UTAH DEPARTMENT OF HEALTH

Report Immediately

Yellow Fever

Disease Plan

Quick Links

Last updated: January 26, 2017 by Dallin Peterson.

Questions about this disease plan?

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✓ WHY IS YELLOW FEVER IMPORTANT TO PUBLIC HEALTH?

Yellow fever virus is found in tropical and subtropical areas in South America and Africa. The virus is transmitted to people by the bite of an infected mosquito. Yellow fever is a very rare cause of illness in U.S. travelers with a high case fatality rate. Illness ranges in severity from a self-limited febrile illness to severe liver disease with bleeding.

✓ DISEASE AND EPIDEMIOLOGY

Clinical Description

Arboviral infections may be asymptomatic, or may result in febrile illnesses of variable severity which are sometimes associated with central nervous system (CNS) involvement. When the CNS is affected, clinical syndromes include meningitis, myelitis and encephalitis, which are clinically indistinguishable from similar syndromes caused by other viruses. Febrile syndromes associated with arboviral infections include:

- Arboviral meningitis - usually characterized by fever, headache, stiff neck, and white blood cells in the cerebrospinal fluid (pleocytosis).
- Arboviral myelitis - usually characterized by fever and acute bulbar (pertaining to crainial nerves IX, X, XI and XII which may affect the circulatory or respiratory system) or limb paresis (partial paralysis) or flaccid paralysis.
- Arboviral encephalitis - usually characterized by fever, headache, and altered mental status ranging from confusion to coma with, or without, additional signs of brain dysfunction. Less common neurological syndromes can include cranial and peripheral neuritis or other neuropathies, including Guillain-Barré syndrome (ascending paralysis).

Non-neuroinvasive syndromes caused by these viruses can include myocarditis (inflammation and damage of the heart muscle), pancreatitis, or hepatitis. In addition, they may cause febrile illnesses (e.g., dengue fever) that are non-localized, self-limited illnesses with headache, myalgias, arthralgias, sometimes accompanied by skin rash or lymphadenopathy. Laboratory-confirmed arboviral illnesses lacking documented fever can occur, and overlap among the various clinical syndromes is common.

Causative Agent

There are about 570 viruses worldwide that are spread through arthropods (insects). More than 30 of these arboviruses have been identified as human pathogens in the western hemisphere. In Utah, three mosquito-borne arboviruses that cause encephalitis in humans have been identified: Western equine encephalitis (WEE), Saint Louis encephalitis (SLE) and West Nile virus (WNV).

- WEE is of the genus Alphavirus and in the family Togaviridae.
- SLE is a member of the family Flaviviridae.

- WNV, also a member of the Flaviviridae family and Flavivirus genus, has recently appeared in the West.

Other important arboviral encephalitides in the Americas include:

- Powassan encephalitis,
- Venezuelan equine encephalitis (VEE),
- Eastern equine encephalitis (EEE),
- LaCrosse encephalitis (part of the California encephalitis virus serogroup),
- Tensaw encephalitis,
- Everglades encephalitis,
- Ilheus encephalitis, and
- Snowshoe hare encephalitis.

Differential Diagnosis

The differential diagnosis for yellow fever includes:

- Viral hepatitis (hepatitis A, B, C, D, and E) – These entities are characterized by transaminitis; hepatitis A and E are acute infections transmitted by the fecal-oral route, whereas hepatitis B, C, and D can present acutely or chronically and are transmitted by body fluids.
- Influenza – Influenza is associated with fever, headache, malaise, and myalgias. It is not generally associated with severe hepatic involvement or jaundice. The diagnosis is established by viral detection.
- Dengue – Dengue and yellow fever are similar in that both are associated with fever, headache and body aches, and hemorrhagic manifestations. Hepatic involvement can occur in the setting of severe dengue infection. The diagnosis of dengue is established by serology.
- Malaria – Malaria is characterized by fever and anemia; clinical manifestations include jaundice due to hemolysis. The diagnosis of malaria is established by visualization of parasites on peripheral smear.
- Typhoid – Manifestations of typhoid fever include fever and gastrointestinal symptoms. Abnormal liver function tests are observed, but jaundice is not a typical clinical feature. The diagnosis is established by culture.
- Leptospirosis – Leptospirosis is a bacterial infection characterized by fever, myalgia, headache, and conjunctival suffusion. Modest elevation of hepatic transaminases may be observed. The diagnosis is established by serology.
- Q fever – Q fever occurs as a result of infection with *Coxiella burnetii*; hepatic involvement includes transaminitis, hepatomegaly without jaundice, and granulomas on liver biopsy. The diagnosis is established by serology.
- Hemorrhagic fever – Yellow fever may be distinguished from other viral hemorrhagic fevers (Lassa fever, Marburg virus, Ebola virus, Bolivian and Argentine hemorrhagic fevers, Congo-Crimean hemorrhagic fever, and Rift Valley fever) in that other viral hemorrhagic fevers are not usually associated with jaundice.

Laboratory Identification

Diagnosis is made by serology, detection of viral genome by polymerase chain reaction (PCR), viral isolation or histopathology, and immunohistochemistry on postmortem tissues.

Serology - Serologic diagnosis is best accomplished using an enzyme-linked immunosorbent assay (ELISA) for IgM. The presence of IgM antibodies in a single sample provides a presumptive diagnosis; confirmation is made by a rise in titer between paired acute and convalescent samples or a fall between early and late convalescent samples.

Persistence of antibodies from earlier receipt of the live-attenuated vaccine can complicate interpretation of IgM results. In addition, cross-reactions with other flaviviruses complicate the diagnosis of yellow fever by serologic methods, particularly in Africa where multiple flaviviruses circulate. The neutralization test is more specific, but requires a specialized laboratory.

Rapid diagnostic tests - Rapid diagnostic tests include PCR to detect viral genome in the blood or tissue, and ELISA for determination of IgM antibody. Next-generation sequencing of RNA directly amplified from blood has been used to confirm the diagnosis and compare the patient's strain to known geographic clades of the virus. These tools are increasingly available in national and regional laboratories in endemic areas.

Virus isolation - Virus isolation is accomplished by inoculation of mosquito or mammalian cell cultures, intracerebral inoculation of suckling mice, or intrathoracic inoculation of mosquitoes. The virus may also be recovered from postmortem liver tissue. During a yellow fever outbreak in Ivory Coast in 1982 including 90 confirmed cases, 30% were diagnosed by virus isolation from the blood; the majority of patients had detectable virus prior to onset of jaundice.

Treatment

The treatment of yellow fever consists of supportive care; there is no specific antiviral therapy available. Management of patients may be improved by modern intensive care, but this is generally not available in remote areas where yellow fever often occurs. Travelers hospitalized after return to the United States or Europe have experienced fatal outcomes in spite of intensive care, demonstrating the inexorable course of severe yellow fever.

Supportive care should include maintenance of nutrition, prevention of hypoglycemia, nasogastric suction to prevent gastric distention and aspiration, treatment of hypotension by fluid replacement and vasoactive drugs if necessary, administration of oxygen, management of metabolic acidosis, treatment of bleeding with fresh-frozen plasma, dialysis if indicated by renal failure, and treatment of secondary infections.

Case Fatality

The estimated risks of illness and death due to yellow fever in an unvaccinated traveler to an endemic area are relatively high (1 in 1,000 and 1 in 5,000 per month, respectively). In the United States, the risks of yellow fever vaccine-associated neurotropic disease (YEL-AND) and yellow fever vaccine-associated viscerotropic disease (YEL-AVD) in travelers are estimated at 0.8 and 0.4 cases per 100,000 doses distributed respectively, although the risk is higher in older adults.

Reservoir

In urban areas, humans and *Aedes* mosquitoes; in forest areas, vertebrates other than humans, mainly nonhuman primates and possibly marsupials and forest mosquitoes. Transovarian transmission of the infection in mosquitoes has been documented, but its contribution to maintenance of infection is unknown. Humans have no essential role in transmission in jungle yellow fever, but are the primary amplifying host in the urban cycle.

Transmission

Transmission occurs through the bite of an infected *Aedes* or *Haemagogus* spp mosquito. There are three transmission cycles: sylvatic (jungle), intermediate (savannah), and urban:

- Urban and rural areas transmission – This occurs through an infected *Aedes spp.* mosquito. Large epidemics occur when infected individuals bring the virus into a population with a high number of non-immune people and *Aedes* mosquitos.
- Sylvatic transmission - In South America, this occurs through forest mosquitos, known as *Haemagogus spp* and *Sabethes spp.* In Africa, the primary vector is *Aedes africanus.* Mosquitos can become infected by feeding on monkeys who have yellow fever.
- Intermediate transmission - In humid or semi-humid parts of Africa, minor epidemics occur. Transmission is through a semi-domestic *Aedes spp* vector known as *Aedes furcifer, Aedes luteocephalus,* and *Aedes simpsoni* complex.

Mosquitos can be infected by blood shortly before onset of fever and for the first 3-5 days of the illness. However, the virus has been found in blood up to 17 days after onset. The disease is not transmissible through contact or fomites; however, it is likely that the virus may be transmitted through breastfeeding or exposure to infected blood or organs.

Susceptibility

Anyone who travels to locations with yellow fever unvaccinated is susceptible to infection. The disease is highly communicable where many susceptible people and plentiful vector mosquitos coexist. Transient, passive immunity in infants born to immune mothers may persist for up to six months.

Incubation Period

From 3-6 days.

Period of Communicability

Arboviral infections or agents of transmission are not communicable from person-to-person, except in rare instances (e.g., blood transfusion, organ donation).

Epidemiology

Yellow Fever occurs in tropical areas such as Sub-Saharan Africa and South America. It is considered a large epidemic disease problem. The incidence of disease is not well-known; however, approximately 1% of individuals diagnosed with hepatitis in endemic regions of Africa may have been triggered by yellow fever. Serological and epidemiological data demonstrated that there were 130,000 cases with viscertropic disease, and 78,000 deaths in Africa in 2013.

Yellow fever occurs in epidemics, but the incidence differs. There is a continuing epidemic in Angola in south/central Africa that started in December 2015. Mosquito-borne epidemics appear in regions where large human populations live in crowded urban areas and immunization coverage is low. Human to human transmission without the mosquito does not occur.

It is more prevalent in Africa than South America because transmission occurs from enzootic sources (primarily monkey to human via mosquito vectors) in Africa. Also, vaccination is as high as 80-90% in endemic regions of South America.

In both Africa and South America, only a small amount of disease is recorded and reported because the disease frequently occurs in secluded areas, recognition of outbreak is delayed, and there is a lack of diagnostic facilities. In Africa, reports dated in the 1980s showed outbreak incidence to be 20-40%, incidence of severe disease to be 3-5%, and the case fatality rate to be 20-30%. However, in South America, case fatality rates are up to 50-60%. It is unknown if these differences reflect a reporting artifact, variations of the virus strain virulence, and/or differing genetic susceptibility of the human populations.

The urban vector (*Aedes aegypti*) is found in Asia and there is no background data regarding specific immunity. Fortunately, there hasn't been a yellow fever case reported in Asia. The 2016 outbreak in Angola may have caused a threat of introduction of the virus, and possible secondary spread in China, because at least 10 Chinese workers were infected and have traveled home to China.

It is uncommon for refugees and travelers to and from Africa and South America to be infected by yellow fever because of the vaccination, which was introduced after World War II. Since that time, only 10 cases had been recorded up to the time of the 2016 Angolan outbreak. The cause of the outbreak in Angola appears to be connected to a large amount of Chinese construction workers who entered the country without vaccination.

✓ PUBLIC HEALTH CONTROL MEASURES

Public Health Responsibility

- Investigate all suspect cases of disease, and fill out and submit appropriate disease investigation forms.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention.
- Identify clusters or outbreaks of disease.
- Identify sources of exposure and stop further transmission

Prevention

- Use EPA-registered insect repellent, preferably those containing DEET, picaridin, IR3535, or oil of lemon eucalyptus on exposed skin.
- Wear protective clothing.
- Use bed nets.

- Make sure there are screens on windows.
- Stay in air conditioned areas.
- Be aware of peak mosquito hours which are during the day for the *Aedes aegypti* mosquito that transmits yellow fever.

If recommended, a vaccine is available for children age nine months and older. The live-attenuated vaccine against yellow fever was developed in 1936 (yellow fever 17D vaccine).

Chemoprophylaxis

None.

Vaccine

The yellow fever vaccine is safe and affordable; a single dose provides life-long immunity against the disease. It is effective in more than 90% of recipients with antibodies appearing 7-10 days after receiving the dose, and effective in virtually 100% of recipients within 3-4 weeks after vaccination. Over 600 million doses of the 17D vaccine have been given since it was first developed. It is extremely rare to experience serious adverse reactions to the vaccine. Vaccine virus can be transmitted via blood transfusion and breastfeeding, so it is recommended that vaccine recipients should not donate blood for at least two weeks. In addition, an allergic reaction can occur to individuals who have a known egg allergy.

Anyone aged nine months or older who is risk due to residence, travel, or occupation should be vaccinated. The vaccine will be recommended if the risk of exposure exceeds the risk of vaccine-associated complications in other groups, e.g.,:

- Persons age 6-8 months
- Persons age ≥60 years
- Persons with asymptomatic HIV infection and CD4+ T-lymphocytes 200 to 499/mm^3 (15-24% of total in children aged <6 years)
- Pregnant women
- Breastfeeding women

Isolation and Quarantine Requirements

Isolation: None.

Hospital: Standard body substance precautions.

Quarantine: None.

✓ CASE INVESTIGATION

Reporting

Healthcare providers or institutions should submit information to governmental public health agencies about illness that meets criteria for yellow fever. Report any illness to public health that meets any of the following criteria:

An 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, and any of the following:

- demonstration of yellow fever virus in tissue, blood, or other body fluid,
- demonstration of yellow fever antigen in tissue, blood, or other body fluid,
- demonstration of yellow fever genome in tissue, blood, or other body fluid,
- four-fold or greater rise in yellow fever antibody titer in a patient AND no history of recent yellow fever vaccination AND no cross-reactions to other flaviviruses,
- positive serology for yellow fever AND no history of yellow fever vaccination AND no cross-reactions to other flaviviruses,
- a person whose healthcare record contains a diagnosis of yellow fever, not related to yellow fever vaccination, or
- a person whose death certificate lists yellow fever as a cause of death or a significant condition contributing to death, but not related to yellow fever vaccination.

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

Criterion	**Reporting**		
Clinical Presentation			
Fever		C	C
Chills		C	C
Severe headache		C	C
Back pain		C	C
Myalgia		C	C
Nausea		C	C
Vomiting		C	C
Hemorrhagic diathesis (gastrointestinal bleeding)		C	C
Petechiae		C	C
Purpura		C	C
Jaundice		C	C
Proteinuria		C	C
History of recent yellow fever vaccination		A	
History of yellow fever vaccination			A
Healthcare record contains a diagnosis of yellow fever	S		
Death certificate lists yellow fever as a cause of death or a significant condition contributing to death	**S**		

Laboratory Findings			
Fourfold or greater rise in yellow fever antibody titer		N	
Cross-reactions to other flaviviruses		A	A
Demonstration of yellow fever virus in tissue, blood, or other body fluid	S		
Demonstration of yellow fever antigen in tissue, blood, or other body fluid	S		
Demonstration of yellow fever genome in tissue, blood, or other body fluid	S		
Antibody titer to yellow fever virus $\geq$ 32 by complement fixation			O
Immunofluorescence assay			
Antibody titer to yellow fever virus $\geq$ 320 by hemagglutination inhibition			O
Antibody titer to yellow fever virus $\geq$ 160 by neutralization			O
Positive serology for yellow fever by immunoglobulin M-capture enzyme immunoassay			O
Epidemiological Risk Factors			
Recent travel to area with endemic yellow fever		C	C

Notes:
S = This criterion alone is sufficient to report a case
N = All "N" criteria in the same column—in conjunction with at least one of any "O" criteria, if present, in each category (e.g., clinical presentation and laboratory findings) in the same column—are required to report a case.
O = At least one of any "O" criteria in each category (e.g., clinical presentation and laboratory findings) in the same column—in conjunction with all other "N" criteria in the same column—is required to report a case.
A = This criterion must be absent (e.g., NOT present) for the case to meet the reporting criteria or case definition.
C = This finding corroborates (e.g., supports) the diagnosis of—or is associated with—yellow fever, but is not included in the case reporting definition and is not required for reporting.

Disease Specific Data Elements

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

Clinical information:
Date of onset of fever
Date of onset of other constitutional symptoms consistent with yellow fever infection

Epidemiologic risk factors:
Destination(s) of recent travel (if any)
Date of return from travel
Epidemiologically linked to a traveler with confirmed yellow fever

Immunization history
Yellow fever vaccination history

Case Definition

Clinical description

A mosquito-borne, viral illness characterized by acute onset of constitutional symptoms, followed by a brief remission and a recurrence of fever, hepatitis, albuminuria, and, in some instances, renal failure, shock, and generalized hemorrhages.

Laboratory criteria

- Fourfold or greater rise in yellow fever antibody titer in a patient who has no history of recent yellow fever vaccination, and cross-reactions to other flaviviruses have been excluded, or
- Demonstration of yellow fever 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 yellow fever virus [e.g., ≥32 by complement fixation, ≥256 by immunofluorescence assay, ≥320 by hemagglutination inhibition, ≥160 by neutralization, or a positive serologic result by immunoglobulin M-capture enzyme immunoassay]. Cross-reactive serologic reactions to other flaviviruses must be excluded, and the patient must not have a history of yellow fever vaccination.)

Confirmed

A clinically compatible case that is laboratory confirmed.

Classification Tables

Table B. Proposed table of criteria to determine whether a case is classified.

Criterion	Case Definition		
	Confirmed		Probable
Clinical Presentation			
Fever	O	O	O
Chills	O	O	O
Severe headache	O	O	O
Back pain	O	O	O
Myalgia	O	O	O
Nausea	O	O	O
Vomiting	O	O	O
Hemorrhagic diathesis (gastrointestinal bleeding)	O	O	O
Petechiae	O	O	O
Purpura	O	O	O
Jaundice	O	O	O
Proteinuria	O	O	O

History of recent yellow fever vaccination		A	
History of yellow fever vaccination			A
Laboratory Findings			
Fourfold or greater rise in yellow fever antibody titer		N	
Cross-reactions to other flaviviruses		A	A
Demonstration of yellow fever virus in tissue, blood, or other body fluid	O		
Demonstration of yellow fever antigen in tissue, blood, or other body fluid	O		
Demonstration of yellow fever genome in tissue, blood, or other body fluid	O		
Antibody titer to yellow fever virus ≥ 32 by complement fixation			O
Antibody titer to yellow fever virus ≥ 256 by immunofluorescence assay			O
Antibody titer to yellow fever virus ≥ 320 by hemagglutination inhibition			O
Antibody titer to yellow fever virus ≥ 160 by neutralization			O
Positive serology for yellow fever by immunoglobulin M-capture enzyme immunoassay			O
Epidemiological Risk Factors			
Recent travel to area with endemic yellow fever	C	C	C

Notes:
S = This criterion alone is sufficient to classify a case
N = All "N" criteria in the same column—in conjunction with at least one of any "O" criteria in each category (e.g., clinical presentation and laboratory findings) in the same column—are required to classify a case.
O = At least one of any "O" criteria in each category (e.g., clinical presentation and laboratory findings) in the same column—in conjunction with all other "N" criteria in the same column—is required to classify a case.
A = This criterion must be absent (e.g., NOT present) for the case to meet the reporting criteria or case definition.
C = This finding corroborates (e.g., supports) the diagnosis of—or is associated with—yellow fever, but is not included in the case classification definition.

Period of surveillance

Surveillance should be on-going.

Case Investigation Process

- Fill out morbidity form.
- Verify case status.
- Fill out disease investigation form.
- Determine whether patient had travel/exposure history consistent with acquisition of disease in Utah or elsewhere.
- If patient acquired disease in Utah, identify the source of transmission and eliminate it.

Outbreaks

An outbreak will be defined as: a larger than normal number of cases by county, one case of an unusual or exotic arboviral etiology, or one non-travel associated case.

Identifying Case Contacts

Case contact identification is not needed since this disease is not spread person to person.

Case Contact Management

None.

✓ REFERENCES

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✓ VERSION CONTROL

Updated 12/12/2016: Updated Case Investigation Tab, Minimum Data Set and References.

✓ UT-NEDSS Minimum/Required Fields by Tab

Demographic
- ☑ County
- ☑ State of Utah
- ☑ Date of Birth
- ☑ Birth Gender
- ☑ Ethnicity
- ☑ Race
- ☑ First Name
- ☑ Last Name
- ☑ Middle Name
- ☑ Area Code
- ☑ Email Address
- ☑ Phone Number

Clinical
- ☑ Date Diagnosed
- ☑ Date of Death
- ☑ Died
- ☑ Disease
- ☑ Onset Date
- ☑ Asymptomatic
- ☑ Febrile Illness
- ☑ Neuroinvasive Disease
- ☑ Other
- ☑ Unknown
- ☑ Has the patient ever received the yellow fever vaccine?
- ☑ Has the patient ever received the Japanese encephalitis vaccine?
- ☑ Has the patient ever had a dengue virus infection?
- ☑ Has the patient ever had Powassan virus infection?
- ☑ Has the patient ever had yellow fever virus infection?
- ☑ Has the patient ever had Japanese encephalitis virus infection?
- ☑ Has the patient ever had St. Louis encephalitis virus infection?

Laboratory
- ☑ Lab Test Date
- ☑ Organism
- ☑ Specimen Source
- ☑ Test Result

Epidemiological
- ☑ Imported From

Investigation
- ☑ Is the patient being breastfed?
- ☑ Is the patient breastfeeding?
- ☑ During the above period, has the patient seen mosquitos or standing water at home?
- ☑ During the above period, has the patient seen mosquitos or standing water at work?
- ☑ During the exposure period, has patient traveled outside of Utah?
- ☑ During the above period, has the patient received a blood transfusion?
- ☑ During the above period, has the patient donated blood or blood products?
- ☑ During the above period, has the patient received an organ transplant?
- ☑ During the above period, has the patient donated organ or tissues?
- ☑ During the above period, has the patient received a bloodborne exposure (e.g., needlestick)?

Contacts
- ☑ N/A

Reporting
- ☑ Date first reported to public health

Administrative
- ☑ State Case Status
- ☑ Event Name