Chikungunya fever: A review of a re-emerging mosquito-borne infectious disease and the current status

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Chikungunya virus is an arbovirus, borne by Aedes mosquitoes. It belongs to the family Togaviridae and genus Alphavirus, which can be further classified into encephalitic viruses and arthritic viruses. Chikungunya is grouped under arthritic viruses along with O’nyong-nyong virus, Ross River virus, Sindbis Virus, Mayaro, Barmah Forrest Virus and Semliki Forest virus. It was first isolated in 1953 in Tanzania and is now an emerging infectious disease, causing epidemics in Africa, Asia and Europe. Explosion in global travel, increasing volumes of traffic and speed coupled with the enlarging geographic range of Aedes mosquitoes have fueled the rise in chikungunya infections and its medical importance. Infection by chikungunya virus is characterized mainly by fever, joint pain with or without swelling, and rash. In some infections, chronic arthritis results and has a debilitating effect. In recent epidemics, there have been atypical presentations as well, including vertical transmission and deaths. Diagnosis of chikungunya is usually clinical however it may be clinically indistinguishable from dengue fever caused by dengue virus. Diagnosis can also be achieved using serology, nucleic acid amplification, immunohistochemistry and virus culture. Currently, there is no vaccine or specific treatment for chikungunya and treatment is only supportive.

This review will discuss the epidemiology of chikungunya infection, the symptoms and signs of infection, diagnosis and treatments available. Potential methods of diagnosis and treatments will also be outlined.

Keywords Chikungunya, alphavirus, Aedes, arthritis

1. Introduction

Chikungunya virus (CHIKV) is an arbovirus belonging to the family Togaviridae and genus Alphavirus, which can be further classified into encephalitic viruses and arthritic viruses. There are 29 viruses belonging to the genus Alphavirus with 6 under the arthritic virus group. They are O’nyong-nyong virus, Semliki forest virus, Ross River virus, Sindbis virus, Mayaro virus and CHIKV [1]. Examples of encephalitic viruses are Western equine encephalitis and Venezuelan equine encephalitis virus [2].

The name Chikungunya originates from Makonde, a language spoken in Tanzania where it was first isolated, and means “that which bends up” or “stooped over” or “walking bent over” or “bent walker”, referring to the posture patients assume with the resulting arthralgia [3]. With drastic increases in global travel resulting in increased volume and speed of traffic coupled with environmental change resulting in increased vector distribution, there have been numerous new and re-emerging diseases, creating new challenges for policy makers, researchers and modern medicine to surmount.

2. Chikungunya virus

CHIKV is a single-stranded, positive-sense RNA virus and has a diameter of 60-70nm that comprises of a nucleocapsid enclosed within a phospholipid envelope (Figure 1). The genome is about 11.8Kb and has 2 open reading frames (ORF), encoding a non-structural polyprotein and a structural polyprotein. The non-structural polypeptide is processed to form 4 non-structural proteins and the structural polyprotein is cleaved to form protein C, E3, 6K, E2 and E1 [1]. Three phylogenetically distinct groups with distinct antigenic properties, based on differing partial CHIKV E1 protein sequences, have been identified namely the Asian phylogroup, West African phylogroup and East, Central and Southern African phylogroup [1, 4].
3. Reservoirs and Vectors

CHIKV can be both endemic and epidemic. It is maintained by two different transmission cycles, specifically sylvatic and human – mosquito – human [4]. In sylvatic cycles, the main reservoirs for CHIKV are mainly non-human primates, rodents, birds and potentially other vertebrates [5-8]. During epidemics, human beings become a reservoir as well.

In areas where CHIKV is endemic, there is usually a range of vectors, reservoirs and a local population with high herd immunity probably due to numerous and continuous transmission [5]. On the other hand, in epidemics, there is usually just one or two vectors, namely *Aedes aegypti* and *Aedes albopictus* and a local population with low herd immunity.

For sylvatic cycles, various vectors such as *Aedes furcifer*, *Aedes taylori* and *Aedes luteocephalus* and other species such as *Culex ethiopicus*, *Anopheles costanti* and *Mansonia fuscopennata* have been implicated [5, 8]. Otherwise, the usual main vectors in epidemics are the anthropophilic *Aedes aegypti* and *Aedes albopictus* with *Aedes aegypti* considered to be the primary vector traditionally.

New and re-emerging arboviruses usually have associated changes in vector characteristics as well [9, 10]. There has been data suggestive of *Aedes albopictus* superseding *Aedes aegypti* in different areas [11]. The recent 2005-2006 Réunion outbreak, was primarily caused by *Aedes albopictus*, traditionally considered to be a secondary vector for CHIKV in previous outbreaks. The virus strain implicated was also associated with a mutation in the E1 envelope gene, where there is a change of alanine to valine at position 226 [12, 13]. This mutation appeared to provide a selective advantage for replication and transmission via that species. *Aedes albopictus* was also implicated as the primary vector in the 2007 Italy and 2007 Gabonese outbreaks [13].

The ability of CHIKV to be transported by infected globetrotters to disease-naïve locations but with established vectors and generate epidemics is typical of an emerging infectious disease. In countries where *Aedes aegypti* and *Aedes albopictus* are endemic, imported cases can result in epidemics regardless of the economic development. In the case of *Aedes albopictus*, there has been an increase in the geographical distribution via increased human mobility and trade of water-containing objects such as car tyres [14]. It can now be located in South East Asia, its origin, Madagascar, Indian Ocean, Africa, Southern Europe and North and South America [11, 14].

4. Epidemiology and Geographical Range

CHIKV was first isolated and described in 1953 in Newala, Tanzania, a central East African nation, where patients were described to have acute onset of fever associated with rigor, joint pain and rash [15].
In the 1960s, CHIKV was considered an uncommon tropical infection and was largely unknown. From 1954-2000, epidemics occurred mainly in Africa and Asia (Thailand, Cambodia, India, Vietnam, Malaysia, Burma, Indonesia, Pakistan, and the Philippines) [16, 17]. In the period between 2000 to 2005, there were relatively few epidemics with only a few areas reporting outbreaks. By 2000, CHIKV was considered endemic in 23 countries [17]. From 2001-2003, Indonesia reported at least 24 outbreaks of CHIKV infection out of which 11 were serologically or virologically confirmed and the remaining based on clinical grounds. In 2001, Malaysia and bordering countries also reported outbreaks [16]. In 2004 however, epidemics occurred in Kenya and in 2005, spread to the Comoros where it then subsequently spread to the Indian Ocean islands [17]. This caught global attention and thereafter, epidemics occurred in India, Sri Lanka, Singapore, Malaysia and Italy [18-20]. From 2004 onwards, the outbreaks were caused by a variant of the East, Central and Southern African phylogroup [20]. Re-emergence of CHIKV is unpredictable, with intervals between consecutive epidemics ranging from 7 to 20 years, as it is in the case of Indonesia, where cases were reported from 1973 to 1988 and then from 2001 to 2003 [16].

There have been imported cases identified in Europe as well, specifically Germany, Switzerland, United Kingdoms, Belgium, Czech Republic, Spain, Italy, France and Norway [17]. China, Taiwan and Japan have also reported imported cases and the United States of America have documented cases too [17]. With the occurrence of imported cases, there is a risk of a following epidemic. Imported cases into countries with established vectors can result in epidemics as in the case of the 2005 Réunion outbreak. Trade and travel was implicated in the introduction of CHIKV onto Réunion island which consequently resulted in 266,000 cases [21].

5. Symptoms and Signs

The incubation period for CHIKV typically ranges from 2-4 days but can range from 1-12 days [15, 22]. Viremia typically lasts 2-10 days [22] and is higher in newborns and adults above the age of 60 [23] at more than $10^8$ copies/mL. Unlike other arbovirus infections, CHIKV infection appears to be mostly symptomatic, [24] with serological surveys reporting asymptomatic infection in only 3-25% of people. [25, 26] These people have detectable serum antibodies but no self-reported symptoms.

5.1 Typical presentation

The classic triad of symptoms includes fever, arthralgia and rash distributed on the trunk, limbs and face. Among the patients, the most common clinical features were fever (100%), arthralgia (90%), rash (50%) and conjunctivitis (40%) [27]. Other less common symptoms include tenosynovitis, myalgia, headache, retro_orbital pain, pharyngitis, nausea, vomiting, lymphadenopathy, asthenia and dysgeusia [28, 29]. For example, lymphadenopathy was only reported in around 9% of patients, [29] with the posterior cervical lymph nodes being the most commonly involved group [30].

5.1.1 Fever

Onset of fever is usually acute and is associated with chills and rigor. It precedes the rash and joint pain and usually reaches as high as 40°C and can remit after 4-5 days resulting in a “saddleback” fever [15, 17]. Convulsions have been reported to occur as well [29].

5.1.2 Arthralgia

The arthralgia is often symmetrical, migratory, polyarticular and involves peripheral joints, most commonly, the fingers, wrists, elbows, toes, ankles and knees [30, 31]. However, 27% of cases may have asymmetrical oligoarthralgia or polyarthralgia or involvement of the proximal joints [29, 31]. Atypical presentations such as Baker’s cyst and hygromas may also occur [31].

Arthritis with joints involved being swollen has been reported in 31.8% of cases [30] but fluid accumulation is rare and there are usually no other signs of inflammation such as redness or warmth.

The pain is intense and is worse in the morning, improved with mild exercise but exacerbated if exercise is strenuous [32, 33]. Patients who suffer from arthralgia often have limited ability to perform the activities of daily living [31, 34]. Activities most commonly affected include difficulty in sitting, lying down, standing straight as well as walking [35].

5.1.3 Chronic arthralgia

Most symptoms would resolve on day 10 of infection but arthralgia may persist. Chronic arthralgia is a characteristic feature of CHIKV infections in adults and can persist for months to years [33-38]. A depressive reaction is often associated with chronic arthralgia [22].

A prospective observational study in 2007 on 47 imported cases in France reported arthralgia in 80% of cases after 10 days [31]. In a study on 69 travellers involved in the 2005 outbreak of CHIKV in Indian Ocean islands, India and Asia,
69% of infected travellers had arthralgia for more than 2 months and 13% had arthralgia for more than 6 months [37]. However, in two other studies with 88 and 147 participants, 63.6% and 57% of participants reported arthralgia more than 1 year after infection [34, 38]. In a study on 107 cases in the 1970s northern Transvaal epidemics, 12.1% continued to have symptoms even after 3-5 years later with 3.7% having occasional stiffness, 2.8% having persistent stiffness and 5.6% having persistent stiffness and pain [33].

Patients most affected by post-CHIK arthralgia were the elderly [36] and adults with comorbidities of diabetes, alcoholic liver disease and impaired renal functions. Thus this chronic stage of disease does not occur in all patients but appears to be dependent on age, as arthralgia is milder in children, and presence of comorbidities.

The pathogenesis of chronic arthralgia is unknown, however cytokines are believed to play an important role. Symptoms experienced are similar to those of rheumatoid arthritis, a systemic inflammatory disease primarily involving joints and inflammatory cytokines such as IL-1beta, IL-6 and TNF-alpha [22]. However, post-CHIKV arthritis can be differentiated from rheumatoid arthritis via normal radiological findings [36].

Adding weight to the roles of these cytokines, global analysis of sera for cytokines, chemokines and growth factors from infected patients have associated increased levels of IL-1beta, IL-6 and TNF-alpha with severe CHIKV infection, defined as high fever of more than 38.5°C or heart rate of more than 100 beats per minute or platelet count less than 100 X 10^9 g/L [27]. This also suggests the potential of using these biomarkers in identification of patients with serious infection and that modulation of these biomarkers may reduce the severity of disease.

5.1.4 Chronic tenosynovitis
Chronic hypertrophic tenosynovitis is also more common in the chronic stage and may progress to nerve tunnel syndromes in the wrists and ankles such as carpal tunnel syndrome. Extensors and flexors of the wrist and finger joints are commonly involved. There may also be associated peripheral vascular disorders such as Raynaud’s phenomenon [31].

5.1.5 Chronic myalgia
Patients may also suffer from persistent myalgia [22, 39]. The pathogenesis is currently unclear but CHIKV antigens have been isolated in human muscle satellite cells via immunofluorescence and immunoperoxidase staining [40]. This is suggestive of infection by CHIKV within human muscle cells. Therefore, these cells may function as reservoirs, leading to chronic myalgia.

5.1.6 Rash
Proportion of patients developing skin lesions is variable, ranging from 27-75% [37, 41] and lesions associated with CHIKV infection are also variable [42]. Vesiculobullous lesions, especially in infants, aphthous ulcerations and subungal hemorrhages have been described. The rashes usually occurs on day 3-4 but can occur earlier [15] and starts as a flush which develops into a rash which lasts 3-4 days. The commonest rash affecting 35.7% of suspected CHIKV-infected cases with eruption is a mobiliform or maculopapular rash. [43] The skin lesions mainly involve the trunk and peripheries but may also involve the palms, soles and face. It may be non-pruritic or pruritic. [29, 41, 43] They can be similar to those described in dengue fever infection with islands of sparing and cannot be differentiated clinically [44].

5.2 Atypical presentation
CHIKV is traditionally considered to be benign and non-life-threatening. However, recent outbreaks had atypical presentations of the disease. The Réunion outbreak was the first outbreak with descriptions of severe cases of CHIKV. The more common complications include respiratory failure, heart failure, meningoencephalitis, acute hepatitis, severe skin involvement, other central nervous system involvement and kidney failure. Most occurred in patients above 65 years old with underlying medical conditions [45].

For the Réunion outbreak, the relatively high number of severe presentations may be attributed to mutations found in the viral strains isolated and to the population being immunologically naïve to CHIKV. The outbreak was the first introduction of CHIKV to Réunion which has no other tropical disease except for dengue. In addition, these severe forms occurred mainly in patients with underlying medical conditions such as diabetes, ischemic heart disease, alcoholic liver disease or renal failure or iatrogenic conditions such as Reye syndrome [34, 46].

The important negative prognostic factors were age and concomitant diseases [34]. Multivariate analysis of the Réunion outbreak identified age above 60 years and underlying medical conditions as independent risk factors for severe complications and age above 85 years as the only risk factor for mortality [47].

5.2.1 Mortality
Excess deaths were reported during the Réunion and Mauritius outbreaks, mainly in the older age group. The estimated case-fatality rates for CHIK infection were 3/10 to 1/1000 and 47/1000, respectively. [45, 46, 48] In the Réunion
outbreak, 213 deaths could be attributed to the viral infection [45]. 96 serologically confirmed cases required intensive care with a 1:4 male to female ratio and a 4:1 adult to children ratio [49].

5.2.2 Neurological complications

Neurological complications have been described in several other encephalitic alphavirus such as Western equine encephalitis. As aforementioned, CHIKV is grouped under arthritic viruses however, reports in the 1960s-1970s in Asia have documented neurological complications of CHIKV infection including seizures, meningitis and encephalitis [44, 50].

Onset of these neurological symptoms is usually early, within 24 hours after onset of fever in children and on the 2nd-3rd day for adults [51]. In a 2006 retrospective hospital-based study on 30 children, the more common neurological complications with infection include encephalitis (40%), febrile fits (33%), meningitis (13%) and acute encephalopathy (13%) [52]. Other neurological complications are encephalomyelitis, Guillain-Barre, acute flaccid paralysis, optic neuritis and encephalomyeloradiculitis [51, 53, 54]. Mortality was around 10% in a review on the Réunion outbreak [55]. In a prospective study in India, the mortality rate was 30% for patients with neurological symptoms [51].

In vertical transmission cases, encephalopathy occurred in about 90% of the neonates, 40% of whom developed permanent disabilities. Hypotonia was also very common and was followed by coma, seizures and epileptic status [51, 53]. Other rare complications such as sensorineural hearing loss and hypokalemic periodic paralysis have also been described [56, 57]. Cerebrospinal fluid findings were largely normal and radiological findings unspecific. On magnetic resonance imaging, majority were normal and only in 40% of cases, were there pathological changes, specifically restricted diffusion in the white matter [58].

In vitro experiments utilizing mouse brain cells have also shown that the virus is capable of infecting and replicating in central nervous system tissue [58]. In neonatal mice and in adult mice lacking type I interferon signaling (interferon-alpha/beta receptor −/−), peripheral inoculation of CHIKV resulted in CNS dissemination through the choroid plexus with infection of ependymal and leptomeningeal cells but not neurons or glial cells [60]. This is unlike other alphaviruses affecting the CNS, where the primary cells infected are the neurons [51]. Thus CHIKV shows tropism for meninges which share a common mesenchymal origin with the peripheral muscle satellite cells.

5.2.3 Other complications

Petechiae, purpura, epistaxis, mucosal bleeding, hematemesis and melena have been reported. [34, 54] Hepatitis and cardiovascular complications such as myocarditis, arrhythmia, pericarditis and myocardial infarction have also been documented [53, 54].

5.3 Pregnancy and newborns

Prior to the Réunion outbreak, there was very little data on the risks and effects of CHIKV infection on pregnancy itself. A prospective multicenter study was conducted on 1400 pregnant women in the Réunion outbreak. 705 cases reported symptoms and infection was confirmed in 658 by serology or RT-PCR tests. 15% of the cases were infected in the first trimester, 59% the second trimester and 26% the third trimester [62].

The data showed no significant difference in risk for stillbirths, congenital malformations, pre-term delivery, low birthweight or admission to neonatal care. There was also no significant difference in hemorrhagic complications such as vaginal bleeding during pregnancy and obstetric hemorrhages [61].

Vertical transmission of CHIKV was also first documented in the Réunion outbreak. In a multidisciplinary prospective study, 7504 pregnant women were recruited and they gave birth to 7629 viable neonates. 678 of the mothers were infected during antepartum and 61 pre- or intrapartum [62].

The attack rate was 8.3% in pregnant women during the peak of the epidemic. However, most maternal CHIKV infections do not result in vertical transmission, with an overall transmission rate of only about 2.5%. Unfortunately, if delivery occurs during viremia, transmission rate may increase up to around 50% [62, 63].

Transmission during the birthing process was supported by the same study, with infection probably occurring when free virus particles in maternal blood passively passed through breaches in the placental barrier. Investigations have shown that the placenta during ante-partum was effective as a barrier for the virus, with only three documented cases of vertical transmission occurring during then. In addition, cesarean delivery was not protective and this may be attributed to the breaches occurring in the placental barrier when pregnancy is near-term, allowing transmission to occur [62].

In another study, 38 neonates were enrolled [63]. Infected neonates were initially asymptomatic and were not viremic. Symptoms only started at about day 4 after birth but this can range from day 3-7 [62, 63]. All neonates had fever, 82% had rashes and 58% had distal edema. Thrombocytopenia was found in 76-89%, lymphopenia in 47%, decreased prothrombin in 65% and increased levels of aspartate aminotransferase in 77% [62, 63]. MRI and echocardiography also revealed abnormalities [63]. 23 out of 38 neonates had typical or uncomplicated CHIKV infection which resolved by 2 weeks while 15 had complications such as hemorrhagic syndromes, hemodynamic compromise, seizures and encephalopathy as mentioned above [63].

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6. Diagnosis

In the absence of commercial vaccines and specific treatment for CHIKV, early detection and diagnosis is imperative for adequate control of infection. Clinically, CHIKV infection can be confused easily with dengue virus infection due to the similar initial presentation, geographical distribution and vectors [64]. There are differences including conjunctivitis, arthralgia and arthritis being more common in CHIKV infection however these are not definitive.

Dual infection with both dengue virus and CHIKV has occurred with both viruses isolated from the serum of the patient too, thus concurrent disease is possible [44, 50, 65]. Other alphavirus infections, especially Onyong-nyong virus and Sindbis virus infection may also present with fever and arthralgia and while some form of differentiation can occur by the different geographical range [66], it is not definitive as well. Thus, CHIKV infection usually requires a diagnostic test.

Available diagnostic methods are reverse transcriptase-polymerase chain reaction (RT-PCR), culture isolation and serology. [4, 67, 68] RT-PCR is useful in the first week of the viraemic phase, during which viremia can reach exceedingly high levels at around 3.3 X10^9 copies/ml [66]. When antibody responses appear, viral RNA levels decrease and become negligible by day 7 after onset of symptoms in almost all cases [52]. Benefits of RT-PCR include high sensitivity, reproducibility and reduced risk of contamination but serological investigations are more commonly done in the clinical setting as they are simpler, faster and cheaper [67].

IgM against CHIKV is detectable at day 5 after onset of symptoms via enzyme-linked immunosorbent assay (ELISA) and can remain detectable for 3 months while IgG is detectable in convalescence and remains so for years [55]. For serodiagnosis to be made, demonstration of CHIKV IgM antibodies in acute-phase serum sample or demonstration of a 4-fold increase in CHIKV IgG antibody titer between the acute and convalescent phase serum sample can be done. However, cross-reaction with other arboviruses such as dengue and o’nyong-nyong virus is possible, resulting in false-positives [69]. Thus in the absence of an epidemic, diagnosis should be carefully considered.

Isolation of CHIKV is considered the gold standard of strain identification and is conducted on C36/6 mosquito cells, Vero cells or mice [49, 68]. However, this is not commonly used in the clinical setting. Other methods include viral culture RT loop-mediated isothermal amplification, immunofluorescence assays and plaque reduction neutralization test [70, 71].

7. Vaccination

With the advent of increasingly numerous and widespread epidemics with significant sequelae, there is a need for an effective vaccine. CHIKV appears to elicit lasting protective immunity and there have been no reports on recrudescence or reinfection. In addition, epidemic peaks decrease as the population gains immunity. Development of vaccines which can induce similar lasting protective immunity has been ongoing through the years however many trials have been stopped due to limited demand and funding [22].

More than two decades ago, a live CHIKV vaccine was developed via 18 serial passages through MRC-5 cell cultures by the U.S. Army [72]. This attenuated vaccine, specifically 181/clone 25 (181/25) is immunogenic in humans but phase II safety trials have resulted in around 8.5% participants developing transient arthralgia [73]. There is potential reversion due to the inherent instability of RNA genomes coupled with little attenuating mutations and further work was halted. Since then, the most recent development regarding this vaccine was an agreement signed in 2006 following the Réunion outbreak. The agreement was between the United States Army Medical Research Institute for Infectious Diseases and the French National Institute of Health and Medical Research Transfert Inserm’s technology-transfer organization, to allow the transfer of information and material.

There are also new strategies implemented in the development of a CHIKV vaccine including the development of DNA chimeric vaccines and epitope based vaccines [22]. Three chimeric alphavirus/CHIKV vaccine viruses, VEE/CHIKV, EEE/CHIKV and SIN/CHIKV created using recombinant DNA technology have been used in mice with efficient immune response, little reactivity and significant protection [74].

8. Treatment

Presently, there is no targeted antiviral treatment for CHIKV infection and treatment is mainly supportive. Majority of the cases are still relatively mild although there are now more known significant sequelae. Thus an anti-viral treatment is most useful for prophylaxis in vulnerable groups such as the immunocompromised and for management of severe cases.

8.1 Present treatment options

Main pharmacological agents used currently include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS) for alleviation of symptoms and corticosteroids. For chronic symptoms, relapse is unpredictable and dosage increase is required. Short term and low dose systemic corticosteroids can be initiated during relapse. However, abuse of these
drugs can result in side effects such as thrombocytopenia, gastrointestinal bleeding, nausea, vomiting and gastritis. This can then progress on to dehydration, pre-renal acute renal failure, electrolyte disturbances and occasionally hypoglycemia and all this can contribute to the mortality rate attributed to CHIKV infection [75].

8.2 Potential treatment options

8.2.1 Chloroquine

Currently, chloroquine use is not justified as there is no conclusive evidence to its effectiveness. The antiviral effects of chloroquine were first described in 1969. [76] Subsequently, in the early 1980s, it was shown to have an inhibitory effect against replicaton of Sindbis and Semliki Forest virus. [77-79] Recent in vitro experiments using chloroquine have successfully decreased CHIKV growth [80] and use of chloroquine phosphate solution provided relief in patients [81]. However, in a 2006 double blind placebo controlled trial with 54 participants, no statistical difference in the mean duration of febrile arthralgia between the placebo and chloroquine group was found [82].

8.2.2 Ribavirin and Interferon

Ribavirin has been described to inhibit a variety of RNA viruses. Mechanism of action is through the inhibition of IMP dehydrogenase, error catastrophe mechanism by causing mutations and by interaction with viral polymerase [82]. Ribavirin coupled with interferons may have a synergistic effect on CHIKV in vitro [83]. However, use of this treatment option has many hurdles. For example, it is hard to administer and is ill-suited for large scale use in outbreaks. In addition, chronic symptoms in CHIKV infection may be immune-related and interferons boost immune response by activating B lymphocytes, T lymphocytes and natural killer cells and stimulating the release of inflammatory cytokines. Thus theoretically, it may exacerbate disease [82], however more research must be conducted for conclusive evidence.

8.2.3 Immunotherapy

Immunotherapy, in the form of human polyclonal antibody, has been used for treatment of human viral infections [84], and in alphavirus-infected animal models, passive immunization with convalescent sera from animals was protective [85, 86]. Sera from patients and monkeys who have recovered from acute alphavirus-infections have been shown to contain neutralizing antibodies in suckling mouse models. These neutralizing antibodies may bind to virions and prevent the virions from binding to cell receptors hence, blocking entry of virions into cells. When neutralizing antibodies bind to the virions, they may also cause opsonization and induce phagocytosis by macrophages. Binding of antibodies to the virion can also activate the complement system. In addition, the Fc portions of bound neutralizing antibodies may cross link with Fc receptors on natural killer cells and initiate antibody-dependent cell-mediated cytotoxicity, resulting in death of infected cells [87].

Human polyonal antibodies (CHIKV Ig) have been purified from plasma of convalescent donors and used in mouse models of CHIKV infection [88]. Results are promising with CHIKV Ig showing both prophylactic and therapeutic potential. In both IFN-α/βR-/- and immunocompetent mouse neonates, a single prophylactic dose of CHIKV Ig was found to be protective against lethality associated with CHIKV, with undetectable viral levels in the serum and no dissemination to the central nervous system. Degree of protection correlated to dose of antibodies administered. CHIKV Ig also has a therapeutic effect as it is protective against lethality when given up to 8 hours post infection. The results also support the hypothesis that viremia precedes CNS dissemination and controlling viremia prevents neurologic complications [88].

This mode of treatment is viable given the high prevalence of CHIKV infection, especially in the case of Réunion island outbreak. Large amounts of CHIKV Ig can be produced from plasma donors and can be used for prophylaxis and treatment in particular for neonates and in persons with underlying medical conditions that predispose them to severe disease.

9. Conclusion

A multitude of factors including virus evolution, climate change, absent herd immunity, change in vector characteristics and increased global trade and travel have been associated with CHIKV re-emergence. The question now is no longer if another epidemic occurs but rather when and whether we would be prepared for it. With an increase in incidence and number of severe atypical cases, there is a need to develop a better prophylactic and therapeutic strategy.

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