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Chikungunya Infection: a Global Public Health Menace

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Abstract Chikungunya virus (CHIKV) has been involved in epidemics in African and Asian subcontinents and, of late, has transcended to affect the Americas. *Aedes aegypti* and *Aedes albopictus* are the major vectors for CHIKV infection, which results in dissemination of virus to various vital organs. Entry of virus into these tissues causes infiltration of innate immune cells, monocytes, macrophages, neutrophils, natural killer cells, and adaptive immune cells. Macrophages bearing the replicating virus, in turn, secrete pro-inflammatory cytokines IL-1β, TNF-α, and IL-17. Together, this pro-inflammatory milieu induces osteoclastogenesis, bone loss, and erosion. CHIKV is characterized by fever, headache, myalgia, rash, and symmetric polyarthritis, which is generally self-limiting. In a subset of cases, however, musculoskeletal symptoms may persist for up to 3–5 years. Viral culture and isolation from blood cells of infected patients are the gold standards for diagnosis of CHIKV. In routine practice, however, assays for anti-CHIKV IgM antibodies are used for diagnosis, as elevated levels in blood of infected patients are noted from 10 days following infection for up to 3–6 months. Early diagnosis of CHIKV is possible by nucleic acid detection techniques. Treatment of acute CHIKV is mainly symptomatic, with analgesics, non-steroidal anti-inflammatory agents (NSAIDs), and low-dose steroids. No vaccines or anti-viral medicines have been approved for clinical therapy in CHIKV as yet. Hydroxychloroquine and methotrexate have been used in chronic CHIKV infection with variable success.

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Introduction

Chikungunya virus, belonging to the family *Togaviridae* and genus *Alphavirus*, is an arthritogenic virus, first isolated in the southern province of Tanzania in 1952–1953 [1]. Initial infectious outbreaks were locally confined and were of low intensity. Ever since its re-emergence in 2000 after a hiatus of 39 years, the virus has evolved into a major public health concern globally. It has transcended international geographic boundaries with frequent epidemics, affecting millions of people mainly in countries within African and Asian subcontinents and Reunion islands in the Indian Ocean [2]. The first local cases of Chikungunya infection (CHIKV) in the Americas were reported in 2013 [3•]. Since then, it has spread swiftly across the continent, affecting about one million people in Latin America, and cases are being reported from 36 states in the USA [4]. CHIKV is characterized by fever, headache, myalgia, rash, and polyarthritis. Generally, these episodes are self-limiting and resolve within a few weeks. However, in 10–60% of cases, musculoskeletal symptoms may persist for up to 3–5 years [5••, 6]. This wide variation may be because of geographical diversity, lack of uniform methodology in detection, and incomplete and heterogeneous follow-up period in published reports. A recent meta-analysis of 18 studies, involving 5702 patients around the world, has described the pooled prevalence of CHIKV which related all chronic inflammatory rheumatism and chronic arthritis to be 40.22 and 14%, respectively [7].

Over the past decade, there has been profound interest in understanding the etio-pathogenesis and management strategies for chronic CHIKV across the globe. This review aims at

emphasizing the epidemiology, pathogenesis, clinical features, and management aspects of CHIKV, focusing on rheumatic symptoms.

Epidemiology

Global Scene

CHIKV is currently geographically distributed in over 60 countries, remaining endemic in Africa, India, and several Southeast Asian countries as well as Latin America (Fig. 1). Four lineages, distinguished by genotypic and antigenic characteristics, have been identified: The West African lineage, the Asian lineage, the East, Central, and South African (ECSA) lineage, and the Indian Ocean (IO) lineage, a monophyletic descendant from the ECSA [8, 9]. Sporadic and intermittent outbreaks of CHIKV are being reported from Asia, Africa, and Reunion islands in the Indian Ocean following the initial isolation 40 years ago. Global attention to this pathogen came later in 2005 following a large epidemic in the coast of Kenya. Massive sequential outbreaks by the IO CHIKV lineage ravaged the islands of the southwest Indian Ocean and the Indian subcontinent in 2005–2006, affecting millions [10•, 11]. The precise reason for resurgence after a long hiatus is still an enigma. Mutated CHIKV genome, adaptations by the vector, reduced herd immunity, and frequent travel are the speculated explanations. Cases attributed to travel were reported for the first time in various parts of Europe, Americas, Canada, and Australia [12]. Indigenous cases were also reported from Italy (2007), France (2010), and the Caribbean islands (2013) [13–15].

Vectors

The highly anthropophilic *Aedes aegypti*, a vector closely associated with humans and widely prevalent in the tropical and subtropical nations, has been the primary vector in CHIKV transmission [16]. After the 2006 outbreak, the Asian tiger mosquito "*Aedes albopictus"* surfaced as a major vector, responsible for perpetuating the epidemic in regions lacking the typical vector [17]. This species, widely distributed in the western hemisphere, can adapt to different climatic conditions and colonize new geographical locations, making it a competent vector for efficient viral transmission [18]. During the Indian Ocean epidemic, a mutation found in the E1 protein of CHIKV (A226V) permitted enhanced vector specificity, virus uptake, replication, and transmission by *Ae. albopictus* [19]. Few other *Aedes* species, *Culex*, and *Anopheles stephensi* have also been reported to transmit CHIKV [20, 21].

Reservoirs and Modes of Transmission

During the inter-epidemic period, monkeys, rodents, and birds serve as reservoir hosts for the virus. Humans replace them as the hosts during epidemics. Periodicity has been noted with occurrence of disease in the community, which probably may be due to the oscillations in monkey herd immunity [22]. The established modes of CHIKV transmission include enzootic, urban, nosocomial, and vertical transmissions. Transmission

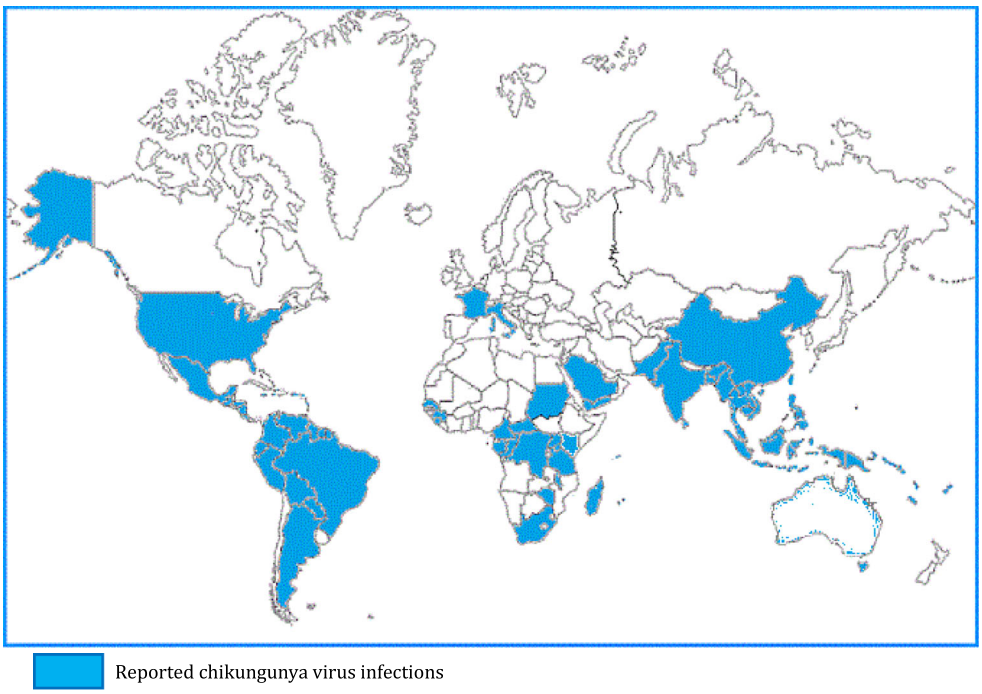

Fig. 1 Geographical distribution of reported Chikungunya cases (source: CDC website as of April 22, 2016)

by needle-stick injury, blood donations, and corneal grafts has been reported [23–25]. Vertical transmissions in an estimated 48.7% of population were described during the epidemic in Reunion islands [26].

Pathogenesis

Evidence From Animal Studies

Mice and primate models have been used for studying CHIKV. Symptoms in primates following CHIKV resemble human infection. Genetic background, age, route, and site of CHIKV transmission significantly affect clinical presentation, development of musculoskeletal involvement, and immune profile in animal models of CHIKV [27]. Clinical presentations in animals depend on the initial viral load [28]. CHIKV infection results in dissemination of virus to various vital organs like liver, spleen, lymph nodes, skin, muscles, bones, and central nervous system [29, 30]. Entry of virus into these tissues causes infiltration of innate immune cells-monocytes, macrophages, neutrophils, natural killer cells, and adaptive immune cells of CD4 as well as CD8 T cell lineage [28, 30]. The virus survives and replicates for longer periods in these targeted organs and in macrophages of infected animals, even when the viral load is low in blood. Infiltration of immune cells results in pathological musculoskeletal features such as inflammatory arthritis, chronic active tenosynovitis, and myositis during acute CHIKV infection [31•]. In a recent study, Goupil et al. used histological and micro-computed tomography techniques to view the clinical progression of musculoskeletal changes in C57BL/6J mice infected with CHIK virus. Necrosis of skeletal muscles, extensive peri-osteitis, lymphoplasmacytic infiltration of synovium, and cartilage necrosis in joints were observed 21 days following infection [32].

Role of Type I Interferon

Cells infected with CHIKV induce secretion of interferon (IFN) α/β. IFN α/β produced in local infected sites by non-hematopoietic cells controls dissemination of virus to other organs [33]. Macrophages act as hosts for CHIK virus survival and also mediate inflammation in joints [27].

Mediators of Inflammation—Chemokines and Cytokines (Table 1)

Increased production of pro-inflammatory cytokines by infiltrating myeloid cells has been shown in CHIKV. Tumor necrosis factor (TNF), IFN-α, IL-6, IFN-γ, and monocyte chemoattractant protein-1 (MCP-1) were major cytokines and chemokines secreted by macrophages [29, 34•, 35]. A cytokine secretion pattern observed a trend towards Th1-type response in mouse models [36].

Role of Immune Cells in Pathogenesis

Neutrophils which are recruited at the site of infection exceed any other immune cells in the joints [36]. Natural killer (NK) cells play an important role in the acute phase of infection through its cytotoxic activity by secreting IFNγ and granzyme B [27, 36]. The role of T cells in pathogenesis of CHIKV infection is evident in RAG2−/−, CD4−/−, and CD8−/− mouse models. CHIKV-infected RAG2−/− mice harbor persistent viral load in blood, and no inflammation was observed in joints. A similar observation was noted in CD4−/− but not in CD8−/− mice [37]. B cells have been shown to enhance natural antibody response to CHIKV and control viral load in circulation [38]. The anti-CHIKV IgM antibody was detected in plasma before IgG and peaked between 4 and 6 weeks post infection. After 6 weeks, IgM levels decreased, whereas IgG (exclusively of IgG3 isotype) levels increased gradually. Kam et al demonstrated delayed mounting of IgG3 response in some patients with low viral load during the active phase. These patients complained of persistent arthralgia in the chronic phase of disease [39].

Innate and Adaptive Immunity in CHIKV

Innate immune cells, including plasmacytoid dendritic cells and NK cells, exhibit robust activation from day 1 of infection, and adaptive cells subsequently contribute to immune responses in circulation for elimination of virus [40••]. Terminally differentiated NK cells expressing high levels of NKG2C and CD57 have been described in circulation of CHIKV-affected individuals. This increased level of NKG2C+ CD57+ NK cells was transient and mostly confined to the early phase of infection. However, in some convalescent patients, the NK cells were increased more than 30 days after infection; eventually on follow-up, these patients developed chronic arthralgia [41].

CHIKV Arthritis Resembles Rheumatoid Arthritis

CHIKV-infected human osteoblasts show increased expression of IL-6 and RANKL and decreased expression of osteoprotegerin (OPG), a decoy receptor for RANKL [42]. Altered RANKL/OPG ratio levels in synovium lead to enhanced osteoclastogenesis [43•]. These changes are similar to the pathogenesis of rheumatoid arthritis. CHIK viruses persist in synovial fibroblasts and osteoblasts of infected individuals. Upon induction, fibroblasts produce IL-6 and MCP-1. Monocytes or macrophages are recruited to the site of infection. Virus replicates in macrophages, which in turn secrete pro-inflammatory cytokines IL-1β, TNF-α, and IL-17. These pro-inflammatory cytokines and RANKL induce osteoclastogenesis, bone loss, and erosions in chronically infected individuals [44].

Table 1 Cytokines, growth factors, and chemokines during acute phase (within 10 days) and chronic phase (between 3 and 12 months)—their association with Ab titer

Cytokine	Acute	Chronic	High titer	Persistence of symptoms
IL-1α				Elevated levels
IL-1β	Elevated levels	Highly elevated levels		Elevated levels
IL-1R	Elevated levels			
IL-1RA	Highly elevated levels	Elevated levels		Elevated levels
IL-2	Elevated levels			
IL-2R	Elevated levels	Elevated levels		
IL-4	Elevated levels			
IL-5	Elevated levels	Highly elevated levels		
IL-6	Highly elevated levels	Elevated levels	Elevated levels	Elevated levels
IL-7	Highly elevated levels	Elevated levels		
IL-10	Elevated levels	Highly elevated levels	Decreased levels	Decreased levels
Il-15	Highly elevated levels	Elevated levels		Elevated levels
IL-12	Highly elevated levels	Elevated levels		
IL-17	Elevated levels	Highly elevated levels		
GM-CSF	Highly elevated levels	Elevated levels		Elevated levels
IFN-α	Highly elevated levels	Elevated levels		
IFN-γ	Elevated levels	Highly elevated levels		
TNF-α	Elevated levels	Highly elevated levels		
FGF-basic	Highly elevated levels	Elevated levels		
HGF	Highly elevated levels	Elevated levels		Decreased levels
SDF-1α	Elevated levels			
VEGF	Elevated levels			
PDGF-ββ	Elevated levels			
Chemokines	Acute	Chronic (3–12)	High titer	Persistence of symptoms
IL-8/CXCL8	Highly elevated levels	Elevated levels		
MCP-1/ CCL2	Highly elevated levels	Elevated levels		Elevated levels
RANTES/CCL5	Highly elevated levels	Highly elevated levels		
MIG/CXCL9	Highly elevated levels	Elevated levels	Elevated levels	Elevated levels
IP-10/CXCL10	Highly elevated levels	Elevated levels	Elevated levels	Elevated levels
MIP-1α/CCL3	Highly elevated levels	Highly elevated levels		Elevated levels
MIP-1β/CCL4	Highly elevated levels	Elevated levels		Elevated levels
Eotaxin	Highly elevated levels	Elevated levels		Decreased levels

References: Schilte et al., Kelvin et al., Chow et al., Chaaithanya et al., Wauquier et al., Venugoplan et al., Ng et al., Chirathaworn et al.

Clinical Features

CHIKV can affect any age group of either sex. The incubation period varies between 3 to 7 days (range 1 to 12 days) [45, 46]. Acute chikungunya fever presents most commonly as fever (92%), arthralgia (87%), backache (67%), and headache (62%). Other less common clinical manifestations include skin manifestations like rash, oral ulcer, hyperpigmentation, and exfoliative dermatitis. Rarely, photophobia, retro-orbital pain, vomiting, diarrhea, and meningo-encephalitic features are seen, especially in the pediatric age group [4]. Fever, lasting for 3–5 days is low to high grade and can be associated with chills and rigors. Polyarthralgia begins 2 to 5 days after the onset of fever and can involve multiple joints. Arthralgia is symmetrical in most of the cases, predominantly involving distal joints, which include hands (50 to 76%), wrists (29 to 81%), and ankles (41 to 68%) [7, 47]. Skin manifestations can be seen among 40–75% of patients. Most often, maculopapular rash is seen, predominantly affecting the limbs and the trunk, but can involve face as well [48]. Physical examination can reveal peri-articular edema or swelling, which is seen in 32–95% of cases. Apart from this, lymphadenopathy (9–41%) and conjunctivitis have also been reported [49•, 50].

Data on the effect of CHIKV on pregnancy outcomes and its effect on infants born to infected mothers is scarce. Torres et al. reviewed pregnancy outcomes during the 2014–15

epidemic in Latin America. Vertical transmission was observed in 27.7 to 48.29% of patients. Case fatality rate was 5.3%. Commonest symptoms included fever, irritability, meningoencephalitis, rash and bullous dermatitis. Serious complications including myocarditis, seizures and acute respiratory failure were documented [51•].

In general, CHIKV has a good prognosis and resolves without any sequelae. However, in a certain group of patients it causes chronic rheumatologic manifestations. Some of the risk factors for developing chronic infection, based on retrospective and small prospective studies, include female gender, older age, co-morbid conditions, and severity of symptoms at onset of infection [5••, 52]. Gerardin et al. have noted the presence of two or more co-morbidities like hypertension, diabetes, osteoarthritis and dyslipidemia to be associated with higher chances of developing chronic infection [53]. Various rheumatic manifestations including polyarthralgia or arthritis, multiple tendonitis, tenosynovitis, enthesopathies, carpal tunnel syndrome, classical rheumatoid arthritis like course, cryoglobulinemia, and psoriatic arthritis have all been observed as post-infectious sequelae [5••, 6, 54–56]. Polyarthralgias or arthritis frequently involves fingers, wrists, knees, ankles, and toes. Rarely, elbows, shoulders, neck, sacroiliacs, and hip joints are also affected [5••, 52, 53]. Studies have indicated the close association of CHIKV with autoimmunity in susceptible individuals [57, 58]. The clinical manifestations of CHIKV may resemble those of other rheumatologic diseases like RA, seronegative inflammatory arthropathies, and systemic lupus erythematosus [59, 60]. In a study from India, 36% of patients with persistent arthralgia 10 months following CHIKV infection met the American College of Rheumatology (ACR) classification for rheumatoid arthritis [58]. CHIKV has been documented to be a precipitating event for development of RA in many studies [6, 55, 59, 61]. These studies have also documented presence of rheumatoid factor (RF) and anti-citrullinated protein (CCP) antibodies, joint space narrowing, effusions and bone erosions.

The frequency of chronic rheumatic symptoms during the post-CHIKV infection period varied in different studies. In a 10-month prospective study from India on 203 CHIKV-infected patients, it was found that 46% experienced persistent joint pain after acute infection [59]. Schilte et al. described 69% patients in their cohort developing persistent arthralgia, 90% reporting symmetric joint involvement, 63% complaining of associated local joint swelling, and 39% suffering from chronic myalgia [5••].

Diagnosis

Currently available tests for diagnosis of CHIKV include viral culture, detection of viral antigen, viral nucleic acid and anti-CHIKV IgM and IgG antibodies. Viral culture and isolation from blood cells of infected patients is the gold standard technique. However, this technique is cumbersome and usually done only in advanced centers, with biosafety level (BSL) 3. Anti-CHIKV IgMs are elevated in the blood of infected patients after 10 days of infection and remain elevated for 3–6 months [62]. Anti-CHIKV IgG is detectable only after 2 weeks of infection and remains elevated for 6 months. Capture ELISA and immune-chromatographic tests are two common techniques for estimation of CHIKV titers in blood. Early diagnosis of CHIKV is possible by nucleic acid detection techniques such as reverse transcription polymerase chain reaction (RT-PCR) and real-time loop-mediated isothermal amplification (RT-LAMP) methods [63]. In low resource centers the difficulties in using RT-PCR can be overcome by RT-LAMP, which does not require a PCR instrument as the assay is carried out in a water bath [64].

Role of Biomarkers

Few studies have reported the role of cytokines and chemokines like IL-1β, IL-6, IL18, MIF, RANTES, CXCL9, CCL2, and CXCL10 [65, 66]. Because of the heterogeneity of these biomarkers in different populations and lack of validation, these tests have not been used in regular clinical practice.

Management of CHIKV

Treatment of acute CHIKV is mainly symptomatic, with analgesics, antipyretics and non-steroidal anti-inflammatory agents (NSAIDs). So far, no vaccines or anti-viral medicines have been approved for clinical therapy in CHIKV.

Chloroquine phosphate (CQ) has long been reported to be effective in the treatment of chronic CHIKV arthritis [67]. In a community intervention trial of chloroquine in 509 CHIKV-infected patients during the 2006 CHIK epidemic in India, 70 patients with early persistent musculoskeletal pain and arthritis were randomized into a 24-week, two-arm, parallel efficacy trial of CQ (250 mg/day) ($n = 38$) and meloxicam (7.5 mg/day) ($n = 32$). There was no significant efficacy difference between the meloxicam and CQ groups. Though the patients reported good improvement in symptoms, it did not reach statistical significance [68]. In a very recent randomized controlled trial on 72 patients with persistent post-CHIKV arthritis (>1 year after infection), the efficacy of a combination of disease-modifying anti-rheumatic drugs (DMARD), namely, methotrexate, sulfasalazine, and hydroxychloroquine (HCQ), was compared with HCQ monotherapy. Both groups received oral steroids for 6 weeks. Combination DMARDs was found to be superior to HCQ monotherapy [69•]. Ganu et al. studied 16 patients with persistent arthritis in spite of treatment with NSAIDs and HCQ for 3 months and observed good response in 71.4 and 12.5% among those treated with sulfasalazine with and without methotrexate, respectively [70].

Ravichandran et al. reported the efficacy of ribavirin 200 mg twice daily for 1 week in 10 patients with chronic CHIKV, as compared to placebo. All patients in both the groups reported reduction of pain. Reduction in swelling was reported by 8 and 6 out of 10 in the antiviral and placebo groups, respectively [71]. Rulli et al. have reported the efficacy of bindarit, an inhibitor of MCP-1 in the treatment of chronic CHIKV [34•]. Inhibitors targeting the mannose-binding lectin (MBL) pathway of the complement system may also be useful in the treatment of alphavirus-induced arthritis/myositis [72]. Experiments reported an autophagy-inducing peptide, beclin, to be effective against CHIKV in cell culture and in mice [73].

The French Infectious Disease Society has come up with recommendations to aid clinicians in diagnosis, assessment, and management of acute, post-acute, and chronic patients. Analgesics, NSAIDs, and low-dose steroids have been mentioned as initial therapeutic options for post-acute and chronic CHIKV infections. Methotrexate can be considered for chronic patients (3 months post-infection) not responding to the initial therapy [74•].

In the authors' experience, a short course of low-dose steroid (<0.5 mg/kg per day of deflazacort) with rapid weekly tapering and withdrawal by 4 to 6 weeks is effective and safe for acute CHIKV infection (unpublished data). Steroids need to be started at least a week after NSAID intake once the acute viremic period is over. Hydroxychloroquine probably does not have much effect in the acute phase, as it takes few weeks to act; by then, the arthritis tends to settle in majority. However, all DMARDs have COX-2-inhibiting actions and hence, may act like NSAIDs initially, thus giving relief before the arthritis self-limits.

Experimental Drugs

Wang et al. looked at the potential of anti-CHIKV drugs in vitro through a high-throughput screening system based on the CHIKV 26S-mediated insect cell fusion inhibition assay. Four compounds were identified, of which niclosamide and nitazoxanide were found to inhibit CHIK virus entry and transmission. This may prove to be a future target for therapy [75]. Suramin, a competitive inhibitor of glycosaminoglycans and heparin, has been shown to have anti-CHIKV action [76, 77]. Kuo et al. demonstrated the efficacy of suramin in reducing viral loads substantially, mitigating acute foot lesions and restoring cartilage integrity in a C57BL/6 mouse model infected with CHIK virus [78]. These results need to be replicated in clinical trials. Intranasal use of a single dose of mDEF201 (adenovirus-vectored IFN-α) prophylactically administered 21 days to 24 h prior to infection significantly reduced synovitis in an experimental mouse model for CHIKV arthritis [79].

Control of Infection

Emphasis should be on early detection of suspected human cases and improved environmental control measures against the vectors. The primary target would be to curtail the urban viral transmission by avoiding mosquito bites. Infection control can be emphasized at two levels—individual and community.

Individual Level

The adult female mosquito bites during daytime. Physical protection measures including full-sleeved clothing, application of mosquito repellent over the exposed body parts, use of permethrin-treated clothing, insecticide-treated bednets, and wire mesh/nets on doors and windows should be encouraged. The Center for Disease Control and Prevention (CDC) and the World Health Organization (WHO) suggest use of 30–50% *N*,*N*-diethyl-m-toluamide (DEET), picaridin, IR3535, and oil of lemon eucalyptus or para-menthane-diol as repellents providing long-lasting protection [80, 81]

Community Level

The foremost step would be to target the mosquito breeding grounds. Extensive regional awareness and effective national control programs should be employed. *Aedes* mosquito breeds in stored/stagnant fresh water in domestic settings such as flower vases and water storage containers, and in peridomestic areas such as construction sites, coconut shells, unused abandoned tires, plastic, and metal cans. Such breeding sites must be destroyed and treated with insecticide [80]. Vector control can be done through anti-adult and anti-larval control of mosquitoes. The WHO recommends applying appropriate products in intervals that are shorter than the incubation period of pathogen in the vector and in accordance with the generation cycle of vector. Adult mosquitoes can be controlled by the use of chemical insecticides (pyrethrum extract, malathion) for indoor spray, ultra low volume spray, and thermal fogging [82]. However, larval control has been found to be more economical and provides sustainable control by eliminating the source of newly emergent adult mosquitoes [83].

Challenges for Future

The rapid spread of CHIKV involving virgin territories over the last few years has earned renewed interest in the pathogenesis, preventive, and surveillance strategies for this arthritogenic virus. Gaps in the understanding of viral replication and processes contributing to chronic arthritis still exist, which hinder optimal drug discovery. Vaccines are still in the infancy stage and need to be tested in clinical trials to prove their efficacy. Patient surveillance and vector control methods

need significant improvement. Consensus on uniform case definitions and evidence-based clinical management guidelines continue to be unmet needs in this area. A global virus network task force on CHIKV was constituted in 2014, outlining clear future plans [84].

Conclusion

CHIKV continues to be a global public health, clinical, and economic challenge. The rheumatologic injury following CHKV seems more often to be immune mediated than direct viral injury. A short course of steroid following the acute viremic phase should suffice to treat the acute complications. Though DMARDs have been tried for this mostly self-limiting disease, use of these agents should be restricted to cases with a more chronic course. Better insight into the factors attributing to chronic complications is warranted for attaining optimal solution to this menace.

Compliance with Ethical Standards

Conflict of Interest Drs. Mathew, Ganapati, Jayakanthan, Nair, Gupta, Chebbi, Mandal, and Danda declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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