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REVIEW

Chikungunya Virus in 2025: Epidemiology, Immunopathogenesis, and Vaccine Development — A Narrative Review

Chenxi Zhao*, Ziruo Ge*, Tingyu Zhang, Zhouling Jiang, Di Tian, Zhihai Chen

National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhihai Chen; Di Tian, National Key Laboratory of Intelligent Tracking and Forecasting for infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, People's Republic of China, Email chenzhihai0001@126.com; tiandi412@hotmail.com

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Abstract: Chikungunya is an arboviral disease caused by infection with chikungunya virus (CHIKV), an alphavirus transmitted primarily by *Aedes aegypti* and *Aedes albopictus*. Over the past two decades, chikungunya has re-emerged across Africa, Asia, the Indian Ocean, Europe, and the Americas, with 119 countries and territories reporting local transmission up to 2024. This expansion reflects a widening geographic range with greater risk of introduction and spreads through mosquito vectors, leaving larger populations susceptible to infection. Following inoculation by an infected mosquito, viral replication leads to viremia and the abrupt onset of fever, severe joint pain with swelling, myalgia, and rash. These clinical manifestations are driven by the host immune response to infection, which also influence disease severity and clinical outcomes. Although most patients recover within weeks, a proportion develop persistent arthralgia or chronic arthritis lasting months to years, contributing to the overall disease burden. Although both the live-attenuated vaccine IXCHIQ and the virus-like particle vaccine VIMKUNYA have been approved, the license for IXCHIQ was recently suspended due to safety concerns. Recent outbreaks of chikungunya fever have driven sustained research, leading to deeper insights into disease pathogenesis, host immune responses and chronic inflammation. In this narrative review, we summarize recent advances up to 2025 in the epidemiology, host receptors, pathogenesis, clinical manifestations, immune responses, mother-to-child transmission, and vaccines development of CHIKV.

Keywords: chikungunya, arthritis, cytokine, mother-to-child transmission, vaccine

Introduction

Chikungunya was first described and epidemiologically documented during 1952–1953 in the Tanganyika Territory (present-day United Republic of Tanzania),[1] after which sporadic cases and localized outbreaks were recorded across multiple African regions, reflecting early endemic circulation. In 1958, Thailand reported the first recorded urban outbreak in Asia.[2] In 2004, an outbreak in Kenya initiated the spread to the Indian Ocean islands, and in 2005–2006 Réunion Island experienced a major epidemic with approximately 244,000 infections, bringing chikungunya virus (CHIKV) to prominence as a global public health concern.[3] In 2007, the first reported autochthonous transmission event in Europe occurred in northern Italy, linked to an imported case from India.[4] In 2013, CHIKV was detected in the Caribbean and then spread widely in the Americas.[5] According to the Pan American Health Organization (PAHO)/World Health Organization (WHO), 411,560 confirmed cases with 515 deaths were reported in 2023,[6] and 431,223 cases with 243 deaths were reported in 2024.[7] In the first seven months of 2025, about 240,000 chikungunya cases and 90 related deaths had been reported across 16 countries and territories.[8] As of August 23, 2025, 10,258 laboratory-confirmed cases were reported in Foshan, the largest recorded outbreak of chikungunya in China.[9] Recent modeling study suggests that under current climate conditions, about 15% of global land area is suitable for CHIKV transmission, placing an estimated

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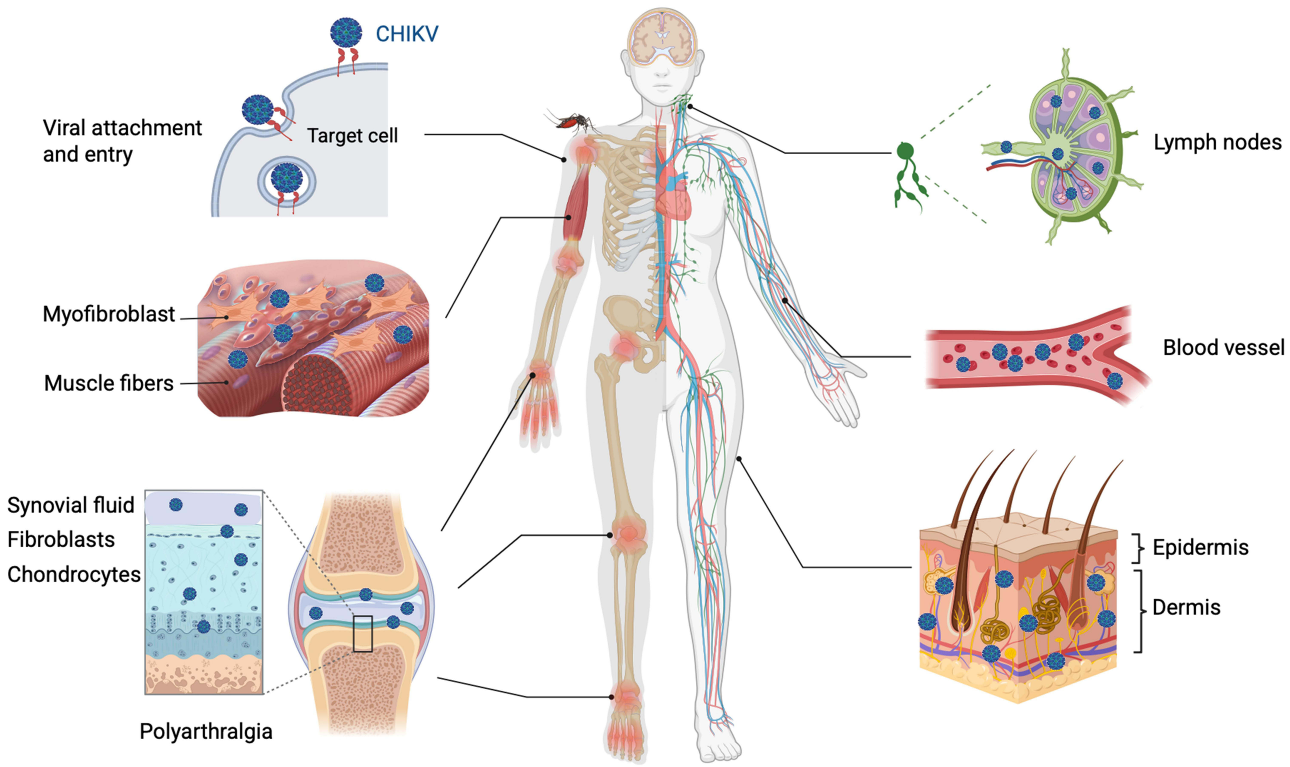
Graphical Abstract



6.78 billion people at risk, mostly in tropical and subtropical regions.[10] As of December 2024, local transmission had been documented in 119 countries and territories worldwide, predominantly in Africa, Asia, and the Americas.[11]

This narrative review synthesizes current evidence on CHIKV, covering its epidemiology and transmission, viral structure and receptors, insights from animal models and human pathogenesis, clinical manifestations and immune responses, mother-to-child transmission, and vaccine development. Relevant literature was identified through targeted searches of PubMed and Web of Science, supplemented by key references and reports from international public health agencies. Epidemiological and vaccine-related data were reviewed up to August 2025, which served as the cutoff date for this review.

Epidemiology and Transmission

CHIKV is an enveloped positive-sense single-stranded RNA virus belonging to the genus Alphavirus within the family Togaviridae.[12] Most alphavirus are broadly classified into two groups according to the clinical syndromes they cause: arthritogenic and encephalitic.[13] The arthritogenic alphaviruses, CHIKV, Ross River virus (RRV), Barmah Forest virus (BFV), Sindbis virus (SINV), Mayaro virus (MAYV) and O'nyong-nyong virus (ONNV), predominantly induce acute and chronic arthralgia.[14] The encephalitic alphaviruses, Eastern equine encephalitis virus (EEEV), Venezuelan equine encephalitis virus (VEEV) and Western equine encephalitis virus (WEEV), cause central nervous system disease such as meningitis and encephalitis.[15] Arthritogenic alphaviruses are transmitted chiefly by *Aedes* mosquitoes and circulate in two epidemiologically distinct cycles.[16]

CHIKV is maintained in a rural enzootic (forest/savannah) transmission cycle between *Aedes* (*Aedes* africanus and *Aedes* furcifer) and vertebrate amplifying hosts, including nonhuman primates considered the principal reservoirs.[17] A meta-analysis estimated CHIKV seroprevalence in nonhuman primates was as high as 35% (95% CI: 9–66%) in Africa, 7% (95% CI: 0–28%) in the Americas, and 6% (95% CI: 5–34%) in Asia.[18] Moreover, CHIKV has been isolated from bats, rodents, palm squirrels, and birds, and CHIKV-specific antibodies have been detected in rats, birds, elephants, and reptiles, suggesting that these animals may participate in the natural transmission cycle of the virus and serve as potential reservoir hosts to some extent.[19] However, evidence that other wild vertebrates, such as rodents, bats and birds, serve as maintenance hosts remains limited and inconsistent.[20] Enzootic transmission mainly affects rural areas, with humans as incidental hosts infected via spillover mediated by sylvatic or bridge vectors. The urban cycle consists of sustained human–mosquito–human transmission driven by *Aedes aegypti* and *Aedes albopictus*,[19] these species also transmit dengue virus (DENV), Zika virus (ZIKV), and yellow fever virus (YFV).[21] Climate change and anthropogenic forces, such as land-use change, deforestation, urbanization, and human mobility, are expanding vector ranges and seasonal suitability, increasing opportunities for spillover from enzootic cycles and subsequent urban amplification.[22] A recent systematic review of *Aedes*-borne arboviral infections in Europe (2000–2023) reported that climate change and international travel are key drivers of the increasing risk of autochthonous transmission by promoting vector expansion, enhancing viral replication within mosquitoes, and facilitating repeated viral introductions into previously unaffected regions.[23] These trends are expected to increase the risk of arbovirus transmission and have prompted the exploration of emerging vector control strategies, including Wolbachia-based endosymbiont control, genetically modified mosquitoes, and integrated vector management.[24,25]

Following ingestion of an infectious blood meal, CHIKV replicate in the midgut epithelial cells of *Aedes* mosquitoes.[26] Viral particles become detectable in saliva by 2 days post infection (dpi), are transmissible from this time point, and reach peak transmissibility around 6 dpi.[27] CHIKV can disseminate to the ovaries, with virus detected in eggs by 6 dpi.[28] Vertical transmission in *Aedes* mosquitoes has been demonstrated, with CHIKV persisting to F5 and F6 progeny, indicating maintenance of the virus across successive mosquito generations.[29] This mode is considered an important mechanism for viral persistence under adverse environmental conditions. The desiccation-resistant eggs remain viable for long periods, allowing CHIKV retention and maintaining infectivity during dry seasons and winter when mosquito densities are low.[30] Mavale et al observed that CHIKV-infected male *Aedes* mosquitoes transmitted the virus to females during mating, and the infected females subsequently infected suckling mice, highlighting the potential epidemiological significance of venereal transmission.[31]

Phylogenetic analyses classify CHIKV into three major lineages: West African, Asian, and East/Central/South African (ECSA), the latter of which includes the Indian Ocean lineage (IOL).[32] Within the IOL, selection in *Aedes albopictus* has driven sequential adaptive changes in the envelope glycoproteins. The E1-A226V substitution increases *Aedes albopictus* infection by approximately 50~100-fold, followed by E2-L210Q, which provides an additional four to six-fold increase.[33,34] These adaptive mutations markedly enhance transmission in *Aedes albopictus* while exerting little measurable effect on *Aedes aegypti* competence or on experimental models of human infection.[35] Ongoing evolution of CHIKV envelope glycoproteins may therefore promote adaptation to more widely distributed vectors and facilitate further geographic spread.[36] To date, no specific amino acid substitution has been linked to increased viral fitness in humans, such as higher viremia, greater clinical severity, or shifts in tissues and organs tropism.[37]

Viral Structure and Receptors

The CHIKV genome is approximately 11.8 kb and contains 5′ and 3′ untranslated regions and two open reading frames (ORFs) separated by a short junction region. The 5′ ORF is translated from genomic RNA to yield the non-structural polyprotein P1234, which is proteolytically processed into nsP1, nsP2, nsP3, nsP4.[38] The nsP3 is a key component of the plasma-membrane–associated replication complex and forms cytoplasmic condensates/tubular networks that concentrate genomic RNA, capsid and requisite host factors, thereby promoting efficient replication and infection.[39] The 3′ ORF is expressed from a subgenomic RNA and encodes the structural polyprotein that is processed into capsid (C), envelope (E)3, E2, 6K, and E1.[40,41] The capsid protein is essential for selectively packaging the viral genome.[42] E1 contains a hydrophobic fusion loop that drives membrane fusion process,[43] while E2 is a major target of neutralizing antibodies that inhibit attachment, membrane fusion, and subsequent viral entry or egress.[44] The E2 forms a complex with the E1, and three E2-E1 complexes form a trimeric envelope protein.[45] E3 stabilizes the E2-E1 heterodimer and prevents premature exposure of the E1 fusion loop.[43] CHIKV virions are spherical, enveloped particles approximately 65 nm in diameter.[46] The T=4 icosahedral nucleocapsid encloses the positive-sense RNA genome and is wrapped by a host-derived lipid bilayer, within which 240 E1–E2 heterodimers assemble into 80 trimeric spikes that arrange an outer quasi-icosahedral glycoprotein lattice.[47,48]

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Matrix remodeling–associated protein 8 (MXRA8), also known as DICAM, ASP3, or limitrin, is an adhesion molecule conserved across mammals, birds, and amphibians, with expression on epithelial, myeloid, and mesenchymal cells.[49] Zhang et al identified MXRA8 as a host entry factor for several arthritogenic alphaviruses, including CHIKV, RRV, MAYV, and ONNV.[50] Structural and functional studies show that MXRA8 binds CHIKV within the canyon between two adjacent protomers of the trimeric E spike, involving multiple interactions with E2–E1 heterodimers and the MXRA8 hinge region.[45] Human MXRA8 facilitates CHIKV attachment to and infection of dermal fibroblasts, synovial fibroblasts, osteoblasts, chondrocytes, and skeletal muscle cells, and serves as a key receptor for viral entry into host cells.[50] Consistently, an MXRA8-Fc fusion protein or anti-MXRA8 monoclonal antibodies effectively block CHIKV infection in vitro and reduce viral infection and joint swelling in mice.[38] Live cell imaging indicates that MXRA8 binds CHIKV at the cell surface and co-internalizes with viral particles, many of which remain colocalized with MXRA8 during endosomal membrane fusion, further supporting its role as a bona fide entry receptor.[51] Kim et al demonstrated that MXRA8 from mouse, rat, chimpanzee, dog, horse, goat, sheep, and human supports CHIKV infection in cell culture, whereas bovine MXRA8 does not because a 15-amino acid insertion in its ectodomain prevents viral binding. Deletion of this insertion in bovine MXRA8 enhances CHIKV binding and infection, while introducing the insertion into mouse MXRA8 blocks binding in cells and mitigates CHIKV-induced pathogenesis in mice. In contrast, avian MXRA8 (chicken, turkey, and duck) does not support CHIKV infection.[52] However, MXRA8 is not expressed on all target cell types, and CHIKV infection of MXRA8 knockout mice leads to a reduced but not abolished level of replication, suggesting that the virus likely engages additional receptors in vivo.[53,54] Other studies have identified the four-and-a-half-LIM domain protein 1 splice variant A (FHL1A) as a crucial host factor that interacts with the hypervariable domain of CHIKV nsP3 and is essential for viral RNA replication, with high expression in CHIKV target cells and marked abundance in muscle.[55] In humans, FHL1 levels are elevated in both acute and chronic chikungunya disease, and FHL1 knockout mice infected with CHIKV exhibit reduced arthritis and myositis, fewer immune infiltrates, and decreased production of proinflammatory cytokines and chemokines compared with infected wild type controls.[56] In addition, prohibitin, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN), basigin (CD147), and T cell immunoglobulin and mucin domain-containing protein 1 (TIM1) have also been proposed as entry or attachment factors for CHIKV.[57–59]

Animal Models and Human Pathogenesis

Mouse models of CHIKV infection provide useful tools for investigating viral and host factors that drive CHIKV pathogenesis.[60,61] In mice with mild CHIKV infection, the virus primarily targets fibroblasts in muscle, joints, and skin, while in severe disease, it disseminates to the central nervous system and specifically targets the choroid plexus and leptomeninges.[62] Several studies have reported that CHIKV-infected mice develop active synovitis with articular cartilage erosion, periostitis with cortical bone involvement, and myositis characterized by muscle fiber degeneration.[63,64] Legros et al using an in vivo mouse model encompassing acute and chronic CHIKV infection, confirmed that the metatarsal joints supported viral replication after the acute phase and that chondrocytes were the main targets.[65]

In macaque models, CHIKV targets lymphoid tissues, liver, central nervous system, joints, and muscles, mainly infecting macrophages, dendritic cells, and endothelial cells during the acute phase. In the later stages, the virus persists in lymphoid organs, liver, joints, and muscles, and can be detected in macrophages for up to three months after inoculation.[66] Macrophages have been identified as the primary cellular reservoir of persistent CHIKV infection during the chronic phase. Studies in rhesus macaques have revealed age-related differences, with older animals showing a general decline in both innate and adaptive immune responses and infectious CHIKV persisting in the spleen, liver, and muscle for up to 44 days postinfection.[67] In cynomolgus macaques, higher inoculation doses correlate with earlier viremia peaks and higher peak viremia levels.[68]

CHIKV exhibits broad cellular tropism and infects various human cell lines and primary cells in vitro, including epithelial (HeLa, HEK293, Huh7), hepatocytic (HepG2), microglial (CHME5), and neuroblastoma lines, as well as primary fibroblasts (MRC5), skeletal muscle myoblasts (HSMMs), and monocyte-derived macrophages.[69] These in vitro findings are supported by animal studies showing that CHIKV replicates in fibroblasts, muscle, joint, and immune cells, and disseminates to multiple organs under severe conditions. In natural infection, when an infected mosquito probes the host skin, saliva together with virus is injected, carrying a cocktail of molecules with anti-hemostatic and immunomodulatory properties.[70] At the cutaneous inoculation site, CHIKV initially replicates in epidermal keratinocytes, melanocytes, and Langerhans cells, following which it spreads to dermal stromal cells such as fibroblasts and endothelial cells. Infected Langerhans cells and dermal dendritic cells subsequently undergo maturation upon antigenic stimulation and migrate to draining lymph nodes, where they initiate adaptive immune responses.[71–73] By interacting with antigen-presenting cells in the skin, CHIKV enters the lymphatics, reaches the bloodstream and induces viremia.[74] In this process, infiltrating monocytes support viral replication at the inoculation site and promote systemic dissemination.[75] CHIKV subsequently disseminates hematogenously to organs including the liver, kidneys, spleen, lymph nodes, muscle, and joints.[76] Type I interferons (IFN) induced during infection activate resident macrophages toward a classical phenotype, enhancing microbicidal activity and the production of proinflammatory mediators.[77] Activated dendritic cells also secrete cytokines and chemokines.[78] Human fibroblast-like synoviocytes have been shown to be permissive to CHIKV replication, creating a synovial environment that favors osteoclastogenesis, the resulting osteoclasts may contribute to CHIKV-associated arthralgia and arthritis.[79] Quadriceps muscle biopsies from infected patients revealed scattered myofiber atrophy and necrosis with minimal inflammatory infiltration at the end of the acute phase. Around three months after infection, biopsies demonstrated extensive interstitial inflammation with polymorphonuclear cells, lymphocytes, and histiocytes, along with large areas of necrosis and collagen deposition.[80] An autopsy study of fatal chikungunya cases demonstrated that CHIKV antigen exhibited marked tropism for mesenchymal cells (fibroblasts, adipocytes, and endothelial cells) and mononuclear cells, including tissue macrophages, blood monocytes, splenic follicular dendritic cells, and Kupffer cells, although no overt cytopathic effects were observed.[81]

Clinical Manifestations and Immune Responses

Chikungunya symptoms usually develop within 4 to 8 days (range 2–12 days) after the bite of an infected mosquito and most cases are self-limiting.[82] Approximately 15–35% of infected individuals remain asymptomatic.[83] Chikungunya typically presents with fever, often accompanied by joint pain, while other common manifestations include myalgia, rash, headache, nausea, and fatigue (Figure 1). Joint pain usually resolves within days but may persist for weeks, months, or

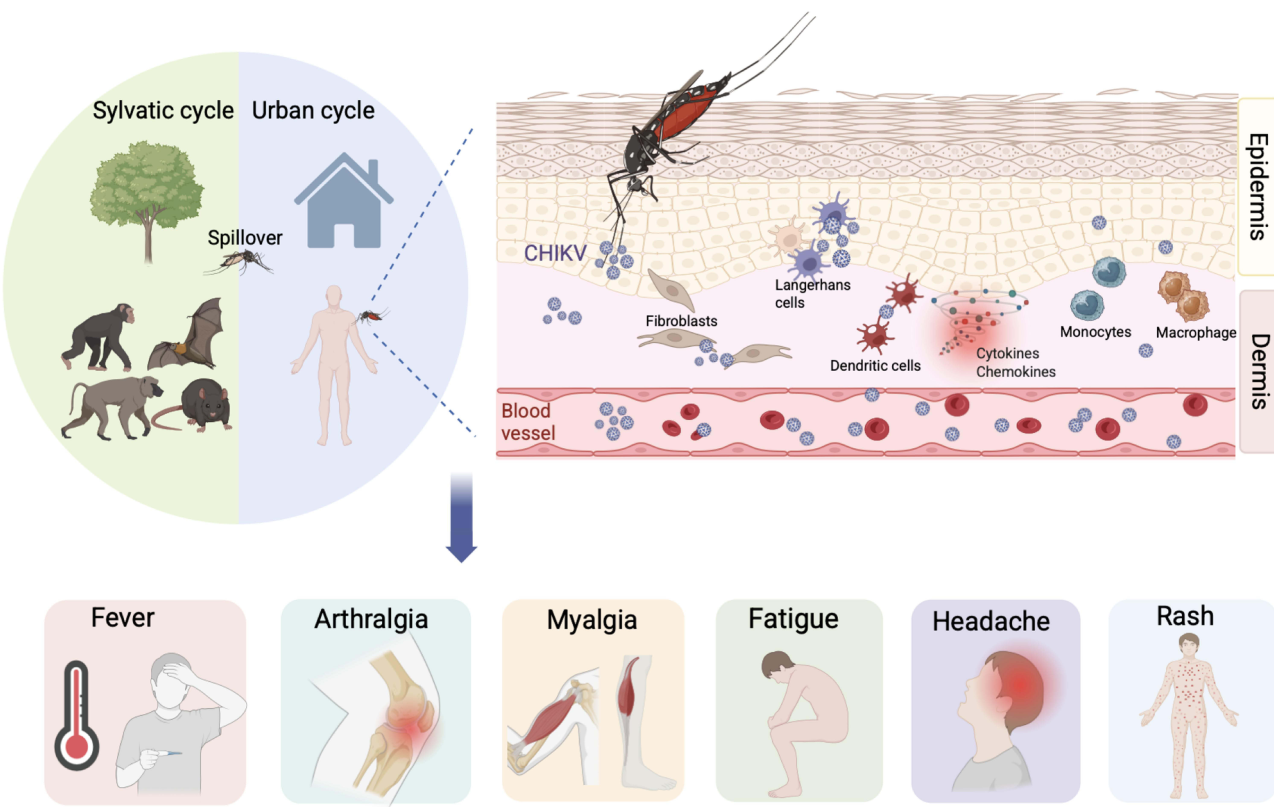

Figure 1 Chikungunya virus transmission, host infection, and clinical manifestations.

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even years in some patients.[84] Clinically, chikungunya progresses through acute, post-acute, and chronic phases, defined by the duration of joint symptoms ranging from transient arthralgia to chronic arthritis.[85]

The acute phase lasts up to two weeks and is characterized primarily by abrupt onset fever, severe arthralgia, joint swelling, and rash.[46,69] Fever usually lasts for 4–5 days.[86] Joint symptoms are usually symmetrical, predominantly affecting distal joints such as the wrists, ankles, and small joints of the hands, while the spine and sacroiliac joints are rarely affected.[87] Older age has been associated with a higher risk of acute arthralgia.[88] Skin manifestations often present as a transient macular or maculopapular rash involving the extremities, palms, feet, trunk, and face, usually appearing within 2–5 days of illness onset, pruritus occurs in approximately one quarter of cases.[89] A recent meta-analysis of symptomatic adults found that arthralgia was the most common manifestation, affecting 89.7% of patients, followed by fever in 87.8%, myalgia in 62.9%, fatigue in 56.0%, joint swelling in 50.0%, headache in 49.5%, rash in 44.3%, and nausea in 34.7%, whereas arthritis was reported less frequently at 17.6%.[90] Other atypical features include lymphadenopathy, conjunctivitis, optic neuritis, photosensitivity, exfoliative dermatitis, hyperpigmentation, vasculitic eruptions, erythema nodosum–like lesions, exacerbation of pre-existing dermatoses, encephalitis, meningitis, and mucosal ulceration.[89,91–93] Chikungunya-associated neurological disease is regarded as the most common severe complication of infection.[94] Autopsy findings from fatal cases confirmed the anatomical sites underlying these clinical manifestations, with CHIKV antigen detected in multiple tissues, including the skin, bone, muscle, spleen, liver, kidney, lung, and heart.[81] CHIKV infection is highly symptomatic and marked by high-titer viremia that peaks within the first three days and can persist for up to eight days.[95] Acute infection elicits robust activation of innate immune responses.[96] The acute phase inflammatory response is characterized by elevated immune mediators and infiltration of immune cells into affected tissues, dominated by interleukin (IL)-6, IL-8, IFN-α, interferon gamma–induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1, and monokine induced by gamma interferon (MIG).[97–99] Higher circulating levels of IL-1β, IL-17A, IL-27, and granulocyte–macrophage colony-stimulating factor (GM-CSF) correlate with more severe joint pain.[100] Consistent with other reports, IL-27, a member of the IL-6/IL-12 family, is associated with rheumatoid arthritis disease activity and correlates with tender joint counts in CHIKV infection.[101] In mouse models, replication in skeletal muscle cells and IL-6 release are key mediators of disease, and IL-6 receptor blockade significantly reduces joint swelling.[102] Correspondingly, high IL-6 levels have been most consistently associated with disease severity.[103] Type-I IFN signaling is critical for controlling infection, and its deficiency is associated with severe disease.[62] MCP-1 is produced primarily by monocytes, and its induction requires IFN-β–mediated communication with other leukocytes.[104] IL-6 is one of the IFN-β–responsive cytokine produced by non-monocytic cells that further promotes this response.[105] Despite early correlations between MCP-1 levels and viral titers, MCP-1 does not directly contribute to CHIKV replication.[98,105] Overall, the balance among pro- and anti-inflammatory mediators is critical for an appropriate host response to CHIKV and is a key determinant of disease severity. Moreover, galectin-9 (GAL-9) and high mobility group box 1 protein (HMGB1) have been identified as potential biomarkers of acute infection.[106,107] Several studies have indicated that $CD8^{+}$ T cells are recruited early during CHIKV infection, where they play an important role in adaptive immunity by mediating cytolytic activity against target cells through granules exocytosis and granule-independent pathways.[108,109] These cytotoxic functions contribute to viral clearance in the circulation.[108]

The post-acute phase spans from two weeks to three months after onset, during which joint manifestations may either persist continuously or recur intermittently following symptom-free periods.[110] Most infected individuals recoverfully after the acute phase, but 30–40% progress to chronic arthritis that may last for months or even years.[111] The chronic phase is defined by persistent of joint manifestations such as pain, edema, or stiffness for more than three months after the acute phase. During this stage, patients may also develop chronic arthritis attributable to chikungunya.[85,112] Recent data suggest that arthritis can persist for up to seven years in some patients.[113] Chronic CHIKV disease is characterized by ongoing inflammation and immune activation.[114] Previous study reported that, in a patient 18 months postinfection, CHIKV RNA and antigens were detected in perivascular synovial macrophages surrounded by infiltrating NK cells, CD4+ T cells, and fewer cytotoxic CD8+ T cells.[115] CHIKV antigen has also been detected in human muscle specimen more than three months after acute infection.[80] However, synovial fluid analysis from 38 participants with CHIKV-associated arthritis at a median of 22 months postinfection was qRT-PCR negative, showed no viral proteins by mass spectrometry, and was culture negative.[116] A meta-analysis shows that chronicity rates decline over time, from 43.9% at three months to 34.4% at six months and 31.9% at twelve months.[87] Similarly, a Latin American cohort study reported that approximately 25% of participants experienced persistent joint pain after 20 months of follow-up, highlighting the long-term burden of chikungunya-related arthritis.[117] Higher viral loads and acute symptoms such as arthralgia, myalgia, and weakness are associated with an increased risk of developing chronic arthralgia.[46] Elevated levels of IL-6 and GM-CSF have also been linked to persistent joint pain.[99] In addition, elevated acute-phase levels of IL-6, IL-1β, TNF-α, IL-5, or IL-12 are associated with a greater risk of chronic joint pain, whereas low levels of IL-13, IL-2, and IL-4 are predictive of chronic outcomes, and a vigorous cytokine response appears necessary for effective viral clearance.[103,118]

Although severe disease and mortality are rare in chikungunya, neurological, cardiac, and renal involvement may result in high morbidity and mortality.[119] Older adults (≥65 years), infants, young children, pregnant women, and individuals with comorbidities such as hypertension, diabetes, or cardiovascular disease are at increased risk of severe disease and prolonged recovery.[82] After infection, IgM antibodies appear within days of symptom onset, with neutralizing anti-CHIKV IgG antibodies typically emerging by the second week, and the IgG3 isotype predominates in the humoral response.[120] Current evidence suggests that recovery is followed by durable immunity against reinfection.[121]

Accurate laboratory diagnosis of CHIKV infection is essential for clinical management and epidemiological surveillance. Diagnostic testing is typically performed on plasma or serum samples from suspected cases. During the acute phase, viral RNA can be detected by RT-PCR, which offers high sensitivity and specificity and is considered the reference method for early diagnosis. Viral isolation using cell culture is largely restricted to research and reference laboratories.[69] In later stages of infection, serological assays detecting CHIKV-specific IgM and IgG antibodies are widely used, including enzyme-linked immunosorbent assays (ELISA) and emerging point-of-care tests that facilitate rapid diagnosis in resource-limited settings.[122] However, serological testing may be complicated by cross-reactivity among antigenically related arboviruses, potentially reducing diagnostic specificity in regions with overlapping transmission. Recent studies have demonstrated the feasibility and performance of affordable multiplex qRT-PCR assays for the simultaneous detection of CHIKV, DENV, ZIKV, YFV, and co-infections, as well as broader panels capable of identifying multiple medically important flaviviruses and alphaviruses in parallel.[123–125] These multiplex platforms improve diagnostic efficiency and support outbreak response in endemic regions.

Mother-to-Child CHIKV Transmission

CHIKV infection does not increase the risk of miscarriage, intrauterine fetal death, or congenital malformations. However, maternal–neonatal transmission can occur in viremic women during childbirth.[126] A meta-analysis estimated the overall risk of mother-to-child transmission at 15.5% (206/1331). The pooled risks of neonatal death were 0.6% (5/832) among maternal infections and 2.8% (5/182) among neonatal infections, while the risk of CHIKV-confirmed antepartum fetal death was 0.3% (3/1203). Symptomatic infection occurred in 50.0% (23/46) of intrapartum cases but in none of the 712 antepartum or peripartum maternal infections. Infected neonates were either asymptomatic or developed symptoms during the first week of life, rather than at birth, including fever, irritability, rash, hyperalgesia, diffuse limb edema, bullous dermatitis, and occasionally meningoencephalitis. Long-term neurodevelopmental delay was observed in 50% of symptomatic neonatal infections.[127] In a two-year follow-up study from the Réunion Island outbreak, children exposed to perinatal mother-to-child CHIKV infection had significantly lower neurocognitive scores than unexposed peers (development quotient: 86.3 vs 100.2, $p < 0.001$). Among exposed children, those with severe encephalopathy had significantly worse outcomes than those with non-severe disease (mean development quotient: 77.6 vs 91.2, $p < 0.001$). Of 12 infants with neonatal encephalopathy, five developed microcephaly and four matched the criteria for cerebral palsy.[128]

Gérardin et al conducted a prospective study showing that mother-to-child CHIKV transmission occurs almost exclusively during intrapartum maternal viremia and is frequently associated with severe neonatal disease. Among 39 viremic mothers at delivery, 19 neonates became infected (vertical transmission rate, 48.7%), with severe illness observed in 10 cases, predominantly neonatal encephalopathy. Notably, placentas from infected neonates had significantly higher mean viral loads than those from uninfected neonates ($p = 0.021$).[129] Another study reported similar findings, with a transmission rate of approximately 62% (18/29) among viremic pregnant women during delivery.[130] Immunofluorescence labeling with anti-CHIKV antibodies failed to detect viral antigen in placentas or in an animal model of maternal–fetal CHIKV infection.[62] In addition, RT-PCR on placental cells isolated by mechanical dissociation was consistently negative.[129] These findings support passive contamination of the placenta by maternal blood-borne free viral particles rather than true placental infection. Mother-to-child transmission of CHIKV may result from placental barrier disruption caused by uterine contractions, allowing maternal blood with high viral loads to cross into the fetal circulation. Notably, emergency cesarean section delivery does not prevent transmission.[129] Consistently, Leglet et al reported that among 151 women infected with CHIKV during pregnancy, 118 delivered outside the viremic period and no neonate showed evidence of infection. In contrast, among 33 women who delivered while viremic, 16 newborns (48.5%) developed neonatal chikungunya.[131] Regarding management, Escobar et al suggested that deferring delivery in women with acute CHIKV infection may be an appropriate management strategy in the absence of obstetric contraindications. The mean interval from maternal symptom onset to delivery was 6.3 ± 1.4 days, which may provide sufficient time for passive transfer of maternal antibodies and thereby reduce the risk of symptomatic infection in the newborn.[132]

Vaccine Development

In November 2023, the US Food and Drug Administration (FDA) approved IXCHIQ (VLA1553), a live-attenuated vaccine developed by Valneva, as the first licensed vaccine against chikungunya (Table 1). IXCHIQ was approved for individuals ≥ 18 years at increased risk of CHIKV exposure and was administered as a single intramuscular dose. Its prescribing information included a warning that the vaccine contains live attenuated virus and may cause symptoms in recipients that are similar to those of natural chikungunya infection.[133] In June 2024, the vaccine was unanimously endorsed by the Member States following a stringent assessment by the European Medicines Agency (EMA).[134] Owing to the unpredictable nature of CHIKV epidemiology, vaccine licensure was based on a correlate of protection rather than traditional Phase 3 trials.[135] On May 9, 2025, the FDA and the Centers for Disease Control and Prevention (CDC) issued a safety communication recommending suspension of IXCHIQ use in adults ≥60 years while post-marketing reports of serious neurologic and cardiac adverse events were under investigation. The suspension was lifted on August 6, 2025, following a risk-benefit assessment. Subsequently, on August 22, 2025, the FDA's Center for Biologics Evaluation and Research (CBER) suspended the biologics license for IXCHIQ. CBER's benefit–risk analysis concluded that the clinical benefit had not been adequately confirmed in clinical studies and the potential benefits of IXCHIQ did not outweigh the associated risks. Accordingly, CBER determined that the vaccine was not safe and that continued administration would pose a public health risk.[136]

In February 2025, the FDA approved VIMKUNYA (PXVX0317) for individuals ≥ 12 years, a virus-like particle vaccine developed by Bavarian Nordic. Phase 3 clinical trial results demonstrated a seroresponse rate of 97.8% with significantly elevated serum neutralizing antibody titers at day 22. In addition, VIMKUNYA also showed a favorable safety profile, with most adverse events reported as mild and self-limiting.[137] In April 2025, the Advisory Committee on Immunization Practices (ACIP) issued recommendations for the use of VIMKUNYA in travelers to chikungunya endemic countries or territories and in laboratory workers at risk of exposure.[138]

Table 1 Current Landscape of Licensed Chikungunya Vaccines (Updated to August 2025)

Vaccine Name	Platform	Developer	Regulatory Status	Approved Population	Key Features
IXCHIQ (VLA1553)	Live-attenuated	Valneva	FDA approved (Nov 2023); EMA endorsed (Jun 2024); biologics license suspended by FDA CBER (Aug 2025)	≥18 years (initial approval)	Single-dose vaccine; licensure based on correlate of protection; post-marketing reports of serious neurologic and cardiac adverse events
VIMKUNYA (PXVX0317)	Virus-like particle	Bavarian Nordic	FDA approved (Feb 2025); ACIP recommended (Apr 2025)	≥12 years	High seroresponse rate (97.8% at day 22); favorable safety profile with mostly mild adverse events

Future Recommendations

The geographic suitability for CHIKV transmission continues to expand. Long-term studies of international travelers show that chikungunya cases in returning travelers reflect transmission activity in endemic regions and often provide early evidence of virus circulation beyond affected areas.[139,140] Retrospective epidemiological analyses in mainland Europe from 2007 to 2023 indicate that the majority of human CHIKV infections were travel-related and that imported cases were frequently observed either before or closely associated with autochthonous transmission in areas where competent *Aedes* vectors are established.[141] Travelers returning to non-endemic regions with CHIKV infection may initiate local clusters or outbreaks where competent mosquito vectors are present. Accordingly, individuals travelling to areas with active CHIKV circulation should be informed of infection risk and advised on appropriate preventive measures.[142] An exploratory surveillance study conducted in Portugal demonstrated that continuous and active surveillance is essential for the timely detection and management of potential CHIKV outbreaks.[143] These observations support the incorporation of travel-associated case detection into integrated surveillance frameworks, together with entomological monitoring and laboratory confirmation, to facilitate early risk assessment and timely public health response.

Conclusions

In conclusion, chikungunya remains a significant global health threat, with *Aedes* mosquitoes well adapted to urban environments and expanding their range due to climate change and human activity. Future studies should clarify how early innate and adaptive immune responses lead to chronic joint disease and develop validated biomarkers that predict persistence and severity. Differences in these responses between asymptomatic and symptomatic CHIKV infection, and between self-limited and chronic courses, need clearer definition. Mother-to-child care should be optimized to reduce transmission at the time of delivery. Developing effective therapeutic approaches is essential to shorten the disease course and reduce the incidence of chronic arthritis. Vaccine strategies should provide safe, durable, and broadly accessible protection for high-risk populations, with continuous monitoring of effectiveness and safety in real-world settings. Progress against chikungunya will require multidisciplinary efforts that integrate fundamental and translational research, clinical investigation, epidemiology, and public health practice.

Abbreviations

CHIKV, chikungunya virus; PAHO, Pan American Health Organization; WHO, World Health Organization; RRV, Ross River virus; BFV, Barmah Forest virus; SINV, Sindbis virus; MAYV, Mayaro virus; ONNV, O'nyong-nyong virus; EEEV, Eastern equine encephalitis virus; VEEV, Venezuelan equine encephalitis virus; WEEV, Western equine encephalitis virus; DENV, dengue virus; ZIKV, Zika virus; YFV, yellow fever viruses; dpi, days post infection; ORF, open reading frame; C, capsid; E, envelope; ECSA, East/Central/South African; IOL, Indian Ocean lineage; MXRA8, Matrix remodeling–associated protein 8; FHL1A, four-and-a-half-LIM domain protein 1 splice variant A; DC-SIGN, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin; TIM1, T cell immunoglobulin and mucin domain-containing protein 1; IL, interleukin; IFN, interferon; IP, interferon gamma–induced protein; MCP, monocyte chemoattractant protein; MIG, monokine induced by gamma interferon; GM-CSF, granulocyte–macrophage colony-stimulating factor; GAL-9, galectin-9; HMGB1, high mobility group box 1 protein; ELISA, enzyme-linked immunosorbent assays; FDA, Food and Drug Administration; EMA, European Medicines Agency; CDC, Centers for Disease Control and Prevention; CBER, Center for Biologics Evaluation and Research; ACIP, Advisory Committee on Immunization Practices.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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