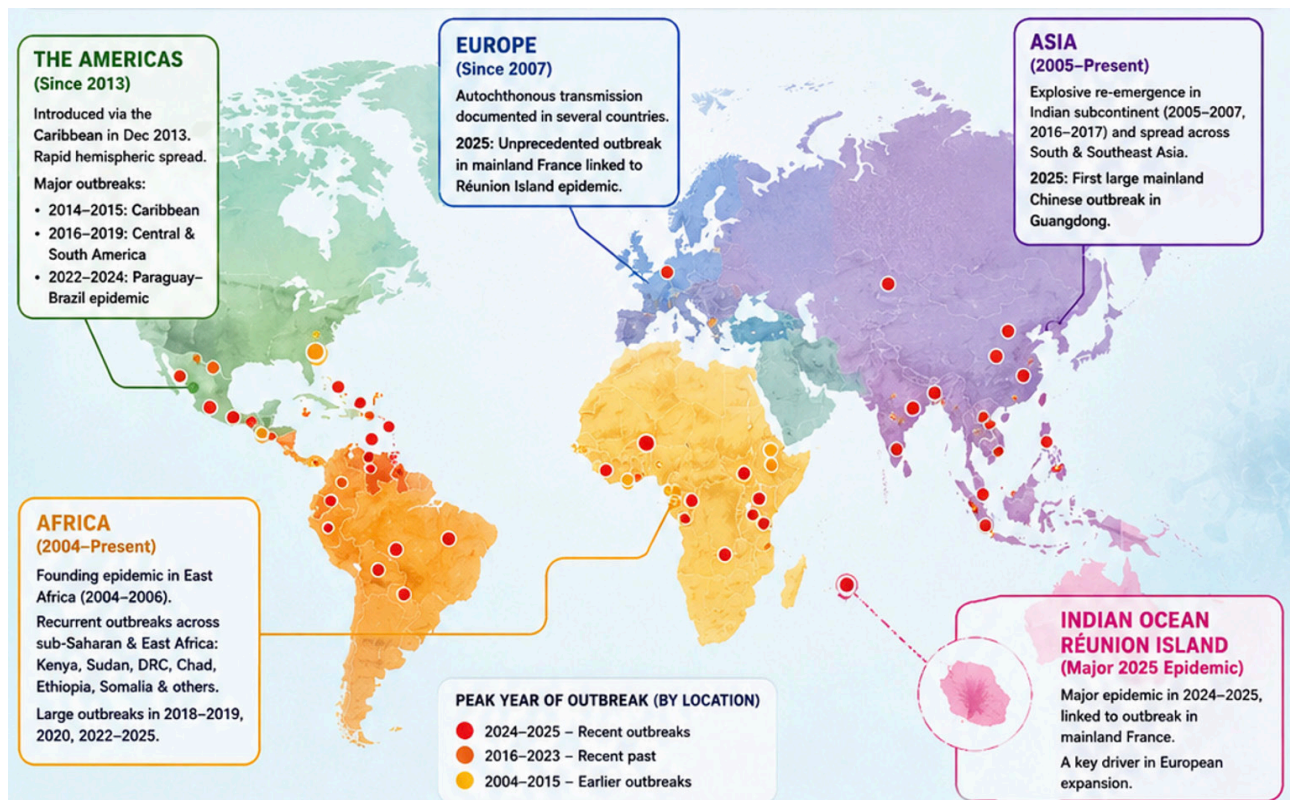


Figure 3. Schematic global map of selected chikungunya outbreaks, 2004-2025, showing peak-year reported case counts (bubble size, log scale) and outbreak era (colour) for representative countries and territories. Case estimates are drawn from the WHO, PAHO, ECDC, Africa CDC and national-surveillance sources cited in Table 1; continent outlines are simplified for illustrative purposes.

Table 1. Summary of major CHIKV outbreaks, 2004-2025

Region/Country	Year(s)	Genotype/ lineage	Principal vector	Reported cases (approx.)	Key mutation(s)	Notable feature
Kenya (coastal)	2004	ECSA	<i>Ae. aegypti</i>	>13,500	-	Seeded the Indian Ocean epidemic ²⁷
Comoros/Réunion/ Mauritius/ Madagascar/ Seychelles	2005– 2006	ECSA (IOL)	<i>Ae. aegypti</i> → <i>Ae. albopictus</i>	~35% of Réunion's population; ≥260 deaths	E1-A226V emerges ¹⁰	Founding vector- switch epidemic
India (nationwide)	2005– 2007	ECSA (IOL)	<i>Ae. aegypti</i> , <i>Ae. albopictus</i>	~1.3 million across 16 states ²⁸	E1-A226V (Kerala) ¹⁶	Largest single- country epidemic of the era
India (nationwide, second wave)	2016– 2017	ECSA	<i>Ae. aegypti</i>	64,057 suspected; 26,364 confirmed	Novel capsid/ E2 mutations	Resurgence after decade-long relative quiescence
Caribbean (Saint Martin/Sint Maarten)	Dec 2013	Asian	<i>Ae. aegypti</i>	>100,000 by May 2014 across 17 territories ²⁹	—	First autochthonous transmission in the Americas
Paraguay	2022– 2023	ECSA (newly introduced)	<i>Ae. aegypti</i>	>120,000 regionally; ~1,150– 1,216/100,000 in Paraguay ³⁰	—	Among the highest cumulative incidence ever recorded
Sudan	2018– 2019	ECSA	<i>Ae. aegypti</i>	~14,000–49,000 (range across sources)	—	Seven states affected; case- count range reflects surveillance uncertainty
Italy (Emilia- Romagna)	2007	ECSA	<i>Ae. albopictus</i>	~200	E1-A226V- adapted strain	First autochthonous transmission in mainland Europe
Mainland France	2025	ECSA (IOL, Réunion- linked)	<i>Ae. albopictus</i>	787 indigenous; 1,053 imported by mid-Nov 2025 ^{31,32}	E1-A226V- adapted strain	Largest cluster: Bergerac (100 locally acquired cases)
Réunion (2025 epidemic)	Aug 2024– Jun 2025	ECSA (IOL)	<i>Ae. albopictus</i>	~54,550 confirmed indigenous cases; 40–43 deaths ²⁴	—	Case-fatality 2.4% in adults ≥65 vs 0.4% overall
Guangdong, China (Foshan)	Jul 2025	Not yet fully characterised in the reviewed literature	<i>Ae. albopictus</i>	>7,000 within one month	—	Largest-ever mainland Chinese outbreak; imported introduction

Sources and case definitions vary across rows (suspected vs. laboratory-confirmed cases; passive vs. enhanced surveillance) and are given per row in the citations above

The Indian Ocean islands and the founding 2005-2006 epidemic

The single most consequential epidemic in modern CHIKV history began in the Comoros in early 2005 and rapidly spread through Réunion Island, Mauritius, Madagascar and Seychelles, ultimately affecting an estimated 35% of Réunion's roughly 750,000 inhabitants and causing at least 260 confirmed deaths²³. Genomic surveillance during this epidemic first documented the E1-A226V vector-adaptive

substitution^{10,11}. The Indian Ocean epidemic subsequently seeded the massive 2005-2007 CHIKV wave across the Indian subcontinent.

Two decades later, the Indian Ocean region experienced an even larger resurgence. After no reported transmission on Réunion between 2010 and 2024, a new epidemic began in August 2024 and, by the time it was declared over on 24 June 2025, had produced approximately 54,550 biologically confirmed indigenous cases - infecting roughly one in

nine islanders - and at least 40-43 deaths, almost entirely among people aged over 70 with underlying comorbidities. Neighbouring Mayotte simultaneously reported over 1,200 cases²⁵. An ecological time-series analysis of the epidemic found a mortality-rate ratio of 1.34 among older adults at the outbreak's April 2025 peak, with an estimated case-fatality rate of 2.4% in those aged 65 and above versus 0.4% in the general population²⁴ - quantitative evidence that, contrary to CHIKV's historical reputation as a low-fatality infection, large epidemics in ageing populations can carry a substantial mortality burden. This epidemic also triggered a large-scale IXCHIQ vaccination campaign and the associated 2025 vaccine safety crisis.

The Indian subcontinent and South/Southeast Asia

CHIKV was first isolated on the subcontinent in Calcutta in 1963 (Asian genotype), with further outbreaks in the 1960s and 1970s (African genotype strains detected in isolates from 1973) before a 32-year hiatus^{28,34}. The virus re-entered southern India at the end of 2005, with initial reports from Andhra Pradesh and Karnataka in October 2005. By early 2006 transmission had spread across Kerala, Tamil Nadu, Goa, Maharashtra and the Andaman and Nicobar Islands³⁵⁻³⁷, then to the central and western states of Gujarat, Madhya Pradesh and Rajasthan³⁸, and finally, by the last quarter of 2006, to northern India, where sporadic CHIKV cases coincided with a large concurrent dengue outbreak in Delhi^{39,40}. By 2007, cases had been reported from nearly every Indian state, in an outbreak that ultimately affected an estimated 1.3 million people across 16 states. Phylogenetic analyses of isolates from southern, central, western and northern India consistently placed the causative strains within the ECSA genotype (IOL sublineage) and confirmed their close relationship to the Indian Ocean strains of 2005-2006^{16,41-43}.

India experienced a second major resurgence in 2016-2017: national surveillance recorded 64,057 suspected and 26,364 confirmed cases, with central India - where genomic analyses identified newly emergent mutations in the capsid and E2 genes relative to strains circulating in 2010-2016 - particularly affected. A separate hospital-based prospective study in Delhi documented ongoing transmission during 2010-2011²². The epidemiological pattern in South Asia has been notably heterogeneous: some settings show classic episodic transmission separated by extended quiescent periods, as reconstructed for the Philippines over 60 years⁴⁴ and for Burkina Faso and Gabon⁴⁵, whereas a nationwide serosurvey in India in 2017 found evidence consistent with more continuous, endemic-level transmission in parts of the country⁴⁶. Neighbouring countries have also reported substantial outbreaks: Pakistan recorded its first large epidemic in Karachi and across Sindh province in December 2016-2017, and Bangladesh experienced a major outbreak in Dhaka between April and September

2017, with more than 13,000 clinically confirmed cases in the city and a genetically distinct viral cluster nested within the broader Indian Ocean clade; a further Bangladeshi outbreak was reported in 2024.

In July 2025, mainland China recorded its largest-ever chikungunya outbreak, centred on Foshan City in Guangdong Province, with more than 7,000 confirmed cases within a single month following imported introductions - a landmark event given China's previous near-absence of sustained local CHIKV transmission and a further illustration of the virus's 2025 global resurgence. At the time of writing, a genomic characterisation of the Guangdong outbreak strain had not yet appeared in the peer-reviewed literature indexed by our search; this is noted explicitly in Table 1 and identified in the last section as a surveillance gap rather than glossed over.

The Americas

CHIKV was entirely absent from the Western Hemisphere until December 2013, when the first autochthonous transmission in the Americas was confirmed on the French/Dutch island of Saint Martin/Sint Maarten, involving the Asian genotype²⁹. The virus spread with extraordinary speed: by May 2014, over 100,000 suspected and confirmed cases had been reported from 17 Caribbean and South American territories, with the highest attack rates on Saint Martin (115 per 1,000 population), Martinique (76 per 1,000) and Saint Barthélemy (74 per 1,000). Multiple independent introductions subsequently seeded outbreaks throughout Central America (notably Nicaragua, from mid-2014) and limited autochthonous transmission in Florida, United States. CHIKV reached Brazil in 2014 via two separate introductions - an Asian-lineage strain entering Amapá at the border with French Guiana, and an ECSA-lineage strain entering Bahia in the northeast²⁶ - establishing the two co-circulating lineages that would drive subsequent Brazilian epidemics.

Across the region as a whole, 3,684,554 suspected and confirmed cases were reported to PAHO/WHO from 50 countries and territories between December 2013 and June 2023⁴⁷. Transmission has been markedly cyclical: after a period of relatively low activity, a severe resurgence began in 2022 and peaked in 2023, when more than 120,000 cases and 51 deaths were recorded regionally, the great majority in Paraguay, where genomic surveillance identified a newly introduced ECSA lineage driving an epidemic that reached a cumulative incidence of roughly 1,150-1,216 cases per 100,000 population - among the highest ever recorded for CHIKV anywhere³⁰. Brazil was simultaneously affected, with the state of Minas Gerais reporting 395 cases per 100,000 and documented excess mortality during the 2023 epidemic⁴⁸. Case numbers remained high in 2024, with over 420,000 cases reported across the Americas. Retrospective epidemic modelling of the 2022-2023 Paraguayan outbreak

estimates that a hypothetical three-month vaccination campaign reaching 40% of the eligible population could have averted approximately 34,200 cases and 73 deaths, a projection that quantifies the theoretical value of timely vaccine deployment but must be weighed against the real-world safety experience⁴⁹.

Europe

The first autochthonous chikungunya transmission recorded in mainland Europe occurred in Italy's Emilia-Romagna region in 2007, imported via a viraemic traveller and transmitted locally by resident *Ae. albopictus* populations. Between 2007 and 2022, 4,730 CHIKV cases were reported across 22 European countries, with a single pronounced peak in 2014 (1,461 cases, 30.9% of the total) coinciding with autochthonous outbreaks in Italy, France, Spain and the United Kingdom^{50,51}. A systematic analysis of local transmission events (LTEs) across Europe found their frequency increasing by an average of 1.24-fold per year, with 43 LTEs recorded in the six years to 2023 compared with only 13 between 2007 and 2017 - a trend associated with, though not thereby proven to be caused solely by, the ongoing northward and westward expansion of *Ae. albopictus*⁵¹.

Mainland France exemplifies this acceleration. Only 32 autochthonous CHIKV cases were recorded there in total between the first two cases in 2010 and the end of 2024. In 2025, this pattern broke decisively: driven by an unprecedented volume of imported infections linked to the Réunion epidemic (1,911 imported cases identified by early July 2025, 89% associated with travel to Réunion) and the vector-adapted strain, autochthonous transmission began unusually early in the vector season and expanded to 15 mainland départements, including - for the first time - the Grand Est and Nouvelle-Aquitaine regions³². By mid-November 2025, France had recorded 787 indigenous and 1,053 imported cases; the largest single cluster, in Bergerac (south-west France), comprised 100 locally acquired cases between June and October 2025, with door-to-door surveys and vector-control measures credited with helping to contain its spread³¹. Italy also reported autochthonous cases in 2025. Collectively, these developments mark a transition in Europe from sporadic, imported-case-driven clusters toward a more sustained seasonal risk of local CHIKV transmission.

Western Pacific and Oceania

The Western Pacific region has historically reported the lowest CHIKV burden of the six WHO regions, but has not been immune to episodic transmission: the Philippines experienced repeated, geographically focal outbreaks over a 60-year period reconstructed through serological and case-based analysis⁴⁴, and Pacific Island states have periodically reported outbreaks, including alongside dengue and Zika co-circulation. The unprecedented 2025

Guangdong, China outbreak - while occurring within a country conventionally grouped in the Western Pacific region - was epidemiologically linked to introductions from South and Southeast Asia and illustrates that this region, too, is not insulated from the global resurgence.

Factors associated with the 2004-2026 global resurgence

Several converging, associated factors help explain CHIKV's transformation from a regionally confined pathogen into one with near-pandemic reach; the evidence below is predominantly ecological and correlative rather than experimental, and causal claims are limited accordingly. First, vector adaptation: the E1-A226V substitution and subsequent compensatory mutations measurably increased CHIKV infectivity for *Ae. albopictus* in controlled laboratory experiments - this is the one link in this section supported by direct experimental causation rather than ecological association¹⁴. Second, the geographic range of *Ae. albopictus* itself has expanded substantially into temperate latitudes over the same period, facilitated by international trade (notably used-tyre shipments) and associated with climate warming; the global burden analysis found a statistical association between mean temperature and CHIKV incidence above approximately 17°C, but this association-based analysis cannot by itself establish that warming has directly driven the observed incidence rise¹. Third, rapid and often unplanned urbanisation is associated with dense peri-domestic breeding habitat and large susceptible populations in close proximity; however, this relationship is non-linear rather than simply additive and again reflects ecological correlation. Fourth, lower GDP per capita at low-to-moderate income levels is independently associated with higher incidence in the same model, plausibly reflecting constrained vector-control infrastructure and diagnostic capacity, though the model cannot exclude residual confounding. Fifth, international travel and migration continue to seed new introductions into previously unaffected or long-quiescent regions, as illustrated repeatedly in 2025 in France, China and elsewhere - a mechanism for which the epidemiological evidence (documented travel-linked index cases) is close to direct rather than merely correlative. Finally, the co-existence of episodic, immunity-limited transmission dynamics in some settings (e.g., the Philippines, Burkina Faso/Gabon) alongside more continuous endemic circulation in others (e.g., parts of India) means that large, susceptible populations can accumulate over years between recognised outbreaks, setting the stage for the kind of explosive resurgence seen in Réunion in 2025 after 15 years without local transmission.

Vaccine development, deployment and safety

No antiviral therapy exists for CHIKV infection, and

management remains supportive. This section separates, throughout, what regulators formally decided, what was reported as an adverse event, and what represents the authors' own interpretation of the evidence.

Regulatory approvals

Two chikungunya vaccines have been licensed to date. IXCHIQ (VLA1553), a live-attenuated vaccine developed by Valneva, received accelerated approval from the US FDA in November 2023 for adults aged 18 and older at increased risk of CHIKV exposure⁵². VIMKUNYA, a virus-like-particle (non-live) vaccine developed by Bavarian Nordic, was approved by the FDA in February 2025. Because of the historically unpredictable, episodic nature of CHIKV outbreaks, both agencies granted licensure on the basis of an immunological correlate of protection rather than a conventional phase 3 efficacy trial - a regulatory pathway (accelerated approval) that explicitly requires post-marketing confirmatory studies, a requirement directly relevant to the events⁵³.

Post-marketing safety signal and regulatory response (factual chronology)

The 2025 Réunion epidemic became the first large-scale real-world test of IXCHIQ deployment, with a vaccination campaign extended to adults, including those over 65. Post-marketing surveillance subsequently identified a safety signal: by early May 2025, 17 serious adverse events had been reported globally among recipients aged 62-89, including two deaths. On 9 May 2025, the FDA and CDC jointly recommended a pause in IXCHIQ use in adults aged 60 and older while the reports were investigated, and the European Medicines Agency initiated a parallel review⁵⁴. On 6 August 2025, the FDA lifted the pause for this age group, concurrently approving updated prescribing information describing the observed serious adverse event pattern in older, comorbid recipients⁵⁴. Further review of accumulating reports - including one death from vaccine-strain encephalitis confirmed by CSF PCR, more than 20 serious adverse events in total, 21 hospitalisations and 3 deaths - led the FDA's Center for Biologics Evaluation and Research (CBER) to suspend IXCHIQ's biologics licence altogether on 22 August 2025⁵⁴.

Regulatory rationale and interpretation

CBER's own stated rationale was that the vaccine's confirmatory clinical benefit had not yet been verified under the accelerated-approval pathway, and that its benefit-risk balance did not favour continued use under most plausible scenarios⁵⁴. In the authors' interpretation, this sequence - an initial age-restricted pause, a labelling-based reinstatement, and a subsequent full suspension within weeks - illustrates how quickly the benefit-risk calculus for a live-attenuated arbovirus vaccine can shift once real-world, large-scale

post-marketing data accumulate, and underscores that accelerated approval based on an immunological correlate of protection is not a substitute for completed confirmatory efficacy and safety data. VIMKUNYA, as a non-live vaccine platform, was not implicated in these reports and was not subject to the same suspension.

Implications for future deployment

Epidemic modelling of the 2022-2023 Paraguay outbreak suggests that timely, well-targeted vaccination could substantially reduce cases, hospitalisations and deaths in a future epidemic⁴⁹; set against the IXCHIQ experience, this juxtaposition - rather than either finding alone - is the central lesson of the 2025 vaccine episode: live-attenuated arbovirus vaccines require intensive, real-time, age-stratified pharmacovigilance before broad deployment can be considered safe at scale, and the theoretical epidemic-averting benefit of vaccination cannot be assumed to translate into real-world net benefit without such monitoring in place.

Surveillance gaps, data limitations and critical synthesis

Substantial gaps continue to limit accurate global burden estimation, and several of the figures cited earlier in this review illustrate those limitations directly rather than being free of them. Clinical overlap with dengue and Zika impairs syndromic diagnosis, and laboratory confirmation rates for suspected cases remain well below 100% even in relatively well-resourced surveillance systems such as Brazil's²⁶. This means the case counts summarised in Table A, are best read as a heterogeneous mixture of suspected and confirmed cases collected under different case definitions and surveillance intensities across countries and years, not as directly comparable like-for-like figures; the wide reported range for the 2018-2019 Sudan epidemic (roughly 14,000-49,000 cases) is a case in point. Seroprevalence studies - including India's 2017 nationwide cross-sectional serosurvey and pooled East African estimates of roughly 20% - reveal considerably more silent circulation than passive case-based surveillance captures, implying that essentially all of the passive case counts discussed in this review substantially underestimate true infection burden, and by an amount that itself varies by setting^{33,46}.

The global burden model is a useful synthesis but rests on the same heterogeneous underlying case data, so its absolute incidence estimates should be treated as indicative of relative regional and temporal trends rather than as precise counts; its temperature, urbanisation and GDP associations, are statistical correlations from an observational model and have not been established as causal mechanisms. Similarly, the vaccine-impact modelling depends on assumptions about vaccine efficacy and coverage that had not, at the time of that analysis, been confirmed in a completed phase

3 trial - a limitation that the subsequent IXCHIQ safety suspension makes directly material rather than theoretical, since it means the projected benefits of vaccination cannot be assumed to hold under the vaccine's actual, post-marketing risk profile.

Genomic surveillance capacity also remains highly uneven between high- and low-resource settings, constraining real-time tracing of lineage introduction and spread during fast-moving epidemics such as those in Paraguay (2023) and Réunion (2025), and, a peer-reviewed genomic characterisation of the 2025 Guangdong outbreak strain was not available at the time of this review. Addressing these gaps will require integrated dengue-chikungunya-Zika surveillance platforms, wider deployment of affordable point-of-care diagnostics, harmonised case definitions that would make cross-outbreak comparisons in tables such as Table A more meaningful, sustained investment in *Aedes* vector control, climate-informed early-warning systems attentive to the associations (not proven causal mechanisms) identified in global burden modelling, and a renewed, safety-first approach to vaccine development and post-marketing surveillance of the kind.

CONCLUSIONS

Two decades of accumulating molecular and epidemiological evidence show that chikungunya virus has been transformed from a regionally confined arbovirus into a pathogen with near-pandemic geographic reach, now confirmed in 119 or more countries and territories. Mechanistically, this trajectory has been shaped principally by a single, recurring, experimentally validated event - vector-adaptive evolution in the structural glycoproteins, epitomised by E1-A226V - layered onto factors that remain associational rather than proven causal: expanding *Ae. albopictus* vector range, climate warming, rapid urbanisation and global mobility. The 2025 suspension of the IXCHIQ vaccine licence is a cautionary reminder that vaccination, while a genuinely promising tool against future epidemics, must be paired with rigorous, age-stratified safety monitoring.

Rather than restate these epidemiological findings, we highlight the microbiological knowledge gaps that should set the research agenda for the next phase of CHIKV work: (i) the relative contribution of true viral persistence versus immune-mediated pathology to chronic post-CHIKV arthralgia remains unresolved and is directly relevant to both prognosis and any future antiviral development; (ii) the phenotypic consequences of the post-A226V compensatory mutations identified in India's 2016-2017 resurgence and in other recent lineages have not been characterised experimentally to the same standard as A226V itself, including for the still-uncharacterised 2025 Guangdong strain; (iii) the immunological correlate of protection used to license both IXCHIQ and VIMKUNYA requires confirmation against real-world efficacy data, and

the IXCHIQ experience specifically requires a mechanistic explanation for vaccine-strain reversion or persistence sufficient to cause vaccine-strain encephalitis; and (iv) harmonised, molecularly informed genomic surveillance - capable of detecting new vector-adaptive substitutions in near-real time rather than retrospectively, as occurred in 2005-2006 - remains the principal infrastructure gap standing between the field and genuinely predictive, rather than reactive, management of CHIKV resurgence.

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AUTHORS' CONTRIBUTION STATEMENT

Pradeep Kumar Singh: Conceptualization, literature review, synthesis of evidence, and drafting of the manuscript. Shweta Kusmakar Singh: Conceptualization, critical review, and editing of the manuscript. Both authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

DECLARATION OF GENERATIVE AI USE

Generative AI was used to assist with language editing and formatting of the manuscript. The authors reviewed and approved the final text and remain responsible for the accuracy and integrity of the manuscript.

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