Submission Date: February 26, 2016

Committee: Infectious Disease

Title: Zika Virus Disease and Congenital Zika Virus Infection Interim Case Definition and Addition to the Nationally Notifiable Diseases List

I. Statement of the Problem

Zika virus (ZIKV) is an emerging infection spread by mosquito vectors and whose incidence and prevalence has exploded in the Americas in 2015. Preliminary investigations demonstrate vertical transmission of ZIKV to the fetus in pregnant women. These *in utero* infections have been associated with the potential for devastating outcomes including microcephaly and spontaneous abortions. There is also an association with ZIKV infection and post-infectious Guillain-Barré syndrome (GBS) under investigation. Because of these epidemiological and clinical features, the World Health Organization declared ZIKV disease a Public Health Emergency of International Concern under the International Health Regulations 2005 on February 1, 2016.[1]

II. Background and Justification

ZIKV, a flavivirus transmitted by *Aedes spp.*mosquitoes, was discovered in the Zika Forest by the Virus Research Institute in Uganda in a non-human primate in 1947 and from *Aedes africanus* mosquitoes in 1948.[2] Before 2007, there had been only 14 human ZIKV illness cases documented. In 2007, an outbreak of ZIKV disease occurred on Yap Island, Federated States of Micronesia and the ensuing investigation included the first population-based epidemiological study of ZIKV infection and disease.[3] It was estimated that 75% (attack rate) of the island's inhabitants were infected with ZIKV resulting in 18% symptomatic and 82% asymptomatic infections. The most common symptoms documented in this outbreak were maculopapular rash, fever, arthralgia, and conjunctivitis. From 2013 to 2014 there was a large outbreak in French Polynesia where *Aedes aegypti* was considered the most important vector. There continues to be ongoing transmission in the Pacific Islands.

In May 2015, the Pan American Health Organization issued an alert regarding the first confirmed ZIKV infection in Brazil. Since that time, local transmission has been reported in many other countries and territories in Latin America and the Caribbean. Brazil reported widespread ZIKV disease in adults and children, and a concomitant and significant rise in the number of infants born with microcephaly, as well as increases in miscarriages. Although not yet confirmed, there is increasing clinical and epidemiologic evidence to support ZIKV as a cause of significant congenital defects and fetal losses. Additionally, reports of increasing incidence of GBS have surfaced in countries experiencing ZIKV epidemics and this syndrome is now being linked to ZIKV. Lastly, sexual transmission of ZIKV has been documented. The extent to which sexual transmission is driving the current outbreak is not known.

Due to the rapidly evolving epidemic of Zika virus infection, the CSTE Executive Board has developed this interim position statement to establish standardized case definitions for Zika virus disease and ZIKV congenital infection. CSTE recognizes that asymptomatic persons will be tested for ZIKV infection and will meet laboratory criteria for infection. At the time of this interim position statement, it is not yet understood what proportion will be false positives and what proportion will be epidemiologically significant. Individual public health jurisdictions are encouraged to evaluate and monitor identified asymptomatic ZIKV infections on a case-by-case basis.

III. Statement of the desired action(s) to be taken

☒ 1. Utilize standard sources (e.g. reporting*) for case ascertainment for ZIKV disease. Surveillance for ZIKV disease should use the following recommended sources of data to the extent of coverage presented in Table III.

Table III. Recommended sources of data and extent of coverage for ascertainment of cases of ZIKV disease

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	x	
Laboratory reporting	x	
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers)	x	
Death certificates	x	
Hospital discharge or outpatient records	x	
Extracts from electronic medical records	x	
Birth Defect Registries or birth certificates	x	
Telephone survey		
School-based survey		
Other _____		
2016 Template		

☐ 2. Utilize standardized criteria for case identification and classification (Sections VI and VII) for [disease/condition] but do not add [disease/condition] to the *Nationally Notifiable Condition List*. If requested by CDC, jurisdictions (e.g. States and Territories) conducting surveillance according to these methods may submit case information to CDC.

☒ 3. Utilize standardized criteria for case identification and classification (Sections VI and VII) for ZIKV disease and add ZIKV disease to the *Nationally Notifiable Condition List.*

- ☐ 3a. Immediately notifiable, extremely urgent (within 4 hours)
- ☐ 3b. Immediately notifiable, urgent (within 24 hours)
- ☒ 3c. Routinely notifiable

CSTE recommends that all States and Territories enact laws (statue or rule/regulation as appropriate) to make this disease or condition reportable in their jurisdiction. Jurisdictions (e.g. States and Territories) conducting surveillance (according to these methods) should submit case notifications** to CDC.

Expectations for Message Mapping Guide (MMG) development for a newly notifiable condition: NNDSS is transitioning to HL7-based messages for case notifications; the specifications for these messages are presented in MMGs. When CSTE recommends that a new condition be made nationally notifiable, CDC must obtain OMB PRA approval prior to accepting case notifications for the new condition. Under anticipated timelines, notification using the Generic V2 MMG would support transmission of the basic demographic and epidemiologic information common to all cases and could begin with the new *MMWR* year following the CSTE annual conference. Input from CDC programs and CSTE would prioritize development of a disease-specific MMG for the new condition among other conditions waiting for MMGs.

☒ 4. CDC should publish data on ZIKV disease as appropriate in *MMWR* and other venues (see Section IX).

CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined above.

IV. Goals of Surveillance
To provide information on the emerging temporal, geographic, and demographic occurrence of ZIKV disease to facilitate prevention and control for this vector-borne infection.

Terminology:
* Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance TO local or state public health.
**Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Condition List TO CDC.

V. Methods for Surveillance: Surveillance for ZIKV disease should use the recommended sources of data and the extent of coverage listed in Table III.
Surveillance for ZIKV disease should use the recommended sources of data and the extent of coverage listed in Table III.

VI. Criteria for case identification

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

Report any illness or laboratory finding to public health authorities that meets any of the following criteria:

- Any person with a clinically compatible illness for ZIKV infection that includes one or more symptoms of acute fever (reported or measured), rash, arthralgia, or conjunctivitis; OR Guillain-Barré syndrome; AND potential ZIKV exposure:
    - Residence or travel to an area with ongoing ZIKV transmission within 2 weeks of symptom onset; or
    - Epidemiologic link to a person with laboratory evidence of recent ZIKV infection.

- Any person with laboratory evidence of recent ZIKV infection as indicated by:
    - Culture of ZIKV from blood, body fluid, or tissue
    - Demonstration of specific ZIKV antigen or nucleic acid in serum, cerebrospinal fluid (CSF), tissue, or other specimen (e.g., amniotic fluid, urine, semen, saliva)
    - ZIKV-specific immunoglobulin M (IgM) antibodies in CSF or serum
    - ZIKV neutralizing antibody titers $\geq$ 4-fold higher than neutralizing antibody titers against dengue or other flaviviruses endemic to the region where exposure occurred

- An infant with microcephaly[4] or intracranial calcifications or central nervous system abnormalities:
    - Whose mother lived in or traveled to an area with ongoing ZIKV transmission during the pregnancy; or
    - Maternal evidence of ZIKV or unspecified flavivirus infection during the pregnancy.

- A person whose healthcare record contains a diagnosis of a ZIKV infection

- A person whose death certificate lists ZIKV infection as a cause of death or a significant condition contributing to death.

B. Table of criteria to determine whether a case should be reported to public health authorities

Table VI-B. Table of criteria to determine whether a case should be reported to public health authorities.

Criterion	Zika Virus Disease	Congenital Zika Virus infection
Clinical Evidence		
Rash	O	
Reported or measured fever	O	
Arthralgia	O	
Conjunctivitis	O	
Guillain-Barré syndrome not known or associated with another diagnosed etiology	O	
Microcephaly		O
Intracranial calcifications		O
Congenital central nervous system abnormalities		O
Healthcare record contains a diagnosis of Zika virus disease	S	S
Death certificate lists ZIKV as a cause of death or a significant condition contributing to death	S	S
Laboratory Evidence		
Detection of ZIKV or ZIKV-specific nucleic acids from specimens of serum, CSF, urine, semen, amniotic fluid, saliva, or tissue	S	S
Detection of ZIKV antigen by immunohistochemical staining of tissue specimen	S	S
Detection of ZIKV IgM antibodies in serum or CSF	S	S
4-fold or greater difference in neutralizing antibody titers between ZIKV and dengue or other endemic flaviviruses	S	S
Epidemiologic Evidence		
Residence or travel to an area with known ZIKV transmission	O	
Mother lived in or traveled to an area with ongoing ZIKV transmission during pregnancy		O
Sexual contact with a laboratory-confirmed case	O	
Laboratory evidence of flavivirus infection in mother during pregnancy		O
Blood transfusion within 30 days of symptom onset	O	
Organ transplant recipient	O	

Notes:
S = This criterion alone is Sufficient to report a case.
N = All "N" criteria in the same column are Necessary to report a case.
O = At least one of these "O" (One or more) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to report a case.
* A requisition or order for any of the "S" laboratory tests is sufficient to meet the reporting criteria.

C. Disease-specific data elements

Clinical information
Underlying chronic illness
Immune suppression
Blood transfusion in past 30 days
Blood donation in past 30 days
Organ transplant recipient in past 30 days
Organ donor
Pregnant
Prenatal exposure
Breast fed
Congenital abnormalities
Outcome of pregnancy (full term, premature, abortion, etc.)
Fetal demise (and evidence of ZIKV infection in the fetus, if available)
Laboratory exposure
Hospitalized
Fatality

Epidemiologic Risk Factors
Occupation
Travel within14 days prior to onset of illness
If pregnant, any travel during pregnancy
Sexual contact with a person with laboratory confirmed or probable ZIKV infection
Country and state or territory where infection was presumably contracted
Mosquito exposure
Association in time and place with a person with laboratory confirmed or probable ZIKV infection

VII. Case Definition for Case Classification

A. Narrative: Description of criteria to determine how a case should be classified.

Clinical Criteria

Mosquito-borne or sexually transmitted case
A person with one or more of the following:

- acute onset of fever (measured or reported)
- maculopapular rash
- arthralgia
- conjunctivitis
- complication of pregnancy
    - fetal loss in a mother with compatible illness and/or epidemiologic risk factors; or
    - in utero findings of microcephaly and/or intracranial calcifications with maternal risk factors
- Guillain-Barré syndrome not known to be associated with another diagnosed etiology.

Congenital case

- live birth with microcephaly or intracranial calcifications or central nervous system abnormalities

Laboratory Criteria

1. detection of ZIKV or ZIKV specific nucleic acids in specimens of serum, CSF, urine, saliva, amniotic fluid, placenta, umbilical cord, or fetal tissue, OR
2. detection of ZIKV antigen by immunohistochemical staining of maternal or fetal tissue; OR

3. detection of ZIKV specific IgM antibody in serum, CSF, or amniotic fluid; AND
   ZIKV neutralizing antibody titers ≥4-fold higher than neutralizing antibody titers against dengue virus or other flaviviruses endemic to region of exposure.

Epidemiologic Linkage

- Travel to a country or region with known ZIKV transmission, OR
- Sexual contact with a laboratory confirmed case of ZIKV infection, OR
- Receipt of blood or blood products within 30 days of symptom onset; OR
- Organ transplant recipient within 30 days of symptom onset; OR
- Association in time and place with a confirmed or probable case.
- For congenital syndrome, a pregnancy with maternal epidemiologic linkage.

CASE CLASSIFICATION

Zika Virus Disease

Clinical Criteria

A person with one or more of the following:

- acute onset of fever (measured or reported)
- maculopapular rash
- arthralgia
- conjunctivitis
- complication of pregnancy
  - fetal loss in a mother with compatible illness and/or epidemiologic risk factors; or
  - in utero findings of microcephaly and/or intracranial calcifications with maternal risk factors
- Guillain-Barré syndrome not known to be associated with another diagnosed etiology.

Probable case

Meets clinical criteria AND

- resides in or has recently traveled to an area with ongoing ZIKV transmission, OR
- has direct epidemiologic linkage to a person with laboratory evidence of recent ZIKV infection (e.g. sexual contact, in utero or perinatal transmission, blood transfusion, organ transplantation), OR
- association in time and place with a confirmed or probable case

AND meets the following laboratory criteria:

- positive ZIKV-specific IgM antibodies in serum or CSF; and
- negative dengue virus-specific IgM antibodies; AND
  - No neutralizing antibody testing performed; or
  - Less than four-fold difference in neutralizing antibody titers between ZIKV and dengue or other flaviviruses endemic to the region where exposure occurred.

Confirmed case

Meets clinical criteria AND

Has laboratory evidence of recent ZIKV infection by:

- Detection of ZIKV by culture, viral antigen or viral RNA in serum, CSF, tissue, or other specimen (e.g. amniotic fluid, urine, semen, saliva); OR
- ZIKV IgM antibodies in serum or CSF **with** ZIKV neutralizing antibody titers 4-fold or greater than neutralizing antibody titers against dengue or other flaviviruses endemic to the region where exposure occurred.

Zika Virus Congenital Infection

Clinical Criteria
An infant with microcephaly[4] or intracranial calcifications or other central nervous system abnormalities.

Probable Case
An infant meets the clinical criteria AND:

- Mother lived in or traveled to a country or area with ongoing ZIKV transmission during the pregnancy; OR
- Mother has laboratory evidence of ZIKV or unspecified flavivirus infection during pregnancy;

AND the infant meets the following laboratory criteria:

- ZIKV IgM antibodies detected in serum or CSF; and
- Tests negative for dengue or other endemic flavivirus-specific IgM antibodies; AND
  - No neutralizing antibody testing performed; or
  - Less than four-fold difference in neutralizing antibody titers between ZIKV and dengue or other flaviviruses endemic to the region where exposure occurred.

Confirmed Case
An infant meets the clinical criteria AND meets one of the following laboratory criteria:

- ZIKV detection by culture, antigen test, or polymerase chain reaction (PCR) in serum, CSF, amniotic fluid, urine, placenta, umbilical cord, or fetal tissue; OR
- ZIKV IgM antibodies present in serum or CSF with ZIKV neutralizing antibody titers 4-fold or greater than neutralizing antibodies against dengue or other flaviviruses endemic to the region where exposure occurred.

B. Classification Tables

Table VII-B. Criteria for defining a case of Zika virus disease.

Criterion	Zika Virus Disease			Congenital Zika Virus Infection		
	Probable	Confirmed		Probable	Confirmed	
Clinical Evidence						
Fever	O	O	O			
Maculopapular rash	O	O	O			
Arthralgia	O	O	O			
Conjunctivitis	O	O	O			
Guillain-Barré syndrome not known or associated with another diagnosed etiology	O	O	O			
Complications of pregnancy	O	O	O			
Microcephaly				O	O	O
Intracranial calcifications				O	O	O
Other congenital central nervous system abnormalities				O	O	O
Laboratory Evidence						
Detection of ZIKV by culture, viral antigen or viral RNA in serum, CSF, urine, amniotic fluid, placenta, umbilical cord, or fetal tissue		N			N	
Detection of ZIKV-specific IgM antibody in serum or CSF	N		N	N		N
A 4-fold or greater difference in neutralizing antibody titers between ZIKV and dengue, or other endemic flaviviruses			N			N
Negative dengue-specific IgM antibody test	N			N		
Less than 4-fold difference in neutralizing antibody titers between ZIKV and dengue, or other flaviviruses endemic to the region where exposure occurred	O			O		
No neutralizing antibody testing performed	O			O		
Epidemiological Evidence						
Resides in or has recently traveled to an area with ongoing ZIKV transmission	O					
Direct epidemiologic linkage to a person with laboratory evidence of recent ZIKV infection (e.g., sexual contact, in utero or perinatal transmission, blood transfusion, organ transplantation)	O					
Laboratory evidence of maternal infection with ZIKV or unspecified flavivirus infection during pregnancy				O		
History of maternal residence in or travel to a country or area with ongoing ZIKV transmission during pregnancy				O		
Association in time and place with a confirmed or probable case	O					
						2016 Template

Notes:
S = This criterion alone is Sufficient to classify a case.

N = All "N" criteria in the same column are Necessary to classify a case. A number following an "N" indicates that this criterion is only required for a specific disease/condition subtype (see below). If the absence of a criterion (i.e., criterion NOT present) is required for the case to meet the classification criteria, list the Absence of criterion as a Necessary component.
O = At least one of these "O" (One or more) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case. (These "O" criteria are alternatives, which means that a single column will have either no O criteria or multiple O criteria; no column should have only one O.) A number following an "O" indicates that this criterion is only required for a specific disease/condition subtype.

VIII. Period of Surveillance

Surveillance should be ongoing. While a national strategy is being developed to track reproductive and fetal outcomes among pregnant women with asymptomatic ZIKV infections, state and territorial health departments are encouraged to develop a surveillance method to compile these surveillance data until standardized guidance from CDC is finalized.

IX. Data sharing/release and print criteria

- State and territorial health departments should report confirmed and probable cases of ZIKV and other nationally notifiable arboviral diseases to CDC.
- CDC Division of Vector-Borne Diseases (DVBD) staff review, analyze, and summarize the national data at least weekly. Provisional state-specific arboviral disease case counts are provided and updated at regular intervals in national summary reports displayed on the CDC website; tables and maps are also provided on the CDC DVBD and U.S. Geologic Survey (USGS) websites. These provisional data are used to: 1) Monitor the epidemiology and geographic spread of ZIKV and other arboviral diseases; 2) Provide timely information regarding regional and national trends in ZIKV disease reporting to public health officials and others; and 3) Identify geographic areas where additional prevention and control efforts may be needed. In circumstances where there is a potential for an international health impact, data from these notifications may be shared with international partners (e.g., PHAC, ECDC, WHO, PAHO).
- Final data are published annually in the MMWR Summary of Notifiable Diseases, posted on the CDC DVBD website, and presented or published at scientific meetings and in peer-reviewed literature. Additional tables and limited use datasets are available to researchers, pharmaceutical companies, media, and the general public upon request to the CDC DVBD. These final data are used to: 1) Monitor the epidemiology, incidence, and geographic spread of arboviral diseases; 2) Identify geographic areas in which it may be appropriate to conduct analytic studies of control methods, risk factors, disease severity, or other public health aspects; and 3) Evaluate ZIKV preparedness and response funding needs and allocate resources.
- All cases are verified with the state health departments before publication. Individual case notifications are made to state and local health departments depending on circumstances. For example, transplant or transfusion-associated cases require rapid notification and investigation.
- To facilitate access to ArboNET data while maintaining patient confidentiality, and to ensure that users understand the limitations of the data, the CDC Arboviral Diseases Branch has developed data sharing and release guidelines, a data request form, and a data use agreement. These policies and procedures are consistent with those developed by CDC and the CSTE for the release and sharing of data reported to the Nationally Notifiable Diseases Surveillance System (NNDSS).

X. Revision History

Position Statement ID	Section of Document	Revision Description
16-ID-01 Interim		New

XI. References

1. World Health Organization (WHO). WHO statement on the first meeting of the International Health Regulations (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/ Accessed February 18, 2016.

2. Haddow AJ, Williams MC, Woodall JP, et al. Twelve isolations of Zika virus from Aedes (Stegomyia) africanus (Theobald) taken in and above a Uganda forest. *Bull World Health Organ*. 1964; 31(1):57-69.

3. Duffy MR, Chen T, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009; 360:2536-2543.

4. CDC. Zika Virus Interim guidance for U.S. state and territorial health departments. Appendix D: Congenital microcephaly case definitions.

XII. Coordination

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