Arrival of Chikungunya Virus in the New World: Prospects for Spread and Impact on Public Health

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For the first time in modern scientific history, chikungunya virus has established its mosquito-human transmission cycle in the Americas. The history of dengue control, recent findings on chikungunya strain variation, and public health preparedness indicate the likelihood of the further spread of this outbreak.

The mosquito-borne chikungunya virus (CHIKV; Togaviridae: Alphavirus) causes a febrile illness (chikungunya fever, or CHIK) typically accompanied by rash and severe, debilitating arthralgia. Pain and swelling are usually focused in the hands, wrists, ankles, and feet and can persist for years to cause not only major public health effects but also economic damage due to lost human productivity [1]. Most cases are not life threatening, although slightly increased mortality is associated with CHIKV infection. The virus is believed to have originated in Africa, where it still circulates enzootically among nonhuman primates, and is transmitted by arboreal Aedes mosquitoes (Figure 1) [2,3]. These cycles lead to regular outbreaks of spillover infection in Africa, but most human cases result from CHIKV emergence into a human–mosquito cycle in urban areas of Africa, followed sometime by spread beyond Africa. Evidence from historic accounts suggest that this emergence began as early as the 18th century in Indonesia and possibly the Americas, presumably via sailing ships that carried the essential ingredients for on-board circulation: susceptible humans and the peridomestic mosquito vector, Aedes aegypti [4]. Two other viruses that circulate in the same cycle, dengue and yellow fever, are also known to have caused outbreaks in port cities where this tropical mosquito was introduced, either temporarily during the summer in temperate climates where it cannot survive cold winters or permanently throughout tropical and subtropical regions of Asia, Europe, Australia, and the Americas.

Following its discovery in 1952, the first documented CHIKV emergence spread to generate urban outbreaks in India and Southeast Asia (Figure 1). This introduction has been traced to an Eastern/Central/Southern African (ECSA) enzootic CHIKV lineage that evolved sometime during or before the early 1950s [2,3]. The resultant “Asian” endemic/epidemic CHIKV lineage persisted in Southeast Asia, where it continues to circulate sporadically in the urban cycle, transmitted among humans by A. aegypti without conclusive evidence of an enzootic component (Table 1). The second documented CHIKV emergence began in coastal Kenya in 2004 [5] and spread independently into islands in the Indian Ocean and to India, presumably via infected air travelers, a documented source of introductions [6–8]. Later, autochthonous transmission occurred in Italy [9] and France [10], initiated by infected travelers from India (Table 1). Although many imported cases were also detected in the Americas [6], including in dengue-endemic locations with both A. aegypti and A. albopictus vectors, no local transmission was detected. As with the Asian lineage, the etiologic CHIKV strain, called the Indian Ocean lineage (IOL) was again identified as a descendent from an enzootic ECSA strain [11]. However, some IOL adapted to a new vector, A. albopictus, through adaptive mutations in the E1 [12,13] and E2 [14,15] envelope glycoprotein genes. These mutations allowed the new epidemic IOL strains to use both A. aegypti and A. albopictus as vectors, resulting in millions of human cases. Because A. albopictus can survive cold winters and is generally less adapted to urban habitats than A. aegypti, IOL CHIKV strains adapted to this vector circulated both in temperate climates such as Italy [9] and in more rural habitats where the former species is more common than the latter [16].

During the ongoing IOL CHIK epidemics, the nearly completely naive human populations in the Americas and the presence of both epidemic vectors, combined with the arrival of infected travelers, raised major concerns that an epidemic in the Caribbean and/or Latin America was inevitable [17]. However, with the gradual subsidence of epidemic transmission in many parts of Asia, this risk was perceived to have declined, because fewer infected travelers were documented in recent years. Thus, the detection of active CHIKV circulation in Saint Martin beginning in October 2013 [18] was somewhat surprising. Furthermore, the characterization of the etiologic strain as belonging to the old Asian lineage rather than to the IOL was unexpected, considering that the former was viewed as displacing the latter in many parts of Asia [19]. However, because it apparently infects A. aegypti slightly more efficiently than CHIKV strains with the A. albopictus-adaptive E1 protein substitution...
The Asian lineage may remain prevalent in urban areas of Asia, from which infected travelers are more likely to depart for global travel.

There is much bad news and only very limited good news in the 2013 CHIKV introduction into the Caribbean. The bad news includes: (1) CHIKV appears to be spreading nearly uncontrolled in the Caribbean, with over 4,300 confirmed cases as of May 23rd (Pan American Health Organization data). (2) Autochthonous transmission has resulted in at least 176 CHIK cases in French Guiana on the South American mainland. If transmission cannot be controlled quickly there, the historic inability to control dengue suggests that CHIKV will spread throughout Latin America. (3) Most of the Latin American population is presumably naïve, setting the stage for major epidemics and rapid spread. (4) Diagnostic capabilities for CHIKV in Latin America remain very limited, and it is possible that undetected circulation is already occurring in the region because of the difficulty in clinically distinguishing dengue from CHIK. And finally, (5) there could be the potential for CHIKV to establish an enzootic, monkey–human cycle in the Americas, as occurred for yellow fever virus hundreds of years ago after its importation from Africa [21].

If there is any good news related to this CHIK outbreak, it is that the etiologic strain, a member of the old Asian lineage, does not infect A. albopictus as efficiently as the adapted IOL strains, and is epistatically constrained in its ability to adapt to this vector via the E1-226 protein substitution [22]. This suggests that most CHIKV transmission in the Americas will occur via A. aegypti, which may limit geographic spread, particularly to temperate climates where this mosquito does not normally occur. However, A. aegypti reinfestation of most tropical and subtropical regions of Latin America since the 1970s [23], along with its persistence in the southern United States, leaves hundreds of millions of persons at risk for CHIKV infection. The presence of the closely related Mayaro alphavirus in South America could provide limited cross-protection [24], but this virus circulates enzootically, mainly in forested areas, where A. aegypti-borne CHIKV is expected to be less prevalent. Finally, the introduction of CHIKV during the beginning of the dry season in the Caribbean and northern hemisphere of Latin America may improve prospects for containing its spread, at least temporarily.

In summary, the prospects for controlling CHIKV circulation in Latin America since its arrival on the mainland of South America are not good, and many parts of the Americas are now at high risk for major epidemics. Because vaccines and specific antiviral therapies for CHIKV are not yet available [25], the only means for controlling its spread are reductions in A. aegypti populations and limiting human contact with this vector. It is therefore critical that public health officials implement robust surveillance based on existing dengue programs, establish local diagnostic capacity to test mosquitoes and patient sera from suspected cases, and develop outbreak response plans, including educational efforts to reduce contact with vectors. Health care workers should also be trained to include CHIK in their differential diagnoses for dengue-like illness and to optimally use available medications to alleviate the severe symptoms of CHIK.
Table 1. Representative chikungunya fever outbreaks documented in the literature.

| Year          | Location                                      | Estimated number of cases | Virus genotype* | Notes                                                                 | References |
|---------------|-----------------------------------------------|---------------------------|-----------------|----------------------------------------------------------------------|------------|
| 1952–1953     | Tanzania                                      | Incidence estimated at 23%| ECSA            | Suspected vector A. aegypti                                          | [26,27]    |
| 1961–1963     | Cambodia                                      | Six confirmed             | Not determined  |                                                                      | [28]       |
| 1956, 1975–1977 | South Africa                                 | Not reported              | ECSA            | No A. aegypti involvement                                            | [29]       |
| 1957, 1961–1962, 1971 | Zimbabwe                                    | 38 suspected (one confirmed), 1962 | ECSA            | No A. aegypti involvement                                            | [29–31]   |
| 1958, early 1960s | Thailand (Bangkok and other locations)       | Estimated 40,000 cases in early 1960s | Asian           | Suspected vector A. aegypti                                          | [32]       |
| 1962–1965     | India (various locations including Calcutta, Madras) | 273 confirmed             | Asian           | Up to 38% human seroprevalence after outbreak, incidence in some locations estimated at 40%; principal vector A. aegypti | [33–36]   |
| 1962–1964     | Bangkok, Thailand                            | 44,000–72,000 estimated   | Asian           | Principal vector A. aegypti                                          | [37]       |
| 1966          | Viet Nam                                     | Ten confirmed             | Not determined  | U.S. soldiers                                                        | [38]       |
| 1969          | Nigeria                                      | 55 confirmed              | Not determined  |                                                                      | [39]       |
| 1999–2000     | Democratic Republic of Congo                 | 40,000 estimated           | ECSA            |                                                                      | [41]       |
| 2004–2005     | Coastal Kenya, Lamu Island                    | Not reported              | IOL             | Principal vector A. aegypti on Lamu Island                          | [5,42,43]  |
| 2005–2011     | Comoros, Mauritius, La Reunion                | 300,000 estimated in La Reunion | IOL             | Principal vector A. albopictus on La Reunion                         | [11,44,45] |
| 2005–2008     | India, Sri Lanka                             | 1.4–6.5 million           | IOL (E1-226A or V in different outbreaks) | Vectors A. albopictus or A. aegypti, depending on location          | [46,47]    |
| 2006          | Bagan Panchor, Malaysia                       | >200 reported             | Asian           |                                                                      | [48]       |
| 2006          | Douala and Yaoundé, Cameroon                  | 54 confirmed              | ECSA            | Suspected vector A. africanus                                        | [49,50]    |
| 2006–2007     | Libreville, Gabon                            | Seven confirmed, 20,000 estimated | ECSA            | Suspected vector A. albopictus                                       | [51–53]    |
| 2007          | Emilia Romagna, Italy                         | 205 confirmed             | IOL (introduced by a traveler from India) | Principal vector A. albopictus                                      | [9]        |
| 2007–2008     | (nonepidemic period)                         | 55 confirmed              | Not determined  |                                                                      | [54]       |
| 2008          | Thailand                                     | 224 confirmed, 46,000 estimated | IOL             | Suspected vector A. albopictus                                       | [55,56]    |
| 2008          | Rural Malaysia                               | 34 confirmed              | IOL             | Suspected vector A. albopictus                                       | [57]       |
| 2008          | Singapore                                    | 231 confirmed             | IOL (E1-226A)   | Principal vector A. aegypti                                          | [58,59]    |
| 2010          | Fréjus, France                               | Two confirmed             | IOL (E1-226A; imported from India) | Suspected vector A. albopictus                                      | [10,60]    |
| 2010          | Ndangui, Gabon (forested region)             | 12 confirmed              | Not determined  | Principal vector A. albopictus                                       | [61]       |
| 2010          | Guangdong Province, China                    | 173 suspected, ten confirmed | IOL             | Suspected vector A. albopictus                                       | [62]       |
| 2011          | Cambodia                                     | 24 confirmed              | IOL             |                                                                      | [63]       |
| 2012          | Bhutan                                       | 78 suspected              | IOL (E1-226A)   |                                                                      | [64]       |
| 2013–present  | Caribbean Sea islands                        | >3,000 confirmed as of March 2014 | Asian           | Principal vector A. aegypti                                          | [18]       |

*IOL strains had E1-226V unless otherwise noted.

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