Chikungunya Virus

Disease Agent:

- Chikungunya virus (CHIKV)

Disease Agent Characteristics:

- Family: *Togaviridae*; Genus: *Alphavirus* including 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 and O'nyong-nyong 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 >58°C and drying. Relatively stable at –40°C.

Disease Name:

- Chikungunya

Priority Level:

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

Background:

- First isolated in 1953 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 with occasional outbreaks in 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 2005-2007, the ECSA genotype has been 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 December on Martinque. 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* has been 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.

Common Human Exposure Routes:

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

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.

At-Risk Populations:

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

Vector and Reservoir Involved:

- Mosquitoes, mainly of the *Aedes* family: *A. aegypti, A. albopictus, A. polynesiens*, as well as: *Culex, Anopheles, Mansonia, Eretmapodites*, and *Coquillettidia*
- Infected species: Birds, humans, chimpanzees, some domestic animals, reptiles
- Human-to-mosquito-to-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, *Aedes aegypti* present in most of the tropical world, has been

found to be an extremely efficient urban vector since it preferentially feeds on humans, often bites several persons during interrupted blood meals, and has adapted to live and breed peridomestically. *A. albopicus* 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; however, transovarial CHIKV transmission has not been documented so there is no means of viral persistence in the winter.

Blood Phase:

- Viremia is present in most patients during the first few days of disease. Viremia usually disappears by day 6 to 7.
- Viral loads in the range of 1.7×10^3 to 1.2×10^{10} copies per mL have been documented in patients during epidemics.
- The duration of presymptomatic viremia is unknown.
- 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-day duration of viremia for donors remaining asymptomatic. It is interesting that, despite these high estimates, no cases of transfusion transmission were recognized. Estimated risk, had collections continued during the outbreak, were 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 per 100,000 donors, 0.13 potentially infectious blood components and a severe outcome in 0.0001 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 completely and persistently asymptomatic control 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 8.4×10^1 to 2.9×10^5 pfu/mL. In contrast, 91% (122/134) of symptomatic cases had viral titers that ranged from 1.3×10^1 to 2.9×10^8 pfu/mL.

Survival/Persistence in Blood Products:

- Unknown

Transmission by Blood Transfusion:

- Theoretical, since transfusion transmission has not been described despite widespread, very large epidemics.
- Animal models using intravenous inoculation are able to transmit infection with CHIKV. Limited data suggests that clinical manifestations may correlate with the dose of CHIKV in the inoculum.

Cases/Frequency in Population:

- Outbreaks are sporadic and explosive.
- 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 US and in European travelers returning from endemic areas. From 1995-2009, 109 cases of CHIKV were reported to the US CDC (ArboNET) from travelers, most of whom had traveled to to India; no cases were autochthonous and 12% of cases were viremic.

Incubation Period:

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

Likelihood of Clinical Disease:

- No unbiased data are available, but it is assumed that inapparent infections are common with estimates varying from 3% of infections to as high as 38%.

Primary Disease Symptoms:

- High fever (39.5-40°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.

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.

Mortality:

- Overall mortality may reach 1/1000.

Chronic Carriage:

- No

Treatment Available/Efficacious:

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

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. The utility of any such intervention is speculative in the absence of proven CHIKV transfusion transmission despite the magnitude of prior epidemics.
- Another strategy is the use of information sheets to enhance postdonation symptom reporting to facilitate quarantine and withdrawal of potentially infectious components.

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 HI, detection of neutralizing antibody by hemagglutination inhibition assay (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. A NAT screening test will also be introduced in the French Antilles for all donations involving a red cell component.

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.

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

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

Leukoreduction Efficacy:

- Unknown

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.

Other Prevention Measures:

- Mosquito control
- Education
- 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 are being held in quarantine for 3 days to facilitate receipt of post donation information, pathogen inactivation for platelets is being used, and plasma is being imported from the mainland. In addition, a sample of all donations will be sent to France and tested individually by a commercial RT-PCR assay (Altona).

Suggested Reading:

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