Dengue Viruses

Disease Agent:

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

Disease Agent Characteristics:

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

Disease Name:

- Dengue, dengue fever, dengue hemorrhagic fever (DHF), dengue shock syndrome
- Sometimes referred to as "breakbone fever" because of the nature of the symptoms

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Low in the US; priority is related to asymptomatic viremia that may result in transfusion transmission and substantial potential for emergence in the US. This risk is mitigated by the low prevalence of autochthonous transmission in the continental US and deferrals for malaria that would exclude most travelers coming from endemic countries. Concern is moderate to high in non-US endemic areas.
- Public perception and/or regulatory concern regarding blood safety: Very low/Absent in the US; Moderate/high in non-US endemic areas
- Public concern regarding disease agent: Very low/Absent in the US; Moderate/high in non-US endemic areas

Background:

- Dengue is among the most important mosquito-borne viral diseases in the world.
- Emergent in populations outside the US; in the last 50 years, dengue incidence has increased 30-fold.
- Although clinical cases of travel-associated dengue and limited outbreaks do occur in the continental US, most clinical dengue cases in US citizens occur as endemic transmission among residents in some of the US territories.
- 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.

Common Human Exposure Routes:

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

Likelihood of Secondary Transmission:

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

At-Risk Populations:

- Tropical areas of Asia, Oceania, Africa, Australia, and the Americas usually in the monsoon or rainy season, especially among persons residing in substandard living conditions
- 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

Vector and Reservoir Involved:

- *Aedes* species mosquitoes
- Both urban (human–mosquito) and sylvatic (monkey–mosquito) cycles are observed, but the relative importance of the sylvatic cycle to human infection is uncertain.

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 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%, and 0.40%, respectively. Virus was cultured from some of these donors.

Survival/Persistence in Blood Products:

- Unknown

Transmission by Blood Transfusion:

- The first documented transfusion-associated case of dengue occurred during a local outbreak in Ma Wan, Hong Kong, in 2002, 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 dengue virus type 1. IgM-specific antibody also developed in the recipient posttransfusion.

- The second documentation of transfusion transmission was a transmission cluster reported from Singapore, an area endemic for dengue. 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 dengue virus type 2. Both the RBC and FFP recipients reported fever 1-2 days posttransfusion and tested positive by RT-PCR for dengue virus type 2; the donor's and the two recipients' virus were confirmed by sequencing to be dengue type 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.
- 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 worldwide, an estimated 100 million cases of dengue fever and 250,000 cases of life-threatening DHF occur annually.

Incubation Period:

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

Likelihood of Clinical Disease:

- Low; most cases are subclinical.
- Case-infection ratio reported to be 1:10 to 1:100
- Homologous immunity to a single serotype is complete and probably lifelong, but cross-protection between serotypes lasts less than 12 weeks.

Primary Disease Symptoms:

- Classic dengue fever presents as an abrupt onset of high fever sustained for up to 5-7 days, accompanied by a transient maculopapular or morbilliform rash (~50%), 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 trunk and spreads centripetally but spares the soles and palms. It may desquamate. In some cases, a biphasic course may occur.
- Hemorrhagic phenomena may occasionally be seen with petichiae, epistaxis, intestinal bleeding, and menorrhagia, along with central neurologic disorders (encephalopathy, peripheral mononeuropathy, polyneuritis, etc.).
- Convalescence may be prolonged.

- DHF and dengue shock syndrome are primarily diseases of children and are thought to occur in persons previously infected with another serotype of dengue. The distinctive feature of DHF is capillary leakage (pleural effusion, ascites, or hypoproteinemia) accompanied by hemorrhagic manifestations that occur 4-7 days after onset of the disease.

Severity of Clinical Disease:

- Moderate to high; leading cause of hospitalization and death among children in Asia

Mortality:

- High with DHF in many endemic regions (10-20% mortality rate or 25,000 deaths/year if untreated), but lower death rate (0.2%) with staff experienced in the management of the disease

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 most dengue endemic areas.
- Travel questions could be broadened to include areas where malaria is not present and dengue outbreaks are occurring.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists; however, research NAT assays have been used for blood donor prevalence studies.
- Virus isolation or serologic tests (IgG and IgM EIA, HI, CF or plaque-reduction neutralization) and NAT using serotype-specific primers
- Virus-specific IgM antibody can be detected by EIA 4-5 days after onset of symptoms and remains detectable for 3-6 months.

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.
- One possible approach would be to adopt the criteria for WNV, another flavivirus, which would be a deferral of 120 days after resolution of symptoms.

Impact on Blood Availability:

- Agent-specific screening question(s): Not applicable

- 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 applicable
- 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

Other Comments:

- In 2007, an outbreak of Zika virus, a flavivirus related to dengue virus (and WNV) but never before 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 having only mild symptoms. Although some patient sera had IgM antibody against dengue virus, 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 flaviviruses and the need for robust epidemiologic and laboratory surveillance systems.

Suggested References:

1. Ajariyakhajorn C, Mammen MP Jr, Endy TP, Gettayacamin M, Nisalak A, Nimmannitya S, Libraty DH. Randomized, placebo-controlled trial of non-pegylated and pegylated forms of recombinant human alpha interferon 2a for suppression of dengue virus viremia in rhesus monkeys. Antimicrob Agents Chemother 2005;49:4508-14.

2. Bausch DG, Ksiazek TG. Viral hemorrhagic fevers including hantavirus pulmonary syndrome in the Americas. Clin Lab Med 2002;22:981-1020.

3. Brunkard JM, Lopez JL, Ramirez J, Cifuentes E, Rothenberg SJ, Hunsperger EA, Moore CG, Brussolo RM, Villarreal NA, Haddad BM. Dengue fever seroprevalence and risk factors, Texas-Mexico border, 2004. Emerg Infect Dis 2007;10:1477-83.

4. Chuang WW, Wong TY, Leung YH, Ma ES, Law YL, Tsang OT, Chan KM, Tsang IH, Que TL, Yung RW, Liu SH. Review of dengue fever cases in Hong Kong during 1998-2005. Hong Kong Med J 2008;14:170-7.

5. Duffy MR, Chen T, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, Guillaumot L, Griggs A, Bel M, Lambert AJ, Laven J, Kosoy O, Panella A, Biggerstaff BJ, Fischer M, Hayes EB. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med 2009;360:2536-43.

6. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, Keystone JS, Pandey P, Cetron MS; GeoSentinel Surveillance Network. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med 2006;354:119-30.

7. Gubler DJ, Suharyono W, Tan R, Abidin M, Sie A. Viraemia in patients with naturally acquired dengue infection. Bull WHO 1981;59:623-30.

8. Guzman MG, Kouri G. Dengue diagnosis, advances and challenges. Int J Infect Dis 2004; 8:69-80.

9. Linnen JM, Vinelli E, Sabino EC, Tobler LH, Hyland C, Lee TH, Kolk DP, Broulik AS, Collins CS, Lanciotti RS, Busch MP. Dengue viremia in blood donors from Honduras, Brazil, and Australia. Transfusion 2008;48:1355-62.

10. Mohamed H, Linnen JM, Munoz-Jordan JL, Tomashek K, Foster G, Broulik AS, Petersen L, Stramer SL. Dengue virus in blood donations, Puerto Rico, 2005. Transfusion 2008;48:1348-54.

11. Nemes Z, Kiss G, Madarassi EP, Peterfi Z, Ferenczi E, Bakonyi T, Ternak G. Nosocomial transmission of dengue. Emerg Inf Dis 2004;10:1880-1.

12. ProMed. Dengue virus, transfusion transmission—China (HK), Archive number 20021011.5526; 2002. [cited May 2009]. Available from: http://www.promedmail.org

13. Tambyah PA, Koay ES, Poon MLM, Lin RV, Ong BK; Transfusion-Transmitted Dengue Infection Study Group. Dengue hemorrhagic fever transmitted by blood transfusion. N Engl J Med 2008;359:1526-7

14. Wilder-Smith A, Schwartz E. Dengue in travelers. New Engl J Med 2005;353:924-32.