Future Integrative Medicine **2026** vol. 000(000) | 000–000 Epub
DOI: 10.14218/FIM.2025.00046

Review Article

Chikungunya Fever: Etiology, Pathogenesis, and Management, with a Particular Focus on Evidence-based Application of Traditional Chinese Medicine

Maoyu Ding[1,2,3#], Tengfei Chen[1,2,3#], Xiaolong Xu[1,2,3*] and Qingquan Liu[1,2,3*]

[1]*Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China;* [2]*Beijing Institute of Traditional Chinese Medicine, Beijing, China;* [3]*Beijing University of Chinese Medicine, Beijing, China*

Received: September 13, 2025 | **Revised:** March 19, 2026 | **Accepted:** April 13, 2026 | **Published online:** April 29, 2026

Abstract

Chikungunya fever, caused by the Chikungunya virus (CHIKV), has re-emerged as a significant global health concern in recent decades. A notable event was the largest-ever local outbreak in China in 2025, marking a critical juncture in its epidemiology. Although conventional treatment remains predominantly supportive, the integration of traditional Chinese medicine (TCM) offers promising complementary strategies for alleviating both acute symptoms and chronic polyarthralgia. This narrative review aims to consolidate current knowledge on the etiology, pathogenesis, clinical manifestations, and management of Chikungunya fever, with a particular focus on the evidence-based application of TCM. By integrating molecular virology with clinical and epidemiological insights, this review offers a comprehensive perspective on the challenges posed by CHIKV and underscores the strategic imperatives essential for its future management. In conclusion, addressing the expanding threat of CHIKV necessitates a multipronged public health strategy that integrates standard clinical and preventive measures with evidence-based TCM therapies, highlighting the urgent need for rigorous clinical trials to globally validate these integrative treatments.

Introduction

Chikungunya virus (CHIKV), an arbovirus transmitted by *Aedes* mosquitoes, specifically *Aedes aegypti* and *Aedes albopictus*, is responsible for Chikungunya fever, a disease recognized for its debilitating and often persistent musculoskeletal pain.[1,2] Originally identified in Tanzania in 1952, CHIKV has been associated with periodic outbreaks in Africa and Asia.[3,4] However, the 21st century has seen a notable increase in its global spread.[5] Commencing with a significant epidemic in Kenya in 2004,[6] the virus has spread to over 119 countries, impacting millions across regions such as the Indian Ocean, the Americas, and Europe.[7] This expansion has been facilitated by viral adaptations that enhance vector competence, particularly in *A. albopictus*, an invasive mosquito species that has established itself in temperate areas worldwide.[8,9]

The disease burden of Chikungunya fever is substantial, with global estimates indicating around 18.7 million annual cases and an estimated loss of approximately 1.95 million disability-adjusted life years between 2011 and 2020.[10] While traditionally associated with tropical regions, CHIKV now presents a predictable seasonal risk in temperate zones. A significant recent occurrence highlighting this shift took place in July 2025 in Guangdong Province, China, where the largest local outbreak of Chikungunya fever was reported, with over 4,000 confirmed cases originating from an imported case in Foshan City.[11,12] This event signifies a crucial transition from sporadic imported cases, which have been documented in China since 2008, to widespread and sustained local transmission. The outbreak emphasizes the heightened vulnerability of immunologically naive populations in regions with established *Aedes* vectors and emphasizes the pressing need for robust surveillance, clinical readiness, and effective control measures on a global scale.[11,13] Although conventional treatment remains predominantly supportive, integrating traditional Chinese medicine (TCM) offers promising complementary strategies for alleviating both acute symptoms and chronic polyarthralgia.

Therefore, this review aims to consolidate current knowledge on the etiology, pathogenesis, clinical manifestations, and manage-

Keywords: Chikungunya fever; Etiology; Pathogenesis; Management; Traditional Chinese medicine; TCM.

***Corresponding to:** Xiaolong Xu, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, 23 Meishuguan Backstreet, Dongcheng District, Beijing 100010, China. ORCID: https://orcid.org/0000-0003-3333-0906. Tel: +86-18811554937, E-mail: xiaolong_xu3013@126.com; Qingquan Liu, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, 23 Meishuguan Backstreet, Dongcheng District, Beijing 100010, China. ORCID: https://orcid.org/0000-0003-0828-0361. Tel: +86-13910055687, E-mail: liuqingquan_2003@126.com

[#]These authors contributed equally to this work.

How to cite this article: Ding M, Chen T, Xu X, Liu Q. Chikungunya Fever: Etiology, Pathogenesis, and Management, with a Particular Focus on Evidence-based Application of Traditional Chinese Medicine. *Future Integr Med* 2026;000(000):000–000. doi: 10.14218/FIM.2025.00046.

ment of Chikungunya fever, with a particular focus on the evidence-based application of TCM.

Etiology and viral replication

CHIKV is a positive-sense, single-stranded RNA virus enclosed in an envelope, categorized within the Alphavirus genus of the Togaviridae family.[14] The viral particle, about 70 nm in diameter, features an icosahedral nucleocapsid comprising the capsid (C) protein that envelops the 11.8 kb genome.[15,16] This genome harbors two open reading frames (ORFs): the 5′ ORF encodes the four non-structural proteins (Nsp)1–4 essential for the formation of the viral replicase complex, while the 3′ ORF, translated from a subgenomic RNA, encodes the structural polyprotein (C-E3-E2-6K/TF-E1).[17–19] Through phylogenetic assessments, CHIKV is classified into four principal genotypes: West African, East/Central/South African, Asian, and the Indian Ocean lineage (Fig. 1a and b).[20] Recent molecular analyses have identified the East/Central/South African genotype as the primary strain responsible for current regional outbreaks.[12] Notably, specific adaptive mutations within this lineage may correlate with the severity of chronic polyarthralgia, a hypothesis that requires further longitudinal studies.[2,21]

The replication cycle of CHIKV commences with the attachment of the E2 envelope glycoprotein to host cell receptors. The cell adhesion molecule matrix remodeling-associated 8 (MXRA8) has been recognized as a key entry mediator on various cell types, including fibroblasts and osteoblasts. In addition to MXRA8, other host factors such as glycosaminoglycans, including heparan sulfate, and phosphatidylserine receptors also facilitate viral attachment to the cell surface.[22–24] Subsequent to attachment, the virion is internalized through clathrin-mediated endocytosis. Within the acidic milieu of the endosome, a conformational alteration in the E1 glycoprotein occurs, exposing its fusion peptide. This event facilitates the fusion of the viral and endosomal membranes, leading to the release of the nucleocapsid into the cytoplasm.[18,25] Upon entry into the cytoplasm, the genomic RNA of CHIKV undergoes translation to generate the non-structural polyprotein precursor (P1234), which is subsequently cleaved by the Nsp2 protease to yield individual Nsps. These Nsps form a replicase complex on the inner face of the plasma membrane, organizing into vesicular replication compartments known as spherules.[15,22,26] Within these compartments, the replicase complex initiates the synthesis of a full-length negative-strand RNA template, which serves as the basis for generating new genomic RNA and the transcription of a 26S subgenomic RNA.[27] The subgenomic RNA is translated into the structural polyprotein, with the capsid protein undergoing autocatalytic cleavage and associating with newly synthesized genomic RNA to form nucleocapsids in the cytoplasm.[25] Concurrently, the remaining envelope glycoproteins (pE2-6K-E1) are translocated into the endoplasmic reticulum and processed through the secretory pathway, culminating in mature E1/E2 heterodimers being embedded in the plasma membrane.[28] The replication cycle culminates as the cytoplasmic nucleocapsids interact with these glycoproteins at the cell surface, leading to the budding and release of new enveloped virions (Fig. 1c).

Pathogenesis

The pathogenesis of Chikungunya fever involves a multifaceted interplay between direct viral cytopathic effects and a robust, often dysregulated, host immune response.[29] Following inoculation by a mosquito bite, CHIKV initiates replication in dermal fibroblasts, macrophages, mesenchymal stromal cells, Langerhans cells, and endothelial cells.[30] Subsequently, the virus disseminates through the lymphatic system and bloodstream, leading to the attainment of notably high viral loads (>10^9 particles/mL) and the establishment of infection in distant tissues. These tissues include the musculoskeletal system (muscles, joints, tendons), as well as the liver, spleen, and, in severe cases, the central nervous system.[31,32]

The onset of clinical symptoms in Chikungunya fever is concomitant with a vigorous innate immune response characterized by elevated levels of type I interferons (IFN-α/β) and a cascade of proinflammatory cytokines and chemokines, such as interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1.[33–36] This systemic inflammatory state can also lead to hemodynamic disturbances, including the dysregulation of coagulation factors and complement pathways. While the type I IFN response is critical for controlling viral replication, the pronounced inflammatory environment significantly contributes to tissue pathology. This inflammation drives a massive recruitment of immune cells—including monocytes, macrophages, T cells, B cells, osteoclast cells, and natural killer cells—into infected musculoskeletal tissues,[37–40] serving as the primary driver of the characteristic myalgia and arthralgia. Simultaneously, the adaptive immune response is activated, with acute CHIKV infection eliciting a robust $CD8^+$ T cell response aimed at killing virus-infected cells. However, the high initial viral loads can lead to $CD8^+$ T cell exhaustion, potentially decreasing the efficiency of viral clearance.[41,42]

A defining feature of CHIKV disease is the high prevalence of chronic arthralgia, the mechanisms of which remain incompletely elucidated but are thought to involve two primary pathways. Firstly, viral RNA and antigens persist in protected tissue reservoirs, such as synovial macrophages and muscle satellite cells, even after viremia has resolved.[43] This persistent viral presence may serve as a constant stimulus for chronic inflammation. The second proposed mechanism is a virus-triggered immune dysregulation, leading to a state resembling autoimmune disorders like rheumatoid arthritis (RA), with shared clinical and immunopathological characteristics.[44] Several studies have failed to detect persistent viral RNA in the synovial fluid of some patients,[45] supporting the hypothesis of a purely host-driven, virus-triggered autoimmune-like immune response similar to RA. Moreover, a key pathway implicated in CHIKV-induced bone pathology is the upregulation of IL-6, which augments the receptor activator of nuclear factor-κB ligand/osteoprotegerin ratio, facilitating osteoclastogenesis and ultimately leading to bone erosion and loss (Fig. 2).[46,47]

Clinical manifestations

The clinical course of Chikungunya fever is conventionally categorized into three phases: acute, post-acute, and chronic.[5] The acute phase, lasting approximately 14–21 days and commencing abruptly following a 3–7 day incubation period, is characterized by a classic triad of high fever (>39 °C), a maculopapular rash, and severe, often debilitating polyarthralgia.[48] The polyarthralgia typically manifests bilaterally and symmetrically, predominantly affecting distal joints such as the wrists, ankles, and phalanges. The intensity of the pain can be severe, leading to a characteristic “bent-over” posture that lends the disease its name. Additional common symptoms include myalgia, headache, back pain, and fatigue.[49]

Following the acute phase of Chikungunya fever, many patients progress to a subacute phase lasting from 3 weeks to 3 months, during which fever and rash subside but joint symptoms may persist or recur. A substantial proportion of patients (estimated be-

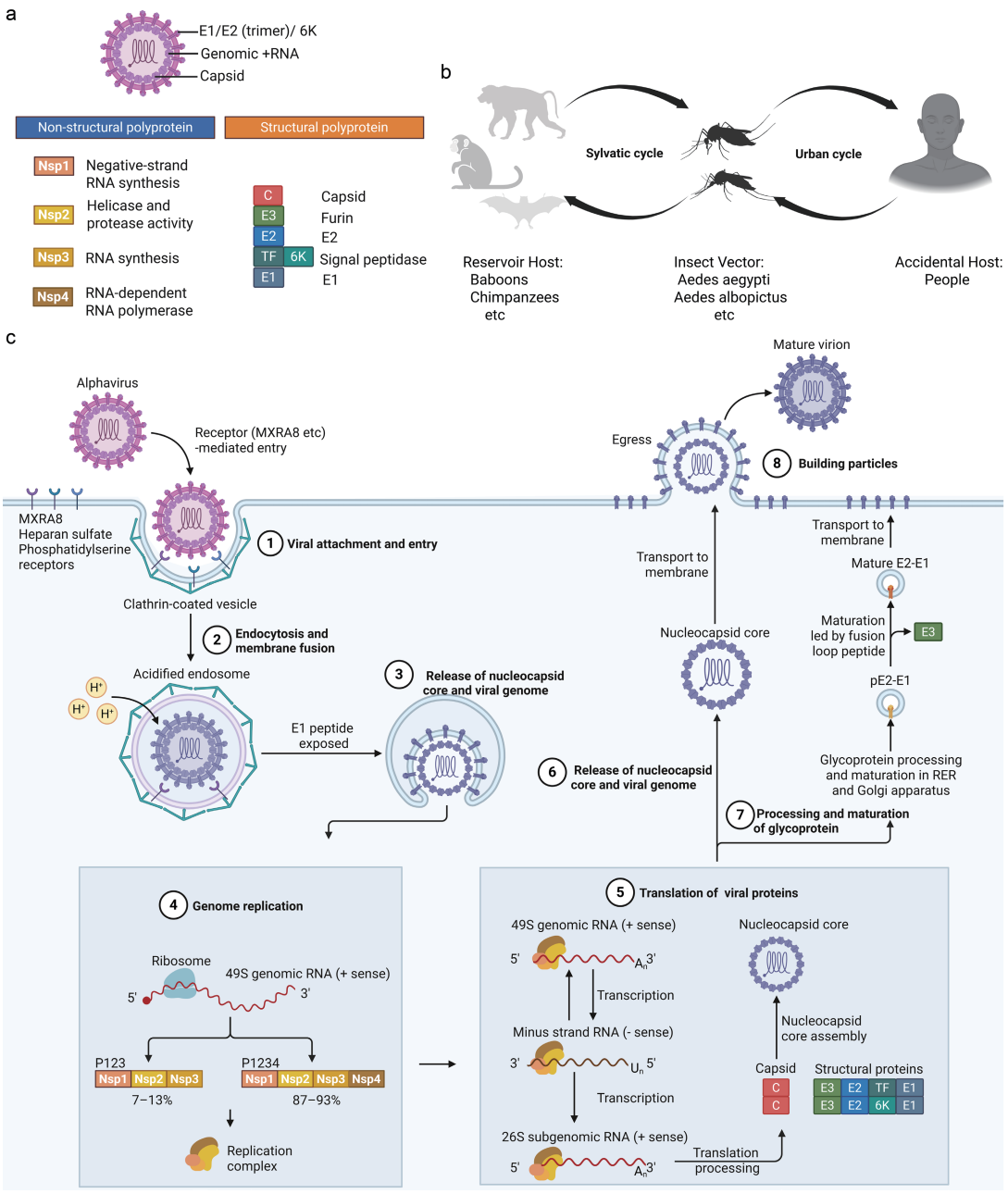

Fig. 1. CHIKV genomic organization, transmission cycles, and cellular replication. This figure provides a comprehensive overview of CHIKV biology, covering structural components, ecological transmission routes, and intracellular replication mechanisms. (a) Schematic representation of the CHIKV virion structure and genome. The genome is organized into two open reading frames that encode a non-structural polyprotein (processed into Nsp1–4) and a structural polyprotein (processed into C, E3, E2, 6K/TF, and E1). Key functions of these proteins in viral replication and immune evasion are indicated. Mature virions are icosahedral particles, approximately 70 nm in diameter, composed of 80 trimeric E2–E1 heterodimer spikes. (b) Depiction of the transmission cycles of CHIKV. The virus is maintained in a sylvatic cycle between non-human primate reservoir hosts (e.g., baboons, chimpanzees) and forest-dwelling *Aedes* mosquitoes. Spillover to humans can initiate an urban cycle, where the virus is transmitted efficiently between people by *Aedes aegypti* and *Aedes albopictus*, often leading to large-scale epidemics. (c) Detailed overview of the CHIKV cellular replication cycle. (1) Infection begins with the virus binding to specific host factors on susceptible cells, such as the primary receptor MXRA8, or attachment factors like heparan sulfate and phosphatidylserine receptors. (2) The virus enters the cell via endocytosis and is transported to the endosome, where the acidic environment triggers conformational changes in the viral envelope. (3) This exposes the E1 fusion peptide, which mediates the fusion of viral and host membranes, releasing the viral genome into the cytoplasm. (4) The viral genome is translated into non-structural polyproteins, which are processed into Nsp1–4 to form the viral replication complex. (5) Translation of viral structural proteins. (6–7) The precursor is processed to release the capsid protein, which assembles with genomic RNA into a nucleocapsid, while glycoproteins pE2 and E1 are processed in the Golgi apparatus and transported to the plasma membrane. (8) Viral assembly is completed by the recruitment of envelope glycoproteins, followed by budding from the cell surface. Additionally, CHIKV can spread via cell-to-cell transmission by inducing the formation of intercellular extensions, facilitating efficient transfer to neighboring cells. CHIKV, Chikungunya virus; RER, rough endoplasmic reticulum.

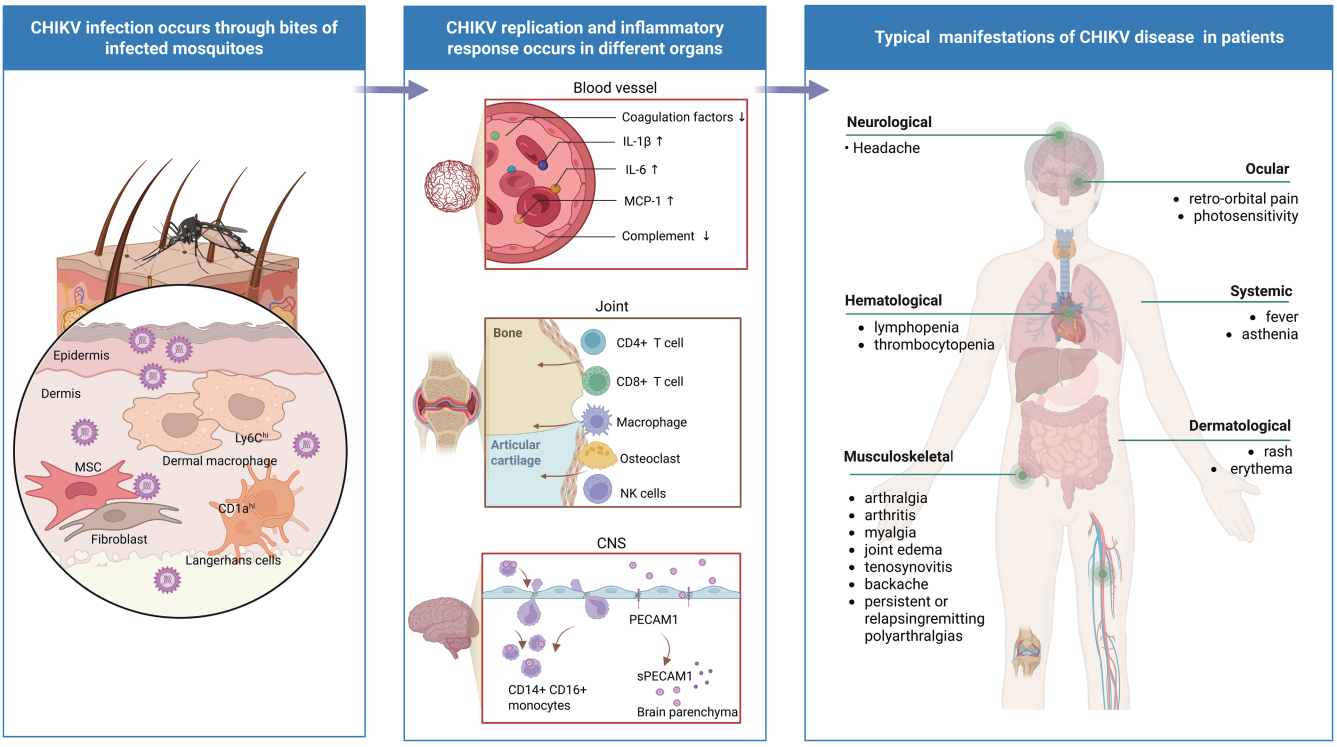

Fig. 2. Pathogenesis and systemic manifestations of Chikungunya fever. This figure illustrates the pathogenic cascade of CHIKV infection from initial inoculation to systemic disease. Infection begins with a mosquito bite, leading to viral replication and immune response in dermal cells, including fibroblasts, macrophages, and Langerhans cells. The virus then disseminates systemically, triggering a multi-organ inflammatory response through the lymphatic system and bloodstream. In the vasculature, this response can lead to endothelial dysfunction and altered levels of coagulation factors and cytokines (e.g., IL-1β, IL-6, MCP-1). In the joints, viral replication and the infiltration of immune cells (such as T cells and macrophages) drive the characteristic inflammatory arthritis and promote osteoclast-mediated bone pathology. In severe cases, neuroinvasion can occur, potentially facilitated by infected monocytes crossing the blood-brain barrier. For instance, CHIKV infection can cleave platelet endothelial cell adhesion molecule 1 (PECAM-1) on blood-brain barrier cells, which may facilitate viral entry into the brain parenchyma. This pathogenic process results in the typical clinical manifestations of Chikungunya fever, which are categorized by the affected organ systems, including the classic triad of fever, rash, and severe polyarthralgia. CHIKV, Chikungunya virus; CNS, central nervous system; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MSC, mesenchymal stromal cell; NK, natural killer.

tween 40% and 80%) advance to the chronic phase, characterized by prolonged rheumatic symptoms lasting over three months and, in some instances, extending for several years.[50–52] This chronic and relapsing-remitting polyarthralgia represents the main contributor to long-term morbidity and exerts a substantial detrimental impact on quality of life.[53,54]

Although mortality rates in Chikungunya fever are low, ranging from 0.024% to 0.8%,[55–58] severe and atypical manifestations can occur, particularly in neonates, the elderly (>65 years), and individuals with underlying comorbidities.[59] These complications encompass neurological disease (such as encephalitis, meningoencephalitis, Guillain-Barré syndrome), cardiovascular issues (including myocarditis and pericarditis), ocular inflammation (such as uveitis and retinitis), and, rarely, fulminant hepatitis or renal failure.[1] Vertical transmission from mother to child during the intrapartum period poses a significant risk, often leading to severe neonatal disease, including encephalopathy (Fig. 2).[60–62]

Arthropod-borne viruses (arboviruses), such as dengue, chikungunya, and Zika viruses, are transmitted by mosquitoes of the genus *Aedes* (Stegomyia).[63] Driven by climate change and urbanization, their co-circulation has become increasingly common, posing significant risks for concurrent outbreaks and human co-infections. Clinically distinguishing among these three infections is challenging due to their similar acute manifestations, including fever, rash, and myalgia. Table 1 summarizes pertinent distinctions that may facilitate differentiation.[64]

Therapeutic and preventive strategies

Currently, there are no specific licensed antiviral drugs for Chikungunya fever, and management primarily involves supportive and symptomatic care. Treatment strategies are tailored to the clinical phase of the disease.[64]

During the acute phase, treatment emphasizes rest, hydration, and analgesia to address fever and pain.[65] Acetaminophen or paracetamol is recommended for pain and fever management.[64] In cases of severe, debilitating pain, mild opioids like tramadol or codeine may be considered, and in refractory situations, stronger opioids may be required under the guidance of a specialist. Corticosteroids are not recommended during the acute phase due to the risk of symptom rebound.[2] The use of intravenous immunoglobulins is generally not indicated except in rare instances of severe cases with life-threatening complications.[66]

For patients progressing to the post-acute and chronic phases, management becomes more complex, often resembling that of chronic inflammatory arthropathies. Non-steroidal anti-inflammatory drugs continue to be a fundamental aspect of treatment. For persistent inflammatory symptoms, low-dose corticosteroids may

Table 1. Clinical manifestations of dengue, chikungunya, and Zika that may help differentiate them from each other

Certainty of the evidence	Manifestations of dengue	Manifestations of chikungunya	Manifestations of Zika
HIGH (findings that differentiate them)	Thrombocytopenia; Progressive increase in hematocrit; Leukopenia	Arthralgia	Pruritus
MODERATE (findings that probably differentiate them)	Anorexia or vomiting; Abdominal pain; Chills; Hemorrhage (includes bleeding on the skin, mucous membranes, or both)	Rash Conjunctivitis; Arthritis; Myalgia or bone pain	Rash Conjunctivitis
LOW (findings that may differentiate them)	Retro-ocular pain; Hepatomegaly; Headache; Diarrhea; Dysgeusia; Cough; Elevated transaminases; Positive tourniquet test	Hemorrhage (includes bleeding on the skin, mucous membranes, or both)	Adenopathy Pharyngitis or odynophagia

be beneficial. In cases of chronic inflammatory rheumatism that mimic RA, disease-modifying antirheumatic drugs such as methotrexate, hydroxychloroquine, and sulfasalazine have shown efficacy, either as monotherapy or in combination. Non-pharmacological interventions, including physiotherapy and physical rehabilitation, are essential for preserving joint mobility and alleviating chronic pain.[65,67] In addition to conventional therapies, complementary approaches such as TCM may have a significant role in management. Notably, the National Health Commission of the People's Republic of China has incorporated TCM into the "Diagnosis and Treatment Protocol for Chikungunya Fever (2025 Edition)," which provides specific herbal formulas for the febrile and recovery phases of the disease.[68] Within the TCM framework, chikungunya is categorized as a "dampness-heat" disease. The protocol recommends phase-specific interventions: (1) Acute phase: The primary therapeutic principle is "clearing heat, resolving dampness, and dispelling wind." Recommended oral herbal formulations include ingredients such as *Pogostemonis Herba* (Guanghuoxiang), *Puerariae Lobatae Radix* (Gegen), and *Forsythiae Fructus* (Lianqiao). (2) Recovery phase: For patients experiencing persistent polyarthralgia, classified as "dampness stagnating in the collaterals," the focus shifts to "dispelling cold and removing dampness." Representative herbs include *Notopterygii Rhizoma et Radix* (Qianghuo), *Angelicae Pubescentis Radix* (Duhuo), and *Gentianae Macrophyllae Radix* (Qinjiao). (3) External therapies: Complementary external treatments, including targeted bloodletting therapy (e.g., at the Dazhui acupoint or inflamed joints) to clear heat and unblock collaterals, as well as topical cold compresses with herbal decoctions (e.g., *Lonicerae Japonicae Caulis* (Rendongteng)), are also highlighted for directly alleviating local joint inflammation and cutaneous pruritus. However, it must be acknowledged that high-quality international evidence supporting these TCM interventions remains limited, underscoring the urgent need for rigorous, multicenter randomized controlled trials to validate their global efficacy and safety.

A significant advancement in preventive measures for Chikungunya fever occurred with the recent regulatory clearance of two vaccines. Ixchiq, a live-attenuated vaccine, received approval from the US Food and Drug Administration (FDA) in late 2023 and the European Union (EU) in 2024 for individuals aged 18 years and older.[69] Vimkunya, a virus-like particle vaccine, was approved by the FDA and EU in 2025 for individuals aged 12 years and older. These vaccines serve as crucial tools for outbreak prevention, particularly benefiting travelers and populations residing in regions at risk of Chikungunya transmission.[70] Despite their potential, challenges persist regarding safety concerns in specific populations (e.g., severe adverse events reported with Ixchiq in adults over 65 years),[69] cost considerations, and ensuring equitable distribution in endemic low- and middle-income countries.

In addition to vaccination, integrated vector control stands as a cornerstone of prevention, encompassing community-driven initiatives to eradicate mosquito breeding grounds, targeted insecticide application, and innovative strategies such as the release of Wolbachia-infected mosquitoes.[13,63]

Outlook

CHIKV has solidified its status as a globally significant arbovirus, with its geographical reach and epidemic capacity steadily widening. The convergence of climate change, which extends the habitat of *Aedes* vectors, and continuous international travel guarantees the enduring presence of CHIKV as a persistent and unpredictable menace. The recent extensive outbreak in China serves as a compelling reminder that no region harboring competent vectors is immune from the risk posed by this virus.[11,12]

Future endeavors should prioritize several key areas. Firstly, a comprehensive understanding of the mechanisms underpinning chronic arthralgia is crucial for the development of targeted therapeutics aimed at alleviating the enduring suffering of patients. There is an urgent need for reliable predictive biomarkers and the development of targeted, host-directed anti-inflammatory therapies to alleviate chronic arthralgia. Secondly, while the regulatory approval of two vaccines marks a significant milestone, the emphasis should now shift towards implementing effective and equitable strategies, including the establishment of regional vaccine reserves and ensuring affordability in the most impacted regions. Post-licensure surveillance to monitor long-term safety and effectiveness is also essential. Thirdly, the development of specific, affordable therapies such as TCM remains a high priority, particularly for managing severe acute infections and potentially averting the progression to chronic conditions.

Limitations

Despite the comprehensive synthesis of current literature, several limitations in the present research landscape must be acknowledged. Firstly, regarding the mechanisms of TCM interventions, there is currently insufficient elucidation of the molecular interactions between CHIKV and specific TCM therapeutic targets, requiring further robust *in vivo* and *in vitro* studies to bridge classical theories with modern virological pathways. Secondly, although novel CHIKV vaccines have shown promise, there is a notable lack of comprehensive clinical vaccine data in populations from low-income countries, which are regions that often bear the highest disease burden. Lastly, the sample sizes of long-term follow-up

studies focusing on CHIKV-induced chronic polyarthralgia remain limited, thereby restricting a comprehensive understanding of the pathophysiological transition from acute viral infection to chronic immune-mediated joint destruction.

Conclusions

A holistic and enduring response to CHIKV and emerging arboviruses demands a comprehensive and multi-pronged public health strategy, including the integration of TCM. This strategy necessitates the fusion of human clinical surveillance with entomological and environmental monitoring, cross-border data exchange, and active community involvement. Through enhancing global cooperation and dedicating resources to pioneering research and public health systems, the global community can enhance preparedness and minimize the repercussions of this formidable viral challenge.

Adapted from the Pan American Health Organization guidelines for diagnosis and treatment of dengue, chikungunya, and Zika in the Region of the Americas.

Acknowledgments

Not applicable.

Funding

The research was supported by the National Natural Science Foundation of China (82474428); the National Multidisciplinary Innovation Team Project of Traditional Chinese Medicine (ZYYCXTD-D-20220); and the National Administration of Traditional Chinese Medicine (NATCM) High-Level Key Discipline of TCM project (zyyzdxk-2023001).

Conflict of interest

QQL has served as Co-Editor-in-Chief, and XLX has been an Editorial Board member of *Future Integrative Medicine* since November 2021. The authors declare that they have no other competing interests.

Author contributions

Study concept and design (XLX, QQL), acquisition of data (MYD, TFC), analysis and interpretation of data (MYD, TFC, XLX, QQL), and drafting of the manuscript (MYD, TFC). All authors have approved the final version and publication of the manuscript.

References

[1] Silva LA, Dermody TS. Chikungunya virus: epidemiology, replication, disease mechanisms, and prospective intervention strategies. J Clin Invest 2017;127(3):737–749. doi:10.1172/JCI84417, PMID:28248203.

[2] Bartholomeeusen K, Daniel M, LaBeaud DA, Gasque P, Peeling RW, Stephenson KE, *et al*. Chikungunya fever. Nat Rev Dis Primers 2023;9(1):17. doi:10.1038/s41572-023-00429-2, PMID:37024497.

[3] Weaver SC, Chen R, Diallo M. Chikungunya Virus: Role of Vectors in Emergence from Enzootic Cycles. Annu Rev Entomol 2020;65:313–332. doi:10.1146/annurev-ento-011019-025207, PMID:31594410.

[4] Levi LI, Vignuzzi M. Arthritogenic Alphaviruses: A Worldwide Emerging Threat? Microorganisms 2019;7(5):133. doi:10.3390/microorganisms7050133, PMID:31091828.

[5] de Souza WM, Lecuit M, Weaver SC. Chikungunya virus and other emerging arthritogenic alphaviruses. Nat Rev Microbiol 2025;23(9):585–601. doi:10.1038/s41579-025-01177-8, PMID:40335675.

[6] Sergon K, Njuguna C, Kalani R, Ofula V, Onyango C, Konongoi LS, *et al*. Seroprevalence of Chikungunya virus (CHIKV) infection on Lamu Island, Kenya, October 2004. Am J Trop Med Hyg 2008;78(2):333–337. PMID:18256441.

[7] Liao CX, Du HP, Wang B, Lyu J, Li LM. Epidemiology, clinical characteristics and prevention strategies of Chikungunya fever (in Chinese). Zhonghua Liu Xing Bing Xue Za Zhi 2025;46(8):1468–1472. doi:10.3760/cma.j.cn112338-20250726-00527, PMID:40854778.

[8] Laporta GZ, Potter AM, Oliveira JFA, Bourke BP, Pecor DB, Linton YM. Global Distribution of Aedes aegypti and Aedes albopictus in a Climate Change Scenario of Regional Rivalry. Insects 2023;14(1):49. doi:10.3390/insects14010049, PMID:36661976.

[9] Mercier A, Obadia T, Carraretto D, Velo E, Gabiane G, Bino S, *et al*. Impact of temperature on dengue and chikungunya transmission by the mosquito Aedes albopictus. Sci Rep 2022;12(1):6973. doi:10.1038/s41598-022-10977-4, PMID:35484193.

[10] de Roo AM, Vondeling GT, Boer M, Murray K, Postma MJ. The global health and economic burden of chikungunya from 2011 to 2020: a model-driven analysis on the impact of an emerging vector-borne disease. BMJ Glob Health 2024;9(12):e016648. doi:10.1136/bmjgh-2024-016648, PMID:39627007.

[11] Feng Y, Chang F, Yang Y, Lu H. From dengue to chikungunya: Guangdong as a sentinel for arboviral threats in East Asia. Biosci Trends 2025;19(4):368–373. doi:10.5582/bst.2025.01228, PMID:40754456.

[12] Li Y, Jiang S, Zhang M, Li Y, He J, Yang Z, *et al*. An Outbreak of Chikungunya Fever in China - Foshan City, Guangdong Province, China, July 2025. China CDC Wkly 2025;7(32):1064–1065. doi:10.46234/ccdcw2025.172, PMID:40837139.

[13] Zumla A, Ntoumi F, Ippolito G, PANDORA-ID-NET Consortium. Chikungunya virus disease returns to Europe: a turning point for the global arboviral landscape. Lancet 2025;406(10506):891–894. doi:10.1016/S0140-6736(25)01458-8, PMID:40713986.

[14] Martelossi-Cebinelli G, Carneiro JA, Yaekashi KM, Bertozzi MM, Bianchini BHS, Rasquel-Oliveira FS, *et al*. A Review of the Biology of Chikungunya Virus Highlighting the Development of Current Novel Therapeutic and Prevention Approaches. Pathogens 2025;14(10):1047. doi:10.3390/pathogens14101047, PMID:41156657.

[15] Solignat M, Gay B, Higgs S, Briant L, Devaux C. Replication cycle of chikungunya: a re-emerging arbovirus. Virology 2009;393(2):183–197. doi:10.1016/j.virol.2009.07.024, PMID:19732931.

[16] Singh A, Kumar A, Yadav R, Uversky VN, Giri R. Deciphering the dark proteome of Chikungunya virus. Sci Rep 2018;8(1):5822. doi:10.1038/s41598-018-23969-0, PMID:29643398.

[17] Frolov I, Frolova EI. Molecular Virology of Chikungunya Virus. Curr Top Microbiol Immunol 2022;435:1–31. doi:10.1007/82_2018_146, PMID:30599050.

[18] Sahoo B, Gudigamolla NK, Chowdary TK. Acidic pH-Induced Conformational Changes in Chikungunya Virus Fusion Protein E1: a Spring-Twisted Region in the Domain I-III Linker Acts as a Hinge Point for Swiveling Motion of Domains. J Virol 2020;94(23):e01561–e01520. doi:10.1128/JVI.01561-20, PMID:32938768.

[19] Petitdemange C, Wauquier N, Vieillard V. Control of immunopathology during chikungunya virus infection. J Allergy Clin Immunol 2015;135(4):846–855. doi:10.1016/j.jaci.2015.01.039, PMID:25843597.

[20] Khongwichit S, Chansaenroj J, Chirathaworn C, Poovorawan Y. Chikungunya virus infection: molecular biology, clinical characteristics, and epidemiology in Asian countries. J Biomed Sci 2021;28(1):84. doi:10.1186/s12929-021-00778-8, PMID:34857000.

[21] Paixão ES, Rodrigues LC, Costa MDCN, Itaparica M, Barreto F, Gérardin P, *et al*. Chikungunya chronic disease: a systematic review and meta-analysis. Trans R Soc Trop Med Hyg 2018;112(7):301–316. doi:10.1093/trstmh/try063, PMID:30007303.

[22] van Duijl-Richter MK, Hoornweg TE, Rodenhuis-Zybert IA, Smit JM. Early Events in Chikungunya Virus Infection-From Virus Cell Binding to Membrane Fusion. Viruses 2015;7(7):3647–3674. doi:10.3390/v7072792, PMID:26198242.

[23] Zhang R, Kim AS, Fox JM, Nair S, Basore K, Klimstra WB, *et al*. Mxra8 is a receptor for multiple arthritogenic alphaviruses. Nature 2018;557(7706):570–574. doi:10.1038/s41586-018-0121-3, PMID: 29769725.
[24] Jose J, Snyder JE, Kuhn RJ. A structural and functional perspective of alphavirus replication and assembly. Future Microbiol 2009;4(7):837–856. doi:10.2217/fmb.09.59, PMID:19722838.
[25] Mangala Prasad V, Blijleven JS, Smit JM, Lee KK. Visualization of conformational changes and membrane remodeling leading to genome delivery by viral class-II fusion machinery. Nat Commun 2022;13(1):4772. doi:10.1038/s41467-022-32431-9, PMID:35970990.
[26] Strauss JH, Strauss EG. The alphaviruses: gene expression, replication, and evolution. Microbiol Rev 1994;58(3):491–562. doi:10.1128/mr.58.3.491-562.1994, PMID:7968923.
[27] Hakim MS, Aman AT. Understanding the Biology and Immune Pathogenesis of Chikungunya Virus Infection for Diagnostic and Vaccine Development. Viruses 2022;15(1):48. doi:10.3390/v15010048, PMID: 36680088.
[28] Voss JE, Vaney MC, Duquerroy S, Vonrhein C, Girard-Blanc C, Crublet E, *et al*. Glycoprotein organization of Chikungunya virus particles revealed by X-ray crystallography. Nature 2010;468(7324):709–12. doi:10.1038/nature09555, PMID:21124458.
[29] Gonçalves WA, de Sousa CDF, Teixeira MM, Souza DG. A brief overview of chikungunya-related pain. Eur J Pharmacol 2025;994:177322. doi:10.1016/j.ejphar.2025.177322, PMID:39892450.
[30] Matusali G, Colavita F, Bordi L, Lalle E, Ippolito G, Capobianchi MR, *et al*. Tropism of the Chikungunya Virus. Viruses 2019;11(2):175. doi:10.3390/v11020175, PMID:30791607.
[31] Broeckel R, Haese N, Messaoudi I, Streblow DN. Nonhuman Primate Models of Chikungunya Virus Infection and Disease (CHIKV NHP Model). Pathogens 2015;4(3):662–681. doi:10.3390/pathogens4030662, PMID:26389957.
[32] Das T, Jaffar-Bandjee MC, Hoarau JJ, Krejbich Trotot P, Denizot M, Lee-Pat-Yuen G, *et al*. Chikungunya fever: CNS infection and pathologies of a re-emerging arbovirus. Prog Neurobiol 2010;91(2):121–129. doi:10.1016/j.pneurobio.2009.12.006, PMID:20026374.
[33] Teng TS, Kam YW, Lee B, Hapuarachchi HC, Wimal A, Ng LC, *et al*. A Systematic Meta-analysis of Immune Signatures in Patients With Acute Chikungunya Virus Infection. J Infect Dis 2015;211(12):1925–1935. doi:10.1093/infdis/jiv049, PMID:25635123.
[34] Ruiz Silva M, van der Ende-Metselaar H, Mulder HL, Smit JM, Rodenhuis-Zybert IA. Mechanism and role of MCP-1 upregulation upon chikungunya virus infection in human peripheral blood mononuclear cells. Sci Rep 2016;6:32288. doi:10.1038/srep32288, PMID:27558873.
[35] Her Z, Malleret B, Chan M, Ong EK, Wong SC, Kwek DJ, *et al*. Active infection of human blood monocytes by Chikungunya virus triggers an innate immune response. J Immunol 2010;184(10):5903–5913. doi:10.4049/jimmunol.0904181, PMID:20404274.
[36] Schilte C, Couderc T, Chretien F, Sourisseau M, Gangneux N, Guivel-Benhassine F, *et al*. Type I IFN controls chikungunya virus via its action on nonhematopoietic cells. J Exp Med 2010;207(2):429–442. doi:10.1084/jem.20090851, PMID:20123960.
[37] Young AR, Locke MC, Cook LE, Hiller BE, Zhang R, Hedberg ML, *et al*. Dermal and muscle fibroblasts and skeletal myofibers survive chikungunya virus infection and harbor persistent RNA. PLoS Pathog 2019;15(8):e1007993. doi:10.1371/journal.ppat.1007993, PMID:31465513.
[38] Labadie K, Larcher T, Joubert C, Mannioui A, Delache B, Brochard P, *et al*. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. J Clin Invest 2010;120(3):894–906. doi:10.1172/JCI40104, PMID:20179353.
[39] Wilson JA, Prow NA, Schroder WA, Ellis JJ, Cumming HE, Gearing LJ, *et al*. RNA-Seq analysis of chikungunya virus infection and identification of granzyme A as a major promoter of arthritic inflammation. PLoS Pathog 2017;13(2):e1006155. doi:10.1371/journal.ppat.1006155, PMID:28207896.
[40] Michlmayr D, Pak TR, Rahman AH, Amir ED, Kim EY, Kim-Schulze S, *et al*. Comprehensive innate immune profiling of chikungunya virus infection in pediatric cases. Mol Syst Biol 2018;14(8):e7862. doi:10.15252/msb.20177862, PMID:30150281.
[41] Dias CNS, Gois BM, Lima VS, Guerra-Gomes IC, Araújo JMG, Gomes JAS, *et al*. Human CD8 T-cell activation in acute and chronic chikungunya infection. Immunology 2018;155(4):499–504. doi:10.1111/imm.12992, PMID:30099739.
[42] Mueller SN, Ahmed R. High antigen levels are the cause of T cell exhaustion during chronic viral infection. Proc Natl Acad Sci U S A 2009;106(21):8623–8628. doi:10.1073/pnas.0809818106, PMID:19433785.
[43] Kam YW, Simarmata D, Chow A, Her Z, Teng TS, Ong EK, *et al*. Early appearance of neutralizing immunoglobulin G3 antibodies is associated with chikungunya virus clearance and long-term clinical protection. J Infect Dis 2012;205(7):1147–1154. doi:10.1093/infdis/jis033, PMID:22389226.
[44] van Aalst M, Nelen CM, Goorhuis A, Stijnis C, Grobusch MP. Long-term sequelae of chikungunya virus disease: A systematic review. Travel Med Infect Dis 2017;15:8–22. doi:10.1016/j.tmaid.2017.01.004, PMID: 28163198.
[45] Chang AY, Martins KAO, Encinales L, Reid SP, Acuña M, Encinales C, *et al*. Chikungunya Arthritis Mechanisms in the Americas: A Cross-Sectional Analysis of Chikungunya Arthritis Patients Twenty-Two Months After Infection Demonstrating No Detectable Viral Persistence in Synovial Fluid. Arthritis Rheumatol 2018;70(4):585–593. doi:10.1002/art.40383, PMID:29266856.
[46] Chow A, Her Z, Ong EK, Chen JM, Dimatatac F, Kwek DJ, *et al*. Persistent arthralgia induced by Chikungunya virus infection is associated with interleukin-6 and granulocyte macrophage colony-stimulating factor. J Infect Dis 2011;203(2):149–157. doi:10.1093/infdis/jiq042, PMID:21288813.
[47] Noret M, Herrero L, Rulli N, Rolph M, Smith PN, Li RW, *et al*. Interleukin 6, RANKL, and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. J Infect Dis 2012;206(3):455–457. doi:10.1093/infdis/jis368, PMID:22634878.
[48] Suhrbier A. Rheumatic manifestations of chikungunya: emerging concepts and interventions. Nat Rev Rheumatol 2019;15(10):597–611. doi:10.1038/s41584-019-0276-9, PMID:31481759.
[49] Burt FJ, Rolph MS, Rulli NE, Mahalingam S, Heise MT. Chikungunya: a re-emerging virus. Lancet 2012;379(9816):662–671. doi:10.1016/S0140-6736(11)60281-X, PMID:22100854.
[50] Hoarau JJ, Jaffar Bandjee MC, Krejbich Trotot P, Das T, Li-Pat-Yuen G, Dassa B, *et al*. Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol 2010;184(10):5914–5927. doi:10.4049/jimmunol.0900255, PMID:20404278.
[51] Sissoko D, Malvy D, Ezzedine K, Renault P, Moscetti F, Ledrans M, *et al*. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS Negl Trop Dis 2009;3(3):e389. doi:10.1371/journal.pntd.0000389, PMID:19274071.
[52] Chopra A, Anuradha V, Ghorpade R, Saluja M. Acute Chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. Epidemiol Infect 2012;140(5):842–850. doi:10.1017/S0950268811001300, PMID:21767452.
[53] Schilte C, Staikowsky F, Couderc T, Madec Y, Carpentier F, Kassab S, *et al*. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. PLoS Negl Trop Dis 2013;7(3):e2137. doi:10.1371/journal.pntd.0002137, PMID:23556021.
[54] Warnes CM, Bustos Carrillo FA, Zambrana JV, Lopez Mercado B, Arguello S, Ampié O, *et al*. Longitudinal analysis of post-acute chikungunya-associated arthralgia in children and adults: A prospective cohort study in Managua, Nicaragua (2014-2018). PLoS Negl Trop Dis 2024;18(2):e0011948. doi:10.1371/journal.pntd.0011948, PMID:38416797.
[55] Silva Junior GBD, Pinto JR, Mota RMS, Pires Neto RDJ, Daher EF. Impact of Chronic Kidney Disease on Chikungunya Virus Infection Clinical Manifestations and Outcome: Highlights during an Outbreak in Northeastern Brazil. Am J Trop Med Hyg 2018;99(5):1327–1330. doi:10.4269/ajtmh.18-0531, PMID:30226152.
[56] Soumahoro MK, Boelle PY, Gaüzere BA, Atsou K, Pelat C, Lambert B, *et al*. The Chikungunya epidemic on La Réunion Island in 2005-2006: a cost-of-illness study. PLoS Negl Trop Dis 2011;5(6):e1197.

doi:10.1371/journal.pntd.0001197, PMID:21695162.
[57] Freitas ARR, Alarcón-Elbal PM, Paulino-Ramírez R, Donalisio MR. Excess mortality profile during the Asian genotype chikungunya epidemic in the Dominican Republic, 2014. Trans R Soc Trop Med Hyg 2018;112(10):443–449. doi:10.1093/trstmh/try072, PMID:30085307.
[58] Jaffar-Bandjee MC, Ramful D, Gauzere BA, Hoarau JJ, Krejbich-Trotot P, Robin S, *et al*. Emergence and clinical insights into the pathology of Chikungunya virus infection. Expert Rev Anti Infect Ther 2010;8(9):987–996. doi:10.1586/eri.10.92, PMID:20818943.
[59] Cerqueira-Silva T, Pescarini JM, Cardim LL, Leyrat C, Whitaker H, Antunes de Brito CA, *et al*. Risk of death following chikungunya virus disease in the 100 Million Brazilian Cohort, 2015-18: a matched cohort study and self-controlled case series. Lancet Infect Dis 2024;24(5):504–513. doi:10.1016/S1473-3099(23)00739-9, PMID:38342106.
[60] Robillard PY, Boumahni B, Gérardin P, Michault A, Fourmaintraux A, Schuffenecker I, *et al*. [Vertical maternal fetal transmission of the chikungunya virus. Ten cases among 84 pregnant women]. Presse Med 2006;35(5 Pt 1):785–788. doi:10.1016/s0755-4982(06)74690-5, PMID:16710146.
[61] Sagay AS, Hsieh SC, Dai YC, Chang CA, Ogwuche J, Ige OO, *et al*. Chikungunya virus antepartum transmission and abnormal infant outcomes in a cohort of pregnant women in Nigeria. Int J Infect Dis 2024;139:92–100. doi:10.1016/j.ijid.2023.11.036, PMID:38056689.
[62] Ramful D, Carbonnier M, Pasquet M, Bouhmani B, Ghazouani J, Noormahomed T, *et al*. Mother-to-child transmission of Chikungunya virus infection. Pediatr Infect Dis J 2007;26(9):811–815. doi:10.1097/INF.0b013e3180616d4f, PMID:17721376.
[63] Tan CH, Wong PJ, Li MI, Yang H, Ng LC, O'Neill SL. wMel limits zika and chikungunya virus infection in a Singapore Wolbachia-introgressed Ae. aegypti strain, wMel-Sg. PLoS Negl Trop Dis 2017;11(5):e0005496. doi:10.1371/journal.pntd.0005496, PMID:28542240.
[64] World Health Organization. WHO guidelines for clinical management of arboviral diseases: dengue, chikungunya, Zika and yellow fever. Geneva: World Health Organization; 2025.
[65] Chopra A, Venugopalan A. Chikungunya and other viral arthritis. Best Pract Res Clin Rheumatol 2025;39(2):102068. doi:10.1016/j.berh.2025.102068, PMID:40360316.
[66] Selvam S, Youron P, Singh H, Shree R, Suri V, Goyal M, *et al*. A case series of post-infectious chikungunya myeloradiculoneuropathy. J Neurol Sci 2024;459:122955. doi:10.1016/j.jns.2024.122955, PMID:38593523.
[67] Chopra A, Anuradha V, Lagoo-Joshi V, Kunjir V, Salvi S, Saluja M. Chikungunya virus aches and pains: an emerging challenge. Arthritis Rheum 2008;58(9):2921–2922. doi:10.1002/art.23753, PMID:18759351.
[68] National Health Commission of the People's Republic of China. Diagnosis and Treatment Protocol for Chikungunya Fever (2025 Edition) (in Chinese). Beijing: National Health Commission of the People's Republic of China; 2025.
[69] Iacobucci G. UK pauses chikungunya vaccine (IXCHIQ) in over 65s to conduct safety review. BMJ 2025;389:r1277. doi:10.1136/bmj.r1277, PMID:40537215.
[70] Richardson JS, Anderson DM, Mendy J, Tindale LC, Muhammad S, Loreth T, *et al*. Chikungunya virus virus-like particle vaccine safety and immunogenicity in adolescents and adults in the USA: a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2025;405(10487):1343–1352. doi:10.1016/S0140-6736(25)00345-9, PMID:40158526.