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Abstract. In January 2005, an epidemic of chikungunya fever broke out in the Comoro Islands and lasted until May 2005. In April, cases were also reported in Mayotte and Mauritius. On Réunion Island, the first cases were reported at the end of April. Surveillance of this epidemic required an adaptive system, which at first was based on active and retrospective case detection around the cases reported, then relied on a sentinel network when the incidence increased. Emerging and severe forms of infection were investigated. Death certificates were monitored. By April 2006, the surveillance estimate was 244,000 cases of chikungunya virus infection, including 123 severe cases and 41 of maternal-neonatal transmission, with an overall attack rate of 35%. Chikungunya infection was mentioned on 203 death certificates and significant mortality was observed. This epidemic highlighted the need for a mutual strategy of providing information on arboviral diseases and their prevention and control between countries in the southwestern Indian Ocean.

INTRODUCTION

Chikungunya virus is a vector-borne alphavirus transmitted to humans by mosquitoes of the genus Aedes. It was first isolated in 1953 during an epidemic that occurred in several neighboring villages of Tanganyika (now Tanzania).1 Within three weeks, the attack rate reached 60–80% and more than 100 villages were infected. Numerous local epidemics have since been reported in Africa2–6 and Asia7–12 that involved a few hundred to several thousand cases. Chikungunya fever is thus developing in an endemico-epidemic pattern in many rural areas of tropical Africa and urban areas of Asia, where it may re-emerge after years or even decades of absence.13–17

Chikungunya infection is generally described as a febrile illness of sudden onset, often accompanied by headache, myalgia, rash, and the characteristic arthralgia that led to its name. Chikungunya means “that which bends up” in the language of the inhabitants of the Tanzanian Makonde plateau. Other less frequent clinical manifestations include nausea, vomiting, and hemorrhagic symptoms such as epistaxis or gum bleeding. Most patients recover quickly without sequelae and acquire immunity against the virus.18 However, chronic forms are sometimes observed, which are characterized by persistent arthralgia that may be incapacitating.19 Neurologic and sensory complications have been reported but are poorly documented.20

On March 16, 2005, the World Health Organization (WHO) sent an alert to the Global Alert and Response Network about an epidemic of chikungunya fever in the Comoro Islands. This was the first known emergence of the virus in the southwestern Indian Ocean region. By mid-April, suspected cases imported from Grande-Comore were reported in Mayotte, and the epidemic reached Mauritius at the end of the month. In Réunion, a serologically confirmed case of chikungunya virus infection imported from Grande-Comore was reported on April 29, and three local suspected clinical cases were reported on May 3. A field survey conducted by the vector control team in the neighborhood of the cases already reported identified numerous additional suspected cases, most of them autochthonous, and three more confirmed cases were reported. These findings were consistent with the presence of viral circulation on Réunion Island, where it persisted until the beginning of year 2007, although with a sporadic pattern. The present work describes the course of this epidemic, one of the largest so far observed.

METHODS

Réunion Island is a French overseas district located in the southwestern Indian Ocean, east of Madagascar (Figure 1). Its population in 2004 was estimated to be 766,000.

Case definitions. Suspected cases were defined as patients with a sudden onset of fever > 38.5°C accompanied by incapacitating joint pain. A confirmed case was defined as a person with positive IgM serologic results and/or the chikungunya genome detected by reverse transcriptase–polymerase chain reaction (RT-PCR). Emerging severe forms of chikungunya were defined as hospitalized patients > 9 days of age with at least one lesional syndrome other than articular, requiring the maintenance of at least one vital function, and a biologically confirmed chikungunya infection. A suspected case of matero-neonatal chikungunya infection was defined as a newborn with biologically confirmed chikungunya infection occurring during the first nine days of life, and was defined as a confirmed case if the mother had had biologically confirmed chikungunya infection during the last week of pregnancy.

Biologic confirmation methods. Serologic confirmation was based on IgM antibody-capture enzyme-linked immunosorbent assay using anti-human IgM as the capture antibody, chikungunya antigen obtained from cellular culture and hyperimmune mouse ascitic fluids detected with peroxidase-conjugated anti-mouse antibodies. Results were considered positive when the optical density of the assay exceeded the mean optical density of negative controls plus 3 standard deviations.26 The RT-PCR was performed using a Superscript™ One-Step RT-PCR with a Platinum Taq kit. (Invitrogen, Carlsbad, CA).21 Physicians were encouraged to seek biologic confirmation of every atypical case.
Community surveillance. After the international WHO alert of March 2005, the local health authorities set up an island-wide operational epidemiologic surveillance system for chikungunya infections as soon as the first cases were identified and reported in April 2005. The objectives of this surveillance system were to monitor epidemic trends, characterize cases, and detect new transmission clusters to provide orientations for prevention and vector control. Until December 2005, it relied on vector control teams, which conducted active and retrospective case-finding around the cases reported by a sentinel physician network, medical laboratories, private practitioners, and patients themselves. After validation, data were seized and duplicates were eliminated in an EpiData database managed by the team of the Cellule Inter-régionale d’Épidémiologie. However, by December 2005, the number of cases exceeded the capacity of this surveillance system, which was no longer able to follow the epidemic trends. Surveillance was then entirely based on the sentinel network. The validity of the epidemic curve was assessed by comparison with a variety of other indicators, including reports from physicians outside the sentinel network, hospital activity, data from health insurance funds, and self-reports by the population to a toll-free telephone line. To extrapolate the total number of cases from the sentinel network data, a coefficient was calculated after confirmation of the correlation between the number of suspected chikungunya cases reported by the 31 network physicians and the number of suspected symptomatic cases identified by the vector control teams during the first 40 weeks of the epidemic. It was thus determined that in Réunion, one case reported by a physician belonging to the sentinel network corresponded to 67 symptomatic chikungunya cases (95% confidence interval = 0–150). From week 51 of 2005 onwards, this central value was applied to the weekly consolidated number of cases reported by the network to estimate the total number of cases.

Mortality and hospital-based surveillance. Mortality data were recorded from the death certificates on which physicians mentioned chikungunya among the causes of death. An active search for emerging severe forms of the disease and for materno-neonatal transmission was also implemented in the island’s hospitals from patients’ medical files.

RESULTS

Epidemic curve. Between March 28, 2005, and April 16, 2006, the surveillance system estimate was 244,000 cases of chikungunya infection, with an overall attack rate of 35%. Figure 2 shows the epidemic curve, which includes two epidemic waves. The peak incidence of the first wave occurred in 2005 during week 19 (May 9–15, 2005) with 450 cases reported. At the beginning of July, the weekly number of cases decreased, stabilized at approximately 100 until the end of September, and gradually increased again in early October. The second and largest wave began at the end of December 2005 with an exponential increase in the number of weekly cases, peaking at week 5 (January 30–February 5, 2006) with more than 47,000 estimated cases.

Case characteristics. As shown in Table 1, the epidemic involved both sexes and all age groups. During the entire study period, the distribution of cases by age group and sex differed significantly from that of the general population, with a predominance of adults and women. Before December 19, 2005, as reported by the active case finding system, the least-affected age group was persons 0–9 years of age and incidence increased continuously up to 89 years of age ($\chi^2 = 2,518$, degrees of freedom [df] = 9, $P < 0.001$). During the subsequent epidemic period, the age distribution of cases reported by the sentinel network was closer to that of the general population. However, significant differences were still noted ($\chi^2 = 89$, df = 9, $P < 0.001$): persons more than 79 years of age, young adults 20–29 years of age, and children less than 10

Figure 1. Map of the western Indian Ocean. Reprinted with permission of Intute Publishers (Oxford, United Kingdom).

Figure 2. Number of weekly incident cases of chikungunya, Réunion Island, March 28, 2005–April 16, 2006 (n = 244,000). *Reported by the active case-finding system between weeks 9 and 50 of 2005 and estimated from the sentinel physician network between week 51 of 2005 and week 15 of 2006.
years of age were the least affected age groups. Women were over-represented in both epidemic periods ($\chi^2 = 217, df = 1, P < 0.001$ and $\chi^2 = 11, df = 1, P < 0.001$) and in all age groups except those less than 20 years of age.

**Clinical symptoms.** The nature and distribution of symptoms has remained stable since the onset of the epidemic. Nearly all cases reported by sentinel physicians had fever (96.3%) and joint pain (96.6%). A few atypical cases without fever or joint pain who did not meet the clinical suspected case definition were included in the analysis because they were biologically confirmed. Headaches (71.2%), muscle pain (61.6%), and cutaneous eruptions (32.5%) were the other signs most often reported.

**Laboratory results.** Over the entire study period (January 2005–May 2006), 16,050 cases were laboratory confirmed, 991 of them by RT-PCR only, 14,727 by serologic analysis only, and 332 by both methods.

**Emerging severe disease.** By April 16, 2006, 123 cases with emerging severe disease suspected by physicians to be associated with biologically confirmed chikungunya infection had been recorded among patients more than 9 days of age. The most frequent complications associated with these confirmed cases were respiratory failure (n = 19), cardiovascular decompensation (n = 18), meningoencephalitis (n = 16) or another central nervous system problem (n = 7), severe acute hepatitis (n = 11), severe cutaneous effects (n = 10), and kidney failure (n = 7). More than half of these serious cases (65 [53%]) involved patients ≥ 65 years of age, and more than one-third (43 [35%]) died.

Also, by April 16, 2006, 55 cases of materno-neonatal transmission were reported in infants less than 10 days of age; 41 of these cases were confirmed and included 10 infants with meningoencephalitis and 1 death.

**Deaths.** By April 16, 2006, 203 death certificates reporting chikungunya infection had been received at the Regional Health and Welfare Office; 121 of these certificates (60%) mentioned the infection among the diseases leading directly to death, whereas the others listed it as a morbid condition that may have contributed to death. According to the 203 certificates, the overall mortality rate associated with chikungunya virus infection was 0.3/1,000 persons, and age-specific mortality rates increased markedly with age. The median age at death was 79 years (Figure 3).

**DISCUSSION**

With an estimated 244,000 cases between March 28, 2005, and April 16, 2006, Réunion Island has had to deal with an exceptionally severe epidemic of chikungunya virus infection. Neighboring islands, including Mayotte, Madagascar, the Seychelles, Comoros, and Mauritius, were also affected. However, because the sensitivity of their surveillance systems seemed to vary, it is difficult to estimate the precise incidence of the epidemic in the area. Since the virus was identified in 1953, it has circulated in many countries of Africa and Asia, sometimes sporadically, but essentially during epidemics, and usually involves a maximum of several hundred cases. The most recent large-scale outbreak occurred in 2002 in the Congo, where after seven years of absence, the virus reappeared and infected 50,000 persons during three separate epidemics.

The epidemic reported here has affected every locality on Réunion Island, both sexes, and all age groups. The two epidemic peaks identified were separated by the austral winter, during which the number of cases decreased considerably, but viral transmission did not cease completely. Several factors may have contributed to the exceptionally dynamic characteristics of the epidemic: the immune status of the population relative to this emerging virus, housing density, vector density and other entomologic characteristics, knowledge of and behavior of the population towards individual protection, and control of larval habitats.

As already observed in Indonesia between 2001 and 2003, children less than nine years of age were one of the least affected age groups, especially during the first epidemic period. Similarly, over-representation of women among the cases has also been reported. One explanation is that men may be more exposed to the vector because of greater home and gardening activities because backyards are especially liable to contain vectorial breeding sites. Another possible explanation might be the differences between clothing of men and women regarding exposure of the skin, especially
the ankles and legs. Similar differences in sex-related attack rates were observed during a limited dengue outbreak that occurred on Réunion Island in 2004. Further studies are underway to determine whether the change in age and sex distribution of cases observed when the epidemic became massive may be explained by a change in the epidemiologic pattern or by the modification of the surveillance system.

Until December 2005, the surveillance system established for this epidemic of chikungunya virus infection was based on active case-finding conducted by vector control teams. Transmission areas could thus be identified even when the incidence was low and geographically heterogeneous. However, this surveillance system and its subsequent adaptation when the epidemic reached massive proportions were based on symptomatic suspected cases. The real number of infected persons and the resulting herd immunity may therefore have been underestimated by the omission of asymptomatic forms. The ratio of the total number of cases to the number reported by sentinel network physicians may have changed during the course of the epidemic. Despite these limitations, the data obtained made it possible to describe the epidemiologic trends, target disease control measures, and generate research hypotheses.

The most frequent clinical symptoms, sudden onset of high fever and joint pains, fitted the definition of suspected cases. Approximately 3% of the reported cases did not meet this definition, perhaps in part because of errors in reporting, but mainly because laboratory testing confirmed some atypical cases because physicians were encouraged to seek laboratory confirmation if in doubt. Thus, it cannot be excluded that some of these confirmed cases were consulting for unrelated problems and happened to have had an asymptomatic chikungunya virus infection in the recent past.

Only one study has dealt with neurologic effects in patients infected with chikungunya virus. During the epidemic on Réunion Island, other severe forms of the disease were recorded in addition to neurologic forms. These forms include respiratory, cardiovascular, hepatic, cutaneous, and renal syndromes, although cause-and-effect relationship has not been ascertained. Whatever relationship they might have with the virus, these forms only account for a tiny fraction of the total number of estimated cases. Clinical studies are under way to determine the physiopathologic processes involved. At this stage, however, health professionals dealing with a large outbreak of infection with chikungunya virus should be aware that such forms might emerge, as occurred on Réunion Island, where they greatly affected the work of intensive care units.

Conversely, before this epidemic, mortality linked to infection with chikungunya virus had never been reported. In January 2006, numerous death certificates, mainly concerning the elderly, began to mention chikungunya, either among the diseases that led directly to death or as an associated morbid event. It is nonetheless difficult to determine to what extent these deaths can be attributed to chikungunya virus in the absence of autopsies that might have confirmed a direct link between death and infection. Studies of global mortality were conducted to compare the number of deaths recorded on Réunion Island during this epidemic with the number of deaths expected, which were estimated from mortality data for previous years that included demographic information. These studies confirmed significant excess mortality that coincided with the epidemic incidence peak in 2006.

Vector control of *Aedes albopictus*, which was identified as the main epidemic vector, continues throughout the island and combines measures against both adult mosquitoes and larvae. Deltamethrin is the insecticide currently used against adult mosquitoes, and has replaced fenitrothion, which was used initially. Larval control is mainly based on mechanical destruction of breeding sites; when this not possible, *Bacillus thuringiensis* israelensis, a biologic larvicide that has replaced temephos, is used. Fenitrothion and temephos were replaced in February 2006 to reduce hazards for non-professional users and possible damage to the environment when vector control activities became massive. These activities, combined with individual measures of protection and community action in the management of solid waste and of containers that may serve as breeding sites in a tropical climate, are the fundamental measures of control of chikungunya virus on Réunion Island.
Their impact on the course of the epidemic remains to be evaluated. More rigorous entomologic surveillance and vector control appear to be critical for the reduction of the health risks linked not only to chikungunya virus but also to other arboviruses likely to emerge on Réunion Island because this island is accessible to their introduction.

The scale of the epidemic on Réunion Island has required the adaptation of the surveillance system. Further adaptation will be necessary when the number of cases decreases. An early detection system for cases of infection with chikungunya virus will be an important issue once the incidence on Réunion Island decreases to a low level. With this in view, an automated system of teletransmission is under study to facilitate and accelerate the communication of reports by local physicians.

At the same time, research is under way to improve understanding of the characteristics of the epidemic and monitor its repercussions, especially the course of chronic forms of infection and of children born to infected mothers. At the end of the epidemic, a seroprevalence survey will be conducted to estimate the proportion and characteristics of the population infected by chikungunya virus, including its asymptomatic forms.

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