Journal of Advanced Veterinary and Animal Research
ISSN 2311-7710 (Electronic)
http://doi.org/10.5455/javar.2017.d211
A periodical of the Network for the Veterinarians of Bangladesh (BDvetNET)

June 2017
Vol 4 No 2, Pages 125-131.

Mini-Review

Chikungunya virus infection in developing countries - What should we do?

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• **Received:** April 5, 2017 • **Revised:** May 13, 2017 • **Accepted:** May 16, 2017 • **Published Online:** May 26, 2017

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ABSTRACT

Chikungunya fever, a serious global public health problem, is a mosquito-borne disease caused by Chikungunya virus belonging to the family *Togaviridae*. The virus was first detected in Tanzania in1953. At present, the virus has been detected over 60 countries across the globe. The virus is transmitted mainly through *Aedes* mosquitoes. Although not fatal, the affected persons suffer a lot from high fever, severe pain and other complications. Currently there is no effective treatment or vaccine for the Chikungunya virus. The situation is severe in developing countries that lack sufficient diagnostic facilities and control measures. Adequate coordinated efforts comprising active surveillance, early detection, vector control and public awareness at local, national and international level need to be adopted in endemic areas for the effective control of Chikungunya virus infection. This mini review highlights some of the advances recently have made in our understanding of Chikungunya virus.

KEYWORDS

Chikungunya fever; Dengue; Diagnosis; Epidemiology; Vaccine; Zika; Zoonoses

How to cite: Rahman MT (2017). Chikungunya virus infection in developing countries - What should we do? Journal of Advanced Veterinary and Animal Research, 4(2): 125-131.

INTRODUCTION

Chikungunya virus (CHIKV), the etiological agent of Chikungunya fever, is a mosquito-borne virus. The virus is a serious global public health problem (Gubler, 2001). The virus is transmitted mainly through *Aedes* mosquitoes. Chikungunya fever is endemic in many countries of Africa and Asia including Bangladesh where the *Aedes* mosquitoes (*A. aegypti* and *A. albopictus*) (**Figure 1**) are found (Vazeille et al., 2007). The virus affects all age groups, but severe illness occurs in older people (≥65 years) and children (Hoque and Ahmed, 2012). The disease is primarily manifested by acute painful fever and joint illness. Currently there is no effective vaccine or antiviral drugs for the prevention and treatment of Chikungunya infections. However, in acute cases, symptomatic treatment with analgesics, low-dose steroids and non-steroidal anti-inflammatory agents are used against CHIKV infection (Mathew et al., 2017).

The name "Chikungunya" derived from local Tanzanian language means "that which bends up" or "stopped walk" due to contorted posture resulting from joint pain (Bettadapura et al., 2013). Although morbidity and mortality is not that high, patient suffers a lot from high fever and severe pain of the body, particularly the joints pain. In fact, patients may suffer with the joint pain for weeks or months. During this period they cannot work properly and thus causing severe economic loss. Recently, complicated case of CHIKV infection has been reported where systemic involvement such as involvement of cardiovascular system was found (Alvarez et al., 2017).

Chikungunya virus is ssRNA positive sense enveloped virus with a genome of approximate 1.8 KB size that encode four non-structural (nsP1 to nsP4) and five structural (C, E3, E2, 6K, and E1) proteins. The virus is spherical in shape with a diameter of about 60–70 nm (**Figure 1**). These arthropod-borne viruses belong to the genus *Alphavirus* of the family *Togaviridae*. Like many other arboviruses, CHIKV are zoonoses (Powers and Logue, 2007). Humans are the major host of the virus, but non-human primates, rodents, and birds are also infected. During the epidemic periods human serve as the amplifying host and reservoir for CHIKV. Outside these periods the main reservoirs are birds, bat, monkeys and rodents (Pialoux et al., 2007).

Chikungunya fever is a global health problem. Outbreak of fever, rash and arthritis, similar to Chikungunya fever has been recorded as early as 1824 in India and elsewhere. However, the CHIKV was first isolated in 1953 from Tanzania and then in Asia (Robinson, 1955). Later on several outbreaks of the disease occurred in Africa and Asia between 1960s to the 1980, but the global emergence of CHIKV actually started in 2004. In addition to Africa and South-East Asia (India, Bangladesh) where it is endemic, sporadic cases are regularly reported from other part of the world (Pialoux et al., 2007). In fact, according to WHO, chikungunya virus has been identified over 60 countries (**Figure 2**). Among the developing countries, beside Bangladesh, the disease has been identified in Bhutan, Cambodia, East Timor, India, Indonesia, Laos, Malaysia, Maldives, Myanmar, Nigeria Pakistan, Philippines, Réunion, Seychelles, Singapore, South Africa, Sudan, Senegal, Thailand, Tanzania, Uganda, Vietnam, and Zimbabwe (Cavrini et al., 2009; Duong et al., 2012; Chen et al., 2013; Wangchuk et al., 2013; Adam et al., 2016; Murugan and Sathishkumar, 2016; Simon et al., 2017). Phylogenetic based analysis of viral sequences has identified 3 distinct clades: West African, Central/ East African and Asian (Chhabra et al., 2008).

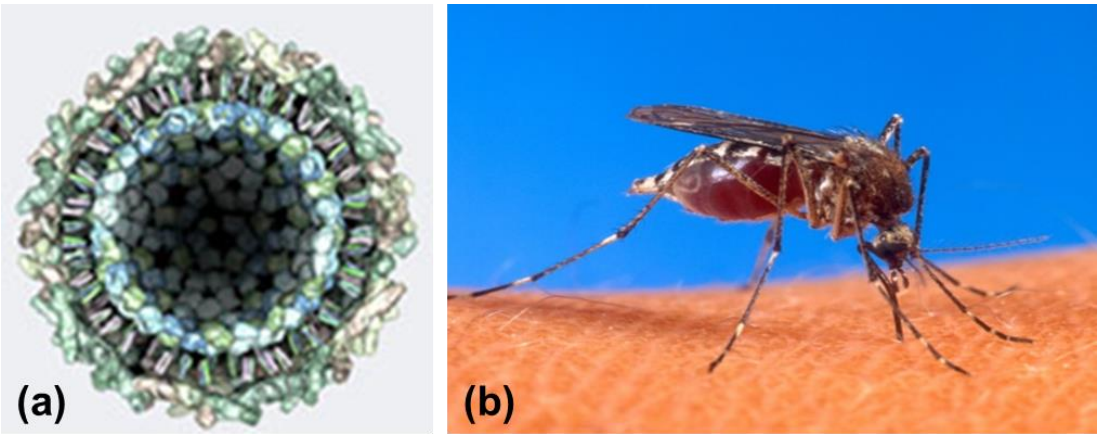

Figure 1. Chikungunya virus particle (a) and *A. aegypti* mosquito (b). (http://www.chikungunyavirusnet.com/chikungunya-virus.html; https://en.wikipedia.org/wiki/Chikungunya)

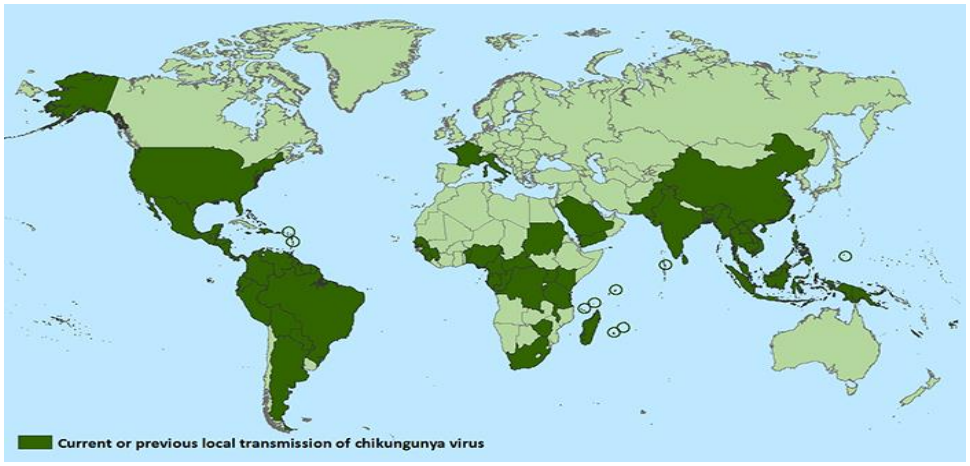

Figure 2. Countries and territories where chikungunya cases have been reported (as of April 22, 2016). The map does not include countries or territories where only imported cases have been documented. (https://www.cdc.gov/chikungunya/geo)

In December 2008, the first outbreak of Chikungunya fever was observed in Bangladesh (Chowdhury et al., 2012). This emerging arboviral disease is currently spreading rapidly across south Asia. During 1960s major outbreak of CHIKV infection was reported in India. In 2014, the first case of CHIKV was reported in Nepal (Pun et al., 2014). The disease in Bangladesh is now considered as an emerging infection (Hassan et al., 2014) since its first detection, from time to time cases of CHIKV are reported from different parts of Bangladesh (Khatun et al., 2015; Faruque et al., 2017;).

CHIKUNGUNYA VIRUS LIFE CYCLE

The CHIKV enters the human body through bite of infected female *Aedes* mosquito (Chhabra et al., 2008). Usually both the *A. aegypti* and *A. albopictus* species are found biting outdoors, but *A. aegypti* also feed indoors. After entry into the blood stream, it spreads across the body and localizes in various target tissues such as in the oral and nasal mucosa and in throat. The replication of the viral genome takes place in the nucleus of the infected cells. Viral protein synthesis and nucleocapsid assembly takes place in the cytoplasm. After replication the virus is released from the infected cells and enters the blood steam (viremia) to spread and affect other tissues to clinical symptoms. From these viremic patients, it goes back to mosquitoes by mosquito bite. In mosquito, the replication of the virus takes place in cells of mid-gut, ovary, neural cells etc. Healthy patients get infection from the infected mosquito during blood sucking. Avoidance of contact between the infected mosquitoes and healthy persons should be taken under consideration for the control of the disease. Detail about the biology and pathogenesis of CHIKV has been reviewed by Schwartz and Albert (2016) and Burt et al. (2017).

CLINICAL FINDINGS AND DIAGNOSIS

The clinical findings of CHIKV infection is very much similar to those of Dengue and Zika and in areas lacking laboratory diagnostic facilities, CHIKV is probably frequently under diagnosed or misdiagnosed as Dengue or Zika. The incubation period of CVIKV varies from 2 to 12 days following the bite of infected mosquito, with an average of 2 to 7 days. The disease is characterized by sudden onset of high fever and arthralgia or arthritis (Hoque and Ahmed, 2012) (**Table 1**). Several joints of the body may be affected, that are found swollen. The fever may persist for 8 to 10 days. In some patients, a biphasic pattern of fever is also noticed. There may be also appearance of rash in the body (Adebajo, 1996). Severe joint pain is one of the most important signs of the disease that may persist for a long time even after recovery from the fever. Other clinical findings of the disease include headache, weakness, malaise, nausea and vomition.

Quite similar types of clinical findings are also found in patients suffering from Zika virus infection, a viral disease also transmitted by *Aedes* mosquito (**Table 1**). In Zika virus infection, generally the symptoms are mild. In many cases, affected patients may fully recover without complications. However, one important characteristics of Zika virus infection is that, unlike CHIKV or Dengue, in pregnant woman, Zika virus may affect the fetus to cause birth defects and Guillain-Barré syndrome (**Table 1**). On the other hand, Chikungunya fever like symptoms is also noticed in Dengue, a viral disease also transmitted by *Aedes* mosquitoes. But in this case, the disease is quite fatal and the patient could die from within 24 h due to massive blood loss as a result of hemorrhage and shock (Dengue hemorrhagic fever).

Table 1. Distinguishing differential points among Chikungunya, Dengue and Zika.

Features	Chikungunya	Dengue	Zika
Agent characteristics			
Genus (Family)	Alphavirus (Togaviridae)	Flavivirus (Flaviviridae)	Flavivirus (Flaviviridae)
Approximate genome size	11.8 KB	10.7 KB	10.8 KB
Serotype	One	Five (DENV-1 to 5)	One
Clinical manifestation			
Fever	High fever	High fever	Low grade fever
Arthralgia	Very common	Moderate	Less common
Edema of limb	Absent	Absent	Present
Conjunctivitis	Present (mild)	Absent-	Very Common
Hemorrhage	No	Present (may be severe)	No
Guillain-Barré syndrome	No	No	May be observed in pregnant women

Adapted from Beltrán-Silva et al. (2016)

The diagnosis of CHIKV is based on ELISA and immunofluorescence test that detect anti-CHIKV IgM and IgA present in serum. Within 2-3 days after the onset of symptoms, the IgM antibodies are developed and may persist for several months (Malvy et al., 2009). On the other hand, the IgG antibodies developed in the convalescent phase, and are reported to be found after several months or even years following recovery (Cavrini et al., 2009). In addition, plaque reduction neutralization test and indirect hemagglutination test are also used for its diagnosis. Confirmatory diagnosis of CHIKV at molecular level is done based on detection of its genome by RT-PCR and real-time RT-PCR (Edwards et al. 2,007). These are highly sensitive, specific and rapid test for CHIKV detection. For the isolation of the virus, insect and mammalian cell lines such as C636 and Vero cell lines are widely used (Mardekian and Roberts, 2015; Deeba et al., 2016).

PREVENTION AND CONTROL

Aedes mosquitoes are the principal vector for CHIKV. Preventive measure therefore primarily targets the *Aedes* mosquito control. *Aedes* mosquito uses a wide range of confined natural and man-made larval habitats. The prevalence of CHIKV infection is significantly linked with mosquito breeding sites (Islam et al., 2011). Detection of such habitants (mosquito breeding sites) and their removal or destruction is an effective way of controlling vector population. Protection against exposure to mosquito at personal level through the use of mosquito net, protective cloths in addition to use of repellents, aerosol products, mosquito coils and insecticides need to be practiced where applicable. During vector control, WHO recommended ecologically sound and sustainable vector control system known as Integrated Vector Management (IVM) should be adopted to ensure optimum use of resources available in the country. Seasonal variation in the occurrence of the disease has to be taken under consideration during the control of mosquito. The risk of infection is highest in the rainy season when numbers of mosquitoes are at their greatest due to available of stagnant water that act facilitate mosquito larvae development.

In nature, there is always equilibrium among the host, agent and the environment and any factors (risk factors) disturbing this equilibrium result in the outbreak of disease. CHIKV control strategies should therefore also include identification of these risk factors linked with the onset of outbreak of CHIKV infection and their management. Among these risk factors increased population of mosquito vectors and their migration within and between countries, frequent cross-border trafficking of passengers and goods and increased movement of CHIKV positive persons across borders should be taken under consideration for the effective control of CHIKV infection (Derraik et al., 2010).

Information on vector biology is crucial for the control of vector borne disease. There are reports suggesting that some of the vector borne viruses (arbovirus) such as Chikungunya, Dengue and Zika viruses are evolving them to expand their natural principal vectors (Nasci, 2014). Moreover, vector biology including their distribution is greatly under the influence of climate change (global warming) and habitat changes (Capinha et al., 2014; Khormi and Kumar, 2014). It is therefore now vital to know the extent of distribution of CHIKV vector in nature for successful vector control to reduce or stop the spread of pathogen they carry. Approaches involving GIS and CLIMEX system now can be applied for monitoring the vector distribution for effective vector control (Khormi and Kumar, 2014).

The present CHIKV infection surveillance and prevention strategies practiced in Bangladesh are not sufficient (Khatun et al., 2015). Implementation of more effective active surveillance system will allow us in early

detection of CHIKV vector, host and reservoir for implementation of effective control program. In the developed world, such active surveillance systems are in full function. This type of surveillance system requires adequate skilled manpower and diagnostic resource and most of the developing countries lack these skilled manpower and diagnostic facilities. Governments in the developing countries should give emphasis on implementation of such active surveillance system along with its neighboring country for the control of CHIKV infection.

CHIKUNGUNYA VIRUS VACCINE

Vaccine is antigen that provides protective immunity against a pathogen. A number of potential vaccine candidates have been tested on humans and animal models during clinical and preclinical trials, but at present there is no licensed vaccine available against the CHIKV (Deeba et al., 2016). Roques et al. (2017) has developed an attenuated strain of CHIKV (Δ5nsP3) and found safe in nonhuman primate model. Use of capsid protein as a potential antigen for CHIKV vaccine is also under investigation (Taylor et al., 2017). Recently, Erasmus et al. (2017) has developed a chimeric virus where CHIKV structural protein encoding gene was cloned as cDNA of insect-specific alphavirus Eilat virus (EILV). This newly developed recombinant EILV/CHIKV was found effective against CHIKV in mouse models and nonhuman primates. The vaccine provided complete protection against CHIKV infection. Although in these animal the newly developed vaccine induced a rapid and robust immune response against CHIKV, but its application in human yet has to be carried out to evaluate its efficacy as vaccine. This vaccine is claimed to be the first of its kind against CHIKV. Further work is needed for the development of an effective and safe vaccine to control the disease in human.

A. aegypti is a day biting mosquito, meaning that the mosquito is most active during daylight, for approximately 2 h after sunrise and several hours before sunset. So, personal protection has to be used at day time for avoiding mosquito bite.

RECOMMENDATIONS

Public awareness

Improving general knowledge of people about the importance of vector control and consequences of CHIKV infection also has to be taken under consideration for successful prevention and control of the CHIKV epidemics. Newspaper, mass media, electronic media, radio, TV and social media like Facebook and Twitter could also play viral role in public awareness against the disease. Awareness of people on reporting of occurrence of any clinical illness resembling CHIKV infection to nearby health authority has to be promoted. More coordination at national and international level between the Government and concern agencies like FAO and CDC are needed to be established for successful control of CHIKV and other vector borne diseases in the developing countries.

Active surveillance

Implementation of active surveillance for early detection of CHIKV has to be in full function across the whole country. In areas where more than one neighboring countries are affected, surveillance should also include monitoring of movement of people, their goods and vector across the border to prevent the entry of CHIKV into the country. Early detection of CHIKV through surveillance will allow us time for preparedness against the CHIKV disease outbreak. Similarly, workers entering into the country from the CHIKV prevalent areas have to be screened properly in the airport, seaport or in land border office to check entry of new cases. If required, quarantine and isolation of suspected and infected cases has to be done at entry point.

Mosquito control

Chikungunya virus is an emerging pathogen of great concern particularly in the developing world. *Aedes* mosquitoes are directly involved in the transmission of the disease. Preventive measures have to be adopted involving various physical, biological and chemical methods targeted against the *Aedes* mosquitoes for the control of CHIKV infection. Existing local and national programs for control of mosquitoe population need to be strengthened.

ACKNOWLEDGEMENT

Sincere thanks to Prof. Nazir at the Department of Microbiology and Hygiene for his critical checking and comments during preparing this mini-review.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

AUTHORS' CONTRIBUTION

MTR reviewed the related articles and prepared this mini-review.

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