Epidemiological History of Chikungunya Virus

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Introduction

Chikungunya virus (CHIKV) is a mosquito-transmitted virus that has been known to cause human disease since 1952 when the virus was first characterized in an outbreak in East Africa. The virus became widely known on a global scale in 2013 when it entered the Western hemisphere and began to rapidly move through 45 counties in under 2 years. Although this expansion was highly visible and on a virtually unprecedented scale, CHIKV actually has a long history of both epidemic and low-level transmission throughout its endemic distribution in Africa and Southeast Asia. The historical epidemiological patterns of CHIKV are different from more recent activity. Apart from a few large outbreaks, activity in Africa has tended to involve only a few human cases at a time that are typically linked to close associations with the enzootic transmission cycle. In contrast, in Asia, where there is no known enzootic cycle, on-going, low-level activity is typical with large periodic urban outbreaks. The epidemiology of CHIKV since its re-emergence in 2004 in coastal Kenya has been characterized by large attack rates, rapid movement and geographic expansion, utilization of alternate mosquito vectors, and adaptation to novel ecologies. Understanding of the historical patterns of the virus as described below provides a framework for appreciating the modern movement of the virus.

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Discovery of CHIKV

In 1952–1953, the local populations of southern Tanganyika (current Tanzania) were affected by an epidemic of disease characterized by a fever with a rapid onset, joint pain, and rash. The pain was so debilitating and prolonged or recurring that the local word *chikungunya*, meaning "that which bends up" was given to the syndrome describing the stooped posture that resulted from the pain of the disease (Robinson 1955; Lumsden 1955). An alphavirus was later identified as the causative agent and given the name chikungunya virus (CHIKV) (Ross 1956). The outbreak occurred both in river valley lowlands as well as on the nearby Makonde Plateau where interestingly, the incidence was highest overall. It was speculated the incidence was highest on the plateau because no pre-existing antibodies were prevalent in this population as was the case in the valley areas. In contrast to the plateau areas, the lower valleys had mosquito populations that were continuously high (Jupp and McIntosh 1989) and the population was therefore likely more frequently exposed to CHIKV. However, distinct mosquito species may also have been involved in the contrasting affected ecologies which would have influenced the patterns of disease.

Approximately 150,000 people resided in the affected areas of Tanzania scattered among numerous small villages. Many of these villages on top of the plateau were far enough away from water sources that storage of fresh water was required (Lumsden 1955); this likely led to large populations of *Aedes aegypti* in close association with their homes promoting epidemic transmission as has been observed in recent epidemics (Chretien et al. 2007). A resulting overall morbidity rate of 47–50 % was reported among affected individuals on the plateau (Lumsden 1955). Although it has been speculated that there had been historical confusion between dengue and CHIKV outbreaks and that CHIKV outbreaks may actually have occurred as early as 1779 (Carey 1971), this first confirmed CHIKV epidemic in coastal Tanganyika demonstrated that this newly discovered virus was capable not only of significant human disease but also epidemics of arboviral disease at an unprecedented scale and rate.

Early Outbreaks and Periodic Detections

After the identification of CHIKV, a number of outbreaks occurred over the next 30 years that were attributed to this agent. These ranged geographically across central Africa from Senegal to Uganda south to South Africa, across the Indian Ocean to India and throughout Southeast Asia. However, although the outbreaks in Africa were more numerous, they tended to be small in scale whereas large urban outbreaks were primarily documented in Southeast Asia. Large urban outbreaks were first reported in Thailand in the late 1950s and early 1960s (Jupp and McIntosh 1989) and the scope of these outbreaks was staggering. For example, in Bangkok in 1962, up to 70,000 outpatient children were affected with CHIKV and the attack rate for the city was estimated to be 31 % (Halstead et al. 1969a). Clear evidence that the virus had been previously established in the area was seen in age-dependent

immune rates. Antibodies were found in 10–20 % of 1–2 year olds but 70–85 % of adults (>20 years) had CHIKV antibodies. Similarly high rates were found in rural Thailand (Halstead et al. 1969b) and in Vietnam after a 1964 outbreak (Deller and Russell 1968) further supporting the idea of long-term endemicity in the region. Curiously, after ~1982, CHIKV activity was virtually undetected in Bangkok even though most conditions for transmission remained present (Burke et al. 1985).

India also experienced large urban outbreaks of CHIKV in both the early 1960s to 1970s. A series of outbreaks was reported in Calcutta in 1963 and in Madras State from 1962 to 1964. The Madras activity involved an estimated 400,000 individuals in this single region in Southern India where the virus had not previously been documented (Myers and Carey 1967; Rao 1966). Even with an estimated 40 % of the population affected by CHIKV, the outbreak ended abruptly with activity nearly nonexistent by 1965 (Rao 1966). Interestingly, involvement of the central nervous system in children was identified in these outbreaks demonstrating early the ability of CHIKV to cause "atypical" disease (Jadhav et al. 1965; Carey et al. 1969) as had been reported in outbreaks since 2005. A later 1973 outbreak in central India (Barsi) also involved large attack rates and resulted in over 37 % of the population being infected (Padbidri and Gnaneswar 1979). Even though these outbreaks in India were significant, there was no reported epidemic activity from the country for the next 30 years. This curious apparent lack of CHIKV transmission does suggest the lack of establishment of an enzootic cycle in India after the cessation of epidemic activity.

During the 1950s to 1970s, a number of smaller scale outbreaks were recorded in Africa as well. Cases were reported in Zaire, Zambia, Senegal, Uganda, Zimbabwe, Nigeria, Angola, Central African Republic, and South Africa (Jupp and McIntosh 1988; Rodger 1961; Macrae et al. 1971; McIntosh et al. 1963, 1977; Moore et al. 1974; Tomori et al. 1975; Filipe and Pinto 1973). In some of these outbreaks, cases were reported in multiple areas of the country yet they had low attack rates in individual locations. This pattern suggested only low levels of transmission from the local vectors (McCrae et al. 1971). When low levels of activity were reported, it was postulated that the infections were a result of humans entering forest habitats when they were bitten by infected sylvatic vectors that tended to have a lower vectorial capacity than urban vectors due to a lower preference for human hosts compared with other vertebrates. These small outbreaks were periodic and covered a wide geographic range but rarely caused significant numbers of cases. This epidemiological pattern was quite distinct from that seen in Asia during the same time frame, perhaps most significantly due to the association of enzootic maintenance of CHIKV in Africa with a number of alternate vector species.

Re-Emergence of CHIKV

Perhaps not unexpected, due to the maintenance of CHIKV in zoonotic transmission in Africa, there was a re-emergence of epidemic CHIKV in 2004 in coastal Kenya. During July, an unusual increase in the number of malaria-like illnesses was detected in the island community of Lamu. However, local physicians noted that the

degree of joint pain associated with these cases was significantly more severe than that seen in standard malaria infections. In addition, 91 % of the blood smears were negative for parasites; thus, the increase in cases could not be accounted for by malaria. Additional testing for likely etiologies revealed positive CHIKV-specific antibodies and nucleic acid results (Sergon et al. 2008). The scope of this outbreak was quite large for eastern Africa with an estimated 13,500 cases. Yet recognition of the outbreak on a global scale was minimal.

Approximately eight months later, an outbreak of febrile illness began on the island of Comoros just off the coast of Tanzania. The outbreak was initially believed to be dengue but laboratory testing showed no evidence of dengue infections. Because of the recent CHIKV activity in Kenya, testing of samples for CHIKV was undertaken. Of 25 samples analyzed, 9 were positive for CHIKV antibody and 6 additional samples were RT-PCR positive. Similar to what was found in Lamu, a high percentage of patients reported fever and joint pain (>89 %) and a serosurvey performed during the outbreak revealed an attack rate of 63 % (Sergon et al. 2007). Molecular epidemiology further revealed that the virus originated from the Lamu/Mombasa outbreaks, demonstrating that the activity in Comoros was simply an extension of the Kenyan outbreaks rather than novel outbreaks (Kariuki Njenga et al. 2008). The total number of cases estimated in Comoros was nearly 215,000 resulting in a grand total of approximately 230,000 cases in just 1.5 years (Sergon et al. 2007). This outbreak also suggested the movement of epidemic activity rather than the cessation of a particular outbreak followed by periodic re-emergence of the virus elsewhere. This was a pattern that would characterize CHIKV outbreaks for the next decade.

Coincident with the large outbreak in Comoros was a smoldering outbreak in nearby La Réunion. Cases were first identified there in March of 2005 but the number of cases remained low until December with the onset of the rainy season (Bessaud et al. 2006). The peak of the outbreak occurred beginning the last week of January, 2006 when 45,000 cases were reported (Josseran et al. 2006) and an overall estimate of >244,000 cases was described (Renault et al. 2007). Intense curiosity regarding the reason for the very slow progression of this outbreak compared with the sweeping activity in Kenya and Comoros was addressed by microevolutionary analysis indicating a single amino acid change likely altered the mosquito infectivity of the strains that were isolated in 2006 (Schuffenecker et al. 2006). This mutation was postulated to enable the virus readily to infect the mosquito *Aedes albopictus*, which was far more abundant on the island than the traditional vector, *Aedes aegypti* (which was virtually absent from the island). The viral variant without this mutation was thought to be limited in ability to infect *Ae. albopictus*. This hypothesis was quickly confirmed using local mosquitoes and viral strains from early and late in the La Réunion outbreak (Vazeille et al. 2007) as well as infectious clones with engineered point mutations (Tsetsarkin et al. 2007). This was a significant finding demonstrating that a single mutation could affect the course of a global outbreak; had this mutation not emerged in the viral population late in 2005, the epidemic may have ended before the increase in cases in La Réunion and subsequent movement to India and Southeast Asia.

This Indian Ocean lineage of CHIKV continued its expansion by moving to India in 2006. After a 32-year absence of the virus, India reported an estimated one million cases in just one year in multiple areas of the country (Dash et al. 2007). From India, the virus was exported to a number of other countries in Southeast Asia including both endemic areas as well as locations with no previous documentation of transmission. Perhaps most notably, an exportation event from India to Italy resulted in the first autochthonous transmission in a subtropical area (Angelini et al. 2007). The activity in Italy was limited in both scope and duration, however, it further demonstrated the risk of transmission in areas where only *Ae. albopictus* were present as well as the ability of the virus to adapt to novel ecologies (Rezza et al. 2007).

Ongoing Threat of CHIKV from Endemic Areas

Although a viral mutation kept the Indian Ocean lineage outbreak alive, the threat of future CHIKV emergence from a different source was still present. Prior to and during the early re-emergence activity in 2004, CHIKV was continuing to circulate and cause large numbers of cases without substantial media attention. In particular, small yet substantial outbreaks were being reported in Central Africa and Indonesia. In 2000 in the Democratic Republic of Congo, an urban outbreak of CHIKV was detected after a 39-year absence of virus isolation in the country (Pastorino et al. 2004). An estimated 50,000 cases occurred in this outbreak with little awareness outside the area. Later, in 2006, CHIKV was identified as the causative agent in a number of febrile illness cases in Cameroon. The virus sequence obtained from this cluster revealed a high degree of homology with the strains from the Republic of Congo in 2000 suggesting continuous circulation of this lineage over at least 6 years in central Africa (Peyrefitte et al. 2007). Only about 400 cases of illness were reported during this outbreak, however, a follow-up cross-sectional serosurvey suggested that the recent infection rate was over 50 % (Demanou et al. 2010). Further evidence of transmission of this central African lineage was found in 2006–2007 in Gabon where a dengue-like outbreak occurred involving 20,000 suspected cases (Leroy et al. 2009). All this activity in central Africa was of the ECSA genotype, however, the lineage was distinct from that of the isolates associated with the Indian Ocean outbreaks (Peyrefitte et al. 2008). This outbreak in Gabon also linked transmission of the virus to the mosquito *Aedes albopictus* further signifying the importance of this species as an epidemic vector (Pages et al. 2009). The same virus lineage was also retrospectively linked to a cluster of febrile illness cases in children in Equatorial Guinea in 2002–2003 and again with travelers who visited this country in 2006 (Collao et al. 2010). Although samples from both time frames in Equatorial Guinea were of the same lineage, the 2006 samples were more closely related to samples more temporally similar from neighboring countries indicating continuous movement of the virus throughout this region over time. In 2011, a CHIKV outbreak affecting approximately 8000 individuals was reported in the Republic of Congo (Kelvin 2011). Genetic data from this outbreak were not

reported, but given the geographic location, it is reasonable that the continuously circulating central African lineage was progressing in both distribution and human infections with little global awareness.

Concurrent with this continuous transmission of the virus in central Africa was endemic transmission in Southeast Asia, particularly in Indonesia. Although antibodies against CHIKV were detected in Indonesia as early as 1972 (Kanamitsu et al. 1979), the virus was only first detected in Indonesia in 1982 when an outbreak was identified in South Sumatra. The epidemic quickly moved to numerous cities throughout Sumatra and a number of other islands of the archipelago were subsequently affected over the next 2 years including Java, Kalimantan, Bali, East Timor, East Nusa Tenggara, Papua, and Sulawesi. The attack rates ranged from 40 to 90 % depending upon the region (Porter et al. 2004). However, there were no additional reports of epidemic CHIKV illness in Indonesia for 15 years until a number of small outbreaks were reported between 1998 and 2003 on Java. Renewed activity was first reported in 1998–1999 in Yogyakarta, Java with a handful of clusters of febrile illness associated with arthralgia and rash. Interestingly, approximately 40 % of these cases exhibited either mild or asymptomatic infections. As activity increased, 24 distinct outbreaks were reported between 2001 and 2003 (Laras et al. 2005) moving across the country from northern Sumatra to Java to northeast Sulawesi and to Nusa Tenggara with the vast majority occurring on the main island of Java (83 %). Most of these epidemics lasted only 2–3 months and involved fewer than 200 individuals. The limited scope of each outbreak may have been due to the fact that most were in rural settings with only 21 % occurring in urban centers. The two most well- characterized outbreaks, in Bogor and Bekasi, showed repeated periods of peak activity with intermittent weeks of fewer cases. Both outbreaks also had approximately 10 % of the “asymptomatic" controls confirmed as positive for CHIKV infection in laboratory tests. Interestingly, approximately 8 % of the suspect cases reported having hemorrhagic manifestations. Given the lack of laboratory testing through most of the country, it is easy to understand how CHIKV outbreaks could easily be mistaken for dengue. Although this would be considered atypical for CHIKV infection, previous outbreaks in Thailand (Burke et al. 1985) and Myanmar (Thein et al. 1992) also showed similar levels of hemorrhagic fever. One other commonality between the two outbreaks was that there were dramatic increases in the amount of rainfall leading up to the initiation of the outbreaks. This link to seasonal increased rainfall has also been reported with previous CHIKV activity in Thailand (Thaikruea et al. 1997) whereas in Asian areas where rainfall is less seasonal (Halstead 1966) or in Africa where drought preceded CHIKV epidemics (Chretien et al. 2007), cases have been reported to occur at any time during the year.

For almost the next decade, numerous small foci of CHIKV illness were reported from multiple islands across much of Indonesia. Case counts were never above 5000 in any location but lack of reporting and diagnostics combined with logistical challenges may have led to underestimates of the scope of each of these events (Kosasih et al. 2013). Febrile illness studies performed in Bandung, Java during 2000–2008, but not specifically associated with any outbreak, provided an estimated CHIKV infection incidence rate of 10.1/1000 persons/year with nearly 7 %

of the febrile episodes due to CHIKV (Kosasih et al. 2013). Overall, the number of cases identified during the course of the study (2000–2004 and 2006–2008) remained relatively consistent over the years with cases being identified year round. The study included follow-up serology over 2 years and revealed that IgM antibodies persisted for 3–22 months and IgG titers peaked at 3–4 months post illness but persisted at high titers for up to 2 years following infection. This study also found only the Asian genotype in all samples sequenced even though the ECSA genotype had been identified in other regions of Southeast Asia beginning in 2006. Curiously, in the first phase of the study (2000–2004), arthralgia was not particularly prominent with only 38 % of the patients exhibiting this symptom. In contrast, 87 % of the individuals had arthralgias in the 2006–2008 cohort which is much more typical during investigated CHIKV outbreaks. However, the first cohort was not specifically asked about the presence of arthralgia so the percentage reporting this particular symptom could have been an underestimate. Overall, these nonoutbreak infected individuals exhibited mild infections with one third missing no work and one third missing only 1–3 days. One significant finding of this study was that many CHIKV cases in endemic regions were not associated with large outbreaks but rather were found throughout the year in affected regions without any apparent clustering. Whether severe disease is linked specifically to outbreaks and milder illness is associated with endemic transmission remains an important topic to be further evaluated. Additionally, the importance of this ongoing endemic activity throughout Indonesia would be realized in late 2013 on a small Caribbean island.

Global Expansion

Although the dramatic movement of CHIKV from Kenya throughout the Indian Ocean, India, and Southeast Asia from 2004 to 2010 was previously unprecedented, the virus was still constrained to the Eastern hemisphere. The most significant global expansion of CHIKV distribution occurred from 2011 to 2014 when outbreaks occurred in the western Pacific, the South Pacific, the Caribbean, and the Americas from Florida to central Brazil.

The year 2011 saw the expansion of CHIKV to New Caledonia (Cao-Lormeau and Musso 2014). The number of cases was small, but the arrival of the virus there was not surprising given the movement of the virus around Southeast Asia (Roth et al. 2014a). What was unexpected was the determination that the genotype associated with these cases was the Asian genotype rather than the broadly circulating ECSA Indian Ocean lineage. However, because the first two cases were travelers who had recently been in Indonesia and because the Asian genotype was circulating in Indonesia (Mulyatno et al. 2012), the finding of the Asian genotype was not unreasonable. This Asian genotype continued to be detected across the Western and South Pacific islands with activity in Papua New Guinea in 2012, the Federated States of Micronesia in 2013, Tonga, Samoa, American Samoa, Tokelau, and numerous islands of French Polynesia in 2014 (Roth et al. 2014b), and Kiribati

and the Cook Islands in 2015 (Nhan and Musso 2015; Musso et al. 2015). Interestingly, molecular epidemiology suggests that the virus was actually not just circulating among these islands but was likely reintroduced to the area from affected areas in the Americas and Asia. For example, the Yap outbreak appears to have been initiated by travelers from the Philippines (Lanciotti and Valadere 2014) where a large outbreak was on-going whereas strains characterized from cases in French Polynesia were genetically more similar to isolates from the Caribbean than from nearby Tonga (Aubry et al. 2015). Identifying these movement patterns further depicts the ease of global movement of arboviral pathogens and demonstrates the value of rapid molecular characterization to identify high-risk areas (Powers 2011).

While CHIKV was quietly moving throughout the Pacific Ocean islands, it very noticeably began autochthonous transmission in the Caribbean in late 2013. Transmission in the Western hemisphere was first documented on the island of St. Martin in December (Leparc-Goffart et al. 2014). Before the year ended, three other islands, Guadeloupe, Martinique, and St. Barthelemy, also reported local cases. At the time, awareness of the prevalence of the Asian genotype activity was unappreciated and initial assumptions were that the ECSA genotype, which was still broadly circulating in India and Southeast Asia, had finally made its way to the Americas (Powers 2015b).

The speed with which the virus moved throughout the Caribbean islands was startling with stepwise progression of transmission being reported in virtually every country within just 9 months demonstrating the intensity of movement between the islands. Within the first year of the virus presence in the Americas, 26 island countries and 14 mainland countries were affected with nearly one million cases reported (Powers 2015a). Although activity in many of the island countries has declined or ceased completely, countries in Central and South America continue to report increasing activity suggesting the virus has indeed become endemic in the Americas. At just under 2 years of transmission in the Western hemisphere, PAHO reports approximately 1.6 million cases in 45 countries (PAHO 2015). Interestingly, the vast majority of the cases in the Americas are Asian genotype, but the ECSA genotype (not the Indian Ocean lineage, however) has also been identified in central Brazil (Teixeira et al. 2015). The genetic evidence links this cluster to strains in Gabon and clearly demonstrates that at least two introduction events in the Americas have resulted in establishment of localized transmission.

Conclusions

CHIKV has had an interesting historical journey from its initial discovery, to enzootic pathogen with opportunistic and sporadic infections, to urban epidemic agent, and finally to global vector-borne virus. The range of CHIKV now covers all tropical and some subtropical areas of the globe encompassing the same distribution as pathogens such as dengue viruses. Even with this tremendous number of at-risk individuals, the concern due to CHIKV is still not high, likely due to its lack of mortality.

However, the rapid global expansion of CHIKV provides a lesson for what will come. There are literally hundreds of vector-borne viruses that could move worldwide within a very short period of time, and there will be more that will follow the path that CHIKV has taken. A global surveillance network is critical for monitoring movement of zoonotic pathogens and preparing for the next such introduction event.

Disclaimer The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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