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CHIKUNGUNYA FEVER: A RE-EMERGING VIRAL INFECTION

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Abstract

Chikungunya (CHIK) fever is a re-emerging viral disease characterized by abrupt onset of fever with severe arthralgia followed by constitutional symptoms and rash lasting for 1-7 days. The disease is almost self-limiting and rarely fatal. Chikungunya virus (CHIKV) is a RNA virus belonging to family Togaviridae, genus Alphavirus. Molecular characterization has demonstrated two distinct lineages of strains which cause epidemics in Africa and Asia. These geographical genotypes exhibit differences in the transmission cycles. In contrast to Africa where sylvatic cycle is maintained between monkeys and wild mosquitoes, in Asia the cycle continues between humans and the Aedes aegypti mosquito. CHIKV is known to cause epidemics after a period of quiescence. The first recorded epidemic occurred in Tanzania in 1952-1953. In Asia, CHIK activity was documented since its isolation in Bangkok, Thailand in 1958. Virus transmission continued till 1964. After hiatus, the virus activity re-appeared in the mid-1970s and declined by 1976. In India, well-documented outbreaks occurred in 1963 and 1964 in Kolkata and southern India, respectively. Thereafter, a small outbreak of CHIK was reported from Sholapur district, Maharashtra in 1973. CHIKV emerged in the islands of South West Indian Ocean viz. French island of La Reunion, Mayotte, Mauritius and Seychelles which are reporting the outbreak since February, 2005. After quiescence of about three decades, CHIKV re-emerged in India in the states of Andhra Pradesh, Karnataka, Maharashtra, Madhya Pradesh and Tamil Nadu since December, 2005. Cases have also been reported from Rajasthan, Gujarat and Kerala. The outbreak is still continuing. National Institute of Communicable Diseases has conducted epidemiological, entomological and laboratory investigations for confirmation of the outbreak. These have been discussed in detail along with the major challenges that the country faced during the current outbreak.

Key words: Alphaviruses, chikungunya, Chikungunya virus, re-emerging infections

Chikungunya (CHIK) fever is a viral disease caused by an alpha virus that is spread by bite of Aedes aegypti mosquito. The name is derived from the Makonde word meaning “that which bends up” in reference to the stooped posture developed as a result of the arthritic symptoms of the disease. The sudden onset of the disease including cripplng arthralgia and frequent arthritis that accompany fever, chills, headache, nausea, vomiting, low back pain and rash are clinically distinctive. The disease is almost self-limiting and rarely fatal.

Chikungunya virus (CHIKV) was first isolated from the serum of a febrile human in Tanganyika (Tanzania) in 1953. Between the 1960s and 1980s, the virus was isolated repeatedly from numerous countries in central and southern Africa as well as in Senegal and Nigeria in western Africa. During the same period, the virus was also identified in many parts of Asia. Since 1953, CHIKV has caused numerous well documented outbreaks and epidemics in both Africa and South East Asia, involving hundreds and thousands of people. Phylogenetic analysis confirms two distinct CHIKV lineages, one containing western African and the second comprising all southern and East African strains, as well as isolates from Asia. This finding corroborates that CHIK virus originated in Africa and subsequently was introduced into Asia. Within the eastern Africa and southern Africa/Asia lineage, Asian strains can be grouped together in a genotype distinct from the African groups. These different genotypes exhibit differences in their transmission cycles: in Asia, the virus appears to be maintained in an urban cycle with Ae. aegypti vectors, while CHIK virus transmission in Africa involves a sylvatic cycle, primarily with Ae. furcifer and Ae. africanus mosquitoes. Complete genomic sequence of CHIKV has been determined. The complete genome was found to be 11,805 nucleotides in length. Coding sequences consisting of two large open reading frames of 7422 nucleotide and 3744 nucleotide encoding the non-structural polyprotein (2474 amino acids) and the structural polyprotein (1248 amino acids), respectively. The non-structural polyprotein is the precursor of proteins nsP1 (535 amino acids), nsP2 (798 amino acids), nsP3 (530 amino acids) and nsP4 (611 amino acids) and the structural polyprotein is the precursor of protein C (261 amino acids), E3 (64 amino acids), E2 (423 amino acids), 6K (61 amino acids) and E1 (439 amino acids).

Aetiology

CHIKV is a Group IV (+) (RNA) belonging to family Togaviridae with genus Alphavirus and species CHIKV.

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the Aedes genus, which usually bite during daylight hours.[6] Vertical maternal foetal transmission of CHIKV has been observed in recent outbreak at La Reunion Island.[7]

In Africa, CHIK virus appears to be maintained in sylvatic cycle involving wild primates and forest dwelling Aedes spp. mosquitoes viz. *Ae. furcifer*, *Ae. taylori*, *Ae. luteocephalus*, *Ae. africanus* and *Ae. neoafricanus*. Monkeys and possibly other wild animals may also serve as reservoirs of the virus.[1] Serological studies have repeatedly demonstrated the presence of antibodies in humans and primates throughout the moist forests and semi-arid savannas of Africa. A vertebrate reservoir or sylvan transmission cycle has not been identified outside Africa, supporting the historical evidence that CHIKV originated in Africa and was subsequently introduced into Asia where it is now typically associated with *Ae. aegypti* mosquitoes. *Ae. albopictus* (the Asian tiger mosquito) may also play a role in human transmission in Asia.[6]

**Pathogenesis**

In humans, CHIKV produces disease about 48 hours after mosquito bite. Patients have high viraemia during the first 2 days of illness. Viraemia declines around 3 or 4 days, usually disappearing by day 5.[8,9] Haemagglutination inhibition (HI) and neutralizing antibodies can usually be detected after day 5 with fading viraemia.[8] Neuro-invasive cases and haemorrhagic manifestation related to CHIKV infection have been conclusively documented in scientific literature. “Silent” CHIKV infections do occur, but how commonly this happens is not yet known. CHIKV infection (whether clinical or silent) is thought to confer lifelong immunity.[9]

Clinical laboratory findings are not remarkable. Few patients may present with leucopoenia with relative lymphocytosis; however, most patients will have normal blood count. The platelet count may be moderately less. Erythrocyte sedimentation rate is significantly elevated and C-reactive protein is positive in acute cases.[9,11,12]

**Clinical Features**

Chikungunya is an acute infection of abrupt onset, heralded by fever and severe arthralgia, followed by other constitutional symptoms and rash lasting for a period of 1-7 days. The incubation period is usually 2-3 days, with a range of 1-12 days. Fever rises abruptly, often reaching 39-40 °C accompanied by intermittent shaking chills. This acute phase lasts 2-3 days. The temperature may remit for 1-2 days, after a gap of 4-10 days, resulting in a “saddle back” fever curve.[5,11,12]

The arthralgias are polyarticular, migratory and predominantly affect the small joints of hands, wrists, ankles and feet with lesser involvement of larger joints. Patients in acute stage complain bitterly of pain when asked to move. They characteristically lie still in the attitude of flexion. Pain on movement is worse in the morning, improved by mild exercise and exacerbated by strenuous exercise. Swelling may occur but fluid accumulation is uncommon. Patients with milder articular manifestation are usually symptom-free within a few weeks, but more severe cases require months to resolve entirely.[3] A study indicated that over 12% of patients develop chronic joint symptoms. Generalized myalgias, as well as back and shoulder pain is common.[13]

Cutaneous manifestations are typical with many patients presenting with a flush over the face and trunk. This is usually followed by a rash generally described as maculopapular. The trunks and limbs are commonly involved, but face, palms and soles may also show lesions. The rash may simply fade or desquamate. Petechiae may occur alone or in association with rash. A positive tourniquet test is found in a small portion of patients.[3]

During the acute disease, most patients will have headache, but it is not usually severe. Photophobia and retrobulbar pain may also occur. Conjunctival redness is present in some cases. Some patients complain of sore throat and have pharyngitis on examination.[3]

Although rare, the infection can result in meningoencephalitis especially in new-borns[14,15] and those with pre-existing medical conditions. Pregnant women can pass the virus on to their foetus. The Reunion South Hospital Group observed, 84 pregnant women who were laboratory-confirmed to be suffering from CHIK infection. In 88% of these - all involving infections relatively distant from delivery, the newborns appeared asymptomatic. Conversely, 10 newborns had severe attacks (four with meningoencephalitis and three with intravascular coagulation) after birth and required intensive care support. No infant died; however, one suffered from intracerebral haemorrhage after severe thrombocytopaenia.[7] Severe cases of CHIK can occur in elderly, newborns and in those who are immuno-compromised. CHIK outbreaks typically result in several hundreds or thousands of cases, but deaths are rarely encountered.

Symptoms of CHIK infection are clinically indistinguishable from dengue fever (DEN). Presence of dual infection of CHIK and DEN has been reported, where both the viruses were simultaneously isolated from sera of the same patient.[16] Both the infections can cause disease at the same time. Other differential diagnosis of CHIK include Onyong-nyong virus infection and Sindbis virus infection.[4,17,18]

**Management of Patients**

There is no specific treatment for CHIK. The illness is usually self-limiting and resolves with time. Supportive care with rest is indicated during the acute joint symptoms. Movement and mild exercise tend to improve stiffness and
morning arthralgia, but heavy exercise may exacerbate rheumatic symptoms. Non-aspirin and non-steroidal anti-inflammatory drugs (NSAID) are recommended. In unresolved arthritis refractory to NSAID, Chloroquine 250 mg has proved to be useful.[13]

Infecive persons should be protected from further mosquito exposure (staying indoors and/or under mosquito net during the first few days of illness) so that they cannot contribute to the transmission cycle.[10]

Epidemiology

A few centuries ago, CHIK virus was probably an infection of primates in forests of Savannahs of Africa maintained by sylvatic Aedes mosquitoes as it continues to be today. However, today, CHIK is also responsible for extensive Ae. aegypti-transmitted urban disease in the cities of Africa and major epidemics in Asia.

Global

Africa: CHIK virus is transmitted in the savannahs and forests of tropical Africa by Aedes mosquito that belong to the subgenera Stegomyvia (Ae. africanus, Ae. luteocephalus, Ae. opok) and Diceromyia (Ae. furcifer, Ae. taylori, Ae. cordellieri). The vertebrate portion of the cycle is provided by non-human primates such as Cercopithecus, monkeys or baboons which amplify and maintain virus circulation. It is thought that endemic circulation and moving epidemics in troops of primates are responsible for survival of the virus and local spillover into human population. In African villages or rural areas, these mosquitoes may then infect humans and the substantial viraemia measures suggest that humans, in appropriate setting, may contribute to mosquito infection, leading to further virus amplification. This becomes particularly important when domestic breeding Ae. aegypti are present in large numbers, a situation that may lead to village and large urban epidemics in Africa.[2,19,20]

The prototype CHIK epidemic which occurred in Tanzania in 1952 to 1953, resulted when Ae. aegypti-borne disease moved through multiple villages over an expanse exceeding 5000 km².[2] Another interesting feature of CHIK epidemiology was observed from Tanzania. In Studies of individual dwellings, there was a highly significant trend for multiple cases to occur in a hut once a single case occurred. This, if course, could be a reflection of flight range of Ae. aegypti vectors and human habits, as also a phenomenon that could occur as a result of mechanical transmission or interrupted feeding of competent biological vectors.[2]

Asia: Different patterns of transmission of disease are observed in Asia as compared to Africa. The disease is primarily transmitted from human to human by Ae. aegypti. Although Asian monkeys have develop significant viraemia after CHIK inoculation and have been found to harbour antibodies to CHIK, they have never been shown to participate in any important way in the maintenance or amplification of the virus in the continent. CHIK activity in Asia has been documented since its isolation in Bangkok, Thailand in 1958,[3] in a setting of intense Dengue virus activity. Antibodies surveys indicated that the virus continued to be transmitted until 1962-1964.[21] During this period, human infections occurred at formidable rates in Bangkok area and its environs. In 1962, an estimated 40,000 patients sought medical attention in the urban complex of 2 million inhabitants. This intensive transmission in mosquitoes was accomplished by large population of Ae. aegypti breeding in water storage jars ubiquitous in Thai homes as a consequence of the lack of piped water distribution system.[21] Similar conditions were observed through the mid-1970s, before CHIK transmission nearly disappeared. CHIK antibodies were rare in Bangkok children born after 1976 and virus isolation was not obtained from febrile outpatients and haemorrhagic fever suspects tested in 1979-1980.[22] The reasons for the decline in the CHIK transmission are unclear because Ae. aegypti were abundant and dengue transmission continued. In 1988, evidence of CHIK transmission in Thailand was obtained once again. But the subsequent pattern has been one of the occasional outbreaks rather than severe epidemic disease. Widespread outbreaks of CHIK have been reported from South-East Asian countries which include Cambodia, Vietnam, Burma, Sri Lanka and India. CHIK has also been active further east in the Pacific, including Indonesia and the Philippines.[23]

India: India, in 1963, experienced an extensive outbreak of dengue-like haemorrhagic fever in Kolkata,[12,24] Sarkar and his colleagues isolated CHIKV from cases with severe haemorrhagic manifestation.[23] A multidisciplinary epidemiological investigation was performed for this epidemic of severe febrile illness, sometimes associated with haemorrhagic manifestations and occasionally terminating in death. It began in July, became serious in August, reached a peak in November and then rapidly declined by December coincident with the end of the monsoon rains. Data from hospital records and death registers showed that serious cases were most frequent among infants and young children, least frequent among young adults and frequent again among adults over 40 years of age. By contrast, data from home visits suggested that milder illnesses may have been of nearly equal frequency among children and adults, leading to a hypothesis that there is an association between age and the likelihood that an infection will eventuate in serious illness or death. It was not possible to make any reasonably precise estimate of the number of infections and mild illnesses that occurred during the course of this epidemic. However, they must have been in lakhs. Similarly, it was not possible to obtain a precise count of the number of cases requiring hospitalization, because the medical profession was unprepared to make definitive diagnosis, but they may have numbered in thousands. Examination of death registers revealed that this epidemic may have resulted in nearly 200 deaths within the corporate limits of Kolkata. Thirty-five
of the 36 virus isolates from intracerebral inoculation of suckling mice were identified as CHIK by “Quick” CF test. One was tentatively recognized as a Group B virus.\(^{[25]}\)

The origin of this epidemic remains unknown, although purely circumstantial evidence suggests an introduction from endemic centres in the countries of South East Asia. Kolkata, an important air and sea port, probably provided an optimal opportunity for any such introduction.\(^{[12]}\)

The CHIK epidemic in Southern India (Vellore, Chennai, Puducherry), in 1964, was well-documented as Vellore was the site of ongoing dengue studies.\(^{[8,11,26]}\) As the rainy season progressed into July, August and September 1964, \textit{Ae. aegypti} population increased to peak. By the end of October, only occasional human cases were seen, as numbers of \textit{Ae. aegypti} decreased with cool temperatures and drier weather. Same transmission season had been seen with Dengue in previous years. Febrile illness usually accompanied by characteristic joint pains, varied from 8 to 86\% in different neighbourhoods and correlated with \textit{Ae. aegypti} density. Males and females were equally affected, but the clinical attack rates were lower to those in infants. It is difficult to accurately assess the impact on Vellore but it was substantial. An estimated 21\% of Chennai city population was affected.\(^{[27]}\) There were 288 laboratory-confirmed CHIK infections from whom 233 virus isolations were made including one infant that died.

The activity of CHIKV appeared to decline during the period 1965-1972. In 1973, a small localized outbreak was reported from Barsi, Sholapur district, Maharashtra state.\(^{[18]}\) This happened after 8 years of relative quiescence, and the cause remains to be understood. No outbreaks were reported from India after 1973 till 2005.

**Current Scenario - Re-emergence of Chikungunya Infection**

**Global**

The outbreak of CHIK was discovered in Port Klang in Malaysia in 1999 affecting 27 people. In February, 2005, an outbreak was recorded on the French Island of La Reunion. As on 18 May 2006, 2,58,000 residents have been hit by the virus in the last 1 year out of the population of about 777,000. Two hundred and nineteen official deaths have been associated with CHIK infection.\(^{[28]}\) Twenty-four distinct outbreaks of probable CHIK aetiology were identified throughout Indonesia from September 2001 to March 2003, after a near-20-year hiatus of epidemic of CHIK activity in the country. Of these, 11 have been confirmed by serological/virological method with attack rate of 2.8-6.7 per 1000 population.\(^{[29]}\) The presenting clinical symptoms were consistent with CHIK infection. Since the beginning of January 2006, other countries in the South West Indian Ocean have reported CHIK cases: Mayotte (9 January-10 March, 2833 suspected cases), Mauritius (1 January-5 March, 6000 suspected cases including 1200 confirmed cases and the Seychelles (1 January-26 February, 8818 suspected cases). Several European countries have reported imported cases in people returning from these islands: France (160 imported cases), Germany, Italy, Norway and Switzerland.\(^{[28]}\)

**India**\(^{[18]}\)

After quiescence of about three decades, an outbreak of CHIK with sporadic cases of dengue is being reported from different parts of India. A total of 6421 cases of fever have been reported from districts of Rayalseema, Nalagonda and Hyderabad in the State of Andhra Pradesh since December 2005. The attack rate varied from 2.3 to 39.1\%. Three hundred and eighty-six sera samples were collected and tested at National Institute of Virology (NIV), Pune. Six samples were positive for IgM antibodies to dengue and 139 samples were positive for IgM antibodies to CHIKV by MAC ELISA. Eighty-six samples were tested at NICD; of these, three were positive for Dengue IgM antibodies and 43 showed HI antibodies for CHIKV in high titres. Out of the 10 samples tested, seven were positive for CHIK by RT-PCR. There was increase in incidence of fever cases in Maharasthra since December 2005. Two hundred and fifty-eight villages from 15 districts have reported 34,725 fever cases till 5th April 2006. Representative samples were collected from Malegaon, Nashik district, Beed and Latur districts. Of the 68 samples tested, 13 showed high titres of HI antibodies against CHIKV and 3 were positive for IgM antibodies to Dengue virus. Similarly, 18,529 cases of fever with arthritis/arthralgia have been reported from seven districts (Gulbarga, Bidar, Bellary, Raichur, Tumkur, Koppal and Chitradurge) of Karnataka State since December 2005. Attack rate varied from 4 to 45\% in different affected villages. Out of 76 sera samples collected from Bidar, 43 showed IgM antibodies against CHIKV at NIV Pune. None were positive for Dengue. Seven paired sera samples were tested at NICD; of these, four showed a four-fold difference in HI antibody titre confirming the diagnosis of CHIK. NICD teams also collected 34 convalescent sera samples each from Kerala and Tamil Nadu. Of these, 3 and 10 samples, respectively, showed HI titres suggestive of CHIK infection. Samples had been received and tested from the states of Gujarat (\(n = 34\)), Rajasthan (\(n = 24\)) and Madhya Pradesh (\(n = 36\)). Fifteen, 14 and 4 samples, respectively, showed HI titres suggestive of CHIK infection. Out of the 70 acute samples processed from the different states, CHIK virus could be isolated in 39 samples. The isolates were confirmed by RT-PCR.

In these states, the onset of illness was observed to be acute with moderate to high fever, chills and associated joint pain. The joints affected are knee, ankle, wrist, elbow and small joints of hands. Lymphadenopathy and rash was not a significant presentation. All ages and both sexes were affected with preponderance above 15 years age. No deaths due to this disease have been reported. Three to four cases
from the same family report illness in 2-3 days duration. Cases have been reported from urban and peri-urban areas. The piped water supply in these areas is only for half an hour duration forcing people to adopt water storage practices mainly in big cement and plastic tanks. These containers act as potential breeding places for \textit{Ae. aegypti}. Entomological surveys carried out in most affected areas revealed high House, Container and Breteau Aedes indices. The outbreak is currently ongoing.

\textbf{Laboratory Diagnosis}

The definitive diagnosis can only be made by laboratory means, but CHIK should be suspected when epidemic disease occurs with characteristic triad of fever, rash and rheumatic manifestations (Table 1).

\textit{Laboratories working on chikungunya}

National Institute of Virology, Pune, a WHO Collaborating Centre for arboviral diseases, is engaged in diagnosis, outbreak investigations and preparation of reagents for diagnosis of arboviral infections. It has provided remarkable support in diagnosis and outbreak investigations of ongoing outbreak of CHIK and is the only institute in the country which prepares reagents for laboratory diagnosis of CHIKV.

National Institute of Communicable Diseases, Delhi, has assisted State governments in investigation of the ongoing outbreaks through multidisciplinary teams constituted by epidemiologists, microbiologists and entomologists. NICD laboratory is fully equipped and has performed virus isolation, serology, molecular diagnosis by PCR and strain characterization of CHIKV for confirmation of diagnosis. To enhance awareness among the health professionals, a CD Alert issue on CHIK fever has been published covering all aspects of the disease.\textsuperscript{[18]} For development of trained manpower, training courses on diagnosis of JE, Dengue and other exotic viral infections including CHIK infection are conducted as WHO Biennium activity.

\textit{Laboratory tests}

Laboratory diagnosis depends on the quality of sample and the time when the sample is obtained during the course of the disease (Table 2).

\textit{Serological diagnosis}

Virus-specific IgM antibodies are readily detected by capture ELISA in patients recovering from CHIK infection and they decline within 3-6 months.\textsuperscript{[3,30]} No commercial tests are yet available in India. However, NIV, Pune has developed a test kit for in-house use.

\begin{table}[h]
\centering
\caption{Case definition of chikungunya fever\textsuperscript{[8]}}
\begin{tabular}{|l|}
\hline
\textbf{Suspected case}  \\
An acute illness characterized by sudden onset of fever with several of the following symptoms: joint pain, headache, backache, photophobia, arthralgia, rash.  \\
\hline
\textbf{Probable case}  \\
As above and positive serology (when single serum sample is obtained during acute phase or during the convalescence).  \\
\hline
\textbf{Confirmed case}  \\
A probable case with any of the following:  \\
\begin{itemize}
\item Four-fold HI antibody difference in paired serum samples  
\item Detection of IgM antibodies  
\item Virus isolation from serum  
\item Detection of chikungunya virus nucleic acid in sera by RT-PCR
\end{itemize}  \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Collection, storage and transportation of sample\textsuperscript{[8]}}
\begin{tabular}{|l|}
\hline
\textbf{For serology}  \\
\textbf{Blood}  \\
Acute sample - collect upto 5 days after the onset of illness.  \\
Convalescent or paired sample - collect 10-14 days after the first sample.  \\
\hline
\textbf{Transportation}  \\
Transport specimens to the laboratory at 2-8 °C as soon as possible. Do not freeze whole blood, as haemolysis may interfere with serology test results.  \\
If more than 24 h delay is expected before specimen can be submitted to the laboratory, the serum should be separated from the red blood cells and stored frozen.  \\
\textbf{For isolation of the virus and RT-PCR}  \\
\textbf{Blood} - collect within first 5 days of illness.  \\
These samples should be immediately transported (within 48 hours) to the referral laboratory in cold, preferably frozen.  \\
\hline
\end{tabular}
\end{table}
Haemagglutination inhibition antibodies appear with the cessation of viraemia. All patients will be positive by day 5-7 of illness. Neutralization antibodies parallel HI antibody. The CHIK antigen for HI Test is available from NIV, Pune.

**Virus isolation**

CHIK virus isolation can readily be accomplished by intracerebral inoculation of mice and mosquito inoculation. In vitro cell culture methods using mosquito cell lines (C6/36) and other mammalian cell lines have comparable sensitivity to in vivo methods and are quick and less cumbersome.

**Molecular diagnosis**

RT-PCR for detection of CHIKV has been standardized using primers from structural and non-structural domains. Specific detection of CHIKV can be performed using RT-PCR/nested PCR combination amplifying fragment of E-2 gene. Combined detection and genotyping of CHIKV has been developed targeting nsP1 and E1 genes. More recently, specific and sensitive one-step TaqMan RT-PCR assay has been developed as a tool for diagnosis of CHIKV and rapid indicator of active infection by quantifying viral load in clinical samples and cell culture supernatant.

**Vector of chikungunya**

*Aedes aegypti* mosquitoes are considered as the vector of CHIKV. The vector bites humans during daytime. It breeds in several types of domestic and peri-domestic water containers (metallic, plastic, rubber, cement, earthen materials etc.). This mosquito is mainly found in urban areas, but during the past 2 decades, due to developmental activities, it has spread to many rural areas of the country.

**Prevention and Control of Chikungunya**

There is no vaccine or specific medication available against CHIK infection. Vector control is thus very important in controlling or preventing CHIK transmission. Elimination of breeding sites or source reduction is an effective method of control. *Aedes aegypti* is typically a container-habitat species and breeds primarily in artificial containers and receptacles.

**Control of mosquito breeding**

- All water tanks, cisterns, barrels, trash containers, etc., need to be covered tightly with a lid.
- Remove or empty water in old tyres, tin cans, buckets, drums, bottles or from other places where mosquitoes breed.
- Clogged gutters and flat roofs that may have poor drainage need to be checked regularly.
- Water in bird baths and plant pots or dip trays, at least twice each week, should be changed.
- Pets’ water bowls need to be emptied daily.
- In ornamental water tanks/garden, larvivorous fish (e.g. gambussia, guppy) need to be introduced. They eat mosquito larvae.
- Weeds and tall grass should be cut short; adult mosquitoes look for these shady places to rest during the hot daylight hours.
- In case water containers cannot be emptied on daily/weekly basis, Temephos (1 ppm) should be applied.

**Protection from mosquito bites**

- Insecticide-treated mosquito curtains/nets should be used (ITN). Especially children should sleep under ITNs during daytime.
- Insecticide spraying should be done to kill mosquitoes. For knockdown, well-planned fogging operations are strongly recommended with 2% pyrethrum space spray in high-risk villages/wards where clustering of cases has been reported.
- Use an insect repellant containing DEET (N,N-diethyl-m-toluamide) or another registered active ingredient on exposed skin.
- Wear long sleeves and pants.
- Have secure screens on windows and doors to keep mosquitoes out.

**Surveillance**

Epidemiological and entomological surveillance should be intensified. Reporting of fever cases should be monitored closely.

Active surveillance by health workers using the case definitions (Table 1) for cases presenting with acute fever associated with Arthralgia/Arthritis (Painful and stiff joints) to detect new cases early for treatment should be undertaken. This will help in identifying the affected areas so that control measures may be initiated.

Vector surveillance (both adult and aquatic stages of mosquitoes) should be done. This will help in identifying the areas for initiating control measures and assess the impact of the measures taken.

Medical and health institutions, professional associations, private practitioners and NGOs should be involved for fever reporting and proper case management.

**IEC activities**

IEC activities are crucial for community sensitization and participation. People need to be educated about the disease, mode of transmission, availability of treatment and adoption of control measures. The activities have to be identified particularly to effect changes in the practice of storage of water and personal protection. They should also be reassured that this is a preventable disease. People should be encouraged to use personal protective measures in the
form of full-sleeve clothes, use of mosquito repellants and insecticide-treated mosquito nets (even while sleeping during daytime)/curtains etc. They should be advised to cooperate in fogging and take measures for eliminating breeding places. Community ownership has to be encouraged in the long term for sustaining low larval and adult densities of mosquitoes and use of personal protection measures.

Special campaigns may be carried out with the involvement of mass media, including local vernacular newspapers/magazines, radio and TV as well as outdoor publicity like hoardings, miking, drum beating, rallies etc. Health education materials should be developed and widely disseminated in the form of posters, pamphlets and handbills. Inter-personal communication through group meetings, traditional/folk media particularly must be optimally utilized. Involvement of NGOs, Faith-Based Organizations, Community-Based Organizations, Women’s Self-Help Groups and professional associations like Indian Medical Association, Nehru Yuvak Kendras and NSS/NCC units in schools and colleges in control activities should be promoted actively.

Points to ponder on the ongoing outbreak and the challenges ahead

Why CHIKV re-emerged after a gap of decades is yet to be understood. Post CHIKV outbreak in 1963, serosurvey conducted in Kolkata in 1994 showed sero-positivity only in 4.37% of the samples. The highest (12.5%) sero-positivity was observed in the age group of 51-55 years and no CHIK antibody was detected in young adults.[34] Similarly, CHIK sero-survey conducted in Chennai city in sera samples collected in 1956 showed 10.8% sero-positivity and the majority of positives were in the higher age group (>40 years).[35] Chennai city experienced CHIK outbreak in 1964. These findings indicate that the virus was active some decades ago in these areas and the immune response shows a declining trend in the country in the course of time. Hence, waning of herd immunity could be the reason for large CHIK epidemics recurring at intervals of several years as susceptible accumulate.

Analysis of strains of recent outbreaks (Madagascar, Mauritius, Mayotte, Reunion and Seychelles) has suggested that the increased severity of the disease may be due to the change in the genetic sequence, altering the virus coat protein (E1), which potentially allows it to multiply more easily in mosquitoes.[35]

Thus, genetic evolution of the virus along with waning herd immunity could be the reason for CHIKV infection in South West Indian ocean and rapid travel may have led to wider spread of the virus.[36] However, it would be interesting to unravel the mystery of re-emergence by planned research during and after the outbreak of ongoing CHIKV.

The major challenge faced by the country during the current outbreak was laboratory confirmation of CHIKV infection.[37] No commercial kits for diagnosis are available in the country. The entire burden of production of reagents fell on the single institute. The need of the hour, therefore, is to develop and standardize the diagnostic reagents/kits and make them commercially available. It is also necessary to identify, train and strengthen the regional laboratories for undertaking diagnosis of CHIKV

Continuous sero-surveillance needs to be maintained in outbreak and non-outbreak areas to have the baseline data and learn about immunity, and in apparent CHIK infections. The role of animal reservoir in maintenance and transmission of the disease needs to be explored. Further studies are required to characterize Indian isolates from the current outbreak to learn about the molecular epidemiology of CHIKV infection. No vaccine is currently available for use; however, phase II safety and immunogenicity study of live CHIK vaccine TSI-GSD-218 had been undertaken in Maryland.[38] Although there were indications that other alpha virus vaccines may interfere with the immune response of live CHIK vaccine, this was found to be highly immunogenic as neutralizing antibodies were detected in 85% of the volunteers after 12 months. Long-term follow-up studies would be needed to determine the durability of immune response. The vaccine was found to be safe; it produced well-tolerated side-effects such as transient arthralgia in 8% of individuals.[39] Further results are awaited as this appears to be a promising vaccine for use in alpha virus naïve individuals. Until then, prevention and control activities are to be targeted at vector source reduction.

References

8. Carey DE, Meyers RM, DeRanitz CM, Jadhav M. The 1964 Chikungunya epidemic at Vellore, South India, including


