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Review

Chikungunya fever – A new global threat[☆]Antonio Montero^{a,b}^a Miembro de la Carrera del Investigador Científico, Consejo de Investigaciones de la Universidad Nacional de Rosario (CIUNR), Rosario, Santa Fe, Argentina^b Centro de Medicina Tropical y Enfermedades Infecciosas Emergentes, Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Rosario, Santa Fe, Argentina

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ABSTRACT

The recent onset of epidemics caused by viruses such as Ebola, Marburg, Nipah, Lassa, coronavirus, West-Nile encephalitis, Saint Louis encephalitis, human immunodeficiency virus, dengue, yellow fever and Venezuelan haemorrhagic fever alerts about the risk these agents represent for the global health.

Chikungunya virus represents a new threat. Surged from remote African regions, this virus has become endemic in the Indian ocean basin, the Indian subcontinent and the southeast of Asia, causing serious epidemics in Africa, Indic Ocean Islands, Asia and Europe.

Due to their epidemiological and biological features and the global presence of their vectors, chikungunya represents a serious menace and could become endemic in the Americas. Although chikungunya infection has a low mortality rate, its high attack ratio may collapse the health system during epidemics affecting a sensitive population.

In this paper, we review the clinical and epidemiological features of chikungunya fever as well as the risk of its introduction into the Americas. We remark the importance of the epidemiological control and mosquitoes fighting in order to prevent this disease from being introduced into the Americas.

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Fiebre chikungunya – Una nueva amenaza global

RESUMEN

Las epidemias causadas, entre otros, por los virus Ébola, Marburgo, Nipah, Lassa, coronavirus, virus del Nilo Occidental, virus de Saint Louis, virus de la inmunodeficiencia humana, dengue, fiebre amarilla y fiebre hemorrágica venezolana han puesto sobre el tapete el riesgo que estos agentes representan para la salud pública global.

Entre las nuevas amenazas destaca el virus chikungunya, que ha extendido rápidamente su área endémica desde regiones remotas de África hacia la cuenca del océano Índico y el Pacífico Oriental, causando importantes epidemias en África, Asia, islas del Índico y Europa Occidental, llegando a establecerse recientemente en islas del Caribe.

Debido a su comportamiento dual endémico y epidémico, a sus propiedades virológicas y a la presencia global de sus vectores, este virus entraña el riesgo de causar grandes epidemias e instalarse en el territorio continental de las Américas a partir de la introducción de casos importados y a la circulación local vista en la región caribeña.

Se revisan las principales características epidemiológicas y clínicas de la fiebre chikungunya y el riesgo de introducción de esta enfermedad en las Américas, enfatizando el rol de la vigilancia y la lucha contra los mosquitos en su prevención.

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Palabras clave:

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Introduction

Chikungunya is an emerging viral disease that manifests as a febrile syndrome with severe arthralgia and skin rash. It is caused by Chikungunya virus, an alphavirus transmitted by mosquitoes.

The risk of Chikungunya epidemics from imported cases is especially high in the Americas, where vectors are sufficiently abundant and the population does not possess immunity against the virus.

Fig. 1. Countries affected and year of onset of Chikungunya fever. Underlined and in bold: countries where the disease has become endemic or local outbreaks have occurred.

Vectors

The main vectors for Chikungunya virus in Asia and the Indian Ocean are the mosquitoes *Aedes aegypti* and *Aedes albopictus*, but other species of *Aedes* (*A. furcifer*, *A. vittatus*, *A. fulgens*, *A. luteocephalus*, *A. dalzieli*, *A. vigilax* and *A. camptorhynchites*) can transmit the infection. Other mosquitoes, such as *Culex annulirostris*, *Mansonia uniformis* and *Anopheles stephensi*, have occasionally been involved as vectors.^{13–16}

A. aegypti and *A. albopictus* are invasive species that inhabit tropical and temperate regions of the globe located between 35° N and 35° S. During the hot season, they advance towards latitudes as extreme as 45°, although they do not survive the winter at these extreme latitudes. Their ability to breed in artificial containers facilitates their passive spread through the main transport routes.¹⁷

A. aegypti has domestic and peridomestic habits. It usually does not occupy territories at altitudes higher than 1000 m, although it has occasionally been found at altitudes as high as 2400 m.

A. albopictus has non-domestic habits and proliferates in wilderness environments. It is a wild and rural species, responsible for transmitting the virus in rural and semi-urban areas.

The eggs of *Aedes* withstand desiccation and extreme temperatures, remaining viable for 7 months to a year. This property represents an evolutionary advantage that makes vector eradication particularly difficult.

As with other mosquitoes, only female *Aedes* mosquitoes bite. These females are anthropophilic and prefer to bite people rather than animals.

Given that it is also the vector for yellow fever and dengue, *Aedes* was fought hard and eliminated from Central and South America at the beginning of the 20th century. However, since the eradication campaigns were suspended in the early 1960s, it has returned in the regions from which it was eradicated, and has even expanded its habitat to places it did not occupy during the eradication campaign.

As they share the same vectors, the epidemiology of dengue and that of yellow fever are closely linked to the risk of introducing Chikungunya virus in the Americas. Owing to the wide distribution of *Aedes* in the Americas, the entire region is susceptible to the invasion and spread of this virus, and the recent occurrence of urban epidemics of dengue in South America highlights the potential danger of Chikungunya fever.

Transmission

During epidemic periods, humans are the main reservoir of the virus, which, like dengue, remains in alternate circulation between mosquitoes and humans. In inter-epidemic periods, various vertebrates have been involved as reservoirs, including non-human primates, rodents, birds and some small mammals. In East-Central Africa, the virus circulates in a non-domestic cycle that involves *Aedes* mosquitoes and primates.

Chikungunya virus is transmitted to humans by means of the bite of an infected female mosquito. After a mosquito has ingested blood from a viraemic person, the virus must replicate in the mosquito for at least 48 h (extrinsic incubation period) before the mosquito can transmit the disease by another bite.¹⁸ As occurs in dengue, infected humans remain viraemic for several days, approximately the same length of time as the duration of the fever (Fig. 2).

Vertical transmission of the Chikungunya virus has been well documented. Although the rate of vertical transmission seems low throughout gestation, when the infection occurs during or shortly before childbirth, the rate of transmission increases and approaches 50%.¹⁹

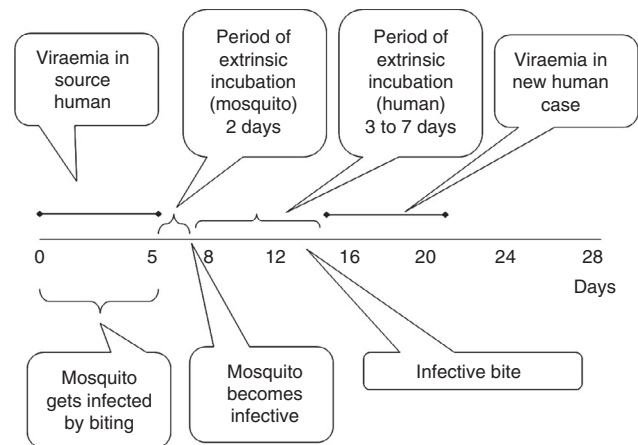


Fig. 2. Extrinsic (mosquito) and intrinsic (human) incubation cycles of Chikungunya virus.

Transmission by means of breast milk has not been reported, but it has been reported through exposure to infected blood. This shows that transmission is possible by means of transfusions of blood or blood products.²⁰

Clinical characteristics

The name “Chikungunya” means “one who bends over” in the Makonde language (Bantu language of Tanzania), and makes reference to severe arthralgia, which causes patients to assume a stooped posture in an effort to relieve pain.

The infection can cause acute, sub-acute and chronic manifestations.

Acute disease (Chikungunya fever)

A high percentage of infected individuals (72–97%) develop symptoms after an incubation period that ranges from 3 to 7 days (limits: 1–12), while the rest remain completely asymptomatic.^{21,22}

Chikungunya fever mimics dengue in its sudden onset with fever, which tends to exceed 39°C, skin rash and headaches. However, it has the distinguishing feature of the presence of severe arthralgia. Typically, the fever persists for 48 h and abruptly subsides, although in some cases it lasts up to a week. This fever tends to be accompanied by non-specific symptoms such as headache, bloodshot eyes and photophobia.

Chikungunya is not life-threatening, but recovery can be prolonged and joint pain can persist for months.²³

Involvement of multiple joints affects 70–100% of patients. Such involvement tends to be symmetrical and affects the small joints of the hands and feet, although occasionally it attacks the large joints of the limbs. It can be limited to arthralgia, or there can be joint swelling, often due to tenosynovitis. The combination of pain, sensitivity, inflammation and joint stiffness tends to be very debilitating, and disables many patients, who remain confined to bed during the acute phase.

Two to five days after the start of the fever, 50% of patients develop a maculopapular skin rash, or occasionally a petechial skin rash, that affects the trunk and, less commonly, the limbs, sometimes spreading to the palms, soles of the feet and face. The skin rash tends to be fleeting, although it persists for more than 2 days in 10% of cases. It occasionally manifests as diffuse erythema that pales when pressure is applied. In small children, skin involvement consists of vesicular and bullous lesions.

Table 1
Normal manifestations of Chikungunya virus infection.

Clinical characteristic	Percentage of frequency
Fever	76–100
Polyarthralgia	71–100
Polyarthritits	12–32
Myalgia	46–72
Dorsalgia	34–52
Nausea and vomiting	50–70
Skin rash	30–77
Headache	17–74
Conjunctivitis	3–56

Among adults, 25% experience stomatitis, and 15% develop mouth ulcers (Table 1).

Symptoms last 5–7 days, and never more than 10 days. However, arthralgia can persist up to 2 years, depending on the patient's age (Fig. 3).

Sub-acute disease

The majority of patients improve after 10 days of having the disease. However, some patients experience a recurrence of joint symptoms 2 or 3 months after their initial recovery, developing arthralgia in the previously affected joints and bones, distal polyarthritits, and sub-acute hypertrophic tenosynovitis in the wrists and ankles. They can also develop Raynaud's syndrome, depression, asthenia and weakness.

Sub-acute Chikungunya infection does not persist for more than 3 months and affects a variable percentage of patients, ranging from 43% to 70% of cases.

Chronic disease

When symptoms persist for more than 3 months, it is considered a chronic disease. The percentage of patients who develop chronic manifestations is highly variable, ranging from 12% to 57%.^{24,25}

Chronic disease tends to resolve with time: 93% of cases remain symptomatic 3 months after the disease has been identified as chronic, but this percentage drops to 57% after 15 months and 47% after 2 years.²⁶

Miscarriages have been reported in infected pregnant women.²⁷ In cases of vertical transmission during or immediately before childbirth, it is normal for the child to be born asymptomatic and develop symptoms after a few days.^{28,29}

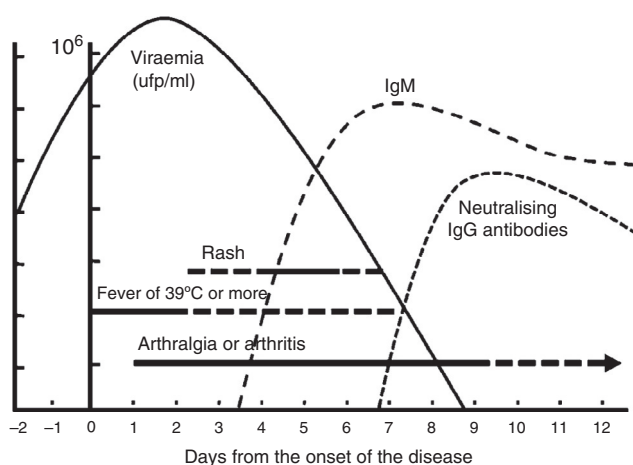


Fig. 3. Clinical graph of Chikungunya fever. PFU/ml, plaque-forming units per millilitre of blood.

Table 2
Uncommon manifestations of Chikungunya virus infection.

Target system or organ	Manifestations
Central nervous system	Meningitis, encephalopathy, paresis, paralysis, neuropathy, cerebellar syndrome, Guillain-Barré syndrome, seizures
Cardiovascular system	Myocarditis, pericarditis, arrhythmias, haemodynamic instability, heart failure
Kidneys	Nephritis, acute kidney failure
Eyes	Uveitis, episcleritis, iridocyclitis, optic neuritis, retinitis
Skin	Nephritis, acute kidney failure
Respiratory system	Pneumonia, respiratory failure
Endocrine system	Adrenal insufficiency, syndrome of inappropriate vasopressin secretion
Miscellaneous	Hepatitis, pancreatitis, bleeding diathesis

Rarely, serious forms of the disease can occur with atypical manifestations including myocarditis, meningoencephalitis and minor bleeding.³⁰ Guillain-Barré syndrome, loss of hearing acuity,^{31–34} uveitis and retinitis^{35–37} have also been observed (Table 2).

Chikungunya fever has a very low mortality rate. However, epidemics can have different mortality rates. The epidemics in India and Mauritius showed a significant increase in mortality.^{38,39}

The elderly are most prone to experiencing serious episodes of Chikungunya fever: in one study, those over 65 years of age had a mortality rate 50 times greater than those under 45 years of age.⁴⁰

Differential diagnosis

The prominent manifestations of Chikungunya fever, such as fever, arthralgia, skin rash, myalgia and conjunctivitis, are common in other diseases for which it may be mistaken, or with which it may coexist, such as dengue. This mandates a meticulous differential diagnosis.

Dengue: this is the entity that most closely resembles Chikungunya fever, and the one that calls for the most important differential diagnosis, owing to the overlap in terms of vectors, geographic area and signs and symptoms, as well as the possibility of both diseases simultaneously affecting a single patient. In the single comparative study conducted, Chikungunya showed a more abrupt start; the fever was of a shorter duration than in dengue, and the skin rash, bloodshot eyes and arthralgia were more common than in dengue⁴¹ (Table 3).

The finding of bleeding diathesis, petechiae or purpura, together with severe dorsalgia, supports a diagnosis of dengue. Laboratory tests help in distinguishing between the two entities. It must always be borne in mind that dengue and Chikungunya fever may simultaneously affect a single patient.

Table 3
Frequency of symptoms present in dengue and Chikungunya fever.

Clinical characteristics	Chikungunya (%)	Dengue (%)
Fever	70–100	40–69
Headache	40–69	40–69
Skin rash	40–69	10–39
Arthralgia or arthritis	70–100	<10
Myalgia	10–39	40–69
Bleeding diathesis	<10	40–69
Shock	0	<10
Leukocytopenia	40–69	70–100
Lymphocytopenia	70–100	40–69
Neutropenia	10–39	70–100
Thrombocytopenia	10–39	70–100

Leptospirosis: severe myalgia in the calf muscles, together with subconjunctival bleeding or conjunctival congestion, which may or may not be accompanied by oliguria or jaundice in a person who has been in contact with water, mud or rodents in an endemic area, aid in arriving at a diagnosis. The presence of neutrophilia and high titres of creatine phosphokinase in blood point to a diagnosis of leptospirosis.

Malaria: a fever that comes and goes, as well as an altered level of consciousness and seizures, point to a diagnosis of malaria. The intermittent fever typical of malaria may not occur in the first few days of having the disease (acclimatisation fever).

Meningitis: a combination of high fever with signs of meningitis or disorders of consciousness supports a diagnosis of meningitis. However, during a Chikungunya epidemic, all cases of meningoencephalitis should be suspected as being due to this infection.

Rheumatic fever: this is most common in children and presents as migratory polyarthritis that predominantly affects the large joints. The Jones criteria should guide diagnosis.

Laboratory findings

A complete blood count tends to show leukocytopenia. Unlike in dengue, thrombocytopenia tends to be absent or only very mild ($>100,000$ platelets/ mm^3). Unlike in other viral diseases, inflammation markers, such as erythrocyte sedimentation rate and C-reactive protein, tend to be high. A slight increase in transaminases also occurs.

Diagnosis

A diagnosis may be made by direct or indirect methods. Direct methods include molecular procedures such as reverse transcription polymerase chain reaction and virus isolation by culture, while indirect methods are based on detecting specific antibodies, whether they are IgM antibodies or, in the case of IgG antibodies, demonstrating an elevation of at least 3 times the baseline values after 2 or 3 weeks.

IgM antibodies do not reach a demonstrable titre by enzyme-linked immunosorbent assay (ELISA) before 2 weeks have elapsed since infection. For this reason, it is not recommended that this test be performed during the first week of having the disease. In some cases, the ELISA test becomes positive after 6–12 weeks (Fig. 4).

Treatment and prevention

There is no known effective anti-viral treatment for Chikungunya fever, which limits therapeutic measures to administration of non-salicylate analgesics and non-steroidal anti-inflammatory drugs.

Although interferon alfa and ribavirin have been demonstrated to have a synergistic effect on Chikungunya virus, there are no

clinical tests that support the use of this combination. Chloroquine does not seem to have efficacy for the treatment of arthralgia.

As there is no effective vaccine, prevention is focused on preventing mosquito bites. In endemic areas, these measures are complemented with a fight against vectors by means of sanitation and fumigation measures that tend to limit the number of mosquitoes.

Those who travel to endemic areas can apply insecticides such as permethrin directly to their clothing. This insecticide has a long residual effect, withstanding 4–5 washings. Repellents for topical use that contain N,N-diethyl-m-toluamide in concentrations of 30–35% can also be used. Repellents should be applied directly to exposed skin, avoiding contact with the conjunctiva and other mucosae owing to the substances' toxicity. It is recommended that concentrations lower than 30% be used in children.

Perfumes should be avoided, since they attract mosquitoes. Air conditioning aids in limiting the movement of mosquitoes inside houses.

Conclusions

In the Americas, the management of viruses transmitted by arthropods has not been very successful. Dengue continues to occur in a region that stretches from the United States to Patagonia. In recent years, there have been outbreaks of a never-before-seen magnitude. West Nile virus, an arbovirus that was recently introduced in the Americas, is now endemic in the region. In the last decade, this virus expanded its area from Canada to Argentina. Recently, another related arbovirus, St. Louis encephalitis virus, caused several confirmed cases in Argentina.

The recent occurrence of cases with autochthonous transmission of Chikungunya in the Caribbean region significantly increases the risk of introduction in the Americas, especially in tropical and sub-tropical areas where *A. aegypti* is widely distributed, and the presence of a population that is sensitive to the infection creates ideal conditions for the virus's introduction and spread.

Considering the high attack rate during Chikungunya epidemics, the resulting major outbreaks have the potential to overwhelm existing healthcare systems and public health infrastructure. Given this scenario, both health authorities and primary care physicians should be alert to the potential risk and the need to manage and fight against insect vectors.

Conflict of interests

The author declares that there are no conflicts of interest.

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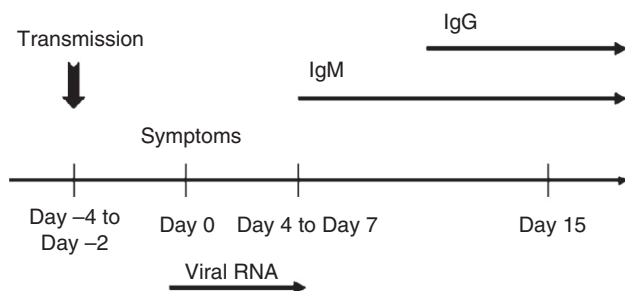


Fig. 4. Chronology of diagnosis of Chikungunya fever. Optimal time in the clinical course to perform the different diagnostic tests.

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