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Review Article

Chikungunya Virus Infection: Epidemiology, Pathogenesis, Clinical Manifestations, and Prevention Strategies

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ABSTRACT

Chikungunya is a re-emerging arboviral disease caused by the Chikungunya virus (CHIKV), a member of the genus Alphavirus in the family Gaviidae. Originally isolated in Tanzania in 1952, CHIKV has become a major global health threat due to its increasing geographic spread and significant impact on public health, particularly in economically weak countries. The virus is primarily transmitted to humans through the bites of infected Aedes aegypti and Aedes albopictus mosquitoes, both of which are highly adaptive vectors prevalent in urban and peri-urban environments. The disease manifests acutely with high fever, severe polyarthralgia, rash, headache, myalgia, and fatigue. While most infections are self-limiting, a substantial proportion of patients experience persistent joint pain that may last for months or even years, especially among the elderly and individuals with pre-existing health conditions. The etiology of Chikungunya involves a complex interplay between viral genetics, vector ecology, host immune response, and environmental determinants. CHIKV exists in three main genotypes—West African, East/Central/South African (ECSA), and Asian—each associated with distinct epidemiological patterns. The ECSA genotype, in particular, has exhibited mutations such as E1-A226V that enhance viral fitness and expand vector competence, notably in Aedes albopictus, facilitating outbreaks in temperate and tropical regions alike. These genetic adaptations, combined with rapid urbanization, poor vector control infrastructure, climate change, and increased global mobility, have led to the expansion of Chikungunya into non-endemic areas, including parts of Europe and the Americas. socioeconomic factors, including inadequate housing, limited access to healthcare, poor sanitation, and lack of public awareness, exacerbate the vulnerability of low-income populations to CHIKV infection. Additionally, comorbidities such as diabetes, cardiovascular disease, immunosuppression, and malnutrition increase the risk of severe and chronic outcomes.

Keywords: *Aedes mosquitoes; Arboviral disease; Polyarthralgia; Vector-borne illness.*

Introduction

Chikungunya virus (CHIKV) infection is an emerging and re-emerging mosquito-borne viral disease that has posed significant public health challenges across tropical and subtropical regions of the world. First identified during an outbreak in Tanzania in 1952, the term “chikungunya” is derived from the Makonde

language, meaning "that which bends up," reflecting the characteristic stooped posture of affected individuals due to severe joint pain. Over the past several decades, Chikungunya has evolved from a relatively localized infection to a globally significant arboviral disease, with frequent outbreaks reported in Africa, Asia, Europe, and the Americas. The increasing incidence and geographic spread of CHIKV infection have been attributed to a combination of factors, including globalization, climate change, rapid urbanization, and the widespread distribution of competent mosquito vectors such as *Aedes aegypti* and *Aedes albopictus* [1].

Chikungunya virus belongs to the genus *Alphavirus* within the family *Togaviridae*. It is an enveloped, single-stranded, positive-sense RNA virus with a genome approximately 11.8 kb in length. The virus is primarily transmitted to humans through the bite of infected female *Aedes* mosquitoes, which are also responsible for the transmission of other arboviral diseases such as dengue and Zika. The co-circulation of these viruses in endemic regions often complicates diagnosis and management, as they share overlapping clinical features. Despite similarities in transmission and early symptoms, Chikungunya is particularly distinguished by its debilitating and persistent arthralgia, which can significantly impact the quality of life of affected individuals [2].

The epidemiology of Chikungunya virus infection has undergone a dramatic transformation in recent decades. Historically confined to sporadic outbreaks in Africa and Asia, the virus re-emerged in the early 2000s with large-scale epidemics affecting millions of individuals. A major turning point occurred during the 2005–2006 outbreak in the Indian Ocean region, particularly on Réunion Island, where an estimated one-third of the population was infected. This outbreak was notable not only for its magnitude but also for the emergence of a viral mutation that enhanced the adaptability of CHIKV to *Aedes albopictus*, a mosquito species with a broader geographic distribution, including temperate regions. Consequently, the risk of Chikungunya transmission expanded beyond traditional tropical zones, leading to outbreaks in Europe, including Italy and France, and later in the Americas, where autochthonous transmission was first reported in 2013 [3].

The global burden of Chikungunya continues to rise, with millions of cases reported annually. In endemic regions, the virus exhibits cyclical patterns of transmission, often associated with seasonal variations in mosquito populations. Factors such as increased international travel and trade have facilitated the introduction of the virus into previously unaffected areas, while inadequate vector control measures have contributed to sustained transmission. In countries like India, Chikungunya has become a major public health concern, with recurrent outbreaks causing significant morbidity and economic burden. The widespread presence of *Aedes* mosquitoes, coupled with favorable climatic conditions, underscores the need for effective surveillance and preventive strategies [4].

The pathogenesis of Chikungunya virus infection involves complex interactions between the virus and the host immune system. Following inoculation through a mosquito bite, the virus initially replicates in skin fibroblasts and disseminates via the bloodstream to various tissues, including the joints, muscles, liver, and lymphoid organs. The acute phase of infection is characterized by high viremia and a robust innate immune response, including the production of type I interferons and pro-inflammatory cytokines. While this immune response plays a crucial role in controlling viral replication, it also contributes to the inflammatory processes responsible for the clinical manifestations of the disease.

One of the hallmark features of Chikungunya infection is the involvement of musculoskeletal tissues, particularly joints. The virus has been shown to infect synovial fibroblasts and macrophages, leading to persistent inflammation and tissue damage. In some patients, the immune response fails to completely eliminate the virus, resulting in chronic infection and prolonged symptoms that may last for months or even years. This chronic phase is often associated with immune-mediated mechanisms, including the persistence of viral antigens and the activation of autoreactive immune cells. The resulting chronic inflammatory arthritis can resemble rheumatoid arthritis, posing challenges in diagnosis and management [5].

Clinically, Chikungunya virus infection presents with a wide spectrum of manifestations, ranging from mild febrile illness to severe and debilitating disease. The incubation period typically ranges from 2 to 7 days, after which patients develop an abrupt onset of high-grade fever, severe polyarthralgia, headache, myalgia, and rash. The joint pain is usually bilateral and symmetrical, commonly affecting the wrists, ankles, fingers, and knees. Unlike other arboviral infections, the arthralgia associated with Chikungunya is often intense and incapacitating, significantly impairing daily activities. Additional symptoms may include conjunctivitis, nausea, vomiting, and fatigue [6].

Although the acute phase of the disease is usually self-limiting, lasting for 1 to 2 weeks, a substantial proportion of patients develop chronic symptoms,

particularly persistent joint pain. Studies have reported that up to 40–60% of individuals may experience chronic arthralgia, which can persist for months or years. The severity and duration of symptoms are influenced by factors such as age, pre-existing comorbidities, and the intensity of the initial immune response. Elderly individuals and those with underlying conditions are at a higher risk of severe disease and complications.

In addition to musculoskeletal manifestations, Chikungunya virus infection can occasionally lead to severe and atypical complications. These may include neurological disorders such as encephalitis, meningoencephalitis, and Guillain–Barré syndrome, as well as cardiovascular, hepatic, and renal involvement. Neonates, pregnant women, and immunocompromised individuals are particularly vulnerable to severe outcomes. Vertical transmission of the virus from mother to child has also been documented, especially during the perinatal period, leading to neonatal complications.

The diagnosis of Chikungunya virus infection is primarily based on clinical presentation and laboratory confirmation. During the acute phase, viral RNA can be detected using reverse transcription-polymerase chain reaction (RT-PCR), which is highly sensitive and specific. Serological tests, including enzyme-linked immunosorbent assay (ELISA), are used to detect CHIKV-specific IgM and IgG antibodies, particularly in the later stages of infection. However, cross-reactivity with other arboviruses can pose diagnostic challenges, necessitating the use of confirmatory tests in certain cases [7].

Currently, there is no specific antiviral treatment for Chikungunya virus infection, and management is largely supportive. Treatment focuses on relieving symptoms, particularly pain and inflammation, using analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). In cases of chronic arthritis, disease-modifying antirheumatic drugs (DMARDs) may be required. Given the absence of targeted therapy, prevention remains the cornerstone of controlling Chikungunya outbreaks.

Prevention strategies for Chikungunya virus infection are primarily centered on vector control and personal protective measures. Reducing mosquito breeding sites through environmental management, such as eliminating stagnant water, is a key component of vector control programs. The use of insecticides, larvicides, and biological control agents can also help reduce mosquito populations. Personal protection measures, including the use of mosquito repellents, wearing protective clothing, and using bed nets, are essential in minimizing exposure to mosquito bites.

In recent years, significant progress has been made in the development of vaccines against Chikungunya virus. Several vaccine candidates, including live-attenuated, inactivated, and virus-like particle vaccines, are currently under various stages of clinical development. Some candidates have shown promising results in terms of safety and immunogenicity, raising hopes for effective prevention in the near future. However, challenges related to large-scale production, distribution, and accessibility remain to be addressed before widespread implementation can be achieved.

The growing global impact of Chikungunya virus infection highlights the urgent need for comprehensive strategies to address this public health threat. Enhanced surveillance systems, improved diagnostic capabilities, and effective vector control measures are essential for early detection and containment of outbreaks. Additionally, increased awareness among healthcare professionals and the general public can facilitate timely diagnosis and management, reducing the burden of disease.

Epidemiology of Chikungunya

The Chikungunya Virus Phylogenetic analysis has shown four different genotypes of CHIKV based on geographical regions. The west African genotype (Senegal and Nigeria), The East/ Central/South African (ECSA) genotype, the Asian genotype and the Indian Ocean Lineage (IOL) genotype [4]. CHIKV is an enveloped, spherical, single-stranded positive-sense RNA alphavirus belonging to the family Togaviridae [5]. It has a genome size of ~12 kb and it consists of two open reading frames cleaved into four non-structural proteins (nsP1, nsP2, nsP3, and nsP4) and five structural proteins (C, E3, E2, 6 K, and E1). E1 and E2 are surface glycoproteins, 439 and 423 amino acid-long, respectively. E1 and E2 carry the major viral epitopes and participate in the attachment and the entry of the virus into target cells, where E2 is responsible for receptor binding, and E1–for membrane fusion. E3 consists of 64 amino acids that are required for E3-E2-6K-E1 or E3-E2-TF polyprotein translocation into the endoplasmic reticulum for virus spike formation [6].

Transmission by mosquito bites: CHIKV is transmitted to people through the bites of the mosquitoes Ae aegypti, Ae. albopictus and Ae. Polynesians the same mosquitoes which transmit the Dengue virus. [7]. These mosquitos breed in or near human habitations and prefer to feed on humans during the daytime in shady areas, and early in the evenings. Horizontal

transmission in Aedes spy can occur and contribute to the maintenance of CHIKV cycles. Vertical transmission is rare but has been observed under natural and experimental conditions. In Africa, CHIKV circulates primarily in an enzootic cycle, with occasional spillover infections of humans. Infection with more than one arbovirus: Co-infection with Dengue virus and CHIKV, and of CHIKV with Dengue virus, Zika virus, yellow fever virus and West Nile virus have been described [8].

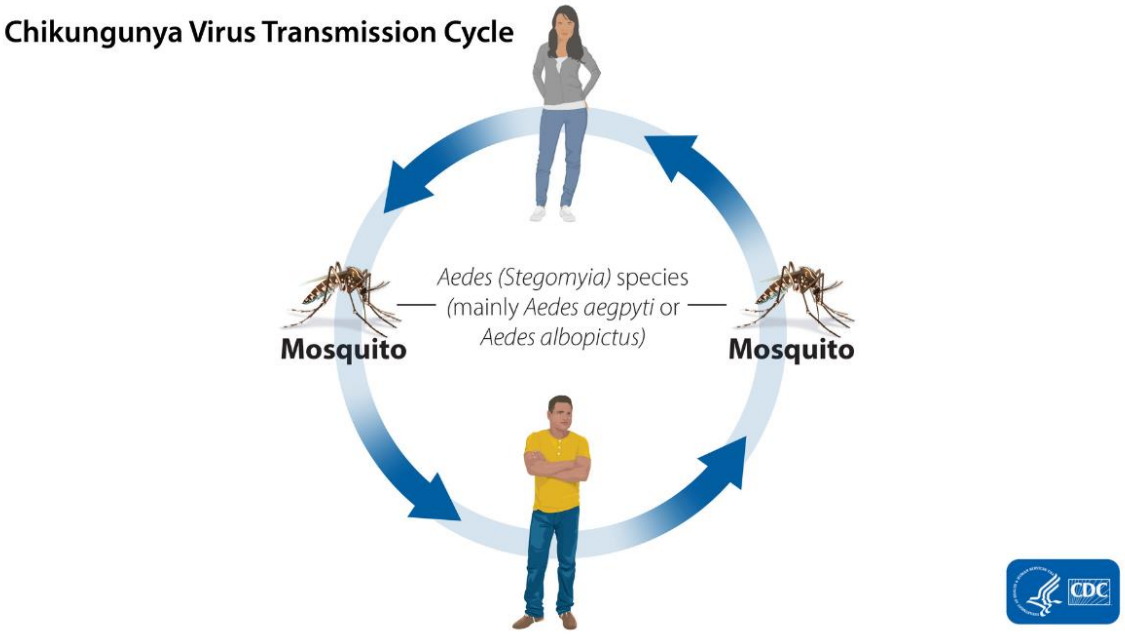

Figure 1: Chikungunya transmission cycle

Diagnosis of Chikungunya

Laboratory diagnosis relies upon the detection of the virus on early samples and/or specific anti-CHIKV IgM and IgG on blood samples. Numerous quantitative reverse transcription-polymerase chain reactions (RT-PCR) have been developed for CHIKV detection. Commercial kits are available, sometimes with excellent sensitivity and specificity [8]. CHIKV-RNA is detected in plasma samples within the first week after symptom onset, commonly with extremely high levels of viremia [9]. RT-PCR can also be used to screen various fluids and tissues, including corneas or other graft tissues. CHIKV can also be isolated from early samples on C6/36 or Vero cell lines. This method is only performed in Biosafety Level 3 laboratories, and is therefore mainly used for epidemiological purposes and research studies. Anti-CHIKV antibodies can be detected in patients shortly after symptom onset, usually after 5 days for IgM and only a few days later for IgG. Commercial enzyme immunoassays and immunofluorescence assays are available, but are of poor performance when expertized [10]. Interpretation of serological results must be cautious because of (1) possible false negativity due to CHIKVinduced mixed cryoglobulinemia [9], (2) cross-reactivity with viruses of the Semliki Forest serocomplex requiring seroneutralization, and (3) long-term persistence of antiCHIKV IgM months after disease onset. Synchronous testing of a sample from the acute stage and a sample collected at least 3 weeks later is sufficient to demonstrate a recent CHIKV infection in most cases. Any doubt should lead to a request for assistance from an expert laboratory. The good management of patients with acute CHIKV infection is essential for public health in susceptible areas with current Aedes sp. activity. In these areas, most health authorities recommend prompt suspicion of imported or autochthonous cases, adequate use of diagnostic tools, isolation of suspect patients, rapid contact with the local health department, and sometimes mandatory case declaration. The final aim is to avoid epidemics spreading around the new cases.

Chikungunya Infection, a Two-Stage Disease

Acute Stage

Most patients infected with CHIKV develop acute symptoms, usually 2 to 6 days after the infective mosquito bite. In Reunion Island in 2005–2006, the prevalence of asymptomatic infections was about 5% to 10% [4]. The first symptoms start abruptly and last for about a week before spontaneous improvement. The acute stage is defined as the first 10 days after disease onset [9]. The most frequent symptoms are high fever, arthralgias, back pain, and headache [8].

Fever is usually high, and is poorly responsive to antipyretics. Illness is associated with intense fatigue, anorexia, myalgias, nausea, and vomiting in adults, and even transient confusion in elderly patients. In Reunion Island in 2006, 47.3% of adults infected considered their fatigue as significant or very significant, 6% were depressed, and 35.5% were demoralized during the acute phase [10]. The acute bilateral and symmetrical rheumatism is typically extensive and progressive within a few days [6,9]. Peripheral joints are frequently very painful and swollen, especially interphalangeal joints, wrists, and ankles. The axis and proximal joints can also become inflamed with large joint effusions in the knees and elbows. The intensity of the symptoms prompts most patients to search for efficient treatment. Unfortunately, no antiviral drug has proved effective against human CHIKV infection [8]. Thus, the treatment of the acute stage is limited to painkillers and nonsteroidal anti-inflammatory drugs (NSAIDs). Their efficacy is not complete, and adverse effects are not rare as a result of excessive selfmedication. Acetaminophen is the elective drug. Aspirin should be avoided because of the risk of bleeding. Although sometimes dramatically effective, systemic corticosteroids are not recommended because of the strong rebound effect after stopping. A transient maculopapular rash, sometimes edematous and/or pruritic, can also be observed on the face and the trunk of half the patients [9]. Miscellaneous cutaneous and mucosal changes have been reported during the acute stage of the disease: photosensitivity, stomatitis, mouth ulcers, exfoliative dermatitis, vesicles, bullae, and purpura [31]. Gastrointestinal symptoms are common [11]. Initial biological changes are transient leukopenia and lymphopenia, mild thrombocytopenia, low rises in C-reactive protein, and hepatic cytolysis [9,11]. After a week of intense discomfort, pain, and incapacity, most CHIKV-infected patients experience a significant improvement of their condition. The fever drops, and the asthenia and joint pain become more acceptable. This period usually lasts for 1 to 2 weeks before a very common relapse. Beside the typical fever-arthralgias-rash association, some clinical features and complications were recently described. Atypical features of CHIKV infection leading to hospitalization and/or death were prospectively recruited in Reunion Island, reflecting their incidence, clinical aspects, and outcome. The most frequent complications involved the CNS: convulsions, meningoencephalitis, and Guillain-Barré syndrome; the direct role of CHIKV is evident in these early manifestations. Other severe acute complications have been reported since 2005: myocarditis, fulminant hepatitis in patients with chronic liver diseases [11], pancreatitis, acute endocrine disorders, extensive epidermolysis [11], kidney failures, respiratory failures, and decompensation of cardiovascular diseases. Although minor bleedings were observed [11], CHIKV infection is no longer considered as a viral hemorrhagic fever. CHIKV infection in children resembles that of adults, but can occasionally be complicated with neuropsychological changes, including lethal meningoencephalitis, with myocarditis or extensive epidermolysis [12].

The most surprising discovery was the mother-to-child transmission, with CHIKV neonatal infections [13]. The risk is not negligible when considering that, in Reunion Island in March 2006, about one pregnant woman in five had serological markers of recent infection [4]. In India, the risk of abortion and fetal death increased before the 22nd week of pregnancy. There was no increased risk for malformation [14]. Mother-to-child transmission were only observed in near-term deliveries for CHIKV-viremic mothers [12]. Under these conditions, half the neonates were infected. Neonatal CHIKV infection was symptomatic after 4 days in one in two cases, with fever, pain, prostration, poor feeding, diffuse pain, distal joint edema, and miscellaneous skin alterations (petechiae, exanthema). Viral meningoencephalitis was the most common complication, with pathological MRI findings and poor outcomes (death, persistent disabilities).

Chronic Stage

After the short-lived improvement following the acute stage, the life of the patient recently infected with CHIKV can be impaired by early exacerbation, inflammatory relapses, long-lasting rheumatism, and a significant loss in the quality of life [9]. This deterioration is more frequent in patients over 40 years of age and/or with underlying diseases, notably rheumatic or traumatic diseases [14]. High CHIKV viral loads in the acute stage are also associated with the persistence of symptoms [12]. Within the first 3 months, most patients experience a rebound of general discomfort, inflammation in the joints and tendons, and an increased handicap in daily life [9]. Disabilities in the extremities are from a severe polyarthritis involving most distal joints and multiple hypertrophic tenosynovitides that are sometimes responsible for carpal or tarsal tunnel syndromes. Difficulties in walking and handling objects can induce frequent and/or prolonged sick leave. Transient vascular disorders (eg, Raynaud syndrome) are present in one patient in six at that period [9], possibly in relation with the concomitant presence of mixed cryoglobulinemia [13]. Ocular changes may also develop a few weeks after disease onset: anterior uveitis, retinitis, episcleritis, and optic neuritis, sometimes leading to blindness. In Reunion Island,

80% to 90% of CHIKV-infected patients complained of persistent symptoms after the first 3 months. Whether this prevalence of nonrecovery is similar in other epidemic countries remains to be determined. However, CHIKV-induced rheumatism is the most frequent manifestation of the chronic stage. It consists of three clinical components, singly or in combination: (1) distal polyarthritis or monoarthritis mildly improved with NSAIDs, (2) frequent tenosynovitides in the hands, wrists, or ankles, highly sensitive to short-term systemic corticotherapy, and (3) exacerbation of pain in previously injured joints and bones requiring painkillers [9]. Most of the time, chronic peripheral polyarthritis is not associated with significant biological changes or the appearance of autoantibodies [9], but mild mixed cryoglobulinemia is frequent [12]. First radiographs of the joints involved usually do not reveal significant changes, even in disabled patients. Relapses are common during the chronic stage, often triggered after exposure to cold. They include mild fever, asthenia, increased inflammation in previously involved joints, and occasionally in new joints. Intensification of symptomatic treatment is often necessary and additional localized treatments and physiotherapy can be of benefit to some patients. The chronic stage can severely deteriorate the patient's quality of life for months. At 6 months, 97% of French CHIKV-infected active adults complained of joint symptoms. They considered their fatigue as totally disabling in 4.6% of cases, very significant or significant in 42.8%, and 37.8% described their mood as demoralized, weakened in 43.9%, and normal in only 16.2% of cases [10]. Another study showed that, on average, only 56% of 199 CHIKVseropositive patients considered themselves as cured 17 months after infection, being significantly longer in older patients. Arthralgia, fatigue, depression, and sleep disorders were twice as common in these patients as among seronegative controls. However, the SF-12 questionnaire evaluated the physical component of the quality of life to be significantly lower among seropositive patients, but not the mental component [11]. De Andrade et al. [14] evaluated the link between pain and quality of life in symptomatic patients, with a main impact on mood, work, and sleep. Over time, unexpected, delayed rheumatic complications have manifested years after acute CHIKV infection. A small percentage of patients with persistent arthralgia develop authentic inflammatory destructive rheumatisms. The most common feature is a rheumatoid arthritis (RA)- like polyarthritis following CHIKV infection. Criteria for this new entity are the presence of anti-CHIKV IgM and IgG antibodies, RA based on the 1987 American College of Rheumatology criteria, no other definite diagnosis for arthritis, and persistent arthritis symptoms from the onset of CHIKV infection to the RA diagnosis. Bouquillard and Combe reported a series of 21 cases of severe RA after CHIKV infection in Reunion Island. All patients were over 45 years old and most of them developed symmetric polyarthritis (18/21) within an average of 10 months. The biological characteristics of the disease were significant systemic inflammation, the presence of rheumatoid factors and HLA DRB1*04 or 01 alleles in more than half the patients, and variability of antiCCP antibodies. Erosions and/or joint space narrowing were present on initial radiographs of hands and feet in half the patients. During a 2-year follow-up, most patients received systemic corticotherapy and were treated with disease-modifying antirheumatic drugs (DMARDs), mostly methotrexate (19/21) and tumor necrosis factor blockers (6/21). Other forms of joint destruction have been described, such as the severe relapse of previously well-controlled psoriatic arthritis, entesopathies, or periostitis [15]. MRI scans seem sensitive in detecting early changes in joints and tendons in CHIKV-induced rheumatism. This could prompt intensification of therapy, including the use of DMARDs, if validated by further studies. To date, there is no evidence of viral reactivation in patients treated with such immunosuppressive drugs, but the benefits/risks balance must be cautiously and regularly evaluated for each patient. However, if indicated for a patient with post-CHIKV destructive arthritis, prescription of a first-line treatment with methotrexate should not be excluded just because of the viral origin of the rheumatism.

Pathogenesis of Chikungunya Virus Infection

The pathogenesis of Chikungunya virus (CHIKV) infection is a multifaceted process involving viral replication, host cell tropism, and a complex interplay between innate and adaptive immune responses. Understanding these mechanisms is essential for elucidating disease progression, chronicity, and potential therapeutic targets.

Viral Entry and Initial Replication

CHIKV is transmitted to humans through the bite of infected Aedes mosquitoes, primarily Aedes aegypti and Aedes albopictus. Upon inoculation into the dermis, the virus first infects susceptible cells at the site of the mosquito bite, including dermal fibroblasts, keratinocytes, and resident immune cells such as macrophages and dendritic cells. Viral entry is mediated by receptor-dependent endocytosis, followed by fusion of the viral envelope with the host cell membrane, allowing the release of viral RNA into the cytoplasm.

The positive-sense RNA genome is directly translated into nonstructural proteins that form the replication complex. This complex facilitates the synthesis of a negative-strand RNA intermediate, which serves as a template for the production of new viral genomes and subgenomic RNA encoding structural proteins. Newly synthesized virions are assembled and released through budding, leading to local viral amplification.

Systemic Dissemination and Tissue Tropism

Following initial replication, CHIKV enters the bloodstream, resulting in viremia that can persist for several days during the acute phase. The virus disseminates to various organs and tissues, exhibiting a marked tropism for musculoskeletal structures. Key target tissues include:

- Synovial membranes of joints
- Skeletal muscles
- Tendons and ligaments
- Liver and lymphoid tissues

Within these tissues, CHIKV infects fibroblasts, muscle satellite cells, endothelial cells, and macrophages. The infection of synovial fibroblasts and macrophages is particularly important in the development of joint inflammation and chronic arthralgia.

Innate Immune Response

The innate immune system plays a critical role in the early control of CHIKV infection. Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and RIG-I-like receptors, detect viral RNA and trigger signaling pathways that lead to the production of type I interferons (IFN-α and IFN-β). These interferons induce the expression of interferon-stimulated genes (ISGs), which inhibit viral replication and spread.

In addition to interferons, infected cells produce pro-inflammatory cytokines and chemokines, including:

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-6 (IL-6)
- Interleukin-1β (IL-1β)
- Monocyte chemoattractant protein-1 (MCP-1)

These mediators recruit immune cells such as monocytes, neutrophils, and natural killer (NK) cells to the site of infection. While this response is essential for viral clearance, excessive or dysregulated cytokine production contributes to tissue inflammation and clinical symptoms.

Adaptive Immune Response

The adaptive immune response is crucial for the resolution of CHIKV infection and the development of long-term immunity. Both humoral and cellular immune components are involved.

Humoral Immunity

B cells produce CHIKV-specific antibodies, including IgM and IgG. IgM antibodies appear within the first week of infection and are indicative of recent exposure, while IgG antibodies develop later and provide long-lasting protection. Neutralizing antibodies target viral envelope proteins, particularly E1 and E2, preventing viral entry into host cells.

Cellular Immunity

T cells, including CD4+ helper T cells and CD8+ cytotoxic T lymphocytes, play a role in controlling viral infection. CD8+ T cells eliminate infected cells, while CD4+ T cells support antibody production and coordinate immune responses. However, excessive T-cell activation may contribute to immunopathology, particularly in chronic disease.

Mechanisms of Joint Involvement and Chronic Disease

A defining feature of CHIKV infection is its propensity to cause persistent joint pain. Several mechanisms have been proposed to explain this phenomenon:

Viral Persistence: Evidence suggests that viral RNA or antigens may persist in joint tissues, particularly within macrophages, leading to prolonged immune activation.

Immune-Mediated Damage: Chronic inflammation is driven by sustained production of cytokines and chemokines, resulting in synovial inflammation and tissue damage.

Autoimmune Responses: Molecular mimicry and the activation of autoreactive immune cells may contribute to chronic arthritis resembling rheumatoid arthritis.

Histopathological studies have demonstrated synovial hyperplasia, infiltration of inflammatory cells, and cartilage damage in affected joints.

Host and Viral Factors Influencing Disease Severity

The severity and outcome of CHIKV infection are influenced by multiple factors:

- Host Factors: Age, genetic predisposition, and pre-existing conditions such as diabetes and cardiovascular disease
- Viral Factors: Genetic mutations that enhance viral replication and vector adaptability
- Immune Response: The balance between antiviral defense and inflammatory damage

Elderly individuals and those with comorbidities are more likely to develop severe disease and chronic complications.

Clinical Manifestations of Chikungunya Virus Infection

The clinical presentation of CHIKV infection ranges from asymptomatic or mild illness to severe and debilitating disease. The infection is typically divided into three phases: acute, subacute, and chronic.

Incubation Period

The incubation period ranges from 2 to 7 days following the mosquito bite. During this time, viral replication occurs without noticeable symptoms.

Acute Phase

The acute phase is characterized by the sudden onset of symptoms, including:

Fever

High-grade fever (often exceeding 39°C) is one of the earliest and most prominent symptoms. It is usually abrupt in onset and may last for several days.

Polyarthralgia

Severe joint pain is the hallmark of CHIKV infection. The pain is typically:

- Bilateral and symmetrical
- Involving small and large joints (wrists, ankles, knees, fingers)
- Debilitating, often leading to reduced mobility

Myalgia and Fatigue

Muscle pain and generalized weakness are common and contribute to the overall morbidity of the disease.

Rash

A maculopapular rash may appear 2–5 days after the onset of fever. It is usually distributed over the trunk and extremities and may be associated with itching.

Other Symptoms

- Headache
- Nausea and vomiting
- Conjunctivitis
- Photophobia
- Subacute Phase

The subacute phase occurs after the resolution of acute symptoms and may last for several weeks to months. During this phase:

Joint pain persists or recurs

Swelling and stiffness may be observed

Tenosynovitis and bursitis can develop

Patients may experience intermittent exacerbations of symptoms, often triggered by physical activity.

Chronic Phase

The chronic phase is defined by the persistence of symptoms beyond three months. It is a major contributor to the long-term burden of CHIKV infection.

Chronic Arthralgia and Arthritis

Persistent joint pain is reported in a significant proportion of patients. Clinical features include:

- Morning stiffness
- Joint swelling
- Reduced range of motion
- Functional impairment

In some cases, the condition resembles chronic inflammatory rheumatic diseases such as rheumatoid arthritis.

Neurological Manifestations

Although less common, neurological complications can occur, including:

- Encephalitis
- Meningoencephalitis
- Peripheral neuropathy
- Guillain–Barré syndrome

Cardiovascular and Other Complications

Rare complications include myocarditis, hepatitis, and renal dysfunction.

Special Populations

Neonates

Vertical transmission can occur, particularly during the perinatal period. Infected neonates may develop severe disease, including neurological complications.

Pregnant Women

While maternal infection is generally not associated with severe outcomes, perinatal transmission poses risks to the newborn.

Elderly and Immunocompromised Individuals

These groups are at higher risk of severe disease, complications, and prolonged recovery.

Prevention Strategies for Chikungunya Virus Infection

Given the absence of specific antiviral therapy, prevention remains the most effective approach to controlling CHIKV infection.

Vector Control

Vector control is the cornerstone of CHIKV prevention and involves reducing mosquito populations and interrupting transmission.

Environmental Management

- Elimination of stagnant water in containers, tires, and drains
- Proper waste disposal
- Community participation in sanitation efforts

Chemical Control

- Use of insecticides to target adult mosquitoes
- Application of larvicides to breeding sites

Biological Control

- Introduction of natural predators such as fish that feed on mosquito larvae
- Use of bacteria such as Wolbachia to reduce mosquito competence

Personal Protective Measures

Individuals can reduce their risk of infection through:

- Use of mosquito repellents containing DEET, picaridin, or IR3535
- Wearing long-sleeved clothing and pants
- Using insecticide-treated bed nets
- Installing window screens and using indoor insecticides

Surveillance and Public Health Measures

Effective surveillance systems are essential for early detection and response to outbreaks.

- Monitoring of mosquito populations
- Reporting and tracking of human cases
- Public awareness campaigns

Health authorities play a key role in coordinating vector control efforts and disseminating information.

Vaccine Development

The development of a safe and effective vaccine is a priority in CHIKV research. Various vaccine platforms are under investigation:

- Live-attenuated vaccines
- Inactivated vaccines
- Virus-like particle (VLP) vaccines
- mRNA-based vaccines

Several candidates have shown promising results in clinical trials, demonstrating strong immunogenicity and favorable safety profiles.

Challenges in Prevention

Despite advances in prevention strategies, several challenges remain:

- Resistance of mosquitoes to insecticides
- Urbanization and population growth
- Climate change affecting vector distribution
- Limited access to healthcare and resources in endemic regions

Addressing these challenges requires integrated and sustainable approaches involving multiple stakeholders.

Future Challenges and perspectives

Scientific Progress

Despite dramatic progress in our understanding of CHIKV infection, research must be continued into the pathogenesis of the long-lasting osteoarticular involvement. Studies should determine whether viral tissue sanctuaries exist in all chronic patients or not,

and if any drug could help the immune system to eliminate CHIKV and improve patients. In parallel with the search for efficient antiviral drugs, a new strategy is being developed with human anti-CHIKV immunoglobulins. Specific immunoprophylaxis or immunotherapy could provide a rapid antiviral action for persons at risk of severe acute CHIKV disease, notably neonates born from viremic mothers [16].

Management of CHIKV-Infected Patients

The most important challenge is to reduce chronic pain and handicap during the chronic stage of the disease. Neuropathic pains in persistently symptomatic patients require a specific pharmacological approach in regard to their association with a more aggressive clinical picture, and their impact on the quality of life. While awaiting future antiviral therapy for the chronic stage, an urgent need exists to study the efficacy and safety of corticotherapy and DMARDs, especially methotrexate, to establish a strategy for the early treatment of destructive arthritis.

Globalization and Prevention

The size and speed of international population movements and the progressive worldwide dissemination of the tiger mosquito increase the risk of new epidemic emergence of CHIKV. International collaboration in preparedness and response to CHIKV introduction in susceptible regions should limit this threat. Controls in epidemic countries can be improved by prompt vector control and the isolation of infective patients under bednets, efficient action that is still neglected. To date, there is no commercial vaccine against CHIKV. Because of the possible risk of viral persistence, live CHIKV vaccines have been abandoned in favor of new candidates such as consensus-based DNA vaccines.

Gaps in Current Knowledge

Chikungunya can have longstanding effects on health and quality of life. Alongside the recent approval of the world's first chikungunya vaccine by the US Food and Drug Administration in November 2023 and with new chikungunya vaccines in the pipeline, it is important to understand the perspectives of stakeholders before vaccine rollout. Our study aim is to identify key programmatic considerations and gaps in Evidence-to-Recommendation criteria for chikungunya vaccine introduction. We used purposive and snowball sampling to identify global, national, and subnational stakeholders from outbreak prone areas, including Latin America, Asia, and Africa. Semi-structured in-depth interviews were conducted and analysed using qualitative descriptive methods. We found that perspectives varied between tiers of stakeholders and geographies. Unknown disease burden, diagnostics, non-specific disease surveillance, undefined target populations for vaccination, and low disease prioritisation were critical challenges identified by stakeholders that need to be addressed to facilitate rolling out a chikungunya vaccine. Future investments should address these challenges to generate useful evidence for decision-making on new chikungunya vaccine introduction.

Conclusion

Several challenges are involved in the development of tools and strategies for prevention of zoonotic and re-emerging infections with epidemic potential, including CHIK. The early identification of human cases, developing rapid point of care diagnostics, effective treatments and vaccines. The establishment of more effective collaborative research networks involving different disciplines, such has medical entomologists, virologists, veterinarians, Infectious diseases clinicians, social science experts, anthropologists, community leaders and policy makers is required to enable more effective definition of host reservoirs, improving outbreak response and control activities. Given the unpredictability and paucity of CHIK and other zoonotic outbreaks, public health response and preparedness should be ready to perform research immediately during an outbreak, allowing for evaluation of existing and newer diagnostics, treatments and vaccines. These are being addressed through increasing research capacity during inter-epidemic periods with an integrated 'One Human-environmental-Animal Health' to assist in rapid investigations of zoonotic outbreaks and developing local capacity to improve national public health institutions. Most of the patients with Chikungunya virus remain undiagnosed or misdiagnosed with dengue. This is due to the lack of diagnostic facilities and people presenting similar symptoms caused by the dengue virus. A successful vaccine against Chikungunya virus can be produced in the future, but caution should be taken during its design and development. Since vectors are the most important determinants for spreading Chikungunya virus in the epidemic form, house-to-house measures need to be taken to eliminate vector breeding places by encouraging public awareness.

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Conflict of Interest

None declared.

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