Emergence of chikungunya virus in Indian subcontinent after 32 years: a review

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Abstract

An outbreak of chikungunya virus is currently ongoing in many countries in Indian Ocean since January 2005. The current outbreak appears to be the most severe and one of the biggest outbreaks caused by this virus. India, where this virus was last reported in 1973, is also amongst affected countries. Chikungunya virus has affected millions of the people in Africa and Southeast Asia, since it was first reported in 1952 in Tanzania. Even then, natural history of this disease is not fully understood. The intra-outbreak studies, point towards recent changes in the viral genome facilitating the rapid spread and enhanced pathogenicity. The available published scientific literature on chikungunya virus was searched to understand the natural history of this disease, reasons for the current outbreak and the causes behind re-emergence of the virus in India.

The paucity of the scientific information on various epidemiological aspects of chikungunya virus threatens off an epidemic as control of spread of virus might be difficult in the absence of appropriate knowledge. There is an immediate need of the research on chikungunya virus, for an effective vaccine besides strengthening the existing diagnostic laboratory facilities. The current outbreak can also be taken as a lesson for establishment of a system for continuous surveillance of diseases, considered disappeared from the countries. The re-emergence and epidemics are unpredictable phenomena but the impact of such events can be ameliorated by appropriate knowledge and by being in the right state of preparedness.

Key words  Aedes aegypti – alpha virus – chikungunya – dengue – India – outbreak

Introduction

Chikungunya fever (CHIK fever) is a mosquito-borne illness of humans caused by chikungunya virus (CHIKV)\(^1\). The virus is currently causing one of the largest reported outbreaks of CHIK fever in last 40 years\(^2,3\). The virus, first reported in 1952 in Tanzania\(^4,5\), has been attributed to many outbreaks in a number of countries, since then. Chikungunya virus is geographically distributed in Africa\(^6-11\), Southeast Asia\(^7,12-14\) and India\(^15-16\). Sporadic cases are regularly reported from different countries in the affected regions\(^1,7-9,13,15,17\). Since January 2005, countries in the Indian Ocean are facing an unparallel outbreak caused by chikungunya virus. The cases of chikungunya fever have been reported from Reunion Island (more than one third population has been affected since the outbreak), Mayotte, Seychelles, Mauritius, Madagascar (Toamasania), Maldives and India. More than a million cases of chikungunya fever have been report-
ed in countries in the Indian Ocean since the beginning of the current outbreak in January 20052,18-20.

Epidemiology

The chikungunya fever is caused by chikungunya virus of genus *Alphavirus*, of Togaviridae family and, spread by Culicine mosquitoes1,21. Chikungunya fever was first reported in 1952 from Makonde plateaus, along the borders between Tanzania and Mozambique4,5. Chikungunya virus was first isolated by Ross in 1953 during an epidemic in Newala district of Tanzania6. Chikungunya is a Makonde word meaning ‘The one which bends up’ referring to the posture of the affected patient acquired due to excruciating pain in the joints4. The virus alternatively affects vertebrates and arthropods1. The arthropods remain infecting all its life. It has been reported from Congo8, Uganda9, East Africa10, Senegal11, Central African Republic16, Cameroon21, Portugal and Guinea1. Philippines, Malaysia, Mayotte and Reunion Island are commonly affected in Asia2. The spread of chikungunya has never been reported from outside the tropical region although the vector invades the planet11,22.

Chikungunya is believed to have originated in Africa1,3 where it has maintained in ‘sylvatic cycle’ involving wild primates and forest dwelling mosquitoes such as *Aedes furcifer*, *Ae. luteocephalus*, or *Ae. taylori*1,21-23. It was subsequently introduced in Asia where it is transmitted from human to human mainly by *Ae. aegypti* and, to a lesser extent by *Ae. albopictus* through an urban transmission cycle23.

Since Tanzania outbreak in 1952, chikungunya virus has caused outbreaks in East Africa (Tanzania3 and Uganda), in Austral Africa (Zimbabwe and East Africa10), in West Africa (Senegal17), and in Central Africa (Central African Republic10 and Democratic Republic of the Congo23). The most recent epidemic re-emergence in Africa was documented in 1999–2000 in Kinshasa8. Since the first documented Asian outbreak in 1958 in Bangkok, Thailand, outbreaks have been documented in Cambodia, Vietnam, Laos, Myanmar, Malaysia, Philippines and Indonesia12-14,23. The outbreaks in Africa and Asia, were unpredictable, with an intervals of 7 to 20 years between two consecutive epidemics.

Chikungunya virus in India

There is a confirmed history of outbreaks during 1963–64 in Kolkata15 (earlier known as Calcutta) and 1965 in Chennai (earlier known as Madras)24,25 when more than 3,00,000 people were affected. Last epidemic in India was reported from Barsi, Maharashtra in 197316 when a morbidity of 37.5% was reported for the whole town. The Kolkata outbreak in 1963 had started in July reaching a peak in November and then rapidly declining in December that year. Hospital record for that period suggests that children and elderly were the most severely affected group26,27. The entry of chikungunya virus in India is unknown although Calcutta sea and air roots are believed to be the probable entry points in India. There were lakhs of cases during the 1963–64 outbreaks with haemorrhagic manifestations and deaths26. Chikungunya virus had almost disappeared from India after 1973 and since then, no case was reported till end of 200528,29.

The current outbreak in India started in the end of 2005 when cases of suspected fever were reported from coastal parts of Andhra Pradesh and Karnataka2,27. Most of the initial reports were in media and in newspapers30 when hospitals were flooded by patients complaining of fever and joint pain. The outbreak was first investigated in February 2006 in Andhra Pradesh and then in March 2006 in Karnataka by health officials of the country2 who(
Till August 4, 2006, the confirmed cases of chikungunya fever have been reported from Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Madhya Pradesh and Gujarat states. Total 129 districts in 8 states have been affected by the virus. National Institute of Communicable Diseases, Delhi and National Institute of Virology, Pune had tested 10,809 samples and 1015 were found to be positive. Total cases of chikungunya fever are in the range of 10,00,000—(Personal communication: Dr. Charan Singh, National Vector Borne Diseases Control Programme, Delhi; Details in Table 1).

Current outbreak

Since the beginning of 2005, chikungunya virus has emerged in the islands of the southwestern Indian Ocean. The outbreak was first reported in Comoros in the beginning of the 20053,33. Later in the same year, the virus had circulated to the other islands and countries—Mayotte, Seychelles, Reunion and Mauritius, Madagascar and India. Since the end of 2005, the rainy season renewed the circulation and led to the intensification of the epidemic2. The most affected island is Reunion where almost 35% of the population (2,60,000 out of 7,70,000) has been affected by chikungunya virus till mid of May 20062,33.

Transmission

The virus is transmitted by culicine mosquitoes1,21. *Ae. aegypti*, *Ae. albopictus* and *Ae. polynesiensis* are commonly involved in the transmission although *Culex* has also been reported for the transmission in some cases3,11,22. A recent Indian study reported transmission of chikungunya virus by *Anopheles stephensi* also34. The current outbreak is caused by transmission by *Aedes* only3. The common reservoirs for chikungunya virus are monkeys and other vertebrates. In the current outbreak suspected reservoirs were macaque monkeys, lemurs and bald mouse. In the epidemic period, men also act as reservoir1,21. Among the potential vectors, species of sub genus *Ae. diomorphus*, *Ae. dalzieli*, *Ae. vittatus* and *Ae. argenteopunctatus* are also thought to be involved in the transmission3,23. The role of cattles and rodents has also been reported in the transmission of the virus11. Chikungunya virus usually shows a periodicity with occurrence of disease in the community with the si-

### Table 1. The reported number of chikungunya fever cases in India

<table>
<thead>
<tr>
<th>State</th>
<th>No. of districts affected</th>
<th>Total fever cases/suspected chikungunya fever cases</th>
<th>No. of samples sent to NIV/NICD</th>
<th>No. of confirmed cases</th>
<th>No. of deaths</th>
<th>Period of reporting (up to)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andhra Pradesh</td>
<td>20</td>
<td>1,10,618</td>
<td>1,224</td>
<td>150</td>
<td>0</td>
<td>4.8.06</td>
</tr>
<tr>
<td>Karnataka</td>
<td>27</td>
<td>6,70,438</td>
<td>4,376</td>
<td>266</td>
<td>0</td>
<td>5.8.06</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>31</td>
<td>2,16,455</td>
<td>4,443</td>
<td>507</td>
<td>0</td>
<td>26.7.06</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>34</td>
<td>43,580</td>
<td>413</td>
<td>59</td>
<td>0</td>
<td>25.7.06</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>4</td>
<td>44,966</td>
<td>36</td>
<td>4</td>
<td>0</td>
<td>31.7.06</td>
</tr>
<tr>
<td>Gujarat</td>
<td>12</td>
<td>22,963</td>
<td>317</td>
<td>26</td>
<td>0</td>
<td>28.7.06</td>
</tr>
<tr>
<td>Kerala</td>
<td>1</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27.7.06</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>129</strong></td>
<td><strong>11,09,033</strong></td>
<td><strong>10,809</strong></td>
<td><strong>1,015</strong></td>
<td><strong>0</strong></td>
<td></td>
</tr>
</tbody>
</table>

(Source: Personal communication with Dr. Charan Singh, NVBDCP, Delhi)
ence interval of 3–4 years\textsuperscript{11}. The periodicity is probably due to their cycle in monkeys\textsuperscript{11,21}. The monkeys are common reservoirs for the virus and following one cycle of circulation, all monkeys might become exposed and, therefore, immunologically protected. Following a gap of 3–4 years, when another group of susceptible and non-immune population becomes available for infection\textsuperscript{11,35} the virus spreads. Mother to child transmission has also been reported in recent studies\textsuperscript{3,35}.

The agent

Chikungunya virus is an enveloped, positive strand RNA virus\textsuperscript{1,21}. The species chikungunya belongs to Alpha virus genus which consists of 28 viruses of around 70 nm in diameter\textsuperscript{1,21}. The alpha viruses are characterised by inactivation by diethyl ether or sodium deoxycholate. The complete nucleotide sequences of chikungunya virus have been determined thrice till date, once in 1953 of Tanzania strain by Ross and, then in 1983 of Senegal strain\textsuperscript{3} and third time in Japan in 2002\textsuperscript{36}. Phylogenetic analyses based on partial E1 sequences from African and Asian isolates revealed the existence of three distinct chikungunya virus phylogroups: first containing all isolates from West Africa, second containing isolates from Asia, and third corresponding to East, Central, and South African isolates\textsuperscript{37}. They have worldwide distribution and all alpha viruses are antigenetically related. The viruses are inactivated by acid pH, heat, lipid solvent, detergents, bleach, phenol, 70% alcohol and formaldehyde. Most of the viruses possess haemagglutinating activities\textsuperscript{1}.

Vector

The disease is spread by culicine mosquitoes in general and Aedes in particular\textsuperscript{4,29}. In the current outbreak, only Aedes has been found to be involved\textsuperscript{2}. It is a diurnal vector with peak of the activities at the end of the day and is a day biter. The vector mosquito, Aedes, has a body divided into three parts: a pair of antennae, three pairs of legs which are white striated. One pair of wings and a pair of beams, long antennae, a long horn, a body covered with scales decorated with white or silver plated spots are other characteristics of the mosquito. Aedes measures 8 to 10 mm in length\textsuperscript{37}. The different species of the Aedes can not be identified by naked eye\textsuperscript{11,22,38}. Ae. albopictus is more active outdoors, while Ae. aegypti feeds and rests indoor.

Pathogenesis

Detailed studies are not available on the pathogenesis of the chikungunya fever. It is expected that once after inoculation, primary viral multiplication occurs in lymphoid and myeloid cells. The arthropod vectors acquire the virus by sucking blood during this period. The virus then spreads to the targeted organs and immune system starts functioning at this stage leading to the activation of both humoral and cellular immunity. This response of the body leads to the clinical features of the disease\textsuperscript{1-3}. The convincing evidence and studies are not available.

Clinical features

The infection is of acute onset and variable clinical features are common findings\textsuperscript{3,22}. The symptoms develop after an incubation period of 4 to 7 day (Incubation period lies between 1 and 12 days). In most of the cases the disease is self-limiting and the symptoms disappear within 5 to 7 days even without treatment. Rarely the symptoms may persist for a longer period and occasionally complications may develop\textsuperscript{3,4,33}.

A clinical triad of ‘fever, rashes and arthralgia’ is suggestive of chikungunya fever. The clinical features vary from high fever (more than 40°C, rapid in rise and sometimes associated with rigor), severe headache, chills and rigors, nausea and vomiting. The fever may disappear to return in one or two days giving it the name of ‘Saddle back fever’\textsuperscript{27,33}. The occur-
rence of poly-arthritis along with myalgia, is a typical feature of the illness\textsuperscript{3,27}. The joint pain is frightening in severity, completely immobilising many patients and preventing sleep in first few days of the illness. The joint becomes very painful to touch. Movement at the joints causes excruciating pain to the person forcing to make bend up position giving it the name ‘Chikungunya’. Different joints of the same patient may be involved at different times\textsuperscript{3,33}.

The maculo-pauplar rashes and gingival haemorrhages are uncommon signs although more frequent in children. Rashes occur mainly on trunks or extensor surfaces of the limbs and are itching in nature\textsuperscript{3,4,33}. Rashes are usually accompanied by secondary rise in the temperature. The haemorrhagic features are more frequently reported in Indian outbreaks than those occurring in other countries\textsuperscript{15,26}. Chikungunya fever is usually self-limiting but person can also develop chronic phase marked by persistent and severe arthropathies. The deaths have also been reported due to chikungunya virus but are very rare\textsuperscript{26}.

The other body systems are infrequently affected by chikungunya virus although; mild tachycardia is noted at the time of rise in fever\textsuperscript{4}. The rare complications include myelomeningoencephalitis, Guillain barre syndrome, fulminant hepatitis, myocarditis and pericarditis\textsuperscript{3}. The asymptomatic infections are also frequent and the resulting immunity is durable and second attack is not reported\textsuperscript{1,3,4}. The infection is severe in infants, elderly and immunocompromised people\textsuperscript{27}.

**Differential diagnosis**

The clinical illness of chikungunya fever needs to be differentiated from dengue and its variants. Rashes occur in both the diseases but are more common in dengue in which, decreased platelet count leads to the severe haemorrhagic signs\textsuperscript{24,39}. Similarly, there is no retro orbital pain, a characteristic of dengue, in chikungunya fever. Severe joint pain, which may or may not be associated with swellings is characteristic of chikungunya fever\textsuperscript{25}.

The other common viral illness similar to chikungunya fever is infection by O’nyong-nyong virus. This infection can be differentiated on the basis of circulation of the O’nyong-nyong virus in the community at the time of clinical diagnosis and confirmation by the serological diagnosis. O’nyong-nyong virus is also different from chikungunya virus as it is transmitted by anopheline mosquitoes\textsuperscript{22}. Sometimes, similar clinical presentation is made by Sindbis virus infection. The confirmatory diagnosis of chikungunya fever from dengue or O’nyong-nyong can be made by the laboratory investigations only.

**Laboratory diagnosis**

The probable diagnosis of chikungunya fever can be made on the basis of presence of the virus in community, and a clinical triad of fever, rashes and arthralgia is suggestive of the illness. The definition of cases is given in Table 2.

The virus produces neutralising and haemagglutination inhibiting (HI) antibodies and that helps in making serological diagnosis. HI test is a simplest diagnostic test, but it identifies the group rather than specific virus. Confirmation of the illness is done by detection of the antigen or antibody to the agent in the blood sample of patient\textsuperscript{1,21}. Reverse transcriptase polymerase chain reaction (RT-PCR) is confirmatory for the identification of chikungunya virus\textsuperscript{1,21}. IgM capture ELISA is the most sensitive serologic assay, and is necessary to distinguish the disease from dengue. The virus isolation procedures need to be done under bio safety level 3 (BSL-3) precautions\textsuperscript{11,21} although such precautions may not be necessary in the countries where chikungunya virus is endemic.

**Prognosis and management**

The disease is considered to be self-limiting and be-
The available literature does not report mortality due to this virus. The current outbreak is being considered the most severe in the history as more number of cases in the current outbreak has developed complications than any previous report. Besides, a few deaths have also been attributed to chikungunya virus. There is no specific antiviral therapy available for chikungunya virus and treatment is mostly, supportive, bed rest, fluids, and symptoms may be treated with analgesics and antipyretics but not by Salicylate. Paracetamol is used for control of fever. Anti-inflammatory drugs are also used. Chloroquine has been tried as empirical treatment without any proven efficacy. Rare cases may require hospitalisation and appropriate management is done for the complications. All persons affected by the illness should be protected from further mosquito bites to reduce the risk of further transmission of the virus.

### Prevention and control

The vaccination is not available and research is on for an effective vaccine although a vaccine trial which had started in 2000 was discontinued due to shortage of funds. The only mode of prevention is use of physical means of protection from mosquito bite—full sleeve clothing, mosquito nets, repellents, etc. The use of repellent should be done with the advice of doctors specially in case of pregnant mothers and children less than 12 years. Center for Disease Control and Prevention (CDC) has advised a repellent containing 30 to 50% DEET (N, N-diethyl-m-toluamide). The repellents with lower concentration need to be applied more frequently.

A community-level action to fight the vector must be implemented:

- Reduction of mosquito breeding sites, specially stagnant water reserves (uncovered barrels, flower vases or cisterns). Water containers should be emptied, if in possible then Temephos in 1 ppm strength should be applied on weekly basis.

World Health Organization (WHO) has strongly recommended the use of communication for behavioural impact (COMBI) approach for mobilisation of both individuals and communities during the outbreaks.

### Public health measures

- Monitoring and reporting of fever cases in the affected area should be done on regular basis to
keep an eye on trends of infection.

- Active surveillance and case detection for chikungunya fever in affected area can be done by health workers. This will help in identifying the area and starting control measures.

- Vector surveillance and control measures in affected area.

- Training to health service providers including health workers, anganwadi workers, private practitioners in identification of cases and control measures.

- IEC activities for general public and NGO through all possible means—Radio, TV, newspapers and local available resources.

**Lessons from the current outbreak**

The current outbreak is considerably larger than all previous ones, and has affected many countries in the Indian Ocean. It is a major public health concern besides a challenge for policy makers and scientists as very little scientific information is available about the chikungunya virus, disease, pathogenesis, treatment and prevention.

The microbiologists have also postulated that re-emergence is due to a variety of social, environmental, behavioral and biological changes and appropriate combination which made spread of virus easier and calls for further studies.

The virus strain in the current outbreak has been studied for possible genome change along with change in behaviour and morbidity in detail to understand the causes of emergence and rate of rapid spread. A recently published study has reported some changes in the virus at E1-226V portion of the genome, which possibly have made it possible for the virus to release its cholesterol dependence. Now, this strain of chikungunya virus is probably able to survive without cholesterol in humans and mosquitoes, and could have survived and multiplied better in mosquito, explaining partially, to its rapid spread. The increased pathogenicity, higher complication rate and mortalities are newer characteristics associated with this current outbreak. It’s also a probability that the virus could have genetically changed over a period of time leading to increased pathogenicity and increased infection rate.

A pertinent issue pointed out by experts that, despite infecting millions of the people for more than 50 years since its first report in 1952, chikungunya virus has been neglected and there is lack of knowledge about the biology of the virus. Furthermore, chikungunya virus has clearly been responsible for disabling and persistent arthralgia, even then it is unresolved whether the symptoms are due to persistence of the virus or inappropriate immune response.

The factors mentioned above, call for more and immediate researches on vaccine, treatment and pathogenicity of chikungunya virus. Secondly, the worldwide distribution of *Aedes* mosquitoes, gives a possibility that chikungunya virus can spread to hitherto unaffected regions of the world affecting larger population, which is still unknown.

Another attempt in explaining rapid spread of the current outbreak in India points toward the absence of the ‘herd immunity’ in this population, as chikungunya virus was last reported in 1973 in India and people here since then have not been exposed to the virus and are susceptible to the infection. A survey in Kolkata in 1995 reported that only 4.37% people reported antibodies against chikungunya virus. The sero-positivity was highest in >50 yrs age group. Only a small proportion had shown antibodies in young and adults. The findings led to the conclusion by the experts that there is no effective immunity against this virus in this population, making the large population, specially of children, vulnerable to the infection.
The other challenge is the scarcity of the diagnostic laboratory facilities for the confirmation of the antibodies against this virus which would be crucial in case of large outbreaks and management of the illnesses. The immediate need is of strengthening the existing infrastructure and trained manpower to deal with such situation. A media report\textsuperscript{30} indicated that it took two months for national laboratory to confirm the disease, when it was first detected in Gulbarga district of Karnataka.

The current outbreak is being termed as re-emergence but there was no active or passive surveillance carried out in the country and the virus was assumed to have disappeared from the subcontinent\textsuperscript{28,43}. Although, the strains of present and past outbreaks of chikungunya virus in India have not been studied in detail, an important lesson is of continuing some form of surveillance for the diseases which cease to exist from community for long. During a recent dengue like outbreak in eastern India, the \textit{Aedes} mosquitoes were found to be positive for chikungunya virus. The evidences of dual infection of dengue and chikungunya virus have been reported\textsuperscript{29,39} and a widely circulating low-virulent chikungunya virus was given as possible explanation for the epidemiological pattern of the chikungunya virus disease in this region\textsuperscript{29}.

Countries like India where dengue is a frequent visitor, special attention need to be paid in the diagnosis of dengue cases and a differential diagnosis of chikungunya fever can be kept in the mind when such symptoms are reported. Public health measures for control of chikungunya virus should also be strengthened in such settings.

**Conclusion**

Chikungunya fever is an emerging disease in Indian Ocean region. The current outbreak has occurred after a gap of many years in number of countries—India has reported outbreak after a gap of 32 years. The clinical features and number of people affected by this outbreak suggest of this virus shedding its earlier benign form and becoming more pathogenic. There appears a wide gap in the knowledge about natural history of the disease. Data on activities during inter-epidemic period, and possible extra human spread. The reports suggest of the changes in the genome of the chikungunya virus making it more virulent, and are indicative of that chikungunya virus is emerging in the region. It only makes sense that world community and public health experts are empowered with appropriate knowledge for control and prevention strategies to avoid an epidemic, otherwise long disappeared diseases like this would keep returning to affect humanity, time and again.

**Acknowledgement**

Special thanks are due to Dr. Charan Singh, NVBD-CP, Delhi for providing necessary information on the activities carried out by NICD and Government of India besides providing updated information on chikungunya virus in India.

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Received: 8 June 2006 Accepted in revised form: 12 August 2006