UNIVERSITY OF GRONINGEN

The burden of chikungunya disease

The spread of chikungunya virus and its social consequences

J.M.Slager

March-April 2015

Chikungunya is a virus transmitted mainly by the Aedes aegypti mosquito. Outbreaks have been witnessed in Africa and Asia, but the Caribbean now also faces the threat of the virus, with epidemics already being reported. Chikungunya consists of an acute and a chronic phase. The acute phase lasts 7-10 days, with fever joint pain and rash being the main symptoms. The chronic phase consists of (poly) arthralgia in most cases. Patients have indicated that their quality of life Is significantly worse prior to infection, mainly due to arthralgia and arthritis. Depressions and demoralization are common in chronic CHIK patients. This review gives further insight in the need of a standard treatment guideline and provides data about epidemics in the past, which can be used to improve the reaction to new upcoming CHIK epidemics.

Introduction

In 1953 a virus now called chikungunya was discovered; since then many tropical countries suffered from epidemics of chikungunya virus. ''To walk bend over'' is the meaning of chikungunya in some countries in Africa; referring to one of the main symptoms of the disease which is incapacitating pain in multiple joints of the body. [1] Countries in Africa and Asia witnessed epidemics in the years after the CHIKV was first isolated; one of the most recent outbreaks was on the island La Reunion near Madagascar. Chikungunya has the same vector as the dengue virus, namely the *Aedes aegypti* mosquito.[1] Countries where dengue is endemic are therefore in danger of CHIK outbreaks, infection with both viruses is also a possibility. Symptoms of dengue and CHIK are comparable, however the incapacitating arthralgia is specific for CHIK The Americas now also face the threat of the CHIKV, as there are more confirmed cases each day. Epidemic proportions of CHIKV have already been reached in certain areas in the Caribbean.[3] Data from the outbreak in the Americas are scarce, and therefore the epidemics on La Reunion and India will be the main sources of data in this paper.

The disease and epidemics have been well described in several articles, but clear insight in the aftermath of chikungunya is still lacking, especially during the chronic phase of the disease. The typical joint pain can last years after infection.[2] This phenomenon leaves patients in physical hindrance; some are now incapable to perform their occupation previous to CHIK infection.[3] Deterioration of mental status has also been witnessed; depressions and demoralization are common in chronic phase CHIK patients. [4]

The goal of this paper is to describe and evaluate the current spread of the chikungunya virus, and to determine what the social burden is of the disease. The economic burden of CHIK disease will also be assessed. Moreover we review how the threat of CHIK is being handled, and asses the treatment and prevention of infection.

Chapter 1: Chikungunya virus: transmission and symptomatology

1.1 The virus chikungunya

The virus chikungunya (CHIK) is a RNA arbovirus which belongs to the genus of Alphavirus [1]. An arbovirus is handled by a vector, which in this case is a mosquito of the Aedus genus. [1] The same mosquito is also responsible for transmitting the dengue virus in several tropical countries. CHIK outbreaks have been witnessed in places close to the equator, as the climate there is ideal for its vector, namely: a high humidity and temperature.[1,2] Dengue epidemics are already common in over 100 countries in Africa, The Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific.[5] Introduction of a virus in those countries could easily lead to an outbreak of CHIK as its vector is already present in high numbers. The populations in those countries are all susceptible to infection of CHIK, since they had no previous CHIK infection; this is called a naïve population. Herd immunity is not in place in those countries as there are no immune people. As for today, there are no working vaccines for CHIK.[2,6]

1.2 Clinical manifestations of CHIK disease

When people are bitten by the *Aedes mosquito* and get infected with CHIK, an incubation period of 4 till 7 days follows.[7] The onset of the disease is not gradually as most patients suffer from high fever and incapacitating joint pain right after the incubation time.[2] The joint pain is the most typical symptom for CHIK; chikungunya itself means ''to walk bend over'' in the Makonde-language, typifying a standard CHIK patient. [1,5,7] The joint pain is caused by both arthralgia and arthritis that can manifest in most joints of the body. Pain in the wrists, ankles and phalanges are most observed, but the larger joints are also affected in most cases [2]. While other symptoms usually disappear, the arthralgia and arthritis can remain for years after infection [1,2]. The joint paint makes people incapable of performing certain actions, which can prevent them from doing their previous profession. [8]

Besides arthralgia and arthritis, several other symptoms are related to CHIK. For example: nausea, fatigue, vomiting and diarrhea are also common symptoms.[1,2,7] In a CHIK outbreak in 2007 on the island of La Reunion, 244.000 cases of CHIK were confirmed. Out of those cases, 96.3% presented themselves with a fever and 96.6% were confirmed to have pain in the joints. Headaches were reported in 71.2% of the cases, muscle pain in 61.6% and the other most common symptom was cutaneous eruptions (32.5%) [9]. This specific study is representative for multiple other studies about CHIK, and is consistent with the data provided by the World Health Organization. [1,2,7]

The CHIK symptoms usually disappear within 7-10 days. As mentioned before, the joint pain can last longer than all the other symptoms, this Is called the chronic phase of the disease. Patients in the chronic phase of CHIK are in a state where the quality of life of a patient may be strongly affected.[8,10,11,1] Depressions and demoralization are common in chronic CHIK patients.[11] The virus is present in the blood for a longer period of time. If in this period a mosquito feeds on the blood of the patient, it will acquire the CHIK-virus and will be able to spread it further on to other persons, starting the cycle of infection over again. This is how the virus is maintained in an epidemic status. In periods outside epidemics, animals serve as ''reservoir'' for the CHIK virus.[1]

1.3 Atypical presentation of CHIK

While CHIK is usually not associated with fatality, there are multiple cases of atypical presentation of the disease in which patients died[12] . These manifestations are most frequent during periods of epidemics.[12] Atypical presentation of CHIK during the outbreak on La Reunion was researched in several (observational) studies.[12,13] The definition of an atypical CHIK case was given as following: ''A patient who has laboratory confirmed CHIKV infection, but shows symptoms other than fever and arthralgia.''[13] There was also a severe disease category meaning that maintenance was required for at least one vital function. [13] In a study about this phenomenon performed in 2009, the sample size of the study consisted of 610 patients of which 222 were diagnosed with the severe form; 65 patients passed away. Median age of the patients was 70 years, range 15-95. The most common observed atypical presentations on La Reunion are the following: heart failures (n=84), encephalitis (n=69), and pneumonia (n=102). Cardiovascular complication in general was witnessed in most of the patients (n=226). The study gives the following possible reasons for the appearance of these new symptoms which can now be associated with CHIK. One explanation is that patients already were suffering from a disease prior to infection with CHIK, for example the prevalence of hypertension previous to a cardiovascular complication. Another explanation is that it could be a stronger reaction to the virus infection than usual. Also, elderly people seem to be more at risk to fall under the severe category of CHIK disease. In conclusion, this study suggests that CHIK might not be as non-fatal as previously thought, and that this should change the way how CHIK is managed in the future.[13]

1.4 Current treatment for CHIK

As of today there are neither working vaccines nor specific anti-viral medication for CHIK. Full protective immunity is only achieved after infection of CHIK.[1,14] Medication is given to relieve the patient of the pain and fever. The medication includes paracetamol, ibuprofen and other non-steroid anti-inflammatories (NSAIDS).[14,15] All of the above drugs are non-specific, and are mainly to ease the incapacitating joint pain. Researches for vaccines against CHIK date from 1967, several vaccines have been developed but none seem to be effective as there are no licensed vaccines available. All of the developed vaccines have not been tested in humans.

1.5 Prevention of CHIK infection

The current and most effective way of preventing infection with CHIK is to control the vector.[1] Strategies for this are already in place because of the dengue virus, which has been more common than CHIK in a lot of countries. These strategies are simple yet effective. Mosquito repellents, long sleeved clothing and insecticide treated bed nets are just a few ways to protect a person from a mosquito bite.[15] However, these methods of prevention are not efficient enough to protect a population. The vectors *Aedes aegypti* as well as its larvae are also being controlled. This has been handled by the eradication of breeding sites by using insecticide.[1,2,15] However total vector control is unsustainable, mosquitos have shown to develop resistance against the insecticide. Full vector control is therefore very difficult to achieve; it is costly, labor intensive and because of the development of resistance it is a path without an end.[1,2,15] It is also not well accepted by the population, which is an issue because cooperation with the local

population is important in achieving CHIK prevention.[1,2,15] Another way to control the mosquito population is preventing mosquitos to lay their eggs in their preferred environment. Mosquitos lay their eggs in or near water, so covering and cleaning water reservoirs are potential easy methods to control the vector, if community participation can be achieved.[5] Examples of such ''reservoirs'' could be a spare tire with a base of water inside of it, or an open rainwater barrel. It is important that the human population is aware of the preferred breeding grounds of the mosquitos, that way everyone can help sustain the population of the vector. These measures will not only prevent the spread of the CHIKV, but also the spread of the dengue virus. Until there is a working and tested vaccine, the only potential effective measures taken against the CHIK virus is by controlling its vector.[6]

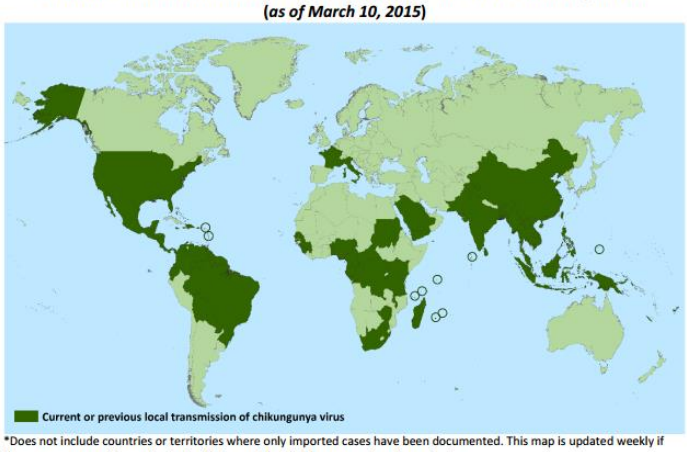
Chapter 2: The worldwide spread of CHIK

2.1 CHIK spread overview

Since its discovery in Tanzania in the year 1952, CHIK has been confirmed in endemic or epidemic state in approximately 40 countries in Asia and Africa by the WHO.[7] However this is outdated, as the most recent outbreak in the Caribbean has not yet been accounted for. CHIK outbreaks were first witnessed in the Caribbean in December 2013. Guyana, French Guiana and Suriname are just a few of the countries where CHIK was reported in 2014.[16] All countries with confirmed cases of CHIK are shown in the figure of the world map. The Americas are now also included in the list of countries where local transmission of CHIK had occurred.

2.2 CHIK epidemic on Reunion Island (Africa 2005-2006)

To give a clear example on how a CHIK epidemic proceeds, we take a look at the outbreak on La Reunion. This epidemic has been widely described in several articles, atypical presentation was the main subject in those studies.[12] A retrospective study was performed in 2007, in which the epidemic has been well documented.[9]



Center for disease control of prevention.
http://www.cdc.gov/chikungunya/geo/index.html

The epidemic on the island of Reunion started in March 2005. CHIK had not been documented on this island before this date.[6] When the rain season was in full effect so was the epidemic as the mosquitos prefer the damp, hot and wet environment. Out of 770,000 people who were living on the island, 244,000 were infected.[6,9] During the epidemic people showed atypical presentation of the disease, as is discussed earlier in this paper. The attack rate during this epidemic was 35%.[9] There were two epidemic curves in this period, and during both periods women were most affected. Also in all of the age groups

except less than 20 years of age, women were the most affected. The study suggests that the latter finding could be explained by the observation that women may be more exposed to the vector because of greater home and gardening activities. Backyards are liable to contain breeding sites for the mosquito; therefore the incidence of infection could be higher in woman.[9] By April 2006, 203 people were confirmed to have died during CHIK infection on La Reunion; median age of death was 79 years.[9]

2.3 CHIK outbreak in India

In the same period as the Reunion epidemic, there was also an epidemic ongoing in India. According to data from the World Health Organization, there were 1.25 million suspected cases spread over 151 districts. The attack rate in some areas reached 45%. [17] There were also patients with atypical presentation of CHIK; however no deaths were accounted for.[1] Women were again most affected, as were the elderly. In the period of this CHIK epidemic, lab results showed that dengue was also still present in the country. The fact that both viruses were prevalent means that the public health status of India has been deteriorating, vector control was also deemed to be inadequate.[1]

2.4 The spread of CHIK in the Americas

The introduction of CHIK in the Americas was anticipated because of the prevalence of the *Aedes aegypti*. *Aedes aegypti* mosquito in a lot of areas. Travel between the Americas and countries where CHIK is endemic was also very common.[18] The first report of CHIK in America was in December 2013. Six months later in May 2013, 55.992 cases have been reported, and the outbreak was not over by then.[19] One year after the first sighting, CHIKV has been reported in 43 countries were previously only travel-associated infections were prevalent. Over one million suspected and confirmed cases of CHIK were reported in these areas.[16] It is important that a surveillance system for CHIK is established to monitor CHIK infection in the Americas. At present time, 500 million people live in areas where dengue is endemic in the Americas. Those people now also face at risk of CHIK infection because of its shared vector *Aedes aegypti*. Strict surveillance is crucial to prevent CHIK from infecting all these people, as attack rate in the past have shown to be as high as 30-75%. This high attack rate will in turn lead to herd immunity, which is profitable on population level. Herd immunity is a term used in the immunology used when there are sufficient immune people in a population, which significantly decreases the chance of infection for naïve people.[16]

M. Johnson et al (2014) analyzed the threat of CHIKV in the Americas and came to the conclusion that the current epidemic is expanding, and not deteriorating. Awareness should be raised in areas where infection is a possibility.[19] Making people aware of the dangers of the CHIKV could hence community preventive practices and decreases chance of local infection. [20,18]

2.5 CHIK in Europe

Intercontinental travel is common nowadays; therefore there is always a risk of introducing foreign viruses or bacteria in naïve populations. Prevention of bringing viruses in a naïve population is crucial. There are a few cases in which people in Europe were diagnosed with CHIK, but no epidemics have occurred. The threat of a CHIK epidemic in Europe is low, because of the non-prevalent vector.[6] A study published in 2015 researched the threat of vector-borne diseases in the United Kingdom, in relation to

global warming. They ruled out the threat of *Aedes aegypti* in the United Kingdom because the climate will not suit the establishment of the mosquito until at least the year 2100.[23] Another vector for dengue (and chikungunya), *Aedes Albopictus*, which already caused some dengue infections in Europe, could be a threat however.[21] *Aedes Albopictus* was responsible for a CHIK outbreak in Italy during the summer of 2007. This was the first time that local transmission occurred in Europe. An estimated 200 people were affected by CHIK. This vector has already established itself in Italy, but also in parts of Spain and France.[22] Used tires were the most probable source of the mosquito, as they are often used as a breeding place. (Inter)Continental Trade of these tires can lead to outbreaks of CHIK in various countries. Tourism is also a common cause of introducing foreign diseases in naïve populations. [6] The most recent local-acquired infection was in France October 2014, where four people from the same family were infected. The source of the virus was a person who had recently come back out of Cameroon. French public health authorities acted accordingly and implemented several health measures like vector control and improving public awareness. [23]

Chapter 3: The burden of CHIK disease

3.1 Chronic CHIK disease and its negative effect on the quality of life

Chikungunya is not seen as a life threatening disease; however the physical and mental burden of the disease is substantial. This is mostly due to the long lasting joint pain, which is seen as the chronic stage of CHIK infection. After months and in some cases years after infection patients indicated that they were in a health status worse than prior to infection with CHIKV.[11,20]

In a research performed in 2008 about the clinical burden of CHIK on La Reunion, 757 military policemen on duty were asked to fill in a detailed questionnaire. A blood sample was also taken from the patients to confirm the infection with CHIK.[11] The impact on the quality of life (QOL) was evaluated during the acute phase of the disease and the chronic phase of the disease. During the acute phase 4.6% felt that they were totally depressed, 35.5% were demoralized, 47.4% were morally weakened, and only 12.5% felt normal. [11] Most of the patients (93.7%) also indicated that they suffered from the chronic stage of the disease. The study suggests that there is little difference in quality of life in the acute and chronic phase. In the chronic phase 2.0% were totally depressed, 37.8% were demoralized, 43.9% morally weakened and 16.2% felt normal.[11] This data indicates that there is a long lasting effect on the quality of life of CHIK patients. Not only the symptomatic period of the disease has a high impact on the QOL, the chronic stage consisting of joint pain has an almost equal negative impact.

The impact of CHIK on the QOL was evaluated in patients from La Reunion and India in several different studies. In the study about the QOL in India, which was performed in 2012, people were divided in two groups; clinically recovered (n=308) and not recovered (n=95). A control group was also added to this study for a baseline, consistent of 308 healthy normal people with the same frequency in age/gender. These people were given a SF-36 questionnaire to determine their estimated health related quality of life (HRQoL) The study concludes that there is a heavy reduction in the HRQoL scores of patients during acute illness but also the following months after clinical recovery from illness.[20]

In a follow up study in 2014, from the same author as the study discussed above, they

researched the incidence of (chronic) poly-arthritis in CHIK patients. Out of the 403 people in the study, 80% suffered from long-term arthralgia. Knees, ankles and wrists were the most commonly affected areas. The study concludes that the outbreaks are unique because of the chronic phase of the disease which impairs the physical functioning of patients. They suggest that there should be more attention to long-term care and treatment, and that there should be a standard treatment guideline for both the acute and chronic phase of CHIK.[10]

A similar study about the QOL was performed in 199 people who had serologically confirmed CHIKV (CHIK+) from the island of La Reunion. They were compared to a group of 199 sero-negative (CHIK-) people, who were again matched for age and gender. The CHIK+ patients were interviewed on an average time of 17 months following the acute phase CHIK infection. The CHIK+ people complained more about arthralgia, fatigue, depression and hair loss. Patients under the age of 30 recovered faster in comparison to patients over the age of 30. The study mentions that there is no clear indication but suggest that underlying medical conditions like osteoarthritis, could result in delayed recovery. The study concludes that the impact on quality of life is moderate, despite the given complaints. [4] According to the authors this is due to the fact that after a year, CHIK-associated symptoms did not increase health care consumption.[4]

3.2 Community burden of CHIK and chronic arthralgia

Eighteen months after the outbreak of a CHIK virus on La Reunion a study was set up to determine the long term and community burden.[24] This study had a large sample size in comparison to the previously discussed studies, namely 1094 CHIK positive patients. People from both La Reunion and India were interviewed about their current symptoms. Symptoms on account of CHIK were discovered in 43 to 75% of the CHIK positive people. The authors conclude from their results that chronic CHIK disease has a heavy impact on rheumatologic, neurological and sensorineural health. This study confirms that CHIK disease is not over after the acute phase, and carries a significant community burden.[24,25] When referred to the chronic phase of CHIK, in most cases this means arthralgia. In a study performed in 2009, the chronic arthralgia was the main subject. CHIK patients from La Reunion (n=147) were interviewed 15 months after infection about their current status. Potential risk factors were also investigated. More than half of the interviewed people still had rheumatic symptoms three months after infection. Two third of the patients were also not content with the prescribed form of medication.[26]

A recent study published in March, 2015 will conclude the subject of chronic CHIK and arthralgia in particular. Medical files of 159 CHIK patients from Reunion Island were reviewed from 2006-2012. The goal was to improve treatment of chronic CHIK patients with rheumatic disorders in particular. [8] Data was gathered in six years following the CHIK epidemic. Patients who are infected with CHIK show different symptoms in comparison to other CHIK patients in many occasions. CHIK should therefore not be seen as simply one disease, as it seems that several people react differently to the virus, especially in the chronic stage. The study agrees with Ramachandran et al (2014) that there should be a guideline for treatment of chronic CHIK patients. The current study therefore provides a diagnostic and therapeutic

algorithm for physicians. This algorithm provides information of proper treatment based on the time that has gone by since CHIK infection. This guideline should help physicians to properly treat the chronic patients. This in turn limits the functional and economic impact of CHIK disease.[8]

3.3 Economic impact of CHIK in India and La Réunion

The acquired joint pain of CHIK can lead to the inability to perform certain actions, including continuing daily jobs. One sick person does not have a huge impact on the economy, however when many people are sick at the same time; this leads to additional costs besides hospitalization and drug consumption. [3] Man-Koumba Soumahoro et al (2011) researched the cost of CHIK disease in the epidemic period 2005-2006 on La Reunion. A patient who only had visited the hospital due to CHIK was estimated to cost €90 euros, while a patient who had to stay overnight €2000 euros.[3] France had already made an estimate of the costs of the epidemic on La Reunion, to provide the needed medical assistance. However the costs were higher than the budget France had set aside, thus an extra €31,5 million out of emergency funds was allocated to assist La Reunion. The study concludes that the medical management was associated with a heavy economic burden.[3]

The data of the costs of this epidemic can be used to estimate the costs of a new epidemic, as it is now known how much an individual costs. With the specific costs for each person known, the data can also be used to determine cost/efficiency. For example, if there is a working vaccine, there is now data available provided by Man-Koumba Soumahoro et al (2011) to know if it is more beneficial for the economy than the current treatment.[3]

A similar study was performed in 2010 to determine the economic costs of CHIK in 2005-2006 in a specific part of India. They estimated the burden of disease by a term called disability-adjusted life years (DALY). The term is defined as the following: ''Time, ability or activity lost by an individual from disability or death resulting from a disease.''[27] The DALY burden of chikungunya was estimated to be moderate in this study. The economic burden for the population however was substantial as the population of India is poor, patients had to pay for their treatment themselves. The study suggests that there should be better communication leading to rational use of medication to lower the costs for the poor part of the population. Improving surveillance and vector control are also suggested, as was suggested in previous studies in this review as well.[27]

Discussion

This review describes the spread of the chikungunya virus and the social and economic impact of the disease on the community. The studies performed in India and La Reunion indicate that the QoL of acute as well as chronic CHIK patients has deteriorated since infection with the CHIK virus. Depression and demoralization were common in the studies, the cause was mainly due to the poly-arthralgia and arthritis. There still is no treatment guideline for acute and chronic phase CHIK patients; this should be a priority to improve the way how CHIK epidemics are handled in the future. A first guideline was set up by E. Javelle et al (2015), and can only lead to improvement for chronic CHIK patients.

A consistent factor in most studies was the call for a better surveillance system to prevent CHIK

infection. The epidemic in the Caribbean was expected for a period time due to the suitable environment and the endemic state of dengue, however it seems that not enough precautions were made. Vector control was also deemed to be inadequate, no proper method has been found to fight the vector efficient. The epidemic could have been limited by making public awareness of CHIK a priority. The population should know the basic principles of CHIK, that way people can help eliminate breeding places, causing the vector to reduce, and therefore reducing the rate of infection.

Chikungunya has been reported in cases in Europe, and a vector (*Aedes albopictus)* for CHIK has already established in parts of Italy, Spain and France. Especially Italy is at risk of a CHIK outbreak, because the vector has established itself in the whole country. Surveillance and community awareness is required to prevent the spread of CHIK in Italy. The World Health Organization already acknowledged the risk of CHIK in the countries where *Aedes albopictus* is prevalent and have taken precautions to prevent local infection of CHIK.

In most studies, the elderly and women were the most frequent infected group. The elderly also seem to be more at risk of becoming chronic-CHIK patients, and there are suggestions that this could be due to underlying medical manifestations. Women were most frequent gender, because most women in the affected countries were housewives. They work in areas, like in gardens, where breeding places of the vector are common.

CHIK also has an impact on the economy because of the inability of people to work during the acute and chronic phase. Medication in the form of drugs, and hospitalizing had the largest impact. There were no universal guidelines available for the treatment of CHIK. While the epidemic in India did not impact the economy of the nation as a whole, it did have a large impact on the poor part of the population who had to pay for the treatment. Due to the now available data of the costs of epidemic, an estimate can be made for the cost of treating one patient. This is useful data for ongoing or nearing CHIK epidemics, as money can be made available before an epidemic has occurred.

In conclusion this review gives insight on the current status of the CHIKV, and opts for a universal treatment guideline and raising community awareness in countries at risk. Chronic CHIK patients are not treated properly, because of the lack of insight in how the chronic CHIK manifestations occur. Further research about the mechanism of chronic CHIK manifestations are needed to develop a treatment guideline. This all to improve the quality of life of chronic CHIK patients, and get them back to a status they were prior to infection.

References

1. Pialoux G, Gauzere BA, Jaureguiberry S, Strobel M. Chikungunya, an epidemic arbovirosis. *Lancet Infect Dis*. 2007;7(5):319-327.

2. Caglioti Claudia C. Chikungunya virus infection: An overview. *New Microbiologica*. 2013-7;36(3):211-27.

3. Soumahoro Man-Koumba MK. The chikungunya epidemic on la réunion island in 2005-2006: A cost-of-illness study. *PLoS Neglected Tropical Diseases*. 2011-6;5(6).

4. Soumahoro Man-Koumba MK. Impact of chikungunya virus infection on health status and quality of life: A retrospective cohort study. *PLoS ONE*. 2009;4(11).

5. Dengue and severe dengue. http://www.who.int/mediacentre/factsheets/fs117/en/.

6. Christopher Nero. Chikungunya, the traveling virus. *Elsevier*. 2008;30(13):97-100.

7. World health organization: Chikungunya. http://www.who.int/denguecontrol/arbo-viral/other_arboviral_chikungunya/en/.

8. Javelle Emilie E. Specific management of post-chikungunya rheumatic disorders: A retrospective study of 159 cases in reunion island from 2006-2012. *PLoS Neglected Tropical Diseases*. 2015-3;9(3).

9. Renault Philippe P. A major epidemic of chikungunya virus infection on reunion island, france, 2005-2006. *American Journal of Tropical Medicine and Hygiene, The*. 2007-10;77(4):727-31.

10. Ramachandran V V. Persistent arthralgia among chikungunya patients and associated risk factors in chennai, south india. *J Postgrad Med*. 2014 Jan-Mar;60(1):3-6.

11. Queyriaux Benjamin B. Clinical burden of chikungunya virus infection. *Lancet Infectious Diseases, The*. 2008-1;8(1):2-3.

12. Rajapakse Senaka S. Atypical manifestations of chikungunya infection. *Trans R Soc Trop Med Hyg*. 2010-2;104(2):89-96.

13. Economopoulou A, Dominguez M, Helynck B, et al. Atypical chikungunya virus infections: Clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on reunion. *Epidemiol Infect*. 2009;137(4):534-541.

14. CDC. Chikunguna symptoms, diagnosis & treatment. http://www.cdc.gov/chikungunya/symptoms/index.html. Updated 03-2015.

15. Ligon B Lee BL. Reemergence of an unusual disease: The chikungunya epidemic. *Seminars in Pediatric Infectious Diseases*. 2006-4;17(2):99-104.

16. Johansson Michael A MA. Chikungunya on the move. *Trends Parasitol*. 2015-2;31(2):43-5.

17. WHO. Global alert and response (GAR) chikungunya in india. http://www.who.int/csr/don/2006_10_17/en/.

18. Olowokure Babatunde B. The caribbean response to chikungunya. *Lancet Infectious Diseases, The*. 2014-11;14(11):1039-40.

19. Johansson Michael A MA. Nowcasting the spread of chikungunya virus in the americas. *PLoS ONE*. 2014;9(8).

20. Ramachandran Vidya V. Impact of chikungunya on health related quality of life chennai, south india. *PLoS ONE*. 2012;7(12).

21. Medlock Jolyon M JM. Effect of climate change on vector-borne disease risk in the UK. *Lancet Infectious Diseases, The*. 2015-3-20.

22. WHO. Chikungunya in the WHO european region. http://www.euro.who.int/__data/assets/pdf_file/0005/246164/Fact-sheet-Chikungunya-Eng.pdf. Updated 2014.

23. WHO. Global alert and response: Chikungunya - france. http://www.who.int/csr/don/23-october-2014-chikungunya/en/. Updated 2014.

24. Gérardin Patrick P. Perceived morbidity and community burden after a chikungunya outbreak: The TELECHIK survey, a population-based cohort study. *BMC Medicine*. 2011;9.

25. Gérardin P P. [Perceived morbidity and community burden of chikungunya in la reunion]. *M?decine tropicale*. 2012-3;72:76-82.

26. Sissoko Daouda D. Post-epidemic chikungunya disease on reunion island: Course of rheumatic manifestations and associated factors over a 15-month period. *PLoS Neglected Tropical Diseases*. 2009;3(3).

27. Seyler T T. Estimating the burden of disease and the economic cost attributable to chikungunya, andhra pradesh, india, 2005-2006. *Trans R Soc Trop Med Hyg*. 2010-2;104(2):133-8.