Current status of dengue and chikungunya in India

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ABSTRACT

Dengue, a Flavivirus and chikungunya, an Alphavirus, transmitted by Aedes mosquitoes, are a cause of great concern to public health in India. Every year, thousands of individuals are affected and contribute to the burden of health care. Dengue outbreaks have continued since the 1950s but severity of disease has increased in the last two decades. Chikungunya outbreaks started in the 1960s and dwindled to sporadic cases until a resurgence in 2006. Based on the data of National Vector Borne Disease Control Programme (NVBDCP), the number of cases reported in 2013 was about 74 454 for dengue with 167 deaths and 18 639 for chikungunya. The number of cases reported is increasing, probably because of the availability of IgM detection kits produced and distributed by National Institute of Virology through NVBDCP and better reporting. In the absence of well-structured epidemiological studies, this review attempts to summarize reports on dengue and chikungunya outbreaks from various regions of India. For dengue, young adults are the major group affected; the severity of disease in India is still lower than that reported elsewhere in South-East Asia; and paediatric cases of dengue haemorrhagic fever have a high mortality. For chikungunya, all age groups are affected but severe manifestations are more often seen in children. Persisting arthralgia, neurological syndromes and non-neurological manifestations are recorded. Changes in the genotype and mutations in the genome have been detected for both dengue and chikungunya viruses. The review ends with a short summary of the most recent vector-control studies.

Key words: dengue, chikungunya, India, symptoms, outbreaks, evolution

INTRODUCTION

Dengue and chikungunya are two mosquito-borne viral diseases of great public health concern in India. Dengue virus (DENV) and chikungunya virus (CHIKV) are transmitted by the same species of mosquito, Aedes aegypti and share spatiotemporal territories. Both viruses are known to cause acute febrile illness with almost identical symptoms in the early phase of infection, although the clinical profiles differ as the infection progresses. DENV belongs to the Flaviviridae family and CHIKV belongs to the genus Alphavirus of Togaviridae. Before the genome organization and replication strategy was discovered the two viruses were placed in arboviruses, group-A and group-B, by virtue of being arthropod-borne viruses and having single-stranded positive-sense RNA genomes. Both viruses are believed to have originated in Africa about 200–300 years ago as shown by molecular clock analysis. However, for DENV, the Malay Peninsula is also considered as a possible place of origin.1

GLOBAL DISTRIBUTION

Dengue

The name dengue originated from the Swahili word for “bone-breaking fever” or the word for “the walk of a dandie” in Spanish. The first probable case of dengue fever (DF) was recorded during the Jin Dynasty (265–420 AD) in China. The first recognized epidemics occurred almost simultaneously in Asia, Africa and North America in the 1780s, shortly after the identification and naming of the disease in 1779 by Benjamin
Chikungunya

Chikungunya was first detected in 1952 in Makonde, United Republic of Tanzania (formerly Tanganyika) and derives its name from *kunguynala*, the Swahili word for the contorted posture of patients because of their arthritic symptoms. It was first described by Robinson and Lumsden in 1953.7 Epidemics were subsequently noted in the Philippines (1954, 1956 and 1968), Thailand, Cambodia, Viet Nam, India, Myanmar and Sri Lanka.8 In India, major epidemics of chikungunya were reported in 1963 in Kolkata, in 1965 in Pondicherry (formerly Pondicherry), Tamil Nadu, Andhra Pradesh, Madhya Pradesh and Maharashtra and again in 1973 in Maharashtra.9 Thereafter, sporadic cases continued to be recorded in Maharashtra during 1983 and 2000.10 Since 2003, there has been a resurgence of chikungunya outbreaks in the islands of the Pacific Ocean, including Madagascar, the Comoros, Mauritius and Reunion Island.11 In January 2006, there was a very large epidemic in Reunion Island followed quickly by the one in India.12 Almost 1.3 million suspected chikungunya fever cases were reported in India.13 Resurgence of chikungunya has been attributed to various factors including globalization, increase in the mosquito population, loss of herd immunity and the mutation A226V in the E1 gene causing a significant increase in CHIKV infectivity for *Ae. albopictus*.11

**DISTRIBUTION IN INDIA**

Since 2007, diagnosis and data assimilation for dengue and chikungunya in India have been facilitated by the National Vector Borne Disease Control Programme (NVBDCP). The programme has 347 sentinel centres in 35 states and 14 apex referral laboratories, which are supplied with DENV- and CHIKV-specific IgM detection kits produced by the National Institute of Virology (NIV).

**Dengue**

The history of dengue outbreaks in India has been recently reviewed.14 More recent and systematic data are now available because of the NVBDCP. The data on the web site of NVBDCP16 and earlier publications by NIV3 show that dengue has been endemic in 16 states since the beginning: Andhra Pradesh, Goa, Gujarat, Haryana, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh, West Bengal, Chandigarh, Delhi and Puducherry. During 2010–2012, dengue encroached into the remaining states. Figure-1 shows the distribution of dengue cases among the states of India in 2013.

Although the number of dengue cases has shown a steady rise with every passing year, the mortality has reduced (Figure-2). The overall mortality rate of 1.2% in 2007 dropped to 0.25% in 2013. This reduction is probably the result of the cumulative effects of better patient management, increased diagnostic capabilities and better reporting. Compared with the rest of South-East Asia, the number of dengue shock syndrome (DSS) cases in India remains low.

The execution of well-designed epidemiological studies has been difficult. We carried out a pilot age-stratified, cross-sectional dengue prevalence study in collaboration with Vadu Rural Health Programme, KEM Hospital Pune. Dengue prevalence was determined in two villages that differed in the level of urbanization and population density. A significantly higher seropositivity of 58.5% for DENV was found in the urbanized village, compared with 41.2% for the rural village.15

**Figure 1:** Distribution of dengue cases in Indian states in 2013 (based on NVBDCP data)

**Figure 2:** Total dengue cases reported to NVBDCP (left axis) and percentage mortality (right axis) in India, 2007–2013
There have been a few longitudinal studies based on single/multiple hospital data. A study on samples received at the All India Institute of Medical Sciences, New Delhi, during 2003–2005 reported 44.56% positivity in 1820 samples. The maximum number of cases belonged to the 21–30 years age group and the peak was in October. Co-circulation of all four serotypes was observed in 2003 and emergence of DENV-3 as the dominant serotype in 2005. Another study from a tertiary care hospital in Delhi covering 7 years (2002–2008), reported 30.15% positivity in 7846 samples and circulation of all four serotypes in 2003 followed by DENV-3 in 2004–2006, DENV-2 in 2007 and DENV-1 in 2008. We carried out a longitudinal study for a period of 6 years (2005–2010) in Pune city involving 24 private and government clinics/hospitals. On testing 5106 samples we observed a positivity of 48.45%. The 21–30 years age group was most affected by dengue throughout the 6 years. The cumulative number of cases observed per month during the 6-year period showed that the largest numbers were observed in the month of October with a positivity of 57.9% (Figure-3). All four serotypes were found to be circulating in Pune. Each year was characterized by the predominance of one of three serotypes. DENV-1 was dominant in 2005 and 2007, DENV-2 was dominant in 2008 and DENV-3 was dominant in 2009. In 2010 both DENV-2 and DENV-3 were co-dominant. DENV-4 was poorly represented with just one case each in 2007 and 2009. In 2010 both DENV-2 and DENV-3 were co-dominant. DENV-4 was poorly represented with just one case each in 2007 and 2010; both cases were dengue haemorrhagic fever (DHF). Based on the symptoms presented the cases, were classified into DF, DHF or DSS according to World Health Organization (WHO) 2007 criteria. During the 5-year period, 90.5% (n=2239) of the patients were classified as DF and 9.5% (n=235) cases were categorized as DHF. Year-wise analysis revealed that the proportion of DHF cases was about 20% in 2005, 2006 and 2008; the proportion dropped to 6.8% in 2007, 2009 and 2010. This fall probably reflected improved diagnosis and better reporting of non-hospitalized dengue cases. DHF was seen with low severity despite the circulation of multiple serotypes.

There have been isolated reports on mortality in paediatric DHF/DSS cases which are much higher than the cumulative mortality reported by NVBDCP. Cherian et al. reported a case-fatality rate of 26.3% in a study that included 19 children older than 1 year in 1990 in the North Arcot district and the adjoining areas of Tamil Nadu and Andhara Pradesh. In the 1996 outbreak in Delhi, a mortality rate of 6.6% was reported in DHF/DSS patients from a single hospital where the mean age was 25.6 years. Another study, in Mumbai in 2003, reported three deaths in 38 DHF/DSS cases in the paediatric intensive-care unit with a mean age of 4.9 years. Therefore, it is evident that to get accurate data, well-designed epidemiological studies in demographically defined populations are required.

**Chikungunya**

The first recorded chikungunya outbreak was in Kolkata in 1963. This was followed by epidemics in Tamil Nadu, Andhra Pradesh and Maharashtra in 1964–65 and in Barsi in 1973. CHIKV then seems to have disappeared from India. The virus re-emerged in 2006 after a gap of 32 years and caused an explosive outbreak affecting 13 states. The states first affected were Andhra Pradesh, Karnataka, Maharashtra, Madhya Pradesh, Tamil Nadu, Gujarat and Kerala. All ages and both sexes were affected. The virus isolates belonged to the African genotype different from the viruses circulating in 1963–1973, which belonged to the Asian genotype. The A226V shift in the E1 protein that was detected with progression of the epidemic in Reunion Island was absent in all of the Indian isolates. The A226V mutation was found to occur only in the 2007 isolate from India.

In 2008 almost 100,000 people in different villages of Kasargod district, Kerala were affected by chikungunya. This was followed by a large outbreak in Tirunelveli district, Tamil Nadu in 2009–2010. The CHIKV isolate was found belong to the Eastern Central Southern African genotype (E1:226A). During 2009–2010, cases were also reported from Maharashtra. In the subsequent years, CHIKV spread to other states: Goa, Orissa, Rajasthan, West Bengal, Andaman & Nicobar Islands and Puducherry. The year 2011 was exceptional in that cases were reported from all states except Punjab, Dadra and Nagar Haveli and Lakshadweep. Lakshadweep had a chikungunya outbreak only in 2007. Distribution of cases in 2013 is shown in Figure 4.
India reported 1.3 million cases in 2006 but no data on mortality were available except for two reports—one on a subset of patients and one deductive. In one report, among 90 laboratory-confirmed chikungunya cases hospitalized in Ahmadabad, 18 deaths were recorded of which 15 were aged 60 years or older and five had comorbidities.25 The other report was deductive; based on death records during previous years in Ahmadabad, the excess deaths that occurred during the outbreak period was attributed to CHIKV and a mortality rate of 4.9% was reported.26

**SYMPTOMS**

**Dengue**

DENV causes self-resolving DF in the majority of cases, characterized by severe bodyache, retro-orbital pain, headache and at times rash, abdominal pain and nausea. According to the new terminology recommended by WHO in 200915 dengue cases can be classified into dengue without warning signs, dengue with warning signs (abdominal pain/persistent vomiting/mucosal bleed/increase in HCT with decrease in platelet count) and severe dengue (severe plasma leakage, severe bleeding and severe organ involvement).

Several groups have tried to identify prognostic symptoms for progression to severe disease. During a 5-year study conducted by our group on clinical profiling of patients; joint pain, retro-orbital pain and itching were seen in a significantly higher proportion of DF cases. The clinical triad of abdominal pain, rash and conjunctival congestion was found to be a possible prognostic marker of progression towards severe disease due to the strong association of these symptoms with DHF cases. Melaena and haematemesis were the most common haemorrhagic manifestations in DHF. Liver involvement, which has been well documented in DHF, was evident in about 85% of the DHF patients tested.29 Similar observations were reported from Delhi,28 Kerala29 and West Bengal.30 Although dengue is considered a non-neurotropic virus, neurological complications have been reported in dengue cases. The neurological manifestations of dengue infection can be grouped into three categories: neurotropic effect of the virus—encephalitis, meningoitis, myositis and myelitis; systemic complications—encephalopathy, stroke, hypokalaemic paralysis and papilloedema; and postinfection—acute disseminated encephalomyelitis, encephalomyelitis, myelitis, neuromyelitis optica, optic neuritis and Guillain-Barre syndrome.35,32

**Chikungunya**

Symptoms generally start 4–7 days after the mosquito bite. The acute phase is characterized by painful polyarthralgia, high fever, asthenia, headache, vomiting, rash and myalgia. In the chronic phase, incapacitating arthralgia persists for months. Neurological syndromes in cases from Ahmadabad and Pune included encephalitis, encephalopathy and myelopathy or myeloneuropathy. Non-neurological systemic syndromes included renal, hepatic, respiratory, cardiac and haematological manifestations together with atypical manifestations including lymphadenopathy, oral ulcers and encephalitis.33,34 Optical abnormalities have also been associated with CHIKV infections.35,36

Children are at maximum risk for severe manifestations of the disease. Some of the clinical features in children include neurological manifestations, i.e. seizures, altered levels of consciousness, blindness due to retrobulbar neuritis and acute flaccid paralysis.37 Another report on CHIKV infection in infants younger than 12 months old indicated that the most characteristic features of the infection in infants were acrocyanosis, symmetrical superficial vesicobullous lesions and erythematous asymmetrical morbiliform rashes.38 CHIKV infection in neonates is very rare, one case presented with severe thrombocytopenia and features of multisystem involvement.39 Vertical transmission of CHIKV from mother to child has been documented.40

**VIRUS EVOLUTION**

**Dengue**

When dengue first emerged in India during 1950–60s, the disease was mild despite circulation of all four serotypes. The disease profile changed and greater severity was reported from the late 1980s. The circulation of serotypes in different parts of the country and changes in the circulating serotypes in consecutive years has been reviewed recently.41 The Indian isolates obtained over a span of 50 years by NIV were sequenced and analysed with global data.42–44 The phylogenetic analysis of the E gene sequence revealed that the Indian viruses formed clusters that were temporally distinct. For all four serotypes, the viruses circulating in India in the 1950s and causing mild disease were either replaced or evolved into lineages/genotypes with greater virulence and/or transmissibility. Genotype shifts for DENV-2 (American to Cosmopolitan) and DENV-4 (genotype V to I) and lineage changes for DENV-1 (India III to India I and II of American African genotype) and DENV-3 (F to A, B, C and D of genotype III) were observed.9 Genotype III of DENV-3, which originated in India, is more virulent and has caused haemorrhagic outbreaks in many countries. DENV-4 serotype seems to have its origin in India. The evolution of genotype I of DENV-4 in India could be associated with an event of recombination of a genotype V Indian isolate of 1961 with a genotype I Sri Lankan isolate of 1978. Complete genome sequence analyses have confirmed these results for DENV-145 and DENV-2.46

**Chikungunya**

The evolutionary timescale of CHIKV was estimated to be in the last 300 years under a constant-population relaxed-clock model. Phylogenetic analysis based on partial sequences of NS4 and E1 genes showed that all earlier isolates (1963–1973) were Asian genotype, whereas the 2006 and 2000 isolates were African genotype. The progenitor of the 2005–2007 viruses was found to have existed around 9 years ago and may have originated from Uganda.47 The Indian 2006 isolates were closer to the new terminology recommended by WHO in 200915 dengue cases can be classified into dengue without warning signs, dengue with warning signs (abdominal pain/persistent vomiting/mucosal bleed/increase in HCT with decrease in platelet count) and severe dengue (severe plasma leakage, severe bleeding and severe organ involvement).
to the Reunion islands isolates (99.9% identity) than to the 2000 isolate, confirming involvement of the Reunion virus in the outbreak. The A226V shift observed with the progression of the epidemic in Reunion Island was absent in the Indian isolates\(^4\) but was present in isolates obtained from 2007 onwards in different parts of India: Tamil Nadu (2009–2010), Kerala (2009)\(^4\) and Orissa (2010).\(^4\)

### VECTORS

**Ae. aegypti** is the principal vector for both DENV and CHIKV. DENV is maintained in a human–mosquito–human cycle. In Africa, CHIKV is maintained in a sylvatic cycle that involves non-human primates and a number of forest-dwelling mosquitoes. It is not clear how the virus is maintained in Asia. Transovarial transmission (TOT) has been reported for DENV.\(^5\)\(^6\) However, for CHIKV all the earlier studies have shown absence of this phenomenon.\(^5\)\(^7\) There are some scanty reports on TOT of CHIKV\(^5\) on the basis of detection of virus in wild-caught mosquitoes emerged from larvae. DENV and CHIKV are also transmitted by *Ae. albopictus*. During the 2005–2006 chikungunya epidemic in certain Indian Ocean islands and in Kerala, *Ae. albopictus* played an alternative role.\(^5\)\(^8\) Experimental studies substantiated its potential as a vector and the E1:A226V mutation was shown to be responsible for enhanced infectivity and efficient transmission to mice by *Ae. albopictus*.\(^5\)\(^9\)\(^10\)

Some novel methods of vector control have emerged. *Bacillus thuringiensis israelensis* (Bti) was shown to be effective in reducing the number of immature *Aedes* in treated containers.\(^10\) However, further studies of Bti in combination with other insect viruses and other strategies to control dengue vectors are warranted. The sterile insect technique is an environmentally friendly, species-specific population control method. Fu et al.,\(^11\)\(^12\) describe construction of transgenic *Ae. aegypti* that combine all of the genetic features necessary to produce highly penetrant, dominant, late-acting, female-specific lethality. The promoter derived from the *Ae. aegypti* Actin-4 (AeAct-4) gene leads to the expression of tetracycline-repressible transactivator in a stage-, tissue-, and sex-specific manner resulting in female-specific release of insects carrying a dominant lethal (RIDL) strains. The transgenic strain, designated OX3604C of *Ae. aegypti*, allows genetic sexing resulting in male-only releases and permits the release of eggs instead of adult mosquitoes. When OX3604C males were introduced weekly into large laboratory cages containing stable target mosquito populations, the vectors were eliminated within 10–20 weeks.\(^13\) Oxitec, Oxford, UK reported 96% suppression of the dengue mosquito in Brazilian trials conducted in Mandacaru, Bahia state, Brazil. With regard to *Wolbachia pipientis*, resistance to infection was found to persist in transinfected mosquitoes which were released in a field trial for a year.\(^14\) These approaches may help in evolving integrated vector management strategies for the eventual control of dengue.

### REFERENCES

Cecilia: Dengue and chikungunya in India


