Emerging Vector- borne Diseases Caribbean Perspective: Should we be worried about Chikungunya?

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Abstract

Zika virus is currently attracting a huge international attention. Recently concluded Rio Olympics are a testament to the importance of public health planning and preparedness to counter the threat of emerging infections. Zika is a documented condition from 1940's and is not so extensively studied until recently. The similarity of the virus transmission and the presence of a common vector pose a significant threat to the community. The strong link of the vector to the environmental conditions is another factor that has to thoroughly explored to prevent the rapid spread that was evident in other regions of the world.

Three essential steps are proposed in the control and require further studies. Firstly, raising the awareness efficiency towards the disease. Second, the vector control and the impact of climate change on the spread of the vector needs to be understood. And thirdly, true burden of the disease and the cost of prevention to the health system need to be explored in depth.

Introduction

Currently the latest Zika virus epidemic to trigger international attention to vector-born diseases. Previously considered a mild, self-limiting illness, because of the increasing microcephaly incidence among new born babies has drawn considerable media coverage. Zika is a flavi-viral disease caused primarily by the bite of Aedes mosquitoes. The first cases of Zika were identified in monkeys in 1947 through a surveillance network for yellow fever in Uganda. Human cases were identified in 1952 in Uganda and later in Tanzania. Since then, outbreaks were noticed in several regions of the world with the more recent onset in Brazil and the association with microcephaly and Guillian-Barre Syndrome (WHO, 2016). The striking similarity with regards to the spread of the disease reminds of another emerging infectious disease introduced in the continents of Americas not so long ago. Dengue and Chikungunya viral diseases previously unknown to the region were introduced to the region and now are endemic in many countries in the Americas.

Chikungunya fever is also an acute febrile illness caused by an arthropod-borne alpha virus, Chikungunya virus (CHIKV). The virus is primarily transmitted to humans via the bite of an infected Aedes species mosquito. CHIKV was first recognized as a human pathogen during an outbreak in 1952 in southern Tanzania, Africa, and since then, cases have been identified in many countries in Africa and Asia (Robinson, 1955) (WHO, 2006). Chikungunya—often shortened to "chik" by scientists—is a Swahili word that means "that which bends up," a reference to some victims' inability to walk upright. The disease is known to occur in large parts of Southeast and South Asia, as well as in Africa (Enserink, 2006).

It is an RNA virus that belongs to the alphavirus genus of the family Togaviridae (WHO, 2014). Recent research suggests that CHIKV had caused human infections in Africa since the 17th century. In fact, Chikungunya virus itself is characterized by fever, severe myalgias and arthralgias, dermatalogical manifestations and frequently, chronic arthritis (Meason, 2016). However similarities of symptoms between Chikungunya and Dengue Virus has misled the diagnostic of the disease. In fact, both diseases cause high fever and severe joint pain, and with poor clinical knowledge and laboratory testing, DENV and CHIKV were indistinguishable (CDC, 2015). Similarly, Zika virus exhibits similar symptomatology as seen in Chikungunya and Dengue.

After its discovery, and its proper labeling, CHIKV was the cause of sporadic outbreaks in Southeast Asia, Africa and India by 1980 (Meason, 2014). Since then, its epidemiological status is endemic in Africa. However, after a major outbreak in Kenya in 2004, its status became pandemic, by spreading to the islands of the Indian Ocean and infecting over 1 million individuals (Meason, 2014). In 2005, the French island La Reunion, has witnessed a major outbreak causing previously unseen mortality rates which highlighted the virulence of CHIKV (WHO, 2006). Chronic Arthritis was reported in 93.7% of infected individuals (Enserink, 2006). Unfortunately, "Even two years later, up to 75% of infected individuals continued to complain of symptoms attributable to chikungunya" (Gerardin, 2011).

Warmer than average temperatures attributable to the Global warming and changes in rainfall patterns allow mosquito vectors to thrive at higher altitudes and at locations where they previously have not survived, ultimately leading to a spread of mosquito-borne diseases. Introduction of mosquitoes into the environment that is conducive for sustained mosquito populations complicate the situation further. While mutations to the chikungunya virus are responsible for some portion of the re-emergence, chikungunya epidemiology is closely tied with weather patterns in Southeast Asia. Extrapolation of this regional weather patterns, travel patterns combined with known climate factors impacting the spread of malaria and dengue, summate to a dark picture of climate change and the spread of this disease from south Asia and Africa into Europe to Caribbean and North America (Meason, 2016). The capability of Zika virus to undergo mutations is not completely known or researched at this stage. However, the presence of common vector of transmission is worrisome in the case of Zika.

Current Epidemiological Status of Chikungunya, its vectors, risk factors and novel intervention methods and the lessons drawn to understand Zika virus:

According to (PAHO/WHO, 2016), new cases of CHIKV are still being reported in the Caribbean, USA, and Europe. Those CHIKV cases, may be due to different CHIKV virus strains and their most compatible vectors. This differential geographical distribution of strains and vectors is affected by the geographical location of the outbreak, as well as molecular factors affecting the mosquito's infection (WHO, 2011 and Vega-Rua et Al., 2014). CHIKV is carried by two main vectors, Aedes *Aegypti* and Aedes *Albopictus*. (Yoon et al., 2015).
Chikungunya virus underwent a mutation at the E2 level of genomic glycoprotein to become compatible with *Albopictus* species (Salas et Al., 2015 and Vega- Rua et Al., 2014). In fact, Vega-Rua et Al., 2014, distinguish between CHIKV strains and their most compatible vector. The latter study declares the ability of CHIKV vectors to be infectious regardless of the CHIKV strain, however, CHIKV Transmission Efficiency (TE) and Dissemination Efficiency (DE) varied greatly between differently matched CHIKV strains and CHIKV vectors. For an example, one of the two vectors, A. *Albopictus*, has really high TE and DE rates, 96.7% and 83.3% respectively for the mutated Asian strain. For the original Asian strain, *A. Abopictus*' TE and DE are extremely low compared to *A. Aegypti*'s (Vega-Rua et Al., 2014). *A. Abopictus*' high anthropologic preference and resilience, has amplified outbreaks. After the Asian Strain's mutation, CHIKV strains infected both vectors, which have high prevalence in the Americas especially (Vega-Rua et Al., 2014).

High prevalence of Aedes mosquitoes is due to "lack of trash collection, poor municipal piped water supplies, uncontrolled urban development and insecticide resistance, weaknesses of vector control methodologies" (Salas et Al., 2015). Their prevalence is geographically and environmentally influenced. According to a Brazilian study published in 2016, *A. Abopictus*, tend to proliferate in rural outdoor areas and *A. Aegypti* is more adapted to urban indoor environments (Madariaga, 2016). Unlike the latter, *A. Abopictus* has higher resilience caused by many factors like: a higher virus dissemination and infection, a longer life span that can reach 8 weeks, a higher adaptation to cool high altitude environments and a higher rate of larva survival in dry environments (Madagaria, 2016 and Salas Et Al., 2015). Given the following, “Both vectors combined put 99% of the population of Brazil at risk of acquiring CHIKV” (Madariaga, 2016). The ability of Zika virus to use one of the two strains of the vector is completely not known. This is another factor that has to be considered in handling the virus transmission.

Selective prevalence, and acquired resilience explained above, have led to a transcontinental spread of Aedes vectors. An abundance of rich quality information about Global Geographic distribution of different CHIKV strains and their associated vectors provides a clearer understanding of Aedes mosquito migration patterns and CHIKV transcontinental prevalence. According to Gonzalez et Al., *A. Aegypti* was incriminated for the outbreak in Mexico in 2014, since it had a higher prevalence in case clustered areas compared to *A. Abopictus* (Gonzalez et Al., 2015). Gonzalez et Al. also argues that *A. Aegypti* was the main vector in outbreaks caused by CHIKV unaltered Asian strain, since it can only be carried by *A. Aegypti*.

Exploring Aedes mosquitos’ migration trends, and Zika virus strain virulence, play an important role in assessing the true risk factors of the disease for future effective intervention methods.

A very interesting study -about the prevalence of CHIKV neutralizing antibodies conducted in North Eastern Thailand, has shown a significantly low rate of CHIKV symptomatic infection among elderly, whom lived during the time of previous CHIKV exposure. This group of elderly had a prevalence of CHIKV neutralizing antibodies that seemed to be circulating in their blood for years (Nitatpattana et Al. 2014**)**.

This theory is further supported by a study that showed an association between the prevalence of CHIKV Neutralizing Immunoglobulin G3 (IgG3) antibodies their life and long protection from chronic arthritis effect (Kam et Al, 2012). It is also associated with the speed of viral clearance out of the blood (Kam et Al, 2012). Kam et Al. suggested that “The absence of early CHIKV-specific IgG3 may therefore serve as a specific marker of patients with increased risk of disease”**.** In assessing the burden of the disease, and case management techniques, further studies about CHIKV Chronic Arthritis need to be conducted. Coudrec & Lecuit, 2015, raised a very interesting theory explaining the possibility of a relationship between reoccurring CHIKV infections among previously exposed populations, and joint pain. In other words, is joint pain after CHIKV infection, due to reoccurring, continuous infections? It has to be researched if similar pattern is present in cases with Zika infection if any and, such patterns can be used to map the prevalence and spread of the epidemic. Currently, microcephaly and Guillian-Barre syndrome are attributed to the exposure of Zika virus.

A multi-facet exploration of components contributing to costs control and efficiency assurance can do no harm. Components like CHIKV herd immunity, CHIKV human reservoir, asymptomatic prevalence of CHIKV, and CHIKV chronic arthralgia were often studied and considered (Galatas et Al., 2016). Similar approach is necessary to understand the evolution of Zika virus.

Furthermore, a study performed in Mauritius post to its CHIKV epidemic, explored its population's needed herd immunity level that will that will assure protection from future epidemics. (Ramchurn et Al., 2008). In the study conducted in Maritius, cases of CHIKV dropped to 0 after couple of months only. Ramchurn et Al. suggest that seroprevalence studies can be more helpful in finding an answer to the protective effect of previous infections. The life-long immunity to CHIKV acquired after infection is broadly discussed in the literature. In fact, WHO states this statement in one of its CHIKV factsheets (WHO, 2014).

Interestingly, data collected through the history of CHIKV epidemics, statistically prove the protective effect of CHIKV previous infections from current ones (Galatas et Al., 2016 and Nitatpattana et Al. 2014).

Thirdly, accuracy of prevalence measures can be attributed to CHIKV transmission modes among humans (Vazeille et Al., 2007). It was later on proven that "the disease can be transmitted vertically from mother to fetus or theoretically by blood transfusion (although no cases have been reported so far)" (Madariaga, 2016). According to Yoon et Al., 2015, two asymptomatic blood donors in the Caribbean, had Chikungunya viral antigens in their blood.

Also theoretical, or unreported yet, CHIKV infections through saliva are potential. In a study performed on CHIKV infected mice, a high prevalence of CHIKV in their oral cavity was observed (Rolph et Al., 2016). The latter study suggests further investigation in the oral transmission of CHIKV, because if it's true, oral transmission of CHIKV will affect children and immune-deficient individuals and also, the responsibility of public health workers to warn individuals from sharing utensils, or from buccal kissing an infected individual (Rolph et Al., 2016). Currently, sexual transmission of Zika virus is postulated and is seen as a cause for microcephaly. Further investigations might prove any associated neurological conditions attributable to Zika.

As for vectors, not surprisingly, modes of transmission are also affected by geography, human urbanism and the presence of primates in the area of epidemic (CDC, 2015). CDC's public health grounds about the prevention of mosquito borne disease, differentiates between two CHIKV life cycles: 1)The Sylvatic cycle: mostly present in Africa or in jungles, 2) the urban or epidemic cycle: this cycle does not require incorporating other hosts, it can be human-mosquito- human mediated. The urban cycle is threatening, since one infected person can infect a mosquito which in return can infect other individuals. This fear is real, since several outbreaks in Europe were brought by human reservoirs, caught by Aedes, to then cause autochthonous infections to individuals who never left Europe (Baldacchino et Al., 2015). That's why, Europe's focus on effective surveillance on Aedes species is serious and effective. Because the only way to prevent outbreaks in Europe right now is by keeping mosquitoes controlled and not infected. These control methods, previously discussed, are divided into five categories: environmental (source reduction), mechanical (trapping), biological (e.g. copepods, *Bacillus thuringiensis* var. *israelensis*, *Wolbachia*), chemical (insect growth regulators) and genetic (sterile insect technique and genetically modified mosquitoes) (Baldacchino et Al., 2015).

Risk factors of CHIKV are directly linked to risk factors of Aedes *Albopictus* and *Aegypti* proliferation since human infections are solely due to CHIKV being injected in the blood by the bites of infected female Aedes (WHO, 2015). In fact, the failure to previously assess and control *A. Aegypti* in Latin American countries, after several major Dengue outbreaks, has led to the proliferation of the mosquito in those areas. This proliferation has led to the fast dispersal of CHIKV in neighboring Caribbean countries and a peak in Central America after in the recent past years (Salas et. Al., 2015). Sharing the same vectors, this proliferation and high virulence will potentially lead to Zika Virus outbreaks in both areas if Aedes population reduction wasn't addressed urgently. (Salas et. Al., 2015). To target the bull's eye, Salas et Al., identify the major risk factors linked to the Caribbean and the Central American spread. Identified risk factors include environmental factors (Rainy and temperate regions), Social behaviors (intense traveling activity, low education about CHIKV and Mosquito control methods), and biological factors (The nativity of the Mexican population to CHIKV) (Salas et Al., 2015). Addressing those risk factors as well as applying preventative measures (use of insecticides, cleaning still and stagnant water masses, apply screens to windows, conduct awareness campaigns) is the only current approved approach for reducing CHIKV prevalence.

Those methods however, haven't showed a greater efficiency in developing countries. As a proof, starting by education and raise of awareness efficiency: WHO highlights this fact by stating an example from the Ebola outbreak: Most infected individuals, did not know anything about the disease's virulence, transmission or prevention, even though affected African countries were in a state of Public Health Emergency of International Concern (Lucey, 2016). Moreover, in the CHIKV scope, a study exploring explore the link between environmental factors and socioeconomic status (SES)/education level status in the island of Mayotte, shows a close association between high risks of infection and poor education (Raude et Al., 2009). Environmental factors in Mayotte, (urban vs. rural residence) are closely linked with SES, therefore rural residence is not a risk factor of higher rates of CHIKV prevalence, it's rather a reflection of health disparities and inequities (Raude et Al., 2009).

Secondly, application of preventative measures to reduce the proliferation of Aedes mosquitoes, was not successful since the aedes *Albopictus* has been circulating in Brazil for an example, since the 1980s (Madagaria, 2016).

Thirdly, in addressing environmental factors, The Human Rights journal emphasizes the role of humans in controlling this epidemic by allocating international efforts to solve the climate change crisis (Meason, 2014). In fact there's evidence of a correlation between weather trends (precipitation and temperature) and the rise of Aedes *Albopictus* and Aedes *Aegypti* prevalence (Meason, 2014). Changes like prolonged periods of drought, followed by heaving showers - phenomenon observed in the Caribbean, and Grenada – are major environmental risk factors of CHIKV disease (Meason, 2014, Salas et Al., 2015, and Madagaria, 2016). However, knowing that environmental factors are distal risk factors and are hard to control, and given that CHIKV, Zika Virus and Dengue virus are urgent public health issues emerging epidemically, and potentially in a Pandemic manner, other strategies to control and prevent future outbreaks are investigated.
Fourthly, it is true that some insecticides were found efficient in killing Aedes mosquitoes, however, their side effect on other insects or species is unknown (Marini, 2015).

Fortunately, innovational surveillance and intervention strategies including: 1)novel vaccine candidates, 2) better diagnosis and reporting of cases, integrated vector control, and finally, 3) better assessment of CHIKV 's risk factors, its pathology and its transmission modes. These methods, are most likely to play a major role in future CHIKV, DENV and ZIKV outbreak preparedness. (Salas et Al., 2015 and Knerrer et Al., 2013).

Vector Control innovational interventions aim to slash Aedes *Albopictus*' and Aedes *Aegypti*'s virulence and abundance. Gene alteration methods like the Sterile Insect Technique (SIT). SIT, is a technique to genetically sterilize males in order to reduce the number of mosquitoes (Bart, 2014). This technique is indeed successful in producing sterile males, but it will not be applied until revising an assured technique to reverse the genetic sterilization of mosquito males. Such studies may affect the ecosystem greatly, thus its pros and cons have to be thoroughly investigated (Harvard T.H Chan School of Public health, Weekly news). Other genomic based intervention include the alteration of either RNA or a specific protein, or glycoproteins of Aedes mosquitoes. However, such studies are costly and exhibit low stability of altered genome in mosquitoes. (Weaver, 2012).

A cost effective, eco-friendly, efficient intervention is by "Biological Control". Biological control, is the use of a natural predator or parasite that will attack Aedes mosquitoes or alter their infection transmission (Johnson, 2015 and Knerrer, 2013). Infecting mosquitoes by Wolbachia, a self-spreading and self-sustaining parasite that will live within the mosquito, leading to a permeant change through future generations. "Implementation is relatively inexpensive and the benefit/cost ratios of some programs have been more than 100. Classical biological control has been used to suppress over 200 species of invasive insects and 40 species of weeds in many countries around the world" (Knerrer, 2013). Moreover, the article published by Salas et Al. in 2015, emphasizes the success of infecting aedes with different strains of Wolbachia: "*w*MelPol and *w*Mel strains which suppress CHIKV infection in *Ae. aegypti* and *Ae. albopictus*, respectively, leading to complete prevention of infection by CHIKV (Salas et Al., 2015).

Nevertheless, before applying any of these interventions however, a detailed assessment of the true burden of Zika disease should be the guide to allocating resources, and choosing the most effective and feasible methodology (Burt, 2014 and Ramchurn et Al., 2008).

In summary, Zika virus interventions should be only addressed after a complete assessment of Zika's risk factors, transmission modes, pathology, real magnitude, burden, and prevalence. Also, a complete assessment of CHIKV vectors' risk factors migration, prevalence, behavior, virulence should be completed prior to intervention will be able to inform the Zika virus control.

The gap in the literature falls when assessing the prevalence of CHIKV, proving the concept of herd immunity needed or obtained to fight against or obtained from an outbreak.

Should we be worried in Virginia?

This is very pertinent in view of the recent emerging infectious diseases. Chikungunya and Dengue proved to be newly introduced infections and gaining foothold not only in the Americas but more so increasingly seen in the USA. Countries in Central, Southern Americas and the Caribbean accounted for almost half-million cases in 2014 alone. In 2014, in the United States, 2811 cases of Chikungunya were reported, with majority being in travelers returning from endemic zones. This is down to 896 in 2015 and to 75 cases in 2016 respectively. There were documented cases of local transmission in the states of Florida and Texas, but the case count is in single digits. [37, 38]. With regards to Zika virus, currently, there are 81 imported cases in the commonwealth of Virginia. All of these are attributable to travel and none are indigenously acquired (CDC, 2016)

The fact that capable and common vector [Aedes albopictus] presence in our state is matter of concern. Expanding number of cases, ongoing endemic disease transmission in the areas surrounding the United States, increased travel to the States from endemic zones put the Commonwealth on the verge of an impending outbreak.

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