

Chikungunya virus: Outbreaks in SEARO, Transmission, Pathogenesis, Clinical syndrome, Diagnosis and prevention review

Abstract

Chikungunya virus is an alphavirus of the Togaviridae family, positive-strand RNA genome, which was first recorded in Tanzania in 1952 and since then Chikungunya has been reported in Burma, Bangladesh, Thailand, Cambodia, Vietnam, India, Sri Lanka, Indonesia, West Africa and the Philippines. In recent decay, Chikungunya is serious global public health concern. Chikungunya predominantly transmitted by bites of mosquitoes of the Aedes genus (Aedes aegypti and Aedes albopictus) the same mosquito that transmits Dengue fever, only female mosquitoes are infective, because they require blood meal for the formation of the egg. Vertical transmission occurs between mother and fetus. The infected Chikungunya mosquitoes can be found for biting throughout daylight hours specially early morning and late afternoon. The Chikungunya viral disease occurs in victim of all ages in both sexes. Following a bite by an infected mosquito, the disease manifests itself after an average incubation period of 2-4 days (range: 3-12 days), predominant clinical features include, High fever, joint pain, rash, myalgia etc. Serum specimen is collected within 5 day for the Reverse Transcriptase- Polymerase Chain Reaction (RT –PCR) to detect the viral RNA and Anti-Chikungunya antibody (IgM and IgG) is detected by ELISA/ICT after 1st week of infection. Specific treatment and recognize vaccine are not available for Chikungunya, but symptomatic treatments are available like paracetamol and pain killer for high fever and local pain. Eliminate the mosquito habitats is the best way to prevention and control of Chikungunya infection.

Keywords:- Outbreaks, Pathogenesis, Transmission, Clinical syndrome, Diagnosis.

Introduction

The word Chikungunya is derived from Makonde word (Bantu language) meaning of this word “ The one which bends up” referring to the posture that the affected patient acquires as a result of the pain to the joints [1]. Chikungunya virus is an alphavirus of Togaviridae family which is small, spherical, enveloped, positive-strand RNA genome, about 60-70 nanometer diameter capsid, phospholipids and also virus is sensitive to temperatures above 58° Celsius and also to desiccation [2,3,4,5]. Genome of Chikungunya virus is about 12 kb long and is capped in 5' and has a poly-A tail in the 3' end. The genome structure contain two open reading frames (ORFs) that encodes for two polyproteins (non-structural polyprotein and structural polyprotein), which can be cleaved respectively into four non-structural proteins (nsP1, nsP2, nsP3, nsP4) and five structural proteins (C, E3, E2, 6K, E1) by viral and cellular proteases [6].

Chikungunya fever is predominantly transmitted by bites of mosquitoes of the Aedes genus (Aedes aegypti and Aedes albopictus) the same mosquito that transmits Dengue Fever. Only female mosquitoes are infective, because they require blood meal for the formation of the egg. Aedes aegypti breeds in stored fresh water in urban and semi-urban environments [7]. In 1952, Chikungunya fever was first reported in Makonde plateaus, along the borders between Tanzania and Mozambique [8]. Chikungunya virus was first isolated from the serum of a febrile human during an epidemic outbreak

48 by Ross in Newala district of Tanzania in 1953, [9]. Since then, Chikungunya virus has [9] become a
 49 more global concern by the Scientific Leadership Group [10]. Probably Chikungunya virus was
 50 originated in Africa [11,12].where Chikungunya virus maintained in 'sylvatic cycle' involving wild
 51 primates and forest dwelling mosquitoes [13]. After that this virus spread to Asia, Europe, America,
 52 and other part of the world.

53 In Asia, Chikungunya virus was introduced subsequently where it has been transmitted from human to
 54 human mainly by Aedes aegypti and, to a lesser extent by Aedes albopictus through an urban and
 55 semi-urban transmission cycle [12,13]. Since then Chikungunya has been reported in Burma,
 56 Thailand, Cambodia, Vietnam, India, Sri Lanka, Indonesia, West Africa and the Philippines [14].

57

58 **Table 1: Outbreaks of Chikungunya virus in south East Asia region**

59

Name of country	Outbreaks history of Chikungunya
India	In India, first Chikungunya outbreak occurred in Kolkata in 1963, since then a number of other Chikungunya outbreaks occur in Maharashtra, Andhra Pradesh, Tamil Nadu, and Barsi from 1964 to 1973. Chikungunya virus re-emerged in 2006 and badly spread in 13 Indian states [7] including Gujarat, Kerala, Tamil Nadu, Andhra Pradesh, Madhya Pradesh, Maharashtra, and Karnataka. In kerala 2008, one lac people were re-infected with CHIKV. After that subsequent year, other several large outbreaks occurred in many state of india includes Maharashtra, Andaman and Nicobar Islands, West Bengal, Orissa, Rajasthan, and Puducherry [15]. In 2010, the National Capital Region of India was the seroprevalence rate 9.91% [16]. In 2016, Mumbai reported 12.5% seroprevalence rate [17].
Bangladesh	In Bangladesh 2008, First chikungunya 39 cases were reported in northern area of Bangladesh (Rajshahi and Chapainawabganj districts). Chikungunya fever first outbreak investigated by IEDCR and ICDDR,B. In late October 2011, an outbreak of fever with prolonged joint pain was investigated in Dohar of Dhaka District, where house-to-house surveys were carried out to identify suspected cases. About 29% of the village residents experienced symptoms consistent with Chikungunya fever during the three months of the outbreak [18]. In 2014, six confirmed cases of CHIKV were reported. Dhaka, the capital city of Bangladesh, where massive Chikungunya outbreak occurs in 2017. There are so far 2,314 cases have been reported in different hospitals and clinics of Dhaka from May to September 2017 and also kabir et al reported more than 18 million people were affected in the capital city of Bangladesh up to September 2017 [19].
Thailand	In 1960s, Chiungunya suspected 46 000 cases were reported. In 2008, 244 people had confirmed CHIKV. In 1962, approximately 31% of the populations were infected in Bangkok outbreak. Severe outbreak occur in 2013 that reported by Bueng Kan[20].
Indonesia	In Indonesia 972, Chiungunya virus was reported in East Sumatera, Kalimantan, Bali, Java, Sulawesi, and Flores. Since then Chiungunya virus sporadically occur in Indonesia. During the time period 2002 to 2008, CHIKV was confirmed in West Java and Bandung. The annual bio-burden has never exceeded 5000 cases. The overall incidence [20] rate was found to be 10.1 cases per 1000 persons per year.
Burma	In Burma, A high prevalence of CHIKV was reported in 1973 in Myanmar, Mandalay Divisions and Kachin, Arakan and Shan States, Sagaing Division, and Rangoon, Magwe, and Tenasserim Divisions. Another study performed in 2010 revealed that in Myanmar about 6% of DENV patients had CHIKV [20].
Maldives	In Maldives First Chiungunya outbreak occurred in late 2006 and 2007 with 12 000 suspected cases of CHIKV. The incidence rate was found to be 82 to 722 people per 1000 population. In 2009, Chikungunya infected confirmed cases was identified in two German travelers who had returned from the Maldives [20].

Sri Lanka	In Sri Lanka, CHIKV re-emerged in Sri Lanka after 40 years. In 2007 chikungunya suspected 37, 000 cases were reported. The surveillance of chikungunya fever in the Sri Lankan population was 89.2% [20]. In Bhutan, Chikungunya infected 78 cases were reported in the 2012 outbreak [20].
Nepal	In Nepal, first chikungunya infection case was reported in 2013. Two cases were identified in March 2013 and one case was identified in June 2013 [21]. Followed by fifteen cases were identified in 2015 [22].

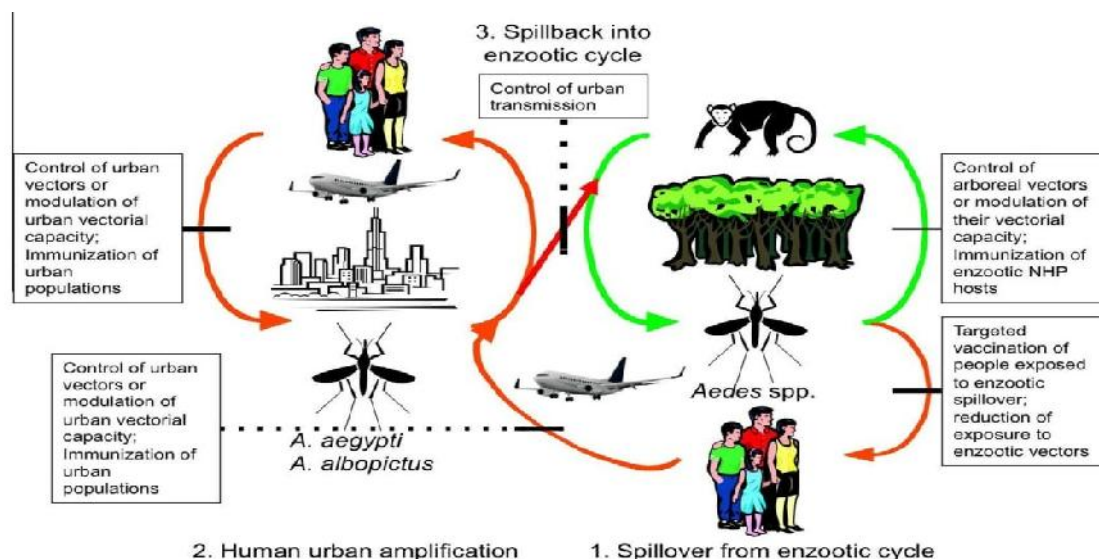
Transmission

In the world three types of Chikungunya viral genotypes are discovered, which has circulated in the different geographical regions, they are named: West African genotype, East Central South African (ECSA) genotype, and Asian genotype. Phylogenetic evidence suggests that the Asian genotype virus derived from the ECSA virus sometime between 1879 and 1927. The Chikungunya virus is transmitted to humans by bite of an infected female *Aedes* mosquito genus, the same mosquito that transmitted dengue. Vertical transmission between mother and fetus has been observed in some cases [23]. Female *Aedes aegypti* and *Aedes albopictus* mosquitoes are the main vectors of Chikungunya in Asia and the Indian Ocean islands (Figure-1) [14].



ECSA lineage, Asian lineage, Indian Ocean Lineage

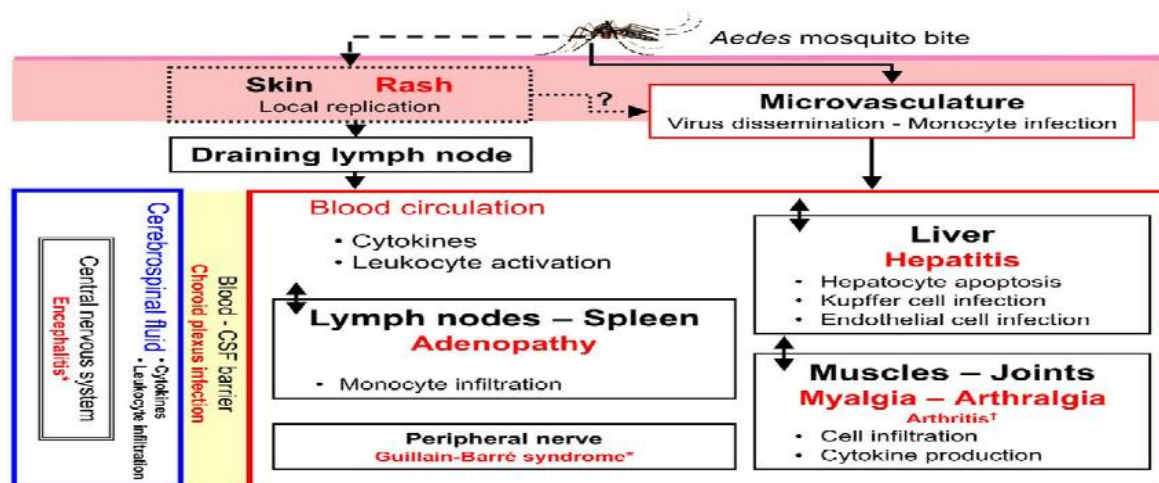
The main causes of chikungunya virus transmission are international travel and global expansion, which enhanced the virus to spread to new regions where environmental conditions are permissive [24]. During epidemic periods humans serve as the reservoir for Chikungunya. Outside these periods, the main reservoirs are (Figure-2) monkeys, rodents, bats and birds [25].



The infected Chikungunya mosquitoes usually bite in daylight specially early morning and late afternoon. Both *Ae. aegypti* and *Ae. albopictus* mosquitoes are found for biting in outdoors, but *Ae. aegypti* are feed readily indoors. *Ae. aegypti* is currently confined within the tropics and subtropics, whereas *Ae. albopictus* is found more readily in temperate/cold temperate regions [26]. Transmission of Chikungunya virus is temperature dependent. In lower temperature (20 °C) displayed decreased virulence of the Chikungunya strain carried by *Ae. aegypti* mosquito [27]. The strain carried by *Ae. albopictus*, does not exhibit the same decreased virulence rather incubated in constant low temperatures. However, it was found that incubated with daily fluctuations in temperature with a mean value of 20 °C, transmission efficiencies and viral loads in *Ae. albopictus* saliva were slightly increased [27]. In recent decades, *Ae. albopictus* has spread from Asia and become established in areas of Africa, Europe and the Americas. The *Ae. albopictus* mosquito thrives in a wider range of water-filled breeding sites than the *aegypti* mosquito, which can include coconut husks, cocoa pods, bamboo stumps, tree holes and rock pools, in addition to artificial containers and vehicle tires. The diversity of possible habitats helps to explain the abundance of *Ae. albopictus* in rural and peri-urban areas [26].

Pathogenesis

Chikungunya virus infected genus *aedes* mosquito usually bite in day time, After bite by a Chikungunya virus infected mosquito, CHIKV spreads rapidly in the body after primary infection. Following Chikungunya virus transmitted and replicates in the skin, and disseminates to the liver, muscle, joints, lymphoid tissue (lymph nodes and spleen) and brain, presumably through the blood (Figure 3) [28].



Chikungunya virus directly enters into the subcutaneous capillaries and some viruses infecting susceptible cells in the skin, such as macrophages or fibroblasts and endothelial cells. Local viral replication seems to be minor and limited in time, with the locally produced virus probably being transported to secondary lymphoid organs close to the site of inoculation. Incubation period of Chikungunya is usually between 2-10 days and mostly affects adult population in comparison to young population [29]. The Chikungunya virus infection resulted in raised concentrations of several proinflammatory cytokines (interferon α , interferon γ , interleukin 6, and others), anti-inflammatory cytokines (interleukin 1 receptor antagonist, interleukin 4, and interleukin 10), and other chemokines such as IP-10 and monocyte chemo-attractant protein 1 [30]. The number of circulating activated and effector T cells is increased in patients with persistent chikungunya-induced arthritis [30] and studies in mice suggest that T cells play a major part in the pathogenesis of chikungunya-induced arthritis [31]. Patients infected with chikungunya develop anti-chikungunya antibody (IgM & IgG) within few days of infection which is measurable in the second week of infection [32]. In addition to T-cell and B-cells, which are involved in pathogenesis of chikungunya virus, multiple other cell types are likely to play a part during infection. Chikungunya virus infects human osteoblasts and causes cytopathic effects [33] which could contribute to the joint pathology and erosive disease. Moreover, large numbers of natural killer cells have been found in the peripheral blood of patients with persistent Chikungunya-induced arthritis than in healthy controls [31]. Most studies have focused on the innate immune response during acute chikungunya virus infection. Why persistent arthritis and chronic symptoms remain that is remains undefined. (Figure-3)^[44]

Clinical presentation

The Chikungunya viral disease occurs in victim of all ages in both sexes. Following a bite by an infected mosquito, the disease manifests itself after an average incubation period of 2-4 days (range: 3-12 days). Chikungunya virus infected patient usually have onset of high fever (39°C), severe arthralgia and myalgia, and an erythematous, maculopapular rash, which can be severe from a mild, localized rash to an extensive rash involving more than 90% of the skin [31]. This symptom occurs after a mean incubation period of 3 days. The rash and fever usually resolve within a few days [34]. Less common symptoms include ocular manifestations such as conjunctivitis; uveitis, episcleritis, and retinitis [35] about 15% of individuals infected with chikungunya virus are asymptomatic. Majority of the chikungunya infected patients suffering from joint pain and swelling with severe morning stiffness, consistent with inflammatory arthritis [31]. In many patients, Chikungunya-related joint pain can persist up to 3 years [36] that's why major impact on society in terms of morbidity and loss of economic productivity [37]. Death rate of chikungunya infection is rare. Neuroinvasion by chikungunya virus, causing seizures, altered mental status, flaccid paralysis, and even death, occurs infrequently [38].

140 **Diagnosis**

141 The patient having onset of fever that lasts 3-5 days along with multiple joint pains that may persist
142 weeks to months [39]. There are different ways for diagnosis the Chikungunya virus; however, since
143 the presentation of Chikungunya virus infection is similar to the Dengue virus infection, the most
144 reliable way to identify the virus is through a blood test [40]. Serum specimen is collected within 5
145 day for the Reverse Transcriptase- Polymerase Chain Reaction (RT –PCR) to detect the viral RNA
146 [41, 42]. High viral counts generally last 4-6 days after the onset of the illness; therefore, the RT- PCR
147 is a useful diagnosis within the first 7 days. Results of the RT- PCR generally take 1 – 2 days, which
148 is also very efficient for diagnosis [42]. The PCR is both very specific and sensitive for the
149 Chikungunya virus [43]. Enzyme-Linked Immunosorbent Assays (ELISA) may detect both anti-
150 Chikungunya virus Immunoglobulin IgM and IgG antibodies from either the acute or the
151 convalescent-phase samples [42]. Serum specimen is collected at the end of first week for ELISA test;
152 because few times require for antibodies production, Serum IgG and IgM are the most for several
153 widely used diagnostic (ICT) tests for chikungunya, as they are the most economical and the easiest to
154 perform on a patient [43]. The IgM antibody levels are highest 3 to 5 weeks after the onset of illness
155 [41]. The Hemagglutination-Inhibition (HI) assay may also be utilized in the detection of a
156 Chikungunya infection [42]. The HI assay determines the level of antibodies to the virus present in
157 serum samples [43]. When a Chikungunya viral infection is present, there is a four-fold HI antibody
158 difference in the serum sample, which turns positive within 5 to 8 days after infection [41].

159 **Prevention & Control**

161 Recognize vaccines are not available for prevention of Chikungunya infection. Vector control
162 is effective preventive measures against mosquito bites. Vector control can be done by use of
163 different insecticide (DDT) during monsoon and pre-monsoon period. However, vector
164 control is an endless, costly and labour-intensive which is not well accepted procedure by
165 local populations [45]. Elimination of breeding sites is an effective method of vector control.
166 Encourage people to eliminate mosquito habitats by emptying water containers once a week
167 & keeping the permanent water containers covered with a tight fitting lid. Personal protection
168 like long sleeve clothes, covering one-self fully, use of repellents, window nets play limited
169 but useful role. Surveillance is important strategies for outbreaks investigation.

170 **Conclusion**

171 Chikungunya has spread to the majority of the countries worldwide since the discovery and there have
172 been explosive outbreaks globally which not remains confined in the Southeast Asia and Central
173 Africa. Public health global initiatives should be focused on these areas in an effort to decrease the
174 spread of the virus to neighboring continents. Global travel and immigration is the main cause of the
175 Chikungunya virus spread. Chikungunya viral infection is self-limiting, rare mortality rate, but
176 morbidity is high in major outbreaks. The best way to the prevention of transmission of Chikungunya
177 to elimination of mosquito habitat. Currently, no recognize vaccine available for prevention of
178 disease. Regular Health educational campaigns to help spread awareness of the Chikungunya virus
179 should focus on the early signs of the infection as well as the preventative measures that will help to
180 reduce transmission. Community empowerment is crucial for the prevention and control of the virus
181 as well as the containment of future outbreaks.

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