**08-ID-01**

**Committee:** Infectious Disease

**Title:** **Improving Detection and Reporting of Dengue Virus Infections: Designating Dengue a Nationally Notifiable Disease**

## I. Statement of the Problem

Dengue is endemic throughout the tropics and subtropics, and more than 900,000 cases were reported in the Americas in 2007 (1). Dengue is the most common mosquito-borne viral disease of humans (2) and the most common arboviral infection in travelers (3). Dengue is more prevalent than malaria among travelers returning to the United States from the Caribbean, South America, south-central Asia and Southeast Asia (4). An estimated 17 million passengers traveled between the U.S. mainland and dengue-endemic areas of Asia, the Caribbean, Central and South America, and Oceania in 2007 (5). Furthermore, the range of areas of dengue transmission has expanded significantly in recent years (6). Hyperendemicity has been established in many urban centers of the tropics where rapid development has favored vector proliferation. Increasing travel and the lack of a vaccine have likely contributed to dengue's geographic expansion.

Although dengue is endemic in tropical and subtropical areas and the risk of infection among US residents is frequently associated with travel to these areas, the evolving ecology and epidemiology of dengue infections suggest that it does pose an increasing risk to public health in the continental United States. A recent commentary in JAMA asserted that "widespread appearance of dengue in the continental United States is a real possibility" (7). Historically, dengue transmission occurred within the continental United States as early as the 18$^{th}$ century. More recently, local transmission was documented as early as 1934 in Florida (8). During 1980, after a 2-year period of intense transmission of dengue in Mexico, the first locally transmitted dengue cases in the U.S. since 1945 were believed to have occurred among residents of Texas (9). More recently, locally transmitted infections in south Texas were thought to have occurred in 9 patients during 1986 (10), in 7 patients during 1995 (11), in 2 patients in 1999 (12), and in single cases of dengue hemorrhagic fever in 2004 (13) and 2005 (14). Recent studies on the Texas/Mexico border have demonstrated a "small, but significant risk for dengue outbreaks in the continental US" (15) and many more infections are believed to occur than are reported (16). Additionally, from July 1943 to July 1944, a total of 1498 locally transmitted cases occurred in Hawaii after dengue was introduced from Fiji (17). In 2001-2002, the Hawaii Department of Health identified 122 infections including the first autochthonous case of dengue fever since 1944 (18). Analysis of data from the CDC's passive surveillance system in Puerto Rico has clearly shown that the number of cases of travel-associated dengue identified in 2005 (96 cases) nearly equals the number identified during the preceding 5 years combined (98 cases) (19).

Dengue is endemic in Puerto Rico, the US Virgin Islands, and US territories in the Pacific. In 2007, approximately 10,500 cases of dengue were reported among American citizens in the continental United States and its territories. Most of these occurred in Puerto Rico, and extensive travel occurs between Puerto Rico and Puerto Rican communities in the northeastern continental United States and Florida. Similarly, heavy travel and migration along the US/Mexican border increase the possibility that imported cases will continue to occur and that local transmission within the United States could result, particularly in southern and eastern states where mosquito vectors (*Aedes aegypti* and *A. albopictus*) are present. Arizona is experiencing increased presence of *A. aegypti* and health authorities are concerned about increased potential for local dengue transmission because of their proximity to Mexico (20).

The risk of transmission through blood transfusion, as occurred with West Nile Virus, is a further public health risk. Because blood donations are not screened for dengue virus, infected persons may unknowingly donate blood, since high levels of viremia can occur before the onset of illness and many dengue infections are asymptomatic. Viremic blood donors infected with dengue virus have been identified (21).

In summary, increasing international travel along with rapidly increasing disease burden world-wide, endemicity in US territories, sporadic instances of autochthonous transmission in the continental United States, and the potential for transfusion-mediated transmission, suggest that the number of dengue cases in the United States is likely to increase in the future

## II. Background and Justification

The purpose of this position statement is to add dengue to the National Notifiable Diseases Surveillance System list of nationally notifiable infectious diseases. Dengue is not currently included in the list of nationally notifiable diseases (http://www.cdc.gov/ncphi/disss/nndss/casedef/arboviral_current.htm). The case definition has not been amended since 1996 and requires updating to reflect current laboratory diagnositic testing as well as World Health Organization (WHO) case criteria. Variation in state-mandated reporting of dengue infections also hinders the collection of representative national surveillance data.

Currently, 26 states mandate the reporting of dengue infections. In an additional 6 states dengue reporting is considered mandatory within the category of arboviruses. In 2006, dengue cases were identified in 12 of the 32 states (37.5%) that mandate reporting, but these cases were not reported to ArboNet. Because state-mandated reporting requirements for dengue do not necessarily result in the submission of cases to ArboNet, current reporting practices do not generate comprehensive national surveillance data on dengue virus infections. Competent mosquito vectors that could transmit dengue have been identified in 21 of the 32 states (65.6%) where dengue is reportable and in 7 of the 18 states (38.8%) where dengue is not reportable.

Dengue reporting in the United States is conducted through 2 passive surveillance systems maintained by the CDC. The system operated by the CDC Dengue Branch in San Juan, Puerto Rico relies mainly on reports by clinicians to state health departments, which forward patient specimens to CDC for diagnostic testing. Dengue cases are also reported through the ArboNet arbovirus surveillance system. ArboNet officially began to record dengue case reports in July 2004. The ArboNet system relies largely on reports by private laboratories and clinicians to state health departments. Under these circumstances the delay between private laboratory testing and reporting means that specimens are rarely available for confirmatory testing. Analysis of data from these two surveillance systems suggests that there is little overlap of reporting. From 2005 through 2007 each system has received reports of approximately 150 cases per year. However, incomplete demographic information and description of symptoms often limits the usefulness of this information. Without systematic national surveillance it is likely that the number of travel-related dengue cases is significantly underestimated. As a result, national epidemiologic information sufficient to improve knowledge about the risk of dengue infection among US citizens is not available.

CSTE position statement 07-ID-06 adopted in 2006 and entitled “Events that May Constitute a Public Health Emergency of International Concern” specifically included dengue as an example of a disease that can spread rapidly internationally and cause substantial morbidity and mortality The need for domestic surveillance to detect such diseases when they occur, consistent with international public health reporting obligations under the newly adopted International Health Regulations (IHR, 2005), necessitates improved dengue surveillance reporting.

## III. Statement of the Desired Action(s) to be Taken

1. Designate dengue a nationally notifiable disease by adding it to the National Notifiable Diseases Surveillance System list of nationally notifiable infectious diseases. Cases of dengue would be reportable through the existing ArboNet surveillance system.

   *and*

2. Update the existing 1996 dengue case definition and standardize laboratory diagnostic criteria.

## IV. Goals of Surveillance

1. Use data from a more comprehensive dengue surveillance system to monitor trends, identify areas of risk and risk factors to US travelers, target prevention efforts, and inform vaccination recommendations when vaccines become available.
2. Enhance surveillance and increase laboratory testing of suspected human cases of dengue to improve knowledge of dengue epidemiology and more accurately assess the public health burden of illness in US citizens.
3. Enhance healthcare provider awareness of dengue so that cases can be rapidly identified, thereby reducing the possibility of local transmission or establishment of endemicity.
4. Potentially improve clinical management of severe dengue infections.

## V. Methods for Surveillance

Case ascertainment will be conducted through population-wide surveillance. Dengue case reports will derive from laboratory and clinician reporting to state and local health departments, which will conduct individual follow-up consistent with available resources. Data will then be transmitted to the existing national ArboNet surveillance system by individual states. CDC laboratories in Fort Collins and San Juan will continue to test specimens submitted by state, county, or city health departments.

## VI. Criteria for Reporting

### A. Narrative

Reporting of dengue is to be on-going and routine and is not limited to occurrences of multiple cases or outbreaks. The data fields that are contained in the ArboNet surveillance system are identified in Section B below. Date of onset is critical for guiding appropriate laboratory testing and is therefore required before samples can be processed if they are forwarded for CDC testing. Confirmatory testing by CDC laboratories is not required for cases to be classified as confirmed. Any laboratory test results meeting the criteria outlined in the case definition section (VII A below) are acceptable for case classification.

### B. Tables

The data fields for reporting are consistent with those currently used for reporting dengue through ArboNet. Bold fields below are required by the ArboNet system. Implementing HL7 messaging will be encouraged to facilitate automatic transfer of data to minimize the reporting burden and reduce the amount of manual data entry that is required. Electronic case reporting for dengue cases using appropriate ICD-9-CM codes is a longer term goal for reporting and is not currently practiced. Appropriate codes for dengue would be 061 (dengue fever) and 065.4 (mosquito-borne hemorrhagic fever) providing that dengue is specified.

| |
|---|
| **StateID** |
| **Year -- this is automatically populated by the system** |
| **State -- this is automatically populated by the system** |
| **County** |
| **Week -- this is populated by system** |
| **OnsetDate** |
| **ImportedFrom –either out-of-state or out-of-country** |
| **Arbovirus** |

| |
|---|
| **CaseStatus** |
| Age |
| AgeUnit |
| BirthDate |
| **Sex** |
| **Race** |
| **Ethnicity** |
| **ClinicalSyndrome** |
| **Fatality** |
| DateOfDeath |
| LabAcquired |
| NonLabAcquired |
| BloodDonor |
| BloodTransfusion |
| OrganDonor |
| OrganTransplant |
| BreastFedInfant |
| InfectedInUtero |
| Pregnant |
| **AFP** |
| **Hospitalized** |
| **IdentifiedByBloodDonorScreening** |
| **DateOfDonation** |
| **CountryOfOrigin –where infection occurred** |
| **DateOfReport -- populated by the system** |
| **Published -- this is a check box that defaults to yes, must uncheck to avoid data being released to the public or on maps.** |

### C. Reporting disease-specific data elements:

In addition to the data elements listed in Table 1, data on “Country of Origin” (i.e., domestically or internationally) would need to be provided in initial case reports to identify if a case resulted from local transmission rather than being an imported from another country. This information is needed to identify instances of potentially autochthonous transmission.

## VII. Case Definition

### A. Narrative

#### 1. Clinical presentation

Infection with any of the 4 dengue virus serotypes (DENV1-4) can cause disease which may result in range of clinical illness from asymptomatic infection to severe systemic disease. Dengue viruses are transmitted from person to person through the bite of infected *Aedes* mosquitoes (principally *A. aegypti*, but also *A. albopictus*) mosquitoes. Humans are the main amplifying viral host. The intrinsic incubation period in humans is 3-14 days with an acute phase of infection lasting 5-7 days. The extrinsic incubation period in mosquitoes is 8-10 days depending on environmental factors. WHO criteria classify symptomatic dengue infections into 1) undifferentiated fever or viral syndrome, 2) classic dengue fever (DF), and 3) dengue

hemorrhagic fever (DHF)/dengue shock syndrome (DSS). Undifferentiated fever associated with dengue infection is characterized by mild symptoms that are insufficient to meet DF criteria.

DF is most commonly an acute febrile illness defined by the presence of 2 or more of the following clinical symptoms: headache, retro-orbital or ocular pain, rash, myalgia, arthralgia, leukopenia, or hemorrhagic manifestations (e.g., petechiae; purpura/ecchymosis; epistaxis; gum bleeding; blood in vomitus, urine, or stool; or vaginal bleeding). Chills, nausea, and vomiting may also occur but are not case-defining criteria for DF.

DHF is characterized by all of the following; 1) fever lasting from 2-7 days; and 2) evidence of hemorrhagic manifestation or a positive tourniquet test;[†] and 3) thrombocytopenia (≤100,000 cells per $mm^3$); and 4) evidence of plasma leakage shown by hemoconcentration (an increase in hematocrit ≥20% above average for age or a decrease in hematocrit ≥20% of baseline following fluid replacement therapy), or pleural effusion, or ascites or hypoproteinemia. While all 4 criteria must be present to meet the WHO DHF case definition, DF and DHF/DSS should be seen as a clinical continuum with increasing plasma leakage as the hallmark of disease severity. Importantly, cases with hemorrhagic manifestations alone do not constitute DHF and should be considered cases of DF.

DSS refers to cases of DHF in which circulatory failure is present as evidenced by rapid and weak pulse and narrow pulse pressure (<20mm Hg) or age-specific hypotension and cold, clammy skin and restlessness.

Asymptomatic infections and undifferentiated fevers are the most common manifestation of dengue virus infection and represent 50%-80% of cases. DF is frequently self-limiting although it can be incapacitating and require hospitalization. Treatment is symptomatic and supportive. Severe manifestations (DHF/DSS) are rare but may be fatal. Without proper treatment, DHF case fatality can exceed 20%. With modern intensive supportive therapy, case fatality can be reduced to <1%. Maintenance of the circulating fluid volume is the central feature of DHF case management. Other, less common clinical syndromes may include myocarditis, pancreatitis, hepatitis, or neuroinvasive disease.

The variability in clinical illness associated with dengue infection and its non-specific symptomology emphasize the need for laboratory confirmation of all suspected cases. Overlap among the various clinical syndromes is common and the CDC Dengue Branch is available for consultation about appropriate case classification.

> [†]The tourniquet test is performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for 5 minutes. A test is considered positive when 20 or more petechiae per 2.5 $cm^2$ (1 $in^2$) are observed. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive, sometimes strongly positive, if the test is conducted after recovery from shock.

**2. Laboratory Criteria for Dengue Diagnosis**

1. Dengue-specific IgM antibodies present in serum at a 2-fold higher level than to another flaviviral antigen in a single sample by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), *or*
2. Seroconversion from negative for dengue-specific serum IgM antibodies in an acute phase (≤ 5 days after symptom onset) specimen to positive for dengue-specific serum IgM antibodies in a convalescent-phase specimen collected ≥6 days after symptom onset, *or*
3. Demonstration of a ≥4-fold rise in reciprocal IgG antibody, hemagglutination inhibition, or neutralization (plaque reduction neutrualiztion test, PRNT) antibody titers to dengue antigens in paired acute and convalescent serum samples; or a 4-fold difference in PRNT titer to a dengue virus in a single convalescent serum sample, *or*

4. Isolation of virus from or demonstration of specific arboviral antigen or genomic sequences in tissue, blood, cerebropspinal fluid (CSF), or other body fluid by polymerase chain reaction (PCR) test, immunofluorescence, or immunohistochemistry. *or*
5. Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF.

**3. Criteria for Epidemiologic Linkage.**

Cases epidemiologically linked to confirmed or probable cases would follow the same classification criteria since the disease is spread by mosquito vectors.

## B. Classification Tables:

**Dengue Case Definition and Classification**

**1. Confirmed Case**

- A clinically compatible case of DF, DHF, or DSS *and*
- Laboratory results meet at least one laboratory criterion for dengue diagnosis.

**2. Probable Case**

- A clinically compatible case of DF, DHF, or DSS *and*
- Dengue virus-specific serum antibodies detected by antibody-capture enzyme immunoassay in a single sample with no second specimen available *or*
- Occurrence at the same time and location as other confirmed dengue cases

**3. Suspect Case**

- A clinically compatible case of DF, DHF or DSS *and*
- Laboratory evidence:
  - Presence of elevated dengue virus–specific IgG serum antibodies demonstrated in a single sample in the absence of dengue virus–specific IgM antibodies

*Note:* When a case has been entered into ArboNet as a suspect case and initial or confirmatory testing is negative state-based arboviral surveillance coordinators can change previously entered case data to “Not a case”. Suspect cases will not be included in final cases counts within ArboNet.

**4. Asymptomatic Cases among Blood or Tissue Donors**

- Specific viral antigen or genomic sequences demonstrated in donated blood or organs during screening and confirmatory testing in the absence of clinically compatible illness.

## VIII. Period of Surveillance:

Unlimited

## IX. Data sharing/release and Print criteria:

Data flow will proceed from state and local health departments to CDC and to WHO. Only fully de-identified case data will be released to the general public. Suspect case data will not be included in final case counts. Case report data will not be used or released until verification procedures are complete and all states have finalized their case counts.

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Table 1. Common core data elements for case reporting to a public health agency from a healthcare provider: To be included in the initial case report.

| | ***Non Condition Specific Data Elements*** | ***Core Data Set*** |
|---|---|---|
| *Reporting Information* | | |
| | Date of report | X |
| | Reporter name | X |
| *Reporter Contact Information* | | |
| | Telephone | X |
| | Address | X |
| *Health Care Provider Information* | | |
| | Health care provider name | X |
| | Facility Name | X |
| *Facility/Provider Contact Information* | | |
| | Phone number | X |
| | Address | X |
| *Subject Information* | | |
| | First Name | X |
| | Middle Name | X |
| | Last Name | X |
| | Street | X |
| | City | X |
| | State | X |
| | ZIP | X |
| | Telephone | X |
| | Age | X |
| | Date of birth | X |
| | Gender | X |
| *Clinical Information* | | |
| | Name of Condition | X |
| | Date of onset | X |