Yellow fever was endemic in the United States from the late 1600s until early 1900s. Devastating epidemics occurred between 1668 and 1905. Philadelphia suffered multiple epidemics (20) as did Boston (8), and Baltimore (7), but it was in the south where the disease would have its greatest effect. Yellow fever reappeared almost every summer in cities on the southeastern and Gulf coasts between the 1850s until 1905, the last major epidemic recorded in the US. The 1853 outbreak that hit New Orleans, for example, caused an estimated 9,000 deaths, while the 1867 epidemic in Galveston resulted in 1,150 deaths (2). At the beginning of the 1900s a special group named the Yellow Fever Commission began an eradication campaign in the United States (1). Measures included community education, mosquito elimination, and vaccine administration, and are still the most effective methods of stopping the yellow fever virus from spreading (1). The virus has since been eradicated from the United States, and only a small number of travel-related cases are reported annually.¹, ²

A. Agent:
The virus that causes yellow fever belongs to the Flavivirus genus and the family Flaviviridae. Yellow fever can exist in two transmission cycles: a sylvatic (jungle) cycle that involves mosquitoes and non-human primates, and an urban cycle usually involving Aedes aegypti or Aedes albopictus mosquitoes and humans. Sylvatic cycle transmission is limited to tropical regions of Africa and South America. Urban transmission can occur in any region populated with mosquitoes carrying the virus.³, ⁴

B. Clinical Description:
Yellow fever causes illness that ranges in severity from a self-limiting febrile illness to hepatitis and hemorrhagic fever. Most yellow fever infections are mild, but the disease can cause severe, life-threatening illness. Symptoms of severe infection are high fever, chills, headache, muscle aches (particularly backache), nausea, and vomiting. After a brief period of recovery, the infection can lead to hemorrhagic manifestations such as blood in vomit or feces, uncontrolled bleeding, shock, and kidney and liver failure. Liver failure causes jaundice, which gives yellow fever its name. Severe yellow fever infections can be fatal. The case fatality rate is 15% to 50%. Infants and children are at greatest risk of severe disease.⁴, ⁵, ⁶

C. Reservoirs:
Humans and non-human primates.

D. Mode(s) of Transmission:
Through the bite of infected mosquitoes, principally the urban mosquitoes Aedes (Ae.) aegypti and Ae. albopictus. Ae. aegypti is a day biting species with increased biting activity for 2 hours after sunrise and several hours before sunset. Both mosquito species are present in the United States.¹ Ae. aegypti is well established in Arizona; Ae. albopictus has not been found to be established in the state.
In the sylvatic cycle outside the United States the principal vectors are forest mosquitoes of the genus *Haemogogous* in South America, and *Ae. africanus, Ae. bromeliae,* and *Ae. simpsoni* in non-human primates and humans in Africa. Uncommonly, the virus can be transmitted through infected blood transfusions, and accidental needle sticks with infected blood.3, 4

**E. Incubation Period:**
The average incubation period for yellow fever is between 3 and 6 days.4, 5

**F. Period of communicability:**
Not transmitted directly person-to-person; however the virus can remain in human blood for 3-5 days after symptom onset and be infectious to mosquitoes. Mosquitoes remain infected for life and can transmit the virus 9-12 days post-feeding.4

**G. Susceptibility and Resistance:**
Individuals who have not been immunized or naturally infected are susceptible. Those who have recovered from a yellow fever infection develop life-long immunity. Transient passive immunity in infants born to immune mothers may persist for up to 6 months. 4, 5

**H. Treatment:**
No specific treatments have been found to benefit patients with yellow fever. Treatment is supportive. Rest, fluids, and use of analgesics and antipyretics may relieve symptoms of fever and aching. Care should be taken to avoid certain medications, such as aspirin or other nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen, etc.) which may increase the risk for bleeding. Infected persons should protect themselves from further *Ae. aegypti* or *Ae. albopictus* mosquito exposure (staying indoors and/or under a mosquito net) during the first few days of illness, so they do not contribute to the transmission cycle.4, 5, 6

**I. Clinical Case Definition:**
A mosquito-borne, viral illness characterized by acute onset and constitutional symptoms followed by a brief remission and a recurrence of fever, hepatitis, albuminuria, and other symptoms and, in some cases, renal failure, shock, and generalized hemorrhages.7

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 ≥ 3 mg/dL, AND
- Absence of a more likely clinical explanation.

**J. Laboratory Criteria for Diagnosis:**

**Confirmatory Lab Criteria**
- 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. 6

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Disease Management
**Presumptive Lab Criteria**
- 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 Classification

<table>
<thead>
<tr>
<th>Confirmed</th>
<th>A case that meets the above clinical criteria and meets one or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• <strong>Isolation</strong> of yellow fever virus from, or <strong>demonstration</strong> of yellow fever viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, <strong>AND no history of yellow fever vaccination within 30 days</strong> before onset of illness unless there is molecular evidence of infection with wild-type yellow fever virus.</td>
</tr>
<tr>
<td></td>
<td>• Four-fold or greater rise in yellow fever virus-specific neutralizing antibody titers in paired sera, <strong>AND no history of yellow fever vaccination within 30 days</strong> before onset of illness.</td>
</tr>
<tr>
<td></td>
<td>• Yellow fever virus-specific IgM antibodies in CSF or serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen, <strong>AND no history of yellow fever vaccination.</strong></td>
</tr>
</tbody>
</table>

| Probable  | A case that meets the above clinical and epidemiologic linkage criteria, and meets the presumptive laboratory evidence **AND no history of yellow fever vaccination.** |

**K. Classification of Import Status:**
A case is considered imported if the person became infected outside of the U.S. This should be considered when there is opportunity for exposure and epidemiological evidence more suggestive of infection elsewhere. A case may also be imported from one state into another, or one local jurisdiction into another. All opportunities for exposure and epidemiological evidence should be documented for assessment of import status. To assess import status, focus on the travel history in the two weeks prior to symptom onset. If the case traveled to an endemic area in that time period they may have imported it, if not, it may be a local case. *Yellow fever is considered an eradicated disease in the U.S., however, there is the potential for re-introduction so it is crucial to always confirm travel history.*

**L. Laboratory Testing:**
Laboratory diagnosis is generally accomplished by testing serum to detect virus-specific IgM and IgG antibodies by serologic assays. Due to cross-reactivity between antibodies raised against other flaviviruses, more specific antibody testing, such as a neutralization test, should be done to confirm the infection. At least 0.5mL of serum and/or 1.0mL of cerebrospinal fluid...
(CSF) are required for serology testing. CSF specimens are routinely tested undiluted and therefore require larger amounts. Whole blood will not be accepted for serology testing.

Early in the course of illness, yellow fever viral RNA can often be detected in serum samples by virus isolation or nucleic acid amplification tests (NAAT). However, by the time more overt symptoms are recognized, the virus or viral RNA is usually undetectable. Therefore, virus isolation and NAAT should not be used as rule-out tests for a diagnosis of yellow fever.

For serology, paired acute and convalescent specimens, if available, should be sent together.

<table>
<thead>
<tr>
<th>Test</th>
<th>Specimen &amp; Transport</th>
<th>Testing Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology (IgM, IgG)</td>
<td>Serum or CSF; keep and send cold</td>
<td>CDC</td>
</tr>
<tr>
<td>Nucleic acid Amplification</td>
<td>Serum, CSF, Fresh frozen tissue; keep tissue frozen at -70°C, ship on dry ice</td>
<td>CDC</td>
</tr>
<tr>
<td>Virus isolation</td>
<td>Serum, CSF, Fresh frozen tissue; keep tissue frozen at -70°C, ship on dry ice</td>
<td>CDC</td>
</tr>
</tbody>
</table>

The ideal timing of specimens for serology are as follows:

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>3 to 10 days after onset of symptoms</td>
</tr>
<tr>
<td>Convalescent</td>
<td>2 to 3 days after acute sample</td>
</tr>
</tbody>
</table>

M. Assessing Laboratory Results

- **SeroLogic cross-reactivity**: In some instances, arboviruses from the same genus produce cross-reactive antibodies. In geographic areas where two or more closely-related arboviruses occur, serologic testing for more than one virus may be needed and results compared to determine the specific causative virus. For example, such testing might be needed to distinguish antibodies resulting from infections within genera, e.g., flaviviruses such as West Nile, St. Louis encephalitis, Powassan, dengue, or Japanese encephalitis viruses.

- **Rise and fall of IgM antibodies**: For most arboviral infections, IgM antibodies are generally first detectable at 3 to 8 days after onset of illness and persist for 30 to 90 days, but longer persistence has been documented (e.g., up to 500 days for West Nile virus). Serum collected within 8 days of illness onset may not have detectable IgM. If case is highly suspected to be an arboviral infection, a second IgM serological test should be repeated during the convalescent phase to rule out arboviral infection in those with a compatible clinical syndrome.
• **Persistence of IgM antibodies:** Arboviral IgM antibodies may be detected in some patients months or years after their acute infection. Therefore, the presence of these virus-specific IgM antibodies may signify a past infection and be unrelated to the current acute illness. Finding virus-specific IgM antibodies in CSF or a fourfold or greater change in virus specific antibody titers between acute- and convalescent-phase serum specimens provides additional laboratory evidence that the arbovirus was the likely cause of the patient’s recent illness. Clinical and epidemiological history also should be carefully considered.

• **Persistence of IgG and neutralizing antibodies:** Arboviral IgG and neutralizing antibodies can persist for many years following a symptomatic or asymptomatic infection. Therefore, the presence of these antibodies alone is only evidence of previous infection and clinically compatible cases with the presence of IgG, but not IgM, should be evaluated for other etiologic agents.

• **Arboviral serologic assays:** Assays for the detection of IgM and IgG antibodies commonly include enzyme-linked immunosorbent assay (ELISA), microsphere immunoassay (MIA), or immunofluorescence assay (IFA). These assays provide presumptive diagnosis and should have confirmatory testing performed. Confirmatory testing involves the detecting of arboviral-specific neutralizing antibodies utilizing assays such as plaque reduction neutralizing test (PRNT).

• **Other information to consider:** Vaccination history, detailed travel history, date of symptom onset, and knowledge of potentially cross-reactive arboviruses known to circulate in the geographic area should be considered when interpreting results.

**N. Outbreak Definition:**
One or more cases for which a known risk factor (i.e., recent travel to an endemic area) cannot be identified should be considered a potential outbreak and adequate resources applied to the investigation, including investigation into potential local transmission of the virus.

**O. Time frame:**
Providers must submit a report to the Local Health Department by telephone or through an electronic reporting system authorized by ADHS within 24 hours after a case or suspect case is diagnosed, treated, or detected or an occurrence is detected.

**P. Forms:**
- [ADHS Arboviral Case Investigation Form](#)

**Q. Steps:**
1. **Confirm diagnosis**
   - Before contacting the patient or family, first determine what information has been released about the patient’s diagnosis and identify if the needed epidemiologic data can be found in the clinical record alone.
• Obtain information that supports the case definition, including travel to endemic areas.
• Obtain information on any laboratory tests performed and results.
• If specimens were sent to CDC for testing, obtain a copy of the CDC Submission Form for onset date, symptoms and travel information.
• If specimens were not sent to CDC, facilitate forwarding specimens to ASPHL who can send specimens to CDC.
• For hospitalizations, obtain medical records, including admission notes, progress notes, lab report(s), and discharge summary.

2. Conduct case investigation
• Collect demographic data (birth date, county, sex, race/ethnicity)
• Determine risk factors and transmission settings. (i.e., travel, outdoor activity, use of repellent) and evaluate the possibility of additional cases. Travel data should be submitted in MEDSIS by filling out the Travel Table.
• Enter all information into MEDSIS.

3. Conduct contact investigation
• In general, contact investigations are not needed for yellow fever investigation because transmission is likely travel-associated from mosquitoes
• If local virus transmission is suspected, individuals living in the same household and local neighborhood could be considered at risk.
  o Follow up with potential contacts to assure adequate treatment and/or medical screening is received if required.

4. Initiate control and prevention measures
Any suspicious cases should be reported to the appropriate health authority. Yellow fever is not transmitted person-to-person, but can be spread by infected mosquitoes. Efforts should focus on identifying suspect cases and cooperating with vector control to apply insecticide at the exposure source and location, when possible. If the case was locally acquired, vector control is considered high priority and should be conducted as soon as possible. Response activities to locally-acquired Yellow Fever would be similar to response measures that would be implemented in the event of locally-acquired chikungunya, dengue, or Zika virus. Additional details regarding response activities can be found in the Arizona Arboviral Handbook.

If the case was imported, vector control should still be notified of the case location and encouraged to focus surveillance and control efforts on that area. The case’s household should also be educated about how to protect themselves from mosquito bites to prevent additional virus transmission into the local mosquito population. Messages can include:
  ● Proper use of DEET and other insect repellents. Always apply after sunscreen and reapply as needed.
  ● When experiencing symptoms it’s best to remain indoors.
  ● Use air conditioning instead of leaving doors and windows open to the outside, or make sure screens are intact and effective.
● Don’t let sitting water accumulate on your property (i.e. don’t leave out buckets, soda cans, or other containers). If water does accumulate, empty and scrub the container.
● If you experience more mosquitoes on your property call your local pest management agencies.

5. Isolation, Work and Child Care Restrictions
None.

6. Case Management
● Follow blood and body fluid standard precautions.
● Patients with acute yellow fever are viremic for about 5 days after symptoms onset, and should be protected from vector mosquitoes that could feed on them and subsequently transmit disease to other people. Useful methods include having screens in windows and doors, using mosquito repellants, spraying rooms with residual insecticide, using insecticide treated bed nets, and wearing long sleeves and long pants.

7. Contact Management
● If disease is travel-associated, no further actions are needed for contacts.
● If others are traveling to endemic areas, or if local disease transmission is suspected, yellow fever vaccination can be recommended.8
   ● Consult with local travel clinics for vaccine; if they do not have it available, consult CDC online information for stocked certified Yellow Fever Vaccination Clinics.10
   ● Consult ADHS or CDC to test patients with serious adverse reactions to the yellow fever vaccine.11

8. Notifications
● Report all cases by telephone or MEDSIS to ADHS within 24 hours of initial report.
● If areas are suspected as having yellow fever transmission, local communities can be notified to take precautions and look for symptoms.
● There are no special notifications or additional reporting requirements.

R. Outbreak Guidelines:
   Refer to Outbreak Section of the Disease Investigation Manual.
References


