Why did Chikungunya Return with a Vengeance?

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ABSTRACT Chikungunya (CHIK) is a mosquito-borne viral disease that is spread by the bite of *Aedes* mosquitoes. It is caused by the chikungunya virus (CHIKV). The disease was first reported from Tanzania in 1952. Since then, outbreaks have been reported from many parts of the globe. The first Indian outbreak was reported in 1963 from Kolkata, followed by others up till 1973. Then, after a gap of 32 years, it re-emerged in 2005 in an explosive outbreak in several Indian states. Several factors have impacted on the re-emergence of CHIK. These include rapid urbanization, increased air travel, loss of herd immunity, climate change, and a mutation in the E1 gene of CHIKV.

KEYWORDS Chikungunya (CHIK), chikungunya virus (CHIKV), CHIK re-emergence, CHIK outbreaks

Introduction

Chikungunya (CHIK) is spread by the bite of *Aedes aegypti* and *Aedes albopictus* mosquitoes. Chikungunya virus (CHIKV) is an arbovirus (*ar*thropod-*bo*rne virus) belonging to the genus Alphavirus under the family *Togaviridae*. CHIKV originated in Africa about 200-300 years ago, based on phylogenetic analysis. It has a single-stranded, positive-sense RNA genome. Chikungunya derives its name from the Swahili word "*kungunyala*", which literally means "that which bends up", referring to the stooped and contorted posture exhibited by CHIK patients due to the excruciating joint pain caused by the infection. Chikungunya was first reported in 1952 from the Makonde Plateau in Tanzania (then Tanganyika).[1,2]

Signs & Symptoms of Chikungunya

Chikungunya is an acute febrile illness characterized by a triad of symptoms, namely, fever, rash, and joint pain. Following the mosquito bite, there is an incubation period of 3-7 days, before symptoms appear. The first symptom to appear is high fever (>102°F), accompanied by polyarthralgia, which is usually bilateral and symmetrical in distribution and can be severely debilitating. Another major symptom is the appearance of maculopapular rashes. Other symptoms include headache, conjunctivitis, myalgia, arthritis, inflammation, swelling, nausea, and vomiting.[3] The joint symptoms usually resolve within a couple of weeks, but in certain cases, these can persist for months or even years.[4] Although CHIK infections are generally not life-threatening, these can cause high levels of morbidity.

Figure 1: Aedes mosquito

Treatment & Prevention of Chikungunya

There is no specific treatment for CHIK. No antivirals or vaccines are currently available. Treatment is essentially symptomatic. For example, fever and pain are controlled by analgesic-antipyretics like paracetamol and aspirin; inflammation and swelling are controlled by non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, indomethacin, and diclofenac;

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while rashes are controlled by antihistamines like cetirizine, fexofenadine, and chlorpheniramine.

Prevention primarily involves avoiding mosquito bites in CHIKV endemic areas as well as effective vector control by eliminating mosquito breeding sites.

Chikungunya Outbreaks in India

Since its first description in 1952, many CHIK outbreaks have been reported from various parts of the globe, since the 1960s. In the Indian context, the first outbreak of CHIK occurred in Kolkata (then Calcutta) in 1963, where 200 deaths were reported.[5] Subsequently, in 1964 epidemics occurred in Chennai (then Madras), Puducherry (then Pondicherry), and Vellore (Tamil Nadu). The following year, outbreaks occurred in Nagpur (Maharashtra), and from three cities in Andhra Pradesh, namely, Kakinada, Rajahmundry, and Visakhapatnam. Then after a gap of 9 years, an outbreak occurred in 1973 in Barsi (Maharashtra).[6] Following these outbreaks, there was a huge hiatus of 32 years, when no outbreaks occurred. The virus again surfaced in 2005, when an explosive outbreak of CHIK occurred in several Indian states during 2005-2006. Andhra Pradesh was worst affected and was the first to report the outbreak in December 2005.[7] Other south Indian states that reported a large number of cases included Karnataka and Tamil Nadu.[8,9] Besides these southern states, the outbreak also spread to Odisha (then Orissa), Madhya Pradesh, Rajasthan and Gujarat.[10] After the outbreak subsided, sporadic cases of CHIK infection still continued to be reported from several districts in Andhra Pradesh.[11,12] Approximately 1,500,000 cases were reported during the 2005-2006 outbreak.[13]

After the 2005-2006 outbreak, there have been five more outbreaks of CHIK infections, one from Meghalaya, two from Andhra Pradesh, and two from New Delhi. These are briefly discussed below.

During November 2010, 64 cases that fell in the category of fever of unknown origin (FUO) were reported from Tura, West Garo Hills district of Meghalaya. The clinical symptoms suggested that these could be cases of CHIK infection. Of the 64 cases, 23 (35.9%) tested positive for CHIKV by IgM-capture enzyme-linked immunosorbent assay (ELISA).[14]

During October-December 2010, New Delhi experienced a CHIK outbreak, which was the first major outbreak to take place in Delhi, where unprecedented number of cases was reported.[15]

During September-October 2013, a huge outbreak occurred in Guntur, Andhra Pradesh. In this outbreak, a total of 1,905 people from 12 villages in Guntur district presented with fever and polyarthralgia. Sixty random blood samples from patients aged 5-65 years were taken for analysis by IgM-capture ELISA, reverse transcription-polymerase chain reaction (RT-PCR), and real time-PCR. Out of 60 samples, 42 were found to be positive for IgM antibodies, and 12 were positive by nested RT-PCR.[16]

During November-December 2013, an unusually large number of fever cases with joint pain (n=1,045) were reported from Atmakur village in Medak district of Andhra Pradesh (this district is now in Telangana). Approximately 50% of suspected CHIK cases tested positive for CHIKV by IgM-capture ELISA.[17]

In August 2016, there was a massive CHIK outbreak in New Delhi and Delhi NCR, resulting in thousands of cases. An investigation was carried out that included 600 patients. The total incidence rate was 58%. Approximately 70% of patients were positive for CHIKV by IgM-capture ELISA, while 24% were positive by quantitative real-time PCR (qPCR). Coinfection with CHIK and dengue was seen in 25% of patients. Clinical features such as restricted joint mobility, swelling, itching, and rashes of varying severity were observed in 97% of patients. Comorbid conditions were observed in 12 patients of whom two died.[18]

Although there has not been any major outbreak after 2016, CHIK has now become endemic in many parts of the country, where sporadic cases are reported every year.

Current Status of Chikungunya in India

Since 2007, diagnosis and data assimilation for CHIK in India has 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. Based on the data of the NVBDCP, the number of CHIK cases reported between 2015-2018 is presented in Figure 2. The number of suspected (47,208) and confirmed (8,499) cases for 2018 are provisional (till 25 November 2018).

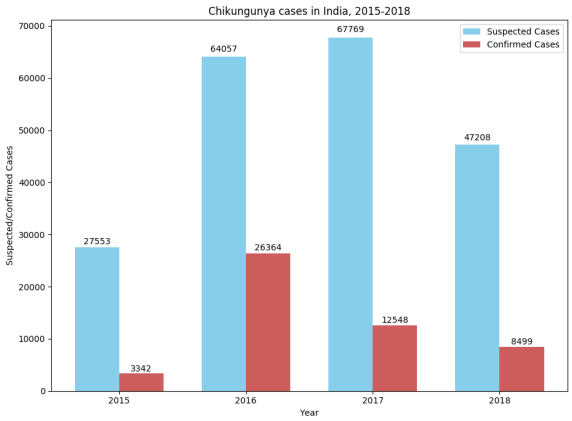

Figure 2: Chikungunya cases in India, 2015-2018.

The number of cases reported is increasing in recent years, particularly between 2016-2017 (Figure 2). This could possibly be influenced by the increased efficiency of case detection due to the availability of CHIKV-specific IgM-capture ELISA kits developed by the National Institute of Virology and made available through the NVBDCP.

Reasons for the Resurgence of Chikungunya in India

It has been suggested that the re-emergence of CHIK in India could be influenced by the under-mentioned factors:

- **Rapid Urbanization:** To keep pace with the burgeoning population, there has been a need for expansion and urbanization. Comparing the Census data on the rate of urbanization, it is seen that the number of statutory towns has increased from 3,799 (2001 Census) to 4,041 (2011 Census). Importantly, in the 2011 Census, 475 Urban Agglomerations (UAs) with 981 outgrowths (OGs) were identified as against 384 UAs with 962 OGs in the 2001 Census.[19] The state of Delhi has the highest percentage of the urban population, compared to all other states and union territories (UTs) in India. Comparing the percentage of urban population to the total population, it is evident that in Delhi, it has

risen from 93.18% in 2001 to 97.5% in 2011.[20] Therefore, this rapid pace of urbanization has led to many unplanned and unsanctioned constructions. These constructions often encroach upon areas which were previously exclusively infested by wild mosquito populations. This encroachment has led to increased mosquito density in these crowded urban areas, providing ideal conditions for the occurrence of CHIK outbreaks.

- **Increased Air Travel:** We live in the jet age, where travelling from one side of the globe to the other can take less than 24 hours. Moreover, air travel has increased dramatically in recent years. For example, in 2017 alone, Indian airports had a footfall of 295 million passengers.[21] Therefore, screening for febrile patients who might be infected is not practically feasible. As a result, a CHIKV infected patient can be rapidly transported from a CHIK endemic country to another part of the globe where the disease is absent, causing a fresh cycle of transmission and possibly, even epidemics.
- **Immunologically Naïve Population:** There are no vaccines that protect 100% of the population, and the maximum duration of protection is usually about 20 years (Hepatitis B vaccine). So after 20 years, the immunity wanes appreciably.[22] Vaccines essentially mimic natural infections. In the absence of a CHIK vaccine, the immunity acquired by natural infection way back in 1973 could not have lasted till 2005, which is a gap of 32 years between the two outbreaks (1973 and 2005). Therefore, the herd immunity of the population would have waned appreciably by 2005. As a result, a large proportion of the population would be immunologically naïve, since they would not have come in contact with the virus, thereby making them more susceptible and vulnerable to CHIKV infections.
- **Climate Change:** Climate change has the potential to affect the development and transmission dynamics of the mosquito vectors. For example, the World Health Organization (WHO) has estimated that over the next 100 years, average global temperatures could rise by 1–3.5°C, thereby facilitating the spread of vector-borne diseases to new geographical niches.[23] Here, both temperature and rainfall have been taken into consideration to explain their influence on vector dynamics. In this regard, it was observed that the average annual temperature of the 10 years (1995-2004) preceding the 2005-2006 outbreak was 24.72°C (Range: 24.1°C–25.29°C), which was marginally higher than the previous two decades (1974-2004).[24] The average monsoon rainfall (June-September) between 1995-2004 was 846.05 mm (Range: 740.1 mm–947.9 mm).[25] It should be remembered that increased rainfall is accompanied by a rise in humidity and when this is coupled with a rise in temperature, it provides ideal conditions for the rapid breeding of mosquitoes and faster maturation of their eggs. Therefore, the variation in the temperature and rainfall patterns could have a direct impact on the vector dynamics and disease transmission.
- **A226V Mutation in the Chikungunya Virus E1 Gene:** During the 2005-2006 CHIK outbreak in India and the preceding outbreak in Reunion Island, *Aedes albopictus* was suspected as the vector, which was substantiated by further experimental studies. It was found that a single mutation (A226V) in the CHIKV E1 gene was responsible for increased infectivity and efficient transmission of the virus in mice by *Aedes albopictus*.[26-28] These studies clearly indicate that the transmission capacity of the mosquito vector can increase appreciably even by a single mutation in the CHIKV gene, thereby enhancing its epidemic potential.

Concluding Remarks

From the preceding discussion, it is evident that several factors have influenced the re-emergence of CHIK in India. These factors have either had a direct or indirect impact, with some having a more significant impact than others. Since CHIK has become endemic in India, there is a need to control the disease so that outbreaks do not occur. In the absence of an effective vaccine or specific antivirals, vector control strategies remain the mainstay for controlling the disease. Besides the conventional chemical and biological control methods, newer strategies based on evidence-based research such as using the bacterium *Bacillus thuringiensis israelensis* (Bti) to kill mosquito larvae or trans-infection of *Aedes* mosquitoes with the endosymbiotic bacterium *Wolbachia* as a biocontrol strategy could be considered. This underscores the need to implement public health strategies using novel approaches for effective vector management in the near future.

Competing Interests

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