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Yellow Fever

Overview^{1, 2, 3, 5, 6, 7, 8, 11}

Yellow fever (YF) is a vaccine-preventable disease caused by a *flavivirus* that is transmitted to humans primarily through the bite of infected *Aedes* or *Haemagogus* species mosquitoes. Mosquitoes acquire the virus by feeding on infected primates (human or nonhuman) and then can transmit the virus to other primates (human or nonhuman). Humans infected with YF virus are infectious to mosquitoes shortly before the onset of fever and for 3-5 days after onset.⁶ YF virus is found in tropical and subtropical areas in South America and Africa. YF is a very rare cause of illness in U.S. travelers; however, ongoing surveillance is necessary to monitor occurrence of the disease and evaluate for possible introduction of the virus into the U.S.

Mosquitoes that spread YF virus typically bite during the daytime, particularly around sunrise and sunset. YF virus has three transmission cycles: sylvatic (jungle), intermediate (savannah), and urban. The sylvatic cycle involves transmission of the virus between nonhuman primates (e.g., monkeys) and mosquito species found in the forest canopy. In Africa, an intermediate cycle also exists in jungle border or savannah areas. In both the sylvatic and intermediate cycles, humans can become infected when mosquitoes seek blood meal hosts outside the forest canopy. The urban cycle, on the other hand, involves transmission of the virus between humans and urban mosquitoes, primarily *Aedes aegypti*, which is also called the yellow fever mosquito. The virus is usually brought to the urban setting by a viremic human infected in the jungle or savannah. Mosquitoes become infectious 9-12 days after a blood meal from a viremic host.

YF gets its name from the yellowing of the skin and eyes (jaundice) that can occur when the *flavivirus* attacks the liver. The majority of persons infected with YF virus, however, have no illness or only mild illness. In persons who develop symptoms, the incubation period is typically 3-6 days. The initial symptoms include sudden onset of fever, chills, severe headache, back pain, body aches, nausea, vomiting, fatigue, and weakness. Most persons improve after the initial presentation. After a brief remission of hours to a day, roughly 15% of cases progress to develop a hemorrhagic form of the disease. This more severe form of YF is characterized by high fever, jaundice, bleeding, and eventually shock and failure of multiple organs.

Laboratory diagnosis of YF is generally accomplished by testing serum to detect virus-specific IgM and neutralizing antibodies. Because YF viremia is transitory, virus isolation and nucleic acid amplification is not used to rule out infection. There is no specific treatment and care is based on symptoms. Steps to prevent infection include getting vaccinated, using personal insect repellents, wearing protective clothing, and being aware of peak mosquito biting hours. Mosquito control is useful in urban environments.

YF vaccine is a live-virus vaccine that has been used for several decades. In February 2015, the Centers for Disease Control and Prevention (CDC) Advisory Committee on

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Immunization Practices (ACIP) approved a new recommendation that a single dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers. The updated recommendations also identify specific groups of travelers who should receive additional doses and for whom additional doses may be considered. Some countries have already adopted this change, however it is uncertain when and if all countries with YF vaccination requirements will adopt this change.⁵

For a complete description of YF, refer to the following texts:

- *Control of Communicable Diseases Manual (CCDM)*, American Public Health Association, 20th ed. 2015.
- American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. 2015.
- *Centers for Disease Control and Prevention (CDC) Health Information for International Travel 2016 - The Yellow Book*. Travelers' Health Branch, CDC.

1997 Case Definition – Yellow fever⁴ - (10/15)

Clinical Criteria

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 symptoms and, in some instances, renal failure, shock, and generalized hemorrhages.

Laboratory Criteria for Diagnosis

- Fourfold or greater rise in YF antibody titer in a patient who has no history of recent YF vaccination and cross-reactions to other flaviviruses have been excluded, **or**
- Demonstration of YF virus, antigen, or genome in tissue, blood, or other body fluid.

Case Classification

Probable: A clinically compatible case with supportive serology (stable elevated antibody titer to YF virus:

- Greater than or equal to 32 by complement fixation, **or**
- Greater than or equal to 256 by immunofluorescence assay, **or**
- Greater than or equal to 320 by hemagglutination inhibition, **or**
- Greater than or equal to 160 by neutralization, **or**
- A positive serologic result by immunoglobulin M-capture enzyme immunoassay.

NOTE: *Cross-reactive serologic reactions to other flaviviruses must be excluded, and the patient must not have a history of YF vaccination.*

Confirmed: A clinically compatible case that is laboratory confirmed.

Comment(s): The 1997 case definition appearing on this page was originally published in the 1990 *MMWR* and re-published in the 2009 CSTE position statement 09-ID-09. Thus, the 1990, 1997, and 2010 versions of the case definition are identical.

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Information Needed for Investigation

Verify the diagnosis: Obtain demographic, clinical, and laboratory information on the case from the health care provider, hospital, and/or laboratory. Does the laboratory test result provide evidence of a recent YF infection? Obtain the other epidemiological information necessary to complete the [Disease Case Report](#) (CD-1) and the [Yellow Fever Surveillance Worksheet](#) from the patient or a knowledgeable family member. Epidemiologically significant attributes of an infection include:

- Demographics (age, sex, race/ethnicity, place of residence, occupation, or other characteristics that can reveal seasonal, geographic, and demographic patterns).
- Date of illness onset.
- Hospitalization and outcome.
- YF vaccination history.

Establish the extent of the illness. Determine if traveling companions, household, or other unvaccinated close contacts are, or have been, ill by contacting the health care provider, patient, or family members. Strongly urge persons with YF-like illness to contact their physician for a medical evaluation. ***NOTE:** Many patients have an uneventful recovery, but in approximately 15% of infected persons, the illness recurs in more severe form within 48 hours following the viremic period. Symptoms include fever, nausea, vomiting, epigastric pain, jaundice, renal insufficiency, generalized hemorrhage, and cardiovascular instability. Among those who develop severe disease, 20-50% may die.⁶ **IMPORTANT:** Prevent access of mosquitoes to the patient for at least 5 days after onset.⁶*

Identify the source of infection. Determine if the case-patient has a history of foreign travel 6 days prior to illness onset. If yes, obtain:

- Travel history (from the patient or the patient’s family, neighbors, co-workers, social worker, or health care provider). Determine the specific dates and location of travel for the 6 days prior to illness onset. ***NOTE:** If there is no history of foreign travel consistent with acquisition of YF, it is important to determine the case-patient’s recent medical history, including blood transfusions, or medical treatments received in or outside the United States.*
- What is the patient’s YF vaccine history, including dates?
 - Rare but serious adverse events can follow YF vaccination, including anaphylaxis, vaccine-associated neurologic disease, and vaccine-associated viscerotropic disease.
 - Encourage healthcare providers to report cases of adverse events possibly caused by vaccination to the CDC/FDA Vaccine Adverse Events Reporting System (VAERS). For more details, go to: <http://www.cdc.gov/yellowfever/healthCareProviders/healthCareProviders-VacAdverseEv.html>



- The Missouri State Public Health Laboratory (MSPHL) can facilitate specimen submission to CDC to determine if an illness is potentially due to their recent YF vaccination. ([Laboratory Procedures](#) are provided below.)
- Is the case-patient:
 - Working in a laboratory or clinical setting?
 - Pregnant or breast feeding?
 - Known to have contacts with a similar illness, or are healthcare providers aware of others with a similar illness in the area?
 - Ill persons should be advised to seek medical attention and alert their medical provider that they may have been exposed to YF virus.
 - A recent organ, tissue (e.g., corneas, skin), bone marrow or blood donor, or recipient?
 - If yes, notify:
 - ✓ Blood or tissue bank. Assure relevant partners have been notified (hospitals, CDC, other health departments).
 - ✓ Quarantine remaining co-component blood or tissues.
 - ✓ Identify other possibly exposed patients. If necessary, investigate recipients of transfused co-components from implicated donation and other potentially contaminated donations from implicated donor(s).
- Notify Bureau of Communicable Disease Control and Prevention (BCDCP).

Provide information on YF to persons at risk for infection and the general public as needed. Efforts should be made to promote YF awareness among international travelers and persons visiting family and friends where this disease is known to occur. To the extent possible, travelers should avoid known foci of epidemic disease transmission.

Residents of and travelers to areas with endemic YF can reduce their risk of infection by receiving YF vaccine. This vaccine can only be obtained from YF vaccination clinics. [Search for a YF vaccination clinic near you.](#) The vaccine is recommended for persons aged \geq 9 months who are traveling to or living in areas at risk for YF virus transmission in South America and Africa.⁶ The vaccine is contraindicated in children younger than 6 months of age and should be considered for those aged 6-8 months only if the risk of exposure is judged to exceed the risk of vaccine-associated encephalitis.¹ **NOTE:** *You should be vaccinated at least 10 days before you travel, as this will allow enough time for your body to develop protection against the YF infection.*¹ YF vaccination requirements and recommendations for specific countries are available on the [CDC Travelers' Health page](#). For information on YF prevention, consult the section on Control Measures below.

YF Surveillance. Medical providers should report YF cases promptly. Local public health agencies (LPHAs) should review WebSurv to determine whether other cases have been reported. When YF cases are reported, every effort should be made to identify the source.

Data collected from YF surveillance is used to monitor trends; identify areas of risk for travelers; and provide vaccination recommendations. Furthermore, public health

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surveillance can enhance healthcare provider awareness of YF so that cases can be rapidly identified, thereby reducing the possibility of local transmission or establishment of endemicity in this country.

Notification

- Contact the Bureau of Communicable Disease Control and Prevention (BCDCP) [District Communicable Disease Coordinator](#), the [Senior Epidemiology Specialist](#) for the District, or MDHSS/Office of Veterinary Public Health (OVPH), phone (573) 526-4780, Fax (573) 751-6185; or for afterhours notification contact the MDHSS/ERC at (800) 392-0272 (24/7) if a YF case is suspected.
- If a case(s) is associated with a childcare center, BCDCP or the LPHA will contact the Bureau of Environmental Health Services (BEHS), phone (573) 751-6095, Fax (573) 526-7377 and the Section for Child Care Regulation, phone (573) 751-2450, Fax (573) 526-5345.
- If a case(s) is associated with a long-term care facility, BCDCP or the LPHA will contact the Section for Long Term Care Regulation, phone (573) 526-8524, Fax (573) 751-8493.
- If a case is associated with a hospital, hospital-based long-term care facility, or ambulatory surgical center, BCDCP or the LPHA will contact the Bureau of Health Services Regulation phone (573) 751-6303, Fax (573) 526-3621.

Control Measures^{1, 2, 5, 6, 7, 8, 11}

Primary prevention for persons potentially exposed to YF-infected mosquitoes is by vaccination. The YF vaccine is a live-virus vaccine that has been used for several decades. *NOTE: ACIP approved a new recommendation that a single dose of YF vaccine provides long-lasting protection and is adequate for most travelers. The updated recommendations also identify specific groups of travelers who should receive additional doses and others for whom additional doses may be considered. The official ACIP recommendations were published on June 19, 2015 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a5.htm>). All current ACIP YF vaccine recommendations can be found on the ACIP website at: <http://www.cdc.gov/vaccines/hcp/acip-recs/index.html>. The World Health Organization adopted the recommendation to remove the 10-year booster dose requirement from the International Health Regulations (IHR) as of June 2016. Some countries have already adopted this change, which is noted under the YF vaccine requirements on each country's [destination page](#). However, it is uncertain when and if all countries with YF vaccination requirements will adopt this change. For additional information on YF vaccine, see the following CDC websites:*

- [Yellow Fever Vaccine Recommendations](#)
- [Contraindications](#)
- [Precautions](#)
- [Reactions to Yellow Fever Vaccine](#)

Additional preventive measures include:

- Avoidance of mosquito-prone areas, **and/or**

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- Awareness of peak mosquito exposure times and places
- Personal protection measures such as long sleeves, mosquito repellents, and **bed nets** when accommodations are not adequately screened or air conditioned
- Mosquito control measures, such as elimination of standing water

Mosquito preventive measures:

- For urban YF, eliminate or control the mosquitoes through disposal of standing water-holding containers and the use of larvicides and insecticides.
- For jungle YF, mosquito control measures are typically not successful. Protective clothing, bed nets, and repellents are advised for those not immunized.
- For travelers who cannot be immunized, using protective clothing, bed nets, and repellents may help lower the risk of disease.

Insecticides to control larval and adult mosquitoes are registered specifically for that use by the Environmental Protection Agency (EPA). Instructions provided on product labels prescribe the required application and use parameters, and must be carefully followed. Properly applied, these products do not negatively affect human health or the environment. More detailed information about pesticides used for adult mosquito control is available from the EPA (<http://www2.epa.gov/mosquitocontrol/controlling-adult-mosquitoes>). Pesticides for adult mosquito control can be applied from hand-held application devices or from trucks or aircraft.

Treatment⁶

No specific treatments have been found to benefit patients with YF. Whenever possible, YF patients should be hospitalized for supportive care and close observation. Treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve symptoms of aching and fever. Care should be taken to avoid certain medications, such as aspirin or other nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen), which may increase the risk of bleeding.

***NOTE:** To prevent further mosquito transmission, YF patients should be protected from further mosquito exposure for 5 days after onset.^{6, 10} Infected patients should be isolated in rooms that are well screened and sprayed with insecticides.¹⁰ This way, YF virus in their bloodstream will be unavailable to other uninfected mosquitoes, thus breaking the transmission cycle and reducing risk to the persons around them.*

Laboratory Procedures⁶

Diagnosis is confirmed by culture, serologic tests, PCR, or identification of characteristic midzonal hepatocyte necrosis at autopsy.¹⁰ MSPHL does not perform YF testing. All requests from medical providers regarding YF testing to be performed by CDC should be coordinated through MSPHL. This can be done by contacting the Virology Unit at: 573-751-3334.

An appropriately complete CDC submission form [CDC 50.34](#) must accompany the specimens. A delay in testing will occur if the CDC 50.34 form does not contain the illness

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onset date, the specimen date, pertinent travel, as well as the patient’s full name and date of birth. Instructions for sending diagnostic specimens to CDC’s Arbovirus Diagnostic Laboratory can be found at [CDC’s Division of Vector-Borne Diseases Arboviral Specimens submission page](#). **IMPORTANT:** *All results will be sent to the state health department. Healthcare providers are asked to notify the state health department of any submissions to CDC by calling MSPHL and/or the Bureau of Communicable Disease Control and Prevention at 573-751-6113.*

Additional YF Information for health care providers can be found on CDC’s website:

- [Clinical and Laboratory Evaluation](#)
- [Diagnostic Testing](#)
- [Testing for Vaccine Adverse Events](#)

NOTE: Health care providers are encouraged to report cases of adverse events potentially caused by YF vaccination to the CDC/FDA Vaccine Adverse Events Reporting System (VAERS). Testing of selected patients with serious adverse events potentially related to YF vaccination should be considered.

For additional information on VAERS and testing related to YF vaccination see CDC’s website:

<http://www.cdc.gov/yellowfever/healthCareProviders/healthCareProviders-VacAdverseEv.html>.

Reporting Requirements

YF is a Category 2 (A) disease and shall be reported to the [LPHA](#) or to the Missouri Department of Health and Senior Services (MDHSS) within one (1) calendar day of first knowledge or suspicion by telephone, facsimile, or other rapid communication.

As a Nationally Notifiable Condition, confirmed and probable YF cases are categorized as **IMMEDIATE, URGENT** reports to the CDC. MDHSS will report these conditions to the CDC EOC at 770-488-7100 within 24 hours of a case meeting the notification criteria, followed by submission of an electronic case notification (WebSurv) in the next regularly scheduled electronic reporting cycle.

1. For confirmed and probable cases complete a [Disease Case Report](#) (CD-1), and a [Yellow Fever Surveillance Worksheet](#).
2. Entry of the completed CD-1 into the WebSurv database negates the need for the paper CD-1 to be forwarded to the District Health Office.
3. MDHSS will report to CDC following the above reporting criteria (see box).
4. Send the completed [Yellow Fever Surveillance Worksheet](#) to the District Health Office.
5. All outbreaks or “suspected” outbreaks must be reported as soon as possible (by phone, fax or e-mail) to the [District Communicable Disease Coordinator](#). This can be accomplished by completing the [Missouri Outbreak Surveillance Report \(CD-51\)](#).



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6. Within 90 days from the conclusion of an outbreak, submit the final outbreak report to the [District Communicable Disease Coordinator](#).

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