

- In water tanks which cannot be emptied or controlled introduce larvivorous fish (*Gambusia*).
- Weeds and tall gras around houses should be kept short.
- Use insecticides for water tanks which cannot be emptied or inhabited with larvivorous fish.

Active surveillance by physicians using an appropriate case definition should be established. This will facilitate the detection of possible cases. Laboratory facilities for rapid diagnosis and confirmation should be established and continuously trained for diagnosing human cases. Public health authorities should be on alert and prepared for an outbreak organizing and training surveillance teams and mosquito combating teams.

Relevance in travel medicine

Many of the known endemic areas of Chikungunya fever, like the islands of the Indian Ocean, India or Malaysia and Indonesia are popular tourist destinations. Therefore in a large number of travellers returning from those countries an acute Chikungunya fever was diagnosed [4, 5, 6]. In a recent publication of a French Tropical Medicine Department 121 human cases were reported with more than half coming from Mauritius and about 10 % each returning from the Seychelles, from India and from La Reunion [5]. Most cases were seen in France as Mauritius and La Reunion are popular destinations for French people [5]. From April 2005 to December 2006 about 900 human cases were diagnosed in travellers returning from endemic and epidemic areas to France [10]. In a study at the Bundeswehr Institute of Microbiology in Munich, Germany 11/192 (5.8 %) patients with fever and additional constitutional symptoms returning from tropical areas were diagnosed with Chikungunya fever. In the

same patient population however 23/192 cases of acute dengue fever were seen at the same time.

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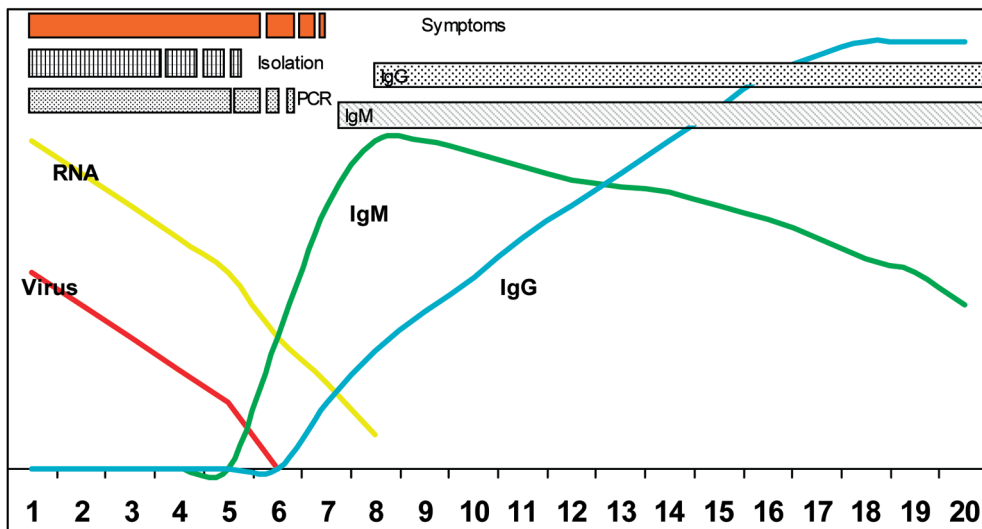


Figure 2. Natural history of Chikungunya virus infection and time course for diagnostic procedures
Slika 2. Prirodni tijek Chikungunya virusne infekcije i vremenski slijed dijagnostičkih postupaka

Laboratory testing relies on the good quality of samples. In case of Chikungunya virus the sample of choice is serum. Physicians should notice as follows:

For isolation or detection of viral RNA, blood taken during the first 7 days can be used. Best results are obtained during the first five days of illness [13]. The blood should be transported at 2–8 °C as fast as possible to the laboratory. Do not freeze the blood. For longer transports (> 48 hours) serum should be separated and transported on dry ice.

Serological detection of antibodies reliably works only after the first week of illness.

For serological antibody detection blood should be transported at 2–8 °C. For longer transports (> 48 hours) serum should be separated and can be frozen.

For serological detection of IgM antibodies ELISA or indirect immunofluorescence can be used.

For serological detection of IgG antibodies ELISA or indirect immunofluorescence can be used. For the confirmation of an acute infection a significant difference in titer in paired sera is required.

For serological testing hemagglutination inhibition test can be used. For the confirmation of an acute infection a significant difference of titer in paired sera is required.

Cross reactions to other alphaviruses do occur in ELISA, hemagglutination inhibition and indirect immunofluorescence.

Unspecific cross reactions have to be excluded by using a neutralisation test.

Treatment

There is no specific treatment for Chikungunya fever. Usually the illness is self limiting. Supportive care is indi-

cated according to the dominating symptoms. Movement and mild exercise may improve stiffness and arthralgia [13]. Non-steroidal anti-inflammatory drugs are used to treat arthralgias [13]. Aspirin should be avoided due to its potency of causing coagulation disorders. In arthritis symptoms which do not respond to anti-inflammatory drugs chloroquine can be useful. Life-threatening symptoms require admission in intensive-care units.

Prophylaxis, prevention and surveillance

There is currently no vaccine against Chikungunya fever available. However, some candidate vaccines are under study and especially various armed forces are interested due to the sudden potential loss of battle capacities during an outbreak in the troops. Otherwise exposure prophylaxis at the moment is the only possibility of individual protection. The individual exposure prophylaxis has to be maintained the whole day as *Aedes* mosquitoes may be active the whole day [8]. This includes:

- Wear long sleeves and pants.
- Use insect repellents containing a registered active ingredient on exposed skin.
- Use insecticide-treated bed-nets.
- Use mosquito-safe screens on windows and doors to keep mosquitoes out.
- Sleep in acclimatised rooms or under insecticide-treated bed nets.

For prevention of outbreaks the following measure have to be taken:

- Control all water tanks, cisterns, barrels, trash containers and use tight fitting lids.
- Remove or regularly empty all stagnant water sources in and around houses.

to mosquitoes of the genus *Anopheles*, the vectors of malaria, mosquitoes of the genus *Aedes* usually are also feeding during daylight hours. Transmission via blood donations seems also possible, however it plays only a minor role during an epidemic situation. Vertical maternal transmission of Chikungunya virus has been observed in the recent outbreak in La Reunion. During an epidemic situation this kind of transmission also seems to be of minor importance.

Mosquitoes are mainly infected by sucking blood from viremic patients. So far, the so-called mechanism of transovarial transmission, the transmission from females to their offspring has only been reported for Chikungunya virus in the laboratory, but it seems to be of little importance during an epidemic for the maintenance of the virus in mosquito population in nature. An urban transmission cycle is defined as a cycle between humans as vertebrate hosts and mosquitoes. In Africa and possibly in Southeast Asia also a transmission cycle between mosquitoes and monkeys as vertebrate hosts has been detected. This cycle is named as sylvatic transmission cycle [10]. Human cases of Chikungunya fever usually peak with the maximum of mosquito populations during or at the end of the rainy season.

Chikungunya virus is endemic in areas of tropical Africa and Asia. In Africa virus could be detected in western, central, eastern and southern Africa. The islands of the eastern Indian Ocean seem to be epidemic, however at the moment few or now cases are reported [11]. Therefore the virus activity seems to be on halt. On the Indian subcontinent the Chikungunya outbreak seems to continue in several states. Furthermore outbreaks continue to occur in Malaysia and Indonesia [12]. The outbreak in September 2007 in Italy seems to be over. No new cases have been detected or diagnosed in the affected region in 2008.

Clinical symptoms and pathogenesis

The incubation time of Chikungunya fever is on average 4–8 days, ranging from 2 to 12 days. The onset of clinical symptoms is abrupt with high fever which rises up to 40 °C accompanied by intermittent chills and joint pain. The acute phase lasts for 2–3 days. Then the temperature may remit for 1–2 days after a gap of 4 to 10 days, resulting in a typical saddle back fever curve. Constitutional symptoms are headache, back pain, myalgia and, as a prominent symptom, intense arthralgia. The arthralgias are polyarticular, migratory and predominantly affect the small joints of extremities (hands, ankles, wrists, phalanges) and, on a lesser extend also the larger joints. Swelling of the affected joints may occur but fluid accumulation is uncommon [13].

Cutaneous manifestations are typical. Many patients present with a flush over the face and trunk, followed by a

maculopapular rash involving trunk and limbs and rarely also face, palms and soles. Rarely petechiae are found. During the acute infection most patients note medium headache, photophobia and retro-orbital pain. Conjunctivitis or conjunctival injections may also occur. Some patients complain of sore throat and pharyngitis.

Patients with milder symptoms are usually free of symptoms within a few weeks. More severe cases require months to resolve completely. According to some studies up to 12 % of infections develop into a chronic form of arthralgias which may persist for months to years [13]. The cutaneous manifestations may fade or desquamate. Chikungunya fever is usually not considered to be a life-threatening disease. However, the very young and very old age groups and immunosuppressed patients have a more severe course of the disease. During the epidemic in La Reunion more than 150 deaths were directly or indirectly associated with Chikungunya fever. Meningo-encephalitis was an uncommon complication. The rare association with multi organ failure is still under investigation. Thrombocytopenia may occur and may also cause complications with intravascular coagulation or intra-cerebral hemorrhage [9].

Laboratory diagnosis

The definite diagnosis of Chikungunya fever can only be made by the laboratory. However Chikungunya fever should be suspected in an epidemic situation in all human cases fitting to a case definition. In a non-epidemic situation or with sporadic or imported cases the physician should take into account this disease. An appropriate virological and/or serological testing should be done in all areas where *Aedes albopictus* and/or *Aedes aegypti* are prevalent and where cases with signs and symptoms that are suggestive of Chikungunya fever occur.

The following case definition is used in countries with endemic or epidemic occurrence of Chikungunya fever [2]:

Suspected case:

Acute illness characterized by sudden onset of fever with one or several of the following symptoms: joint pain, headache, backache, photophobia, arthralgia, rash occurring in an area known to be endemic for Chikungunya fever or in an area where *Aedes aegypti* or *Aedes albopictus* are prevalent

Probable case:

As above and positive serology (when a single serum is obtained during the acute or convalescent phase)

Confirmed case:

A probable case with either:

A significant (minimum fourfold) IgG antibody difference in paired serum samples

Detection of IgM antibodies

Isolation of virus from the serum of the patient

Detection of Chikungunya virus RNA in sera by RT-PCR

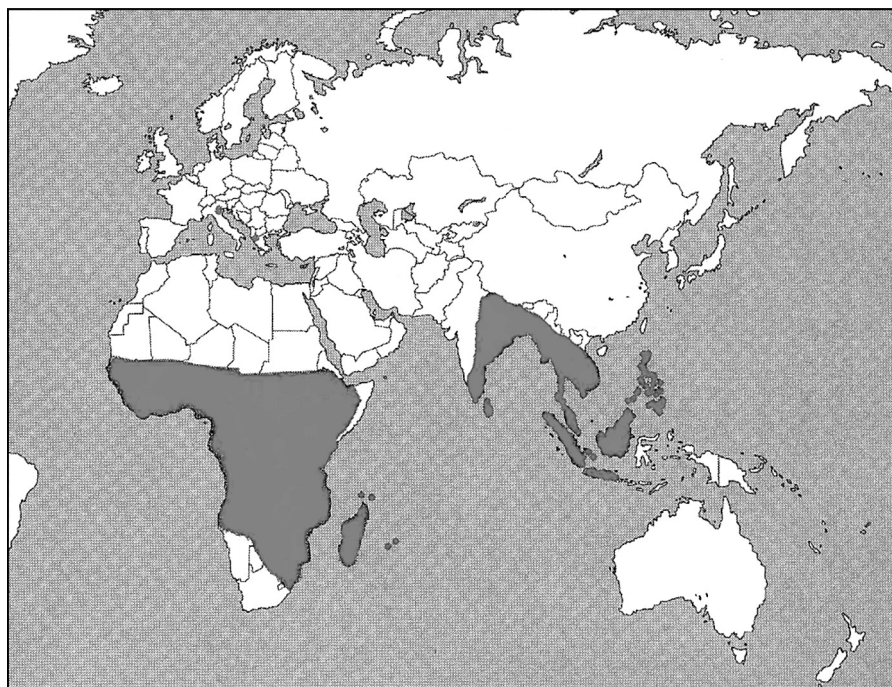


Figure 1. Known global distribution of Chikungunya fever
Slika 1. Globalna rasprostranjenost Chikungunya groznice poznata do sada

few years due to two events: in 2004 a large outbreak started in Kenya, east Africa and moved via the Comoros Islands, the Island La Reunion (266,000 cases out of 750,000 inhabitants) and other islands on the southwest Indian Ocean to reach India in 2005/2006, where a large outbreak occurred (estimated 1,400,000 patients). This current outbreak continues to spread and large numbers of patients are still seen in parts of India, Indonesia and Malaysia [3]. During this outbreak hundreds of travellers from industrialized countries with a temperate climate became infected with Chikungunya virus and returned home while being viremic [4]. Many strains of the virus could be isolated from such patients and the virus could be first isolated from travellers returning to France [5, 6]. During this outbreak it was recognized that the current strain circulating on the islands of the Indian Ocean better adapted to another mosquito species, the Asian tiger mosquito, *Aedes albopictus*, which was found highly prevalent and which efficiently transmitted the virus between humans.

Additional concern among virologists and epidemiologists in Europe was raised by two events: an autochthonous transmission of the virus to a nurse in France, and a recent outbreak at Ravenna, in the North-east part of Italy, very close to a popular touristic area [7]. This is thought to be the first outbreak of a tropical human arboviral disease in modern times in Central Europe. However, introduction and sporadic cases of Chikungunya fever were already reported in 1987 from Albania near Lake Skutari and it was thought that migrating birds from Africa had introduced the virus there. It should also be remembered that the last

big Dengue fever epidemic in the Mediterranean dates back to 1928, a time when *Aedes aegypti* was still highly prevalent in many areas of the Mediterranean coast regions.

The current outbreak of Chikungunya fever in Italy could be traced back to a traveller returning from India (Kerala) in a viremic state and it was favoured by the diffusion of *Aedes albopictus* in the affected area in Italy [7]. *Aedes albopictus* turned out to be an effective transmitter of the virus between humans. It was introduced in the 1990s into the Mediterranean region and spread over total Italy and to parts of France and Spain and to parts of the eastern Adriatic coast (Croatia, Albania, Greece). All together *Aedes albopictus* is currently endemic in 12 European countries [8]. There are now concerns of a wider spread of Chikungunya fever and fears of an endemic or even epidemic situation like in the islands of the Indian Ocean, India and Southeast Asia some years ago. The following paper will provide a review on various aspects of Chikungunya fever emphasizing the practical approach for an early detection in order to start prompt measure to control the spread of this infection.

Transmission and Epidemiology

Chikungunya virus is most commonly transmitted to humans through the bite of mosquitoes. Main vectors of the virus are mosquitoes of the genus *Aedes*, mainly the species *Aedes aegypti* and *Aedes albopictus* [9]. In contrast

Chikungunya Fever – Invading Tropical Virus in the Mediterranean Region?

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Review article

Chikungunya fever is a virus infection caused by a virus of the genus Alphavirus, family Togaviridae. It is transmitted in nature exclusively by mosquitoes of the genus *Aedes*. It causes a febrile illness with prominent arthritis and incapacitating arthralgias, which may last for months. In 2004, a large outbreak started in East Africa, spread over India to Southeast Asia and caused an estimated several million human cases in the affected countries. In 2007, Chikungunya virus was introduced by a viremic traveller into Italy and there caused an outbreak with more than 200 human cases. The virus there was transmitted by the Asian tiger mosquito (*Aedes albopictus*). Chikungunya virus in combination with *Aedes albopictus* forms a complex with high potential for emergence in so far unaffected regions. The actual paper reviews the current situation and presents a case definition for detection of clinically suspicious cases for rapid intervention of transmission.

Chikungunya groznica – invazivni tropski virus u mediteranskoj regiji?

Pregledni članak

Chikungunya groznica je virusna infekcija koju uzrokuje virus roda Alphavirus, iz obitelji Togaviridae. U prirodi se prenosi isključivo komarcima roda *Aedes*. Uzrokuje febrilnu bolest s izraženim artritismom i artralgijskim bolovima koje mogu trajati i do nekoliko mjeseci. Godine 2004., zabilježena je velika epidemija u istočnoj Africi koja se proširila preko Indije do jugoistočne Azije, uzrokujući, prema procjenama, zarazu nekoliko milijuna stanovnika zahvaćenih zemalja. Godine 2007., Chikungunya virus je unesen u Italiju preko zaraženog putnika uzrokujući epidemiju sa više od 200 zaraženih osoba. Virus je tamo prenio azijski tigrasti komarac (*Aedes albopictus*). Chikungunya virus u kombinaciji sa *Aedes albopictus* čini cjelinu s visokim potencijalom za pojavljivanje u do sada nezahvaćenim područjima. U radu se donosi pregled trenutne situacije i definiraju kriteriji za otkrivanje klinički suspektnih slučajeva koji zahtijevaju brzu intervenciju.

Introduction

Chikungunya fever is an infection caused by Chikungunya virus, a so-called arbovirus (arthropod-borne virus) which is transmitted to humans by the bite of mosquitoes of the genus *Aedes*. The name is derived from the African Makonde dialect and means »that which bends up«. In reference to the stooped posture developed as a result of the arthritic symptoms of the disease. The disease itself seems to be an old one and probably was seen in human population since centuries. However there was probably a lot of confusion with dengue fever and other unspecific viral diseases.

Chikungunya virus was first isolated in Tanganyika (Tanzania) in 1953 from the serum of a febrile human [1]. In the following years and decades the virus was isolated numerous times in central, southern and western Africa and in many parts of south-eastern Asia and of the Indian subcontinent. Since its first isolation and identification, Chikungunya virus has caused uncountable outbreaks and epidemics in both Africa and Asia involving hundreds of thousands of people [2].

While until few years ago Chikungunya fever was mainly in the minds of some tropical virologists and travel medicine specialists this disease came to the attention of a broad scientific and medical community during the last