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SUPPLEMENT ARTICLE

Chikungunya: Its History in Africa and Asia and Its Spread to New Regions in 2013–2014

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Chikungunya virus (CHIKV) is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes and causes febrile illness with severe arthralgia in humans. There are 3 circulating CHIKV genotypes, Asia, East/Central/South Africa, and West Africa. CHIKV was first reported in 1953 in Tanzania, and up until the early 2000s, a few outbreaks and sporadic cases of CHIKV were mainly reported in Africa and Asia. However, from 2004 to 2005, a large epidemic spanned from Kenya over to the southwestern Indian Ocean region, India, and Southeast Asia. Identified in 2005, the E1 glycoprotein A226V mutation of the East/Central/South Africa genotype conferred enhanced transmission by the *A. albopictus* mosquito and has been implicated in CHIKV's further spread in the last decade. In 2013, the Asian CHIKV genotype emerged in the Caribbean and quickly took the Americas by storm. This review will discuss the history of CHIKV as well as its expanding geographic distribution.

Keywords. chikungunya; epidemiology; Africa; Asia.

Chikungunya, which means "disease that bends up the joints" in the Tanzanian Makonde dialect, is a mosquito-borne viral disease caused by an alphavirus from the Togaviridae family and transmitted by *Aedes* mosquitoes [1, 2]. It is described as a febrile illness with rash, and associated severe joint pain can persist for months. Severe manifestations can include myocarditis, hepatitis, ocular, and neurological disorders. However, the disease is considered a nonfatal illness. The incubation period ranges from 1 to 12 days. Chikungunya virus (CHIKV) is a 12-kb single-stranded, positive-sense RNA virus and belongs to the Semliki Forest complex. It is closely related to O'nyong nyong virus, another mosquito-borne virus identified in Uganda in 1959 in patients presenting with fever, severe joint pain, and an itchy rash but transmitted by *Anopheles* mosquitoes [1, 2]. Three genotypes of CHIKV have been identified: Asian, West African, and East/Central/South African (ECSA) [2, 3].

The first identified outbreak of chikungunya, with an incidence estimated at 23%, was reported from July 1952 to March 1953 in the Newala and Masisi districts in the Southern Province of former Tanganyika Territory (currently Tanzania). It was considered a new febrile disease with a sharp onset of crippling joint pain and sometimes a rash [1–3]. The virus was isolated in early 1953 from the blood of several febrile patients and several mosquito species, including *Aedes aegypti* [1]. Subsequently, CHIKV was identified in Uganda in mosquitoes and humans and other countries in sub-Saharan Africa, mainly in rural tropical regions. It has also been reported in Asia since the 1960s, where it has been associated with outbreaks of dengue virus (DENV) and hemorrhagic fevers [3, 4]. This article will provide a general overview of the history of chikungunya and its spread and upsurge during the last decade to new regions of the world.

CHIKUNGUNYA VECTORS AND CYCLE OF TRANSMISSION

Chikungunya transmission involves *Aedes* mosquitoes. In Africa, sylvatic *Aedes* vectors include *A. africanus* in East Africa; *A. furcifer, A. taylori, A. dalzieli, A. luteocephalus,* and *A. vittatus* in West Africa; and *A. taylori* and *A. cordellieri* in South Africa [2, 5, 6]. Experimental transmission studies confirmed the role of several of these sylvatic mosquito species [1]. In Asia, transmission of CHIKV has been documented to occur mainly in urban areas, and *A. aegypti* has been identified as the main vector [7]. *Aedes albopictus* has also been reported as a vector in Asia [8]. Venereal transmission of CHIKV in *A. aegypti,* with the identification of male mosquitoes positive for CHIKV, and transovarial transmission has been reported [7]. Experimental vertical transmission of CHIKV in *A. albopictus* has been unsuccessful [9].

The enzootic cycle of CHIKV in Africa is poorly understood. Longitudinal studies conducted in the Zika forest in Uganda in the 1950s detected CHIKV viremia and antibodies in sentinel monkeys [2]. Otherwise, a few isolations of CHIKV have been reported in other mammalian species (eg, golden squirrel and bats) [1, 5]. It has been assumed that the virus is maintained in Africa in a cycle involving nonhuman primates in forest or savannah areas in different types of habitats linked to the presence of competent vectors [1]. Studies conducted in Southeast Senegal showed a periodicity of CHIKV every 4–7 years, in alignment

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with renewal of the monkey population [6]. However, the increase of CHIKV circulation in *Aedes* mosquitoes every 4–7 years did not systematically cause concomitant outbreaks in humans.

It is possible that CHIKV originated in Africa and then spread to Asia. As mentioned earlier, the dynamics of CHIKV in Asia an highlight urban cycle of transmission, and there is very limited evidence of an enzootic cycle outside of Africa. However, CHIKV antibodies have been detected in crab-eating macaques in the Philippines [10], and CHIKV was isolated in several long-tailed macaques in Kuala Lipis, Pahang, Malaysia, in 2007, suggesting perhaps an enzootic cycle with emergence of several limited outbreaks [11].

EPIDEMIOLOGY

Since the 1960s, CHIKV outbreaks have been reported in Africa and Asia, with major activity in the 1960s–1980s and then a decrease in activity until 2004. In 2004, a large epidemic started on the coast of Kenya [12, 13]. CHIKV then spread quickly to several islands in the Indian Ocean, to India, and to Southeast Asia (Figure 1) [14]. The disease reemerged in several countries in Central and West Africa, and small outbreaks have been reported in Europe since 2007 [15]. The Pacific region has experienced several outbreaks since 2011 [16]. CHIKV emerged in 2013 in the Caribbean and rapidly spread to neighboring islands and Central, South, and North America. The following sections will go into more detail on CHIKV's historical landscape.

CHIKV: PRIOR TO 2004

Africa

After the outbreak in Tanzania in 1952–1953, epidemics were reported in South Africa in 1956 and in 1975–1977; in Zimbabwe in 1957, 1961–1962, and 1971; in the Democratic Republic of Congo in 1958 and 1960; in Zambia in 1959; in Senegal in 1960, with recurrent, limited outbreaks up to 1996–1997; in Uganda in 1961–1962 and 1968; in Nigeria in 1964, 1969, and 1974; in Angola in 1970–1971; and in the Central African Republic in 1978–1979 [1, 13, 17]. Sporadic cases were also identified in other countries such as Cameroon and Cote d'Ivoire [1, 5, 13]. In the Democratic Republic of the Congo, resurgence of the disease after 39 years was observed in 1999–2000 during an urban epidemic in Kinshasa, which affected about 50 000 persons [18]. In equatorial Guinea, a few CHIKV cases were identified in 2002 [19].

Asia

In Asia, CHIKV outbreaks were initially associated and confused with dengue epidemics. In Thailand, CHIKV was recognized in 1960 in Bangkok during the first significant documented urban outbreak. It seemed to account for a large proportion of hemorrhagic fever cases [4, 20]. In 1961–1962, the role of *A. aegypti* as the main CHIKV vector in urban settings was confirmed in Thailand [1, 13]. In Cambodia, the presence of CHIKV was identified in 1961 [2]. CHIKV seemed to be widespread in Southeast Asia, with outbreaks reported in Myanmar, Vietnam, Sri Lanka, and Indonesia [14, 16].

In India, a large outbreak was reported in Calcutta in 1963, and the disease spread to other states in 1964–1965 through 1973. In 1964, Chennai, India, experienced a large outbreak with >400 000 cases [1, 2, 13]. One study reported several fatal cases related to CHIKV infection in Calcutta, but several studies conducted in India and Thailand did not confirm these results and reported findings similar to those observed in Africa, with

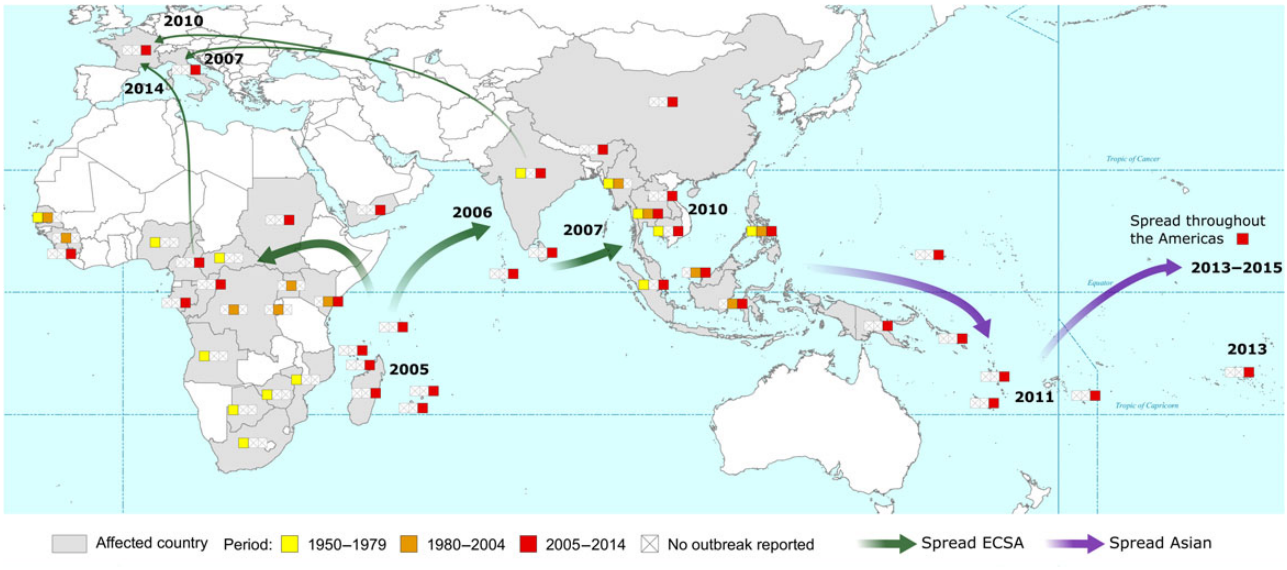

Figure 1. Chikungunya's geographic distribution. This map highlights the spread of East/Central/South Africa (ECSA) and Asian chikungunya virus genotypes in Africa and Asia in new regions in 2005–2014.

only minor hemorrhagic signs and no death [3, 4, 21]. After 1973, no major outbreaks were reported in Asia, rather sporadic cases. For example, cases were reported in Indonesia in 1982 and Thailand in 1988. In Malaysia, the first outbreak was identified in 1998 [22]. In Indonesia, after an interval of 15 years, sporadic outbreaks were identified simultaneously in several regions in 2001–2002 [23].

CHIKV: 2004–2014

Africa and Islands in the Indian Ocean

From April to August 2004, a CHIKV outbreak was reported in Lamu Island, Kenya. The outbreak peaked in July 2004, with an estimated 13 500 cases (70% of the island's population) [12]. The disease reached Mombasa on the Kenyan coast in November–December 2004 and the Comoros, where it resulted in a large outbreak in 2004–2005 [13]. Approximately 63% of the population may have been infected with CHIKV in Grande Comore. The epidemic then spread to other islands [14]. La Réunion, an island with a population of 750 000, experienced a large epidemic from March 2005 to May 2006, with an overall attack rate of 35% [24]. Viral transmission decreased during the cool winter season (June to September 2005), and 2 epidemic waves were identified with peak incidences of 450 cases and 47 000 estimated cases during week 19 in May 2005 and week 5 in February 2006, respectively [24].

The epidemic spread to other islands. Mauritius reported about 13 500 suspected cases from February to May 2006 (1.1% of the population); Seychelles reported 8800 suspected cases (10% of the population) in January–February 2005; and Madagascar and Mayotte reported outbreaks in January 2006 [14, 25, 26]. *A. albopictus* was the main suspected vector species in La Réunion, Mauritius, and Seychelles [3, 13]. From the end of 2005, unconfirmed outbreaks compatible with CHIKV were reported in several Indian states (Andrah Pradesh, Maharashtra, and Orissa) [14, 19].

Particularly during the La Réunion epidemic, unusual clinical complications were reported, and there were 123 severe cases [24]. Forty-one cases of mother-to-child CHIKV transmission in the context of intrapartum maternal viremia led to severe neonatal infections [27]. An overall mortality rate corresponding to the epidemic peak was also reported and then reported in later outbreaks [28].

The viral isolates in La Réunion showed a distinct clade within the ECSA genotype. An alanine-to-valine mutation in the E1 glycoprotein at position 226 (E1-A226V) was reported in isolates obtained from September 2005 in comparison with isolates from the first epidemic wave (March–June 2005) [29]. This E1 glycoprotein mutation at position 226 is located close to the peptide fusion region that is known to induce a loss of dependence on cholesterol and an increase of replication in mosquitoes infected with Semliki forest virus, which is closely related to CHIKV [29]. Experimental infection confirmed that the mutation induced a more efficient dissemination rate in *A. albopictus*, with infectious viral particles detected in the salivary glands from day 2 after infection [30]. Thus, this mutation is regarded as conferring enhanced transmission in the vector.

The resurgence of CHIKV transmission was noticed in several countries with outbreaks reported in major cities in Central and Western Africa from 2005. Some of the affected regions were areas recently colonized by the *A. albopictus* mosquito. In Cameroon, an outbreak of CHIKV and dengue was reported in April–July 2006 in urban/periurban settings of Yaoundé, where *A. albopictus* tended to replace *A. aegypti* [31]. In Tanzania, CHIKV cases were reported at the same time as dengue cases in 2007–2008 [32]. CHIKV emerged in Gabon along with a DENV-2 outbreak between April and July 2007, causing a large outbreak with about 20 000 cases [33]. The outbreak mainly affected the capital, Libreville, where *A. albopictus* was the main vector, but several other towns along the route north, toward Cameroon, were also affected. In Gabon in 2010, several isolated villages in the southern deep forest region were affected as well. In these villages, *A. albopictus* was the main CHIKV vector.

These outbreaks collectively illustrate an increasing public health problem because of the geographic spread of this invasive mosquito vector [34]. In June 2011, another outbreak was identified in Brazzaville, Republic of Congo, affecting 8000 persons, who locally named the disease "robot malaria" because of its specific symptoms affecting posture and locomotion [35]. Phylogenetic analysis of the Gabon 2007 and Republic of Congo 2011 CHIKV isolates identified the E1-A226V mutation as well [36]. CHIKV cases were also reported in equatorial Guinea in 2006 [19]. In West Africa, CHIKV infection was detected in several travelers coming from Senegal in September–December 2006 [37]. More recently CHIKV-DENV coinfection was reported in a traveler returning from Luanda, Angola, to Portugal in January 2014 [38].

Asia

After a gap of 32 years, CHIKV reappeared throughout India, causing >1.3 million cases in 13 states from October 2005 to October 2006 [39]. The CHIKV from the ECSA genotype was the main causative agent in this reemergence, and *A. albopictus* was identified as the main vector in several regions. Since its reappearance in 2005, there has been continuous transmission of CHIKV in India. However, dengue remains the main arbovirus, and coinfections of DENV and CHIKV were reported in several states, such as Orissa and Maharashtra states in 2013 [40].

The disease also reemerged in the rest of Asia, with significant outbreaks in Sri Lanka in 2006, in Malaysia in 2007, and in Thailand and Singapore in 2008–2009 [3, 8, 41]. In Malaysia, CHIKV reemerged in April–May 2006, 7 years after the first outbreak in 1998. The CHIKV strains involved belonged to the Asian genotype [22]. In December 2006, an outbreak linked

to the ECSA genotype was reported in Perak, Malaysia, with possible introduction by a traveler returning from India in November 2006. The virus was also identified in *A. albopictus* pools. Southern Thailand experienced large outbreaks in 2008–2009, and cases were still being reported in 2010 [41]. An outbreak was also reported in Dongguan city, Guangdong province, China, in September–October 2010 [42].

In Cambodia, outbreaks were detected in May–December 2011 in several locations within the country and again in 2012 [41]. Studies of the circulating 2008–2010 strains from Malaysia, Singapore, Thailand, Cambodia, and China highlighted the widespread establishment of the ECSA, with strains harboring the E1-A226V mutation [22, 40–42]. In China, the circulating virus linked to the ECSA virus genotype was most closely related to a 2009 isolate from Thailand [42]. In Papua New Guinea, an outbreak was reported in June 2012 in Vanimo, and in Bhutan, an outbreak was reported in July 2012 [43, 44]. CHIKV from Papua New Guinea was closely clustered with mutant strains that evolved in India and subsequently spread to other countries in Southeast Asia (eg, Malaysia, Singapore, Sri Lanka, and Thailand) [44]. The CHIKV from Bhutan belonged to the ECSA genotype but did not have the E1-A226V mutation [43].

In Indonesia, surveillance investigations in 2001–2004 and 2007–2008 identified CHIKV cases an incidence rate of 7.9–10.1 cases per 1000 persons per year [23, 45]. The clinical picture was mostly mild, and the disease short. Cases were also detected during the dry season but at a lower frequency [45]. In 2011, CHIKV strains belonging both to the Asian genotype and the ECSA genotype were circulating in different regions of Indonesia [46]. In 2013, CHIKV outbreaks occurred in a variety of geographic locations within the Philippines archipelago, including Manila as well as Singapore, India (Gujarat, Tamil Nadu, Kerala, and Odisha states), and Indonesia (East Java and East Jakarta).

The Pacific Region

In the Pacific region, CHIKV was detected in early 2011 in New Caledonia. Other outbreaks were reported in New Caledonia and Yap State (Federated States of Micronesia) in 2013 [16]. In 2014, cases were reported in Tonga, American Samoa, the Independent States of Samoa, and Tokelau. The viruses involved in these outbreaks belonged to the Asian genotype [16]. In October 2014 to January 2015, French Polynesia experienced a large outbreak affecting about 25% of the population. Phylogenetic studies demonstrated that CHIKV was probably introduced to French Polynesia from the Caribbean and not from other Pacific countries [16]. The disease spread further to other islands, such as Cook Island, as early as 2015.

Europe

In 2007, an outbreak was reported for the first time in northeastern Italy. A total of 217 cases were reported in July–September 2007 [15]. The presumed index case came from India in June. The virus isolated from humans and *A. albopictus* mosquitoes was closely related to the ECSA genotype and had the E1-A226V mutation [47]. Vector control measures were implemented to decrease the *A. albopictus* population in the affected areas, and there was no reemergence in 2008.

A limited outbreak was reported in September 2010 in southern France, where an enhanced surveillance of febrile illness, focusing on CHIKV and DENV, has been in place since 2007 in areas where *A. albopictus* is present. The index patient had travelled back from India [48]. Experimental infections with the 2010 strain detected in France have shown that the local *A. albopictus* mosquito populations in southern France exhibited a high efficiency for CHIKV transmission [49]. Another outbreak occurred in Montpellier, a French town recently colonized by *A. albopictus*, in August–September 2014. The index patient had returned from Cameroon. The 11 autochthonous confirmed cases were reported in the same neighborhood.

The virus in both the 2010 and 2014 outbreaks belonged to the ECSA genotype but did not possess the E1-A226V mutation [50]. The efficient transmission in Italy and France provides new insights in the dissemination potential of CHIKV in regions of Europe where *A. albopictus* is present. In the absence of an apparent sylvatic cycle in Europe as well as vertical transmission, the maintenance of the virus and reemergence have not yet occurred. Such a profile is also exhibited for limited autochthonous transmission in southern Europe, with few reports from Croatia in 2010 and France in 2010, 2013, 2014, and 2015.

The Americas

On the Caribbean island of St Martin Island, a cluster of clinical cases with onset of febrile illness starting in mid-October 2013 resulted in negative laboratory results for dengue in November 2013. Additional investigations quickly recognized CHIKV infection, and an alert was issued in early December. The emergent CHIKV belonged to the Asian genotype. The presence of a human population naive to CHIKV, the presence of competent *A. aegypti* and *A. albopictus*, and the intense movement of people into and between islands were factors that most likely contributed to the rapid spread of CHIKV to neighboring islands and Central, South, and North America. More than 1.2 million autochthonous cases were reported to Pan American Health Organization in the Americas for the period 2013–2014.

CONCLUSIONS

Within the last 10 years, CHIKV has become a major arboviral public health threat. The spread of CHIKV particularly coincides with the rapid expansion of the invasive *A. albopictus* mosquito and the E1-A226V mutation in the ECSA genotype that confers enhanced vector transmission. Owing to these factors, CHIKV has become widely distributed, with limited outbreaks now reported in temperate regions. Global vigilance with early recognition in combination with appropriate vector

control measures is needed to decrease the overall burden of the disease.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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