

Dengue Viruses

(with comments on Zika virus, another mosquito-borne flavivirus)

Disease Agent:

- Dengue viruses (DENV-1, DENV-2, DENV-3, DENV-4)

Disease Agent Characteristics:

- Family: *Flaviviridae*; Genus: *Flavivirus*
- Virion morphology and size: Enveloped, ~50 nm in diameter
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~10.7 kb in length
- Physicochemical properties: Susceptible to 70% ethanol, 1% sodium hypochlorite, 2% glutaraldehyde and quaternary ammonium compounds; sensitive to heat; low pH inactivates virus
- Dengue viruses are stable in dried blood and exudates up to several days at room temperature.

Disease Name:

- Dengue, dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS)
 - New WHO classification categorizes dengue into dengue, with and without warning signs, and severe dengue, rather than DHF and DSS
- Sometimes referred to as “break-bone fever” because of the nature of the symptoms

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Low in the continental US; priority is related to asymptomatic viremia that has been shown to result in transfusion-transmitted disease and potential for emergence in those parts of the continental US where the vector exists but disease is not endemic. This risk is mitigated by the low rate of autochthonous transmission in the continental US, and by existing malaria deferrals that would exclude much travel from areas of the world where dengue and malaria coexist. Concern is moderate to high in Puerto Rico and non-US endemic areas.
- Public perception and/or regulatory concern regarding blood safety: Moderate in the continental US; moderate/high in Puerto Rico where the virus is endemic and non-US endemic areas
- Public concern regarding disease agent: Very low in the continental US; moderate/high in Puerto Rico where the virus is endemic and non-US endemic areas

Background:

- Dengue is among the most important mosquito-borne viral disease in the world. The disease is caused by four serologically and genetically distinct viruses termed dengue virus

(DENV) -1, -2, -3 and -4. Each DENV has four or more genetic groups (or genotypes).

- In the last 50 years, dengue incidence has increased 30-fold, worldwide.
- Dengue is highly endemic in most tropical and subtropical areas of Asia and the Americas; dengue exists in Africa but degree of endemicity is not known.
- In the US, dengue is endemic in Puerto Rico, Virgin Islands and most US-affiliated Pacific Islands; incidence increases during the wet, hot season of each year. The intensity of annual epidemics is cyclical.
- Throughout the continental US, dengue is the most frequently diagnosed cause of fever in travelers returning from Asia and the Americas.
- Along the US-Mexico border, outbreaks of dengue have been identified in the US when there are epidemics along the Mexican side of the border. CDC serological surveys have demonstrated prevalence of 40% along the US side of the Texas-Mexico border and 78% on the Mexico side. This high rate suggests endemic transmission.
- During 2009-2010, a locally transmitted dengue outbreak was identified in Key West, FL, and isolated autochthonous cases were found farther north in FL.
- During the summer of 2013, a very localized outbreak of dengue occurred among residents of Martin and St. Lucie Counties in Florida. Twenty-two cases were eventually reported. The major blood collection organization briefly suspended collections in the involved counties. This response was made possible by their relatively few collections in the epidemic area and their ability to enhance collections elsewhere. Whether this approach would be feasible in more extensive outbreaks without jeopardizing the blood supply is unknown and dependent on multiple considerations.
- Evidence exists for additional circulation of genetic variants in nonhuman primates.

Common Human Exposure Routes:

- Vector-borne; transmission occurs through a mosquito-human cycle
- The importance of transmission from the sylvatic mosquito-nonhuman-primate cycle is minimal

Likelihood of Secondary Transmission:

- Isolated cases of parenteral transmission; aerosol transmission does not occur.

At-Risk Populations:

- Tropical areas of Asia, Oceania, Africa, and the Americas usually in the monsoon or rainy season, especially among persons residing in substandard living conditions
- Outbreaks in Queensland Australia are occasional, small and quite tightly restricted to Cairns and Townsville.
- Travelers to endemic region (e.g., 3.4 cases/1000 Israeli travelers to Thailand) with highest proportionate morbidity for travelers to Southeast Asia and the Caribbean

- Secondary infections with a new virus type have been associated with an increased risk of severe dengue.

Vector and Reservoir Involved:

- *Aedes* species mosquitoes
- Both urban (human-mosquito) and sylvatic (primate-mosquito) cycles are observed.

Blood Phase:

- Asymptomatic viremia is recognized. Viremia typically begins 2-3 days before the onset of symptoms, and it continues for 4-5 days during acute illness.
- Viremia for dengue 1, 2, and 3 infections ranges from barely detectable to 10^8 virions per mL for 2-12 days (median of 4-5 days); titers for dengue 4 are about 100-fold lower.
- NAT prevalence studies among blood donors in endemic areas (Brazil, Puerto Rico, and Honduras) have shown rates of 0.06%, 0.07-0.2%, and 0.40%, respectively. Virus was cultured from some of these donors.

Survival/Persistence in Blood Products:

- Frozen plasma, red cells and platelets have been associated with transfusion transmission; one case involved a 38-day old red cell unit.

Transmission by Blood Transfusion:

- The first documented transfusion-associated case of dengue occurred in 2002 during a local outbreak in Ma Wan, Hong Kong, an area that is not endemic for dengue. The index recipient was a 76-year-old seronegative woman who developed fever without rash 2 days after receiving a unit of packed red blood cells collected from a 17-year-old donor who was diagnosed with dengue (generalized rash) 7 days postdonation. The blood had been stored at 4-8°C for 38 days prior to transfusion. RT-PCR testing of the recovered donor plasma and archived specimens from the donor and recipient were found to be positive for DENV-1. IgM-specific antibody also developed in the recipient posttransfusion.
- The second documented transfusion transmission was a cluster reported from Singapore, an area endemic for dengue in which three cases occurred from one donation from an infected donor. The donor was a 52-year-old male whose components were transfused to three recipients. The donor reported fever the day following donation, and a stored serum sample was positive for DENV-2 by PCR. Both the RBC and FFP recipients reported fever 1-2 days posttransfusion and tested positive by PCR for DENV-2. Direct sequencing of PCR amplified products from the donor and two recipients showed alignment of envelope segments for DENV-2. The platelet recipient was asymptomatic for dengue. All three recipients tested antibody positive for IgM and/or IgG with documented seroconversion in the RBC recipient 11 days posttransfusion.
- Another report of transfusion transmission was in Puerto Rico in 2007 following tracing of a patient who received an

RNA-positive packed red cell unit from a donor in which greater than 10^8 copies/mL were detected. Donor screening was part of a research study investigating the frequency of donor viremia in Puerto Rico during the 2007 dengue outbreak. Recipient samples were available from the CDC as part of a repository of all clinical cases reported on the island. Both the donor and recipient samples had identical sequences of DENV-2 covering 1500 nucleotides in the envelope region. The recipient developed DHF 4 days posttransfusion.

- Transmission also has been observed after needle stick exposure and in bone marrow and kidney transplant recipients.

Cases/Frequency in Population:

- The incidence is variable, but can be as high as 1-8% during epidemic periods in endemic countries. Worldwide, the WHO estimates 50 to 100 million cases of infection and 500,000 cases of life-threatening severe dengue occur annually (0.5-1.0% of those infected).
- In 2010, the global burden of dengue was estimated at 390 million total infections, of which 96 million were symptomatic.
- In endemic areas, over 90% of the population may be antibody positive.

Incubation Period:

- 3-14 days (usually 4-7 days)

Likelihood of Clinical Disease:

- Low; the US CDC estimates that one-half or more of all dengue-infected individuals are asymptomatic, that is, they have no clinical signs or symptoms of disease. Other reports indicate significant variability with documented asymptomatic to symptomatic ratios of 2:1 to 13:1 depending on circumstances surrounding the acquisition of the data.
- Homologous immunity to a single serotype is complete and probably lifelong, but cross-protection between serotypes lasts less than 12 weeks.

Primary Disease Symptoms:

- Dengue fever presents as an abrupt onset of fever sustained for up to 5-7 days, accompanied by a transient maculopapular rash that occurs in up to 50% of the patients around day 4, severe headache, retrobulbar pain, lumbosacral aching pain ("break-bone fever"), conjunctivitis, and facial flushing followed by myalgia or bone pain, anorexia, nausea, vomiting, weakness, and prostration.
- The rash begins on the legs and trunk and spreads centripetally but spares the soles and palms. It may desquamate. In some cases, a biphasic course may occur.
- Severe dengue (DHF, DSS) is quite rare with less than 0.5% of secondary cases progressing to this outcome. It occurs more often in persons previously infected with another serotype of DENV. The distinctive feature of severe dengue is the rapid onset of capillary leakage (pleural effusion, ascites, or

hypoproteinemia) leading to hypotension and hemoconcentration. This results in shock with a subset presenting with hemorrhagic manifestations (petechiae, epistaxis, gastrointestinal bleeding and menorrhagia) that occurs 4-7 days after onset of the disease often following a period of defervescence.

- Central neurologic disorders (encephalopathy, peripheral mononeuropathy, polyneuritis, etc.) may occur in severe dengue although this relationship is not fully accepted by all experts.
- Convalescence may be prolonged.
- Differentiation from chikungunya is sometimes difficult, although excruciating, symmetrical joint pain, as opposed to myalgia, is more consistent with chikungunya.

Severity of Clinical Disease:

- Moderate to high

Mortality:

- High with severe dengue in many endemic regions (5-20% mortality rate if untreated), but lower death rate (0.2%) with staff experienced in the management of the disease
- WHO estimates 20,000 deaths annually worldwide.

Chronic Carriage:

- None

Treatment Available/Efficacious:

- Supportive treatment only

Agent-Specific Screening Question(s):

- No specific question is in use; however, the current questions related to travel outside US and Canada for malaria deferral will result in deferral for travel to many dengue endemic areas.
- Travel questions could be broadened to include areas where malaria is not present and dengue outbreaks are occurring.
- Some authorities in the European Union and elsewhere have implemented temporary deferral periods following any travel to the tropics that are not malaria endemic. This would mitigate risk from dengue, chikungunya and other acute pathogens; e.g., Zika virus, by preventing donation until resolution of asymptomatic viremia. It would be associated with a significant operational burden and loss of donors. The utility of any such intervention is speculative even for known transfusion-transmitted agents as no transfusion-transmitted dengue from travelers has been reported in the US.
- 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; however, research NAT assays have been used for blood donor prevalence

studies and the detection of virus in asymptomatic individuals. Data from one NAT-reactive donor with RNA reactivity of at least 29 days and whose index donation was infectious in mosquito cell culture indicates that the duration of DENV RNA by a transcription-mediated amplification (TMA) assay may be longer than previously demonstrated with less sensitive PCR assays. However, associated infectivity in the presence of neutralizing antibody is expected to be considerably shorter than the duration of the RNA detection interval.

- NS1 antigen is not as sensitive as virus-specific RNA (at least by TMA) for blood donor screening, but its detection correlates with high RNA titers.
- DENV-specific IgM antibody can be detected by EIA 4-5 days after onset of symptoms and remains detectable for 3-6 months. The detection rate is lower in secondary DENV infection than in primary infection.
- In blood donors studied retrospectively in Puerto Rico in 2005 and in 2007 and confirmed positive for dengue RNA, 1/12 (3.4%) and 6/29 (20.6%) were IgM positive (using the CDC MAC ELISA), respectively. Variability was likely related to the extent of the dengue outbreaks (2007 > 2005).
- Differential diagnosis for Zika virus (see below) should be considered if travel to French Polynesia or other endemic areas has occurred.

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- The appropriate deferral period for clinical dengue is unknown but would likely be on the order of several weeks after the resolution of symptoms.
- Current available scientific data do not support a temporary deferral for donors living in nonendemic or nonoutbreak areas of the US who have traveled to an outbreak and/or endemic area.

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; data collected using research tests indicate impact would be low

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; potential impact of NAT may be significant in dengue endemic areas but minimal in continental US.

Leukoreduction Efficacy:

- No data available. Plasma viremia makes a clinically significant impact unlikely.

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 and avoidance
- Vaccines are in clinical trials.

Comments Related to Zika Virus:

- In 2007, an outbreak of Zika virus, another mosquito-borne flavivirus that has never before been reported outside of Africa or Asia, occurred on Yap Island, a group of four closely grouped islands in Micronesia. Zika virus was originally isolated in 1947 from a rhesus monkey in the Zika forest in Uganda. The virus is believed to be transmitted to humans by infected *Aedes* species mosquitoes. The outbreak was characterized by rash, conjunctivitis, and arthralgia with most infected individuals having only mild symptoms. Although some patient sera had cross-reacting IgM antibody against dengue virus, especially among patients with evidence of previous dengue infections which is common to Micronesia, the illness was clinically distinct from dengue, and Zika RNA was isolated from 15 cases with no other arboviral RNA. A total of 49 Zika virus cases were confirmed of the 185 suspect cases; serosurveys estimated that approximately three quarters of the islands' population (or ~900 people) had illness attributable to Zika virus infection. This outbreak highlights the risk of further expansion of mosquito-borne flaviviruses and the need for robust epidemiologic and laboratory surveillance systems.
- In October 2013, epidemic Zika virus infection recurred on the islands of French Polynesia. By January 13, 2014, 361 laboratory-confirmed and 7156 clinically suspect cases had been reported; however, estimates are that there are more than 35,000 cases as part of this outbreak. This includes the first autochthonous cases identified in New Caledonia where up to 19 autochthonous cases have been reported and 30 in travelers to French Polynesia (February 7, 2013; <http://www.promedmail.org/direct.php?id=20140210.2268533>). Acute fever with a mild headache is common to most cases along with a maculopapular rash that covers most of the body (median of 6 days with range of 2-14 days), arthritis or arthralgia (median of 3.5 days with range of 1-14 days), and conjunctivitis. The US CDC has issued a travel notice reinforcing standard mosquito avoidance measures. There have been no reported cases of transfusion-transmitted Zika virus. An in-house RT-PCR assay was introduced in January 2014 in French Polynesia.

Suggested Reading:

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