

# Is Chikungunya an Emerging Infectious Disease as a Potential Viral Epidemic?

## *Chikungunya: Potansiyel Epidemik Bir Viral Enfeksiyon*

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Alphaviruses are known to give rise to a spectrum of disease in humans, ranging from silent asymptomatic infections to undifferentiated febrile illness to devastating encephalitis. Alphaviruses have been associated primarily with fever and polyarthrititis. Chikungunya and other mosquito-borne alpha-viruses have been described as causing a similar, dengue-like illness. Chikungunya (CHIKV) is a mosquito-borne viral illness that is endemic in rural areas of Africa and Asia. Chikungunya means “that which bends up” in the reference to the crippling manifestations of the disease. It is suggested that there remains much unknown and unreported information regarding the disease course and pathophysiology of mosquito-borne alpha-viral arthropathic diseases such as CHIKV, Mayaro, O’Nyong, Ross River, Sindbis, and Barmah Forest Fever. CHIKV and other alphaviruses infections are somewhat prevalent in certain foreign countries but are relatively indistinct to Turkish practitioners. CHIKV has to be gain an extremely importance with its epidemics and similar clinic course when the world-wide global pandemic risk of H5N1 avian influenza infection is discussed intensively, today.

Key words: *Aedes albopictus*; alphaviruses; arthralgia; chikungunya; encephalitis.

Alfavirüsler sessiz, belirti vermeden seyreden hastalıklardan tanımlanamamış ateşli hastalıklara ve ağır ensefalite kadar uzanan geniş bir klinik yelpaze içinde enfeksiyonlara yol açan etkenlerdendir. Alfavirüsler başlıca ateş ve poliartritlerle birlikte dir. Chikungunya (CHIKV) *Aedes albopictus* sineği aracılığıyla bulaşan, viral kaynaklı, yüksek ateşle seyreden, kanamalı bir hastalıktır. Chikungunya hastalığı Afrika ve Güney Asya’da Hint Okyanusuna kıyaslı olan ülkelerde görülmektedir. Chikungunya’nın manası hastalarda kas ve eklem ağrılarınin neden olduğu görüntü nedeniyle “kıvrılıp yatıran” hastalık olarak bilinmektedir. Burada CHIKV, Mayaro, O’Nyong, Ross Nehri, Sindbis, and Barmah Orman Ateşi gibi sivrisineklerle geçen artropatik hastalıkların seyri ve patofizyolojisi hakkında kısaca bilgi verilmiştir. CHIKV ve diğer alfavirüs enfeksiyonlarının bazı yabancı ülkelerdeki (İtalya, Fransa gibi) durumu bilinmektedir. Ancak ülkemizde bu durum belirsizdir. CHIKV dünya çapında pandemilerle ortaya çıkan H5N1 avian influenza enfeksiyonu (kuş gribi) gibi salgınlar oluşturması ile günümüzde daha da önem kazanmaktadır.

Anahtar sözcükler: *Aedes albopictus*; alfavirus; artralji; chikungunya; ensefalit.

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sing a similar, dengue-like illness. Chikungunya (CHIKV) is a mosquito-borne viral illness that is endemic in rural areas of Africa and Asia.<sup>(1-4)</sup> Chikungunya means, “That which bends up” in the reference to the crippling manifestations of the disease. International classification of disease codes (ICD)-10 for Chikungunya is A92.0.

AJCI 2007;1(3):205-210

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**Table 1.** Alphaviruses used in Phylogenetic Analyses.

Disease / Virus	Region	Vector
EEE	East of USA, Canada, South America, Caribbean	<i>Culex</i>
WEE	North and South America	<i>Culex tarsalis</i>
VEE	Mid-South America	<i>Culex, Aedes, Mansonia,</i> <i>Psorophora, Deinocerites</i>
Sindbis	Russia, Europe, Scandinavia, Africa (New Zealand, Egypt, Israel)	<i>Culex, Culiseta, Aedes,</i>
CHIKV	Africa, Asia	<i>Aedes</i>
O’Nyong-Nyong	Africa (Uganda)	<i>Anopheles</i>
Ross River	Australia, Oceania	<i>Aedes</i>
Mayaro	Caribbean, Brasil, Bolivia	<i>Haemagogus</i>

EEE: East equine encephalitis; WEE: West equine encephalitis; VEE: Venezuela equine encephalitis; CHIKV: Chikungunya.

Typical clinical manifestations include the abrupt onset of fever, chills, headache, myalgias and arthralgias, and during a 2- to 4-day course may include epigastric pain, backache, nausea, vomiting, photophobia, vertigo, dizziness, retro-orbital pain, and rash. The arthralgias are typically the most severe and prominent manifestation, are often temporarily incapacitating, and may persist for up to 2 months. In addition to CHIKV, five other mosquito-borne alpha-viruses have been described as causing a similar, dengue-like illness.<sup>(1-3,5)</sup>

It is suggested that there remains much unknown and unreported information regarding the disease course and pathophysiology of mosquito-borne alpha-viral arthropathic diseases such as CHIKV, Mayaro, O’Nyong, Ross River, Sindbis, and Barmah Forest Fever (Table 1). CHIKV and other alphaviruses infections are somewhat prevalent in certain foreign countries but are relatively indistinct to Turkish practitioners.

**EPIDEMIOLOGY**

CHIKV is spread by the bite of an infected mosquito. Mosquitoes become infected when they feed on a person infected with CHIKV. Monkeys, and possibly other wild animals, may also serve as reservoirs of the virus. Infected mosquitoes can then spread the virus to other humans when they bite. *Aedes aegypti* (the yellow fever mosquito), a household container breeder and aggressive daytime biter, which is attracted to

humans, is the primary vector of CHIKV to humans (Fig. 1). *Aedes albopictus* (the Asian tiger mosquito) may also play a role in human transmission in Asia, and various forest-dwelling mosquito species in Africa have been found to be infected with the CHIKV.<sup>(6,7)</sup> The *Aedes albopictus* mosquito lays its eggs in any water-containing receptacle, in both urban and non-urban areas. Pots, tyres and tin cans are favoured habitats.<sup>(8)</sup>

CHIKV is responsible for extensive *Aedes aegypti*-transmitted urban disease in cities in Africa and major epidemics in Asia. CHIKV activity in Asia has been documented since its isolation in Bangkok in 1958.<sup>(5,9)</sup> Other countries, which have reported CHIKV activity, include Cambodia, Vietnam, Myanmar, Sri Lanka, India, Indonesia, and the Philippines. CHIKV virus is transmitted in the savannahs and forests of tropical Africa by *Aedes* mosquitoes of the subgenera *Stegomyia* and *Diceromyia*. *Aedes aegypti* is an important vector in urban epidemics in both Africa and Asia.<sup>(4)</sup>

*A. albopictus* is known to be currently spreading around the world. The mosquito can transmit the virus, but its actual vectorial capacity (environment-dependent). *A. albopictus* is also capable of transmitting dengue fever.<sup>(10)</sup> The *Aedes albopictus* mosquito that has been the epidemic vector in Réunion has already been introduced into several European countries, including Belgium, Bosnia and Herzegovina, Croatia, France, Greece, the Netherlands, Serbia



**Fig. 1.** The *Aedes aegypti* mosquito.

**Table 2.** Number of Chikungunya Cases Reported by Various Countries, February 2005 to April 2006\*.

Country	No. of Cases	Suspected (S) or Confirmed (C)	Reporting Period
<b>Indian Ocean and Asia</b>			
Réunion	255.000	S	28 Feb 05 - 30 Apr 06
Mayotte	5.834	S	1 Jan 06 - 16 Apr 06
Seychelles	8.818	S	1 Jan 06 - 26 Feb 06
Seychelles	158	S	29 Mar 06 - 2 Apr 06
Comoros	8	C	20 - 26 Mar 06
Madagascar	2	C	6 - 12 Mar 06
Mauritius	6.000	4800 S + 1200 C	1 Jan 06 - 5 Mar 06
India	> 100.000	S	Dec 05 - 23 Apr 06
Malaysia	200	S	1 Jan 06 - 21 Apr 06
<b>Europe (Imported Cases)</b>			
France	307	C	1 Apr 05 - 28 Feb 06
Germany	17	C	1 Jan 06 - 21 Apr 06
United Kingdom	9	2 C + 7 S	1 Dec 05 - 20 Apr 06
Belgium	12	C	Dec 05 - 26 Apr 06
Czech Republic	1	C	1 Jan 06 - 20 Apr 06
Norway	1	C	1 Jan 06 - 19 Apr 06

\*The data in this table is not meant to be exhaustive, and is based on information supplied by Eurosurveillance editorial advisors and the Institut de Veille Sanitaire in April and May 2006.

and Montenegro, Slovenia, Spain and Switzerland. Importation is thought to have occurred through the trade of used tires (the mosquito lays eggs in pools of water in the tires) and ornamental plants which are transported in water, notably species of *Dracaena* trees and shrubs (including ‘lucky bamboo’). This has resulted in the establishment of this mosquito in Albania, Northern/Central Italy, and limited foci in other countries. Most of southern Europe has potentially favourable climate and ecological conditions for local establishment of *A. albopictus*. However, the vectorial competence and capacity of *A. albopictus* for transmission of CHIKV in infested areas is not yet known, and research is currently being carried out in France. Based on current knowledge, it is considered highly likely that this mosquito species is able to transmit the virus within Europe, but the efficiency of virus transmission is not yet known.<sup>(11)</sup>

CHIKV is certainly underestimated as a causative agent of febrile and arthralgic illness in European travellers coming back from endemic areas.

Moreover, the broad geographic distribution of the mosquito vectors *A. albopictus* and *A. aegyptii* may allow the expansion of CHIKV to new areas, such as Americas and to a lesser extent Europe. By searching more systematically, CHIKV in European travellers it could be inferred some epidemiological information about worldwide CHIKV activity, changes in the local epidemiology of the disease and genotype worldwide distribution. The information gathered by this kind of study may benefit both travellers and the host countries as well.<sup>(11)</sup>

Since the end of 2004, CHIKV has emerged in the islands of the southwestern Indian Ocean (i.e Comoros, Mayotte, Reunion, Mauritius, and Madagascar) and is causing one of the largest outbreaks described in the past 40 years.<sup>(12)</sup> After the Grande Comore Island epidemic, the first cases were reported in the Reunion Island (775.000 inhabitants) with in March 2005. CHIKV led to over 244.000 reported cases and 205 deaths (directly or indirectly linked) as of April 20, 2006 (Table 2).<sup>(11,13)</sup>

In recent CHIKV epidemic of Reunion Island, was a surprise because of its unexpected emergence, its magnitude, and clinical cases rarely or never described before severe forms, central neurological involvement, hepatic cytolysis, severe lymphopenia, severe dermatological involvement, deaths and neonatal infections. This was the first manifestation of the intrusion CHIKV on the island, which benefits from a sub-tropical climate, but also of an occidental healthcare environment, with a non-immune population.<sup>(6,9,11)</sup>

#### CLINICAL FINDINGS AND SYMPTOMS

CHIKV is an acute viral infection characterized by a rapid transition from a state of good to illness that includes several arthralgia and fever. The incubation periods ranges from one day to 2 weeks. Temperatures rises abruptly to as high as 40°C and is often accompanied by shaking chills after a few days fever may abate and recrudescence giving rise to a “saddleback” fever curve.

The arthralgias are polyarticular, migratory, and predominantly affect the small joints of the hands, wrists, ankles and feet, with lesser involvement of larger joints. It is favoring the previous injuries. Pain on movement is worse in the morning, improved by mild exercise, and exacerbated by strenuous exercise. So patients typically avoid movement as much as possible. Joint may swell without significant fluid accumulation. Patients with milder articular manifestations are usually symptom-free within a few weeks, but more severe cases require months to resolve entirely. Generalized myalgia, as well as back and shoulder pain is common.

The rash characteristically appears on the first day of illness, but onset may be delayed. It usually arises as a flush over the face and neck, which evolves to a maculopapular or macular form that may be pruritic. The latter lesions appear on the trunk, limbs, face, palms and soles in that order of frequency. Petechial skin lesions have also been noted.

Headache, photophobia, retro orbital pain, sore throat with objective signs of pharyngitis, nausea and vomiting also occur in this setting.<sup>(3)</sup> Children may display neurological symptom.<sup>(7)</sup> Fifteen cases of meningoencephalitis have been notified, of which 12 have been microbiologically confirmed by the French national reference

centre for arboviral diseases in Lyon. Cases of neonatal encephalopathy and major algic syndrome associated with vertical transmission of the virus were also reported. Six cases occurred in newborns, and mother-to-child transmission is strongly suspected in these cases. The other nine identified cases occurred in adults with pre-existing medical conditions. All cases have since progressed favorably. This is the first time that meningoencephalitis forms of CHIKV, and mother-to-child transmission of the chikungunya virus, have been reported in CHIKV outbreaks.<sup>(8)</sup>

Previously undescribed clinical forms have been reported 1 to 1.000 patients with a confirmed CHIKV infection developed severe clinical signs. These clinical manifestations were acute liver failure in five cases and multi-organ failure in 10 cases, although the direct relationship between CHIKV infection and this multi-organ failure is still under investigation.<sup>(14)</sup>

CHIKV infection (whether clinical or silent) is thought to confer life-long immunity.

#### LABORATORY

The tests available are detection of antigen and antibody in blood by serology by ELISA test. An IgM capture ELISA is necessary to distinguish the disease from dengue fever and other likely illnesses.<sup>(5)</sup> Chikungunya Virus-specific IgM antibodies are readily detected by capture ELISA in patients recovering from CHIK infection and they persist in excess of 6 months. Hemagglutination inhibition (HI) antibodies appear with the cessation of viremia. All patients will be positive by day 5 to 7 of illness. Neutralization antibodies parallel HI antibodies.

A study of chikungunya virus was carried out to establish Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) as a rapid detection technique of the virus.<sup>(6)</sup>

Virus isolation is readily accomplished by inoculation of mosquito cell culture, mosquito, mammalian cell culture or suckling mice. Viremia will be present in most patients during the first 48 hours of disease and may be detected as late as day 4 in some patients. The true incidence of the disease is thought to be much higher, because due to the self-limiting nature of the illness a large proportion of patients did not go to hospital, and even for those who did, laboratory diagnosis

proved difficult as RT-PCR was positive for the virus in samples collected between the first and fourth day only, indicating the viremic phase of the infection.<sup>(15)</sup>

The erythrocyte sedimentation rate is usually markedly elevated and the C-reactive protein is positive. In complete blood count, mild leukopenia with relative lymphocytosis is frequently seen.

#### COMPLICATIONS

Severe arthritic involvement is most commonly seen in adults. Whereas children occasionally present with symptoms referable to the central nervous system (CNS) including seizures and convulsions. Long-term joint involvement has been reported in association with human leukocyte antigen B27.<sup>(3)</sup>

Residual joint symptoms for several years have been described in some patients after CHIKV infection.<sup>(16,17)</sup>

#### DIFFERENTIAL DIAGNOSIS

Acute CHIKV fever typically lasts a few days to a couple of weeks, but as with dengue, West Nile fever, O'Nyong-Nyong fever and other arboviral fevers, some patients have prolonged fatigue lasting several weeks. Additionally, some patients have reported incapacitating joint pain, or arthritis, which may last for weeks or months. The prolonged joint pain associated with CHIKV is not typical of dengue. Co-infection of dengue fever in many areas may mean that CHIKV fever cases are sometimes clinically misdiagnosed as dengue infections, therefore the incidence of CHIKV fever could be much higher than what has been previously reported.<sup>(6,17,18)</sup>

The clinical features of ONNV infections include a low-grade fever, symmetrical polyarthralgia, lymphadenopathy, generalized papular or maculopapular exanthema, and joint pain.<sup>(19)</sup>

Important bacterial diseases that should be mentioned in the differential diagnosis of CHIKV infection are brucellosis, typhoid/paratyphoid and leptospirosis. Malaria as a parasitic disease also should be investigated in CHIKV infection suspected cases.

CHIKV has to gain an extremely importance with its epidemics and similar clinical course when the worldwide global pandemic risk of

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#### TREATMENT AND PREVENTION

The illness is usually self-limiting and will resolve with time. No vaccine or specific antiviral treatment for CHIKV fever is available. Treatment is symptomatic; resting, fluids, and ibuprofen, naproxen, acetaminophen, or paracetamol may relieve symptoms of fever and aching. Acetyl-salicylic acid should be avoided during the acute stages of the illness. Chloroquine phosphate (250 mg/day) has been tried in the treatment of arthralgia associated with CHIKV with promising results.<sup>(5,16,20)</sup>

Prevention tips are similar to those for dengue or West Nile virus:

- Use insect repellent containing a DEET or another suitable active ingredient on exposed skin.
- Wear long sleeves and pants (ideally treat clothes with permethrin or another repellent).
- Have secure screens on windows and doors to keep mosquitoes out.
- Get rid of mosquito breeding sites by emptying standing water from flowerpots, buckets and barrels. Change the water in pet dishes and replace the water in birdbaths weekly. Drill holes in tire swings so water drains out. Keep children's wading pools empty and on their sides when they are not being used.

In concision; prevention includes avoiding mosquito bites in endemic areas by using protective clothing, barriers, and repellents. Infected persons should be protected from further mosquito exposure (staying indoors and/or under a mosquito net during the first few days of illness) so that they can't contribute to the transmission cycle.<sup>(1,16)</sup> The virus is killed by common disinfectants, moist heat and drying. The vector (a mosquito) also needs to be controlled with insecticides.

Edelman et al. were conducted a phase II, randomized, double blind, placebo-controlled, safety and immunogenicity study of a serially passaged, plaque-purified live CHIKV vaccine in 73 healthy adult volunteers. This promising live vaccine was safe, produced well-tolerated side effects, and was highly immunogenic.<sup>(21)</sup>

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