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CHIKUNGUNYA VIRUS INFECTION: A REVIEW

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ABSTRACT
Chikungunya fever is a self-remitting febrile viral illness that has been associated with frequent outbreaks in tropical countries of Africa and Southeast Asia. The illness has only recently become a concern in Western countries and temperate zones around the world. Chikungunya is an arboviral disease transmitted by *Aedes* mosquitoes, caused by Chikungunya virus (CHIKV). It consists of an acute illness characterized by fever, rash and arthralgia. Over the past decades, the virus has dispersed unexpectedly from tropical and subtropical regions of Africa and Asia, affecting millions of people worldwide. Treatment of acute case is symptomatic; treatment of fever and joint swelling includes the use of nonsteroidal anti-inflammatory drugs such as naproxen, non-aspirin analgesics such as acetaminophen. Currently, in the era of globalization and increased international travel, and due to widespread distribution of the mosquito vector, CHIKV is becoming a substantial threat to human health worldwide, including the industrialized countries. Given the lack of effective vaccine or antiviral drug, the long-term consequences of the infection appear to be even more harmful. 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 CHIKV infection.
Keywords: Chikungunya virus, infection, malaria, fever, vaccine, treatment

INTRODUCTION

Chikungunya fever is a self-remitting febrile viral illness that has been associated with frequent outbreaks in tropical countries of Africa and Southeast Asia. The illness has only recently become a concern in Western countries and temperate zones around the world. The recent re-emergence and travel-related spread of Chikungunya infection to Europe and the United States has drawn global attention. In fact, international travel stands out as one of the major risk factors for the rapid global spread of the disease (Morrison, 2014). The term "Chikungunya" often refers to both the virus (CHIKV) and the illness or fever (CHIKF) caused by this virus. It was derived from the African dialect Swahili or Makonde and translates as "to be bent over." In Congo, it is referred to as "buka-buka," which means "broken-broken." These terms refer to the "stooped-over posture" exhibited by individuals with the disease as a consequence of severe chronic incapacitating arthralgias (Lumsden, 1955). The roots of this viral illness date back to 1953, when it was first described during an outbreak in a Swahili village in the Newala district of Tanzania, Africa. Chikungunya virus is transmitted to humans through day-biting mosquitoes that belong to the Aedes genus (Tsetsarkin *et al.*, 2007).

While the disease typically occurs in Africa and Asia, outbreaks have been reported in Europe and the Americas since the 2000s. In 2014 more than a million suspected cases occurred (WHO, 2016).

In 2014 it was occurring in Florida in the continental United States but as of 2016 there were no further locally acquired cases. Chikungunya virus (CHIKV) is a member of the alphavirus genus, and Togaviridae family. It was first isolated in 1953 in Tanzania and is an RNA virus with a positive-sense single-stranded genome of about 11.6kb (Weaver *et al.*, 2012). It is a member of the Semliki Forest virus complex and is closely related to Ross River virus, O'nyong'nyong virus, and Semliki Forest virus (Powers *et al.*, 2000). Because it is transmitted by arthropods, namely mosquitoes, it can also be referred to as an arbovirus (arthropod-borne virus). In the United States, it is classified as a category C priority pathogen, and work requires biosafety level III precautions.

Chikungunya fever (CHIKF) is an arthropod-borneviral disease transmitted by the *Aedes (Ae.) aegypti* and *Ae. albopictus* mosquitoes. It characterized by fever, headache, rashes, and debilitating arthralgia (Robinson, 1955). Chikungunya means ‘‘to walk bent over’’ in the Makonde language; this is the classic posture adopted by CHIKF patients during the acute phase. Caused by the chikungunya virus (CHIKV), an alphavirus belonging to the Togaviridae family, the disease has an incubation period of 3–7 days. The virus is usually detectable in peripheral blood between 1–2 weeks and the peak of viremia (up to 108pfu/mL of plasma) is associated with the onset of the disease (Powers and Logue 2007). Although there can be 5–15% asymptomatic patients, CHIKF is mainly an incapacitating and nonfatal disease. However, since the Indian Ocean islands outbreaks due to the A226V *Ae. albopictus* East-Central- South-African (ECSA)-adapted strains, severe forms and deaths, often associated with co-morbidities, have been reported (Mavalankar *et al.*, 2007; Lemant *et al.*, 2008). Reports have chronicled the new wave of CHIKV outbreaks in the Americas since November of 2013 due to the adaptation of the Asian *Ae. aegypti* strain in the French West Indies and Caribbean islands. The virus has since spread to several parts of Central and Latin America (Morens and Fauci, 2014). But until now, there have been no reports that describe the disease severity in these countries.

Early antibodies can be detected in patient sera as early as after 5 days after the onset of symptoms. These antibodies neutralize the virus, thus preventing its isolation. The serologic response to infections by CHIKV can be detected by enzyme-immune assays (EIAs), an indirect immunofluorescence assay (IFA), a hemoagglutination inhibition (HI) test and a neutralization test (NT) (Caglioti, 2013). Enzyme immunoassay is a rapid and sensitive technique for the detection of specific antibodies and can discriminate between immunoglobulin G (IgG) and immunoglobulin M (IgM). The IgM to CHIKV is typically detectable 3 days after the onset of symptoms and persists up to 3 months. IgG antibodies to CHIKV appear after IgM antibodies and persist for years (Roth *et al*., 2014).

Life Cycle of Chikungunya Virus

The life cycle of chikungunya virus can be divided into three stages as follows:

i) Initial Stage of chikungunya virus Infection

Chikungunya virus enters the human body via the salivary glands of the mosquito. When an infected female *Aedes* mosquito bites, it introduces the virus into the bloodstream of the host. Soon after entering the blood stream, the virus gets attached with permissive cells, especially the one of the nose, throat and mouth.

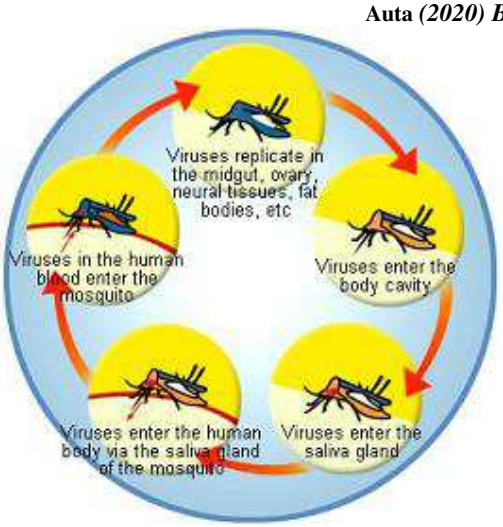

Figure 1: Life cycle of chikungunya virus in its host and vector (Goyal, 2018).

ii) Cellular and Infectious Stage

In cellular stage, the chikungunya virus makes its way to the cytoplasm and then finally to the nucleus. After entering the nucleus, chikungunya virus releases genetic material and replicates genome in the nucleus. After passing the cellular stage, the virus enters into the surrounding tissues and begins infecting the other cells as well. It proliferates in the bloodstream and entire body causing main infection. It is only after two to twelve days of an infected mosquito bite that the symptoms of illness occur. Chikungunya fever is mainly characterized by sudden onset of fever, severe pain in the joints and skin rashes

iii) The Mosquito Stage

When a mosquito bites the above stated viremic host or the human who has been infected, the virus is transmitted to it and it gets replicated in the mid-gut, ovary, neural tissues and fat bodies of the insect. The virus reproduces there and migrates to the 16 salivary glands of the mosquito. As the infected mosquito bite someone the life cycle of chikungunya virus transfers onto another person making another viremic host.

Epidemiology of Chikungunya Infection

Historically, chikungunya has been present mostly in the developing world. The disease causes an estimated 3 million infections each year (Seppa and Nathan, 2015). Epidemics in the Indian Ocean, Pacific Islands, and in the Americas, continue to change the distribution of the disease. In Africa, chikungunya is spread by a sylvatic cycle in which the virus largely cycles between other non-human primates, small mammals, and mosquitos between human outbreaks (Powers Logue, 2007). During outbreaks, due to the high concentration of virus in the blood of those in the acute phase of infection, the virus can circulate from humans to mosquitoes and back to humans. The transmission of the pathogen between humans and mosquitoes that exist in urban environments was established on multiple occasions from strains occurring on the eastern half of Africa in non-human primate hosts. This emergence and spread beyond Africa may have started as early as the 18th century. Currently, available data does not indicate whether the introduction of chikungunya into Asia occurred in the 19th century or more recently, but this epidemic Asian strain causes outbreaks in India and continues to circulate in Southeast Asia. In Africa, outbreaks were typically tied to heavy rainfall causing increased mosquito population. In recent outbreaks in urban centers, the virus has spread by circulating between humans and mosquitoes.

Global rates of chikungunya infection are variable, depending on outbreaks. When chikungunya was first identified in 1952, it had a low-level circulation in West Africa, with infection rates linked to rainfall.

Beginning in the 1960s, periodic outbreaks were documented in Asia and Africa. However, following several decades of relative inactivity, since 2005, chikungunya has re-emerged and caused large outbreaks in Africa, Asia, and the Americas. In India, for instance, chikungunya re-appeared following 32 years of absence of viral activity (Lahariya and Pradhan, 2006). Outbreaks have occurred in Europe, the Caribbean, and South America, areas in which chikungunya was not previously transmitted. Local transmission has also occurred in the United States and Australia, countries in which the virus was previously unknown. In 2005, an outbreak on the island of Réunion was the largest then documented, with an estimated 266,000 cases on an island with a population of approximately 770,000. (Roth, 2014) In a 2006 outbreak, India reported 1.25 million suspected cases (Muniaraj, 2014), Chikungunya was recently introduced to the Americas, and from 2013-14 in the Americas, 1,118,763 suspected cases and 24,682 confirmed cases were reported by the PAHO.

An analysis of the chikungunya virus's genetic code suggests that the increased severity of the 2005–present outbreak may be due to a change in the genetic sequence which altered the E1 segment of the virus' viral coat protein, a variant called E1-A226V. This mutation potentially allows the virus to multiply more easily in mosquito cells (Schuffenecker *et al.,* 2006). The change allows the virus to use the Asian tiger mosquito (an invasive species) as a vector in addition to the more strictly tropical main vector, *Aedes aegypti* (Tsetsarkin *et al*., 2007) Enhanced transmission of chikungunya virus by *A. albopictus* could mean an increased risk for outbreaks in other areas where the Asian tiger mosquito is present (Liumbruno *et al.,* 2008). *A. albopictus* is an invasive species which has spread through Europe, the Americas, the Caribbean, Africa and the Middle East.

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In Nigeria, there is paucity of information on the epidemiology of infections due to Chikungunya virus (CHIKV) especially among patients with febrile illness. Cases of febrile illness are usually associated with malaria and typhoid fever without considering the possibility of viral aetiology. This study was designed to determine the prevalence and identify other epidemiological parameters of CHIKV infections among outpatients with febrile illness attending University of Maiduguri Teaching Hospital, Nigeria. Sera from 370 patients were tested for presence of CHIKV immunoglobin (Ig) IgM and IgG antibodies using the enzyme-linked immunosorbent assay (ELISA). Of the 370 sera tested, 39 (10.5%) were positive for presence of CHIKV antibodies.

A total of 24 (6.5%) tested positive for CHIKV IgM only, while none (0.0%) was positive for the presence of CHIKV IgG only Fifteen (4.1%) of the serum samples simultaneously reacted to both IgG and IgM antibodies. A significant difference ($p<0.0001$) was observed in the distribution of CHIKV antibodies in relation to gender. The males had prevalence of 8.5% IgM antibodies as against 4.6% in females, 4.6% of females were positive for both CHIKV IgG and IgM antibodies, compared to 3.4% in males. The age group ≤60 years and the undisclosed age group were positive for the presence of CHIKV IgG and/or IgM antibodies. No significant difference was observed in the seasonal prevalence of CHIKV antibodies among the study subjects. Analysis of the prevalence of CHIKV antibodies in relation to clinical presentation in the patients revealed that headache and fever were the most frequently encountered ailments (Yusof *et al.,* 2011; Akinola *et al.,* 2017).

Symptoms of Chikungunya Infection

The disease may be asymptomatic, but generally is not, as 72% to 97% of those infected will develop symptoms. Characteristic symptoms include sudden onset with high fever, joint pain, and rash. Other symptoms may occur, including headache, fatigue, digestive complaints, and conjunctivitis. Information gained during recent epidemics suggests that chikungunya fever may result in a chronic phase as well as the phase of acute illness. Within the acute phase, two stages have been identified: a viral stage during the first five to seven days, during which viremia occurs, followed by a convalescent stage lasting approximately ten days, during which symptoms improve and the virus cannot be detected in the blood. Typically, the disease begins with a sudden high fever that lasts from a few days to a week, and sometimes up to ten days. The fever is usually above 39 °C (102 °F) and sometimes reaching 40 °C (104 °F) and may be biphasic—lasting several days, breaking, and then returning. Fever occurs with the onset of viremia, and the level of virus in the blood correlates with the intensity of symptoms in the acute phase. When IgM, an antibody that is a response to the initial exposure to an antigen, appears in the blood, viremia begins to diminish. However, headache, insomnia and an extreme degree of exhaustion remain, usually about five to seven days (Chhabra *et al.,* 2008).

Following the fever, strong joint pain or stiffness occurs; it usually lasts weeks or months, but may last for years. The joint pain can be debilitating, often resulting in near immobility of the affected joints (Capeding *et al.,* 2013) Joint pain is reported in 87–98% of cases, and nearly always occurs in more than one joint, though joint swelling is uncommon. Typically the affected joints are located in both arms and legs, and are affected symmetrically. Joints are more likely to be affected if they have previously been damaged by disorders such as arthritis. Pain most commonly occurs in peripheral joints, such as the wrists, ankles, and joints of the hands and feet as well as some of the larger joints, typically the shoulders, elbows and knees. Pain may also occur in the muscles or ligaments. Rash occurs in 40-50% of cases, generally as a maculopapular rash occurring two to five days after onset of symptoms. Digestive symptoms, including abdominal pain, nausea, vomiting or diarrhea, may also occur (Powers, Ann., 2014). In more than half of cases, normal activity is limited by significant fatigue and pain. Infrequently, inflammation of the eyes may occur in the form of iridocyclitis , or uveitis, and retinal lesions may occur (Powers, 2008). Rarely, neurological disorders have been reported in association with chikungunya virus, including Guillain–Barré syndrome, palsies, meningoencephalitis, flaccid paralysis and neuropathy. In contrast to dengue fever, Chikungunya fever very rarely causes hemorrhagic complications. Symptoms of bleeding should lead to consideration of alternative diagnoses or co Infection with dengue fever or coexisting congestive hepatopathy.

Mode of Transmission

CHIKV is transmitted in two different cycles: urban and sylvatic. The urban cycle refers to transmission from human to mosquito to human, while sylvatic transmission is animal to mosquito to human (Singh and Unni, 2011). The sylvatic cycle is the primary form of maintenance in Africa (Chhabra *et al*., 2008). CHIKV elsewhere in more densely populated areas is primarily maintained in an urban cycle, in which humans act as the major hosts and mosquitos of the genus Aedes act as vectors (Singh and Unni, 2011). Specifically, the virus is primarily transmitted by *Aedes aegypti* and *Aedes albopictus*. The principal vector in CHIKV transmission has historically been *Ae. aegypti*, but *Ae. albopictus* acted as the major vector in several recent outbreaks in Réunion, Europe, and Gabon (Singh and Unni, 2011), although *Ae. Aegypti* continues to be an important viral vector as seen during the Caribbean outbreak in 2013 (Mowatt and Jackson, 2014). The adaptation by *Ae. albopictus* has been theorized to be due in part to a lack of sufficient *Ae. aegypti* vectors (Vazeille *et al*., 2007) , with a mutation in the E1 envelope protein allowing *Ae. albopictus* to serve as a competent vector. The A226V mutation in the E1 envelope protein increased fitness of CHIKV in *Ae. albopictus* and improved transmissibility to vertebrate species (Singh and Unni, 2011). Mother-to-child vertical transmission has been postulated for the post-2005 incidences (Gérardin *et al*., 2007), being especially deleterious when the mother is infected up to four days postpartum (Dotters-Katz *et al.*, 2015), though this hypothesis has been disputed (Vazeille *et al*., 2009).

Laboratory Diagnosis of Chikungunya Infection

Chikungunya is diagnosed on the basis of clinical, epidemiological, and laboratory criteria. Clinically, acute onset of high fever and severe joint pain would lead to suspicion of chikungunya. Epidemiological criteria consist of whether the individual has traveled to or spent time in an area in which chikungunya is present within the last twelve days (i.e. the potential incubation period). Laboratory criteria include a decreased lymphocyte count consistent with viremia. However a definitive laboratory diagnosis can be accomplished through viral isolation, RT-PCR, or serological diagnosis (Morens and Fauci, 2014). The differential diagnosis may include infection with other mosquito-borne viruses, such as dengue or malaria, and infection with influenza. Chronic recurrent polyarthralgia occurs in at least 20% of Chikungunya patients one year after infection, whereas such symptoms are uncommon in dengue (Morens and Fauci, 2014).

Virus isolation provides the most definitive diagnosis, but takes one to two weeks for completion and must be carried out in biosafety level III laboratories (WHO, 2013). The technique involves exposing specific cell lines to samples from whole blood and identifying chikungunya virus-specific responses. RT-PCR using nested primer pairs is used to amplify several chikungunya-specific genes from whole blood, generating thousands to millions of copies of the genes in order to identify them. RT-PCR can also be used to quantify the viral load in the blood. Using RT-PCR, diagnostic results can be available in one to two days. Serological diagnosis requires a larger amount of blood than the other methods, and uses an ELISA assay to measure chikungunya-specific IgM levels in the blood serum. One advantage offered by serological diagnosis is that serum IgM is detectable from 5 days to months after the onset of symptoms, but drawbacks are that results may require two to three days, and false positives can occur with infection due to other related viruses, such as o'nyong'nyong virus and Semliki Forest virus.

Presently, there is no specific way to test for chronic signs and symptoms associated with Chikungunya fever although nonspecific laboratory findings such as ceactive protein and elevated cytokines can correlate with disease activity (Shilte *et al.,* 2010).

Treatment of Chikungunya Infection

Currently, no specific treatment for chikungunya is available (Caglioti *et al.,* 2013). Supportive care is recommended, and symptomatic treatment of fever and joint swelling includes the use of nonsteroidal anti-inflammatory drugs such as naproxen, non-aspirin analgesics such as paracetamol (acetaminophen) and fluids (Caglioti *et al.,* 2013) Aspirin is not recommended due to the increased risk of bleeding (European Centre for Disease Prevention and Control, 2013) Despite anti-inflammatory effects, corticosteroids are not recommended during the acute phase of disease, as they may cause immunosuppression and worsen infection (Burt *et al.,* 2012).

Passive immunotherapy has potential benefit in treatment of chikungunya. Studies in animals using passive immunotherapy have been effective, and clinical studies using passive immunotherapy in those particularly vulnerable to severe infection are currently in progress (Couderc *et al*., 2009) Passive immunotherapy involves administration of anti-CHIKV hyperimmune human intravenous antibodies (immunoglobulins) to those exposed to a high risk of chikungunya infection. No antiviral treatment for chikungunya virus is currently available, though testing has shown several medications to be effective in vitro (Thiberville *et al*., 2013).

Prevention of Chikungunya Infection

Because no approved vaccine exists, the most effective means of prevention are protection against contact with the disease-carrying mosquitoes and controlling mosquito populations by limiting their habitat (Caglioti *et al.,* 2013). Mosquito control focuses on eliminating the standing water where mosquitoes lay eggs and develop as larva; if elimination of the standing water is not possible, insecticides or biological control agents can be added (Weaver *et al.,* 2015). Methods of protection against contact with mosquitoes include using insect repellents with substances such as DEET, icaridin, PMD (p-menthane-3, 8-diol, a substance derived from the lemon eucalyptus tree), or IR3535. However, increasing insecticide resistance presents a challenge to chemical control methods.

Wearing bite-proof long sleeves and trousers also offers protection, and garments can be treated with pyrethroids, a class of insecticides that often has repellent properties. Vaporized pyrethroids (for example in mosquito coils) are also insect repellents. As infected mosquitos often feed and rest inside homes, securing screens on windows and doors will help to keep mosquitoes out of the house. In the case of the day-active *A. aegypti* and *A. albopictus*, however, this will have only a limited effect, since many contacts between the mosquitoes and humans occur outdoors (Hallengärd *et al.,* 2013).

Vaccine for Chikungunya Infection

As of 2017, no approved vaccines are available. A phase-II vaccine trial used a live, attenuated virus; to develop viral resistance in 98% of those tested after 28 days and 85% still showed resistance after one year (Edelman, *et al.,* 2000) However, 8% of people reported transient joint pain, and attenuation was found to be due to only two mutations in the E2 glycoprotein (Gorchakov, *et al.,* 2012) Alternative vaccine strategies have been developed, and show efficacy in mouse models (Plante *et al.,* 2011), In August 2014 researchers at the National Institute of Allergy and Infectious Diseases in the USA were testing an experimental vaccine which uses virus-like particles (VLPs) instead of attenuated virus. All the 25 people participated in this phase 1 trial developed strong immune responses. Phase 2 trial will commence using 400 adults aged 18 to 60 and take place at 6 locations in the Caribbean (Idrus and Amirah, 2015). Even with a vaccine, mosquito population control and bite prevention will be necessary to control chikungunya disease (Morens and Fauci, 2014).

CONCLUSION

Currently, in the era of globalization and increased international travel, and due to widespread distribution of the mosquito vector, CHIKV is becoming a substantial threat to human health worldwide, including the industrialized countries. Given the lack of effective vaccine or antiviral drug, the long-term consequences of the infection appear to be even more harmful.

RECOMMENDATIONS

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 CHIKV infection. 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. 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.

COMPETING INTERESTS

We have declared that no competing interests exist.

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