Chikungunya: A Paradigm of Emergence and Globalization of Vector-Borne Diseases

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KEYWORDS

• Chikungunya • *Aedes albopictus* • Arthritis • Tenosynovitis
• Travel • Emerging disease • Globalization

After a period of 50 years of silence, a disease with an unpronounceable name, ''chikungunya'' (CHIK), has recently become a medical reality that has reached the public throughout the world.[1–3] Although the CHIK virus (CHIKV) is not a newcomer among tropical viruses, it was unknown by most people in the world, including medical doctors. However, during the second half of the twentieth century, CHIKV has been found to be responsible for widespread outbreaks of a two-stage disease, consisting of an intense, acute stage commonly followed by a long-lasting disabling polyarthritis.[4] Before 2000, only a few benign, imported infections had been occasionally observed in North American and European travelers.[5–7] Therefore, until recently CHIKV had generated only minor interest in the global medical community and no fear in developed countries, in contrast to other arboviruses, such as dengue and West Nile.[8] However, the recent large-scale outbreaks that successively swept through eastern Africa, the western Indian Ocean islands, India, and the eastern Indian Ocean Islands demonstrated the strength of this emerging human pathogen.[3] With millions of people

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infected over the few past years,[3,9] the classic clinical features of CHIK have been rediscovered. Moreover, its dramatic emergence in developed countries such as Reunion Island (a French island in the western Indian Ocean) and India rapidly led to the identification of unexpected clinical presentations and enlarged our knowledge of the epidemiology, virology, and pathophysiology of this fascinating arbovirus.[10,11]

Since 2006, CHIKV infection has also been identified in an unprecedented number of travelers (more than 1000) after they returned home from epidemic areas.[12] Among CHIKV-infected travelers were some with high-grade viremia, who returned to countries where competent vectors are present, raising serious concern for the globalization of the disease.[13] Indeed, *Aedes albopictus*, the Asian tiger mosquito (**Fig. 1**), the main vector in Reunion, is also indigenous to Southeast Asia and the western Pacific and Indian Oceans, and has recently spread to Africa, the Middle East, Europe, and the Americas.[14] The outbreak that developed in Italy in August 2007 demonstrated the reality of this threat.[15] Given its explosive spread, severe clinical burden, and negative impacts on health, socioeconomic, and political systems in epidemic countries, CHIKV is a major concern in most African and Asian areas. Because CHIKV infection is an arboviral disease that all physicians should be prepared to encounter, the authors review here the different aspects of this reemerging disease, focusing on the lessons from recent and ongoing outbreaks.

WHAT WAS KNOWN ABOUT CHIKUNGUNYA VIRUS FROM THE PAST CENTURY
A Neglected Arboviral Infection in Africa and Asia

CHIKV infection was first described after outbreaks of febrile polyarthritis in Tanzania in 1952 and 1953.[16,17] The name ''chikungunya'' comes from Kimakonde, a vernacular language in Tanzania and Mozambique. It means ''that which contorts or bends up'' and refers to the contorted posture of infected patients suffering with severe joint pain and dramatic limited ability to ambulate in daily life.[16,17] In Congo, people call the disease ''buka-buka,'' which can be translated as ''broken-broken.''[18]

CHIKV was first isolated from the serum of a febrile human in Tanzania (formerly Tanganyika) in 1953 during the epidemic investigation.[17,19] Thereafter, given its ability to incapacitate those infected, military laboratories studied CHIKV as a natural threat and as a putative biological weapon.[20] CHIKV belongs tot he *Alphavirus* genus and *Togaviridae* family. Like all alphaviruses, CHIKV has a genome consisting of a linear, positive-sense, single-stranded RNA molecule.[11] Other alphaviruses express antigenicity similar to CHIKV. Most of them also share its tropism for joints and induce similar polyarthralgia/arthritis (**Table 1**).[21] Despite numerous experimental studies on other alphaviruses, the pathophysiology of chronic rheumatism following alphaviral infections remains unclear.[22]

Fig. 1. *Aedes albopictus*, the Asian tiger mosquito. (*Adapted from* Parola P, de L X, Jourdan J, et al. Novel chikungunya virus variant in travelers returning from Indian Ocean islands. Emerg Infect Dis 2006;12:1493–9.)

Table 1
Epidemiologic characteristics of arthritogenic alphaviruses

Virus	Main Vectors	Main Areas of Endemicity
CHIKV	*Aedes aegypti, A albopictus*	Africa, India, Southeast Asia, Indian Ocean
O'nyong-nyong virus	*Anopheles* spp	Africa
Ross River virus	*Aedes* spp; rarely, *Culex* spp	Australia, South Pacific
Barmah Forest virus	*Aedes* spp	Australia
Semliki Forest virus	*Aedes* spp	Africa
Sindbis group viruses	*Culex* spp	Africa, Asia, Australia, Northern Europe
Mayaro virus	*Aedes* spp*; Haemagogus* spp	South America

Between the 1960s and 1990s, CHIKV was isolated repeatedly in numerous focal outbreaks and clusters in numerous countries in central, southern, and western Africa (**Fig. 2**).[11] After spreading to Asia (the first documented outbreak was in 1958 in Thailand), frequent CHIKV outbreaks were reported in India, Pakistan, and Southeastern Asian countries from the 1960s to the end of the last century.[11,23]

As CHIK struck focally in only a few tropical developing countries and was anecdotally diagnosed in travelers,[5–7] interest in CHIKV epidemiology was limited before 2000. Most outbreaks had a rapid progression, affected hundreds to a few thousand persons, and were followed by long, silent interepidemic periods. Nevertheless, in Africa, CHIKV infection was endemic, with sporadic clusters of cases and a tendency to cause small outbreaks.[24–26]

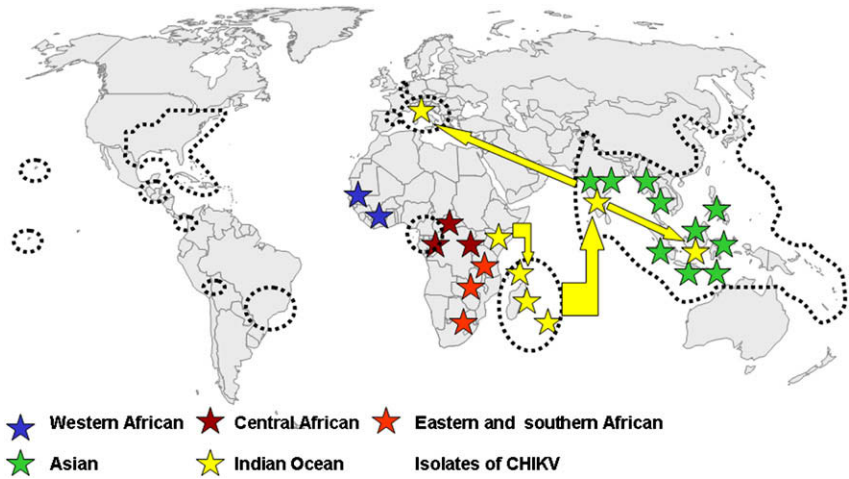

Fig. 2. Estimated global distribution of *Aedes albopictus* (*areas enclosed in dotted lines*) and distribution of CHIKV (*stars*), including the Indian Ocean variant responsible for the 2006 outbreak (*yellow stars*). The color of the stars reflects the main evolutionary lineages of the CHIKV. Arrows indicate the spread of the recent large-scale outbreak. (*From* Parola P, de Lamballerie X, Jourdan J, et al. Novel chikungunya virus variant in travelers returning from Indian Ocean islands. Emerg Infect Dis 2006;12:1493–9; with permission.)

Two epidemiologic profiles of CHIKV infection were described. In Africa, CHIKV was known to be zoonotic and maintained in a sylvatic cycle involving wild primates, rodents, and forest-dwelling *Aedes* spp mosquitoes (particularly members of the *A furcifer-taylori* group).[11,27] The sylvatic mosquito densities that increase with periods of heavy rainfall influenced the epidemiologic pattern of CHIV outbreaks in Africa.[11]

On the other hand, in Asian countries, CHIKV was known to be transmitted by the urban *Aedes aegypti* mosquito (the urban, peridomestic, anthropophilic vector of dengue), with an epidemiologic cycle resembling that of dengue: assumed absence of animal reservoir, human-to-human transmission by mosquito bites, and potential for major epidemics. Other abundant, common, peridomestic species, including *A albopictus,* which colonizes artificial and natural containers in suburban and rural areas, have been suspected in supplementing *A aegypti* in the transmission of CHIKV.[11,27]

Febrile Polyarthralgia Followed by Long-Lasting Rheumatism

Since the first description of the disease in the 1950s, knowledge of its clinical features has been based on the descriptions from South African teams after local epidemics in the late 1970s.[28–30] After a short incubation (2–6 days), two successive stages of the disease have been identified. The acute stage is characterized by a sudden onset of symptoms. Infection is frequently associated with high fever and, synchronous or not, incapacitating polyarthritis and skin manifestations.[29,30] In tropical areas, confusion with dengue fever was common, although the two diseases present characteristic clinical signs (**Table 2**). As early as 1955, Robinson proposed distinguishing CHIKV infection from other epidemic illnesses with febrile diffuse pain, and identified lack of pain when moving the eyes and extended duration of joint pain as more characteristic of CHIKV infection.[19] General manifestations of CHIK are not specific: high fever that decreases only slightly with paracetamol (acetaminophen), intense asthenia, and diffuse myalgia. Patients are often confined to bed because of coexisting multiple inflammatory arthralgias or arthritides. This acute rheumatism is mostly bilateral, symmetric, and cumulative within few days, and it especially involves the peripheral joints: hands, wrists, feet, and ankles. Nevertheless, all joints can be painful, and spinal pain is also frequent. Skin manifestations can include maculopapular rash, diffuse hyperemia, and edema of the face and extremities. These manifestations usually start after 2 to 4 days and last for 3 days. Minor and transient mucosal bleeding is possible at this

Table 2
Main clinical differences between chikungunya and dengue infection

	Chikungunya	Dengue Fever
Fever, asthenia	Common	Common
Rash	Days 1–4, important skin edema	Days 3–7
Retro-orbital pain	Rare	Common
Myalgia	Possible	Very common
Polyarthritis	Very common, edematous	None
Tenosynovitis	Yes	None
Hypotension	Possible	Common, days 5–7
Minor bleeding	Possible	Common
Second stage	Chronic polyarthritis up to 1 year Tenosynovitis at M2–M3 Raynaud's syndrome at M2–M3	Fatigue up to 3 months

stage. Severe hemorrhage and deaths were described in 1960,[31] but some cases may have been confused with dengue.[32] Two cases of acute CHIKV encephalitis were reported in Cambodia.[33] The second stage of CHIKV infection, also named the chronic stage, was identified because of persisting polyarthralgia, which can severely incapacitate the patient for weeks to more than 1 year. In Brighton's experience, 88% of 107 CHIKV-infected patients declared themselves cured 3 years after disease onset, whereas 12.1% mentioned persistent symptoms including occasional discomfort, persistent joint stiffness, or stiffness, pain and effusion.[30] Pain or stiffness was more severe and more prolonged in the oldest patients and in those who had previous rheumatism. Only one case of late articular destruction was reported.[34] The quality of immunity after natural CHIK infection in humans has not been studied, but infecting mice with a vaccinal strain protected them against various CHIKV strains.[35]

The therapy of infected patients was empiric because no well-conducted prospective study or guidelines were available. No antiviral drug with in vitro activity was correctly tested on infected patients. Patients were commonly treated with pain killers or anti-inflammatory drugs, steroidal or not. Only Brighton empirically conducted an open pilot study, which suggested chloroquine sulfate was effective against chronic symptoms, but no clear conclusion could be obtained.[36]

THE LESSONS FROM 2000'S LARGE-SCALE OUTBREAKS

A Chikungunya Virus Outbreak from Africa to Indian Ocean Islands, Asia, and Europe

In addition to the historical outbreaks starting in the 1960s, an unexpected resurgence of CHIKV outbreaks has been observed since the end of the twentieth century, notably in Africa. In 1999 to 2000, a reemergence was documented in the Democratic Republic of the Congo, where an estimated 50,000 persons were infected during an urban epidemic after 39 years without any isolation of the virus.[18,37] Also in Asia, epidemic reemergence was documented in 2001 to 2003 in Indonesia, after a nearly 20-year hiatus of epidemic CHIKV activity.[38]

In 2004, the ongoing giant CHIKV outbreak started. We know now that it began in Lamu Island, Kenya, in 2004, with an attack rate higher than 50% and an estimated 13,500 persons infected. At first, this disease outbreak was suspected to be due to o'nyong-nyong fever virus, another member of the genus *Alphavirus* (ProMED archive number 20,041,214.331; http://www.promedmail.org).[39,40] Then the outbreak spread to the Indian Ocean Islands. More than 5000 cases were reported in the Comoros Islands,[41] and thereafter the virus circulated to other islands including Reunion[42] and Mayotte[43] (two French territories), Mauritius,[44] the Seychelles,[45] and Madagascar (see **Fig. 2**) (**Table 3**).[46]

At the beginning of 2006, after a period of lower transmission during the winter and with the arrival of the Southern Hemisphere summer, the rainy season gave rise to a renewed epidemic circulation of the virus. Reunion Island suffered an explosive outbreak. By September 18, 2006, an estimate of 266,000 residents (population 770,000) infected with CHIKV was reported.[47–49] This CHIKV epidemic was the first in a country with an occidental health care environment.[50] It was first noticed in the southern state of Andhra Pradesh in February 2006.[51,52] By the end of 2006, it had spread to 15 other states. Several million cases have been reported in India and cases have been reported continuously up to December 2007.[9,53,54] Continued expansion was reported in Sri Lanka,[55] Indonesia,[56] and Malaysia.[57] By 2007, the virus had reached Europe.[15]

Furthermore, since 2004, CHIK fever has been identified in an unprecedented number of travelers (more than 1000) after they returned home from epidemic areas to

Table 3
Epidemiologic data on chikungunya outbreaks in islands of the Western Indian Ocean, 2004 to 2006

Island, Country	Epidemic Years (Peak)	Estimated Attack Rate or Seroprevalence	Estimated Number of Cases	Mortality	References
Lamu Island, Kenya	2004 (July)	Seroprevalence: 75%	13,500	No available data	39
Seychelles	2005	No available data	No available data	No available data	None
Grande Comore, Comoros Union	2005 (March)	Seroprevalence: 63%	215,000	No available data	41
Mayotte, France	2005–2006 (March–April)	Attack rate: 39.6 cases per 1000 inhabitants	6,346	1 reported death	43
Mauritius	2005–2006 (February–March)	No available data	~15,500	743 excess deaths in the 3 months after the epidemic peak	44
City of Toamasina, Madagascar	2006 (January)	No available data	No available data	No available data	46
Reunion Island, France	2005–2006 (February–March)	Seroprevalence: 35%	244,000	213 deaths certificates; 260 excess deaths; case-fatality rate: 1/1000	42,112

European countries,[10,58,59] the United States,[60] Australia,[61] and Asia.[62] Imported CHIKV infection in returned travelers paralleled the spread of the explosive outbreaks in the Indian Ocean islands and then India.[10,60] Most patients consulted at the chronic stage. The acute stage developed after return in 14% to 45% of CHIKV-infected travelers.[10,63] CHIKV viremia was identified in some recently infected travelers, raising concern about the potential globalization of the disease,[13,60] focusing on the role of travelers and migrants visiting friends and relatives in their country of origin as unwitting sentinels, transport media, and potential transmitters of infectious diseases.[12,64,65]

As a consequence, the accumulated data and published papers from CHIK epidemic experiences have increased exponentially (**Fig. 3**). Unexpected changes in epidemiology, new clinical complications, improved insights into pathophysiology, and the evolution of the virus have been described. CHIKV is no longer neglected.

Harsh Public Health Consequences in Large Outbreaks

The first characteristics noticed from CHIKV outbreaks are the rapid spread, high attack rates, and severe impact on public health, as demonstrated in Reunion Island[42,66] and India.[9] Regional contiguous extension of the epidemics is partially explained by the intensity of human exchanges, lack of regional strategy to control arboviral infections, and absence of immunity against CHIKV in local populations. In most countries, adequate measures to control CHIKV outbreaks are commonly delayed for weeks to months for several reasons: (1) difficulty in identifying the first cases in a formerly CHIK-free area, (2) underestimation of the epidemic threat, (3) underestimation of the clinical impact, (4) political or economic (tourism) reticence. In this situation, the global CHIKV load exponentially increases in infected patients and mosquitoes. More than 95% of CHIKV-infected adults are symptomatic, and most working adults become disabled, with loss of mobility, hand handicap, and depressive reaction, which can each last for weeks to months.[67] Thus, a CHIKV outbreak has the effect of a brutal epidemic of acute febrile polyarthritis plus endemic chronic rheumatism. Quantity of work and quality of life are commonly altered for a prolonged period. For example, in Grande Comore in 2005, 79% of the CHIKV-seropositive persons were hospitalized or stayed at home in bed for a mean of 6 days, and 52% missed work or school for a mean of 7 days.[41] CHIKV outbreaks generate mild-to-major crises

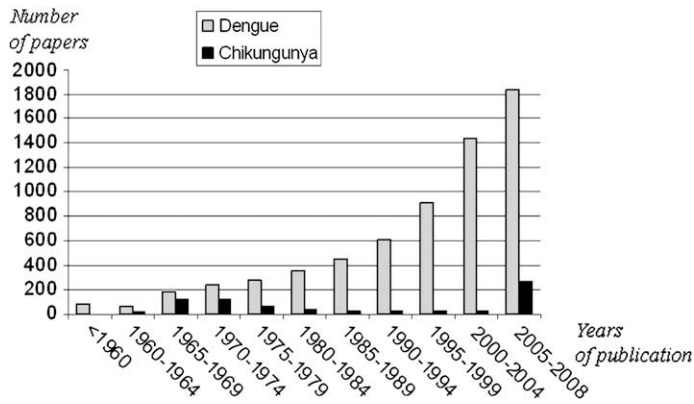

Fig. 3. Evolution of the number of publications on dengue and CHIK over time. (Search performed with PubMed. Available at: www.ncbi.nlm.nih.gov. Accessed July 20, 2008.)

in public health in terms of morbidity and mortality, overloading of medical structures, loss of availability of health care workers, lack of preventive and curative means, loss of patients' confidence, and excessive media coverage. In parallel, social, economic, and political balances are also severely disturbed by the epidemics. The main public health actions consist of public relations exercises, realization of guidelines, community surveillance for suspect or proved cases, hospital-based surveillance for potential severe forms, mortality surveillance, prevention of nosocomial CHIKV-transmission, and vector control measures. Beside the management of the emotional impact in such severe outbreaks, health authorities must promptly disseminate updated medical information, guidelines for diagnosis, and therapy of suspect patients, and must manage saturation of hospitals. Thus, one important challenge is that most patients have to be managed by general practitioners as outpatients with two consequences in an epidemic context: the risk for misdiagnosing serious, treatable diseases (eg, malaria, leptospirosis) when serologic assays are not performed and the risk for intrafamilial spread if the patient is maintained at home without a bed net. Measures are required to limit nosocomial transmission of CHIKV through occupational blood exposure with needlestick, tissues grafts, and blood transfusion.[13,68,69]

No More a Benign Infection: Morbi-Mortality in the Acute Stage, Handicap in the Chronic Stage

The outbreaks in the Indian Ocean, India, and Asia brought new data on clinical spectrum of CHIK infection: improved description of the two stages, unexpected complications and deaths during the exceptional outbreak in Reunion Island. Excess deaths were reported during the Reunion Island and Mauritius outbreaks, mainly in persons older than 75 years of age; the estimated case-fatality rates for CHIK disease were 0.3 to 1/1000 and 47/1000, respectively.[42,47,70] Underlying diseases and age are the most important negative prognostic factors.[42,71] CHIKV infection is more severe in autochthonous than in imported cases, perhaps because travelers are younger and previously healthier than patients who have to be hospitalized in an epidemic situation.[71] All these new data on CHIK morbidity and mortality clearly alter the characterization of CHIK as a benign infection.

Clinical studies from recent outbreaks reported signs and symptoms in the acute stage that appear to vary more than those previously described (**Table 4**).[10,58,67,71,72] The description of the two main clinical components in the acute stage (ie, rash and polyarthralgia) is now enriched with a finer definition of associated symptoms. Polyarthritis commonly involves more than 10 joint groups.[10] It can be edematous, asymmetric, or atypical (Baker's cyst), and is frequently associated with disabling acute tenosynovitis; intense pain provoked by pressure on the anterior part of the wrists is highly evocative.[10]

Some unusual locations are possible (eg, sternoclavicular and temporomandibular), whereas hips are relatively spared.[10,71] Axial involvement is common at any level. Skin involvement consists of patchy to diffuse and edematous exanthema (**Fig. 4**A) and, less frequently, itching, peeling, or epidermolysis; all types can be followed by persisting dyschromic patches on dark skin.[10,58,73,74] Nonspecific gastrointestinal signs are common.[63,71] Borgherini and colleagues[71] also mentioned neurologic signs in 12% of their patients, mainly delirium in the older ones. Respiratory symptoms have been reported in India only, in relation to respiratory syncytial virus, influenza, or adenovirus coinfections.[75] Thrombocytopenia was not prominent and rarely severe in the Reunion experience.[71]

The Reunion hospital-based surveillance allowed description of 123 severe features during the epidemic peak that affected about 244,000 persons.[42] The

Table 4
Early clinical features in chikungunya virus infection during Reunion outbreak

	[71]	[72]	[67]	[58]	[10]
Recruitment of patients	157 cases with acute stage in Reunion Island	20 imported cases from western Indian Ocean, India, Southeast Asia to Germany	125 cases in Reunion Island	22 imported cases from western Indian Ocean to mainland France	47 imported cases from western Indian Ocean to mainland France
Epidemiologic data					
Mean/median age (range)	57.9 1.2	44.4 y (12–66)	40 y (19–55) 17.9	47 y (22–72) 0.57	45 y (0.5–73) 0.88
Sex ratio (M/F)	71%	NR	NR	NR	64%
Underlying disease					
Symptoms and signs					
Fever (duration)	95.9%	100% (4.9 days)	86.5% (3 days)	100% (4 days)	96% (3.7 days)
Asthenia	NR	ND	100%	77%	NR
Headache	47.1%	ND	74%	59%	NR
Myalgia	NR	ND	ND	55%	NR
Nausea, vomiting	ND	30% and 1.5%, respectively	NR	14%	NR
Skin manifestations	40.1%	75%	54.4%	77%	51%
Pruritis	54%	25%	NR	14%	19%
Mucous bleeding	2%	4%	2.6%	0%	4%
Arthralgias/arthritis	96.1%	100%	Most patients	100%	100%
Hands	49.6%	ND	76%	73%	ND
Wrists	29.1%	ND	74%	81%	ND
Feet	41%	ND	68%	NR	ND
Ankles	66.2%	ND	68%	77%	ND
Symmetry of arthralgias	73.2%	NR	Mainly present	Mainly present	64%
Periarticular edema	31.8%	95%	44.8%	NR	41%
Axial involvement	34.4%	NR	Neck: 49%; back: 42%; loins: 52%	NR	47%
Peripheral lymphadenopathy	8.9%	NR	NR	9/22 (41%)	NR
Complication	5 deaths (mean age: 79.4 y) (see reference for more details)	NR	NR	NR	4% (acute myocarditis: 1; pancytopenia: 1)

Abbreviations: ND, not detailed; NR, not reported.

Fig. 4. Clinical manifestations of CHIK infection. (*A*) Edematous exanthema of the face (acute stage). (*B*) Raynaud's phenomenon at the third month after disease onset (chronic stage). (*C*) Polyarthritis in hands and hypertrophic tenosynovitis in wrists at the third month after disease onset (chronic stage). (*D*) Bursitis of dorsal side of the hand (chronic stage). (*E*) Chronic swelling and stiffness of the fingers with loss of grip strength (chronic stage).

most commonly observed complications, in decreasing frequency, were respiratory failure, cardiovascular decompensation, meningoencephalitis, severe acute hepatitis, severe cutaneous effects, other central nervous system problem, and kidney failure. More than half of the severe cases involved patients older than 65 years of age, and more than one third died. A causal relationship between CHIKV and most complications cannot be ascertained. In fact, many patients who had severe acute forms also had underlying diseases that worsened[71] or iatrogenic complications, such as drug-induced hepatitis or Reye syndrome.[4,64] A direct role of CHIKV in severe features seems limited to rare acute central neurologic or cardiac complications, which is consistent with previous experimental studies in mice,[76] but the exact pathophysiologic mechanisms remain unknown. To date, no evidence exists for increased virulence of the recent CHIKV strains. CHIKV-induced meningoencephalitis is the main neurologic complication, especially in children.[42,74] Polyradiculoneuritis and acute flaccid paralysis are exceptional.[77,78] Miscellaneous ocular

complications have been recently described in India: episcleritis, granulomatous and nongranulomatous anterior uveitis, optic neuritis, retrobulbar neuritis, dendritic lesions, and retinitis; recovery is common.[79–81] Acute myocarditis has also been reported in a few cases in adults and children,[74,81–83] but the long-term cardiac prognosis is uncertain.[81] The direct impact of CHIKV infection on pregnancy has also been evidenced: higher risk for abortion in the first trimester and mother-to-child transmission in the last trimester.[64,84] During the epidemic peak in Reunion Island, the attack rate was as high as 8.3% in pregnant women.[84] Vertical transmission was not observed in the intrapartum period (ie, more than 7 days before delivery), but around one half of the mothers with ongoing CHIKV infection in the setting of delivery transmitted the disease to their offspring. Mother-to-child CHIKV virus transmission has been shown to be common in the context of intrapartum maternal viremia, and often leads to severe neonatal infection. Caesarean section did not prevent transmission. Neonatal infection was associated with fever, poor feeding, pain, distal edema, and various skin manifestations. Severe illnesses have been observed and mainly consisted of encephalopathy, including pathologic MRI findings (brain swelling; cerebral hemorrhages) and possible evolution toward persistent disabilities.[84]

Knowledge of the clinical aspects and outcome of the second stage has progressed recently. This stage is not constant, but seems affected by age and underlying diseases, notably rheumatic or traumatic diseases. Its evolution can include early exacerbation, relapses, and long-lasting rheumatism. The first months after disease onset can be marked by a temporary increase of handicap, joint pain and stiffness, and sometimes dysesthesia in the extremities.[10] The authors recently described transitory peripheral vascular disorders, such as Raynaud's syndrome, at this period in about one sixth of CHIKV-infected travelers (**Fig. 4**B).[10] Chronic hypertrophic tenosynovitis are also common and sometimes induce nerve tunnel syndromes in wrists or ankles (**Fig. 4**C).[85] CHIKV-induced chronic rheumatism consists of three clinical components, isolated or associated: finger and toe polyarthritis with morning pain and stiffness (see **Fig. 4**B), severe subacute tenosynovitis/bursitis in hands (**Fig. 4**D), wrists, and ankles, and exacerbation of pain on movement in previously injured joints and bones.[10] The handicap in handling objects during daily life can be major, leading to prolonged sick leave (**Fig. 4**E). A follow-up of cohorts from 2000/2006 outbreaks progressively details the real impact of the chronic symptoms. Patients frequently complain of unpredictable relapses that include sensation of fever, asthenia, and exacerbation of joint pain and stiffness, and often require intensification of symptomatic treatment. Complications of anti-inflammatory treatments for the chronic stage, such as gastrointestinal perforation, are being reported.[86] The psychologic burden and loss of quality of life cannot be neglected; the frequency and intensity of chronic rheumatologic changes remain high after 6 months.[67] The severity of the persisting handicap and depression led some patients to attempt suicide (F. Simon, unpublished data, 2007). An 18-month follow-up identified persistent polyarthralgias in 65.9% of 88 patients previously infected in Reunion (mean age: 58.3 years).[87] Ongoing follow-up will define the long-term handicap and sequelae.

Changing Patterns in Relationship Between the Chikungunya Virus and Mosquitoes

The phylogenetic analyses based on the E1 gene (encoding one of the two major envelope surface glycoproteins) sequences grouped CHIKV isolated worldwide by 2004 into three genotypes: Asian, East/Central/South African, and West African.[11,37]

The CHIKV strains responsible for the massive outbreak in the western Indian Ocean have been isolated from autochthonous patients[88] and from travelers who have

returned to France.[13] Molecular characterization first revealed that the epidemic CHIKV was related to Central/East African CHIKV isolates, from which new variants may have evolved.[13,88] Extensive genome analysis of epidemic isolates identified unique molecular changes in the envelope glycoprotein E1 when compared with the few previously available sequences from laboratory-adapted viruses.[89]

In the successive outbreaks in Kenya, Comoros, and Seychelles, CHIKV was transmitted by *A aegypti*.[90] CHIKV isolates from these islands and early isolates from other islands in this region had an alanine residue at position 226 of the E1 gene.[88] When reaching Reunion and Mauritius Islands, CHIKV met different ecologic environments, characterized by the absence or scarcity of *A aegypti* and the proliferation of *A albopictus* around human habitations. Within 1 year, a new mutation (A226V [ie, a valine residue at position 226]) appeared in CHIKV strains in Reunion. The A226V mutation was identified in all sequenced 2006 Mayotte isolates and in a recent 2007 isolate from Madagascar.[90] This mutation is associated with improved adaptation of CHIV to *A albopictus*, which was previously considered a secondary vector. Indeed, recent entomologic studies[91,92] demonstrated that E1-A226V mutation was directly responsible for significant increase in CHIKV infectivity for *A albopictus*, boosted CHIKV dissemination in *A albopictus,* including into the salivary glands, and improved transmission to vertebrate species, conferring a selective advantage over infection in *A aegypti*. Finally, in all Indian Ocean islands where *A albopictus* was present, the A226V adaptive mutation was observed 1 or 2 years after CHIKV introduction. Overall, the recent efficiency of CHIKV extension can be explained by the combination of: (1) probable first entry of CHIKV among the nonimmune and vulnerable population in Reunion island, (2) the abundance of potential vectors involved in local transmission (*A albopictus*), and (3) the appearance of a viral mutation leading to increased infectivity and faster dissemination of the CHIKV mutant in *A albopictus*. As emphasized by de Lamballerie, it is not known if this mutation was acquired several times independently or if an "*A albopictus*–adapted" strain evolved in one island and then dispersed to neighboring islands.[90] Considering robust phylogenetic analysis, the same investigator suggests separate acquisitions of A226V mutation by CHIKV isolates in India, Cameroon (2006), and Gabon (2007) (two African countries where *A albopictus* has displaced *A aegypti*), independently from the same mutation in Indian Ocean isolates.[90] Therefore, three independent events of virus exposure to *A albopictus*, each followed by the acquisition of a single adaptive mutation, have provided selective advantage for transmission by this mosquito. This unique example of the so-called "evolutionary convergence" occurring in nature illustrates rapid pathogen adaptation to ecologic perturbation.[90]

A Paradigm for the Globalization of Vector-Borne Diseases

In 2006, after having identified high CHIKV viremia in some patients returned from Indian Ocean islands, the authors alerted the scientific community about the risk for CHIKV globalization.[13] Indeed, since the 1980s, *A albopictus* has spread worldwide, having reached the United States in 1985, Brazil in 1986, Central America in 1988, and Africa in 1992 (see **Fig. 2**). In Europe, it was identified in Albania in 1979 and in Italy in 1991, where it has become established. It was reported in France for the first time in 1999 when larvae were discovered in recycled tires imported from the United States and Japan.[14,93] Since 2005, *A albopictus* has become a major pest in the southern French departments of Alpes-Maritimes and Var, and in 2006 it was found in Corsica.[93,94] *A albopictus* probably came from Italy, where it is active from February through December, with a peak in August and September. It is also present in several other European countries, including Belgium, Bosnia and Herzegovina, Croatia,

Greece, Montenegro, Serbia, Slovenia, Switzerland, and The Netherlands, and has recently been found in Spain.[95]

A albopictus can be introduced in a new place through different routes. The eggs can withstand desiccation and survive in miscellaneous containers during long travels around the world. The international trade in used tires, which are optimal breeding sites, has played a major role in the mosquito spread, as has the importation of Dracaena sanderiana plants, also known as ''lucky bamboo.'' Furthermore, public or private transport from infested areas by highway, ferry, or air can contribute to the passive dispersion of *A albopictus*. After its introduction into a new area, the mosquito will disperse actively to nearby areas if environmental conditions are favorable (mean winter temperature higher than 0°C, annual rainfall of at least 500 mm, sufficient rainfall in warm season, and summer temperature around 25° to 0°C).[96] Thus, *A albopictus* is active year round in tropical and subtropical latitudes and it overwinters in the egg stage in the colder latitudes of the Northern Hemisphere. For these reasons, risk for CHIKV implantation from any destination is probably low, if not nil, during the colder months in northern Europe and northern parts of North America. Synchronicity of the vector activity in the epidemic country and of *A albopictus* in the susceptible area seems necessary to allow CHIKV to spread from a viremic traveler to a local resident, which is probably why CHIKV did not spread between January and April 2006 from the epidemic peak in the west Indian Ocean (warm months) to South Europe (cold months). On the contrary, countries in Southern Europe are more susceptible to CHIKV implantation and spread with the arrival of travelers with high CHIKV viremia in warmer months. Risk became reality in Italy, as demonstrated by the outbreak that developed in the summer of 2007 from an infected visitor from India. The overlapping of mosquito seasons in India and Europe permitted travelers returning from India to fuel an epidemic by infecting native mosquito populations in Europe. This seasonal synchronicity made the scenario come true in the province of Ravenna in northeastern Italy, when 205 cases of CHIKV infection were identified between July 4 and Sept 27, 2007. The presumed index case was a man from India who developed symptoms while visiting relatives in one of the villages. *A albopictus*, which is the major human biting pest in this area, was found CHIKV positive by reverse transcription-polymerase chain reaction (RT-PCR)[97] and was considered the most likely vector for this outbreak. The Italian strain ITA07-RA1 (GenBank_EU244823) had the A226V mutation.[98]

HOW TO DIAGNOSE CHIKUNGUNYA VIRUS INFECTION

In the current context of globalization of CHIKV, CHIK fever has to be suspected in any place, whether *A albopictus* is present or not (see **Fig. 2**). Appropriate laboratory tools are available, including serology,[13,99,100] culture isolation,[99] and molecular tools.[13,37,60,100,101] Time after disease onset determines the choice between viral detection and serologic assays. In the acute stage, viremia can be detected on blood sampled in an EDTA tube within the first week of illness onset with culture or molecular tools, both performed in specialized laboratories in nonendemic/epidemic areas. CHIKV isolation is conducted on mosquito cells (C6/36), mammalian cells (Vero), or mice.[4] The test has low sensitivity more than 5 days after disease onset but it remains the gold standard for determining the viral strain. CHIKV can also be detected in the same period with RT-PCR assay, which appears to be more feasible, faster, and more sensitive than culture and is also specific.[100] Serologic assays are performed more often in routine clinical practice. Anti-CHIKV IgM antibodies are detected by direct enzyme-linked immunosorbent assay (ELISA) from the fifth day after the first symptoms.[100] IgG are detected a few weeks later by ELISA, following immunocapture.

These tests have a good sensitivity after the fifth day, but false-negative results have been observed in some patients, for which specific methods should be used.[102] The interpretation of serologic results should consider a possibility of cross-reactions with antigens of o'nyong-nyong, Mayaro, and Ross River viruses in nonepidemic situations.[103] Considering the risk for local spread, all cases detected in nonendemic countries should be reported to health authorities. In France, as in many places in Europe, the disease requires a mandatory declaration.

FUTURE CHALLENGES

To date, at least 12 countries in Europe are susceptible to CHIKV implantation because of the presence of *A albopictus.* Some *A albopictus* specimens collected in Camargue and "Côte d'Azur," southern France, in 2006, experimentally exhibited the same high susceptibility to CHIKV infection as specimens collected in March 2006 in Reunion Island.[93] The presence of this potential vector in such a touristy area as "Côte d'Azur" is now considered a threat for CHIKV introduction in France.[93] Furthermore, it is not known whether infected *A albopictus* can transmit CHIKV to its progeny, and thus persist into the following season, which would expose nonimmune people in the area to the risk for infection and the potential for epidemic resurgence with a strong threat for secondary regional spreading, in Italy as in any previously epidemic country.

Furthermore, other countries are at risk, including the United States.[102] Recently, the potential for a CHIKV outbreak in Florida was examined by the determination of *A aegypti* and *A albopictus* susceptibility to CHIKV; all mosquito strains were susceptible to infection and dissemination, with some variation between strains. Therefore, Florida and probably all the states where *A albopictus* are prevalent in urban and rural areas, would be vulnerable to transmission of CHIKV during the warmer months.[102] In 2006, two viremic CHIKV-infected travelers returned to regions in the United States (South Carolina and Louisiana) known to have populations of *A albopictus*.[60]

Many questions remain unanswered about the pathophysiology of CHIKV and the interactions between CHIKV and humans. What are the mechanisms for CHIKV-induced chronic rheumatism and transient peripheral vascular disorders? Why do anti-CHIKV IgM still persist in about 40% of symptomatic patients 18 months after disease onset?[87,100] Can CHIKV infection become chronic and where could the viral sanctuaries be? Important data are waiting on CHIKV cell tropism and in vivo behavior and on immune disorders. First of all, various human adherent cells (epithelial and endothelial cells, primary fibroblasts, and macrophages) appear susceptible to Reunion CHIKV strains whose replication induces a cytopathic effect and apoptosis.[89] Skeletal muscle progenitor cells, also named muscle satellite cells, contained viral antigen in a muscle biopsy from a patient who had a clinical relapse some weeks after disease onset,[104] which suggests the possibility of persistence of CHIKV in some patients long after initial viremia. It could also explain the low clearance of anti-CHIKV IgM in symptomatic patients. Also, the authors recently identified a high incidence of mixed cryoglobulimia in CHIKV-infected symptomatic travelers in the first months after disease onset, induction for false-negative serologic tests, and long persistence. The association of mixed cryoglobulinemia and Raynaud's phenomenon is under investigation (F. Simon, unpublished data, 2007). A good animal model will probably bring progress on pathophysiology, therapy, and prevention.[105]

Treatment of the acute and chronic stages in CHIKV-infected patients remains empiric. No well-designed trial of therapeutic interventions was conducted during the recent huge outbreaks. Current therapy is solely symptomatic with painkillers or

anti-inflammatory drugs, steroidal or not. Intensity of pain and handicap can require systemic short-term low-dosed corticotherapy when nonsteroidal anti-inflammatory drugs are contraindicated or local treatment fails, but the steady or dramatic improvement can be followed by a painful relapse.[10] However, corticosteroid therapy should not be prolonged or repeated, especially in elderly patients, to limit the severe side effects (eg, hip osteonecrosis, osteoporosis). Rapid replacement with local treatments, including physiotherapy, is recommended when possible. Unfortunately, no alternative systemic drug with evidence-based efficiency exists. Although the efficacy of chloroquine in the acute stage of the disease was recently discussed, no conclusive results have been obtained in clinical studies and it use is currently not justified.[106] New approaches have been proposed for wide screening for curative antiviral drugs against CHIKV.[107,108]

When working on CHIKV as a potential threat, the United States Army developed a live vaccine. Results from a phase II trial on 59 healthy volunteers were consistent with safety, good tolerance (8% with transient arthralgia), and high immunogenicity (98% seroconversion).[109] Unfortunately, funding for this project was discontinued and to date, no vaccine is yet available. Since 2006, research on this topic has been growing again in France (VacciChik project). Nevertheless, recent findings on pathophysiology in CHIKV infection raise questions about a live vaccine: Does wide use in the general population present any risk (chronic infection, viral reversion, mosquito transmission)? Could a vaccine strain induce long-lasting rheumatism? DNA vaccine strategy is an interesting alternative, as suggested by Muthumani and colleagues.[110] However, vaccination policy should also be defined in terms of wide or targeted use during outbreaks and prevention for travelers or military personnel.

SUMMARY

Vector-transmitted infections are evolutionary threats in the modern world, even in temperate, industrialized countries. Their potential for spreading was clearly demonstrated with the West Nile fever that emerged in 1999 in the United States, which has since became the main vector-borne viral disease in this country.[111] The current large-scale CHIKV outbreak has revealed extraordinary adaptive capacity and clear potential for global extension of this previously neglected arbovirus. Within a few years, CHIKV switched from rural endemicity in Africa and focal outbreaks in urban Asia to a worldwide public heath problem. A single adaptive mutation in CHIKV has provided a significant advantage for its transmission to and by *A albopictus,* which is strongly linked to two main human activities, urbanization and international transport. As a consequence, the new epidemiologic profile of CHIK fever is one of global dissemination, in which travelers play a key role. They can be sentinels, whose surveillance helps to alert and define clinical features, and, most of all, transporters and transmitters of the disease to naive populations in nonendemic areas, as demonstrated by the recent Italy outbreak. Also, the potential impact of global warming on mosquito-borne diseases, such as CHIKV infection, in temperate countries deserves consideration.

To be clear, CHIK fever is no longer a disease embedded in tropical and poor countries. It should definitely be considered as a threat to global public health and thus, requires adequate international actions: research programs, surveillance, prompt local alerts, rapid confirmation of outbreaks, diffusion of information on Internet networks, good application of international health regulations, and support for local public health measures. Physicians in CHIKV-free areas should be prepared to suspect and confirm promptly possible cases with two aims, an individual benefit

for the patient and medical intelligence for such a remarkably adaptable pathogen in countries with *A albopictus*.

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