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Chikungunya virus pathogenesis: A global bioterrorism for public health

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Abstract

The recent emergence of Chikungunya has taken the concern of the health authorities of Bangladesh. There was a good number of record of Chikungunya patients in different hospitals as well as clinic. Although the fatality rate of this disease almost negligible, but the suffering due to this viral fever has been the main notable point. The aim of this paper is to make a general understanding of the disease as well as the structural identity of the virus with the symptoms and probable treatment or prevention. Chikungunya virus (CHIKV), a mosquito-transmitted alphavirus, is recurring in epidemic waves. In the past decade and a half, the disease has resurged in several countries around the globe, with outbreaks becoming increasingly severe. Though CHIKV was first isolated in 1952, there remain significant gaps in knowledge of CHIKV biology, pathogenesis, transmission, and mechanism. Diagnosis is largely simplified and based on symptoms, while treatment is supportive rather than curative. Here we present an overview of the disease, the challenges that lie ahead for future research, and what directions current studies are headed towards, with emphasis on improvement of current animal models and potential use of 3D models. Therefore, it is imperative that health care first responders who provide emergency medical services be knowledgeable on the detection, diagnoses and response to biological agents so as to minimize adverse health effects and prevent fatalities. Information contained in this article includes overall awareness of select agents of bioterrorism and brief clinical characteristics of the most common and most likely bioterrorism agents known as Tier 1 select agents with the purpose of better preparing health care first responders in the event of a potential bioterrorism attack.

Keywords: Pathogenesis, symptoms, diagnosis, genome organization, replication, transmission, vector, clinical manifestation, models

Introduction

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus that circulates predominantly in tropical and subtropical regions, potentially affecting over 1 billion people. Recently, an outbreak began in the western hemisphere and has resulted in over 1.8 million reported suspected cases. Infection often results in severe fever, rash and debilitating polyarthralgia lasting weeks to months. Additionally, the current literature reports that CHIKV can result in a severe chronic arthralgia and/or arthritis that can last months to years following the initial infection. The purpose of this review is to evaluate the literature and summarize the current state of knowledge regarding CHIKV-associated disease, including clinical presentation, diagnosis, risk factors for development of severe disease, treatment, and pathogenesis in human patients. Additionally, recommendations are presented regarding avenues for clinical research to help further elucidate the pathogenesis of joint disease associated with CHIKV infection. CHIKV is an enveloped virus that is approximately 70 nm^[1, 2] in diameter in neutral pH and contains a 11.8 kb single-stranded, positive-sense RNA genome^[3, 4]. The genome consists of a 50 methylated terminal cap untranslated region (UTR), followed by RNA coding for 4 non-structural proteins (nsP1–4) and 5 structural proteins (C–E3–E2–6K–E1), and a 30 terminal poly-A tail. Chikungunya (CHK) is caused by an arbovirus that belongs to the genus *Alphavirus* under the *Togaviridae* family. It has a single-stranded RNA genome, a 60-70 nm diameter capsid and a phospholipids envelope^[2, 5]. It is sensitive to temperatures above 58° Celsius and also to desiccation. Believed to be enzootic throughout much of Africa, CHK virus probably spread to other parts of the world from this origin.

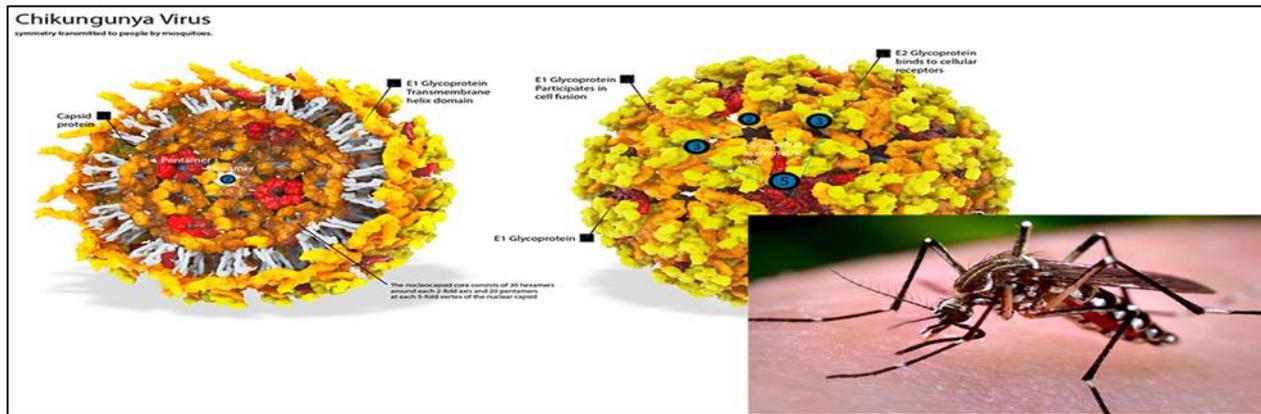


Fig 1: Electron microscopic view of Chikungunya Virus

African and Asian strains are reported to differ biologically with distinct lineages. In Bangladesh in this year 2017, up to the first three weeks of May 240 blood samples of clinically suspected CHIKV infection and 50 of them were laboratory confirmed by IEDCR [5]. But studies regarding CHIKV infection in our country are yet not available. Chikungunya virus (CHIKV) is a mosquito-transmitted alphavirus that belongs to the Togaviridae family, probably originated in Africa.

History/Origins

CHIKV was not recognized in the early 19th century, but what we now know as CHIKF was. It was not until the early 1950s that CHIKV was first characterized in East Africa [6]. It was more specifically outlined in southern Tanzania in 1952, where it was first isolated in a human [7]. Following its discovery, the disease was largely confined to pockets of land in Asia and Africa. The disease was marked by long gaps of inactivity interspersed with sudden outbreaks [8], though this characterization has been disputed [9]. It was not until the late 1990s and early 2000s that CHIKV began to re-emerge on a global scale. Many of these recent epidemics differed from those previously reported in both their increased scale and more rapid movement, with many originating from migrant populations moving from areas with endemic CHIKV. Malaysia had an outbreak in 1998 that was present primarily in adults and speculated to be re-introduced through the movement of workers [10], while Indonesia had a major outbreak in 2001–2003 after a 20-year hiatus of epidemic CHIKV [11]. The 2005 Indian epidemic, one of the most severe of the recent outbreaks, provided a possible template for envisioning future outbreaks and their consequences. This outbreak affected one-third of the island's population and was notable in that its neural, hepatic, and myocardial symptoms led to an unusually high mortality rate as compared to previous CHIKV outbreaks [12].

Bioterrorism

Bioterrorism is terrorism involving the intentional release or dissemination of biological agents. The lack of prophylactic and therapeutic measures, the potential for human-to-human transmission, and this pathogen a serious bioterror threat. The potential to use chikungunya virus (CHIKV) as a bioweapon is further enhanced by the ability to manipulate the virus through either rational genetic approaches or through various passing schemes to produce altered agents that could escape detection and/ or existing prevention and control methods [21]. As such, chikungunya virus (CHIKV) is considered a

potential threat as a biological weapon [22] that could have dramatic direct (morbidity and death) and indirect (international trade restrictions) impact in countries that are currently free of the virus. Because of its clear disease potential, aerosolized chikungunya virus (CHIKV) could be used as a bioterror weapon to threaten humans and ruminants and devastate the economy [23-26]. Importantly, unlike other potential bioterror agents (i.e., Crimean-Congo hemorrhagic fever virus, Nipah virus and Ebolavirus), the vectors for chikungunya virus (CHIKV) transmission are present in the Western hemisphere. chikungunya Viruses can be used by both States and terrorists as biological weapons, but using them on a wide scale requires considerable technical knowledge and facilities. The main defence is education of clinicians and the public as the greatest effect of these weapons is fear and panic.

- Viruses are potential biological weapons, and many viruses are infectious by the aerosol route even if they are normally transmitted by vectors.
- chikungunya Viruses has received most attention as a potential biological threat.
- Knowledge, skills, research and public health infrastructure are the best defence for bioterrorism.
- Standard principles of infection control and public health apply to bioterrorist incidents.
- Nature is the greatest bioterrorist and the infrastructure developed for deliberate acts supports real events.

Epidemiology

In the South-East Asia Region, Chikungunya virus is maintained in the human population by a human-mosquito-human transmission cycle that differs from the sylvatic transmission cycle described on the African continent. A high vector density as seen in the post monsoon season accentuates the transmission. Chikungunya fever epidemics display cyclical and seasonal trends. There is an inter-epidemic period of 4-8 years (sometimes as long as 20 years) [13]. Outbreaks are most likely to occur in post-monsoon period when the vector density is very high. Human beings serve as the chikungunya virus reservoir during epidemic periods. During inter-epidemic periods, a number of vertebrates have been implicated as reservoirs. These include monkeys, rodents, birds, and other vertebrates. The exact nature of the reservoir status in South-East Asia Region has not been documented.

Global Perspective

The first incidence of Chikungunya virus epidemic was first came into light in 1952 with its first ravage in East Africa

followed by several epidemics in Asia.¹⁰ Including Philippines (1954, 1956 and 1968), Thailand, Cambodia, Vietnam, India, Myanmar and Srilanka. The re-emergence of CHIKV infection was also found in democratic Republic in Congo in 1999-2000, Java in 2001-2003 and in the islands of South western Indian ocean i. e Myotte, Seychilles and Mauritius. Imported cases from these islands were found in Europe in the beginning of 21st century. According to Eurosurveillance, 2006; 307 cases were found in France, 197 in Italy, 17 cases in Germany, 9 in United Kingdom, 12 in Belgium and 1 in each Czech Republic and Norway. CHIKV arrived in the America in 2013. The incapacitating arthralgia raised the doubt about the infection in the early period of 2006. The diagnosis was confirmed as Chikungunya virus infection with laboratory findings. During 2006, a total of 13,90. 322 clinically suspected cases of Chikungunya infection were reported from 16 states of India, which came

down to an amount of 27,553 cases in 2015. It confirmed the re-emergence of this virus in this sub-continent. It may be multifactorial, which includes social, environmental, behavioral and biological factors. In 2016, a big CHIKV epidemic affected our neighboring country India which compelled their public health system to formulate guideline to manage acute Chikungunya cases and their sequel.

Bangladesh Situation

In 2006, an increase in the incidence of Chikungunya in India rationalized prompt testing of serum samples collected from febrile patients from two different surveillance projects in Dhaka, Bangladesh. However one hundred seventy-five serum samples tested were found no antibodies against Chikungunya virus¹⁷. In 2008, the first recognized outbreak of Chikungunya in Bangladesh was identified in Paba, Rajshahi, the northwest area of the country.



Fig 2: Chikungunya virus affected Bangladesh

An outbreak investigation team was deployed at the end of November where team from Institute of Epidemiology Disease Control and Research (IEDCR) and International Centre for Diarrhoeal Disease Research, (ICDDRDB) of Bangladesh in Char Kushai village, Dohar, Dhaka. Data collected in all 897 households in the village in 3,840 residents with or without symptoms. Detailed epidemiological data and mathematical models were used to show the transmission pattern and risk factors ^[29]. It was found that viral spread was largely driven by transmissions at distances not much farther away than neighboring households. Human mobility in rural Bangladesh especially in woman is very

limited with individuals spending >50% of the time in and around the home.

Pathogenesis

At present, not many detailed studies are available on the pathogenesis of the Chikungunya fever. In humans, the bite of an infected mosquito leads to deposition of Chikungunya virus (CHIKV) in the subcutaneous tissue resulting in viremia. A febrile response signals viral replication with release of inflammatory cytokines. Lymphocytic perivascular cuffing and extravasation of erythrocytes from capillaries are seen in biopsies of the cutaneous rash.

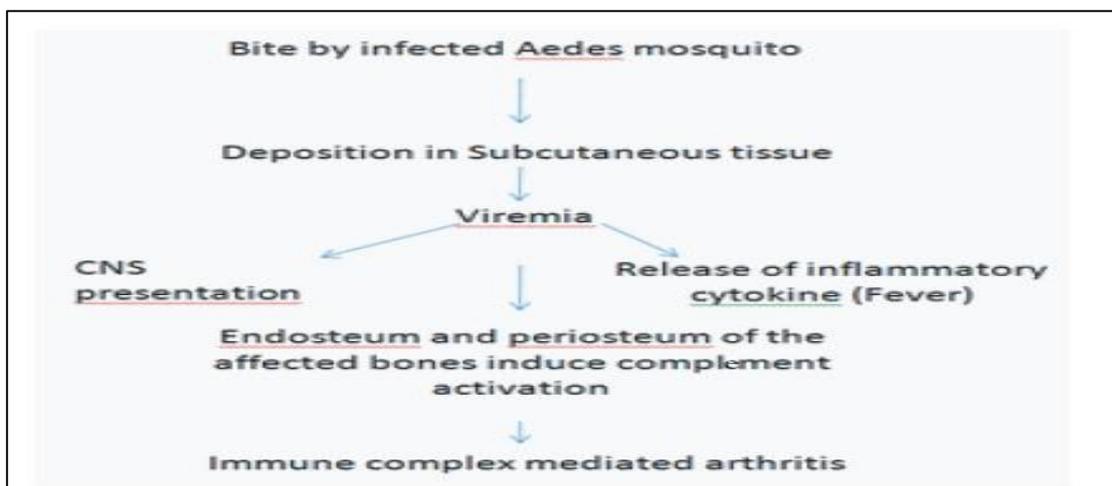


Fig 3: Flow chart of Pathogenesis

Animal studies on related flaviviruses have shown that replicating virus in the synovial fluid, endosteum and periosteum of the affected bones induce complement activated immune complex mediated arthritis [14]. In the later stages, involvement of synovial joint spaces leads to frank arthritis. There is no synovial lymphocytosis, bone or cartilage destruction.

Symptoms

Symptoms of a patient usually begin after he or she has been bitten by an infected mosquito. Symptoms include headache, muscle pain, joint swelling, rash, fever and joint pain. Among these, fever and joint pain are the most common symptoms of chikungunya. Though the result of this disease is not death, the symptoms may persist for months or even more. These may be severe and disabling. Newborns who are infected around the time of birth, adults aged ≥65 years and people with high blood pressure, diabetes or heart disease are more susceptible or at higher risk for more severe disease. It is said that if a person is infected once, he or she will likely to be

protected from further infections in future [15, 16]

When laboratory tests are performed, the primary lab finding is lymphopenia, delineated as having <1000 lymphocytes/mL [16]. Along with the lymphopenia, there is occasional leukopenia, elevated liver enzymes, anemia, elevated creatinine, elevated creatinine kinase, and hypocalcemia [16]. The acute stage of CHIKV is noted to have a high viremic load, with an average of 107 pfu/mL [13].

Diagnosis

Diagnosis can be delayed due to the possible confusion of symptoms with those of dengue fever or Zika. Fever and polyarthralgia give 84% sensitivity, 71% positive predictive value (PPV), and 83% negative predictive value (NPV). Enzyme-linked immunosorbent assays (ELISA) can be used to confirm the presence of anti-CHIKV antibodies, with IgM antibody levels highest three to five weeks post-infection and persisting for up to two months. PCR can also be used to genotype the virus.

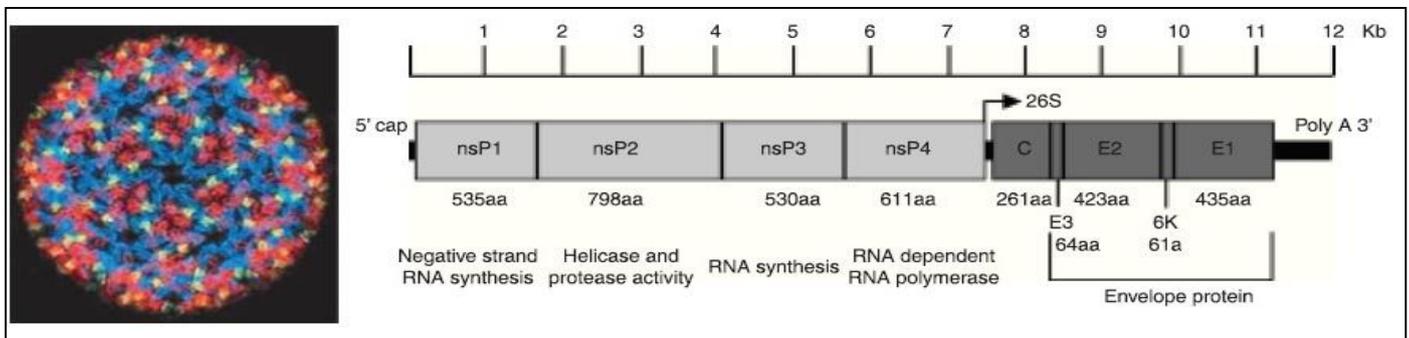


Fig 4: Chikungunya virus and Organization of Chikungunya virus genome

Laboratory diagnosis of Chikungunya fever

As the clinical manifestations of Chikungunya fever resemble those of dengue and other fevers caused by arthropod borne

viruses of the *Alphavirus* genus, laboratory diagnosis is critical to establish the cause of diagnosis and initiate specific public health response.

Differential Diagnosis		
Dengue fever	Chikungunya	Dengue
Fever (>39°C)	+++	++
Arthralgia	+++	+/-
Arthritis	+	-
Headache	++	++
Rash	++	+
Myalgia	+	++
Hemorrhage	+/-	++
Shock	-	+
Lymphopenia	+++	++
Neutropenia	+	+
Thrombocytopenia	+	+++
Hemoconcentration	-	++

Types of Laboratory tests available and specimens required:

Laboratory criteria include a decreased lymphocyte count consistent with viremia. However a definitive laboratory diagnosis can be accomplished through three main laboratory tests: virus isolation, serological test and molecular technique of Polymerase Chain Reaction (PCR). Specimen is usually

blood or serum but in neurological cases with meningo-encephalitic feature, CSF (cerebro-spinal fluid) may also be sent.

Virus isolation

Virus isolation provides the most definitive diagnosis, but takes one to two weeks for completion and must be carried

out in biosafety level III laboratories to reduce the risk of viral transmission. The technique involves exposing specific cell lines to samples from whole blood and identifying chikungunya virus-specific responses. The isolation process is time-consuming and the degree of success is dependent on a number of complicating factors, for example, time of collection, transportation, maintenance of cold chain, storage and processing of samples.

Transmission

Chikungunya fever is a viral disease transmitted to humans by the bite of infected *Aedes aegypti* mosquitoes. Chikungunya virus (CHIKV) is a member of the genus Alphavirus, in the family *Togaviridae*. CHIKV was first isolated from the blood of a febrile patient in Tanzania in 1953.

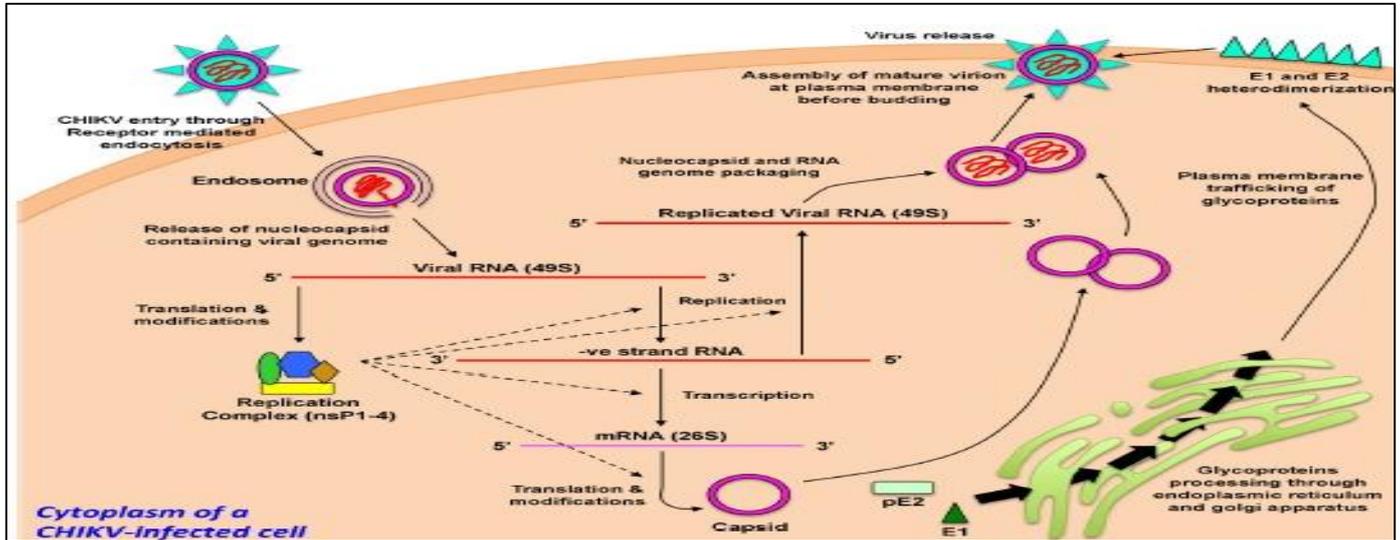


Fig 5: CHIKV replication cycle.

Since then it has been identified repeatedly in west, central and southern Africa and many areas of Asia, and cited as the cause of numerous human epidemics in those areas. The virus circulates throughout much of Africa, with transmission,

thought to occur, mainly between mosquitoes and monkeys. In ‘Swahili’ language, Chikungunya means that which contorts or bends up or illness of the bended walker.

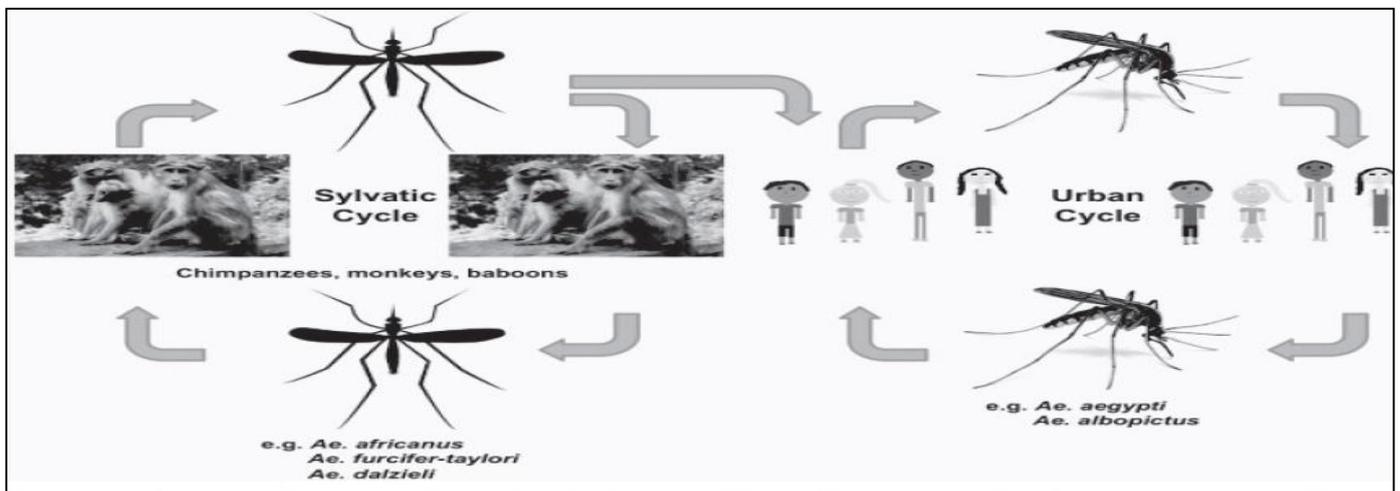


Fig 6: The sylvatic cycle residue in promotes but during outbreak the urban cycle consist of man mosquito man cycle.

This refers to the contorted (or stooped) posture of patients who are afflicted with the severe joint pain (arthritis), a most common feature of the disease. It is a debilitating, but non-fatal viral illness. Since 1960, the outbreaks of the disease in South Eastern Asia were reported from India, Sri Lanka, Myanmar, Thailand, Indonesia, Philippines and Malaysia. Chikungunya outbreaks typically result in large number of cases but deaths are rarely encountered. Chikungunya cases start appearing in post-monsoon season period that is in the month of May onwards with a peak between the month of July and August as during this period vector density remains very high [18]. The last outbreak of Chikungunya infection in

20th century occurred in India during 1973. Thereafter, after a quiescence of 2-3 decades during 2006 reports of large scale outbreaks of fever caused by Chikungunya in several parts of India have confirmed the re-emergence of this virus in the country with 13.9 million clinically suspected and 2001 laboratory confirmed cases [19]. Since then transmission is continuing in various parts of the country. Currently in 2016, big upsurge/epidemic due to Chikungunya is being going on in the capital city of Delhi and reporting case from other States/UT’s too. Till, 11th September, 2016 a total of 14656 clinically suspected cases (including 1724 in Delhi) from 18 states and 2 UT’s have been reported. Against such back drop,

a need was felt to revise and formulate uniform guidelines for management of acute Chikungunya cases and post Chikungunya sequelae.

Transmission Cycle

The human infections are acquired by the bite of infected *Ae. aegypti* mosquitoes, which are day biters and epidemics are sustained by human-mosquito-human transmission. The incubation period (time from infection to illness) can be 2-12 days, but is usually 3-7 days. Acute Chikungunya fever typically lasts a few days to a couple of weeks, but some patients have prolonged fatigue lasting several weeks. Additionally, some patients have reported incapacitating joint pain, or arthritis which may last for weeks or months. The prolonged joint pain associated with CHIKV is not typical of dengue. No deaths, neuro-invasive cases, or hemorrhagic cases related to CHIKV infection have been conclusively documented in the scientific literature.

Neonatal disease and mother-to-child transmission

There have been cases of mother-to-foetus infection which have occurred between 3 and 4.5 months into pregnancy. Vertical transmission has been observed during near-term deliveries in the context of intrapartum viremia; 19 cases of vertical transmission out of 39 women with intrapartum viremia in one series, giving the vertical mother-to-child transmission rate of 48.7%.²² During the outbreak in Réunion island, 38 neonatal cases were studied retrospectively. All of them developed symptoms between Day 3 and Day 7 (mean, Day 4). Mean interval between the onset in mothers and in the babies was five days. Frequent and prominent signs in the neonates were rashes (82%), fever (79%) and peripheral oedema (58%). Raised serum aspartate aminotransferase level (77%), reduced platelet count (76%), diminished prothrombin value (65%), and low lymphocyte count (47%) were observed. Seizures and haemorrhagic and haemodynamic complications were noted. Positive RT-PCR in CSF and abnormalities on magnetic resonance imaging (MRI) studies of the brain were noted in high percentage of neurological cases, (22/24 and 14/25 respectively). Mother-to-child perinatal vertical transmission was deemed responsible [20]. In another study from the same outbreak, three out of nine miscarriages before 22 weeks of gestation were attributed to the CHIK virus infection (RT-PCR positive in amniotic fluid)^[21].

Vector

Aedes mosquitoes- *Aedes aegypti* & *Aedes albopictus*. post-monsoon there is an upsurge of cases. High vector density in the post-monsoon season accentuates virus transmission. Chikungunya is transmitted by *Aedes* mosquitoes (*Ae. aegypti* & *Ae. albopictus*) which breed in clean water collections in containers, tanks, disposables, junk material in domestic and peri-domestic situations besides natural habitats like tree holes, plantations etc. However, *Aedes albopictus* has also been found to be playing a part in some areas. They are principally day biters^[53]. Eggs of these vectors have the ability to withstand desiccation for more than a year. This could result in the virus to remain in nature for long periods and cause outbreaks. *Aedes* mosquitoes take multiple feeds per each feed and it would also result in small focal outbreaks. In the initial part of outbreak, individual population is not protected which could result in larger outbreaks.

Vector surveillance and control

Vector surveillance during pre-monsoon and during the monsoon, if done appropriately, will provide an early warning indicator prior to the outbreak of Chikungunya. Vector control can be done through anti-adult and anti-larval control of mosquitoes

Clinical manifestation of Chikungunya

Incubation period

CHIK virus causes an acute febrile illness with an incubation period of 3-7 days (can be 2- 12 days,). Viraemia persists for upto 5 days from the onset of symptoms. Fever and arthralgia are the hallmark of Chikungunya fever^[22].

Table 1: Clinical feature

Clinical Feature		
Common	Infrequent	Rare in Adults but seen in children
Fever (92%)	Stomatitis	Photophobia
Arthralgia/Arthritis (87%)	Oral ulcers	Retro-orbital pain
Backache (76%)	Exfoliative dermatitis	Vomiting
Headache (62%)	Photosensitive hyperpigmentation	Diarrhoea

Clinical Features

Clinical presentation of Chikungunya is divided in to three phases. In Chikungunya mostly symptoms have an abrupt onset with high grade fever, single or multiple joint pains, skin rashes, headache and myalgia. Clinical presentation of Chikungunya usually follows 3 phases which are as follows:

- Acute phase: Less than 3 weeks
- Sub-acute phase: > 3 weeks to 3 months
- Chronic phase: > 3 months

Clinical presentation may be mild, moderate or severe and most of the symptoms subside within 3 weeks from the onset of symptoms. Some of the symptoms may persist for 3 months and even more. Usually 10 – 15% of the patient those who present with severe Chikungunya progress to Sub-acute or chronic phase.

Common

- Fever
- Arthralgia/Arthritis
- Backache
- Headache
- Skin rash/Itching

Fever: The fever varies from low grade to high grade usually lasting for 24 to 48 hours. It has an abrupt onset usually responds to antipyretics.

Arthralgia/Arthritis: Arthralgias are polyarticular and usually involve peripheral joints. The joint pain tends to be worse in the morning which gets better with mild physical activity. The pain may remit for 2-3 days and then reappear in a saddle back pattern in some patients. It is usually polyarticular, symmetrical involving predominantly small joints of hands and feet. Ankles, wrists and small joints of the hand are the worst affected. Larger joints like knee and shoulder may also be involved. There is a tendency for early and more significant involvement of joints with some previous trauma or degeneration.

Back ache

One of the commonest symptom of Chikungunya giving a typical posture. In initial phase of the disease back ache could be very severe.

Headache

One of the prodromal symptom and could persist during the 1st week of illness.

Rash

Transient maculopapular rash is seen in up to 50% patients.

The maculopapular eruption persists for more than 2 days in approximately 10% of cases. Nasal blotchy erythema and photosensitive hyperpigmentation are more frequently observed. Exfoliative dermatitis affecting limbs and face was seen in around 5% cases. Epidermolysis bullosa was an observation in children. Most skin lesions recovered completely except in cases where the photosensitive hyperpigmentation persisted. Intertriginous aphthous-like ulcers and vesicul bullous eruptions were noticed in some. A few persons had angiomatous lesions and fewer had purpuras.

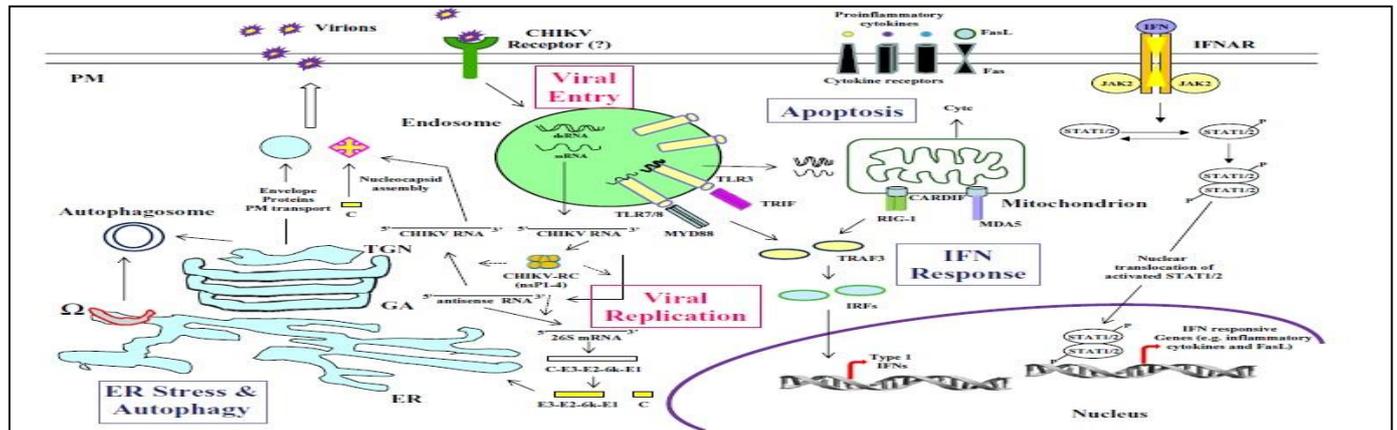


Fig 7: ER Stress and Autophagy

Innate immune response

It is the first line defense mechanism of the body. Monocytes, NK cells are some blood leukocytes that provide innate immunity to various viral infections. These cells accelerate virus dissemination as their main location is in peripheral tissue and circulatory system. In case of CHIKV infection both hematopoietic and nonhematopoietic cells are involved by the innate immune system [23].

Again, monocytes/macrophages in the circulatory system can disseminate virus infection as well as it can also serve as a reservoir for further viral infection [23].

Treatment

Mild and moderate cases can be managed at home. Severe case should be managed at hospital. Home damage. Tablet paracetamol during the periods of fever. Avoid self-

medication with aspirin or other NSAID. Indications for hospitalization are intractable pain, oliguria, bleeding manifestations, pregnancy, high risk group, hemodynamically unstable, comorbid conditions (CLD, CKD, CVD, Diabetes) and any serious complication (CNS, Hepatic, Renal) [16]. In subacute state objective of treatment is to relieve pain and inflammation, Limit the consequences of the inflammatory process. Treatment options are paracetamol, NSAID for joint pain. Amitryptiline, pregabalin, Gabapentin and physiotherapy for neuropathic pain. Prednisolone and DMARD can be used when refractory to NSAID. Chronic phase/chronic joint pain have several categories: Post Chick Rheumatoid Arthritis, Post-CHIK Spondyloarthritis, Post-CHIK undifferentiated polyarthritis, Post-CHIK Musculoskeletal Disorder.

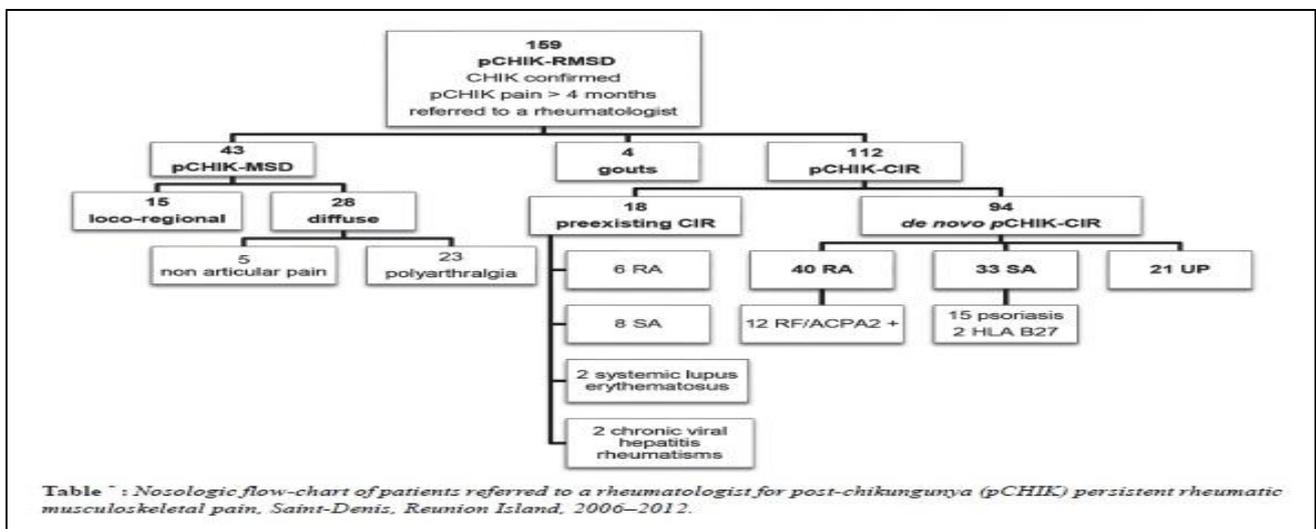


Table 7 : Nosologic flow-chart of patients referred to a rheumatologist for post-chikungunya (pCHIK) persistent rheumatic musculoskeletal pain, Saint-Denis, Reunion Island, 2006–2012.

Post Chick Rheumatoid Arthritis can be treated by Methotrexate, Leflunomide and Sulfasalazine. Post-CHIK Spondyloarthritis can be treated by NSAID. Methotrexate/Sulfasalazine is the second line drugs. Post-CHIK undifferentiated polyarthritis treated with Hydroxychloroquine in excess to NSAID in first line, Corticosteroid and Methotrexate are 2nd line and 3rd line therapy respectively. Post-CHIK Musculoskeletal Disorder is treated with the same principles as the management of sub-acute presentations. No vaccine or medicine is discovered yet to prevent or to treat chikungunya virus. There are some recommendations to treat the symptoms of chikungunya fever which includes:

- a. Plenty of rest should be taken
- b. Prevention of dehydration by drinking fluids
- c. Administration of acetaminophen or paracetamol to reduce pain and fever
- d. Aspirin and other non-steroidal anti-inflammatory (NSAIDs) should be avoided
- e. Consultation with physician before taking other medications for another medical conditions
- f. Prevention of mosquito bites is recommended for the first week of chikungunya attack. This is mandatory as the virus can be transmitted during the first week after attack [16].

Public Health Measures

Patient when infected can spread the infection by spreading the infection through mosquitoes. It is important to break this transmission by minimizing the vector density by community participation and taking appropriate control measures in the hospital setting by following measures.

Minimizing transmission of infection:

This can be done in the following ways:

1. Risk communication to the household members
2. Minimize the vector population
3. Minimize the vector-patient contact (Aedes mosquitoes bite during day time, mostly in the morning and late afternoon)
4. Reporting to the nearest public health authority/ or the DPMO

Risk communication to the household members

Chikungunya is a disease that is transmitted by mosquitoes. House hold members may also come down with Chikungunya infection as they also share the same environment

- Adult could be identified by characteristic white and black band on legs and abdomen. (Known as tiger mosquito).
- The probable potential breeding sites where water could accumulate and acts as

breeding place for *Aedes* in the hospital setting are –

1. In side hospital

Water coolers, AC ducts, flower pots, artificial containers

having ornamental plants, money plants in OPD, overhead / water tanks in wards and sometimes in operation theaters also, toilets/cisterns, canteens /cafeterias

2. over the roof

Overhead water tanks, unused hardware material including condemned furniture and other articles which may accumulate water in rainy seasons

3. in the campus/compound

Unused receptacles (Bottles/tins/buckets/drums), flower pots, cement tanks,

4. in hostels

The probable places are in boys/girls/nursing/training hostels situate in the campus- Coolers/water tanks etc. Kitchens of the hostel are also potential breeding places.

5. Residential houses (Officers/Servant quarters /staff quarters) – House hold

containers /coolers etc.

6. Construction sites within hospital campus –

Articles kept for water storage and unused hardware articles kept in the open

7. Tea shops/Dhabas in compound

Water storage containers and other discarded thrown away articles.

Vaccines

There is currently no commercial vaccine for CHIKV, although some candidate vaccines have been tested in human beings [24]. Several technologies have been used to develop CHIK vaccines, including inactivated viral vaccines, live-attenuated viruses, alphavirus chimeras, recombinant viral vaccines, consensus-based DNA vaccines, recombinant subunit vaccines and more recently, a virus-like particle (VLP) vaccine. Two vaccine candidates have finished phase I trials: alive recombinant measles-virus-based chikungunya vaccine and the VRC-CHKVLP059-00-VP, VLP vaccine.

CHIKV Infection and Models

Accurate modeling of the pathogenesis of CHIKV infection is critical for continued progress against the disease. Most *in vitro* and *in vivo* models of CHIKV have investigated the mechanisms of viral entry and replication, and the efficacy of various antiviral treatments. As CHIKV has been modeled with several different methods, there are several categorizations of CHIKV modeling. There is *in vitro* cell culture modeling, and mouse and non-human primate *in vivo* modeling. Within these various models, acute stage and chronic stage infection models also have been developed. Each model demonstrates unique facets of CHIKV pathogenesis while having unique shortcomings.

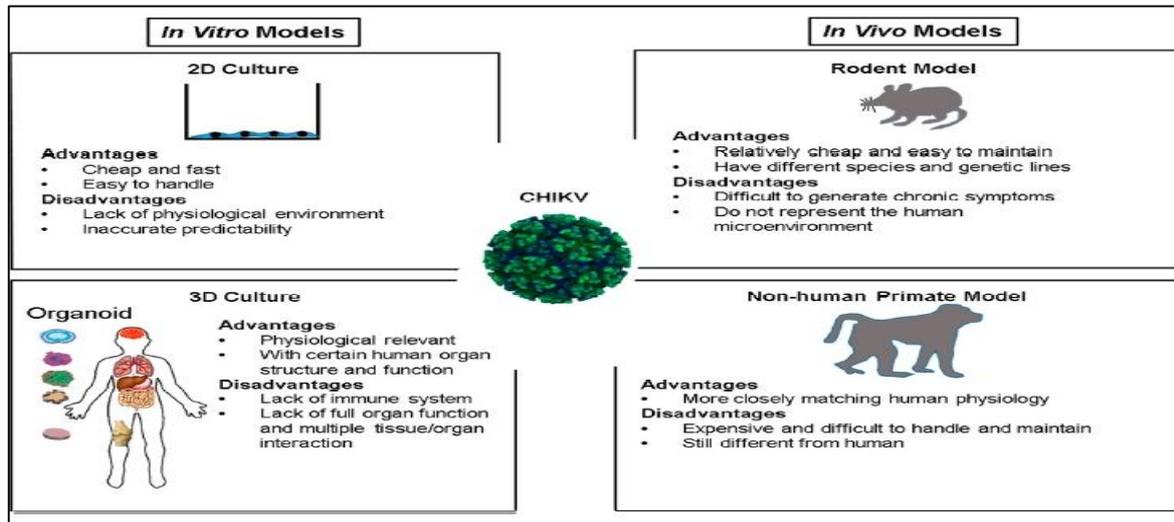


Fig 9: *In Vitro* and *In Vivo* models

Discussion

CHIK is a disease that can present with two phases, acute and late. The acute phase is the period in which symptomatic patients generally report abrupt onset, often characterized by high fever, polyarthralgia, back pain, headache and fatigue.¹⁴ The late phase usually manifests with arthralgia or musculoskeletal pain, with more frequent and lasting signs, interfering for weeks or months, and sometimes for years in the patients' quality of life.¹ Despite the various therapeutic regimens available for CHIK, 40% of patients progress with chronic pain and compromised quality of life,¹⁴ making it critical to research on late-phase therapy. The light from low-power laser therapy produces photochemical reactions within cells that activate enzymes, at the cellular level, with the ability to increase mitochondrial function and ATP synthesis, increasing cell proliferation and accelerating the healing process. But, as reported in the study itself, the sessions are time-consuming, especially considering that patients usually have complaints in several joints, making the sessions longer and rendering it unfeasible to treat a larger numbers of patients. Also, the study is a case report, requiring more research with a larger sample.

Conclusion

In recent years there have been explosive outbreaks of chikungunya fever in several parts of the SEA (South East Asia) Region and elsewhere. Although the disease is self-limiting, morbidity can be very high in major outbreaks resulting in a heavy social and economic toll. The disease should be preventable and it would require a planned approach, besides knowledge and awareness of early warning signs, for prevention. Integrated vector management through the elimination of breeding sites, use of anti-adult and anti-larval measures and personal protection will contribute to preventing an outbreak. Community empowerment and mobilization is crucial for prevention and control of chikungunya. Adult mosquito control measures such as fogging often applied by the civic authorities as a single tool may not by itself contribute to the effective containment of an outbreak. There was a long-term indication of the use of methotrexate and hydroxychloroquine for treatment, but they did not always resolve arthralgia in the chronic phase of CHIK. Thus, other drugs such as ribavirin and colchicine, and the maintenance of analgesics and anti-inflammatory drugs, judiciously used, have been proposed as alternatives.

Physiotherapeutic treatment has shown some satisfactory results through electrothermal therapy. Homeopathy has also been an alternative in therapeutics. But investigations must be intensified, since the literature on CHIK is still scarce. In addition, it is important to emphasize to the public the need for disease prevention, through educational campaigns and more vigorous supervision by competent bodies.

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