ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26mar1925

Chikungunya Virus 2025: An Integrated Review of Epidemiology, Virology, Pathogenesis, Clinical Spectrum, Diagnostics and Vaccine Development

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Publication Date: 2026/04/10

Abstract: Aedes aegypti and Aedes albopictus mosquito bites can infect people with the chikungunya virus (CHIKV), an alphavirus that causes chikungunya, an arboviral disease. In the past two decades, the chikungunya virus has resurfaced as a contagious illness in Africa, Asia, the Indian Ocean Islands, Europe, and the Americas; 119 countries and territories have reported locally transmitted cases of chikungunya virus disease up to 2024. The geographic distribution of chikungunya virus disease is expanding to include a wider geographic distribution and an increased risk of introduction and subsequent spread of the virus through mosquito vectors to an increasing population at risk of infection. Once infected through the bite of an infected mosquito, replication of the virus leads to the onset of symptoms such as fever, severe joint pain and swelling, myalgias, and rash as a result of the body's immune response to the infection. Most people infected with chikungunya virus disease make a full recovery within a period of weeks; however, a small percentage of people may develop prolonged arthralgia or chronic arthritis lasting for months or even years. While both the live-attenuated vaccine IXCHIQ and the virus-like fragment vaccine VIMKUNYA have been approved for use, the former's license has recently been revoked due to safety issues. Recent chikungunya fever outbreaks have led to active and continuous research into the disease, resulting in a better and deeper understanding of the disease and its pathogenesis. In this review article, we highlight the recent advances up to 2025 in the epidemiology, transmission, virology, pathogenesis, clinical manifestations, diagnosis, and vaccines for chikungunya virus disease.

Keywords: *Chikungunya, Vaccine Development, Transmission.*

How to Cite: Vishnu Agrahari; Iva Katiyar; Akhilesh Kumar Dubey; Madhumala Chauhan; Devejya Shukla (2026) Chikungunya Virus 2025: An Integrated Review of Epidemiology, Virology, Pathogenesis, Clinical Spectrum, Diagnostics and Vaccine Development. *International Journal of Innovative Science and Research Technology*, 11(3), 3746-3752. https://doi.org/10.38124/ijisrt/26mar1925

I. INTRODUCTION

The Chikungunya virus (CHIKV) is a virus that is spread by mosquitoes and is a member of the Togaviridae family's Aphavirus genus. It was discovered and isolated for the first time in Tanzania in 1952. It has once again emerged as a major pathogen endangering worldwide public health within the past 20 years (1,2). The virus is mostly spread by Aedes albopictus and Aedes aegypti mosquitoes. High fever, severe polyarthritis, and rash are common clinical signs of acute febrile illness caused by infection (3). However, up to 60% of patients endure months or even years of incapacitating, chronic joint pain. Despite the low fatality rate of CHIKV infection, recurring epidemics have a significant socioeconomic impact due to employment loss, increased strain on healthcare systems, and long-term consequences, all in the context of an aging population and a rise in comorbidities (4).

CHIKV infection saw an unexpected rebound in 2024 and 2025, while being underdiagnosed in many regions of the world (4). The World Health Organization (WHO) received

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26mar1925

reports of more than 160,000 laboratory-confirmed cases and more than 1.6 million probable cases, including the biggest local outbreak in China. There were 108 laboratory-confirmed cases of CHIKV infection and 2197 probable cases reported in Africa by September 2025. As of October 3, 2025, 56,456 CHIKV cases, including 40 fatalities, have been documented in four European countries and regions: France, Italy, Reunion, and Mayotte. Southeast Asia, Central Asia, South Asia, and the Western Pacific subregion of East Asia are the regions with the highest prevalence of CHIKV in Asia (5). Bangladesh, Indonesia, and Pakistan have seen an upsurge in CHIKV cases during the last two years. Over 16,000 local CHIKV infection cases with laboratory confirmation were recorded by Guangdong province in China by September 27, 2025, making it the largest local outbreak of Chikungunya fever in Chinese history. 48 additional local cases had been reported in the province by November 15. CHIKV cases have been reported in 21 cities in Guangdong province, with the majority of them being in Foshan (10,040), Jiangmen (5223), Guangzhou (590), Shenzhen (140), Zhanjiang (112), Zhuhai (60), and Zhongshan (54). Young adults between the ages of 18 and 45 made up the largest percentage of all reported cases (6).

II. VIROLOGY OF CHIKV

The spherical CHIKV particles have a diameter of about 60 to 70 nm. They have a nucleocapsid core made of single-stranded positive-sense RNA and capsid proteins with a single serotype, as well as a lipid envelope (7). There are two open reading frames (ORFs), ORF1 and ORF2, in the coding section of the roughly 11.8 kb viral genome. ORF1 is located in the 5′ end of the genome and constitutes two-thirds of the entire genome sequence and sequentially codes for four non-structural proteins (nsPs), namely nsP1 to nsP4. Five structural proteins such as nucleocapsid protein (C), envelope glycoproteins E1, E2, E3, and 6K protein are coded by ORF2 located in the 3′ end of the genome. (8,9). (Figure.1)

CHIKVnsPs are important molecules that control pathogenic pathways and mediate connections between viruses and host cells. Every protein has extremely specialized roles (10). Both N7-guanine methyltransferase (MTase) and guanylate transferase (GTase) activities, which are essential for preserving the integrity of viral RNA, are carried out by the nsP1 and catalyze the creation of the 5′ cap structure of nascent viral RNA (11). Additionally, nsP1 can bind to cholesterol microdomains in the host cell membrane, which is mediated by the palmitoylation of the protein, creating important sites for the formation of viral replication complexes. (12). The greatest nsP that the alphavirus genome encodes is nsP2. It has a cysteine protease domain at the C-terminus and an RNA-specific helicase domain at the N-terminus. This is an important step in the viral life cycle, and it degrades the viral polyprotein precursor into functional viral replicase components (nsP1, nsP2, nsP3, and nsP4) (13). The domain structure of the nsP3 protein is modular. The N-terminus, with its phosphatase and ADP-ribose hydrolase activity, helps the virus replicate by controlling the metabolism of nucleic acids. (14). In order to facilitate viral replication, this region contains a hypervariable domain (HVD) at its C-terminal end, which binds to different signaling molecules in the host cell, interacting with the host cell and controlling physiological processes in the host cell (15). Additionally, it has the alphavirus-unique domain (AUD), which is essential for transcription and viral genome replication. The primary catalytic component for viral RNA replication is nsP4. Viral RNA synthesis is effectively catalyzed by its RNA-dependent RNA polymerase (RdRp) domain. It plays a crucial regulatory role in viral replication and is an essential enzyme for subgenomic RNA transcription and viral genome replication (16, 17). Different roles are played by CHIKV structural proteins during viral assembly and infection. RNA encapsulation and nucleocapsid production are ensured by the exact contact between the viral genome and the C protein, which is made possible by the N-terminal RNA-binding domain of the C protein (18). A protease domain found in the C-terminal interacts with the E2 protein to facilitate viral release. The E1 protein facilitates the fusion of the viral envelope and the surrounding host cell membrane. The E2 protein promotes particular associations among the viruses and the host's cell receptors, which aids in viral integration, identification, and adherence, and facilitates the endocytosis of viral RNA into the host cell. The E3 protein stabilizes the E1/E2 trimer shape and encourages the proper folding of the E2 protein precursor. The 6K protein and its translational frame shifting end product, transferase (TF), promote the fusion of vesicles inside the endoplasmic reticulum, which serves to create ion channels and aid in viral dispersion (19,20).

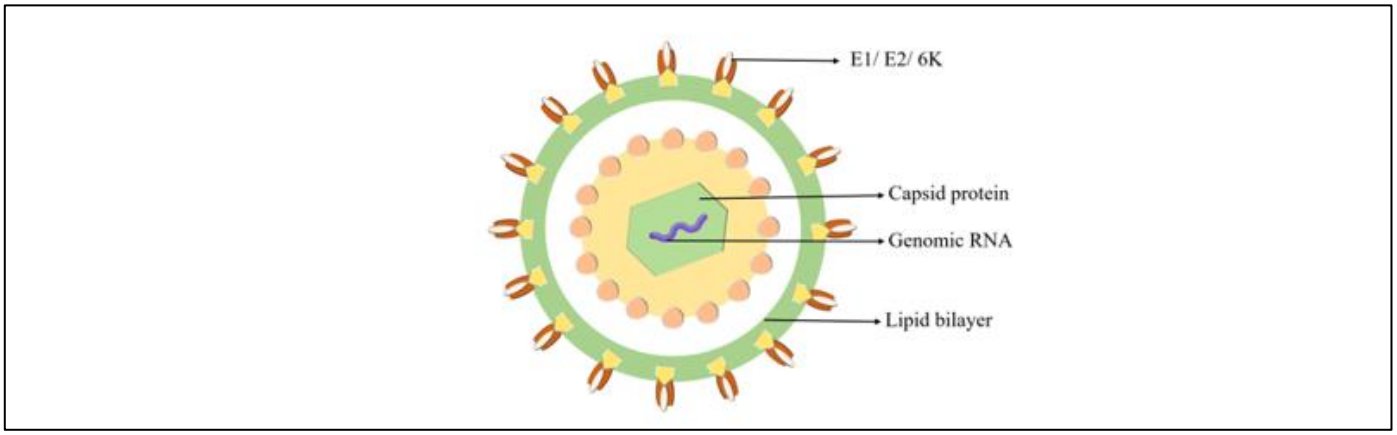

Fig 1 Structure of Chikungunya Virus

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26mar1925

III. EPIDEMIOLOGY AND TRANSMISSION

CHIKV refers to the genus Alphavirus and family Togaviridae. It is an encapsulated positively-sense RNA that is single- Stranded virus (21). The majority of alphaviruses can be roughly categorized into two groups based on the clinical symptoms they cause: encephalitic and arthritogenic (22). Acute and chronic arthralgia are mostly caused by the arthritogenic alphaviruses CHIKV, Ross River virus (RRV), Barmah Forest virus (BFV), Sindbis virus (SINV), Mayaro virus (MAYV), and O'nyong-nyong virus (ONNV) (23). The encephalitic alphaviruses Eastern equine encephalitis virus (EEEV), Venezuelan equine encephalitis virus (VEEV), and Western equine encephalitis virus (WEEV) can cause meningitis and encephalitis, among other illnesses of the central nervous system (24). Arthritogenic alphaviruses circulate in two epidemiologically separate cycles and are mostly spread by Aedes mosquitoes (25).

The primary reservoirs for CHIKV in a rustic enzootic (forest/savannah) transmission cycle are believed to be Aedes (Aedes africanus and Aedes furcifer) and vertebrate augmenting hosts, such as other primates that are not humans (26). According to a meta-analysis, the prevalence of in nonhuman primates, CHIKV reached as high as 35% in Africa, 7% in the Americas, and 6% in Asia (27). Additionally, CHIKV has been isolated from bats, insects, palm squirrels, and birds. Furthermore, CHIKV-specific antibodies have been found in mouse, birds, elephants, and reptiles, implying that these creatures might engage in the natural cycle of CHIKV transmission and serve as eventual hosts for reservoirs (28). Nevertheless, additional wild species, including birds, bats, and rodents, serving as There are few and irregular maintenance hosts (29). The rural cycle is limited to rural areas, with humans acting as accidental hosts through spillover from sylvatic or bridge vectors. The urban cycle is based on the maintenance of an anthropophilic cycle between humans and mosquitoes, mediated by Aedes aegypti and Aedes albopictus. These mosquitoes also transmit DENV, ZIKV, and YFV (30). Moreover, the rising issue for the range and appropriateness of vectors are increasing over longer times of the year due to climate change and human-caused causes such land use changes, urbanization, forest loss, and migration of humans, hence increasing the risk of spillover of the virus from the enzootic transmission cycle and urban amplification (31). A recent systematic review of Aedes-borne Arbo Viral Infections in Europe (2000-2023) has indicated that climate change and international travel are major factors in the rising risk of autochthonous transmission of Aedes-borne Arbo Viral Infections in the region by enhancing the expansion of the range of vectors, the replication of the virus in the vectors, and the re-infestation of the region with the virus(32). This has led to the rising interest in the creation of cutting-edge vector control techniques like holistic vector governance and endosymbiont control with Wolbachia (33-34).

After consuming an infected blood meal, CHIKV replication occurs in the epithelial cells of the midgut of the Aedes mosquito(35). Viral particles in the saliva are detected by 2 days post-infection (dpi), and the virus is transmissible from this period onwards. It is maximally transmissible by 6 dpi (36). CHIKV can also infect the ovaries of the mosquito and is detected in the eggs by 6 dpi(37). Vertical transmission of the virus in the Aedes mosquito has been established. In this mode of transmission, the virus is retained in the F5 and F6 generations of the mosquito(38). This mode of transmission is considered significant in the persistence of the virus under adverse environmental conditions. Desiccation-resistant eggs of the mosquito can remain viable for long periods and enable the retention of CHIKV and the maintenance of infectivity in the dry season and winter when the density of the mosquito population is low (39). Mavale et al.'s finding that CHIKV-infected male Aedes mosquitoes transferred the virus to females during mating, and the infected females subsequently infected nursing rats, underscored the possibility of the epidemiologic significance of venereal propagation (40). According to phylogenetic investigations, CHIKV is divided into three main lineages: East/Central/South African (ECSA), which includes the Indian Ocean lineage (IOL), Asian, and West African (41). Selection in Aedes albopictus has caused successive adaptive modifications in the envelope glycoproteins within the IOL. Aedes albopictus infection is increased by roughly 50–100 times with the E1-A226V alteration, and by an additional four–six times with the E2-L210Q substitution (42, 43). While having little discernible impact on these adaptive changes greatly boost transmission in Aedes albopictus, either in laboratory simulations based on human infection or in Aedes aegypti proficiency (44). Thus, ongoing CHIKV envelope glycoprotein development may encourage adaptation to more widely dispersed vectors and enable additional geographic expansion (45). Increased infection, heightened clinical severity, or altered tissue and organ specificity are examples of elevated viral adaptation in humans, has not yet been associated with any particular amino acid substitution (46).

IV. PATHOGENESIS & CLINICAL MANIFESTATION

Since it has the potential of causing debilitating diseases, either acute or chronic, people worldwide are increasingly concerned about the Chikungunya virus (CHIKV), which is spread by mosquitoes of the Aedes aegypti and Aedes albopictus species. CHIKV enters the body of the host by the skin after a mosquito bite and first replicates in dermal fibroblasts, macrophages, and endothelial cells through specific cell surface receptors such as MXRA8, which allows the viruses to enter and multiply (47). CHIKV then enters the bloodstream and causes severe viremia, leading to the infection of the liver, spleen, muscles, joints, and lymphoid tissues, among other body organs (47, 48). The rapid induction of the innate immune response leads to the production of type I interferons and pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are essential for the control of viruses but are also responsible for tissue damage (48, 49). As RNA and antigens of the virus have been detected months following the onset of the disease, recent studies have indicated that the persistence of the virus in the macrophages and the synovial tissues is essential for the development of the disease (48,50). Moreover, the replication

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26mar1925

of the virus and its survival can be enhanced by altering various cellular mechanisms of the host, such as autophagy, which causes additional damage to the cells (47). Both the direct replication of the virus in the musculoskeletal tissues and the immune-mediated effects leading to synovitis, cartilaginous destruction, and bone destruction contribute to the manifestations of the disease (49,50). Additionally, rheumatoid-like chronic inflammatory arthritis is related to molecular mimicry and abnormal adaptive immunity (50).

From the clinical point of view, the infection with the chikungunya virus is described as having an incubation period of two to seven days, followed by the sudden onset of a high-grade fever and severe, bilateral, and symmetrical polyarthralgia, which is one of the hallmarks of the infection and is often incapacitating (51). Additional acute symptoms include myalgia, headache, fatigue, nausea, conjunctivitis, and a maculopapular rash, which occur a few days after the onset of fever (51, 52). In recent systematic reviews, it has been noted that 30-40% of infected persons enter the chronic phase of the infection, which is characterized by joint pains, stiffness, and swelling, which can last for months and even years, although the acute phase resolves within 1-2 weeks (52, 53). There is no doubt that chronic chikungunya infection is one of the major contributors to long-term morbidity, with the quality of life, functionality, and even the psychological state of the patient being severely impaired, as indicated by depression and sleep disorders.(53) Tenosynovitis, inflammatory arthritis, and exacerbation of pre-existing rheumatologic conditions represent examples of chronic manifestations in some cases (49, 53). Moreover, recent studies have pointed to the occurrence of unusual and severe manifestations of the disease, particularly in newborns, the elderly, and people with compromised immune systems (51). These manifestations include visual manifestations such as uveitis and retinitis, liver or renal failure, cardiovascular manifestations such as myocarditis, and neurological manifestations such as meningoencephalitis and Guillain-Barre syndrome (51,52). Lymphopenia, thrombocytopenia, and abnormal liver enzymes represent examples of abnormal laboratory findings that point to the involvement of various organs and the presence of systemic manifestations of the disease (51).

In conclusion, chikungunya is a complex immunopathological disease with both acute and chronic manifestations. This is attributed to the persistence of the virus in the host and the complex interactions of the host and the pathogen. Long-term clinical management of the disease is therefore required (48, 53).

V. DIAGNOSIS

The shortage of commercial immunochromatographic test (ICT) kits for chikungunya virus (CHIKV), which detect mainly antibodies (IgM/IgG) and only a couple of alternatives for antigen-detection, reduces the effectiveness with which point-of-care testing is performed (54). Among the available IgM-based quick ICT kits, the total pooled sensitivity has been found low at 42.3%, and falls to 26.2% in ≤7 days of sampled patients due to the delayed seroconversion of IgM as well as relative lower viremia status during early acute infection. While >80–86% acute-phase sensitivity (100% in several prototypes) has been achieved, few commercial (RT-) antigen detecting ICTs exist and exhibit genotypic variance regarding efficacy (lower against Asian genotype). ICTs alone cannot be used to reliably diagnose acute-phase infections, because IgM ELISA kits have high sensitivity (93.4%) (54,55). Antibody ICTs vary in specificity (96–97%); however, because they share clinical symptoms with dengue or Zika viruses, these tests can yield false positives when both pathogens co-circulate in endemic zones; furthermore, cross-reactivity is difficult to mitigate except through multiplex testing (the latter remains limited), while antigen ICTs provide 94–96% specificity across lineages but no extensive validation is available (56,57,58). Under conditions of fragmentation (over 43 antibody ICTs with Brazil, the USA and India as predominantly contributing countries; a total of 23 license applications were submitted to ANVISA/4360 or CIB/CNPS approval; no application for FDA or EMA approval), the majority of studies are limited to non-representative case control designs (mostly Phase I/II) lacking population-based phase IV impact investigations. Although there are promising in-house antigen prototypes, they have not yet been commercialized; practical deployment requires meeting REASSURED requirements (cheap, stable, and equipment-free) (54,56).

VI. CHIKUNGUNYA VACCINES

Many vaccines have been developed to prevent CHIKV infection in humans by 2025, and two of the most promising ones are nearly prepared for regulatory authorization (59,60). The first approved vaccine is VLA1553 (IXCHIQ), a live-attenuated CHIKV vaccine created by Valneva SE (59). The FDA authorized its use in November 2023 for people who were 18 years of old or above and at extremely susceptible of contracting CHIKV (61). Because a single intramuscular injection of IXCHIQ produces potent neutralizing antibody responses and recent post-marketing monitoring has revealed concerns regarding safety, , the FDA stopped the drug's use in August 2025 awaiting more safety assessment. involving hospital stays, uncommon deaths, and symptoms similar to chikungunya (59,62). A second sophisticated alternative, the virus-like particle (VLP) vaccine PXVX0317 (Vimkunya), demonstrated remarkable immunogenicity and safety in Phase III clinical trials, attaining seroconversion indices over 97% within 22 days of inoculation (59,63). It is now undergoing priority evaluation by the FDA and the European Medicines Agency (EMA), with approval expected in 2025. In order to produce neutralizing antibodies that stop viral entry and replication, both vaccines target the structural envelope proteins E1 and E2 (59). Long-term protection, effectiveness in endemic communities, as well as safety in certain groups, such as pregnant and immunocompromised individuals, are all being studied in ongoing Phase IV and real-world research. Despite the difficulties with IXCHIQ, the discovery of CHIKV vaccines represents a significant advancement in the management of a disease with a high global burden (64). The CDC now advises those between the age group of 18 and 64 who plan to travel to regions with active CHIKV transmission or recent outbreaks to think about

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26mar1925

being vaccinated, especially for durations exceeding two weeks that entail mosquito encounter. We suggest tailored immunization for these high-risk visitors and epidemic responders where the potential for exposure is large because modeling shows that vaccinations could prevent 70–90% of chronic post-CHIKV arthralgia patients despite 10–20% reactogenicity rates (65). Regular immunization is not advised for elderly people or intermittent, low-risk visitors (less than two weeks) until further safety information on rare neurologic side effects after authorization is acquired. In highly endemic areas where outbreaks are rapidly spreading, tailored mass vaccination campaigns among adults should be taken into consideration along with more stringent vector control measures. When developing vaccination decisions via collaborative medical assessment, individual risk factors, vaccine reaction potential profiles, and region transmission intensity should all be taken into account.

VII. CONCLUSION

Significant illness is caused by CHIKV, it is expanding geographically, and it is still transmitted by Aedes mosquitoes. Therefore, it represents a significant global health problem. The novel vaccines, especially the ones targeting the viral envelope proteins, hold promise to protect against CHIKV and reduce the associated disease burden. However, it must be understood that the problem of controlling the mosquitoes cannot be solved by vaccines alone. To effectively control the mosquitoes and prevent future outbreaks, especially with the emergence of global climate change that will lead to an expansion of habitats of the mosquitoes, it is important that public health officials use a combination of chemical, biological, and genetic approaches to control the mosquitoes rather than just one of them. In addition to this, it must also be understood that future progress against CHIKV will also depend upon a deeper understanding of the pathogenesis of CHIKV infection, host immune responses to CHIKV, and the evolution of CHIKV.

➢ *Declaration:*

- *Conflict of Interest:*
  No conflict of interest was declared by the authors.

- *Ethical approval:*
  Not required.

- *Financial Disclosure:*
  The authors declared that this study received no financial support.

- *Author's contributions*
  Each author has committed to take responsibility for every part of the work after reviewing the final version that will be published.

ACKNOWLEDGMENT

We acknowledge the efforts of healthcare workers and researchers around the world who are working tirelessly to address the chikungunya virus outbreak.

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