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A Scoping Review of Chikungunya Virus Infection: Pathogenesis, Transmission and Prevention Strategies

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Abstract

Chikungunya virus (CHIKV), a re-emerging arbovirus, induces a debilitating musculoskeletal inflammatory disease in humans, *manifesting as* fever, polyarthralgia, myalgia, rash, and headache. CHIKV is transmitted by mosquitoes of the Aedes genus and exhibits a highly efficient epidemic and urban transmission cycle. Since 2004, CHIKV has expanded into new regions, leading to outbreaks on a global scale, and the *risk of future epidemics remains substantial.* The virus's evolution, along with factors such as globalization and climate change, may have facilitated its geographic spread. Despite CHIKV's ability to cause millions of infections and impose a considerable economic burden on affected regions, *no licensed vaccines or antiviral treatments are currently available.* This review explores the epidemiology, recent trends, pathogenesis, transmission dynamics, and diagnostic approaches for CHIKV, while also evaluating potential vaccine candidates and future research directions.

Keywords: Chikungunya virus, Epidemiology, Pathogenesis, Vaccines

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Introduction

The chikungunya virus (CHIKV) is recognized as the causative agent of chikungunya fever (CHIKF), a disease transmitted primarily by mosquitoes of the Aedes genus (1). Initially identified in 1952 in what is now Tanzania, early cases of CHIKF were often misdiagnosed as infections caused by the dengue virus (DENV) (2). Following the isolation of CHIKV from the sera of infected patients, along with *Ae. aegypti* (*Stegomyia*) and *Culex* spp. in 1953, the virus was classified within the arbovirus group A (3). CHIKV is currently categorized under the *Alphavirus* genus within the *Togaviridae* family and is recognized as a member of the *Semliki Forest virus* (SFV) antigenic complex (4).

After its identification in East Africa in 1952, CHIKV was subsequently documented in Central and Southern Africa, specifically in Uganda and the sub-Saharan regions (5). Advancements in molecular evolution tools and nucleic acid sequencing have facilitated the classification and naming of CHIKV strains based on their

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geographical origins: The East, Central, and South African (ECSA) lineage. Phylogenetic analysis of CHIKV isolates from epidemics occurring between 1958 and 1973 in Asia classified them into a monophyletic group known as the *Asian lineage* (6). Similarly, phylogenetic investigations of CHIKV isolated from mosquitoes in West Africa (Senegal) before the end of the 20th century confirmed the existence of a second, more geographically restricted viral lineage known as *West African (WA)* (7).

With over six million suspected cases, CHIKV began to spread throughout the Indian Ocean islands, India, and Southeast Asia following a major epidemic on the Kenyan coast in 2004 (8). Viruses evolving from the ECSA clade were later classified under the *Indian Ocean Lineage (IOL)*, which was consistently linked to CHIKV epidemics between 2005 and 2014 (9). In 2005, a significant CHIKV epidemic occurred in the Comoros, infecting approximately 215,000 individuals (10). From March 2005 to April 2006, 255,000 cases were reported on Réunion Island (11).

More recently, on Réunion Island, where *Aedes albopictus* (Skuse, 1894) is highly prevalent, a non-synonymous mutation in the viral envelope glycoprotein E1 (*E1-A226V*) was detected in 90% of isolates (12). Studies employing reverse genetics have demonstrated that the *E1-A226V* mutation enhances viral fitness in *Ae. albopictus* (13). The *E1-A226V* substitution is believed to increase CHIKV infectivity in the midgut cells of *Ae. albopictus*, as amino acid 226 is positioned near the fusion peptide, which plays a crucial role in the virus's release from the endosome during the early stages of infection. Notably, this mutation did not impair CHIKV replication in *Ae. aegypti* (13). Mutations at similar positions on the *E1* glycoprotein gene have also been identified in other alphaviruses, including *Semliki Forest virus* (SFV) and *Sindbis virus* (SINV), and have been associated with enhanced infection capacity and viral egress in the *Ae. albopictus* (C6/36) cell line (14).

Concerns surrounding CHIKV intensified after 2007, following its detection in northern Italy, likely introduced by an infected traveler from India (15). In September 2010, an autocthonous chikungunya case was reported in southeastern France (16). That same year, CHIKV caused outbreaks in India, Myanmar, Thailand, Indonesia, and the Maldives, while also re-emerging on Réunion Island (17). CHIKV arrived on the American continent in 2013, initially spreading across the Caribbean before reaching Brazil in 2014 (9). In 2015, CHIKV was designated a notifiable disease by the CDC (18). The most recent documented outbreak occurred in Mombasa, Kenya, in February 2018 (19, 20).

At present, CHIKV infection has been reported in multiple countries across all continents except Antarctica (21). In some regions, particularly in South America, the co-circulation of CHIKV alongside other arboviruses—including *ZIKV, DENV, yellow fever virus (YFV), and Mayaro virus (MAYV)*—necessitates robust epidemiological surveillance and differential diagnostic strategies (22). This review examines key aspects of CHIKV epidemiology, pathogenesis, transmission, treatment, diagnosis, prevention, and vaccine development. Furthermore, the publication trends for CHIKV-related research in the PubMed database indicate a steady increase from 1957 to 2024 (Figure 1).

Recent Trends and Emerging Epidemics

As of September 30, 2024, approximately 460,000 cases of CHIKV infection and 170 associated fatalities had been reported globally. Twenty-three countries documented CHIKV cases across the Americas (15), Asia (6), Africa (1), and Europe (1). In September 2024, Grenada recorded its first reported cases of CHIKV, marking the virus's debut in the country that year. The highest CHIKV burden was observed in South and Central America (23).

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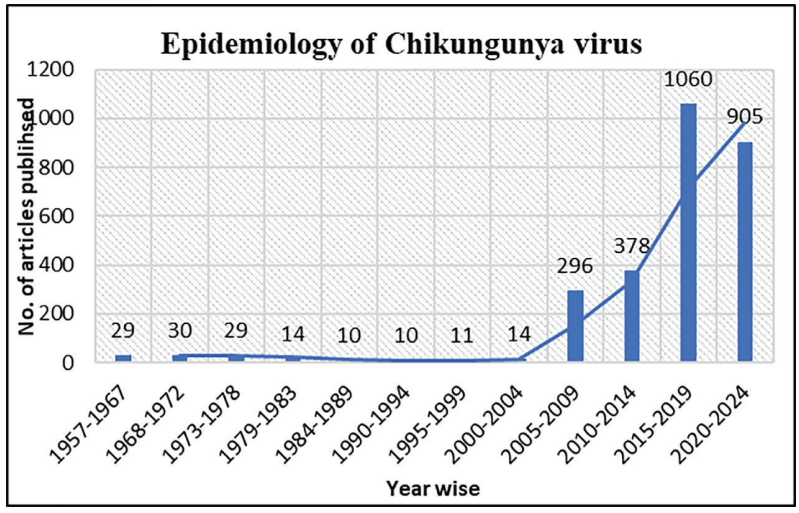


Figure 1. Trends in Chikungunya Virus Epidemiology Publications Based on a Literature Review of the PubMed Database

In 2024, Senegal confirmed nine CHIKV cases. That same year, a single locally acquired case of CHIKV was identified in mainland Europe, specifically in France. Additionally, seven non-travel-related CHIKV cases were reported in La Réunion. The majority of CHIKV-related fatalities occurred in Brazil (170) (Figure 2) (23).

Current Scenario of Chikungunya Virus in India

In India, multiple CHIKV outbreaks occurred between 1963 and 1973 (24). However, no outbreaks were documented between 1974 and 2004 (25). CHIKV re-emerged in India in 2005, triggering widespread epidemics in Southern India (26). The 2006 outbreak resulted in an estimated 25,588 disability-adjusted life years (DALYs) lost, corresponding to a total burden of 45.26 DALYs per million people (Table 1) (25). The burden of CHIKV varied across Indian states, ranging from 0.01 to 265.62 DALYs per million people. The National Vector-Borne Disease Control Program (NVBDCP) recorded over 40,000 clinically suspected cases in India in 2020 (27). The 28-day case fatality rate due to CHIKV was reported at 9.5% (28). Furthermore, a mortality rate of 11.9% was recorded in Ahmedabad, reflecting the case fatality rate in that region (29) (Figure 3).

Structure and Organization of the viral Genome

Like other members of the *Togaviridae* family, CHIKV possesses a single-stranded, positive-sense RNA genome (~12 kb) with a polyadenylated 3' tail and a 5' N7-methylguanylated cap (30).

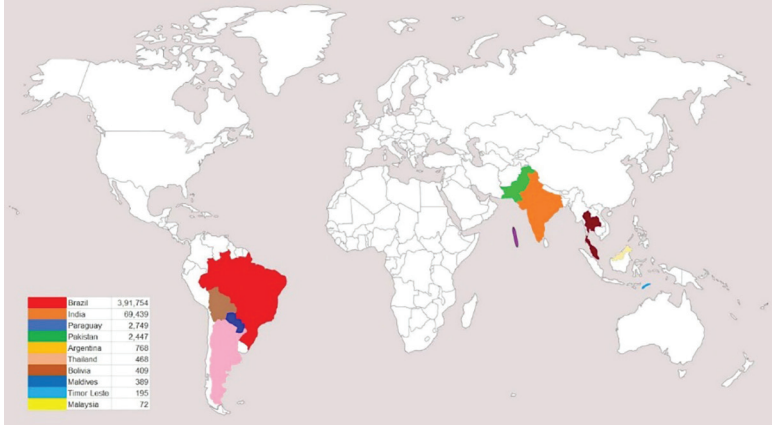


Figure 2. Countries with the Highest Reported CHIKV Cases

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Table 1. Chikungunya Cases Reported in India (2018–June 2024)

Year	No. of Suspected Cases	No. of Confirmed Cases
2018	57,813	9,756
2019	81,914	12,205
2020	43,424	6,324
2021	1,19,070	11,890
2022	1,48,587	8,067
2023	2,00,064	11,477
2024	69395	3066

The genome comprises two open reading frames (ORFs) encoding structural proteins (sP) and non-structural proteins (nsP), flanked by 5' and 3' untranslated regions (UTRs) (31). The 5' ORF encodes four non-structural proteins (nsP1, nsP2, nsP3, and nsP4), which are crucial for genome synthesis and replication. A read-through of an opal stop codon between nsP3 and nsP4 typically facilitates the translation of these proteins as either an nsP1-3 polyprotein or a full-length nsP1-4 polyprotein (32). The 3' ORF encodes a polyprotein that includes the viral structural proteins (*Capsid, E1, E2, E3, 6K, and TF*), which are translated from a subgenomic RNA (sgRNA) produced from the negative-sense antigenome. These structural proteins are essential for virion assembly, host cell entry, and viral budding (33). The processing of both polyproteins by viral and

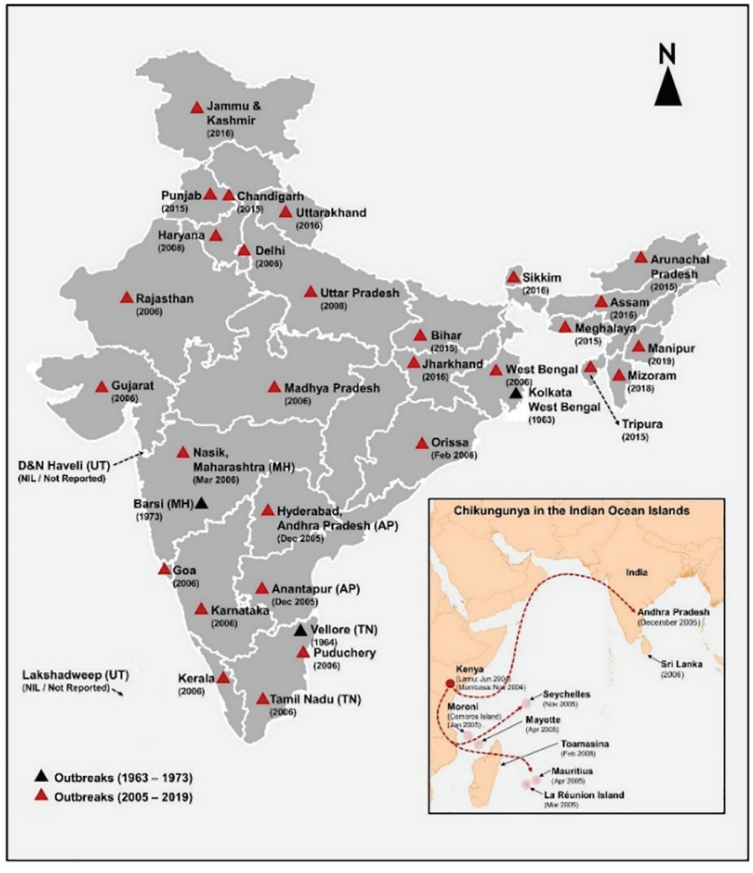


Figure 3. Timeline of Chikungunya Epidemics in India (1963–2019). Black and red triangles indicate the years of epidemic onset, while the transition from the Asian genotype (1963–1973) to the ECSA genotype (2005–2019) is represented by red triangles. Data source: NVBDCP (2014–15), National Health Profile (2019), and National Center for Disease Control (2020).

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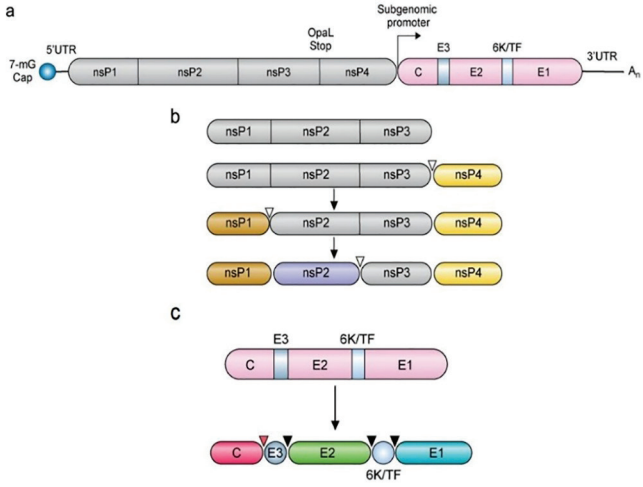


Figure 4. CHIKV Genome Organization, Protein Processing, and Structural Complexes.

host proteases during replication follows distinct temporal and spatial patterns (34). The CHIKV virion, approximately 70 nm in diameter, consists of an icosahedral nucleocapsid enclosing the viral RNA genome within a lipid bilayer. Trimeric spikes composed of E1 and E2 glycoprotein heterodimers are embedded in the viral membrane, forming an external icosahedral protein lattice (Figure 4).

Pathogenesis of CHIKV

The *Alphavirus* genus includes approximately 30 species, which are believed to have diverged several thousand years ago (35). While some alphaviruses do not cause disease in humans, others exhibit significant infectivity, leading to clinical manifestations ranging from mild to severe. Alphaviruses are broadly classified into two groups: New World and Old World viruses (36). These groups have evolved distinct host interactions and differ in pathogenicity, cellular and tissue tropism, cytotoxicity, and virus-induced immune evasion strategies. Most alphavirus infections in humans and domestic animals

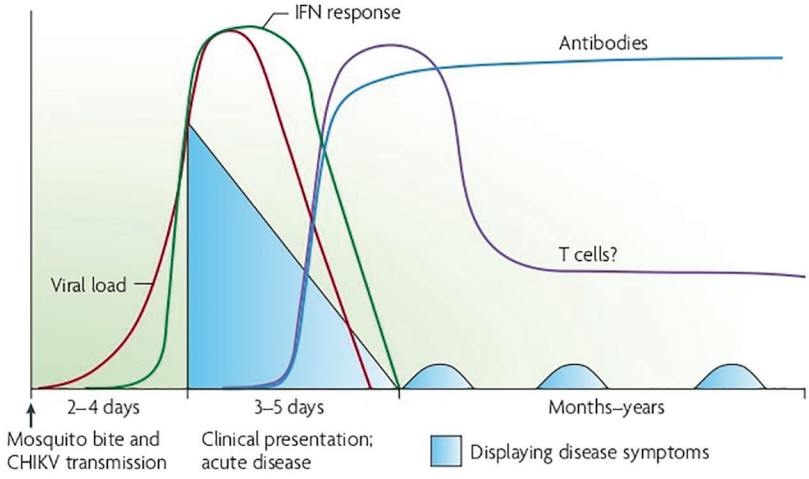


Figure 5. Chikungunya Virus Pathogenesis. Following an infectious mosquito bite, symptoms typically appear within 2–4 days. Fever, chills, headache, and rash are common early symptoms, with most infected individuals experiencing severe joint pain. A rising viral load triggers an innate immune response, leading to the production of type I interferons (IFNs) at disease onset. Within a week, patients clear the virus and develop adaptive immunity, including T-cell and antibody-mediated responses. However, approximately 30% of patients experience persistent arthritis or arthralgia.

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are considered "dead-end" infections, meaning that the virus is not efficiently transmitted to new hosts. This suggests that the evolutionary constraints on viral diversity may be linked to host specificity. However, a comprehensive investigation into potential zoonotic reservoirs of CHIKV remains lacking.

Clinically, alphaviruses are classified into two groups:

1. Neurotropic viruses, which primarily cause encephalitis (New World alphaviruses).
2. Arthritogenic viruses, which mainly cause polyarthritis and rash (Old World alphaviruses) (37).

Although CHIKV is traditionally categorized as an arthritogenic alphavirus, recent outbreaks have reported cases of meningoencephalitis (particularly in neonates) and hemorrhagic manifestations (38). These findings suggest that such severe complications represent significant sequelae of acute CHIKV infection (39). Unlike classical neurotropic alphaviruses, which primarily target neurons, CHIKV appears to infect the stromal cells of the central nervous system, particularly those lining the choroid plexus (Figure 5).

CHIKV transmission primarily occurs through bites from infected *Aedes aegypti* or *Aedes albopictus* mosquitoes, although recent epidemics have demonstrated evidence of maternal-fetal transfer (40). Following transmission, CHIKV multiplies in the skin before spreading to the liver and joints, presumably via the bloodstream (41, 42). The incubation period typically lasts 2–4 days, followed by an abrupt onset of clinical disease without a prodromal phase. The clinical manifestations of CHIKV infection include elevated fever, chills, headache, photophobia, and either a petechial or maculopapular rash. Moreover, the majority of infected persons experience debilitating joint pain (43, 44) (refer to the WHO guidelines on the therapeutic management of chikungunya). Asymptomatic infections are relatively uncommon, occurring in approximately 15% of affected persons (45). During the acute phase, the viral load can reach 108 viral particles per ml of blood. Concurrently, the plasma concentration of type I interferons (IFNs) ranges from 0.5 to 2 ng per ml, accompanied by a significant elevation of other pro-inflammatory cytokines and chemokines (46, 47).

The acute phase of CHIKV infection typically endures from several days to a few weeks. In contrast to the acute phase, the chronic phase of the disease remains incompletely understood. Recurrent joint pain, which may persist for years in certain instances, affects 30–40% of infected individuals; however, this is not considered to be the result of chronic infection, as the infectious virus cannot be isolated from these patients. Radiographic examinations typically appear unremarkable or show minor edema, corresponding with joint discomfort. This persistent joint discomfort is thought to be immune-mediated, similar to the pain induced by the associated alphavirus Ross River virus (RRV) (48). Although not definitively demonstrated, the presence of autoantibodies has been documented in a single case of CHIKV infection associated with significant musculoskeletal sequelae (49).

Transmission of CHIKV

Research has identified two distinct transmission cycles: enzootic and urban. Within African forests, arboreal mosquitoes, particularly *Aedes species*, serve as vectors for an enzootic cycle. Based on substantial evidence, non-human primates appear to function as the primary reservoir and amplification hosts in the enzootic cycle, as demonstrated by their elevated seroprevalence rates, which encompass confirmed infections and viremia both in natural settings and following experimental infection (50). During mild epidemics, enzootic mosquito vectors can facilitate human-to-human transmission, enabling the enzootic cycle to extend to nearby human populations. The introduction of CHIKV into urban areas in

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Africa triggers epidemics, where transmission occurs through the anthropophilic vectors *Aedes aegypti* and *Aedes albopictus*, which enhance human-mosquito transmission. CHIKV can establish a persistent urban transmission cycle through human amplification hosts and these *Aedes* species (51). The proximity of mosquitoes to human populations in this endemic/epidemic cycle intensifies human exposure to mosquito transmission. The behavioral patterns and ecology of adult female *A. aegypti* contribute significantly to epidemic spread, as they preferentially seek human blood, frequently taking multiple partial blood meals within a single gonotrophic cycle, deposit eggs in artificial containers conducive to larval development, and reside indoors in close proximity to human hosts (52). *A. albopictus* exhibits both zoophilic and anthropophilic behaviors, characterized by aggressive, silent, and diurnal activity. Its exceptional lifespan of up to 8 weeks exceeds that of other mosquito species, and it has successfully colonized previously designated *Aedes*-free zones over recent decades (53). The recent surge in *A. albopictus* outbreaks stems from viable eggs transported in tires and lumber shipped from Asia to various countries (54). For both *A. albopictus* and *A. aegypti*, humans present high viremia levels that typically persist for the first four days following symptom

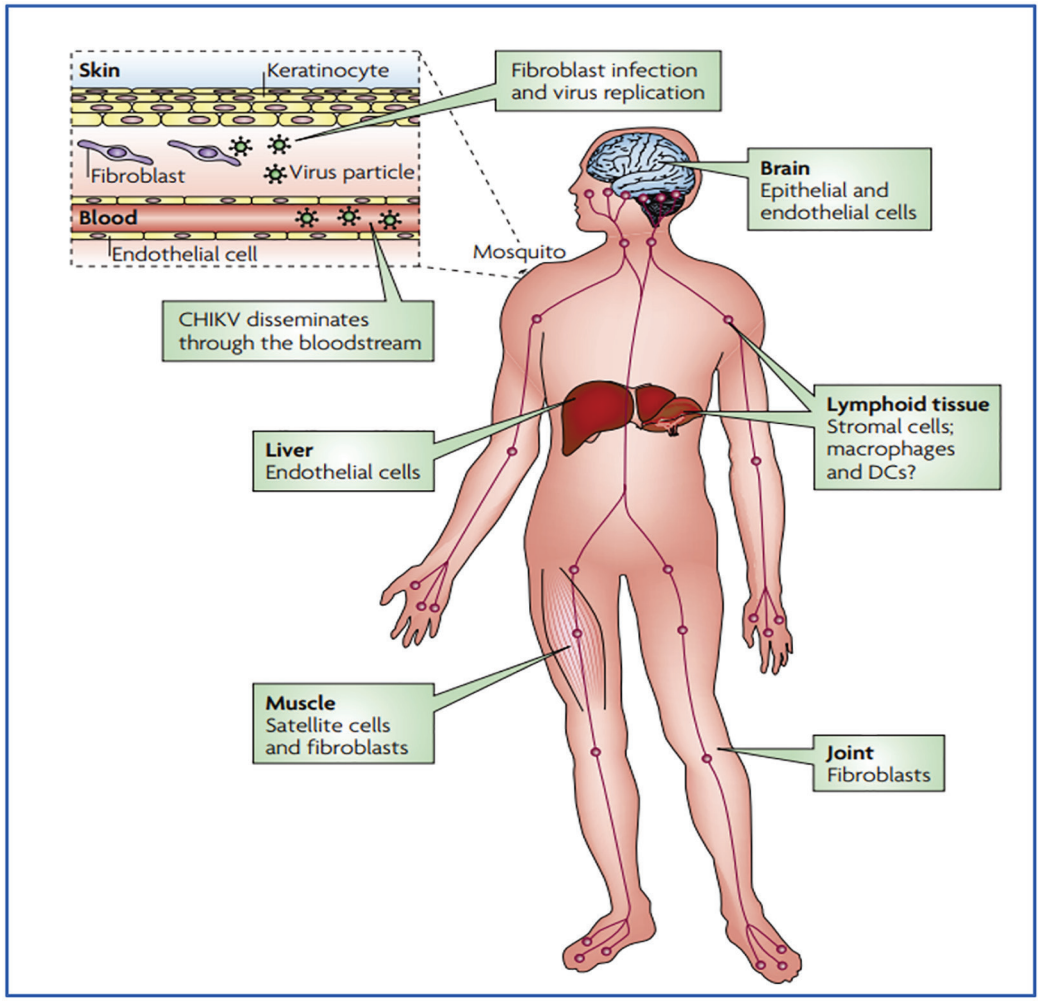


Figure 6. Chikungunya virus transmission in vertebrates. Following mosquito (*Aedes aegypti* or *Aedes albopictus*) transmission, CHIKV multiplies in skin fibroblasts before disseminating to the liver, muscles, joints, lymphoid tissue (including lymph nodes and spleen), brain, and other organs. Target cells are specified for each tissue.

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onset, reaching peak levels of approximately 109 viral RNA copies/ml on the day of onset (55). Although infectivity varies significantly among CHIKV strains, infectious titers can exceed 107 PFU/ml (56). These titers typically surpass the oral infectious dose 50% threshold for both epidemic vector species, enabling efficient mosquito-to-human transmission (57). During epidemic periods, humans function as the principal CHIKV reservoir. In the absence of human cases, monkeys, rodents, and birds serve as viral reservoirs, maintaining viral circulation in the environment (Figure 6).

Diagnostic Approaches for CHIKV

Similar to other arboviral infections, CHIKV manifests with a diverse range of symptoms, including fever, myalgia, skin rash, arthralgia, headache, and neurological complications. It is worth noting that the clinical manifestations of CHIKV and other arboviral infections share numerous overlapping characteristics. This diagnostic challenge becomes particularly evident in regions where CHIKV occurs simultaneously with dengue virus and Zika virus (58). Therefore, laboratory diagnosis plays a crucial role in verifying the differential diagnosis of CHIKV and other etiological agents. Current diagnostic methodologies for CHIKV identification comprise viral isolation through cell culture, viral nucleic acid detection via reverse transcription-polymerase chain reaction (RT-PCR), and the detection of CHIKV-specific IgM antibodies using serological assays (59). The Centers for Disease Control and Prevention (CDC) has established a laboratory diagnostic testing algorithm for confirming CHIKV infection, which takes into account the disease's characteristics and the timing of sample collection. For serological identification, CHIKV-specific IgM antibodies are detected using an enzyme-linked immunosorbent test (ELISA) (60). The effectiveness of antibody detection in CHIKV-infected patients increases significantly in samples collected approximately 5 days after the onset of illness. Notably, cross-reactivity has been documented between antibodies targeting DENV and those of the Semliki Forest antigenic complex group, which includes viruses such as Mayaro and o'nyong-nyong (61).

While viral culture remains the gold standard for diagnosing CHIKV infection, the identification of viral RNA in plasma or serum (or other sample types) through RT-PCR is typically employed during the acute phase. Various molecular techniques, including nested and real-time PCRs, can be utilized to detect viral RNA (40). Both conventional and real-time PCR techniques have proven effective in amplifying the genes of nsP1, nsP2, or envelope proteins (E3, E2, or E1) (62, 63). The spectrum of molecular diagnostic methods available for CHIKV identification encompasses reverse transcription (RT) and polymerase chain reaction (PCR) assays that target specific regions within the nsP1, nsP2, nsP3, nsP4, or E1 sections of the CHIKV genome, predominantly utilizing real-time methodologies (64, 65).

Treatment

Currently, no specific pharmaceutical treatment exists for CHIKV infection. Healthcare providers should administer symptomatic medication only after excluding severe conditions such as dengue, malaria, and bacterial infections. The management of acute infection consists primarily of symptomatic and supportive interventions, including rest and the controlled administration of paracetamol for fever reduction (not to exceed 4 gm per day). For the alleviation of arthritic symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen may be prescribed, provided that dengue infection has been ruled out. In cases of severe joint pain that proves resistant to NSAID therapy, tramadol or opioids such as morphine may be considered (66).

While earlier studies have suggested potential benefits of hydroxychloroquine phosphate in managing arthralgia, further research is necessary to validate these findings. Indeed,

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subsequent investigations have failed to demonstrate its efficacy (67). Recent research has focused on evaluating alternative treatments, including methotrexate (MTX). A retrospective study conducted on La Réunion Island revealed that 54 out of 72 patients demonstrated a favorable clinical response following MTX treatment. In cases where MTX is either contraindicated or ineffective, immunomodulating biological medications such as etanercept, rituximab, or tocilizumab may be considered. Research has demonstrated that individuals with rheumatoid arthritis exhibit reduced vitamin D levels, which correlate inversely with disease activity (68).

Based on these findings, vitamin D repositioning might serve to reduce disease severity. An experimental trial in India administered vitamin D and calcium supplementation to patients with CHIKV-associated persistent arthritis over a period of five months. Beyond pharmaceutical interventions, individuals experiencing arthralgia and joint stiffness may derive significant benefit from a progressive physiotherapy program implemented during both acute and chronic phases of the condition (69).

Prevention

In the absence of a developed vaccine, effective prevention relies exclusively on personal protection against mosquito bites and vector control. The management of adult and larval mosquito populations follows an approach similar to that employed for dengue control, which has demonstrated significant effectiveness across various nations and settings (70). The implementation of comprehensive mosquito control measures represents the most efficacious strategy for preventing CHIKV transmission. Of particular importance is the elimination of breeding sites through systematic emptying, cleaning, pesticide treatment, or complete removal (71). For personal protection, individuals should wear clothing that minimizes exposure to daytime-biting vectors. Approved repellents should be applied to exposed skin or clothing in accordance with product label recommendations. The most effective repellents include IR3535 (3-[N-acetyl-N-butyl]-amino propionic acid ethyl ester), DEET (N, N-diethyl-3-methylbenzamide), and icaridin (1-piperidine carboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). The use of mosquito coils and insecticide vaporizers can significantly reduce indoor biting incidents (72).

Vaccines

While no commercially available vaccine currently exists for CHIKV, several candidate vaccines have progressed to human trials (73). The virus structure includes two glycoproteins (E1 and E2) that are essential for cellular infection. The E1 glycoprotein consists of 442 amino acids forming three β-barrel domains (74)—domains I, II, and III. Similarly, the E2 glycoprotein comprises 423 amino acids organized into domains A, B, and C. Research has established that domain A contains the receptor binding site and facilitates cell-to-cell transmission (75). Domain B primarily functions as a protective cover for the fusion loop on domain II of E1, while domain C, situated adjacent to the viral membrane, retains an unidentified function. Current vaccine development approaches include inactivated viral vaccines, consensus-based DNA vaccines, recombinant viral vaccines, alphavirus chimeras, recombinant subunit vaccines, and live-attenuated viruses. Additionally, virus-like particle (VLP) vaccines have emerged as promising candidates in recent CHIKV vaccine development. Among these, the live recombinant measles virus-based CHIKV vaccine and the VLP vaccine have successfully completed phase I clinical trials, unlike the inactivated VRC-CHKVLP059-00-VP. Notably, the live recombinant measles virus-derived CHIKV vaccine demonstrated robust immunogenicity, even among individuals with pre-existing measles immunity. Furthermore, both this vaccine and the VRC-CHKVLP059-00-VP

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vaccination proved to be safe and well-tolerated (76). The field of CHIKV vaccine research has experienced significant growth over recent decades (77, 78), with initial research focusing primarily on treating CHIKV fever during the first two decades.

Conclusion

The global resurgence of CHIKV can be attributed to multiple factors, including urbanization, human mobility, viral adaptation, insufficient control efforts, and the geographical expansion of new vectors. The unprecedented scale of the current global outbreak is characterized by its magnitude and extensive transmission across numerous countries. This pattern comprises multiple smaller outbreaks that disseminate from one location to another through human mobility, persisting until adequate herd immunity develops in adjacent populations or environmental factors impede further viral spread. In nations with large populations, such as India, transmission can persist for more than a decade. The presence of *Ae. albopictus* as a competent vector in subtropical and temperate climates has significant implications for disease transmission patterns. While promising developments are emerging in CHIKV vaccine research, significant challenges remain before successful commercialization can be achieved. The rapid global dissemination of CHIKV underscores the critical need to develop and implement scalable and cost-effective strategies for managing *Aedes aegypti* populations.

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Conflict of Interests

The authors declare no conflicts of interest.

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Authors' Contribution

Sreedevi conceptualized and supervised the study. Krishna and Thrimothi were responsible for data collection and manuscript preparation. All authors have reviewed and approved the manuscript for publication.

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