

**18-ID-04****Committee:** Infectious Disease**Title:** Update to Yellow Fever Case Definition

Check this box if this position statement is an update to an existing standardized surveillance case definition.

**I. Statement of the Problem**

Yellow fever is a nationally notifiable disease. However, the current case definition, which was originally drafted in 1990 and republished in position statement 09-ID-09, does not include current laboratory diagnostic tests or updated interpretations of test results in persons who previously received yellow fever vaccine (e.g., persistence of IgM antibodies following vaccination). The case definition also was developed before yellow fever vaccine-associated viscerotropic disease was recognized as a rare adverse event that could be misdiagnosed as a case of wild-type yellow fever disease. This position statement proposes a revision to the standardized case definition for yellow fever disease to address changes in diagnostic testing and the possible occurrence of yellow fever vaccine-associated viscerotropic disease.

**II. Background and Justification**

Yellow fever virus is a mosquito-borne flavivirus that is closely related to dengue, Japanese encephalitis, West Nile, and Zika viruses. Yellow fever virus is endemic to sub-Saharan Africa and South America, where it causes an estimated 200,000 disease cases and 30,000 deaths annually. Local mosquito-borne transmission of yellow fever virus has not occurred in the United States in >100 years. On average, only one travel-associated case of yellow fever has been identified among U.S. travelers every 10 years. However, increasing numbers of travelers to and from endemic areas and outbreaks near major urban areas have heightened concern for the possible introduction and spread of the virus in the United States.

Yellow fever virus is primarily transmitted to humans by infected *Aedes (Stegomyia)* and *Haemagogus* species mosquitoes. Yellow fever virus transmission also has been documented through laboratory exposure, blood transfusion, and intrapartum from a viremic mother to her newborn. Transmission could theoretically occur through breastfeeding or organ transplantation. There have been no reports of congenital or sexual transmission of yellow fever virus, though viral RNA was detected in semen of one patient with wild-type disease.

Most yellow fever virus infections are asymptomatic. Following an incubation period of 3–9 days, approximately one-third of infected people develop symptomatic illness characterized by fever and headache. Other clinical findings include chills, vomiting, myalgia, lumbosacral pain, and bradycardia relative to elevated body temperature. An estimated 5%–25% of patients progress to more severe disease, including jaundice, renal insufficiency, cardiovascular instability, or hemorrhage (e.g., epistaxis, hematemesis, melena, hematuria, petechiae, or ecchymoses). The case-fatality rate for severe yellow fever is 30%–60%.

Yellow fever diagnostic testing is available at CDC and several state health departments, and includes: 1) RT-PCR to detect viral RNA in body fluids or tissues; 2) serologic assays to detect IgM or neutralizing antibodies in serum or CSF; and 3) immunohistochemical staining to detect viral antigen in formalin-fixed tissues. Yellow fever viral RNA may be detected in serum up to 10 days after illness onset. Yellow fever virus IgM antibodies usually are detectable several days after onset of illness and can persist for years following infection. Yellow fever virus IgM antibody tests can have false-positive results due to cross-reactivity with related flaviviruses. Neutralizing antibody testing should be performed to confirm positive IgM antibody results and evaluate for other possible flavivirus infections. A  $\geq 4$ -fold increase in virus-specific neutralizing antibodies between acute- and convalescent-phase serum specimens can help confirm recent infection.

Yellow fever is preventable by a safe and effective vaccine. Yellow fever vaccination history is essential to properly interpret yellow fever diagnostic test results. Following routine vaccination, yellow fever vaccine viral RNA can be detected in serum for up to 14 days, and IgM and neutralizing antibodies can persist for years. In addition, yellow fever vaccine-associated viscerotropic disease is a rare serious adverse event in which vaccine virus proliferates in multiple organs within weeks after vaccination; viral RNA and antigen can be detected in serum and tissues, and may be indistinguishable from wild-type disease.

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

CSTE recommends the following actions:

1. Utilize standard sources (e.g. reporting\*) for case ascertainment for yellow fever. Surveillance for yellow fever 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 yellow fever.**

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), specify: hospitals, pharmacies, veterinarians.	X	
Death certificates	X	
Hospital discharge or outpatient records	X	
Extracts from electronic medical records	X	
Telephone survey		
School-based survey		
Other, specify:		

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\*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. Note: notification is addressed in a Nationally Notifiable Conditions Recommendation Statement and is the process of a local or state public health authority submitting a report (case information) of a condition on the *Nationally Notifiable Conditions List* TO CDC.

2. Utilize standardized criteria for case identification and classification (Sections VI and VII and Technical Supplement) for yellow fever.
3. Please see accompanying NNC Recommendation Statement for additional Desired Actions to be Taken (page 8).

### **IV. Goals of Surveillance**

To provide information on the temporal, geographic, and demographic occurrence of yellow fever to facilitate prevention and control for this vector-borne infection through vaccination and vector control measures.

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

Surveillance for yellow fever should use the recommended sources of data and the extent of coverage listed in Table III.

## **VI. Criteria for case ascertainment**

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

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

- Any person with laboratory evidence of recent yellow fever virus infection.
- A person whose healthcare record contains a diagnosis of a yellow fever infection.
- A person whose death certificate lists a yellow fever infection as a cause of death or a significant condition contributing to death.

### **B. Disease-specific data elements to be included in the initial report**

Disease-specific data elements to be included in the initial report are listed below.

#### *Clinical Information:*

- Date of onset of fever or acute illness associated with jaundice
- Other clinical signs or symptoms consistent with yellow fever virus infection
- 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
- Laboratory exposure
- Hospitalized
- Fatality

#### *Epidemiologic Risk Factors:*

- Destination(s) of recent travel (if any)
- Date of return from travel
- Visited or resided in an area with risk of yellow fever virus transmission in the 2 weeks prior to illness onset
- Epidemiologically linked to a confirmed yellow fever disease case
- Mosquito exposure

#### *Immunization History*

- Yellow fever vaccination history (number of doses and date of last vaccination)

## **VII. Case Definition for Case Classification**

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

#### **Clinical Criteria**

A clinically compatible case of yellow fever is defined as:

- Acute illness with at least one of the following: fever, jaundice, or elevated total bilirubin  $\geq 3$  mg/dl  
AND
- Absence of a more likely clinical explanation.

**Laboratory Criteria*****Confirmatory laboratory evidence:***

- Isolation of yellow fever virus from, or demonstration of yellow fever viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid.
- Four-fold or greater rise or fall in yellow fever virus-specific neutralizing antibody titers in paired sera.
- Yellow fever virus-specific IgM antibodies in CSF or serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen.

***Presumptive laboratory evidence:***

- Yellow fever virus-specific IgM antibodies in CSF or serum, and negative IgM results for other arboviruses endemic to the region where exposure occurred.

**Epidemiologic Linkage**

Epidemiologically linked to a confirmed yellow fever case, or visited or resided in an area with a risk of yellow fever in the 2 weeks before onset of illness.

**Case Classifications*****Confirmed:***

A case that meets the above clinical criteria and meets one or more of the following:

- Isolation of yellow fever virus from, or demonstration of yellow fever viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, AND no history of yellow fever vaccination within 30 days before onset of illness unless there is molecular evidence of infection with wild-type yellow fever virus.
- Four-fold or greater rise or fall in yellow fever virus-specific neutralizing antibody titers in paired sera, AND no history of yellow fever vaccination within 30 days before onset of illness.
- Yellow fever virus-specific IgM antibodies in CSF or serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen, AND no history of yellow fever vaccination.

***Probable:***

A case that meets the above clinical and epidemiologic linkage criteria, and meets the following:

- Yellow fever virus-specific IgM antibodies in CSF or serum, AND negative IgM results for other arboviruses endemic to the region where exposure occurred, AND no history of yellow fever vaccination.

***Suspect:***

Not applicable.

**B. Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance**

Not applicable.

**VIII. Period of Surveillance**

Surveillance should be ongoing.

### IX. Data sharing/release and print criteria

- Notification to CDC of confirmed and probable cases of yellow fever is required.
- CDC Division of Vector-Borne Diseases (DVBD) staff review, analyze, and summarize the national data weekly. Provisional state-specific yellow fever disease case counts are provided weekly in the MMWR nationally notifiable diseases tables. These provisional data are used to: 1) Monitor the epidemiology of yellow fever; 2) Provide timely information regarding regional and national trends in yellow fever 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 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 yellow fever; 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 arboviral disease 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, first case resulting from suspected yellow fever virus local transmission or 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).

CSTE recommends the following case statuses be included in the CDC Print Criteria:

- Confirmed
- Probable
- Suspect
- Unknown

### X. Revision History

Position Statement ID	Section of Document	Revision Description
09-ID-09	Section VI. B. Disease-specific data elements to be included in the initial report	ADDED and EDITED clinical information and epidemiologic risk factors
09-ID-09	Section VII. A. Narrative: Description of criteria to determine how a case should be classified	EDITED clinical criteria to include acute illness with fever or jaundice, AND absence of a more likely clinical explanation
09-ID-09	Section VII. A. Narrative: Description of criteria to determine how a case should be classified	EDITED confirmatory and presumptive laboratory evidence
09-ID-09	Section VII. A. Narrative: Description of criteria to determine how a case should be classified	ADDED epidemiologic linkage criteria

09-ID-09	Section VII. A. Narrative: Description of criteria to determine how a case should be classified	EDITED confirmed case classification to include absence of yellow fever immunization OR molecular characterization demonstrating wild-type yellow fever virus
09-ID-09	Section VII. A. Narrative: Description of criteria to determine how a case should be classified	EDITED probable case classification to include specific presumptive laboratory evidence and epidemiologic linkage criteria

## **XI. References**

1. CDC. Case definitions for public health surveillance, 1990. MMWR 1990;39(No. RR-13). <https://ftp.cdc.gov/pub/publications/mmwr/rr/rr3913.pdf>
2. Centers for Disease Control and Prevention (CDC). Case definitions for infectious conditions under public health surveillance. MMWR 1997;46(No. RR-10):1–57. Available from: <http://www.cdc.gov/mmwr/>
3. CSTE. Public Health Reporting and National Notification for Yellow fever. <http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/PS/09-ID-09.pdf>
4. CDC. Yellow Fever Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59(No. RR-07)1-27. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5907a1.htm>
5. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2016. New York: Oxford University Press; 2016.

## **XII. Coordination**

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## Nationally Notifiable Conditions (NNC) Recommendation Statement

**Position Statement Title:** Update to Yellow Fever Case Definition

**Disease/Condition:** Yellow Fever

- This statement updates a disease/condition already on the *Nationally Notifiable Conditions List*.
  - No change to the CDC notification timeframe is recommended.
  - New subtype(s) or additional disease/condition categories are added to the accompanying position statement.

**This NNC Recommendation Statement recommends the following:**

1. Utilize standardized criteria for case identification and classification (based on Sections VI and VII and Technical Supplement of accompanying position statement) for yellow fever and add yellow fever to the *Nationally Notifiable Condition List*
  - Immediately notifiable, extremely urgent (within 4 hours)
  - Immediately notifiable, urgent (within 24 hours)
  - Routinely notifiable
  - No longer notifiable
2. CSTE recommends that all States and Territories maintain or enact laws (statute or rule/regulation as appropriate) to make yellow fever reportable in their jurisdiction. Jurisdictions (e.g. States and Territories) conducting surveillance (according to these methods) should submit case notifications\* to CDC using the revised case confirmation criteria outlined in the accompanying position statement.
3. 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 yellow fever as appropriate (see Section IX of corresponding position statement).
5. CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined here and in the accompanying standardized surveillance position statement.

\*Notification: process of a local or state public health authority submitting a report (case information) of a condition on the *Nationally Notifiable Conditions List* TO CDC.

## Technical Supplement

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

Criterion	Yellow fever virus infection
<i>Clinical Evidence</i>	
Healthcare record contains a diagnosis of yellow fever virus infection	S
Death certificate lists a yellow fever infection as a cause of death or a significant condition contributing to death	S
<i>Laboratory Evidence</i>	
Isolation of yellow fever virus from, or demonstration of yellow fever viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid	S
Four-fold or greater rise or fall in yellow fever virus-specific neutralizing antibody titers in paired sera	S
Yellow fever virus-specific IgM antibodies in CSF or serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen	S
Yellow fever virus-specific IgM antibodies in CSF or serum, and negative IgM results for other arboviruses endemic to the region where exposure occurred.	S

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**Notes:**

S = This criterion alone is SUFFICIENT to report a case.

**Table VII. Classification Table: Criteria for defining a case of yellow fever.**

Criterion	Probable		Confirmed		
<i>Clinical Evidence</i>					
Acute onset of illness	N	N	N	N	N
Fever	O	O	O	O	O
Jaundice	O	O	O	O	O
Total bilirubin $\geq$ 3mg/dl	O	O	O	O	O
Absence of a more likely clinical explanation	N	N	N	N	N
No history of yellow fever vaccination within 30 days before onset of illness	N	N		N	N
No history of yellow fever vaccination	N				N
<i>Laboratory evidence</i>					
Isolation of yellow fever virus from, or demonstration of yellow fever viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid			N	N	
Four-fold or greater rise or fall in yellow fever virus-specific neutralizing antibody titers in paired sera				N	
Yellow fever virus-specific IgM antibodies in CSF or serum	N				N
Confirmatory virus-specific neutralizing antibodies in the same specimen or a later specimen					N
Negative IgM results for other arboviruses endemic to the region where exposure occurred	N				
Molecular evidence of infection with wild-type yellow fever virus			N		
<i>Epidemiologic evidence</i>					
Epidemiologically linked to a confirmed yellow fever case	O				
Visited or resided in an area with a risk of yellow fever in the 2 weeks before onset of illness	O				

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**Notes:**

- 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** (categories=clinical evidence, laboratory evidence, and epidemiologic evidence) **in the same column**—in conjunction with all "N" criteria in the same column—is required to classify a case. A number following an "O" indicates that this criterion is only required for a specific disease/condition subtype.