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Reemergence of an Unusual Disease: The Chikungunya Epidemic

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Since the beginning of 2006, a crippling mosquito-borne disease has shown an explosive emergence in nations in the Indian Ocean area. By March 7, 2006, 157,000 people had been infected in the French island La Réunion, and the disease had spread to the islands of Seychelles, Mauritius, and Mayotte (French). Subsequently, the disease appeared in India, China, and European countries. The World Health Organization is taking measures to assist in fighting the epidemic. This article describes the disease, its recent emergence, and the current epidemic.
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Health officials meeting in Atlanta, Georgia, in March 2006 for a 4-day conference on emerging infectious diseases discussed the increased incidence of animals serving as the leading source of new human diseases and issued a warning that more trained professionals and resources will be needed to combat them. Lonnie King, acting director of a new U.S. research office for studying such diseases, is reported as noting that three-quarters of all new human diseases in the past 3 decades and 80 percent of microbes considered among the most dangerous possible bioterrorist weapons originated in animals.[1] Among these diseases are such global public health threats such as acquired immune deficiency syndrome (AIDS), severe acute respiratory syndrome, avian flu, and, now, the little-known chikungunya, a virus originating in monkeys. Since the beginning of 2006, chikungunya, a crippling mosquito-borne disease, has shown an explosive emergence in nations in the Indian Ocean area. An increased incidence of the disease was reported first in February of the previous year in the French island of La Réunion, with sporadic but regular cases being reported until December. During the next month, however, the incidence increased considerably, causing concern in Paris, where Minister Baroin held a news conference to announce that French authorities were sending military troops to the island to reinforce efforts of 2800 health care workers, administrative staff, and other personnel who were working to eradicate the virus.[2] This article provides a review of the recent emergence and current epidemic and a brief description of the disease.

Historical Incidence of Chikungunya

The first epidemic of the disease was recognized in East Africa in 1952 to 1953.[3] Between 1954 and 1986, the chikungunya virus was implicated as the cause of epidemics in Asian countries, including the Philippines, Thailand, Cambodia, Vietnam, India, Burma, and Sri Lanka. Although the disease later all but disappeared in India, Sri Lanka, Burma,[4] and Bangkok,[5] outbreaks and sporadic cases continued to occur in Thailand and the Philippines. Epidemics were documented in the Philippines in 1954, 1956, and 1968.[6,7] Serosurveys suggested that virus activity occurred in the central and southern part of the archipelago.[8]

Between 1982 and 1985, the virus spread into Indonesia for the first time, with outbreaks occurring in South Sumatra, Java, Kalimantan, Sulawesi, Timor, Nusatengarra, and the Mollucas Islands.[9] In 1986, three cases of chikungunya fever were diagnosed among U.S. Peace Corps volunteers stationed in the Republic of the Philippines. The three cases, the first ones reported from the Philippines since 1968, were diagnosed using an IgM antibody-capture enzyme-linked immunosorbent assay. One case occurred in Mindanao, one of the southernmost islands of the archipelago; the second occurred on Cebu, one of the islands in the central portion; and the third case occurred on the island of Masbate, also in the central part of the country but north of Cebu.[10]

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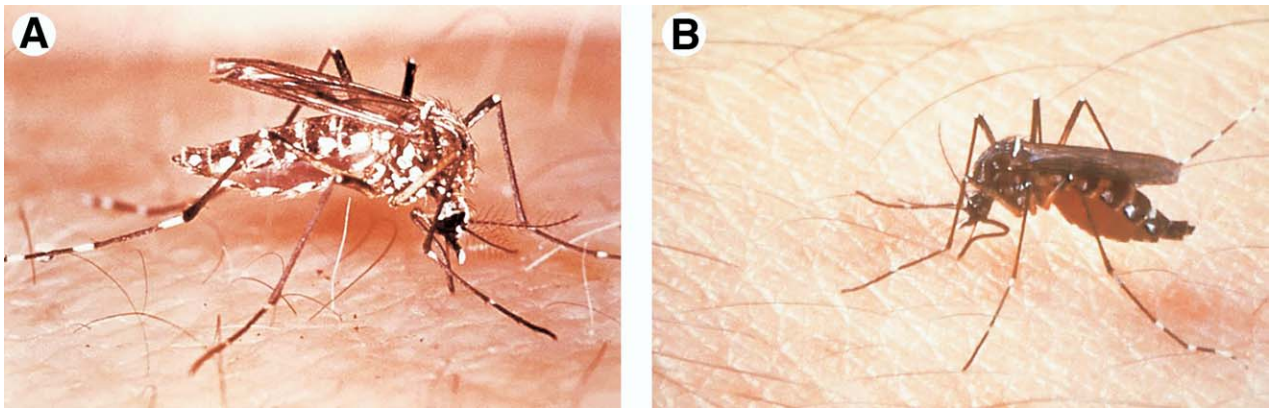

Figure 1 (A) This female *Aedes aegypti* mosquito is shown here after landing on a human host, as it is about to obtain a blood meal. The *Aedes aegypti* mosquito is a known transmitter of Dengue fever, yellow fever, and chikungunya fever. The viruses are transferred to the host when bitten by a female mosquito. (Courtesy of the CDC/WHO, ID# 2740.) (B) A female *Aedes aegypti* mosquito rests on the skin of a human host while she acquires a blood meal. (Courtesy of the CDC and Robert S. Craig, ID#: 6923.) (Color version of figure is available online.)

Three epidemics have been reported in Senegal, in 1966,[11] 1982,[12] and 1999.[13] Between 1972 and 1999, 178 chikungunya virus strains were isolated from mosquitoes caught in Kedougou. Four major sylvatic occurrence of chikungunya virus were observed in 1975, 1979, 1983, and 1992. The major sylvatic vectors (*Aedes furcifer, Aedes taylori*, and *Aedes luteocephalus*) are the same as those for yellow fever virus. The sylvatic form (*Aedes aegypti formosus*) does not appear to be involved in transmission because no strain of the virus has ever been isolated from it. The only domestic vector of yellow fever identified, *Aedes aegypti* (Figs 1A and B), is also the only mosquito species found associated with chikungunya virus in human habitats of Senegal. Researchers also observed periods of 3 or 4 years during which no viruses were isolated, except for the 1987 to 1992 period. In all of Senegal, 185 strains of the virus were isolated from 13 mosquito species.[13]

More recently, 24 distinct outbreaks of probable chikungunya etiology were identified in Indonesia between September 2001 and March 2003. These outbreaks, 13 of which were based on clinical observations alone and 11 confirmed by serological/virological methods, were the first incidences after almost 20 years. The incidences in Bogor and Bekasi, where the rates were 2.8/100 and 6.7/100, respectively, occurred during the rainy season after reported increased densities of *A. aegypti* and *Aedes albopictus* mosquitoes (Fig. 2A and B).[14]

During this same period of time, incidents were reported in Southeast Asia, where in 2001 many countries neighboring Malaysia had outbreaks of human infections. At that time, outbreaks had not occurred in Malaysia since the one that occurred between December 1998 and February 1999, although concern was expressed that the disease might be reintroduced into the country by the movement of migrant workers.[15] The 1999 outbreak had involved 51 confirmed cases in a densely populated urban area.[9] That same year (2001), the first surveillance conducted in India since the previous epidemic of 1971 revealed widely circulating low-virulent chikungunya virus in *A. aegypti* mosquitoes as a possible explanation for an epidemiological pattern of the disease in that region.[16]

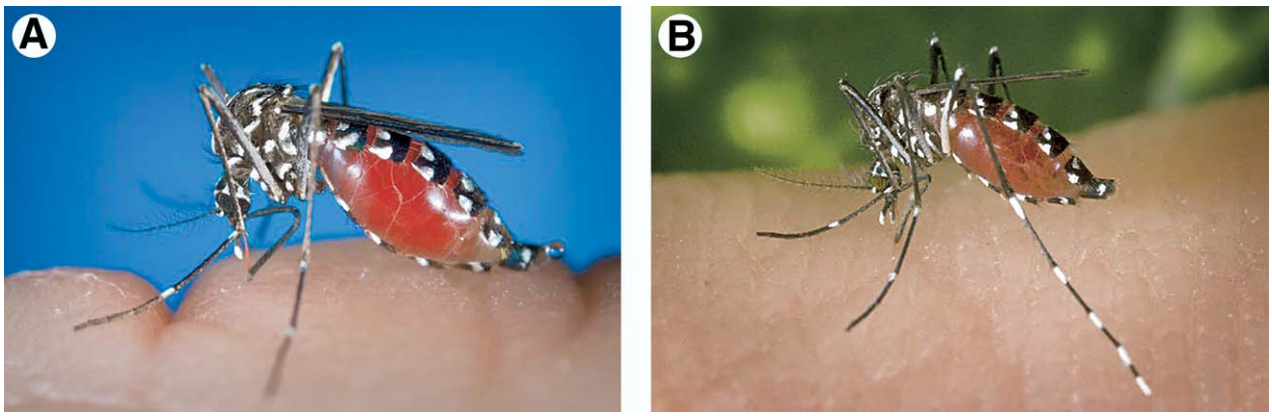

Figure 2 (A) This female *Aedes albopictus* mosquito is feeding on a human blood meal, thereby becoming engorged with blood. (Courtesy of the CDC and James Gathany, ID #4735.) (B) A blood-engorged female *Aedes albopictus* mosquito is feeding on a human host. (Courtesy of the CDC, ID#: 2167.) (Color version of figure is available online.)

The first documentation of epidemic transmission in Yogyakarta, Indonesia since 1982 was reported in 2004.[17] Similarly, a 39-year period without any isolation of the virus was broken by a resurgence of incidence in 2004 in Kinshasa Democratic Republic of the Congo, where the virus was isolated in sera from nine patients with clinical symptoms.[18]

Current Epidemic of Chikungunya

An extensive outbreak of chikungunya fever was reported first on the French island of La Réunion, where between March 28, 2005, and January 15, 2006, an estimated 10,750 suspected cases were reported and 2424 were confirmed by laboratory analysis. A limited peak first occurred in mid-May 2005, the number of cases then decreasing with the onset of the southern hemisphere winter.[19] From mid-July, the incidence remained stable for longer than 3 months before rising again, initially moderately, at the beginning of October and increasing exponentially in December. In addition to the increased incidence, as of January 27, 2006, 15 cases of meningoencephalitis had been reported, 12 of which were microbiologically confirmed. Six of the cases were newborns, with mother-to-child transmission strongly suspected. Six adult cases also were reported and confirmed by the national reference center in elderly patients.[20]

Despite the spraying of pesticides that had been performed throughout the French island of Réunion, 15,000 persons were afflicted in the last week of January, and 20,000 more came down with the disease during the first week of February. By February 8, 2006, French officials had reported that approximately 70,000, nearly one in 10, inhabitants of the island had been infected, and 300 French soldiers were being sent to get the outbreak under control.[2] On February 26th and 27th, Prime Minister Dominique de Villepin visited the island and promised further health research would be implemented, but despite all the efforts exerted, the epidemic continued spreading without so much as slowing (Fig. 3).[21] By the first week of April, the entire island was affected, with particularly high activity occurring in the southern parts. Approximately 236,000 cases were estimated to have occurred, although the weekly number was beginning to decline.[22]

By the first week in March, the virus had spread to the islands of Seychelles, Mauritius, and Mayotte (French). In Seychelles, approximately 2500 cases were reported during January and the early part of February, with the number doubling each week. By the first week in March, that number had jumped to more than 8800 suspected cases.[23] Mauritius, the closest neighbor of Réunion, had reported more than 2500 cases by March 7,[22] the day that Lee Jong-Wook, Director-General of the World Health Organization (WHO), went to Mauritius to meet with Mauritian government officials to discuss how the United Nations (UN) agency could assist in fighting the epidemic.[23] By March 17, that number had increased to 6000 suspected cases and 1200 confirmed cases.[23] On the island of Mayotte, the outbreak did not start until late January, but within 6 weeks 1000 cases had been registered.[21] The number of suspected cases had increased to 2833 on March 10, 2006.[23] The governments of both islands initiated harsh measures, with spraying and fogging machines and some 100,000 liters of insecticides being ordered from abroad once the epidemic spread, but the disease only continued to spread.

Figure 3 French Prime Minister Dominique de Villepin (right) visits La Réunion to observe the campaign launched against chikungunya fever. Copyright Beno"t Granier/Matignon/afrol News (Courtesy of Afrol News). (Color version of figure is available online.)

The worst fears of regional health workers, that the outbreak would spread to the large island of Madagascar, were realized in March. The outbreak, thought to have started sometime in February, was concentrated on the eastern coastal city of Toamasina. Concerns were raised that it might spread across the island and find a permanent refuge there, thereby rendering the eradication of the virus from the Indian Ocean region close to impossible.[21]

In Andhra Pradesh state of India, a mixed outbreak of chikungunya with sporadic cases of dengue has been reported. Between December 1, 2005, and February 17, 2006, 5671 cases of fever with arthralgia were reported. A high density of *A. aegypti* mosquitoes also was observed. During the first 2 weeks of March, more than 2000 cases of chikungunya were reported from the Malegaon town in Nasik district, Maharashtra state, India. Another 4904 cases of fever associated with myalgia and headache were reported between February 27 and March 5, 2006 in Orissa state, India. All of the signs are consistent with an arbovirus outbreak.[23]

Malaysia also reported the first outbreak since 1999, when 27 people were infected in Port Klang, Selangor. In March 2006, the Health Department of Malaysia was alerted by a general practitioner concerning 30 people who were found to have symptoms similar to those of chikungunya infections. Laboratory tests confirmed that the cases were chikungunya, and fogging, cleaning, and other public health strategies were implemented.[24]

The first ever case of chikungunya in Hong Kong SAR was reported on March 31. The case of a 66-year-old Chinese

man was seen in the Prince of Wales Hospital Infectious Diseases clinic on March 24, after returning from a 1-week stay in Mauritius. The case was confirmed by polymerase chain reaction and sequencing at the Public Health Laboratory Centre.[25] "Imported " cases also have been reported in France, Germany, Switzerland, Norway, China, and French Guyana.

Chikungunya: The Disease "That Bends Up"

Chikungunya virus is a member of the genus Alphavirus in the family *Togaviridae*. It was isolated first in 1953 by Ross during an epidemic of dengue that occurred in the Newala district of Tanzania.[26] The virus is so-called because in Swahili the term means "stooped over,"[27] "that which bends up,"[28] or "walking bent over,"[22] reflecting the characteristic symptom of arthralgia.

It is related most closely seriologically to o'nyong-nyong virus and is a member of the Semliki Forest antigenic complex. Two distinct strains, one from Western Africa and the other from southern and Eastern Africa, as well as Asia, have been delineated. The different genotypes of the latter strain exhibit differences in their transmission cycles: in Asia, the virus appears to be maintained in an urban cycle with *A. aegypti* mosquito vectors, whereas transmission of the virus in Africa involves a sylvatic cycle, primarily with *Aedes furcifer* and *Aedes africanus* mosquitoes. Phylogenetic trees demonstrate that the virus originated in Africa and subsequently was introduced into Asia.[29] It has been shown to be distinct from o'nyong-nyong virus.[29,30] In 2002, the complete genomic sequence of chikungunya virus was determined: the complete genome was 11,805 nucleotides in length, excluding the t' cap nucleotide, an I-poly(A) tract and the 3′ poly(A) tail; it comprised two long open reading frames that encoded the nonstructural (2474 amino acids) and structural (1244 amino acids) polyproteins.[30]

Hosts

Chikungunya virus is able to replicate in a broad spectrum of vertebrate species. Newborn mice, hamsters, rats, rabbits, guinea pigs, and kittens all have been infected by subcutaneous inoculation of field strains of the virus. Neutralizing or hemagglutination-inhibition antibodies to chikungunya have been recovered from sera obtained from ungulates. Verbet monkeys and baboons are infected readily, and rhesus monkeys infected by intravenous and intramuscular inoculation had viremia titers in excess of 10^7 mouse LD_{50}. Subhuman primate populations are affected in epizootics that involve large numbers of the susceptible population, followed by disappearance of the virus. Hence, chikungunya virus possibly is maintained in wildlife populations by its constantly moving epizootic activity, much as respiratory and enteric virus infections are maintained in humans.[31] Human acquisition occurs typically by the bite of an infected *A. aegypti* mosquito, although other competent mosquito vectors exist.[27] Epidemics are sustained by human-mosquito-human transmission.[28]

Clinical Manifestations

Clinical symptoms, which manifest after an incubation period of 2 to 7 days, include chills and fever, headache, nausea, vomiting, arthralgia, photophobia, and rash.[27,28,31] The victim suffers significant pain in the joints (ankles, writs) that can persist for several weeks.[27] In contrast to dengue, chikungunya has a briefer febrile episode, persistent arthralgia in some cases, and the fortunate absence of fatalities.[28] Some patients have had hemorrhagic symptoms, such as bleeding from the nose or gums. Age plays a role in the manifestation of symptoms: infants experience an abrupt onset of fever, followed by flushing of the skin, a generalized maculopapular rash that appears 3 to 5 days later, and, frequently, conjunctival infection, swelling of the eyelids, pharyngitis, and symptoms of upper respiratory tract disease; older children have, in addition to acute fever, headache, myalgia, and arthralgia involving various joints; and adults have arthralgia or arthritis as the most conspicuous feature.[31]

Diagnosis

The diagnosis depends on demonstrating a significant increase in antibody after an illness. Neurtralizing and hemagglutination-inhibition antibodies usually are present in samples collected 2 weeks or more after the onset of fever. Clinical diagnosis can be made based on the prevalence of the disease in the area and on clinical signs noted above. Differential diagnosis includes the viral causes of dengue fever syndrome. Although the symptoms of chikungunya are similar to those of dengue, distinct differences exist: chikungunya infections are shorter in duration; a terminal maculopapular rash, arthralgia or arthritis, and conjunctival infection are more common; and hemorrhagic phenomena rarely occur.[31]

Treatment

Currently, no vaccine is available. Treatment is symptomatic only and includes nonsteroid antiinflammatories and anonsalicyclic analgesics. Bed rest is advised during the febrile period, with provision of antipyretics or cold sponging to keep the body temperature less than 40° C (104° F). Mild sedation may be required to control pain. Febrile convulsions should be treated with Phenobarbital given intravenously or orally and continued until the temperature returns to normal. Severe or intractable convulsions may respond to intravenous diazepam. Children who cannot take oral fluids may need intravenous rehydration. Patients with severe hemorrhagic phenomena should be examined for underlying hemostatic disorders.[31]

Prognosis

In addition to hemorrhage, neurologic and myocardial involvement has occurred in some adults, who also may experience arthralgia for weeks. The pain typically shifts from one joint to another and is most severe in the morning. Ankles,

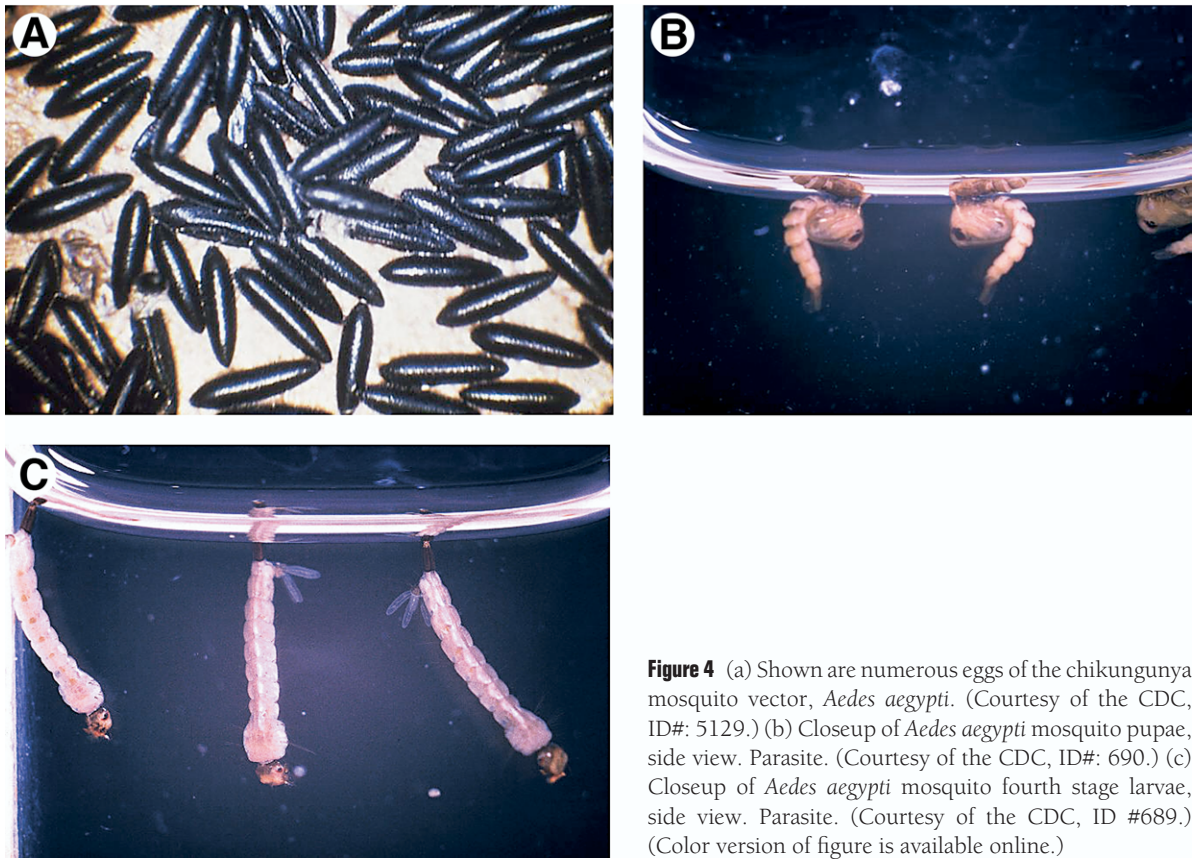

Figure 4 (a) Shown are numerous eggs of the chikungunya mosquito vector, *Aedes aegypti*. (Courtesy of the CDC, ID#: 5129.) (b) Closeup of *Aedes aegypti* mosquito pupae, side view. Parasite. (Courtesy of the CDC, ID#: 690.) (c) Closeup of *Aedes aegypti* mosquito fourth stage larvae, side view. Parasite. (Courtesy of the CDC, ID #689.) (Color version of figure is available online.)

wrists, and fingers frequently swell; the sequelae may resemble rheumatoid arthritis in older patients.[31]

Prevention

Recommended strategies for minimizing exposure to mosquito bites include use of antimosquito devices (insecticide-treated bed nets, coils, smudge pots, spray, and repellents) and wearing long-sleeved shirts and pants. Mosquito repellent based on a 30 percent DEET concentration is recommended. For children younger than 3 months, repellents are not recommended; instead, insecticide-treated bed nets should be used.[22]

A. aegypti mosquitoes deposit their eggs in any outdoor container that can hold water (Fig. 4a–c). These containers include large uncovered jars for drinking water and refuse receptacles such as bottles and food tins. Hence, measures to be taken at the community level include reducing the prevalence of mosquito breeding sites by removing all open containers with stagnant water in and around buildings and/or treatment with larvicides. The quickest way to effectively reduce the mosquito population and to interrupt the transmission to use space spraying application, which knocks down the mosquitoes instantly. Aerial spraying with insecticides may be required in certain areas. The WHO recommends applying the appropriate products in intervals that are shorter than the incubation period of the pathogen in the vector and in accordance with the generation cycle of the vector.[22] Measures must be taken four to five times at 5-day intervals during the "attack phase." This approach ensures that the full generation cycle of the mosquitoes is broken. Thereafter a maintenance program (larvicide and periodical space spraying) should be followed to keep the mosquito population under control.[32]

References

1. Lauerman J. Scientists fear increase in animal diseases jumping to humans. Bloomberg.com, March 23, 2006
2. Chikungunya epidemic spreads in Indian Ocean. afrolNews, 8 February 2006. Available at http://www.afrol.com/articles/18025. Accessed April 26, 2006
3. Robinson MC: An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-1953. I. Clinical features. Trans Royal Society Trop Med Hyg 49:28-32, 1955
4. Pavri K: Disappearance of Chikungunya virus from India and South-East Asia. Trans R Soc Trop Med Hyg 80:491, 1986
5. Burke DS, Nisalak A, Nimmannitya S: Disappearance of Chikungunya virus from Bangkok. Trans R Soc Trop Med Hyg 79:419-420, 1985
6. Campos LE, San Juan A, Cenabre LC, et al: Isolation of chikungunya virus in the Philippines. Acta Med Philippina 5:152-155, 1969
7. Macasaet FF: Further observation on chikungunya fever. J Philippines Med Assoc 46:235-242, 1970
8. Tesh RB, Gadjusek DC, Garruto RM, et al: The distribution and prevalence of group A arbovirus neutralizing antibodies among human populations in Southeast Asia and the Pacific Islands. Am J Trop Med Hyg 24:664-675, 1975
9. Mackenzie JS, Chua KB, Daniels PW, et al: Emerging viral diseases of Southeast Asia and the Western Pacific. Emerg Infect Dis 7:497-504, 2001
10. Centers for Disease Prevention and Control: Chikungunya fever among U.S. Peace Corps volunteers—Republic of the Philippines. MMWR 35:573-574, 1986
11. Roche S, Robin Y: Infections humaines par le virus Chikungunya a

Rufisque (Senegal) Octobre-Novembre 1966. Bull Soc Med Afr Noire League Fr 12:490-496, 1967
12. Saluzzo JF, Cornet M, Digoutte JP: Une poussee epidemique du au virus Chikungunya dans l'ouest du Senegal en 1982. Dakar Med 28: 497-500, 1983
13. Diallo M, Thonnon J, Traore-Lamizana M, et al: Vectors of chikungunya virus in Senegal: current data and transmission cycles. Am J Trop Med Hyg 60:281-286, 1999
14. Laras K, Sukri NC, Larasati RP, et al: Tracking the re-emergence of epidemic chikungunya virus in Indonesia. Trans R Soc Trop Med Hyg 99:138-141, 2005
15. Lam SK, Chua KB, Hooi PS, et al: Chikungunya infection—an emerging disease in Malaysia. Southeast Asian J Trop Med Public Health 32:447-51, 2001
16. Mourya DT, Thakare JR, Gokhale MD, et al: Isolation of chikungunya virus from Aedes aegypti mosquitoes collected in the town of Yawat, Pune District, Maharashtra State, India. Acta Virol 45:305-309, 2001
17. Porter KR, Tan R, Istary Y, et al: A serological study of Chikungunya virus transmission in Yogyakarta, Indonesia: evidence for the first outbreak since 1982. Southeast Asian J Trop Med Public Health 35:408-415, 2004
18. Pastorino B, Muyembe-Tamfum JJ, Bessaud M, et al: Epidemic resurgence of Chikungunya virus in Democratic Republic of the Congo: identification of a new central African strain. J Med Mirol 74:277-282, 2004
19. Paquet, C, Quatresous, I, Solet, J-L, et al Chikungunya outbreak in Reunion: epidemiology and surveillance, 2005 to early January 1006. Bulletin Epidemiologique Hebdomadaire. Special issue, January 31, 2006 (translated and published in Eurosurveillance 11: 2 February 2006. Available at: http://www.invs.sante.fr/beh/1006/hs_310106hs_310106.pdf. Accessed April 26, 2006
20. E-alert. Chikungunya outbreak in Reunion, a French 'overseas departement'. Eurosurveillance 11:January 27, 2006. Available at http://www.eurosurveillance.org/ew/2006/060126.asp#1. Accessed April 26, 2006
21. Mosquitoes in Paradise Chikungunya epidemic spreads. afrolNews, 7 March, 2006. Available at: http://www.afrol.com/articles/18363. Accessed April 26, 2006
22. European Centers for Disease Control. Chikungunya fever—information for travelers. 10 April 2006. Available at http://www.ecdc.eu.int/outbreaks/Chikungunya_reunion.php. Accessed April 26, 2006
23. World Health Organization. Chikungunya and Dengue in the southwest Indian Ocean. Epidemic and Pandemic Alert and Response. Geneva, WHO, 17 March 2006.
24. Doyle, P. Chikungunya Virus Now Spread to Malaysia. Rense. Available at http://www.rense.com/general70/chikd.htm. Accessed April 26, 2006
25. Tang JW-T: Chikungunya-China (HongKong)-confirmed. ProMED-mail post. International Society for Infectious Diseases.
26. Ross RW: The Newala epidemic. III The virus: isolation, pathogenic properties and relationship to the epidemic. J Hyg 54:177-191, 1956
27. World Health Organization. Chikungunya in La Reunion Island (France). Epidemic and Pandemic Alert and Response. Available at http:www.who.org. Accessed April 26, 2006
28. Definition of Chikungunya. MedicineNet. Available at http://www.MedicineNet.com. Accessed April 26, 2006
29. Powers AM, Brault AC, Tesh RB, et al: Re-emergence of Chikungunya and O-nyong-nyong viruses: evidence for distinct geographical lineages and distant evolutionary relationships. J Gen Virol 81:471-479, 2000
30. Khan AH, Morita K, Parquet MMC, et al: Complete nucleotide sequence of chikungunya virus and evidence for an internal polyadenylation site. J Gen Virol 83:3075-3084, 2002
31. Halstead SB. Chikungunya, in Feigin RD, Cherry JD, Demmler GJ, et al (eds): Textbook of Pediatric Infectious Diseases (ed 5). Philadelphia, PA, Saunders, 2004, pp 2178-2184
32. Bayer CropScience coordinates with WHO the fight against Chikungunya. Available at http://www.bayercropscience.com/bayer/cropscience/cscms.nsf/id/NR060317_EN?open&ccm=400. Accessed April 26, 2006