

Chikungunya Fever: A New Concern For the Western Hemisphere

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Abstract: Chikungunya virus has spread from Tanzania and has caused autochthonous transmission throughout Africa and Asia, and most recently in Europe, and the Americas. Transmission into new geographical areas has been facilitated by many factors including international travel, genetic adaptation of the virus to the vectors, and a breakdown of vector control measures. The economic impact on affected countries may be severe as a result of the immediate effect on the healthcare services and loss of man-hours as well as the potential effect on tourism. Effective control will require early diagnosis and isolation of viremic persons as well as enhanced environmental measures. To stop transmission in the region will require a regional effort that involves public education and an interdisciplinary One Health approach.

Keywords: Arthritis, blood, Caribbean, chikungunya, cornea, uveitis, vector-borne, western hemisphere.

INTRODUCTION

The Institute of Medicine described emerging diseases as diseases that are the result of a new agent being introduced e.g. chikungunya fever virus. They further identified 10 factors to be influential in the development of emergence. These are: "(1) increased human intrusion into tropical forests; (2) lack of access to health care; (3) population growth and changes in demographics; (4) changes in human behaviours; (5) inadequate and deteriorating public health infrastructure; (6) misuse of antibiotics and other antimicrobial drugs; (7) microbial adaptation; (8) urbanization and crowding; (9) modern travel; and (10) increased trade and expanded markets for imported foods." [1] In recent years, chikungunya fever has emerged in new geographical locations as a result of increased international travel [2-9], coupled with limited access to adequate healthcare, increase in population size and urbanization, failing public health infrastructures, viral mutation and adaptation, as well as increased global trade. With the emergence of chikungunya fever into new geographical areas it is important that healthcare providers, public health practitioners, and policy makers are aware of the clinical and epidemiological features as well as the potential economic impact associated with this disease to aid them in their efforts to implement effective prevention and control measures and for program planning. In this paper we address the microbiology, epidemiology, clinical presentation, treatment, prevention and control as well the potential economic impact on the areas affected in the Western hemisphere.

MICROBIOLOGY

Chikungunya virus, which was first discovered in Tanzania in 1952 [10], is a positive, single-stranded enveloped ribonucleic acid virus belonging to the *Alphavirus* genus of the *Togaviridae* family [9]. Twenty-seven alphaviruses exist that based on antigen properties, have been grouped into 7 antigen complexes [9]. Of these 7 antigen complexes, chikungunya virus belongs in the Semliki Forest complex [11]. Alphaviruses are spherical, 60-70 nm in diameter, have a single capsular protein, and their envelope contain 3 glycoproteins (E1 to E3). All alphaviruses contain E1 and E2, only the Semliki Forest virus has the third (E3) [12]. Complement fixation, haemagglutination antibodies and neutralization antibodies target primarily the E2 glycoprotein [11]. On the basis of the E1 glycoprotein phylogenetic analysis, chikungunya virus has been divided into 3 groups: West African; Asian; and East, Central, and South African (ECSA) [11]. In 2004 the Indian Ocean Lineage (IOL) evolved from the ESCA group and has been responsible for most outbreaks in Asia to date [13].

Genetic analyses of the E1 and E2 glycoproteins have identified mutations that affect the transmission of the virus by mosquitoes. In the ECSA group, the alanine to valine mutation at the E1-226 position (E1-A226V) increases the infectivity for *Aedes albopictus* mosquitoes [14] thereby making this variant more effectively transmitted by this species of mosquito. Other mutations in the E2 glycoprotein have been shown to influence the infectivity for mosquitoes. When the E1-A226V mutation is present, the glycine to aspartic acid mutation at the E2-60 residue (E2-G60D) increases the infectivity for both *A. albopictus* and *A. aegypti* [14] while isoleucine to threonine mutation at the 211 residue (E2-I211T) increases infectivity for *A. albopictus*

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only [14]. Tsetsarkin *et al.* [13] demonstrated that the presence of the threonine on the E1 protein at position 98 in the Asian group, suppressed *A. albopictus*' response to the E1-A226V mutation in this viral group. The extrinsic period for the virus in either *A. aegypti* or *A. albopictus* ranges from 2 to 10 days depending on factors such as viral lineage, virus variant, and environmental temperature [15-17].

Chikungunya fever virus belongs to the Old World alphaviruses that are typically arthritopathic [18], however, the pathogenesis associated with infection is not fully understood. The virus has been shown to replicate in fibroblast and myoblast cells [19]; macrophages play an integral role in the acute infection with activation of the innate immune system [19-22], and subsequent activation of the adaptive immune system [20-22]. Waquier *et al.* [20] compared the levels of 50 cytokines, chemokines, and growth factors in blood samples obtained from patients during the first week of infection and uninfected controls. The authors showed that there were several proteins that were at significantly higher levels ($p < 0.05$) in patients than in controls irrespective of the time point at which the samples were taken [20]. During the acute stage of infection, multiple chemokines and cytokines such as interleukin (IL) 16, IL-17, monocyte chemoattractant protein (MCP) 1, and Interferon (INF)-gamma-induced protein (IP) 10 were produced in infected patients [20]. However, the primary innate response was associated with IFN α [20]. With time, the host's antiviral defense system increased with the attraction of leucocytes as a result of proinflammatory proteins such as the macrophage migration inhibitory factor (MIF), macrophage inflammatory protein (MIP) 1 β , IL-6, and IL-8. Eventually, anti-inflammatory IL-1 receptor antagonist (IL-1RA) molecules were produced in an effort to reduce the inflammatory process. There was evidence of an adaptive immune response by day 2 with the increase in primarily cluster of differentiation (CD) 8+ T lymphocytes, however, by day 3 the ratio of CD4+ T cells was more than three times that of CD8+ T cells, suggesting a switch from cellular to humoral response [20]. Viral load has been shown to be correlated with the level of the inflammatory response [21] but is not a good predictor of chronic disease [23]. Chronic arthritis is a frequent outcome of infection and the underlying pathway to this outcome is still to be elucidated. However, Gérardin *et al.* [24] in a study of 346 infected adults on Réunion island showed that the predictors for relapsing and lingering chikungunya-associated rheumatism were increased levels of chikungunya virus-specific IgG antibodies, having initial severe rheumatic musculoskeletal pain, and increasing age, while Hawman *et al.* [22] compared experimentally infected wild type and B and T cell deficient mice and demonstrated that chronic musculoskeletal problems may be due to joint tissue specific persistence of chikungunya virus.

EPIDEMIOLOGY

Since its discovery in 1952, chikungunya virus has become endemic throughout sub-Saharan Africa. Due to increased international travel, the virus has also been identified in European and North American travellers returning from endemic areas [5, 25, 26] It has caused several outbreaks in Africa, Asia, and Oceania, the largest

being the outbreak in 2005 on the Island of Réunion that was caused by the ECSA group [27]. Autochthonous transmission subsequent to imported cases has been reported in Europe [28, 29] and most recently an outbreak that started December 2013 in Caribbean has spread to Central, South and North America. As of November 2014, 14,705 autochthonous confirmed cases and 874,103 suspected cases have been reported in this outbreak [30]. Sequence analysis has indicated that this outbreak is associated with the Asian group [31]. These recent outbreaks demonstrate how quickly transmissions may occur within a geographical region. In addition to vectorborne transmission, intrauterine [32], and nosocomial [3] transmission have been documented. While primates are considered to be the main animal reservoirs, some debate continues regarding the range of animal reservoirs that exist [33]. In Africa, the sylvatic cycle is maintained between primates and mosquitoes with spill over into humans. In other parts of the world, an urban cycle exists that is maintained between viremic humans and mosquitoes [11]. The specific role that mosquitoes play in maintaining the cycle is still being studied, however recent studies have shown that both vertical [34] and venereal [35] transmission occurs in *A. aegypti* mosquitoes. Outbreaks occur in cycles when there is a reduction in the local herd immunity [11].

CLINICAL DISEASE

After an incubation period that ranges from 1-12 days (average 2-5) [11, 32], patients develop an acute febrile illness in which the fever can be saddlebacked in nature. One to two days after the fever begins, a noncoalescing macular or maculopapular rash with or without pruritis and a burning sensation lasting 1 to 4 days appears on the face, abdomen, thorax, back, limbs, palms and/or soles [11]. Headache, nausea, vomiting, photophobia, and severe bilateral polyarthralgia that is frequently accompanied by joint swelling also occur [11]. Primarily the wrists, ankles, fingers, knees, and shoulders are affected [36, 37]. Acute disease lasts up to two weeks [21], however acute polyarthralgia lasts on average 2 months [38]. This may evolve into chronic arthritis with affected joints showing on X-rays and magnetic resonance imaging a narrowed joint space, periarticular osteopenia, bone erosions, and synovial thickening in chikungunya infected patients [38] Simon *et al.* [39] described 3 forms of chronic chikungunya fever manifestations, all of which may occur simultaneously in a patient: "(1) finger and toe polyarthrits with morning pain and stiffness; (2) severe subacute tenosynovitis of wrists, hands, and ankles; and (3) exacerbation of mechanic pain in previously injured joints and bones." The authors in that prospective study showed that 48% of persons followed for 6 months remained symptomatic, others have identified persons with severe debilitating pain up to 27.5 months after an outbreak of chikungunya fever [40]. Frequently, disease is benign however, neurological symptoms such as meningoencephalitis and neuropathy, cardiovascular disease presenting as myocarditis and or pericarditis, renal failure, hepatic and multiorgan failure, and ocular disease may occur [41]. Mild haemorrhaging may occur and has been seen more frequently in infections occurring in Asia [42]. Rarely patients may report bilateral erythema and swelling of the

pinnae [43]. The blood profile in both mild and severe cases includes elevated liver and muscle enzymes, mild thrombocytopenia, leucopenia or cytopenia, and nonregenerative anaemia [11]. Disease presentation in children has been thought to be similar to that in adults with some exceptions, (1) the rash may be vesiculo-bullous or epidermolysis bullosa; (2) arthralgia and arthritis are rare, and (3) watery stool may occur in infants [44]. However, the 2005-2006 outbreak on the island of Réunion showed the potential for severe disease in children that may range from encephalitis to death and result in long-term sequelae in survivors [45]. Intrauterine infected neonates born to perinatally infected mothers develop symptoms within 3 to 7 days of birth. These symptoms include, increased evidence of pain as measured on the Echelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale, fever, rash, conjunctival hyperemia, pharyngitis, upper respiratory tract disease, peripheral oedema, feeding problems, diarrhoea, haemorrhaging, neurological problems and occasional death [27, 32]. Congenitally infected children also have evidence of thrombocytopenia, leucopenia, and hypocalcaemia, decreased levels of prothrombin, and elevated liver enzymes [33].

While ocular disease may occur concurrently with systemic disease, it frequently occurs as a unilateral or bilateral disease 1 month to 1-year post-systemic disease [28, 46]. Signs and symptoms include photophobia, conjunctivitis, eyelid swelling, and/or retroocular pain [28]. Collectively, these may be categorized as anterior or posterior uveitis [28]. Anterior uveitis is mild granulomatous or nongranulomatous, accompanied by pigmented diffuse or globular keratic precipitates that are located centrally or over the entire corneal endothelium, and stromal oedema [28, 47]. Posterior synechiae may occur but are rare and increased intraocular pressure occurs in the presence of open angles. Patients may present with ocular hyperemia, pain, photophobia, blurred vision, and floaters. It should be noted that the prognosis is usually good for anterior uveitis [28]. Patients with posterior uveitis may present with a history of blindness, colour vision defect, central or centrocecal scotoma and peripheral field defects [28]. They may have a normal anterior segment and normal intraocular pressure. The posterior pole retinitis is confluent and the vitreous reaction is not intense. Other findings include, optic neuritis, neuroretinitis, and retrobulbar neuritis [28]. Posterior uveitis tends to have a worse prognosis compared to anterior uveitis. Chikungunya infection has been reported in a case of Fuchs' heterochromic iridocyclitis [48].

Although the attack rates are high [12], in general, the case fatality rate is low; approximately 0.1% [11] with the highest death rates noted among infants and persons older than 50 years of age [42]. The symptomatic to asymptomatic infection ratio is approximately 2:1 [49] and it has been shown that asymptomatic persons may develop viremic loads as high as symptomatic persons and therefore present a potential threat to the blood supply [50, 51]. In addition, Couderc *et al.* [52] isolated chikungunya virus from corneal specimens taken from asymptomatic persons on La Réunion, this could also represent a potential for transplant-associated transmission.

Infection with chikungunya virus provides life long immunity and is protective across all 3 genotypes [11, 31]. However transplacentally acquired antibodies will provide protection only until 9 months of age [49].

DIAGNOSIS

Clinically, chikungunya fever must be differentiated from dengue fever, West Nile fever, O'Nyong O'Nyong, Ross River virus, Sindbis virus, urban yellow fever, malaria, Fuchs' heterochromic iridocyclitis associated with cytomegalovirus or rubella virus infections, and rheumatoid arthritis [28, 38, 53]. Compared to dengue fever, the incubation period for chikungunya is much shorter 2 to 5 days vs 2 to 14 days. In addition, decreased platelet counts; severe haemorrhage and shock are rare with chikungunya fever, while rashes are more common with dengue fever [28]. Cytomegalovirus-associated Fuchs' heterochromic iridocyclitis frequently occurs in males, Asians, and older patients, and rubella virus-associated Fuchs' heterochromic iridocyclitis is more frequently seen in European patients [53]. The clinical triad of fever, rashes and arthralgia are suggestive of illness with chikungunya virus [54]. Confirmatory diagnosis requires laboratory confirmation from blood or serum and when neurological symptoms exist, cerebrospinal fluid specimens may be tested. Virus isolation and molecular techniques are valuable during the viremic stage that peaks 3 to 8 days after symptoms appear [50]. Virus isolation can be accomplished using a wide variety of cell lines but must occur in a biosafety-level 3 facility. Molecular biology methods such as the reverse transcriptase polymerase chain reaction or real-time loop-mediated isothermal amplification assay can be used to detect and genotype chikungunya as well as to determine viral load [28, 55]. These methods are best used up to 4 days post onset of illness [56]. Chikungunya-specific IgM antibodies appear on day 5 post-onset of illness and decline 3 to 6 months after infection [32, 55], while IgG antibodies appear on day 15 post-onset of illness and can persist for years [32]. Therefore, serology is most useful when specimens are taken 5 days after the onset of disease and 10 to 14 days post-infection [55, 56]. Antibodies can be detected using an enzyme-linked immunosorbent assay test, the haemagglutination inhibition, or the plaque reduction neutralization test [14, 55]. This outbreak in the Western hemisphere has many unconfirmed cases, as many patients test negative despite having symptoms. This may be a result of the several factors, including the time lag between infection and specimen collection, quality control measures that influence test outcome such as break in the cold chain or laboratory technician skill, or the inherent validity of the tests being used. Blacksell *et al.* [57] reported low sensitivities in two commercially available tests for diagnosing acute chikungunya fever.

The use of tests for anti-nuclear antibodies, urine uric acid in combination with X-rays and magnetic resonance imaging of affected joints as well as chikungunya virus specific tests is of value in diagnosing chikungunya-associated arthritis.

TREATMENT

Treatment for acute systemic disease is primarily symptomatic (pain killers and/or anti-inflammatories), with most patients reporting improvement in 7-10 days [39]. When refractory arthritis, tenosynovitis, nerve entrapment syndromes, or Raynaud phenomenon is present, the regimen may be supplemented with short term systemic corticosteroids and disease modifying anti-rheumatic drugs [28, 38, 39]. Treatment for ocular disease focuses on the management of inflammation. This may be accomplished by the use of topical or systemic steroids [58]. Topical and oral painkillers may be given to control pain. Mydriatics, and non-steroidal anti-inflammatory drugs may be added to the regimen when needed [58]. Antiglaucoma medications may be used in the presence of uveitis-induced glaucoma. The use of acyclovir has also been reported to be successful [41].

ECONOMIC IMPACT TO THE WESTERN HEMISPHERE

Given that once infected, recovery can take months to years mainly as a result of the disability associated with chronic arthralgia [49] the economic burden due to loss of income in persons who are unable to work for extended periods can be devastating. Krishnamoorthy *et al.* [59] in a 2006 study in India estimated a Disability Adjusted Life Years (DALY) of 45.26 per million population associated with chikungunya fever, though lower than what was observed for dengue fever, this estimation did not include mortality data and most likely underestimated the burden of disease associated with chikungunya fever. This outbreak of Chikungunya fever started in the Caribbean where the islands are in close proximity to each other, there is frequent travel between the islands for personal and professional reasons and commerce, as well as the lifestyles and climate also increase the probability of infection and transmission. Adding to this, many people in these affected areas are uninsured, have limited access to healthcare, the countries have limited resources for diagnosis and treatment, and limited ability to respond to vector surveillance and control.

It has been shown that wind-dispersed insects were able to travel across the Torres Strait from Papua New Guinea to Australia [60]. Thus, where islands are close as in the Caribbean, control on one island may be easily destabilized by wind-borne insects from a neighbouring island that has not yet established control. This could result in a cycle of reinfestation and potentially drive up the cost of vector control in the region. Tourism accounts for a high percentage of the gross domestic product of the countries in the Western hemisphere where the outbreak is on-going. This outbreak of chikungunya fever may deter tourists from these areas and have a huge impact on the local economies. Modrek *et al.* [61] looking at the effect of malaria elimination on tourism, suggests that it may be more cost effective to focus efforts on the tourist-concentrated areas, therefore in the resource poor countries of the Western hemisphere, this may be a viable option to retain tourist dollars. Loss of tourism dollars would feed the cycle of having insufficient funds for vector control, diagnosis, and treatment, thus the long-term impact of this outbreak is yet to be felt and measured.

CONTROL AND PREVENTION

No vaccine is currently commercially available for the prevention and control of chikungunya virus. Current options rely on environmental control, personal protection, early diagnosis and isolation of infected persons [62]. To effectively prevent and control outbreaks of chikungunya fever require an integrated approach. Both human and vector surveillance play an integral role in prevention and control efforts because, in addition to providing an early warning signal, surveillance allows on-going revision of control strategies as needed [63]. In warm climates, ideally, surveillance for vector-borne diseases should be continuous, but at a minimum should begin 2 to 3 months prior to and during the rainy season [64], in temperature zones, this should occur during the mosquito season that may be as early as May or as late as November. Important in the control is an understanding of the vector ecology. *A. aegypti* is frequently found in urban areas vs *A. albopictus* which is found most frequently in more rural areas [65, 66]. Environmental factors such as temperature and rainfall affect the distribution of *A. albopictus* and *A. aegypti* with *A. aegypti* preferring warmer climates [65]. Water storage has been shown to be a risk factor for the presence of mosquitoes. However, the container type used for water storage has been shown to affect both species of mosquitoes differently [65]. *A. albopictus* is more frequently found in drums, tyres, and jars while *A. aegypti* is more frequently collected from drums and jars, therefore targeting these specific sites may be of value [65]. Patil *et al.* [67] in India showed that combining personal protective measures such as repellants and bed nets with efforts that reduce water collection sources in the community and around the home was effective in reducing the incidence of chikungunya. They also noted, that in situations when residents were forced to store water as a result of intermittent water supply, by the establishment of “dry days” in which there was weekly emptying of water containers, scrubbing, washing, drying then refilling the containers contributed to effectively reducing the incidence of disease. While the use of “dry days” may be a good supplement, other measures are needed that are tailor-made for specific regions in the Western hemisphere; for example in the Caribbean where in the rural areas many homes have deep in-ground water tanks that collect rain water for domestic use, it is not uncommon to see mosquito larvae swimming in these tanks. Therefore, these water sources should be treated with larvicides. However, the average annual retail cost for treating these water sources at 2015 prices is estimated to be at least \$13 US per year for a tank that is 10 feet by 10 feet in dimension [68].

The use of insecticide-treated bed nets to prevent mosquito bites in infected and uninfected persons is recommended. However, proper education on how to use these nets is essential. Current control efforts of the outbreak in the Western hemisphere are hampered by the fact that at times there are no locally available effective personal protective agents such as insect repellents, due to the increased demand, the lack of funds to meet the demand as well as a sometimes bureaucratic system that prevents or delays importation of these products. Transmission is also influenced by the fact that many people still have limited or

inaccurate knowledge about the disease and assume they are not at risk because of several factors including consumption of special diets, or the use of specially prepared “anti-chikungunya” potions. They may also be unaware of the symptoms of chikungunya and not visit a healthcare provider for diagnosis, treatment, and advice on preventive measures. This is particularly important given that persons should avoid being bitten by mosquitoes from the first 8 days after the onset of symptoms. Further complicating the matter is the fact that conspiracy theories are alive and these compete with proven scientific dogma. Therefore, appropriate and timely education is an essential part of prevention and control.

Other factors in the control and prevention are the role of asymptomatic persons. Given that they can be viremic, there may be a need to make recommendations to travelers returning to nonendemic areas from endemic areas regarding mosquito avoidance during the first 20 days after their return. Similar to West Nile virus, chikungunya shows the potential for blood and transplant-associated transmission that will require additional recommendations for the blood supply and organ and tissue donations during outbreaks and in endemic areas.

CONCLUSION

In recent years, the Americas have experienced several emerging vector-borne diseases. Between 1952 and 1965, 19 countries in Latin and Central America eliminated *A. aegypti* the main vector involved in the transmission of dengue fever, yellow fever, and chikungunya fever. However, by 2007 all of these countries were reinfested as a result of the fact that not all countries were willing to eliminate the vector thus regional *nidi* existed, population shifts occurred to urban areas that overburdened the fragile infrastructure, economic factors limited expenditure on maintaining the vector-free status as well as a slow response to reinfestation [69]. In addition, in the mid-1980s *A. albopictus* was imported into the United States (US) from Asia and is now fully established throughout the region. *A. aegypti* is active mainly at dusk and dawn while *A. albopictus* is active throughout the day and while both species have shown a high affinity for mammalian blood, *A. albopictus* has consistently shown a higher preference for human blood [70-72]. Therefore, this new vector increases the transmission risk to humans. In 1999, West Nile virus was first recognized in New York City and is now endemic throughout the hemisphere. By the early 1960s malaria was eliminated on the island of Jamaica [73], however as a result of increased international travel and or commerce, the recent outbreak in 2006 in Jamaica was linked to a single source introduction of the Haitian isolate [74]. Since 2004, travel to the Americas has shown an overall increasing trend that increases the risk of transmission of diseases in which humans play a role in the transmission. Prior to the outbreak in the Caribbean, between October and December 2012, 84.4% of travellers from chikungunya endemic countries to the Caribbean arrived from South Africa, India, China, the Philippines, and the French territory of Réunion [75]. The recent importation into Miami, Florida from the Caribbean is not surprising as between May and July 2012; The US was the top destination from chikungunya endemic areas of the

Caribbean [75]. The fact that asymptomatic persons infected with chikungunya virus can be infectious for mosquitoes makes this disease even more challenging to control and there may be a need to revisit current guidelines for prevention and control during outbreaks and in travellers from endemic countries. The issue of mosquito eradication needs to be revisited in resource poor areas.

CONFLICT OF INTEREST

Both authors declare that they have no conflict of interest with regard to this work.

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