

### 3 | CHIKUNGUNYA VIRUS

#### 3.1 | Disease agent

- Chikungunya virus (CHIKV)

#### 3.2 | Disease agent characteristics

- Family: *Togaviridae*; Genus: *Alphavirus* includes 29 viruses within the genus comprising three groups. CHIKV is divided into two genotypes: Asian and East Central South African (ECSA). It is a member of the Semliki Forest antigenic complex along with Mayaro, Ross River (RRV) and O'nyong-nyong (ONNV) viruses; all are human pathogens.
- Virion morphology and size: Enveloped, icosahedral nucleocapsid symmetry, spherical particle, 60–70 nm in diameter.
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~11.8 kb in length.
- Physicochemical properties: Susceptible to inactivation by 70% ethanol, 1% sodium hypochlorite, 2% glutaraldehyde and lipid solvents (ether and detergents). Inactivated by dry or wet heat >56°C and drying. Relatively stable at –40°C.

#### 3.3 | Disease name

- Chikungunya

#### 3.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; although no transfusion transmission has been documented, RNA detection in plasma from blood donors, rapid reemergence in 2005–2007 and increased pathogenicity, suggest that transfusion transmissions are possible.
- Public perception and/or regulatory concern regarding blood safety: Low in the United States; Moderate in non-US endemic and threatened areas.
- Public concern regarding disease agent: Very low to absent in the United States; Moderate/High in non-US endemic and threatened areas.

#### 3.5 | Background

- First isolated in 1952 by R. W. Ross from a Tanzanian patient with fever and joint pains. The name, from the

Makonde language, is translated as “that which bends up” referring to the contorted posture of infected patients afflicted with the severe joint pain.

- Endemic in sub-Saharan Africa, India, Southeast Asia, and the Philippines.
- Large-scale outbreaks occurred during 2005–2007 in the Indian Ocean islands of Comoros, Madagascar, Mayotte, Mauritius, Seychelles, and Reunion, then spread to several western states in India, Southeast Asia and northern Italy.
- Local transmission was identified in northern Italy in the summer of 2007.
- From 2005 to 2007, the East/Central/South/Africa (ECSA) lineage was responsible for at least 1.3 million human cases worldwide believed largely due to a point mutation changing alanine to valine at position 226 in the CHIKV E1 gene.
- On December 5, 2013, autochthonous CHIKV transmission was reported for the first time in the Americas, with cases in the Caribbean islands, first in St. Martin in the French Antilles, followed by autochthonous cases reported in Martinique. By late February 2014, over 2,000 laboratory-confirmed cases attributable to both travel within the Caribbean and autochthonous cases in St. Martin, Guadeloupe, St. Barthelemy, Martinique, St. Maarten (the Dutch side of St. Martin), Anguilla, Dominica, the British Virgin Islands, French Guiana and Aruba had been reported, demonstrating rapid dissemination after introduction. *A. aegypti* was the vector in these cases. Next generation sequencing was used to characterize the full-length RNA from the sera of two viremic patients and identified the virus as belonging to the Asian genotype (not the ECSA genotype that was responsible for the prior massive outbreaks in the islands of the Indian Ocean, western India, southeast Asia, Africa and northern Italy). The virus lacks the E1 A226V mutation making *A. albopictus* a less competent vector; the virus is phylogenetically related to strains identified in Indonesia in 2007, in China in 2012 and in the Philippines in 2013.
- During the Caribbean outbreak in 2014, 11 autochthonous cases were reported in South Florida of a total of 2811 cases in the continental US. In 2020, the continental US case count dropped to 33.
- More than 130 arboviruses are known to cause human disease; most of public health importance belong to the genera *Flavivirus*, *Alphavirus* and *Orthobunyavirus*. Many are nationally notifiable via state reporting to the US CDC (ArboNet) and include dengue virus, Zika virus, California serogroup viruses, CHIKV, eastern equine encephalitis virus, Powassan virus, St. Louis encephalitis virus, West Nile virus, western equine encephalitis virus and yellow fever virus.

### 3.6 | Common human exposure routes

- Vector-borne; transmission occurs through a mosquito-human-mosquito cycle

### 3.7 | Likelihood of secondary transmission

- Vertical transmission was reported during the Reunion Island epidemic. This includes *in-utero* infections resulting in fetal deaths and perinatal infection with symptomatic disease in the affected neonates.

### 3.8 | At-risk populations

- Elderly
- Pregnant women
- Immunosuppressed patients
- Travelers to epidemic or endemic areas

### 3.9 | Vector and reservoir involved

- Mosquitoes, mainly of the *Aedes* family: *A. aegypti*, *A. albopictus*, *A. polynesiensis*, as well as: *Culex*, *Anopheles*, *Mansonia*, *Eretmapodites*, and *Coquillettidia*.
- Infected species: birds, humans, chimpanzees, some domestic animals, reptiles.
- Human-mosquito-human infection occurs without the need for an intermediate amplifying host.
- CHIKV is enzootic across tropical regions of Africa and Asia. In West and Central Africa, CHIKV is believed to be maintained in a sylvatic cycle involving wild nonhuman primates and forest-dwelling *Aedes* mosquitoes.
- While forest-dwelling mosquito species have historically been the primary vectors in Africa, the urban mosquito, *A. aegypti* present in most of the tropical world, has been found to be an extremely efficient vector since it preferentially feeds on humans, often bites several persons during interrupted blood meals, and has adapted to live and breed peridomestically. *A. albopictus* is an alternate vector in areas where *A. aegypti* are not present.
- A mutation affecting the CHIKV E1 gene (A226V) allows increased viral loads in *A. albopictus*, which is believed to be responsible for the severity and extent of the 2005–2007 outbreaks in the islands of the Indian Ocean, western India, southeast Asia and northern Italy.
- The distribution of *A. albopictus* extends from tropical and temperate Asia to Europe, the Americas and the

islands of the Indian and Pacific oceans. It survives farther north than *A. aegypti* because it is better adapted to cold weather. Transovarial transmission in mosquitoes is likely to contribute to local viral maintenance and a continuous, low-level incidence of human infections that establishes a higher baseline immunity to these viruses within the local population.

### 3.10 | Blood phase

- Viremia is present in most patients during the first few days of infection in both symptomatic and asymptomatic infections. Viral loads in the range of  $1.7 \times 10^3$  to  $1.2 \times 10^{10}$  copies/mL have been documented in patients during epidemics. Viral loads in the range of  $1.7 \times 10^3$  to  $1.2 \times 10^{10}$  copies/mL have been documented in patients during epidemics.
- The kinetics of any presymptomatic viremia are poorly characterized.
- Modeling on Reunion Island during the 2005–2007 epidemic involving >300,000 clinical cases (40% of the island's population) estimated a mean risk of viremic donations of 132/100,000 donations, peaking at 1500/100,000. The model assumed 15% of infections remain asymptomatic based on serosurveys and assumed 1.5 days of asymptomatic viremia before the onset of clinical illness and 7.5-days duration of viremia for donors remaining asymptomatic. It is interesting that, despite these high estimates, no cases of transfusion transmission were recognized. The mean estimated risk, had collections continued during the outbreak, was 13/10,000 donations overall with a peak of 150/10,000. Subsequent CHIKV RNA testing by NAT of platelet donors demonstrated rates of RNA of 0.4%.
- Another model used data from a 2007 outbreak in Northern Italy involving approximately 250 cases resulting from an index case in a resident returning from India. Like the above outbreak, *A. albopictus* was the vector. The model estimated a peak prevalence of 1.07 infections/100,000 donors, 0.13 potentially infectious blood components, and a severe outcome in 1/100,000 transfused patients during the outbreak based on an assumed 0.1% infected individuals who will develop severe disease.
- During the peak of an intensive epidemic in Thailand in 2009, 9% (12/127) of persistently asymptomatic patients (location, age and gender-matched to cases) were identified who were RNA positive or seroconverted. Of the 12 patients, six seroconverted without detectable viremia while six were viremic with viral titers ranging from 84 to  $2.9 \times 10^5$  pfu/mL (median

$3.4 \times 10^3$ ). In contrast, 91% (122/134) of symptomatic cases had viral titers that ranged from  $13$  to  $2.9 \times 10^8$  pfu/mL (median  $5.6 \times 10^5$ ).

### 3.11 | Survival/persistence in blood products

- Unknown

### 3.12 | Transmission by blood transfusion

- Theoretical, since transfusion transmission has not been described despite widespread epidemics. In a systematic literature review and meta-analysis, the reported prevalence of CHIKV RNA in blood donors was 1.9% in Puerto Rico (2014), 1.0% in Thailand (2009), and 1.0% in French Polynesia (2014–2015).
- Animal models using intravenous inoculation are able to demonstrate transmission of CHIKV. Limited data suggest that clinical manifestations may correlate with the dose of CHIKV in the inoculum.
- From September 2014 to February 2015, 7 pregnant women with serological and PCR-positive test for CHIKV delivered 8 infants with CHIKV.

### 3.13 | Cases/frequency in population

- Outbreaks are sporadic and explosive.
- CHIKV has been identified in over 100 countries in Asia, Africa, Europe and the Americas.
- The number of cases varies depending on the immunity of the exposed population. It has been estimated that about 40% of the 700,000 residents of Reunion Island were infected during the 2005–2007 epidemic, and as part of the same outbreak, a subsequent 1.3 million cases have occurred in India.
- Autochthonous transmission was described in northern Italy in the summer of 2007 involving approximately 250 cases.
- A substantial number of imported cases have been documented in the United States and in European travelers returning from endemic areas. From 1995 to 2009, 109 cases of CHIKV were reported to the US CDC (ArboNet) from travelers, most of whom had traveled to India; no cases were autochthonous and 12% of cases were viremic.
- During September 2014 (the height of the epidemic in the United States), 11 autochthonous cases were identified in South Florida.

- During 2022 (as of Dec 19), 363,206 cases and 76 deaths were reported by the European CDC (ECDC) with the majority reported from Brazil followed by India, Guatemala, Thailand and Paraguay. No autochthonous cases were reported in Europe. According to PAHO, of these, 251,216 cases and 75 deaths were reported in the Americas.

### 3.14 | Incubation period

- Estimated to range from 3 to 12 days, without a prodrome

### 3.15 | Likelihood of clinical disease

- It is assumed that inapparent infections are common with estimates varying from 3% of infections to as high as 38%.

### 3.16 | Primary disease symptoms

- CHIKV is in a group of Alphaviruses (RRV, ONNV, Igbo Ora, Sindbis, Mayaro and Barmah Forest) that are associated primarily with polyarthritides and rash.
- High fever ( $39.5$ – $40^\circ\text{C}$ ) rapidly emerges and is associated with headache, myalgia, and incapacitating joint pain (polyarthralgia), followed by a pruritic, maculopapular rash 4–8 days later, which is concurrent with leukopenia. Joint pain is symmetric and occurs commonly in the wrists, elbows, fingers, knees and ankles.
- Acute febrile phase usually resolves after 1 week. Residual incapacitating arthralgia may persist for many months in 10%–15% of subjects. Occasional eye, heart and neurologic complications have also been reported.
- Symptoms are similar to dengue and Zika virus infections making a clinical diagnosis difficult.
- Once an individual has recovered, current evidence suggests that they are likely immune from future infection.

### 3.17 | Severity of clinical disease

- Meningoencephalitis has been described in the epidemic on Reunion Island; 1/1000 cases were classified as severe. Other rare complications include uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, myelitis, Guillain-Barré syndrome, and cranial nerve palsies.

- Persons at risk for severe disease include neonates exposed intrapartum, older adults (e.g., >65 years), and persons with underlying medical conditions (e.g., hypertension, diabetes, or cardiovascular disease).
- Joint signs and symptoms may persist for months; up to 64% of patients reported joint stiffness and/or pain for more than 1 year after infection.

### 3.18 | Mortality

- Overall case-fatality rates may reach 1/1000.

### 3.19 | Chronic carriage

- No

### 3.20 | Treatment available/efficacious

- No specific antiviral therapy.
- Supportive care with rest and fluids.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve acute pain and fever.
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, and physiotherapy.

### 3.21 | Agent-specific screening question(s)

- No specific question is in use; the current deferral criteria for travel to at-risk malaria areas encompasses many of the regions affected by the recent outbreaks.
- Not currently indicated because transfusion transmission has not been demonstrated.
- Some authorities in the European Union and elsewhere have implemented temporary deferral periods following any travel to the tropics including areas that are not malaria endemic. This would mitigate risk from dengue, CHIKV and other acute pathogens by preventing donation until resolution of asymptomatic viremia. It would be associated with a substantial operational burden and significant loss of donors according to donor travel surveys. The utility of any such intervention is speculative in the absence of proven CHIKV transfusion transmission despite the magnitude of prior epidemics.
- A survey in the United States representing a large proportion of blood from 2014 to 2015 looked at 14- versus 28-day deferral periods following travel to endemic areas to estimate donor loss. Results varied by season and geographic area representing regions that would trigger

deferrals. Less than a 1% deferral rate was projected for a 14-day deferral limited to the Caribbean and the Americas versus 3% or greater if a 28-day deferral for all travel outside of the United States and Canada was used.

- Another strategy is the use of information sheets to enhance postdonation symptom reporting to facilitate quarantine and withdrawal of potentially infectious components.

### 3.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Diagnostic tests include virus isolation from serum, RT-PCR, IgM-specific antibody by EIA or hemagglutination inhibition assay (HI), detection of neutralizing antibody by HI, and demonstration of a rise in serum IgG antibody titer between acute infection and convalescence.
- A NAT screening test was implemented on Reunion Island for platelet components by the Établissement Français du Sang. NAT was also introduced in the French Antilles for all donations involving a red cell component.
- Multiplexed NAT assays are being developed with dengue, Zika and other arboviruses.

### 3.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Some blood collection agencies have implemented a temporary deferral period for donors who have traveled to non-malarious areas experiencing a CHIKV outbreak. The appropriate deferral period for clinical chikungunya is unknown but would likely be on the order of several weeks after the resolution of symptoms.

### 3.24 | Impact on blood availability

- Agent-specific screening question(s): Not generally considered applicable due to concerns of donor loss without demonstrated efficacy
- Laboratory test(s) available: Not applicable

### 3.25 | Impact on blood safety

- Agent-specific screening question(s): Not generally considered applicable due to questions of sensitivity and specificity
- Laboratory test(s) available: Not applicable

### 3.26 | Leukoreduction efficacy

- Unknown

### 3.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in the removal of enveloped viruses.

### 3.28 | Other prevention measures

- Mosquito control and avoidance particularly during dawn to dusk hours; repellents and wearing clothing that minimize skin exposure.
- WHO encourages countries to develop and maintain the capacity to detect and confirm cases, manage patients and implement social communication strategies to reduce the presence of the mosquito vectors.
- Pathogen inactivation technology and NAT for virus detection were introduced in Reunion Island for platelet components. In the French Antilles, following introduction of the virus in 2013, donations were being held in quarantine for 3 days to facilitate receipt of postdonation information, pathogen inactivation for platelets is being used, and plasma is being imported from the mainland. In addition, a sample of all donations were sent to France and tested individually by a commercial RT-PCR assay (Altona).
- No vaccine or specific treatment is currently available.

#### SUGGESTED READING

1. Appassakij H, Khuntikij P, Kemapunamanus M, Wutthananarungsan R, Silpapojakul K. Viremic profiles in asymptomatic and symptomatic chikungunya fever: a blood transfusion threat? *Transfusion*. 2013;53:2567–74.
2. Brouard C, Bernillon P, Quatresous I, Pillonel J, Assal A, De Valk H, et al. Estimated risk of chikungunya viremic blood donation during an epidemic on Reunion Island in the Indian Ocean, 2005–2007. *Transfusion*. 2008;48:1333–41.
3. Centers for Disease Control and Prevention. Chikungunya fever. Available from: <http://www.cdc.gov/chikungunya/fact/index.html>. Accessed 27 Jan 2014
4. Charrel RN, de Lamballerie X, Raoult D. Chikungunya outbreaks—the globalization of vector-borne diseases. *N Engl J Med*. 2007;356:769–71.
5. Chikungunya.net. [cited May 2009]. Available from: <http://www.chikungunya.net/index.html>
6. Enserink M. Tropical disease follows mosquitoes to Europe. *Science*. 2007;317:1485.
7. European Centers for Disease Control. Communicable disease threat report: week 51, 18–24 Dec. 2022 <https://www.ecdc.europa.eu/sites/default/files/documents/communicable-disease-threats-report-week-51-2022.pdf>. Accessed 16 Jan 2023

8. Gibney KB, Fischer M, Prince HE, Kramer LD, St George K, Kosoy O, et al. Chikungunya fever in the United States: a fifteen-year review of cases. *Clin Inf Dis*. 2011;52:e121–6.
9. Giménez-Richarte A, de Salazar MO, Arbona C, Giménez-Richarte M, Callado M, Fernández P, et al. Prevalence of chikungunya, dengue and Zika viruses in blood donors: a systematic literature review and meta-analysis. *Blood Transfus*. 2022; 267–80.
10. Griffin DE. Alphaviruses. In: Knipe DM, Howley PM, editors. *Fields Virol*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 1023–67.
11. Heath CJ, Grossi-Soyster EN, Ndenga BA, Mutuku FM, Saho MK, Ngugi HN, et al. Evidence of transovarial transmission of chikungunya and dengue viruses in field-caught mosquitoes in Kenya. *PLoS Negl Trop Dis*. 2020;14(6):e0008382.
12. Higgs S. Editorial: The 2005–2006 chikungunya epidemic in the Indian Ocean. *Vector Borne Zoonotic Dis*. 2006;6:115–6.
13. International Society for Infectious Diseases. Chikungunya (09): Caribbean. ProMED archive number 20140126.2231647. Available from: [www.promedmail.org](http://www.promedmail.org). Accessed 28 Jan 2014
14. Krastinova E, Quatresous I, Tarantola A. Imported cases of chikungunya in metropolitan France: update of June 2006. *Euro Surveill*. 2006;11:e060824.1.
15. Labadie K, Larcher T, Joubert C, Mannioui A, Delache B, Brochard P, et al. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J Clin Invest*. 2010;120:894–905.
16. Leparac-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the Americas. *Lancet*. 2014; 383:514.
17. Lanciotti RS, Kosoy OL, Laven JJ, Panella AJ, Velez JO, Lambert AJ, Campbell GL. Chikungunya virus in US travelers returning from India, 2006. *Emerg Infect Dis*. 2007;13:764–7.
18. Oei W, Janssen MP, van der Poel CL, van Steenberghe JE, Rehmet S, Kretzschmar MEE. Modeling the transfusion risk of emerging infectious diseases through blood transfusion. *Transfusion*. 2013;53:1421–8.
19. Parola P, de Lamballerie X, Jourdan J, Rovey C, Vaillant V, Minodier P, et al. Novel chikungunya virus variant in travelers returning from Indian Ocean islands. *Emerg Inf Dis*. 2006;12: 1493–9.
20. Petersen LR, Stramer SL, Powers AM. Chikungunya virus: possible impact on transfusion medicine. *Transfus Med Rev*. 2010; 24:15–21.
21. Powers A, Logue CH. Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. *J Gen Virol*. 2007;88: 2363–77.
22. Ramful D, Carbonnier M, Pasquet M, Bouhmani B, Ghazouani J, Noormahomed T, et al. Mother-to-child transmission of chikungunya virus infection. *Pediatr Infect Dis J*. 2007;26:811–5.
23. Spencer BR, Stramer S, Dodd R, Kleinman SH, Hollinger B, Krysztof DE, et al. Survey to estimate donor loss to 14- or 28-day travel deferral for mitigation of CHIKV, DENV, and other acute infections. Abstract P1-030A. *Transfusion*. 2015; 55(S3):3A.
24. Taubitz W, Cramer JP, Kapaun A, Pfeffer M, Drosten C, Dobler G, et al. Chikungunya fever in travelers: clinical presentation and course. *Clin Infect Dis*. 2007;45:e1–4.

25. Touret Y, Randrianaivo H, Michault A, Schuffenecker I, Kauffmann E, Lenglet Y, et al. Early maternal-fetal transmission of the chikungunya virus. *Presse Med.* 2006;35:1656–8.
26. Villamil-Gómez W, Alba-Silvera L, Menco-Ramos A, Gonzalez-Vergara A, Molinares-Palacios T, Barrios-Corrales M, et al. Congenita chikungunya virus infection in Sincelejo, Colombia: a case series. *J Trop Pediatr.* 2015;61:386–92.
27. World Health Organization. Chikungunya. <https://www.who.int/news-room/fact-sheets/detail/chikungunya>. Accessed 15 Jan 2023.