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Epidemiology, clinical features and transmission of re-emerging arboviral infection chikungunya

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ABSTRACT

A number of re-emerging and emerging infectious diseases including chikungunya, West Nile, yellow fever, Zika, dengue, Japanese encephalitis, and others have increased in recent years, which threaten the public health across the globe. Chikungunya is a neglected re-emerging arboviral infection caused by chikungunya virus. Arboviral infections such as chikungunya, Zika and dengue have similar epidemiology, transmission cycles and clinical symptoms, which makes it difficult to diagnose these three infections. Moreover, there is no commercial vaccine or licensed therapy available for chikungunya infection, thus causing severe burden worldwide. Vector control may reduce the disease risk; however, this remains a challenge due to many factors including, but not limited to, evolution of insecticide resistance in mosquitoes, gaps in vector control tools, urbanization, environmental and demographic changes. Effective integrated vector control strategies and surveillance measures along with affordable vaccine development or anti-viral therapy are essential to control the infection. In this review, we discuss the epidemiology of mosquito-borne infection chikungunya which has re-emerged as an international concern in recent decades.

1. Introduction

International travel, tourism and visiting exotic destinations by the travelers have increased in recent decades. Travelers visiting the epidemic places are at a risk of mosquito bites and mosquito-borne illness. Commercial globalization, human migration, mobility of livestock, animals that may have host zoonotic microorganisms, and increasing geographical distribution of disease vectors resulted in increased outbreak of emerging and re-emerging infectious diseases. Environmental changes and natural calamities such as flood, earthquake may also contribute for the outbreak of infectious diseases[1]. Recent epidemics of chikungunya, Zika, dengue and yellow fever serve as reminders that the zoonotic diseases can spread within a short period causing major threat to public health. Most of the mosquito-borne arboviruses pose serious public health issues globally[2]. Chikungunya is a mosquito-borne viral infection caused by chikungunya virus (CHIKV). The primary vectors for this infection are two mosquito species: *Aedes aegypti* (*Ae. aegypti*) and *Aedes albopictus* (*Ae. albopictus*)[3]. The recent outbreaks of vector borne diseases including chikungunya, Zika

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and dengue that are mainly transmitted by these viral vectors exert significant impact on human health and still many lives in tropical and subtropical regions are at great risk[4]. The global expansion of these two mosquito vectors is the major cause of chikungunya outbreaks across continents, affecting many populations in recent years. After its re-emergence in 2004, the virus has spread into new locations in Africa, Europe and Asia and millions of cases have been reported worldwide[5]. The clinical and epidemiological features of chikungunya, dengue and Zika are similar which makes diagnosis complicated[6]. With no vaccine or specific treatment currently available, vector control can be considered as preventive measures to control chikungunya outbreaks; however, this remains challenging due to many factors including, but not limited to, evolution of insecticide resistance in mosquitoes, gaps in vector control tools, urbanization, environmental and demographic changes[7]. Because of the threat imposed by chikungunya, National Institute of Allergy and Infectious Diseases classified chikungunya as a category C priority pathogen[8]. This review elaborately describes the epidemiology, geographical distribution of CHIKV, mosquito vector and clinical features of CHIKV infection.

2. Chikungunya

Chikungunya, one of the neglected diseases, is caused by CHIKV and transmitted by mosquitoes. It is a febrile illness associated with headache, high fever, severe arthralgia, myalgia and rash[9]. Chikungunya was first reported in Tanzania in 1952 and the virus was first isolated from blood of a febrile patient in early 1953[10]. Chikungunya is a Makonde word meaning "The one which bends up" which refers the contorted posture of the affected persons acquired from debilitating joint and muscle pain. CHIKV belongs to the family Togaviridae and genus *Alphavirus*[11-13].

CHIKV is a small, enveloped, positive strand RNA virus of approximately 60-70 nm in diameter. The genome is about 11.8 kb long capped with 5' 7 methylguanosine and 3' poly A tail organized as 5′UTR-nsP1-nsP2-nsP3-nsP4-J-C-E3-E2-6K-E1-polyA-3′UTR[14,15]. CHIKV has two open reading frames that encodes for two polyproteins: non-structural proteins and structural proteins. The RNA encodes for non-structural polyprotein (NSP) precursor which is in turn processed into four different non-structural proteins nsp1, nsp2, nsp3, nsp4 that are mostly involved in viral multiplication and pathogenesis[16]. The subgenomic positive sense mRNA codes for structural proteins including three major structural proteins capsid, E1, E2 and two minor proteins 6K and E3 which are mainly responsible for viral encapsidation and budding. The lipid bilayer envelope on the CHIKV virion that encapsidates the genomic RNA has 240 copies of heterodimeric proteins E1 and E2 arranged as spikes on the nucleocapsid[17]. During infection, both E1 and E2 proteins play a key role in virus attachment and fusion. The replication cycle of CHIKV is similar like other alphavirus replication. The virus enters into the host cell by endocytosis of clathrin coated vesicles. Following endocytosis, the E1 protein undergoes conformational changes resulting in dissociation of E2-E1 heterodimers and formation of E1 homotrimers. Hydrophobic fusion peptide on the E1 trimer binds to the target membrane mediating virus host cell membrane fusion, resulting in the release of viral genome in host cell cytoplasm[18]. The NSPs are synthesized in early stages of infection and are mainly responsible for RNA replication. After the synthesis of structural proteins, capsid protein is cleaved from the structural polyprotein precursor due to its autocatalytic cleavage activity and encapsidates the viral genomic RNA. Further the assembled nucleocapsid containing E1 and E2 proteins results in budding of mature virions. The lipid bilayer on the virion envelope is derived from the plasma membrane of the host cell[11,19].

3. Mosquito vector and transmission

Epidemics and outbreaks of neglected infectious diseases are constantly increasing in frequency where the vectors can establish new geographical territories and become endemic in new environments. Large human population, movement of people, cargo and international trade facilitate the spread of viral vectors such as *Ae. aegypti* and *Ae. albopictus*. It is difficult to avoid mosquito bites since humans and mosquitoes co-exist in urban areas[20]. The factors involving in the transmission of arboviral infections are a vertebrate reservoir, blood sucking mosquito vector and human hosts who act as a secondary reservoir in urban areas[21]. Arboviral infections in humans and animals are mostly caused by the viruses belonging to the families Bunyaviridae, Togaviridae, Flaviviridae, Reoviridae and Rhabdoviridae[22]. Since its outbreak in Tanzania, sporadic cases and epidemic outbreaks have been reported in Africa, Asia, Europe and America[20].

Chikungunya is a zoonotic disease transmitted by *Ae. aegypti* (*Stegomyia aegypti*) and *Ae. albopictus* (*Stegomyia albopicta*) in Asia and *Aedes furcifer*, *Aedes luteocephalus*, *Aedes taylori* in Africa[23,24]. *Ae. aegypti* is the principal vector for disease transmission; however, *Ae. albopictus* is reported to be the major cause of transmission on recent chikungunya outbreaks. *Aedes* genus is highly anthropophilic and lives in urban areas close to humans. The A226 V mutation in the E1 protein of African lineage of CHIKV increases its infectivity, making it adaptable to *Ae. albopictus*. This point mutation in the E1 protein altered the vector competence and epidemic potential of CHIKV[25]. *Ae. aegypti* is diurnally active, feeds human blood and its eggs can resist dessication for several months. All these characters make this as an efficient vector for human disease transmission. *Ae. albopictus* has a wider range of hosts than *Ae. aegypti* and it has larger geographical distribution[26]. *Ae. albopictus* (Asian tiger mosquito) is day biting mosquito that enlarges its territories globally. Although monkeys and other vertebrates are the common reservoirs

of CHIKV, cattles and rodents have also been reported in the virus transmission[23].

4. Outbreaks

CHIKV is likely originated in Central/East Africa and subsequently transferred to Asia. The virus circulates continuously in Africa in sylvatic cycle involving wild primates, mosquitoes and urban transmission cycle involving humans. After its first outbreak in Tanzania, massive chikungunya outbreaks were reported in Uganda, Senegal, South Africa, Kenya, Nigeria *etc*. The outbreaks were unpredictable between two consecutive epidemics[27,28].

In 1958, CHIKV was reported in Bangkok, Asia followed by Cambodia, Vietnam, Myanmar, Malaysia and Indonesia[29]. In 1963, CHIKV epidemic was first recorded in Kolkatta, India followed by Madras in 1965 and Barsi in 1973. After three decades, chikungunya re-emerged as a massive outbreak in India in 2006. The magnitude of outbreak and number of suspected cases were higher than the past. The large chikungunya outbreak was recorded in India; almost 1.3 million cases were reported across 13 states[30,31]. Imported cases have also been reported in European and North American countries (Canada and USA)[32].

During the 2005-2006, chikungunya outbreaks in La Reunion Island, one third of the population were affected. Vertical transmission of CHIKV from infected mothers to fetus through intrapartum transmission causes congenital illness, fetal death and neurological complications like encephalopathy in the CHIKV infected neonates[33]. Transmission through exposure with infected blood and sexual transmission of arboviral infections have also been reported. However, no reports are available showing virus transmission through breast milk[34,35]. Chikungunya is not considered as a life-threatening disease but mortality was reported during the Reunion Island outbreak in 2006[36].

5. Symptoms and treatment

While feeding on the blood, female *Aedes* mosquitoes inject CHIKV intradermally. After initial infection, CHIKV infects the susceptible cells in the skin, replicates in the fibroblasts and then the virus disseminates to liver, muscles, joints and lymph nodes through blood[17].

Incubation period of CHIKV ranges from 2-4 days once after the CHIKV infected mosquito bites humans. The symptoms of chikungunya are divided into an acute stage that lasts approximately for a week, and a chronic stage, which is also known as the persistent stage, that can last from months to years[37]. Symptoms include high fever, rash, headache, weakness, arthralgia, and concomitant abnormalities are also reported. Asymptomatic infections vary between different age groups[38,39]. The affected persons develop devastating chronic polyarthralgia after the onset of fever. Based on disease severity and patient's symptoms analgesics, antipyretics and anti-inflammatory agents are recommended. Animal studies suggested that the fibroblasts and connective tissue are susceptible to CHIKV infection and account for the pain associated with joints[40]. The joint pain occurs mostly in wrists, elbow, fingers, knees and ankles. Arthralgia or musculoskeletal pains may persist for several days to months. The crippling joint pain is debilitating and appearing in 30%-90% of the cases[38,41]. More than 60% of the patients are reported to have persistent arthralgia even after post 18 months of infection. Additional symptoms include rash, headache, fatigue, vomiting and conjunctivitis. Diarrhoea, vomiting and abdominal pain are also reported in 15%-47% of cases[38]. New complications were also noted in recent epidemics like myocarditis, mild hemorrhage, photophobia, Guillain Barre syndrome, uveitis and retinitis *etc*[42-44]. However, serious complications are not common, rare severe symptoms can likely occur to vulnerable people *i.e.*, elderly, neonates and those who are immuno-compromised[45].

Current treatment mainly involves the use of analgesics, non-steroidal anti-inflammatory drugs and antipyretics along with bed rest, fluid intake and supportive care to reduce the severity of the disease[46]. The patients with chronic symptoms may have given disease-modifying anti-rheumatic drugs such as chloroquine, acyclovir, robovrin, corticosteroids, methotrexate and hydroxychloroquine to reduce pain and swelling[47]. The recent outbreak of chikungunya infection in Europe and America showed the ability of the virus to expand geographically and the importance to develop effective vaccine or prophylaxis against this epidemic. Till now, there is no specific vaccine or licensed anti-viral therapy for treating chikungunya infection, many promising candidates are in preclinical studies and clinical trials[20]. A live attenuated candidate vaccine 181/clone25 induced neutralizing antibodies in phase 2 clinical trials[48]. Studies showed the reversion of attenuation following immunization in mice and human volunteers; hence stabilization of attenuation is required before further development[49]. The live attenuated vaccine candidates based on genetically engineered clone are developed recently which showed promising results in animal models[50,51]. The viral-vectored vaccine based on attenuated measles virus vector expressing the chikungunya structural proteins induced neutralizing antibodies in phase Ⅰ studies and now in phase 2 trials[52]. Virus-like particles vaccine (VLPs) has also been developed by electroporation of plasmid encoding chikungunya structural protein open reading frame in mammalian cells. These VLPs protect immunodeficient mice and now in phase 2 trials[53,54].

6. Conclusion

Chikungunya is a neglected re-emerging disease that has been

recently considered as potential global threat. Recent outbreaks have affected many Asian and African countries which proved that mosquito-borne diseases may spread rapidly and infect a large proportion of population in less time unless measures are taken for vector controls. The dramatic spread and geographical distribution of disease caused by mosquito vector and virus urge researchers to develop vaccine, treatment or effective vector control program. Several CHIKV vaccine candidates such as live attenuated, viral vector and VLP based vaccines are highly promising with many of them in the clinical and pre-clinical pipeline. In addition to developing an effective vaccine for disease control, all the countries must have a surveillance system to monitor mosquito borne diseases, effective integrated vector control management, vector control programmes and good healthcare system to protect public health.

Conflict of interest statement

The authors declare no conflict of interest.

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