Reemergence and Global Spread of Chikungunya

Shweta Rana and Palak Lunia

***Abstract*---**Chikungunya is an acute feverish illness associated with severe symptoms of muscle and joint pain. Chikungunya virus (CHIKV) is a mosquito-borne alphavirus responsible for a recent, unexpected severe epidemic in countries of the Indian Ocean region. It was first recognized as a pathogen in 1950 in countries of Asia and Africa. It subsided for almost 20 years after that however, since its reemergence in 2004 in Kenya, it has caused millions of death in Indian Ocean region and has also emerged in new areas including Europe, the Middle East and the Pacific region. Cases of CHIKV were identified in the Caribbean Island of St. Martin, signaling its arrival in Western Hemisphere. The reemergence of the virus indicates its virulence and adaptability to novel ecological niches. The virus does not only cause massive morbidity but it also takes a toll on the economic competencies of countries and their health care systems.

***Keywords*---**Chikungunya, CHIKV, reemergence, spread

I. Introduction

IN 1952-53, reports of an outbreak of dengue-like symptoms (such as sudden fever and rash typically for 10 days) were recorded in Newala and Masasi Districts of the Southern Province of Tanzania. However, the outbreak involved patients complaining about debilitating joint and muscle pain, which are not clinical symptoms of dengue, and also the virus in question had a shorter incubation period than the dengue virus. After further examination of the virus, it was found that the outbreak was not dengue. The patients exhibited severe tenderness and swelling in their joints in ankles, knees, toes, fingers, which would last for weeks, hence, the fever came to be known as Chikungunya. The word 'Chikungunya' originated from the Makonde dialect-describing patient's contorted posture, or that which bends [1].

Chikungunya fever is an acute febrile illness caused by alphavirus, Chikungunya virus (CHIKV). It is a zoonotic disease spread with the help of mosquitoes. Retrospective case reviews have suggested that CHIKV epidemics occurred as early as 1779 but were frequently documented inaccurately as dengue outbreaks [2].

Shweta Rana is Associate Professor with Department of Physical and Natural Sciences in FLAME University, Pune, Maharashtra- 412115, India.

Palak Lunia is at FLAME School of Liberal Education, FLAME University, Pune, Maharashtra- 412115, India

In between 1827 and 1828, an extended outbreak was recorded in Gulf of Mexico and Caribbean islands. The outbreak was recognized to be Dengue although on inspecting clinical evidence, it was found to be Chikungunya. According to the historical records this was the first and only introduction of Chikungunya in the American region as a consequence of American slave trade [3].

The disease became an endemic in African regions after the 1952-53 outbreak in Tanzania. Evidence for the outbreak was seen in Uganda, Democratic of Congo, Kenya, Senegal, Nigeria, and South Africa [4]. In Asia the CHIKV was first observed in Bangkok in 1958. This was followed by outbreak in the countries of Cambodia, Malaysia, Taiwan, and Vietnam [5]. In 1963, several reports of Chikungunya started to crop up in the Indian subcontinent, as well. India was one of the leading countries to be affected by this detrimental disease. The outbreaks were mainly seen in Calcutta (now Kolkata), Vellore and many places in the state of Maharashtra. The numbers of infections were in lakhs and over 200 deaths were reported. From 1970s to 1980s cases of Chikungunya were detected in parts of Srilanka, Myanmar and Indonesia [4]. According to Physician James Christine, Chikungunya fever erupted in the Indian Ocean region in a gap of 40-50 years. Thus, making the re-emerging period the most striking feature of the epidemic. It has created keen interest amongst the epidemiologist to understand its re-emergence and rapid global spread [3].

II. Clinical Manifestation And Biological Diagnosis

Chikungunya is a mosquito-borne viral disease, characterized by acute joint and muscle pain. Illness caused by CHIKV is usually diagnosed based on symptoms, and often confused with dengue given some overlapping symptomology. CHIKV related mortality is rare, but can occur, often in patients with other health conditions.

A. Clinical Symptoms

After a susceptible individual is infected by the CHIKV, there is a silent incubation period of 2-4 days on average; it can also range from 1-12 days. Clinical onset of symptoms is abrupt and random. However, high fever, headache, back pain, muscle pain and joint pain are seen in the early onset, and can intensify with time. Other symptoms involving skin are rash predominating on the thorax, facial edema, bullous rash with pronounced sloughing in children. Hemorrhagic fever has been reported in some patients mainly in Thailand region. Random, erratic, relapsing and weakening joint pain is the

hallmark for determining Chikungunya. There are few precise descriptions of Chikungunya virus, which are associated with joint disorders, however the underlying mechanism is unknown. Joint pain or arthritis appears to affect 73-80% of infected cases. This can persist in 33% of patients for more than 4 months; 15% for 20 months, and 10% patients were recorded to show these symptoms for 3-5 years [6].

In India during the 2006 outbreak of Chikungunya, 4 cases were observed that showed persistent flaccid limbs weakness. This was recorded by Cambridge University; they listed detail case description of the four cases of acute flaccid paralysis associated with Chikungunya virus infection [7]. Infected cases of Chikungunya are rarely seen in children. However the outbreak of 2006 worldwide have shown cases of vertical transmission from mother to child, with new born showing infection of Chikungunya virus without prior involvement with mosquitoes. These cases portrayed infants with fever, pain, poor feeding, distal joints, skin rash, formation of blood clots in small blood vessels, decrease in platelet count, and appearance of red or purple spot on the skin. Some severe cases of neonatal infection involved brain hemorrhages complicated by the presence of internal blood clots [8].

Occasionally, atypical symptoms are seen associated with Chikungunya infection. For example, during the outbreak of chikungunya in Sri Lanka in 1972, individuals infected with Chikungunya revealed evidence of inflammation of heart muscles after acute febrile illness. The individual suffered with cardiomegaly and abnormal electrocardiograms. In other cases, signs of congestive heart failure were documented, even after months of initial illness. Atypical clinical features have been of particular note in the 2005–2007 outbreaks, where descriptions of cases from Réunion Island have included neurological involvement in adults, Fetuses and Neonates Laboratory studies have also shown the potential for neurological involvement [9].

B. Biological Diagnosis

There are various ways in which the CHIKV can be detected in an infected body. For specific diagnosis of Chikungunya is obtained through serological tests, molecular methods or viral cultures. In the serology test the anti-CHIK antibodies are detected using the IgM capture ELISA. However, one needs to remember that IgM antibodies appear only after 4-7 day after the onset of fever and in most of the cases fever is subsided by then. It can also be used to detect IgG antibodies, after onset of symptoms and about day 15 into the disease. Individual serological testing is not particularly useful, except when faced with atypical or severe forms during the epidemic period. The molecular diagnosis of Chikungunya by RT-PCR, therefore, has been in vogue recently. Patients that are infected with CHIKV tend to have viremia that last up to 6 days. This can be detected by PCR, a specific test with a turn-around time in one day. It is important to note that PCR, antigen detection and viral culture can also be used to detect Chikungunya virus in mosquito during the epidemiological studies and also to assess the capacity of the vector to be infected by the virus [6] [10].

III. Treatment And Preventive Measures

A. Treatment

Chikungunya virus infections seem to elicit long-lasting protective immunity. The fever lasts for not more than a few days, although the joint pain associated with infection can be long lasting and unbearable. There is currently no commercial vaccine for the virus. Patients are recommended bed rest and painkillers to reduce the joint pains. Patients are treated according to symptoms manifestation [10]. Homeopathic experts claim for effective drugs avaliable that can prevent as well as speed up the recovery from the disease. These medicines were prescribed to patients in South India during the 2006 outbreak [11]. Chloroquine has been assayed for the treatment of chronic pain associated with CHIKV arthritis. However due to the changing nature of the virus the researchers have to modulate these medicines. Antiviral startegies are being planned keeping in mind the evolutionary pattern of the Chikungunya virus [12].

B. Prevention

Due to pending development of vaccine of CHIKV the only effective preventive measure is to control and protect against the vector i.e. mosquito bites. The vector control includes eradicating both larvae as well as adults. This is achieved by spraying dwellings with residual-action insecticides, biological control, environmental management including source reduction and use of personal protection measures. Large-scale prevention campaigns have been undertaken since 2006 to control the growth of vector. Individually addressed vector control methods can be costly, time consuming and endless. Therefore multifaceted rather than individual level intervention works better as they can address larger variety of breeding places. The resultant decline in the vector-host cycle can reduce transmission of the vector with a consequent decline in the incidence of the disease. These campaigns can be useful when inexpensive, simple and indigenous methods are used. People should be encouraged and made aware about using bed nets, sprays, and repellants. They should be educated about the hazardous and unsafe environment that can be created by mosquito breeding. Personal protection measures such as applying insect repellant to the exposed skin can keep out *A. aegypti*, a daytime biter. Insect repellants containing 30% DEET have been proven to provide an average of 5 hours of complete protection against *A. aegypti* bites after a single application on the exposed skin. It is a known fact that rapid deforestation and urbanization is leading to climate change globally and has led to increase in several virus diseases including Chikungunya. The climate change creates extreme conditions such as droughts in some parts of the world and floods in others, thereby creating habitable places for the mosquitoes to breed and multiply. Manipulation and modification of the environmental factors coupled with right education and awareness can help to reduce the breeding of mosquitoes [6] [10].

IV. Reemergence Of Chikungunya Epidemic

After causing severe burden on the economy of the countries and deterioration of its health of the population, the virus laid dormant for 20 years. It was believed that Chikungunya had been eradicated; however, this belief was challenged in the year 2003 [13]. In few Asian countries reports of fever with muscle and joint pain was recorded. This was first observed in Thailand, Indonesia and southern regions of India around 2003-2004. The reports were also observed in Reunion Islands, Mauritius, Comoros, and Seychelles Islands located in the western Indian Ocean. The reemerged virus was different from the one-recorded 20 years ago. The virus was now more virulent and compatible to the surrounding environment. Beginning in 2005, a large outbreak occurred on Reunion Islands that affected an estimated 266,000 people by 2006. The epidemic peaked with 46,000 new cases in 6 weeks of 2006 [6]. That same year an epidemic of the disease swept across multiple states of India, including Tamil Nadu, Maharashtra, Gujarat, and also Delhi with approximately 1.25 million suspected cases reported among the population of 536 million people [4]. The WHO regional office for Southeast Asia reported that 151 districts located in 10 states of India that had been hit with the CHIKV. In comparison to the outbreak of 1971 in India, the attack rate in Maharashtra province was 37.5% more. Andhra Pradesh was one of the worst affected with more than 80,000 suspected cases. These statistics made epidemiologists wonder about the sudden attack of this virus and on such large scale [6].

Between 2006 -2008, various cases of Chikungunya was reported in the peninsular region of Malayasia. The reports showed that Malays who mainly dewelled in rural areas or forest areas had high frequency of contracting the disease. A total of 13,759 patients were referred to National Public Health Laboratory, from which highest number of cases were referred in 2008 (8320 cases) and lowest in 2001(108 cases) [15].

In 2007, Chikungunya fever appeared for the first time in Europe, causing illness in more than 200 people in Ravenna, a city in Northeastern Italy. This spread to the European continent was believed to be carried by travelers from India to Ravenna. The unexpected outbreak of a tropical disease in the European region of the world prompted concern about the invasiveness and adaptive abilities of Chikungunya vector in cool climates. Thus adding to the curiosity of epidemiologists all over the world [13]. More over, Chikungunya cases were reported in other parts of Europe, especially Germany, Switzerland, United Kingdoms, France, and Norway [4].

Located in Southeast Asia Singapore has never been a victim of on going epidemics. However in 2008 cases of febrile fever with arthralgia was reported in the region [15]. In 2009 a large outbreak of Chikungunya fever occurred in Thailand. Between January and June of that year, some 24,000 cases of the disease were reported. [4].

Over the next several years, outbreaks of Chikungunya fever occurred sporadically, with cases emerging in regions already affected by the disease as well as in previously unaffected countries, such as Bhutan in South-Central Asia and the French portion of the island of Saint Martin in the Caribbean Sea [4]. Between 2006-2013, on average 28 people per year in the United States tested positive on CHIKV, these were mainly travellers returning to United States from affected Asian or African countries. In late 2013 and early 2014, the disease spread to multiple islands in the Caribbean (West Indies) via local transmission, indicating that mosquitoes in the region had become infected with the virus. Infected travelers leaving the islands subsequently carried the disease to other parts of America. In June 2014, health officials estimated that more than 165,000 people in America had been affected by Chikungunya fever through local transmission, though only about 4,500 cases had been confirmed with laboratory testing. Local transmission was also identified in Florida, Puerto Rico and the U.S. Virgin Islands [16].

During the epidemic reign, private and government hospitals were flooded with cases of victims. It inflicted considerable pain and misery among the victims and caused substantial and unexpected local, regional and national financial burden towards healthcare. Patients underwent weeks in pain before they could limb back to their normal self. Hospitals, which were ill-equipped to handle the burden of the epidemic, collapsed. Hospitals were overwhelmed with patients, with lack of adequate health care treatments. The socio-economic impact was tremendous: school attendance dropped, productivity at work declined sharply and farmers could not tend to their crops. Sufferers lost their wages, sold household items and were forced to borrow money at high interest rates [17] [18].

V. Reasons For Reemergence And Spread

The reasons for reemergence and spread are investigated in light of viral structure vector and their interactions with the virus along with other anthropogenic factors.

A. Virology

Chikungunya virus, an arbovirus belongs to the genus *alphavirus* from Togaviridae family; has a single stranded RNA genome, a 60-70 nm diameter capsid and a phospholipid envelope [20]. The virus encodes 9 genes, consisting of coding sequences for non-structural polyproteins, structural polyproteins (precursor for C, E1,E2, E3 and 6K proteins), and polyadenylation site, flanked by 5´ and 3´ sequences. It is sensitive to desiccation and to temperatures above 58°C. E1 protein modulates penetration of the virus in the mosquito species (vector); it is also responsible for the fusion with human host cell [21]. The structural proteins are produced by translation of mRNA strand that is generated from an internal, sub genomic promoter inside the host cell. The polyprotein is processed to produce a capsid protein with two major envelope surface glycoproteins i.e. E1 and E2. E1 and E2 post-translation are modified in the endoplasmic reticulum and Golgi apparatus before being transported to the plasma membrane where they maintain a close association with each other, forming a spike structure. As virion formation proceeds, the cytoplasmic nucleo-capsids are trafficked to the cell membrane where they bind to the surface glycoproteins before budding from the cell [13] [14].

The historic records and genetic analysis of the Chikungunya virus suggests that it originated from the tropical

African region. Subsequently it evolved into 3 distinct genotypes, which are the East African, the West Africa and the Asian genotype. Stark differences are seen in every phylogroup of CHIKV. The Asian genotypes have a high degree of nucleic acid sequence homology among themselves; on the other hand the African strains exhibit wider sequence diversity, and have been shown to undergo genetic microevolutions even during the course of an epidemic. Prior to the 2006 epidemic in India, the 3 genotypes were restricted to the geographical areas denoted by their names. Experts suggest that virus strains isolated from the 2005 epidemic in the Indian Ocean islands, and the strains observed in the epidemic of 2006 in India, have evolved from the East African genotype. The past outbreaks in India were caused by the Asian genotypes [12]. Recently, point mutation was also observed in almost 90% of viral sequences in the strains obtained from Indian Ocean. This mutation has allowed the virus to acquire an ability to invade and thrive in host cells that lack or are low on cholesterol. This mutation was seen specifically in E1 factor, whose fusion mediates the viral entry in low pH cells [13]. Various theories and models have been established to understand the correlation between the various aspects of the disease. It is suggested that conducive environment for the growth of the virus as well as genetic mutation in the virus has led to the re-emergence of the CHIKV. [13].

B. Vector

Chikungunya is a zoonotic disease transmitted with the help of a vector: *Aedes* mosquito. Many species of Aedes are associated with the tramission such as *Aedes aegypti* and *A. albopictus* in Asia and *A. frucifer, A. luetocephalus, A. taylori* in Africa. Only the female *Aedes* mosquito is responsible for causing this viral disease. In the outbreaks that occurred before 2000s globally *A.aegypti* was recognized as the leading vector to transmit the virus amongst humans. Several attributes make *A. aegypti* an efficient vector for the Chikungunya virus. It is highly susceptible to the CHIKV, prefers to inhabit close to human habitations, seek blood meal during the day, which is usually painless. It can seek several people in short period for one blood meal, hence can infect them and simultaneously lead to spread of epidemic in shorter durations. The mosquito, well adapted to life in urban settings, typically breeds in clean puddles of standing water and collections of water in artificial containers such as tin cans, pots, plastic containers, rain barrels, buckets and discarded tyres. The adult female appears to transmit the virus vertically to her eggs, although this remains to be documented in the Indian Ocean outbreak [21]. It is very difficult to control either of the breeds in tropical, human modified ecosystems with modern infrastructure, irrigation and massive solid-waste production [5].

However since the re-emergence in 2003 *A. albopictus* have become the leading cause of transmission of CHIKV. *A. albopictus* has a wide geographical distribution, is resilient and can survive in urban as well as rural environments. The mosquito's eggs are highly resistant and can remain viable throughout the dry season, giving rise to larvae and adults the following rainy season. Originating from Asia, and initially sylvatic, *A. albopictus* has shown a remarkable capacity to adapt to human beings and to urbanization, allowing it to replace *A. aegypti* in many places. This introduction of *A. albopictus* in various Asian cities was marked by vegetative eggs contained in timber, which is exported throughout Asia thus making the vector fit for rural and urban areas, thriving in natural as well as inhabitations and their immediate peripheries. The adaptability of this mosquito is due its long-lived nature and it can take a flight of radius 400-600m in one go [18] [20].

CHIKV has a peculiar characteristic. It is absent for a long period of time and emerges back with an explosion. The question that arises is how does the virus survive during the inter-epidemic period? In Africa, the virus is maintained in the sylvatic cycle during the inter-epidemic season, which involves non-human primates and a number of forest dwelling mosquitoes. However in Asia, no known animal reservoir has been identified to harbor the virus. It is a known fact that female *Aedes* mosquitoes are responsible for the spread of the disease to humans as well as to off springs through vertical transmission. An experiment has proved the transfer of the virus from infected male mosquitoes to females venereally. This has led to the conclusion that the males maintain the virus during the inter-epidemic periods without infecting human population, but the venereally infected females eventually start a new cycle of epidemic [22].

C. Virus–vector interactions

As mentioned earlier, great curiosity was built among researchers to know the cause of the sudden outbreak of 2003. The reasons formulated are three fold. One of which is the point mutation (as mentioned in section A) that helped the vector attain the ability to infect the new vector, *A. albopictus,* thus enhancing the opportunity for transmission to humans. The mutation in virus increased its virility to invade human cells that lacked or had low cholesterol. The second cause could be attributed to the vector *Aedes* mosquitoes. Experimental evidences suggested that mosquitoes that are infected with microfilaria transmit the arboviruses more efficient [14]. As observed from the proportion of reported cases of Chikungunya in India, they are mainly infected by the filarial parasite. Researchers speculate that filarial parasitic infections could be modulating the re-emergence of Chikungunya. Therefore, one can say that change in the position E1 in the Chikungunya virus meant that the virus no longer needs cholesterol, which is usually necessary for virus to infect the cells of human or mosquito host. These in turn lead to better survival and multiplication of the mosquitoes and causes rapid spread of disease [23]. Additionally the virus maintains itself during the inter-epidemic seasons through sylvatic cycles in the African continent and through venereal transmission in Asia .And lastly, the environment also aided the vector and the virus to affect a greater number of people. As the affected population in the subcontinent lacked herd immunity, it increased the number of people that could fall prey to the disease. Introduction of the virus into a non-immune population could have contributed to the 2003 outbreak. In addition, the increased trade and travel has accelerated the wide dissemination of the virus. The mosquito

can only fly a hundred meters beyond which it is transported by various goods traded from one country to another such as timber [14]. These various causes are put together in a structural format in Fig. 1, they together work to strengthen the re-emergence of Chikungunya virus.

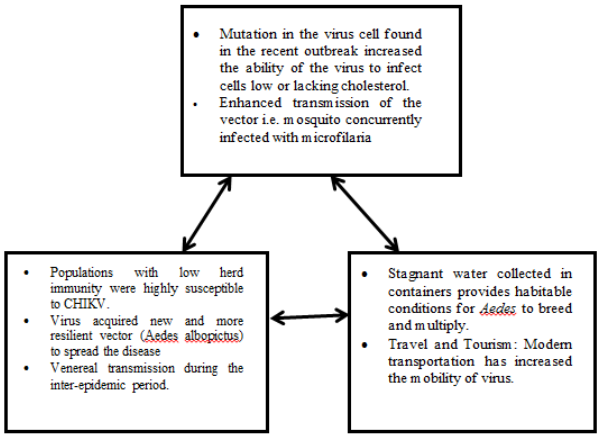

Fig. 1: Factors leading to re-emergence.

D. Other factors

Researchers have contemplated the role of social, environmental or behavioral factors influencing the re-emergence of the 2003 outbreak. They hypothesized that social economic status as well as psycho-cognitive beliefs played a part in boosting the 2003 outbreak. When demographics of the infected population was considered, high probability of contamination was seen in individual with very low income, involved in manual labor such as farm work and little education. These findings correspond with findings of sociology of infectious diseases. Therefore, one can say that socio-economic conditions are a predetermined to contracting Chikungunya. The research also tested frequency of population using household insecticides sprays, coils, mosquito net and other related sources to kill mosquitoes. By this observation they raised a hypothesis testing the exposure to and protection against mosquitoes is the relationship between risk perception based on psycho-cognitive variables and the adoption of protective behaviors. This showed that people with casual behavior towards disease for instance believing in whatever has to happen will happen were more likely to get infected, as they were low on use of preventive measures. Whereas, the section of the population that was more careful and aware about the hazardous causes of disease were less likely to contract the disease. The absences of perceived controllability of risk appears to be consistent with fatalistic attitude, which also is an indication to changing people's behavior for effective protection [24].

Another cause that is associated with erratic onset of Chikungunya worldwide is the climatic change. The change in climatic conditions causes extreme changes in nature's forces. Without a functional healthy ecosystem the chances of a disease thriving is very high. The changing climatic patterns lead to many changes in the ecosystem, which are mostly undesirable to many of its biotic components but can also prove advantageous to some. There are reports of CHIKV vectors becoming better-suited inhabitants of and hence widening their reservoirs to spread more disease. As mentioned earlier *A. aeypti* and *A. albopictus* mosquito species, causative agents of Chikungunya, thrive on rural and urban settings. During drought conditions people maintain water storage, thus attracting the mosquitoes to human dwelling. Whereas in rainy periods, potholes created due to poor urban infrastructure is filled with rainwater. These resources become the reservoirs for mosquitoes to multiply [25]. To make matters worse, the discarded tyres or unchecked timber that act as reservoirs for mosquitoes are exported all over the world. This increases the geographical reach of the vector, and introduces them to new susceptible population. The advancement in transport sector have made matters worst, infected people travel from one place to another exposing a population with low herd-immunity to a new disease [14].

The emergence of Chikungunya is complex and has multifactorial agents, but it appeases in a pattern that follow the extreme weather conditions of drought and rainy season, associated with global climate change. The health and life of people are put at risk due to unwanted developments of the urbanized world. This not only hampers the life of people from low-income group but also is also associated with violation of their human rights [25].

After 200 years, the Chikungunya virus reemerged in America mainly due to large-scale transport of local goods from Africa, China and India. The European continent was affected by Chikungunya due to contact with infected people in India, which could be through tourism to and from India. Africa the continent that housed the outbreak of this devastating epidemic provided conducive environment for development of CHIKV and breeding places for the mosquito species. Lack of awareness and treatment methods about the disease also contributed to the spread. The virus's adaptability to low cholesterol environment largely contributed to its global spread, also due to presence of various species of *Aedes* mosquitoes around the world enhanced the effect.

VI. Conclusion

Re-emergence of Chikungunya has caused detrimental effects globally. The virus, vector and environment are inter-related contributors in the reemergence of Chikungunya. The mutation in the virus increased its virility to survive in mosquitoes as well as humans for longer, the virus also adapted to a new vector increasing its global reach. Venereal transmission during the inter-epidemic period aided the survival of the epidemic. The changing climatic conditions such urbanization and increased travel and tourism has also helped the vector and the virus to travel distance that it could never reach before. A disease of the tropical origin only known to survive in its native regions has affected worldwide population. Due to unavailability of vaccines and medicines, collective community treatments needs to be put into place for the eradication of the disease.

It is also essential that Chikungunya is not considered in isolation to other vector-borne disease such as dengue, malaria. We need to implement robust evidence-based interventions to help prevent future epidemics. Help from variety of fields such clinicians, microbiologists, public health

disciplinary all need to collaborate to mobilize support to eradicate the disease. We must ensure that the virus and the vector, possibly lurking in the dark, do not catch us unaware again.

ACKNOWLEDGMENT

We would like to thank FLAME University, Pune, India, for providing a platform to work in a motivated academic environment.

REFERENCE

[1] Robinson, M.C. "An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-1953. I Clinical features. Transactions of the Royal Society of Tropical Medicine and Hygiene." 49.1 (1952): 28-32 published.

[2] Jupp PG, McIntosh BM. Chikungunya virus disease. In: Monath TP , editor. *The arboviruses: epidemiology and ecology* vol. II. Boca Raton, FL: CRC Press; 1988, pp. 137-157 published.

[3] Halstead B, Scott, Re-appaearance of Chikungunya, formerly called Dengue in Americas. *Emerge Infect Dis*. 2015 Apr; 21(4): 557–561 published.

[4] Powers, A. M. and C.H Logue . "Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus." *J. Gen virol* 88.9, 2007, pp. 2363-2377 published.

[5] Sudeep A B, Parashar D, 'Chikungunya; an overview', *Indian Academy of Sciences*, 2008 November, pp. 444, published.

[6] Pialoux, Gilles, et al. "Chikungunya, an epidemic arbovirus." *Infection the Lacet* 2015 321-323 published.

[7] J S. S. Singh, S. P. Manimunda, A. P. Sugunan, Sahina and P. Vijayachari. "Four Cases of Acute Flaccid Paralysis Associated with Chikungunya Virus Infection ." *pidemiology and Infection*, 2008, pp. 1277-1280 published.

[8] Gérardin, P. B.-S.-Y. (2008). Multidisciplinary Prospective Study of Mother-to-Child Chikungunya virus Infections on the Island of La Réunion. *PLOS Medicine* , *5* (3), pp. 413-423. http://dx.doi.org/10.1371/journal.pmed.0050060

[9] Powers, Ann M. and Christopher H. Logue. "changing patetrns of chikungunya virus- re-emergence of zoonotic arbovirus." *Journal of general Virology* 2007; pp.1-10 published.

[10] Kalantri, S. P., Rajnish Joshi and Lee W. Riley. "Chikungunya epidemic: An Indian perspective." *The National Medical Journal of India* 2006, pp.11

[11] J Ezine, Hpathy, Homeopathy for Chinkunya, *Journal of Medical Epidemiology*, 2014.

[12] Solignat, Maxime, et al. "Replication cycle of Chikungunya: A re-emergence arbovirus." 24.3, 2006, pp.83-84.

[13] V, Ravi. "Re-emergence of Chikungunya virus in India." *Pathogen Detection* 24.2, 2006, pp. 83-84.

[14] Schwartz, Olivier and Mattew Albert. "Biology and pathogenesis of chikungunya virus." *Nature Reviews* 2010, pp. 491 published.

[15] Chua K B, 'Epidemiology of Chikungunya in Malaysia: 2006-2009', *Med J Malaysia*, 65 (4), 2010 December, pp. 278-279 published.

[16] Leo S. Yee, Chow L. P.Angela, Tan Li Kiang, Lye C. David, Lin Li, Ng C. Lee, 'Chikungunya outbreak, Singapore 2008'. Emerg Infect Dis, 2009 May, 15 (5), pp. 836-837. http://dx.doi.org/10.3201/eid1505.081390

[17] Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases, USA, 2015.

[18] Patel, Vinod. Not at ease. *Down to Earth*, 2006, pp. 22 published.

[19] Khan AH, M. K. (2002). Complete nucleotide sequence of chikungunya virus and evidence for an internal polyadenylation site. *83* (3075), 84. http://dx.doi.org/10.1099/0022-1317-83-12-3075

[20] Blackburn NK, B. T. (1995). Antigenic relationship between chikungunya virus strains and o'nyong nyong virus using monoclonal antibodies. . *Res Virol , 146*, 69-73. http://dx.doi.org/10.1016/0923-2516(96)80591-7

[21] Iteman I, M. A. (2006). Genome microevolution of chikungunya viruses causing the Indian ocean outbreak. *PLOS Med* , 263.

[22] Mavale Mangala, et.al, 'Venereal Transmission of Chikungunya Virus by Aedes aegypti Mosquitoes (Diptera: Culicidae)', Am *J Trop Med Hyg*, 2012 December 6, 83(6): pp. 1242-1244.

[23] Schuffenecker, Isabelle et. al. "Genome microevolution of chikungunya viruses causing the indian ocean outbreak." *PLOS Med*, 2006, pp. 1070.

[24] Setbon, Michel, Jocelyn Raude and Dana Pottratz. "Chikungunya on Réunion Island: Social, Environmental and Behavioural Factors in an Epidemic Context ." *Population (English Edition, 2002-)* 63.3, 2008, pp. 491-518 published.

[25] Meason, Braden and Ryan Paterson. "Chikungunya, Climate Change, and Human Rights ." *Health and Human Rights* 16.1, 2014, pp.105-112.