CHIKUNGUNYA

Chikungunya is an arboviral disease transmitted through mosquitoes.
It is important to make a differential diagnosis with other arboviral diseases with similar symptoms, such as dengue, or with other febrile infections, such as malaria in endemic areas.

THE CHIKUNGUNYA VIRUS[1-4]

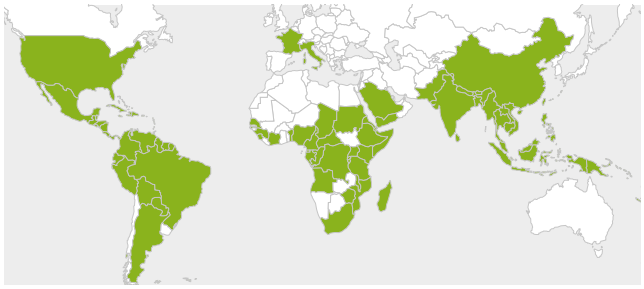
- Chikungunya virus (CHIKV) is an **arbovirus (Arthropod-Borne-Virus)** transmitted through the bites of infected female Aedes mosquitoes (most commonly *Aedes aegypti* and *Aedes albopictus*).
- CHIKV is a **single-stranded RNA virus** that belongs to the genus Alphavirus (family *Togaviridae*).
- CHIKV exists as a **single serotype** thought to confer life-long immunity in recovered individuals.
- CHIKV comprises **three main genetic lineages**: Asian, West African and East/Central/South African (ECSA). ECSA gave rise to the Indian Ocean Lineage (IOL) responsible for epidemics in the Indian Ocean islands, mainland India and Europe since 2004.

EPIDEMIOLOGY AND BURDEN OF CHIKUNGUNYA[1,3-5]

- First identified in Tanzania in 1952, the disease remained quiescent for nearly 50 years with **periodic and limited outbreaks in sub-Saharan Africa and Southeast Asia**.
- Following a **major outbreak in the Indian Ocean and India** in 2005-2006 causing over 1.5 million cases, CHIKV has now spread all over the world and has been identified **in over 60 countries** throughout Asia, Africa, Europe and the Americas. Outbreaks can occur even in temperate regions.
- In addition to regular outbreaks in Asia and Africa, CHIKV has caused **large outbreaks in the Americas** and more **sporadic and clustered cases in Europe**.
- It has been shown that this rapid expansion of the disease was the consequence of a **genetic mutation** directly responsible for a **significant increase in CHIKV infectivity for *Ae. albopictus***. Due to the widespread distribution of *Ae. albopictus*, this mutation facilitated the potential for CHIKV to spread in regions where *Ae. albopictus* is more common than *Ae. aegypti* and to permanently extend its range into Europe and the Americas.

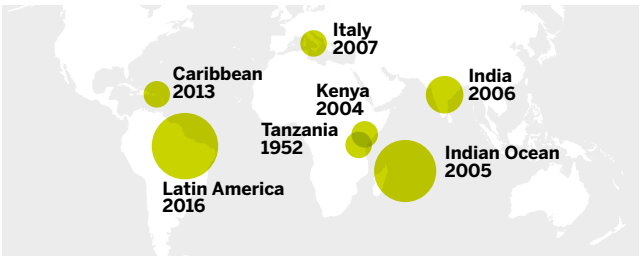
COUNTRIES AND TERRITORIES WHERE CHIKUNGUNYA CASES HAVE BEEN REPORTED* (AS OF MARCH 2, 2022)

Source: CDC https://www.cdc.gov/chikungunya/pdfs/Chik_World_Map_10-30-20-P.pdf
Accessed on March 7, 2022.

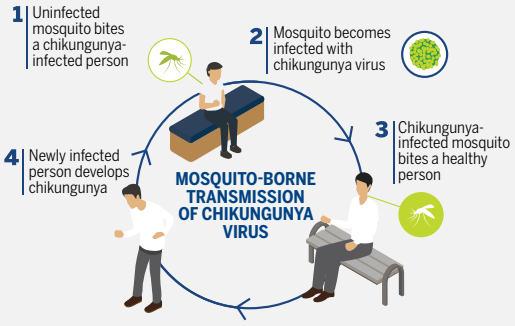


*Does not include countries or territories where only imported cases have been documented.

MAJOR OUTBREAKS OF CHIKUNGUNYA WORLDWIDE



HOW CHIKUNGUNYA IS TRANSMITTED



TRANSMISSION[1]

- Chikungunya virus is transmitted between humans via mosquitoes. When an uninfected mosquito feeds upon a viremic person (with virus circulating in their blood), the mosquito can pick up the virus as it ingests the blood.
- The virus then undergoes a period of replication in the mosquito, after which it can be transmitted back to a new, naïve host, when the mosquito next feeds.
- The virus again begins to replicate in this newly infected person and amplify to high concentrations. If a mosquito feeds on them during the time they have virus circulating in their blood, the mosquito can pick up the virus, and the transmission cycle begins again.

CLINICAL PRESENTATION[2,6,7]

- Chikungunya disease is very similar to other widespread arbovirus infections such as dengue, with some clinical specificities.
- Chikungunya is usually a **mild disease**, and rarely causes death. However, newborns infected around the time of birth, older adults (≥65 years), and people with medical underlying conditions are at risk for more severe and sometimes lethal disease.
- The **incubation period** is silent and lasts for **4 to 7 days**.

STAGES OF CHIKUNGUNYA[7]

Acute phase

- 1 to 2 weeks (up to 3 weeks in some patients)
- Sudden high fever and joint pain (due to inflammatory arthralgia and arthritis)
- Other symptoms may include myalgia, headache, macular to maculopapular rash

Post-acute phase

- Day 21 to end of 3rd month
- Concerns >50% of patients with clinical symptoms
- Persistence of initial inflammatory events, which slowly regress

Chronic phase

- Absence of return to pre-existing condition >3 months after onset of symptoms
- Several months to several years
- Clinical symptoms similar to post-acute stage
- Concerns up to 40% - 60% of patients depending on the population studied
- Can impair patients' quality of life

RELATIVE FREQUENCY OF CHIKUNGUNYA SYMPTOMS[8]

Adapted from Tanabe *et al. Front Cell Infect Microbiol*. 2018;8:345.

Most common symptoms → **Least common symptoms**

DIAGNOSTIC APPROACH[2,3,9]

- As **symptoms are not specific**, chikungunya fever can be confused with other febrile infectious diseases during the acute phase, or with other rheumatologic diseases during the post-acute and chronic phase.
- **Differential diagnosis** relies on residence, travel history, and exposure.
- During the initial febrile phase, it is necessary to consider other Flavivirus infections (most commonly dengue and Zika virus disease), other Alphavirus infections, and other febrile infections such as leptospirosis, malaria, rickettsia.
- In regions where several pathogens are co-circulating, **co-infections are possible**, especially dengue-chikungunya or malaria-chikungunya.
- **Etiological confirmation** of chikungunya requires laboratory testing:
  - routine laboratory tests provide non-specific results: lymphopenia without leukopenia, mild thrombocytopenia, mild transaminase elevations, and an elevated C-reactive protein level;
  - confirmation of CHIKV infection therefore relies on specific laboratory assays.

LABORATORY CONFIRMATION[3,7,9]

The diagnostic approach for chikungunya confirmation is based on:

- **direct methods** which detect the virus in the blood: virus isolation or nucleic acid amplification test, such as PCR;
- **indirect methods** such as serological testing which detect the host immune response to CHIKV infection.

Virus isolation and Plaque Reduction Neutralization Test (PRNT) are considered as reference methods for, respectively, direct virus detection and serology; however they are not used in routine practice (requiring specialized laboratories).

The indication for testing depends on when the samples are collected after onset of symptoms, and interpretation of test results is based on the epidemiological context and clinical information provided by the clinician (time of onset of symptoms is mandatory).

BIOMARKER KINETICS

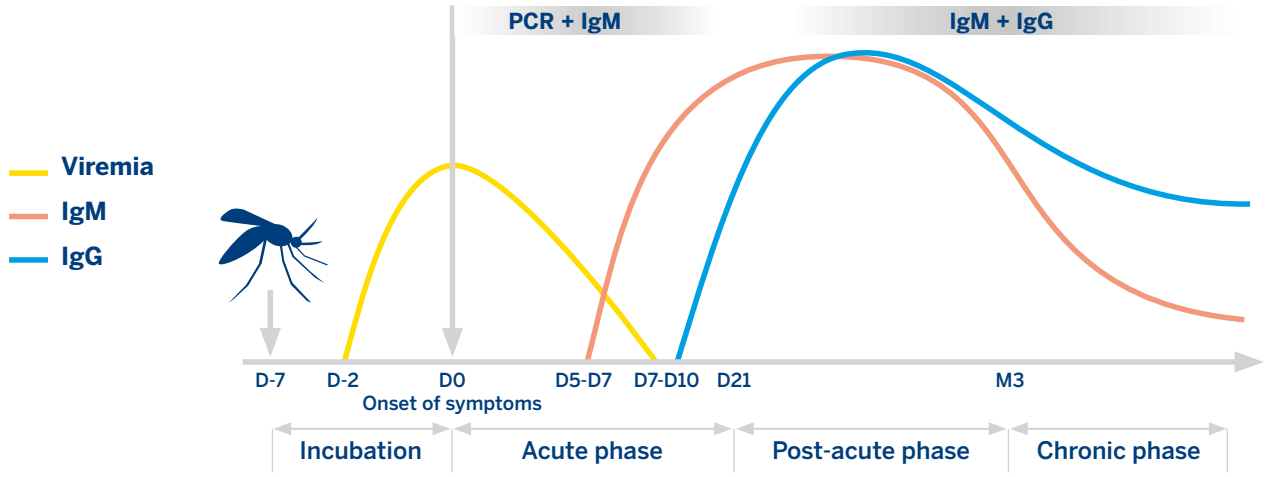
Viremia (presence of the virus in the blood) is detectable up to 5-7 days after onset of symptoms.

Anti-chikungunya IgM and **IgG** are antibodies produced by the immune system after chikungunya infection:

- **IgM** are detectable as soon as 5-7 days post-infection (sometimes earlier). It has traditionally been admitted that IgM persist for several weeks up to 3 months. However, it has now been demonstrated that IgM can be detected in the blood of infected persons up to at least 10-12 months after the acute phase.
- **IgG** are detected a few days after IgM (7-10 days post-infection) and persist for years.

RECOMMENDED DIAGNOSTIC METHODS FOR CHIKUNGUNYA ACCORDING TO THE DELAY AFTER INFECTION[7, 10]

Adapted from Simon *et al. Med Mal Infect*. 2015;45(7):243-263 and Santé Publique France.



TREATMENT AND PREVENTION[1,2,11]

As there is **no effective antiviral treatment**, the management of chikungunya is **symptomatic**.

- Assess hydration and hemodynamic status and provide supportive care as needed.
- Evaluate for other serious conditions (e.g., dengue, malaria, and bacterial infections) and treat or manage appropriately.
- Use acetaminophen or paracetamol for initial fever and pain control:
  - if inadequate, consider using narcotics or non-steroidal anti-inflammatory drugs (NSAIDs);
  - if the patient may have dengue, do not use aspirin or other NSAIDs (e.g., ibuprofen, naproxen, toradol) until they have been afebrile ≥48 hours and have no warning signs of severe dengue.
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, or physiotherapy.

In early 2024, **the first chikungunya vaccine, Ixchiq**, was approved by the U.S. Food and Drug Administration (FDA) for individuals 18 years of age and older who are at increased risk of exposure to chikungunya virus.

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