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Chikungunya

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Summary
Chikungunya is an acute viral disease characterised by fever and painful arthralgia. The arthritic symptoms associated with chikungunya can be debilitating and may persist for months or even years in some patients. Severe neurological complications such as encephalitis have also been reported during recent large outbreaks. The disease is caused by chikungunya virus (CHIKV), a mosquito-borne alphavirus from the *Togaviridae* family, which has recently emerged to become one of the most important exotic viral threats worldwide. Chikungunya is endemic throughout Africa, and over the past decade, it has also spread throughout the Indian Ocean, Asia, the South Pacific, southern Europe, the Caribbean and Central America. The rapid emergence of CHIKV has been linked to expansion of the mosquito vector species, *Aedes aegypti* and *Ae. albopictus*, throughout most tropical and subtropical regions of the world. Furthermore, mutations in some strains of CHIKV have been associated with increased transmissibility of the virus. The lack of a commercial vaccine and the failure of vector control strategies to limit the expansion of chikungunya have prompted the need for further options to prevent the spread of this disease.

Keywords
Aedes – *Aegypti* – *Albopictus* – Alphavirus – Arbovirus – Arthralgia – Chikungunya – Fever.

Introduction

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus that belongs to the *Togaviridae* family. CHIKV was first isolated during a large outbreak in Tanganyika (present-day Tanzania) in 1952–1953 (1, 2). Typically, chikungunya infection results in a febrile illness characterised by painful and potentially protracted arthritic symptoms. The virus is a member of the Semliki Forest virus antigenic complex, which contains important arboviruses such as O'nyong-nyong virus (ONNV) from Africa, Mayaro virus (MAYV) from South America and Ross River virus (RRV) from the Oceania region. All of these viruses cause acute illness in humans, typically characterised by fever, rash and arthralgia (3).

Three distinct genotypes of chikungunya have been reported: Western Africa, Eastern/Central/Southern Africa (ECSA) and Asian genotypes. The geographical distribution of these genotypes has traditionally been restricted to the regions implied by their names. However, in 2005 the ECSA genotype re-emerged, following an outbreak in Kenya, to spread throughout the Indian Ocean and most countries of Asia (4). Interestingly, the Asian genotype also re-emerged during this time and caused outbreaks in the South Pacific and, more recently, in many Caribbean countries (5). The re-emergence of the ECSA genotype is linked to a mutation in the E1 glycoprotein gene which enhances the transmissibility of this virus in the Asian tiger mosquito, *Aedes albopictus* (6). The re-emergence of the Asian genotype has not been linked with any specific adaptive mutations, but may be associated with the efficient transmission of the virus in both *Ae. aegypti* and *Ae. albopictus*, which increases the opportunities for virus spread in many regions (7).

Clinical features and treatment of chikungunya

The incubation period for chikungunya infection has a reported range of 1–12 days, with an average of 2–4 days (8). The acute phase of the disease is characterised by an acute onset of fever and arthralgia, with a maculopapular rash also occurring in 40–50% of cases (9, 10, 11, 12). Although full recovery after 1–2 weeks is reported for many cases, a high proportion of patients report ongoing arthritic

symptoms that may persist for months or even years. The joints most commonly reported with arthritic symptoms are the small peripheral joints such as ankles, wrists and phalanges; however, involvement of the large joints, particularly the knees and shoulders, is also relatively common (9, 13, 14). The arthritic pains from CHIKV infection are the most characteristic symptom of the disease and are commonly very painful and potentially debilitating. In fact, the name 'chikungunya' means 'that which bends up' in the Makonde language of East Africa and describes the severe arthritic pains of the disease (1).

A significant proportion of patients develop chronic arthritic symptoms following CHIKV infection, with studies reporting some patients still suffering symptoms 1–2 years after the acute phase of the disease. After the 2005 outbreak in India and the Indian Ocean islands, Taubitz *et al.* (15) reported that, two months after returning home from affected areas, 69% of 69 travellers were suffering from persistent arthralgia, and 13% were still affected six months after infection. The figures were even higher in a study by Sissoko *et al*. (16), with 57% of 147 participants still reporting arthritic symptoms 15 months following infection on Reunion Island. Following the 2007 chikungunya outbreak in Italy, 67% of 250 patients were still reporting symptoms after 12 months (17). Age (>40 years) and pre-existing arthritis or joint pain are commonly reported as risk factors for chronic arthritic symptoms (10, 16). Many studies report a significant reduction in health-related quality of life of patients suffering from chronic symptoms following chikungunya infection (18, 19, 20, 21, 22).

The mechanism for persistent arthritic symptoms following CHIKV infection has not been fully elucidated. Evidence from patients and animal model studies suggest that persistent arthralgia may be due to host inflammatory mechanisms (23, 24, 25). A study in a cohort of chikungunya patients in India, with no prior history of musculoskeletal disorders, showed that the patients displayed symptoms similar to those of autoimmune rheumatoid arthritis, but without the usual erosion of cartilage and bones (26). Persistent arthralgia is also commonly reported for the related RRV and other mosquito-borne alphaviruses such as ONNV, MAYV, Barmah Forest virus and Sindbis virus (27, 28). The detection of RRV in the synovial joints during infection suggests that viral persistence may be associated with persistent arthralgia following infections with these viruses (29). Recent detection of CHIKV in the synovial macrophages of a patient 18 months post infection provides further evidence for this theory (30), as does the long-term persistence of CHIKV in the joints, muscles, lymphoid organs and liver of experimentally infected macaques (31).

Although fever and arthralgia are the predominant symptoms of chikungunya, occurring in almost 100% of patients, other symptoms such as rash, headache, muscle pain, itching and gastrointestinal disturbances (vomiting and diarrhoea) are also commonly reported (Table I). During the large outbreak on Reunion Island in 2005, and subsequently in other locales, severe illnesses were also associated with CHIKV infection, including neurological complications such as encephalitis, seizures, neuropathy and Guillain-Barre syndrome (33, 34, 35). Although mild haemorrhagic symptoms such as petechiae and bleeding

Table I
Comparison of clinical features reported during outbreaks of chikungunya
Reference numbers are given in brackets

Clinical signs	Reunion Island (13)	Reunion Island (9)	India (14)	India (10)	India (32)	Italy (11)	Gabon (12)
Patients (No.)	180	157	740	203	540	205	270
Fever	100%[a]	89%	97%	85%	100%[a]	100%[a]	85%
Arthralgia	100%[a]	96%	90%[b]	98%	63%	97%	90%
Muscle pain	59%	NR	NR	25%[c]	NR	46%	73%
Joint swelling	26%	32%	NR	53%	28%	NR	NR
Headache	70%	47%	78%	38%	63%	51%	72%
Rash	48%	40%	15%	50%	36%	52%	42%
Itching	14%	54%	12%	NR	NR	20%	25%
Vomiting	43%	NR	NR	11%	44%	19%	32%[d]
Diarrhoea	29%	NR	NR	4%	7%	23%	32%[d]
Bleeding	1%	6%	1%	NR	NR	NR	2%
Lymphadenopathy[e]	9%	NR	2%	2.4%	NR	NR	NR
Red eyes	23%	NR	NR	19%	NR	3%	NR

a) Part of the case definition
b) Reported as body ache
c) Reported as pain in the body other than headache and joint pain
d) Reported as digestive symptoms, consisting of abdominal pain, nausea, vomiting and diarrhoea
e) Enlarged lymph nodes
NR: Not reported

gums or nose are occasionally associated with chikungunya (9, 12, 13, 14), severe haemorrhagic manifestations have not been conclusively established.

The elderly (>65 years) and paediatric patients, in particular newborns, are at increased risk of severe disease, as are patients with underlying medical conditions, as these are associated with a higher risk of complications (neurological, cardiac) and even death. During the Reunion Island outbreak, vertical transmission (mother to child) of CHIKV was documented for the first time and has subsequently been reported from other locales (36, 37, 38, 39). Severe clinical manifestations such as encephalitis were reported from the Reunion Island outbreak in 53% of babies infected by this route, with persistent sequelae in 44% (36). Vertical transmission of chikungunya infection was also associated with one neonatal death and three early fetal deaths in this setting (34, 36).

The attack rate (i.e. the proportion of the population that become infected) during chikungunya outbreaks can often be very high, with over 50% of the population infected. During the 2005 outbreak on Reunion Island, more than 30% of the island's population of 770,000 people were infected with CHIKV (9). Similarly, ongoing (as of July 2014) outbreaks in Martinique and Guadeloupe in the Caribbean also have high estimated attack rates: 11.7% and 13.1%, respectively (40). This can have significant social and financial impacts due to loss of productivity and the need for ongoing support for patients suffering from the protracted, debilitating effects of arthritic symptoms.

Clinical diagnosis of chikungunya is often difficult as the symptoms are similar to many other tropical febrile illnesses, such as dengue, malaria, typhoid, scrub typhus and other arboviral diseases. The viral load in the patient's bloodstream can reach very high levels (>10^9 viral RNA copies/ml), which facilitates nucleic acid detection using methods such as real-time polymerase chain reaction (41). CHIKV is readily grown in common mammalian cell lines such as Vero, Hela and HepG2, but growth on insect cell lines, such as C6/36, is strain dependent (42). Specific IgM antibodies can be detected 2–7 days post infection, and persist for up to three months (43). IgG antibodies are typically detected about one week after infection and persist for several years (44). Although most serological tests are highly sensitive for the detection of CHIKV antibodies, the high antigenic cross-reactivity between other alphaviruses results in reduced specificity and can make definitive diagnosis using antibody-based assays problematic.

An effective antiviral treatment for chikungunya does not yet exist and therefore supportive care is recommended to relieve symptoms. Patients are commonly treated with antipyretics to reduce fever, analgesics/anti-inflammatory drugs to relieve joint and muscle pain, and fluids to prevent dehydration (45, 46).

The life cycle of chikungunya virus

Two distinct transmission cycles have been described for CHIKV (Fig. 1). The sylvatic cycle has been documented primarily in Africa, between non-human primates and forest-dwelling *Aedes* species such as *Ae. furcifer* and other members of the *Ae. furcifer-taylori* group (47). Occasionally, the virus can 'spill over' to human populations encroaching on the natural cycle through hunting and gathering activities, or living close to the sylvatic environment (48). Thus, the sylvatic cycle mostly affects small rural populations. However, recent expansion in the distributions of *Ae. aegypti* and *Ae. albopictus* throughout Africa, coupled with increased urbanisation, have resulted in large outbreaks in Kenya and central African countries such as Cameroon, Congo and Gabon (12, 49, 50). Thus, the urban cycle has evolved in areas where large populations of people and urban *Aedes* mosquitoes exist to maintain a human–mosquito–human cycle. Chikungunya in Asia has been historically associated with an urban cycle between humans and *Ae. aegypti*, and the persistence of the CHIKV virus in this region is thought to be the result of continuous introduction of CHIKV to immunologically naive populations (51). *Ae. albopictus* have traditionally been considered a vector of secondary importance, but recent outbreaks of chikungunya in Asia (and many other regions of the world) have underlined their importance as a primary vector. Studies have suggested that the sylvatic cycle may also occur in Asia, with isolation of CHIKV in wild monkeys in Malaysia (52) and the detection of antibodies on a monkey farm in the Philippines (53);

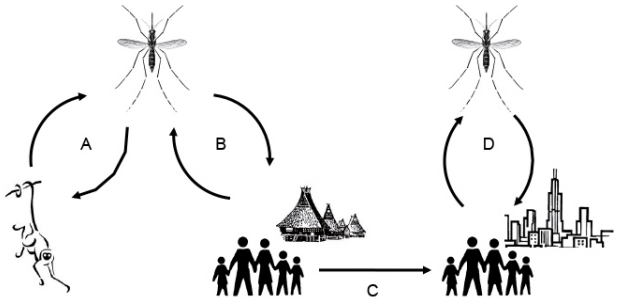


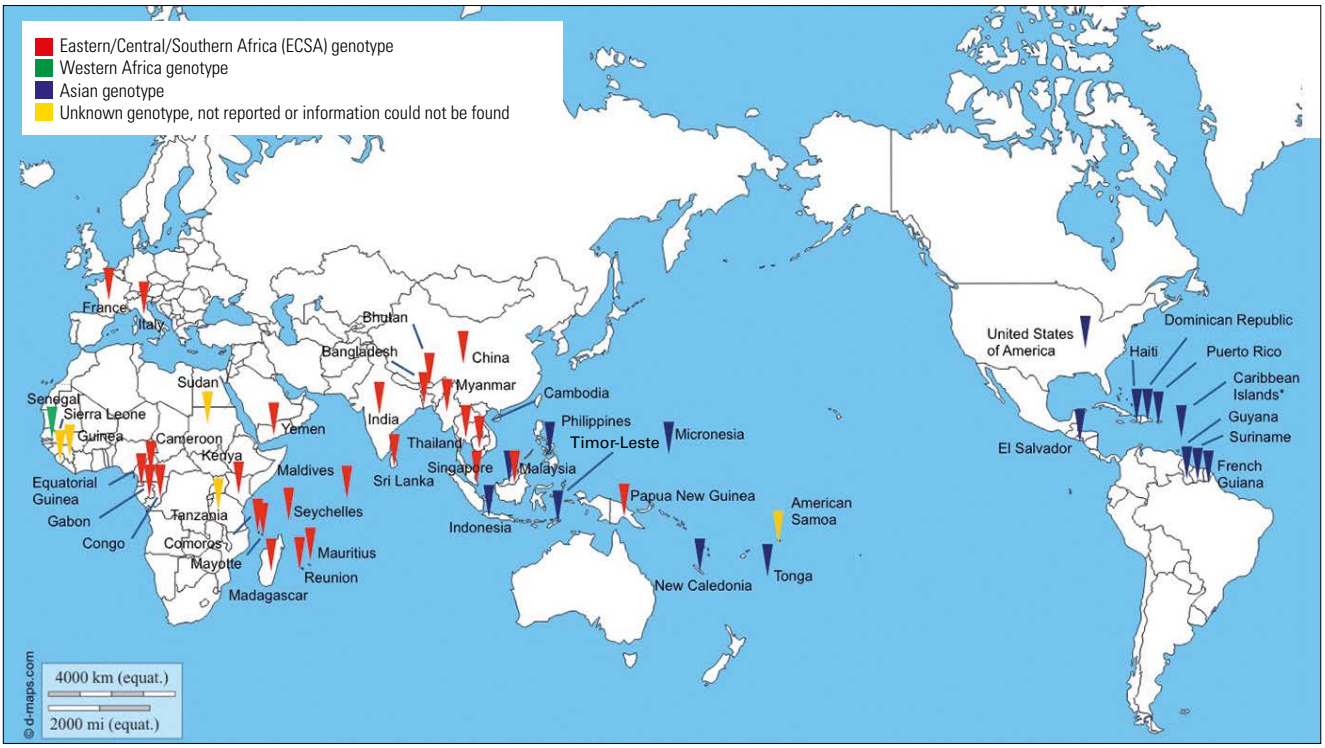
Fig. 1
The transmission cycles of chikungunya virus
A: The sylvatic cycle exists primarily in Africa where the virus circulates between non-human primates and forest-dwelling *Aedes* species
B: Small outbreaks can occur in rural populations when humans encroach on the natural habitat and are bitten by infected forest-dwelling mosquitoes
C: Travel of infected humans to major population centres can result in the establishment of an urban cycle
D: In an urban cycle the virus is maintained between urban *Aedes* species (*Ae. aegypti* and *Ae. albopictus*) and humans in a human–mosquito–human cycle

however, the existence of a persistent sylvatic cycle has not been conclusively established in this region.

Evidence from molecular evolutionary studies suggests that Africa is the geographical origin of CHIKV, based on the genetic diversity in the West African genotype and the presence of an established sylvatic cycle between mosquitoes and non-human primates (25). CHIKV probably emerged from the sylvatic cycle approximately 300 to 500 years ago, with the virus being introduced into Asia within the last 100 years (54, 55).

Recent global expansion

The CHIKV ECSA genotype has recently spread throughout Asia, Southeast Asia and the South Pacific to become the dominant global genotype (Fig. 2). The global expansion of this genotype began following an outbreak in Kenya in 2004 (57). Cases were subsequently detected in Reunion Island, Madagascar, Comoros and other islands of the Indian Ocean where high attack rates and severe cases were reported (58). As many of the islands in this region are popular tourist destinations, the cases spread to most regions of the world, offering opportunities for further spread of the virus, although fortunately autochthonous transmission was limited. In 2006, the outbreak spread to many Asian countries, where the virus continues to circulate (Fig. 2). The outbreak in India affected at least 13 states and more than 1.39 million people (59). Outbreaks with autochthonous transmission were also reported in high-income European countries such as France and Italy (60, 61). The rapid emergence of these strains has been linked to a point mutation in the CHIKV genome, occurring independently in Reunion Island and India. The mutation, called E1:A226V, resulted in an amino acid change from alanine to valine at position 226 in the E1 glycoprotein gene which enhanced the transmissibility of the virus in *Ae. albopictus* mosquitoes (6, 62). A further mutation in the E2 glycoprotein, called E2:L210Q, has also been detected in Indian lineage strains of ECSA, which also increases the infectivity of the virus in *Ae. albopictus* (63). Interestingly, neither of these mutations have any effect on the infectivity of the virus in *Ae. aegypti*.



*Caribbean Islands with local transmission: Guadeloupe, Martinique, St Barthelemy, St Martin, Anguilla, Antigua and Barbuda, Aruba, Dominica, Grenada, St Kitts and Nevis, St Lucia, St Maarten, British Virgin Islands, United States Virgin Islands (note that this situation is rapidly evolving at present [July 2014] and the outbreak is likely to spread to more countries in the region)

Fig. 2

Reported outbreaks of chikungunya throughout the world since 2004

Further endemic circulation of chikungunya virus is evidenced by serological studies and importation of cases into developed countries, but these cases have not been listed on the map

Source: ProMed-mail (www.promedmail.org), the World Health Organization (www.who.int/mediacentre/factsheets/fs327/en), United States Centers for Disease Control and Prevention (www.cdc.gov/chikungunya), Thiberville *et al.* (4) and Weaver (56)

Although recent expansion of the ECSA genotype into Asia has dominated outbreaks in the region, the Asian genotype has not been totally replaced. Outbreaks of the Asian genotype have occurred in recent years in Malaysia, Indonesia and other countries in the region (64, 65). In addition, the Asian genotype has been responsible for outbreaks in the South Pacific region (New Caledonia, Tonga and the Federated States of Micronesia), where chikungunya had never been reported before (66). However, most surprising have been the explosive outbreaks of Asian genotype CHIKV in the Caribbean and Central America (Fig. 2). The virus was first reported in St Martin in December 2013 and cases were rapidly reported throughout the region. By mid-2014 at least 22 countries in the Caribbean and three countries in Central America had reported outbreaks with local transmission (40). Most recently (July 2014), local transmission of CHIKV was reported for the first time in the United States (Florida) (67). There are major concerns that the outbreak will spark devastating epidemics in Central and South America, where climatic and social conditions are highly conducive to arboviral transmission.

Although the emergence of the ECSA genotype has been linked with an adaptive mutation in the virus, the emergence of the Asian genotype has not been associated with any specific viral changes. Thus the expansion of the Asian genotype is probably linked to increased geographical invasion of *Ae. aegypti* and *Ae. albopictus*, coupled with increased urbanisation and international travel. For the same reasons the distribution of endemic and epidemic dengue has increased considerably in recent years (68).

Prevention and control

Currently, the only proven method of controlling *Aedes* mosquitoes in urban settings is through vector control strategies such as insecticidal spraying and management of breeding sites (69). These control efforts have largely failed to restrict the geographical expansion of *Ae. aegypti* and *Ae. albopictus*, resulting in an alarming increase in the global incidence of dengue and chikungunya (68). The successful use of insecticide-treated bed-nets for malaria control is unlikely to have an effect on the distribution of *Aedes* mosquitoes as they are day-biting species. It is evident that public health authorities need more options in their arsenal to combat the spread of chikungunya and dengue.

The transinfection of *Ae. aegypti* with symbiotic *Wolbachia* bacteria has been investigated as a promising bio-control approach for dengue, chikungunya and other mosquito-borne pathogens. These intracellular bacteria are maternally inherited in mosquito populations and can induce reproductive changes in the host (70). Some *Wolbachia* strains are able to shorten the lifespan of their insect host by up to 50% (71). This reduction in the lifespan of the host is expected to result in significant reductions in dengue and chikungunya transmission, as both viruses must replicate in the mosquito before they can be transmitted to a human during blood feeding. Furthermore, some *Wolbachia* strains directly inhibit the reproduction of certain pathogens, including dengue, chikungunya, yellow fever virus and *Plasmodium* (72, 73, 74). Recent field releases of *Wolbachia*-infected *Ae. aegypti* in northern Australia have demonstrated the potential success of this approach to arbovirus control (75). Another interesting option for the control of dengue, chikungunya and other mosquito-borne pathogens is the use of genetically modified (GM) mosquitoes to reduce mosquito populations. This approach involves releasing GM male mosquitoes that carry a dominant lethal gene or other heritable changes that result in a population crash (76). Different strategies using GM mosquitoes are currently being tested in field trials in various locations around the world for the control of dengue and malaria.

Given that humans are the sole amplifying host during urban outbreaks of chikungunya and that infection leads to life-long protective immunity, vaccination is an attractive option for control. Currently, a commercial vaccine is not available for the prevention of chikungunya. However, this is an area of active research, with inactivated viruses, virus-like-particles, live attenuated viruses and recombinant viruses being developed as vaccine candidates (77). The United States Army Medical Research Institute of Infectious Disease developed a live attenuated vaccine from a virus isolated during an outbreak in Thailand in 1962 (78). Although Phase I (79) and Phase II (80) clinical trials demonstrated the safety and immunogenicity of the vaccine, further development has not occurred. Concerns over the lack of a stable, ongoing market base are a potential hindrance to the development of this and other chikungunya vaccines, as is the lower priority attributed to chikungunya compared to diseases with higher mortalities, e.g. dengue and Japanese encephalitis. The epidemiology of chikungunya, characterised by 'boom-to-bust' outbreaks, may also affect the financial appeal of vaccine development (77).

Conclusions

Recently, we have witnessed unprecedented expansion of the ECSA and Asian genotypes of CHIKV. Spread of these viruses into new areas such as southern Europe, the South Pacific, the Caribbean and Central America has sparked fears that the virus could continue to invade new areas (56, 81, 82). South America, northern Australia, southern Europe and the southern United States all contain *Aedes* mosquitoes (*Ae. aegypti* or *Ae. albopictus*) in sufficient densities to sustain local transmission (7, 83, 84, 85). Imported cases of chikungunya have been reported in all of these areas in

recent years, so further spread of CHIKV to new territories is expected, particularly in developing and middle-income countries where quarantine and mosquito control activities are not well developed. In developed countries, rigorous quarantine procedures and active case detection have mostly prevented local transmission of the virus (except for France and Italy). However, the recent re-emergence of CHIKV and the preponderance of outbreaks in widespread locations have resulted in large increases in imported cases, with the potential for autochthonous spread.

Le chikungunya

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Résumé

Le chikungunya est une maladie virale aiguë caractérisée par de la fièvre et des arthralgies douloureuses. Les symptômes arthritiques associés au chikungunya peuvent être invalidants et perdurer pendant des mois, voire des années chez certains patients. Des complications neurologiques graves dont des cas d'encéphalite ont également été rapportées lors de récents foyers majeurs. L'agent causal est le virus chikungunya (CHIKV), un alphavirus d'apparition récente, transmis par les moustiques et appartenant à la famille des *Togaviridae*, rapidement devenu la principale menace sanitaire due à un virus exotique au niveau mondial. Le chikungunya est endémique dans toute l'Afrique et s'est également propagé au cours de la décennie écoulée de part et d'autre de l'océan Indien, en Asie, dans le Pacifique Sud, en Europe méridionale, dans les Caraïbes et en Amérique Centrale. Une corrélation a été constatée entre l'émergence rapide du CHIKV et l'expansion de l'aire de distribution des espèces de moustiques qui lui servent de vecteur, à savoir *Aedes aegypti* et *Ae. albopictus* dans la plupart des régions tropicales et subtropicales du monde. En outre, certaines souches du CHIKV ont subi des mutations qui semblent concomitantes à une transmissibilité accrue du virus. Aucun vaccin n'est disponible et les stratégies de contrôle du vecteur ont jusqu'à présent échoué à contenir l'expansion du chikungunya, de sorte que la mise au point de solutions alternatives pour prévenir la propagation de la maladie est une urgence absolue.

Mots-clés

Aedes – *Aegypti* – *Albopictus* – Alphavirus – Arbovirus – Arthralgie – Chikungunya – Fièvre.

El chikungunya

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Resumen

El chikungunya es una enfermedad vírica aguda que se caracteriza por la presencia de fiebre y fuertes dolores articulares. Los síntomas artríticos asociados a la enfermedad pueden ser debilitantes y durar varios meses, o incluso años en ciertos pacientes. En recientes brotes de grandes proporciones se han descrito graves complicaciones neurológicas, como encefalitis. El agente causal de la enfermedad es el virus chikungunya, un alfavirus de la familia *Togaviridae* que se transmite por mosquitos y ha surgido en fechas recientes para convertirse en una de las más importantes amenazas víricas exóticas en todo el mundo. El chikungunya es endémico en todo el continente africano, y en

el último decenio también se ha extendido al Océano Índico, Asia, el Pacífico Sur, Europa meridional, el Caribe y América Central. Se ha postulado que la rápida emergencia del virus chikungunya guarda relación con la expansión de las especies de mosquito que le sirven de vector, *Aedes aegypti* y *Ae. albopictus*, por la mayoría de las regiones tropicales y subtropicales del mundo. Por otra parte, se han vinculado ciertas mutaciones de algunas cepas del virus con una mayor capacidad de transmisión. La inexistencia de una vacuna comercial y la inoperancia de las estrategias de lucha para contener la expansión del virus hacen necesarios otros procedimientos alternativos para prevenir la propagación de la enfermedad.

Palabras clave
Aedes – *Aegypti* – *Albopictus* – Alfavirus – Arbovirus – Artralgia – Chikungunya – Fiebre.

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