

# Yellow Fever

<b>Signs and Symptoms</b>	<ul style="list-style-type: none"> <li>• Acute onset fever, headache, muscle aches, nausea, vomiting, and jaundice</li> <li>• Pulse may be relatively slow for fever</li> <li>• ~15% progress after 24 hour remission to hemorrhage, hepatorenal failure, and shock marked by jaundice, albuminuria, and leukopenia with 30-60% mortality</li> </ul>	
<b>Incubation</b>	3-9 days	
<b>Case classification</b>	<b>Clinical criteria:</b> acute illness with fever, jaundice, or elevated total bilirubin $\geq 3\text{mg/dl}$	
	<table border="1"> <tr> <td><b>Confirmed:</b> Clinically consistent illness with <math>\geq 4</math>-fold rise or fall in yellow fever antibody titer OR demonstration of yellow fever virus antigen or genome in tissue, blood or other body fluid OR IgM positive with virus-specific neutralizing antibodies, without recent yellow fever vaccine</td> <td><b>Probable:</b> Clinically consistent illness and epi-linked with IgM positive AND negative IgM for other arboviruses AND no history of yellow fever vaccination</td> </tr> </table>	<b>Confirmed:</b> Clinically consistent illness with $\geq 4$ -fold rise or fall in yellow fever antibody titer OR demonstration of yellow fever virus antigen or genome in tissue, blood or other body fluid OR IgM positive with virus-specific neutralizing antibodies, without recent yellow fever vaccine
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<b>Differential diagnosis</b>	Other flavivirus infection, viral hemorrhagic fever (e.g., Ebola, Lassa, dengue, Congo-Crimean), viral hepatitis, arenavirus, louse-borne relapsing fever, toxic hepatitis	
<b>Treatment</b>	Supportive; may require intensive care	
<b>Duration</b>	About a week if uncomplicated, weeks if hemorrhagic disease	
<b>Exposure</b>	Mosquito-borne in sub-Saharan Africa and South America, including Brazil in 2018	
<b>Laboratory testing</b>	<p>Local health jurisdiction (LHJ) and Office of Communicable Disease Epidemiology (CDE) arrange testing if suspected based on illness and travel – <b>urgent</b></p> <ul style="list-style-type: none"> <li>• Washington State Public Health Laboratories can forward specimens to CDC</li> <li>• <b>Best specimens:</b> <u>serum (acute and convalescent), biopsy tissue, autopsy specimen</u></li> </ul> <p><i>Specimen shipping (Section 4):</i></p> <ul style="list-style-type: none"> <li>• Hospital to keep all specimens <b>cold, ship cold</b> with Virology/Serology form <a href="https://www.medialab.com/dv/dl.aspx?d=1615463&amp;dh=e4b87&amp;u=69790&amp;uh=0e2a1">https://www.medialab.com/dv/dl.aspx?d=1615463&amp;dh=e4b87&amp;u=69790&amp;uh=0e2a1</a></li> </ul>	
<b>Public health actions</b>  <b>URGENT</b>	<p>LHJ immediately contacts CDE 877-539-4344 for diagnosis</p> <ul style="list-style-type: none"> <li>• Yellow fever is internationally notifiable</li> <li>• Obtain serum for testing at CDC</li> <li>• Interview for risk exposure, particularly travel to an endemic area</li> <li>• Sequester from mosquitoes (<i>Aedes</i>)</li> <li>• Identify others who travelled with the case and interview for symptoms</li> <li>• Determine if case donated blood, tissues, or body fluids and notify agency</li> </ul> <p><i>Infection Control:</i> standard precautions</p>	

# Yellow Fever

## 1. DISEASE REPORTING

### A. Purposes of Reporting and Surveillance

1. To identify cases of yellow fever associated with travel.
2. To prevent further spread of the disease within the United States.

### B. Legal Reporting Requirements

1. Health care providers and Health care facilities: *immediately* notifiable to **local health jurisdiction**.
2. Laboratories: any positive result except IgG *immediately* notifiable to **local health jurisdiction**; submission required – specimen associated with any positive result excluding IgG, within 2 business days
3. Local health jurisdictions: **suspected and confirmed cases are immediately notifiable** to the Washington State Department of Health (DOH) Office of Communicable Disease Epidemiology (CDE) (206-418-5500 or 1-877-539-4344).

### C. Local Health Jurisdiction Investigation Responsibilities

1. Alert CDE about possible cases.
2. Facilitate transport of specimens to the Washington State Department of Health Public Health Laboratories (PHL) if initial testing or confirmatory testing is needed. Please call CDE prior to submitting specimens (206-418-5500).
3. Report all *confirmed* and *probable* cases to CDE (see definitions below). Complete the Yellow Fever case report form and enter the data into the Washington Disease Reporting System (WDRS) as “Yellow Fever.”  
<https://doh.wa.gov/sites/default/files/legacy/Documents/5100/210-064-ReportForm-Yellow.pdf>

## 2. THE DISEASE AND ITS EPIDEMIOLOGY

### Background

Yellow fever is a very rare cause of illness among travelers arriving in the United States. The disease is known to occur only in tropical and subtropical Africa and South America. CDC recommended vaccine for some areas of Brazil due to an outbreak beginning in 2017.

### A. Etiological agent

The etiologic agent is an RNA virus of the genus *Flavivirus* and family Flaviviridae.

### B. Description of Illness

Symptoms typically begin with fever, chills, headache, muscle aches, nausea and vomiting. The pulse may be slow and out of proportion to the fever (Faget’s sign). Jaundice is moderate early in the disease and increases later. Albuminuria often helps to

distinguish yellow fever from other causes of viral hepatitis. Leukopenia appears early and peaks about the fifth day of illness. Although up to 85% of illnesses resolve at this stage, after a 2-24 hour remission others progress to severe disease. During this stage, patients develop liver failure, renal failure, and hemorrhagic symptoms characterized by epistaxis, gingival bleeding, hematemesis (coffee-ground or black vomit), and melena (black stool). Up to 60% of cases that progress to severe disease are fatal.

### C. Yellow fever in Washington State

No cases of wild-type yellow fever disease have ever been reported in Washington. One case of yellow fever vaccine-associated viscerotropic disease was reported in 2002, and one case of yellow fever vaccine-associated neurologic disease was reported in 2018.

### D. Vectors and Reservoirs

There are three transmission cycles for yellow fever virus – a *sylvatic* (or *jungle*) cycle involving mosquitoes and non-human primates; an *intermediate* cycle involving various *Aedes* mosquito species and humans or nonhuman primates in African savannahs; and an *urban* cycle involving *Aedes aegypti* and humans. The sylvatic cycle is restricted to tropical regions of Africa and South America with a few hundred cases annually, usually young adult males who work in forested areas. The intermediate cycle occurs in the humid savannah of Africa, where infected mosquitoes feed on both monkeys and humans.

Reinfestation with *Ae. aegypti* in many areas (including the southern United States) would raise the risk of urban yellow fever transmission should a yellow fever-viremic person arrive in those areas. Humans are not essential for maintaining the jungle cycle but are the primary amplifying host in the urban cycle.

### E. Modes of Transmission

Except on very rare occasions, yellow fever is acquired through the bite of an infected mosquito. The virus can be transmitted through blood, body fluid, or tissue.

California reported transfusion-associated transmission of the attenuated yellow fever vaccine strain in 2009 <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5902a2.htm>. Despite serologic evidence of transmission, no adverse events in blood recipients were attributed to the transfused virus. Also in 2009, a breast-fed, three-week-old infant had confirmed yellow fever vaccine-associated meningoencephalitis after maternal vaccination.

### F. Incubation Period

Three to nine days.

### G. Period of Communicability

Yellow fever is not directly transmitted person-to-person, but can be indirectly transmitted among persons via a mosquito vector as described above in the intermediate and urban transmission cycles. The disease is readily transmitted where many susceptible people and abundant vector mosquitoes coexist. Viral concentration in blood is adequate to infect mosquitoes from shortly before fever onset through the fifth day of illness. Once infected, mosquitoes remain so for life. See above for vaccine strain transmission.

## H. Treatment

Treatment is supportive, often involving hospitalization with intensive care therapy. NSAIDs should be avoided, as they can increase the risk of bleeding.

## 3. CASE DEFINITION

### A. 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

### B. 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 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, or
- 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, or
- 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.

#### 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, AND no history of yellow fever vaccination.

#### 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.

### C. Case Definition (2019)

*Probable:* a clinically compatible case with epidemiologic linkage AND presumptive laboratory evidence.

*Confirmed:* a clinically compatible case that is laboratory confirmed.

## 4. DIAGNOSIS AND LABORATORY SERVICES

### A. Diagnosis

Laboratory diagnosis is often made by demonstrating the presence of yellow fever-specific RNA by PCR, specific immunoglobulin M (IgM) in early sera, or a rise or fall in yellow fever-specific neutralizing antibody titers in paired acute and convalescent samples. Diagnosis is complicated by serologic cross-reactivity with other flaviviruses and persistent IgM from vaccination. In fatal cases, nucleic acid amplification, histopathology with immunohistochemistry, and virus culture of biopsy or autopsy tissues can also be positive.

### **B. Tests Available at the Washington State Public Health Laboratories (PHL)**

PHL does not perform testing for yellow fever but will forward specimens to the Centers for Disease Control and Prevention (CDC) for testing. Please contact the Office of Communicable Disease Epidemiology (206-418-5500) for approval prior to submitting specimens. Patient history must include recent travel to a known endemic area to be eligible for testing. Serum, CSF, biopsy tissue, and autopsy specimens can be tested.

Note that PHL require all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

### **C. Specimen Collection**

Serum or CSF should be refrigerated and transported cold. Frozen serum or CSF are also acceptable. It is strongly recommended to collect both acute and convalescent (2 weeks later) specimens.

Specimens should be submitted with a completed PHL Virology/Serology Submission form. Please call PHL for instructions for shipping specimens other than serum.

<https://www.medialab.com/dv/dl.aspx?d=1615463&dh=e4b87&u=69790&uh=0e2a1>

## **5. ROUTINE CASE INVESTIGATIONS**

**Since yellow fever rarely occurs in the United States, call Office of Communicable Disease Epidemiology (206-418-5500 / 877-537-4344) to discuss a case investigation.** Interview the case and others who may be able to provide pertinent information.

### **A. Evaluate the Diagnosis**

In general, test for other agents including other arboviruses unless the case is severely ill with liver failure, renal failure, and hemorrhagic symptoms. If the case tests positive for yellow fever at a laboratory other than a public health laboratory or CDC, facilitate transport of the specimen to Washington State Public Health Laboratories for further testing.

### **B. Identify Potential Sources of Infection**

Obtain a travel history and ask about mosquito exposures in endemic areas during the likely exposure period: <https://wwwnc.cdc.gov/travel/diseases/yellow-fever>

### **C. Identify Potentially Exposed Persons**

Identify other persons who traveled with the case. If these contacts have symptoms consistent with yellow fever, refer them to a health care provider and arrange for

laboratory testing. Determine if the patient donated blood during the communicable period. If the patient donated blood, other body fluids, or tissues, inform the agency of the potential exposure.

#### D. Infection Control / Case Management

1. Hospitalized patients should be cared for using standard precautions.
2. Patients being treated for yellow fever in the United States should be sequestered from mosquitoes while viremic to avoid urban transmission. Given that *Ae. aegypti*, the principle mosquito vector, is not endemic to Washington State, the risk of the case infecting mosquitoes which could subsequently infect other humans is very low. This is not true in many other areas in the United States.

### 6. MANAGING SPECIAL SITUATIONS

There have been reports of rare but serious events following yellow fever vaccination. These events include anaphylaxis, yellow fever vaccine-associated viscerotropic disease (YEL-AVD), and yellow fever vaccine-associated neurologic disease (YEL-AND). CDC can provide laboratory testing support for suspected YEL-AVD and YEL-AND cases. Findings of yellow fever virus-specific neutralizing antibodies in a clean (not RBC contaminated) CSF specimen following vaccination support invasion of the vaccine virus into the CNS. Cases of yellow fever vaccine reaction can be reported using the yellow fever form in WDRS. Healthcare providers are encouraged to report all adverse events that might be caused by vaccination to the [CDC/FDA Vaccine Adverse Events Reporting System \(VAERS\)](#).

### 7. ROUTINE PREVENTION

For travel recommendation see <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/yellow-fever> and <https://www.cdc.gov/yellowfever/prevention/index.html>

#### A. Immunization Recommendations

For information about yellow fever vaccine recommendations, please see the 2010 and 2015 Yellow Fever Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP), <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5907a1.htm>, <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a5.htm>, and <https://www.cdc.gov/features/yellow-fever-vaccine/index.html> for travel destinations.

Note that some countries have entry requirements that include yellow fever vaccination.

As a precautionary measure, vaccination of nursing mothers should be avoided because of the small risk for the transmission of vaccine strain virus to the breast-fed infant. When travel of nursing mothers to high-risk yellow fever-endemic areas cannot be avoided or postponed, such persons can be vaccinated.

#### B. Other Prevention Recommendations

When traveling in areas where yellow fever occurs (i.e., areas of Africa and South America), persons should avoid mosquito bites by:

- **Using mosquito repellent.** The most effective mosquito repellents contain the EPA approved active ingredients DEET (N, N-diethyl-m-toluamide), picaridin, oil of lemon eucalyptus, or IR3535. Read and follow instructions on the label.
  - Additional information regarding the use of mosquito repellents can be found on the CDC website at: <https://wwwnc.cdc.gov/travel/diseases/yellow-fever>
- **Wearing proper clothing to reduce mosquito bites.** When weather permits, wear long-sleeves, long pants, and socks when outdoors. Mosquitoes may bite through thin clothing, so spraying clothes with repellent containing permethrin or another EPA-registered repellent will give extra protection. Don't apply repellents containing permethrin directly to skin.
- **Be aware of peak mosquito hours.** *Aedes aegypti*, the main vector of yellow fever virus, feeds during the daytime. Repellent and protective clothing should be used during the daytime as well as evening and early morning. In addition, consider avoiding outdoor activities during these times in areas where yellow fever is a risk. Bed nets can reduce the number of mosquito bites from other mosquito species that transmit communicable diseases other than yellow fever and should be used as appropriate for hospitalized persons with yellow fever viremia to prevent nosocomial transmission.

## ACKNOWLEDGEMENTS

This document is a revision of the Washington State Guidelines for Notifiable Condition Reporting and Surveillance published in 2002 which were originally based on the Control of Communicable Diseases Manual (CCDM), 17<sup>th</sup> Edition; James Chin, Ed. APHA 2000. We would like to acknowledge the Oregon Department of Human Services for developing the format and select content of this document.

## UPDATES

March 2008: In Section 1C, the guideline for timeliness of initiating an investigation was removed.

July 2008: In Section 8B, IR3535 was added as a safe and effective mosquito repellent.

June 2009: In Section 4D, updated laboratory submission requirements.

January 2010: In Section 2D and G, the intermediate transmission cycle was added and in Section 4C, the laboratory form link was updated.

June 2010: In Sections 2 (vaccine transmission) and 4 were updated.

January 2011: The Legal Reporting Requirements section was revised to reflect the 2011 Notifiable Conditions Rule revision.

November 2013. Reviewed and later sections reorganized.

August 2016. Reviewed and front page added.

April 2018. Travel risk to Brazil added.

December 2018: Updated case definition to include bilirubin level, epi link, and travel to an area of risk; added section 6.

December 2022: For 2023 WAC revision combined provider and facility reporting requirement, updated laboratory submission (Section 1B)

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