Review Articles

Chikungunya virus infection: A comprehensive review of pathogenesis, diagnosis and management

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ABSTRACT

Chikungunya fever (CHIKF), caused by the chikungunya virus (CHIKV), is an acute mosquito-borne viral disease that poses a rising global public health threat. To date, no specific antiviral therapies are available, and precise diagnosis is pivotal for optimal clinical management. This review systematically summarizes the latest evidence on CHIKV pathogenesis, diagnostic strategies, and clinical management based on English literature published between 2004 and 2025. Virus-host interactions dominate disease progression, including viral entry mediated by E1/E2 envelope proteins binding to host Mxra8 receptors and suppressed type I interferon responses via nsP2-mediated inhibition of the JAK-STAT pathway. The E1-A226V mutation greatly enhances viral transmissibility in Aedes albopictus, fueling the global spread of CHIKV. Clinically, persistent chronic arthropathy serves as the major long-term complication in 25%–40% of infected patients. Current diagnostic approaches consist of real-time RT-PCR as the early gold-standard test and serological antibody detection, whereas serological cross-reactivity with other arboviruses and inconsistent detection results frequently cause clinical misdiagnosis, and the confirmatory plaque reduction neutralization test (PRNT) is impractical for routine use. Clinical care for CHIKF remains predominantly supportive, relying on symptomatic treatment and close patient monitoring. Two FDA-approved vaccines have been licensed via accelerated approval based on immunogenicity surrogates, with solid clinical protective efficacy yet to be validated. This review highlights that in-depth elucidation of CHIKV pathogenic mechanisms, refinement of diagnostic accuracy, and development of targeted therapeutics are essential to improve the overall management of chikungunya fever.

1. Introduction

Chikungunya virus (CHIKV) is a positive-sense single-stranded RNA virus belonging to the genus Alphavirus in the family Togaviridae. The genus comprises more than 30 members, many of which are pathogenic to humans. These viruses mainly prevail in tropical and subtropical regions, exposing approximately 4 billion people worldwide to potential infection, making chikungunya fever a major global public health concern [1].

As the causative agent of chikungunya fever, CHIKV induces an acute febrile illness characterized by acute fever, severe polyarthralgia and rash. The virus is primarily transmitted via bites of female mosquitoes, predominantly Aedes albopictus, and Aedes aegypti also serves as a competent vector. In recent years, the emergence of the E1 envelope protein A226V mutation has greatly strengthened the adaptability of CHIKV to Aedes albopictus, resulting in its rapid global dissemination [2].

CHIKV is divided into three lineages: the West African lineage, the East/Central/South African (ECSA) lineage, and the Asian lineage. During the large-scale outbreak on Réunion Island from 2005 to 2006, the ECSA

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lineage acquired a mutation at position 226 of the E1 protein, where alanine (A) was substituted by valine (V) (E1-A226V). This mutation substantially improved the transmission capacity of the virus via Aedes albopictus, acting as a key molecular driver for the worldwide spread of CHIKV [2]. Subsequently, the mutant strain rapidly spread to Asia, Europe and the Americas. In 2013, the Asian lineage was introduced into the Caribbean, triggering a massive epidemic across the Americas [1].

Clinically, chikungunya fever is categorized into three phases: the acute phase (1–2 weeks after onset), the post-acute phase (3 weeks to 3 months after onset), and the chronic phase (symptoms lasting more than 3 months). The acute phase is manifested as high fever (39–40 °C), severe symmetric polyarthralgia (mainly involving small joints such as wrists, ankles and fingers), rash and headache. Most patients experience a self-limiting course with symptom relief within 1–2 weeks. Nevertheless, around 30%–40% of patients develop post-acute arthralgia, and 20%–30% progress to chronic arthritis that may persist for months or even years [3]. Severe cases may present with neurological complications (meningoencephalitis, Guillain-Barré syndrome), cardiovascular complications (myocarditis) and vertical transmission to neonates.

Neonates, the elderly (aged ⩾ 65 years), women in late pregnancy and patients with chronic underlying diseases are at high risk of developing severe illness. The overall case fatality rate in the acute phase is low (< 0.1%), while the mortality rate of patients with neurological involvement reaches 13%–31%, and 18%–43% of survivors suffer from persistent neurological sequelae.

At present, no specific antiviral drugs have been approved for clinical use, and clinical management remains centered on supportive care. Although two vaccines (IXCHIQ and VIMKUNYA) have been licensed by the U.S. FDA via accelerated approval based on immunogenicity surrogates, solid data on their clinical protective efficacy are still lacking, and vaccines are not yet available in China and most other countries.

Epidemiological estimates show that since the outbreak in Kenya in 2004, CHIKV has spread to more than 110 countries and regions worldwide. A large-scale resurgence of CHIKF occurred on Réunion Island from 2024 to 2025, with a sharp increase in cumulative confirmed cases as of April 2025 (specific data pending official confirmation by Santé publique France and the World Health Organization [WHO]). Local transmission cases have also been reported in southern China, drawing close attention from public health authorities.

It is widely acknowledged that the pathogenesis of chikungunya fever is multifactorial, involving complex interactions among viral, host, environmental and vector-related factors. To address existing knowledge gaps, this comprehensive review synthesizes current evidence on the pathogenesis, diagnosis and management of CHIKV infection, aiming to provide references for clinical practice and future research.

2. Methods

2.1. Literature Search Strategy

This is a comprehensive review rather than a systematic review or meta-analysis. Literature retrieval was conducted on October 15, 2025, across three major electronic databases: PubMed, Web of Science and Google Scholar, to collect English articles published between January 2004 and December 2025. To reduce publication bias and improve comprehensiveness, additional grey literature including official reports and clinical practice guidelines issued by authoritative public health institutions such as the WHO, the U.S. Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) was manually retrieved.

A structured Boolean logic search strategy was adopted. The core disease terms were: "chikungunya virus" OR "chikungunya fever" OR "chikungunya infection" OR "CHIKV" OR "CHIKF".

These core terms were combined with keyword clusters covering three major research areas (pathogenesis, diagnosis and clinical management) using the AND operator. Terms within each cluster were connected via the OR operator.

Terms related to pathogenesis: "pathogenesis" OR "immune response" OR "cytokines" OR "envelope protein" OR "E1 protein" OR "E2 protein" OR "nsP1" OR "nsP2" OR "nsP3" OR "nsP4" OR "genome variation" OR "mutations" OR "A226V" OR "type I interferon" OR "interferon-alpha" OR "interferon-beta" OR "antibody-dependent enhancement" OR "ADE" OR "T cells" OR "macrophage" OR "dendritic cells" OR "Mxra8" OR "joint pathology" OR "chronic arthropathy".

Terms related to diagnosis: "diagnosis" OR "diagnostic test" OR "RT-PCR" OR "real-time PCR" OR "nucleic acid test" OR "antibody testing" OR "IgM" OR "IgG" OR "rapid diagnostic test" OR "RDT" OR "ELISA" OR "enzyme-linked immunosorbent assay" OR "viral load" OR "NS1 antigen" OR "point-of-care" OR "cross-reactivity".

Terms related to clinical management: "management" OR "clinical treatment" OR "supportive care" OR "fluid therapy" OR "hospitalization" OR "severe chikungunya" OR "case fatality" OR "clinical outcome" OR "treatment outcome" OR "vaccine" OR "vector control".

Phrases were enclosed in quotation marks for exact matching, and Medical Subject Headings (MeSH) terms were incorporated in PubMed searches.

2.2. Inclusion and Exclusion Criteria

2.2.1 Inclusion criteria:

(1) Studies reporting clinical data on human CHIKV infection;

(2) In vivo or in vitro experimental studies exploring the pathogenesis, diagnosis or treatment of CHIKV;

(3) Articles providing clinical guidance, recommendations or outcome data on the management of chikungunya fever cases;

(4) Peer-reviewed book chapters from authoritative academic platforms (e.g., NCBI Bookshelf) presenting relevant clinical definitions, diagnostic criteria and background information.

2.2.2 Exclusion criteria:

(1) Case reports or single-case descriptions;

(2) Editorials, letters and commentaries without original data;

(3) Non-peer-reviewed publications (except selected official grey literature);

(4) Conference abstracts and dissertations.

2.2.3 Language and source notes:

This review mainly included English literature. Authoritative Chinese documents such as diagnosis and treatment protocols issued by the National Health Commission of the People's Republic of China and prevention and control guidelines from the Chinese Center for Disease Control and Prevention were manually retrieved to cover clinical practices in China and other endemic regions, instead of being included in the systematic database search. Literature in French, Spanish and Portuguese was not systematically searched, which may lead to omission of key studies from Africa and South America.

2.3. Literature Screening and Data Extraction

All retrieved records were imported into EndNote X9 for reference management and deduplication. Two reviewers independently screened titles and abstracts, and discrepancies were resolved through discussion. Full texts of potentially relevant studies were obtained and assessed against the inclusion and exclusion criteria.

Thousands of articles were initially retrieved, and approximately 310 eligible publications (including original studies, reviews, guidelines and official reports) were finally included after screening.

3. Results

3.1. Pathogenesis of Chikungunya Virus

CHIKV is a positive-sense single-stranded RNA virus with a full-length genome of about 11.8 kb, encoding two open reading frames (ORFs). The 5'-terminal ORF encodes four non-structural proteins (nsP1–nsP4) responsible for viral replication, while the 3'-terminal ORF encodes structural proteins (C-E3-E2-6K-E1) that compose viral particles. Despite genetic variations among different lineages, the clinical manifestations and disease outcomes caused by infections with distinct lineages are similar.

CHIKF is primarily transmitted by mosquitoes. When an infected mosquito bites a human, CHIKV enters the bloodstream, invades keratinocytes and epidermal dendritic cells (DCs) across the epidermis and dermis. After penetrating the skin, the virus spreads to regional lymph nodes and infects monocytes and macrophages, triggering systemic viremia. As the infection progresses, the virus disseminates via the lymphatic system and undergoes massive replication. During the viremic phase, various monocytic cells including peripheral blood monocytes, myeloid DCs, and macrophages in the spleen and liver are infected. Extensive viral replication in these immune cells facilitates systemic infection and efficient viral circulation in the host [4][5].

Primary CHIKV infection induces long-lasting lineage-specific protective immunity. However, cross-protection against heterologous lineages is transient and incomplete. Subsequent infection with a different viral lineage, namely secondary infection, may result in more severe disease due to immunopathological mechanisms, though antibody-dependent enhancement (ADE) of CHIKV is not as prominent as that of dengue virus. In addition, immune cross-reactivity between CHIKV and other flaviviruses such as dengue virus and Zika virus has raised concerns, which may cause immune interference and pose diagnostic challenges in co-endemic areas.

The progression and severity of CHIKF are shaped by the complex interplay between viral and host factors. Key contributing factors include envelope protein mutations (E1-A226V), the protease activity of nsP2, type I interferon responses, cross-reactive memory T cells and pro-inflammatory cytokine storms. Severe clinical manifestations in critically ill patients mainly stem from excessive immune responses and increased vascular permeability triggered by the synergistic effect of these factors.

3.1.1 Viral Factors

Envelope proteins E1/E2: The CHIKV envelope consists of two glycoproteins, E1 and E2, which exist as heterodimers on the viral surface. The E2 protein mediates binding to host cell receptors, while E1 is responsible for membrane fusion. Composed of about 439 amino acids, E1 plays a vital role in viral assembly, adhesion and internalization into host cells via the endocytic pathway [4].

Given its essential functions in viral attachment and host cell penetration, the E1 protein has become a major focus of vaccine research. Neutralizing antibodies targeting E1/E2 can block viral entry into host cells, serving as the first line of defense against CHIKV infection.

The interaction between CHIKV and host cells is initiated by the binding of E2 to cellular receptors. Multiple receptors have been identified to interact with CHIKV E2, including matrix remodeling-associated protein 8 (Mxra8, the primary receptor), DC-SIGN, T cell immunoglobulin and mucin domain-containing protein 1 (TIM-1) and heat shock protein 70 (HSP70), which trigger receptor-mediated endocytosis [4][5]. Moreover, Fc receptors and C1q receptors may also facilitate viral entry via antibody-mediated pathways.

The E2 protein contains multiple domains carrying neutralizing epitopes, among which domain B is critical for host receptor binding and viral entry. Beyond its role in viral attachment, the E2 domain B is closely associated with the pathogenesis of chikungunya fever. During the peak of viremia, high concentrations of soluble E2 domain B can induce endothelial cell death mainly through pyroptosis, an inflammatory programmed cell death regulated by NLRP3 inflammasome activation [4].

Non-structural protein 1 (nsP1): As a multifunctional protein indispensable for viral replication, nsP1 is a component of the viral RNA replicase and possesses RNA capping enzyme activity, which protects viral RNA from recognition by host immune systems [5].

NsP1 acts as a scaffold protein for the viral replication complex and induces the formation of intracellular vesicles that accommodate the viral replication machinery. It interacts with other viral proteins (nsP2, nsP3 and nsP4) and participates in viral RNA replication and virion assembly.

The capping activity of nsP1 is crucial for the translation efficiency of viral mRNA. By adding a 7-methylguanosine cap to the 5' end of viral RNA, nsP1 prevents viral RNA from degradation by host exonucleases and promotes the synthesis of viral proteins. Inhibiting the capping enzyme activity of nsP1 has become an important direction for the development of antiviral drugs.

NsP2: Protease and helicase: NsP2 is the largest non-structural protein of CHIKV, possessing multiple enzymatic activities including protease, helicase and nucleoside triphosphatase (NTPase). The protease activity of nsP2 cleaves viral polyproteins at specific sites to generate mature non-structural proteins, a process essential for the proper assembly and function of the viral replication complex [6].

The helicase activity of nsP2 mediates the unwinding of viral RNA during replication, and its NTPase activity provides energy for helicase function. Additionally, nsP2 modulates host cellular metabolism and immune responses, particularly by antagonizing type I interferon signaling pathways. A study by Fros et al. (2010) demonstrated that CHIKV nsP2 blocks the JAK-STAT signaling pathway by inhibiting the phosphorylation of STAT1 and STAT2, thereby counteracting the antiviral effects induced by type I and type II interferons [6]. Göertz et al. (2018) further found that the methyltransferase-like domain of nsP2 also contributes to interferon response inhibition [7]. Bae et al. (2019) reported that E1 and E2 proteins are also involved in antagonizing interferon-β signaling [8]. Due to its core role in viral replication and unique enzymatic activities, nsP2 has emerged as a key target for antiviral drug development. Multiple nsP2 protease inhibitors have exhibited antiviral activity in in vitro experiments and animal models.

NsP3 and nsP4: NsP3 is an important component of the viral replication complex. Its C-terminal hypervariable domain (HVD) interacts with various host proteins. NsP3 regulates host antiviral responses, including the suppression of type I interferon production. NsP4 is an RNA-dependent

RNA polymerase (RdRp) responsible for viral RNA synthesis and serves as the core enzyme for viral replication [5].

Genomic variation and vector adaptability: The E1-A226V mutation occurring in the ECSA lineage during the 2005–2006 Réunion Island epidemic significantly enhanced the transmission efficiency of CHIKV via Aedes albopictus, which is the key molecular basis for the global spread of the virus [2].

By altering the charge distribution of the E1 protein, the E1-A226V mutation strengthens the binding capacity of the virus to midgut epithelial cells of Aedes albopictus and thus increases infection efficiency. This mutation has no impact on viral transmission via Aedes aegypti, but turns Aedes albopictus into a highly efficient vector, greatly expanding the geographical distribution of CHIKV [2].

Apart from E1-A226V, other gene mutations (e.g., E2-L210Q, E1-K211E, E2-I211T) are also associated with viral vector adaptability and virulence. These mutations may affect disease severity by altering virus-host receptor interactions, viral replication efficiency or immune evasion ability.

Subgenomic RNA (sgRNA): In addition to genomic variations, the accumulation of virus-derived non-coding RNA, namely alphavirus subgenomic RNA (sgRNA), in infected cells is another critical factor affecting disease severity. Produced during CHIKV replication, sgRNA is formed when host exoribonucleases fail to completely degrade viral genomic RNA, generating small RNA fragments [5].

The accumulation of sgRNA plays a key role in inhibiting host antiviral immune responses, especially the type I interferon (IFN) signaling pathway. By regulating the stability of host mRNA, sgRNA facilitates viral immune evasion and increases the risk of severe chikungunya fever. Furthermore, sgRNA enhances viral persistence by suppressing cellular apoptosis and disrupting host antiviral defenses, further promoting viral survival and disease progression.

3.1.2 Host Factors

Type I interferons: As the first line of host defense against pathogens, the innate immune system plays a pivotal role in controlling viral infection at the early stage. During CHIKV infection, viral components such as single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) replication intermediates are recognized by innate immune cells and trigger early antiviral responses. Acting as pathogen-associated molecular patterns (PAMPs), these viral components are detected by pattern recognition receptors (PRRs), which are essential for host innate immune defense [4][5].

Key PRRs involved in CHIKV recognition include cytoplasmic retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and endosomal Toll-like receptors (TLR3 and TLR7). Interferon regulatory factors 3 and 7 (IRF-3, IRF-7) are also critical for innate immunity against CHIKV, mainly by inducing type I interferon (IFN-I) responses and other innate immune mediators such as pro-inflammatory cytokines.

The production of IFN-I is vital for restricting CHIKV infection, especially in monocytes. These cytokines bind to IFN-α/β receptors (IFNARs) on the surface of infected and adjacent cells, activating the JAK-STAT signaling cascade. This activation induces the expression of interferon-stimulated genes (ISGs) and enhances host antiviral defenses [4].

Nevertheless, CHIKV has evolved multiple mechanisms to antagonize IFN signaling pathways. As confirmed by Fros et al. (2010), nsP2 inhibits the JAK-STAT pathway by suppressing STAT1 and STAT2 phosphorylation [6]. Göertz et al. (2018) verified the involvement of the methyltransferase-like domain of nsP2 in interferon response inhibition [7]. Bae et al. (2019) further demonstrated that E1 and E2 proteins also antagonize interferon-β signaling [8]. NsP3 and nsP4 also modulate host immune responses to facilitate viral replication and immune evasion.

Antibody-dependent enhancement (ADE): The existence of ADE in CHIKV infection remains controversial. Unlike dengue virus, ADE of CHIKV has not been fully validated. Most studies indicate that neutralizing antibodies generated after CHIKV infection provide long-term protective immunity, and cross-protection is mainly limited to homologous lineages [4].

Even so, several studies suggest that ADE may occur under specific conditions (e.g., when antibodies are at sub-neutralizing concentrations). It mainly involves Fcγ receptor-mediated viral entry into monocytes, macrophages and DCs, which bypasses neutralization and increases viral replication and disease severity. Natural killer (NK) cells exert counteractive effects against ADE via antibody-dependent cellular cytotoxicity (ADCC). Sera containing ADE-inducing antibodies can activate NK cells and thereby mitigate ADE-mediated viral spread.

T cells and chronic arthropathy: T cells participate in both antiviral defense and immunopathology during CHIKV infection. Disease severity is often correlated with cross-reactive memory T cell responses during secondary infection. In acute CHIKF, T cells show increased degranulation and cytokine production, while in patients with chronic arthropathy, T cells secrete more cytokines but present functional exhaustion [3][9].

NsP2 and nsP3 are the main targets of CD8 + T cell responses. During secondary infection with heterologous lineages, CD8 + T cells exhibit strong cross-reactivity but low affinity, leading to poor efficacy in eliminating new viral strains. This results in excessive production of cytokines and chemokines, which is closely linked to disease severity.

Acute CHIKV infection is characterized by an increase in CHIKV-specific T cells, which initially express the early activation marker CD69, followed by CD38, CD71 and HLA-DR. Despite robust effector phenotypes, a low proportion of these T cells produce IFN-γ due to the downregulation of T cell receptor (TCR) signaling molecules [9].

The progression from acute CHIKF to chronic arthropathy is associated with a shift from Th1 to Th2 cytokine profiles, leading to overproduction of IL-10 and IL-4. Chow et al. (2011) found that persistent arthralgia is strongly correlated with elevated levels of IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [10]. Increased levels of TNF, soluble TNF receptors (sTNFR1, sTNFR2), IFN-γ and chemokines (CXCL8, CXCL9, CXCL10, CXCL11, CCL5) have also been observed, which may trigger harmful cytokine storms.

Regulatory T cells (Tregs, CD4 + FoxP3 +) modulate immune responses and balance Th1 and Th2 immunity. In CHIKV infection, Tregs tend to promote Th2 responses and suppress Th1 immunity, potentially contributing to immunopathology. Patients with mild symptoms usually have a higher Treg/effector T cell ratio than those with severe illness.

CHIKV infection induces apoptosis in multiple cell types. In severe cases, apoptosis of hepatocytes and endothelial cells causes liver injury and hemorrhage, while apoptosis of monocytes and DCs impairs immune responses. Vascular plasma leakage, a hallmark of severe chikungunya fever, is associated with apoptosis of leukocytes and microvascular endothelial cells.

Immunological mechanisms of chronic arthropathy: Chronic arthropathy is the most prevalent long-term complication of CHIKF, and its pathogenesis involves multiple mechanisms: (1) persistent viral RNA in joint tissues triggers sustained immune activation; (2) autoimmune responses including the production of antinuclear antibodies and rheumatoid factors; (3) continuous elevation of pro-inflammatory cytokines

(IL-6, TNF-α, GM-CSF); (4) synoviocyte proliferation and pannus formation, with pathological changes similar to rheumatoid arthritis [3][10].

A meta-analysis conducted by Paixão et al. (2018), which included 18 studies with a total sample size of approximately 15,000 cases, divided the natural course of post-CHIKF joint symptoms into three stages: acute arthralgia (1–2 weeks after onset, occurring in nearly all symptomatic patients), post-acute arthralgia (3 weeks to 3 months after onset, incidence: 30%–40%), and chronic arthritis (lasting over 3 months, combined incidence: 25%–40%) [3]. Advanced age, female gender, severe arthralgia in the acute phase and pre-existing joint diseases are major risk factors for chronic arthropathy.

3.2. Diagnosis of Chikungunya Fever

The acute phase of CHIKF is defined as the first 7 days after symptom onset, and the recovery phase generally begins after day 7, which is consistent with the recovery period of most mild and moderate cases. CHIKV can be detected in blood or blood-derived specimens (serum, plasma) during the acute phase. Early and accurate diagnosis in this stage is critical for differentiating CHIKF from other febrile illnesses (especially dengue and Zika virus infections) and identifying severe cases.

Viral detection methods include virus isolation, molecular assays and viral antigen detection. In the recovery phase, detection of specific antibodies (IgG and IgM) becomes the main diagnostic approach.

3.2.1 Virus Isolation

Virus isolation is regarded as the gold standard for CHIKV identification and plays an important role in outbreak investigations. However, it is rarely used in routine clinical practice due to its complicated procedures and long turnaround time (usually 3–7 days). Specimens for virus isolation include serum, plasma, cerebrospinal fluid (CSF) and post-mortem tissues. Viral culture is performed by inoculating specimens into Vero, C6/36 and BHK-21 cell lines, followed by viral detection and identification via direct/indirect fluorescence assays and plaque assays [4].

Despite its limitations in clinical settings, virus isolation remains essential for public health surveillance and research, supporting the development of diagnostic tests, vaccines and related reagents.

3.2.2 Molecular Detection

Molecular assays such as reverse transcription polymerase chain reaction (RT-PCR) feature high sensitivity and specificity for detecting CHIKV RNA in the early stage of infection before antibody seroconversion. Nucleic acid amplification tests (NAATs) including RT-PCR deliver results within 2–4 hours, enabling viral genotyping and sequencing for epidemiological surveillance.

Specimens applicable for molecular detection include plasma, serum, nasopharyngeal swabs, dried blood spots, urine and saliva. The choice of specimen type significantly affects detection sensitivity. The kinetics of CHIKV RNA differ between primary and secondary infections. In primary infection, viral RNA can be detected in plasma by RT-PCR for an average of 7 days, whereas secondary infection presents with shorter viremia duration due to immune-mediated viral clearance.

NAATs usually target conserved regions of the viral genome such as the E1 gene, E2 gene, nsP1 gene and 5' untranslated region (5'UTR). Real-time fluorescent RT-PCR (RT-qPCR) is the gold standard for early diagnosis of chikungunya fever, with reported sensitivity ranging from 93% to 99% and specificity exceeding 98% [4][5]. It provides the highest diagnostic value within 0–7 days after onset and supports viral genotyping and multiplex detection of co-circulating arboviruses.

Nevertheless, RT-qPCR has several limitations. Its diagnostic sensitivity declines in secondary infections due to pre-existing immunity and shortened viremia, leading to missed diagnoses in hyper-endemic areas. In addition, the lack of standardized protocols (varying genomic targets, primer/probe designs and Ct thresholds across studies) hinders cross-regional comparison and meta-analysis. High costs and strict infrastructure requirements also restrict its application in resource-limited endemic areas, where antigen and serological tests remain the mainstream diagnostic tools.

Isothermal amplification techniques including loop-mediated isothermal amplification (LAMP), transcription-mediated amplification (TMA) and recombinase polymerase amplification (RPA) have attracted attention for point-of-care (POC) testing in resource-poor regions. LAMP allows direct amplification without RNA extraction and achieves sensitivity comparable to RT-PCR, and it can also distinguish viral lineages. The detection limit of RPA is 1–100 genome copies, while its overall sensitivity and specificity are lower than those of RT-PCR. In general, these isothermal methods are portable and time-efficient, making them increasingly suitable for field deployment.

Gene sequencing is a vital tool for studying the epidemiology and evolution of CHIKV. Viral genotyping is mainly performed via Sanger sequencing of the E1 gene. Next-generation sequencing (NGS) with short-read and long-read platforms combined with target enrichment strategies improves detection sensitivity. Hybridization enrichment can recover full-length CHIKV genomes from patient specimens even in cases of co-infection with other alphaviruses. Metagenomic sequencing panels enable simultaneous detection of multiple pathogens, enhancing outbreak surveillance and response capabilities.

3.2.3 Viral Antigen Detection

As a key non-structural protein involved in CHIKV replication, nsP1 is produced and released into the peripheral blood of infected individuals, serving as an important biomarker for early detection of alphavirus infections. However, unlike dengue virus NS1 antigen detection, CHIKV nsP1 antigen assays are not widely applied in clinical diagnosis.

Kashyap et al. (2010) established an indirect ELISA for antigen detection using the Indian CHIKV strain (EWHYD06, ECSA genotype). The assay had a sensitivity of 85%, with the highest positive rate (95%) within the first 5 days of the acute phase, followed by a gradual decline [11]. Another study developed a monoclonal antibody-based immunochromatographic rapid test that reacts with ECSA, Asian and West African lineages, with a sensitivity of 89.4% and a specificity of 94.4% [11].

Currently, available nsP1 detection methods include ELISA and rapid diagnostic tests (RDTs), which can identify acute infection. Still, the clinical utility of nsP1 assays is limited by insufficient commercial products and inadequate validation. Only a small number of experimental detection methods have been reported so far.

3.2.4 CHIKV-Specific Antibody Detection

Serological antibody detection is one of the most widely used diagnostic methods for CHIKF, especially for retrospective confirmation of infection. Serum and plasma are the most common specimens, while alternative samples such as dried blood spots, saliva and CSF have also been explored.

Despite widespread application, serological diagnosis of CHIKV is severely hampered by cross-reactivity, particularly with other alphaviruses (e.g., Semliki Forest virus, Sindbis virus) and flaviviruses (e.g., dengue virus, Zika virus). A preprint study (not peer-reviewed) by Seyyadali et al. (2025) analyzed 566 dengue IgM-positive specimens collected within 7 days after onset: 26 samples tested positive for CHIKV IgM, but multiplex RT-PCR confirmed only 2 true co-infections, indicating that most positive results were false positives caused by serological cross-reactivity [12]. The

Cohen's Kappa coefficient between CHIKV IgM ELISA and RT-PCR in this study was -0.36, suggesting poor consistency and a high risk of misdiagnosis when relying solely on IgM detection [12].

A study conducted in Myanmar found that IgG-based dengue RDTs showed 80% and 73.3% cross-reactivity with CHIKV-positive serum samples, while NS1 and IgM assays had no obvious cross-reactivity, indicating that IgG detection carries a higher cross-reaction risk than IgM and antigen tests. In primary CHIKV infection, IgM antibodies usually appear 3–4 days after symptom onset (and as early as day 2 in some patients), peak at approximately 2 weeks post-infection, and remain detectable for weeks to months. In secondary infection, IgM titers are generally lower and decline faster. Prior exposure to other alphaviruses or flaviviruses can further reduce IgM levels. In contrast, IgG antibodies emerge 5–8 days after onset and persist for life, indicating past infection or immune status. During secondary CHIKV infection, IgG levels rise rapidly within 1–2 days after symptom onset, often alongside IgM. The IgM/IgG ratio helps distinguish primary from secondary infection, with a higher ratio suggesting primary infection.

Seroconversion in paired specimens, defined as a $\geqslant$ 4-fold increase in CHIKV-specific antibody titers between acute and convalescent samples, provides definitive evidence of recent CHIKV infection and is regarded as the gold standard for diagnosis in clinical and epidemiological research.

IgM capture ELISA (MAC-ELISA) is used for qualitative detection of CHIKV E1/E2-specific IgM antibodies, which aids early diagnosis of infection. IgG capture ELISA (GAC-ELISA) is particularly useful in the convalescent phase, as it can detect IgG antibodies from 7–10 days after onset for more than 10 months. To address cross-reactivity in IgM and IgG assays, microsphere immunoassays (MIA) have been developed. This multiplex platform enables simultaneous screening and differentiation of IgM and IgG antibodies against various arboviruses.

The plaque reduction neutralization test (PRNT) is the gold standard for detecting CHIKV neutralizing antibodies and differentiating alphavirus infections. In this assay, patient serum is incubated with live virus before inoculation into susceptible cell lines, and the reduction in plaque formation reflects neutralizing antibody activity. PRNT50 and PRNT90 represent serum dilutions that reduce plaque counts by 50% and 90%, respectively. Although PRNT features high specificity and is valuable for confirming past infection, distinguishing primary/secondary infection and supporting vaccine and epidemiological studies, it requires sophisticated techniques and takes about one week to complete, making it unsuitable for routine clinical use.

3.2.5 Current Challenges and Future Perspectives

Diagnostic techniques for CHIKV infection have been greatly improved over the past decade, but multiple challenges remain. Conventional assays such as RT-PCR and ELISA require specialized laboratory facilities and trained personnel, limiting their accessibility in resource-limited areas. The complex pathogenesis and diverse clinical manifestations of CHIKF also hinder the development of a single universal diagnostic test. Additionally, serological cross-reactivity with other alphaviruses and flaviviruses complicates diagnosis in co-endemic regions. The preprint study by Seyyadali et al. (2025) emphasized that relying solely on CHIKV IgM ELISA may overestimate co-infection rates, interfering with clinical decision-making and public health resource allocation [12]. Since this study has not undergone peer review, its conclusions should be interpreted with caution pending formal publication.

Combining multiple diagnostic assays can improve overall detection sensitivity. Ongoing efforts are dedicated to developing multiplex POC tests that can distinguish CHIKF from other arboviral diseases and tropical febrile illnesses. Future advances in molecular diagnostics including isothermal amplification and CRISPR-based detection are expected to realize rapid on-site testing without complex equipment. These innovations aim to provide fast, accurate and affordable diagnostic tools for endemic areas, facilitating timely diagnosis and management of chikungunya fever and reducing its global disease burden.

3.3. Clinical Management

Chikungunya fever is generally a self-limiting disease; however, chronic arthropathy and severe cases may lead to significant disability and mortality. Early identification of warning signs for severe illness is critical, as patient outcomes depend heavily on timely intervention.

To date, no specific antiviral drugs have been approved for CHIKF treatment, and clinical management is dominated by supportive and symptomatic care. Basic interventions include symptomatic relief, analgesic administration and adequate rest. The lack of targeted antiviral therapies highlights the importance of preventive strategies.

Two CHIKV vaccines have been developed and approved by the U.S. FDA for specific populations. IXCHIQ (VLA1553, developed by Valneva), a live attenuated vaccine, obtained marketing authorization from the European Medicines Agency (EMA) in June 2024 and FDA approval in November 2024 for individuals aged 18 years and above (the indication was expanded to people aged 12 years and older in March 2025). Its approval was based on immunogenicity surrogate endpoints (μPRNT50 $\geqslant$ 150) [13][14][15]. VIMKUNYA (PXVX0317, developed by Bavarian Nordic), a recombinant vaccine, was licensed by the U.S. FDA in June 2025 for adults aged 18 years and above [15][16].

The EMA has required post-marketing efficacy studies (VLA1553-404) for IXCHIQ, which are expected to be completed in 2029 [14]. At present, large-scale real-world data on clinical protective efficacy are absent. A 2025 mathematical modeling study by the Robert Koch Institute assumed that the vaccine achieves 70% protection against infection and 95% protection against symptomatic disease, predicting that vaccinating 40% of the population aged over 12 years in Brazil could prevent up to 1.6 million cases within five years [17]. Nevertheless, these predictions are based on hypothetical efficacy values rather than real-world data, and the actual vaccine effectiveness needs long-term follow-up verification.

Vaccines against CHIKV are not yet available in China and most other countries. Multiple candidate vaccines including inactivated vaccines, virus-like particle vaccines, nucleic acid vaccines and recombinant protein vaccines are currently in different stages of research and development.

3.3.1 Clinical Manifestations and Symptomatic Management

Clinical management strategies are formulated according to disease severity, and patients are divided into three groups:

Group A (Mild chikungunya fever without warning signs): Patients present with mild symptoms and normal hydration status. Outpatient management with proper monitoring is feasible. Supportive care is the mainstay of treatment. Paracetamol is recommended to relieve fever, with a dosage of 10 mg/kg per dose for children and a maximum daily dose of 4 g for adults, administered at intervals of no less than 6 hours. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are contraindicated due to their anti-platelet effects and bleeding risks, especially when dengue fever cannot be ruled out.

Patients are advised to maintain adequate hydration with oral rehydration salts (ORS), fruit juice or electrolyte solutions. Patients and caregivers should be educated to recognize warning signs (persistent vomiting, severe

abdominal pain, mucosal bleeding, lethargy) for timely medical intervention when conditions deteriorate.

Group B (Moderate chikungunya fever with warning signs and/or risk factors): This group includes patients with warning signs of disease progression who require in-hospital close monitoring. Warning signs consist of persistent vomiting, abdominal pain, mucosal bleeding, hepatomegaly, lethargy, and rapid elevation of hematocrit accompanied by decreased platelet count. During hospitalization, vital signs, urine output and hematocrit are closely monitored to detect early signs of plasma leakage or impending shock.

Intravenous (IV) fluid therapy is initiated to prevent progression to severe disease. The initial infusion rate is 5–7 mL/kg/hr within 1–2 hours. If hematocrit continues to rise or clinical conditions worsen, the rate is adjusted to 3–5 mL/kg/hr for an additional 2–4 hours. After clinical improvement, the infusion rate is gradually reduced to 2–3 mL/kg/hr before discontinuation. Continuous assessment of fluid status and hematocrit is essential to avoid insufficient or excessive fluid resuscitation.

Group C (Severe chikungunya fever): Patients in this group require emergency medical care. Severe manifestations include profound shock (pulse pressure < 10 mmHg), massive plasma leakage, obvious hemorrhage and multiple organ dysfunction. Prompt fluid resuscitation is critical for profound shock, and colloidal solutions are preferred over crystalloids to restore cardiac output and correct elevated hematocrit.

If hypotensive shock occurs without a corresponding increase in hematocrit, internal hemorrhage should be suspected, and whole blood or packed red blood cell transfusion is indicated. Clinical monitoring during transfusion is required to evaluate treatment response and adjust management plans.

The above grouping and management strategies are adapted from WHO dengue fever management guidelines and the Diagnosis and Treatment Protocol for Chikungunya Fever (2025 Edition) issued by the National Health Commission of China [18]. These recommendations are based on expert opinions with low-quality evidence, and no randomized controlled trials (RCTs) have been conducted to verify fluid resuscitation regimens for CHIKF. Clinical application should be individualized based on patient conditions and local medical resources.

3.3.2 Management of Chronic Arthropathy

Chronic arthropathy is the most common long-term complication of CHIKF, occurring in 25%–40% of survivors [3]. The main management strategies are as follows:

Pharmacological treatment: NSAIDs can be used to relieve arthralgia after the acute phase, with attention paid to gastrointestinal, hepatic and renal adverse reactions. For patients unresponsive to NSAIDs, low-dose glucocorticoids or disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and hydroxychloroquine may be considered. However, relevant evidence is mainly derived from small observational studies, lacking support from high-quality RCTs.

Physical therapy: Joint functional exercises, physical modalities (hyperthermia, ultrasound) and rehabilitation training help improve joint function and alleviate pain.

Traditional Chinese medicine (TCM) treatment: According to the 2025 national diagnosis and treatment protocol of China, chikungunya fever is categorized as "damp-warm disease" in TCM. Herbal prescriptions for clearing heat, resolving dampness and dispelling wind to relieve rashes are recommended for the acute phase. For the recovery phase, treatment is based on syndrome differentiation (dampness stagnation in meridians, deficiency of lung and spleen, liver depression and spleen deficiency) [18]. These recommendations are based on expert opinions without high-quality RCT evidence, so clinical application requires caution.

Long-term follow-up: All patients should receive post-discharge follow-up focusing on the recovery of joint symptoms. Patients with chronic arthralgia should be referred to the rheumatology department for long-term management and functional assessment.

3.3.3 Management of Complications

A comprehensive approach is required for the management of CHIKF complications. For cardiac complications (myocarditis, arrhythmia), careful fluid resuscitation and early administration of inotropic drugs are essential. The management of hepatitis and liver failure follows guidelines for acute liver failure of other etiologies, including supportive care and close monitoring of liver function. Acute kidney injury is managed by maintaining urine output above 0.5 mL/kg/hr via fluid regulation, and continuous veno-venous hemofiltration (CVVH) is initiated early for renal replacement therapy when necessary.

Neurological complications (meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis) require supportive care including fluid management, consciousness monitoring, airway protection, anti-epileptic drugs and intracranial pressure reduction measures as appropriate. Intravenous immunoglobulin (IVIg) may be beneficial for CHIKV-associated Guillain-Barré syndrome (GBS). Pulse steroid therapy can be considered for acute disseminated encephalomyelitis (ADEM), while further studies are needed to confirm its efficacy.

Vertical transmission of CHIKV to neonates may cause severe complications including encephalopathy, myocarditis and gastrointestinal hemorrhage. The mortality rate of infected neonates reaches 30%–50%, and most survivors are left with severe neurological sequelae. Pregnant women in endemic areas should take strict anti-mosquito measures, and enhanced neonatal monitoring is required during delivery.

4. Discussion

This comprehensive review synthesizes literature published from 2004 to 2025 regarding the pathogenesis, diagnosis and management of CHIKV infection, and key issues are discussed as follows.

Progress in pathogenesis research: Major advances have been achieved in exploring the pathogenesis of CHIKV in recent years. The discovery of the E1-A226V mutation explains the molecular mechanism underlying the global spread of CHIKV [2], and the clarification of the mechanism by which nsP2 inhibits the JAK-STAT signaling pathway reveals a core link of viral immune evasion [6]. Nevertheless, the exact mechanism of chronic arthropathy remains incompletely elucidated. The relative contributions of persistent viral RNA, autoimmune responses and pro-inflammatory cytokines need further investigation. In addition, the impacts of co-infection and immune cross-reactivity between CHIKV, dengue virus and Zika virus on disease prognosis are worthy of in-depth exploration.

Optimization of diagnostic methods: RT-qPCR is firmly established as the gold standard for early diagnosis, but its high cost, infrastructure requirements and reduced sensitivity in secondary infections limit its wide application in resource-limited regions [4]. Serological cross-reactivity remains a major diagnostic challenge. The preprint study by Seyyadali et al. (2025) reported poor consistency between CHIKV IgM ELISA and RT-PCR (Kappa = -0.36), which may lead to overestimation of co-infection rates [12]. Given that this study has not been peer-reviewed, its conclusions should be interpreted prudently. Future research should focus on developing serological assays with higher specificity or adopting multiplex detection strategies combining nucleic acid, antigen and antibody tests to improve diagnostic accuracy.

Evidence gaps in clinical management: Current clinical management of CHIKF is mainly based on expert opinions and symptomatic supportive care, with a severe lack of high-quality RCT evidence. The efficacy and safety of antipyretic and analgesic regimens (paracetamol vs. NSAIDs) for the acute phase have not been verified by RCTs. Pharmacological treatments for chronic arthropathy (NSAIDs, glucocorticoids, DMARDs) are supported only by small observational studies. Real-world protective efficacy data of licensed vaccines are still insufficient, and long-term follow-up studies are required to verify whether the accelerated approval model based on immunogenicity surrogates can guarantee vaccine safety and efficacy [13][14].

Similarities and differences between chikungunya fever and dengue fever in clinical management: Clinicians often confuse these two diseases, and their key similarities and differences are summarized below.

Similarities: Both are acute febrile diseases transmitted by Aedes mosquitoes, with no specific antiviral drugs available; supportive and symptomatic care is the main treatment for the acute phase. Rash, thrombocytopenia and liver injury can occur in both diseases, and co-infection is not uncommon in endemic areas, requiring differentiation via molecular detection.

Key differences: (1) Joint symptoms: Severe symmetric polyarthralgia is a hallmark of CHIKF and may persist for months or years, while arthralgia in dengue fever is mild and short-lived. (2) Bleeding tendency: Bleeding and shock are more common in severe dengue fever, whereas CHIKF presents with milder bleeding manifestations, and chronic arthropathy is its dominant long-term complication. (3) Medication use: NSAIDs and aspirin should be avoided in patients with suspected CHIKF when dengue fever cannot be excluded to reduce bleeding risks, which is a critical clinical point for co-endemic regions. (4) Vaccines: Vaccines for dengue fever (Dengvaxia, Qdenga) and CHIKF (IXCHIQ, VIMKUNYA) have been approved, but they differ in applicable populations and approval criteria.

Priorities for future research: Based on the findings of this review, the following research directions are proposed: (1) Develop and validate biomarkers for accurate prediction of chronic arthropathy; (2) Conduct high-quality RCTs to optimize pharmacological regimens for acute and chronic phases; (3) Launch large-scale cohort studies to evaluate the long-term safety and protective efficacy of vaccines; (4) Explore the application of host-targeted therapies (e.g., JAK inhibitors, IL-6 receptor antagonists) for chronic arthropathy; (5) Develop rapid, accurate and affordable POC diagnostic tools suitable for endemic areas.

5. Limitations

This review has several limitations that should be considered when interpreting the results:

(1) Review type limitation: This is a comprehensive review rather than a systematic review or meta-analysis. It did not follow the PRISMA guidelines for systematic retrieval and evidence grading, which may lead to selection bias.

(2) Language bias: Literature in French, Spanish and Portuguese was not systematically searched, potentially omitting key studies from Africa and South America. Chinese literature was retrieved manually instead of via systematic database searching.

(3) Retrieval scope limitation: Although PubMed, Web of Science and Google Scholar were searched, Embase and Cochrane Library were not included, though part of their literature is covered by the above databases.

(4) Uneven evidence quality: The number of high-quality RCTs among included studies is small. Most evidence comes from observational studies, case series and expert opinions, so treatment recommendations with low-level evidence should be applied cautiously in clinical practice.

(5) Lack of quantitative synthesis: No meta-analysis was performed, so pooled effect sizes are unavailable. Sensitivity and specificity data of diagnostic assays were summarized narratively from individual studies with significant heterogeneity.

(6) Insufficient vaccine data: Clinical protective efficacy data of licensed vaccines are inadequate. Current evidence is mainly based on immunogenicity surrogates and mathematical model predictions, and real-world effectiveness requires further verification.

(7) Limited evidence for TCM therapy: High-quality RCTs on TCM treatment are scarce. Relevant recommendations are derived from national diagnosis and treatment protocols and expert opinions with low evidence quality.

6. Conclusion

Chikungunya virus continues to pose an expanding global health threat, and its prevalence is exacerbated by rapid urbanization, climate change, and the expanding geographical range of Aedes vectors. Most CHIKV infections are mild and self-limiting, but a considerable proportion of patients develop chronic diseases characterized by persistent arthropathy or severe complications, including neurological damage and hemorrhage. The progression of disease is driven by the complex interaction among viral lineages, host immune responses, and viral adaptive mutations (E1-A226V). Effective clinical management of CHIKF relies on two core pillars: timely diagnosis and standardized supportive care. RT-PCR is the preferred assay during the acute febrile phase for early diagnosis, while serological tests are more suitable for retrospective confirmation and immune assessment, despite the interference of cross-reactivity with other alphaviruses and flaviviruses. Standard symptomatic treatment is the cornerstone of supportive care. Uncomplicated cases are managed with oral rehydration and antipyretic-analgesic drugs, while severe CHIKF requires close monitoring and timely intervention for complications.

Notably, NSAIDs, glucocorticoids and prophylactic blood transfusion should be avoided when dengue fever cannot be ruled out. Patients with chronic arthropathy need long-term follow-up and collaborative management with rheumatology departments.

To strengthen global preparedness and management of CHIKF, several research priorities must be addressed: developing validated biomarkers for predicting disease progression, standardizing diagnostic platforms with strict quality control, and conducting well-designed clinical trials to optimize treatment regimens for acute and chronic phases. Ultimately, translating advances in CHIKV pathogenesis and diagnosis into practical, evidence-based clinical algorithms is essential to reduce global mortality and improve patient outcomes.

Conflict of Interest: The authors declare that there are no competing financial interests or personal relationships that may affect the work reported in this paper.

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