



# Yellow Fever Investigation Guideline

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*Attachments can be accessed through the Adobe Reader's navigation panel for attachments. Throughout this document attachment links are indicated by this symbol ; when the link is activated in Adobe Reader it will open the attachments navigation panel. The link may not work when using PDF readers other than Adobe.*

**Revision History:**

| <b>Date</b> | <b>Replaced</b> | <b>Comments</b>  |
|-------------|-----------------|--|
| 05/2019     | 05/2018         | Updated case definition. Added more information to the Vaccine section of Disease Overview.  |
| 05/2018     | 01/2015         | Updated format. Updated Notification sections with updated regulations.  |
| 01/2015     | 12/2009         | Added notification section and table of contents. Updated Laboratory Analysis Section. More details added to Investigators Responsibilities and Data Management. Reformatted Standard Case Investigation section to assist with EpiTrax system data entry. Reformatted fact sheet. |

# Yellow Fever

## Disease Management and Investigative Guidelines

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### CASE DEFINITION (CDC 2019)

#### Clinical Description for Public Health Surveillance:

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 for Case Classification:

*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 Classification:

##### 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.

##### 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.

## LABORATORY ANALYSIS

**Warning:** Prior consultation with CDC recommended before attempting to collect or send samples. Call the Arbovirus Branch in Ft. Collins, CO at 970-221-6407.

The preliminary diagnosis is based on the patient's clinical features, places and dates of travel, and activities. Laboratory diagnosis is best performed by:

- Serologic assays to detect virus-specific IgM and IgG antibodies. Because of cross-reactivity between antibodies raised against other flaviviruses, more specific antibody testing, such as a plaque reduction neutralization test, should be done to confirm the infection.
- Virus isolation or nucleic acid amplification tests performed early in the illness for YFV or yellow fever viral RNA. However, by the time more overt symptoms are recognized, the virus or viral RNA is usually undetectable. Therefore, virus isolation and nucleic acid amplification should not be used for ruling out a diagnosis of yellow fever.

Clinicians should call 800-CDC-INFO (800-232-4636) for additional assistance with diagnostic testing for yellow fever infections and for questions about antibody response to vaccination.

### To send specimens to CDC for testing:

1. Call Epidemiologic Services at 877-427-7317 before sending any samples to the Kansas Health and Environment Laboratory (KHEL).
2. Prepare and collect serology samples:
  - o Must be accompanied by a [CDC submission form \(CDC 50.34\)](#) with the following provided:
    - Date of onset of symptoms
    - Date of specimen collection (Specimen collection within 8 days after the onset of symptoms, requires a convalescent specimen collection.)
    - Pertinent travel history (3 months prior to the date of symptom onset)
    - Patient's name (REQUIRED for submitting specimens)
  - o Specimen: Blood or serum (3-5 ml). Acute and convalescent specimens, if available, should be sent together.
  - o Collection: blood specimen in serum separator tube (SST). Follow manufacturer's instructions for serum processing.
  - o Timing of collection for serology: Acute obtained 3 to 10 days after onset of symptoms; convalescent 2-3 weeks after acute sample.
3. Forward specimens to KHEL for transport to CDC.  
**Kansas Health and Environment Laboratories (KHEL)**  
**6810 SE Dwight St.**  
**Topeka, KS 6620**

Test results are normally available 4 to 14 days after specimen receipt. Hard copy of results will take at least 2 weeks after testing is completed.

For additional information and/or questions, call (785) 296-1620.

## EPIDEMIOLOGY

Yellow fever virus is endemic in certain regions of Africa and the Americas located between 15°N and 10°S of the equator. There are 2 types of transmission cycles, a sylvatic or jungle cycle that involves mosquitoes and nonhuman primates, and an urban cycle involving *Aedes aegypti* mosquitoes and humans. Sylvatic transmission is restricted to tropical regions of Africa and Latin America, where a few hundred cases occur annually. Historically, urban yellow fever occurred in many cities of the Americas, although in recent years has only been reported in Nigeria. An outbreak of urban yellow fever has not been reported in the Americas since 1942.

## DISEASE OVERVIEW

### A. Agent:

Yellow fever virus; flavivirus.

### B. Clinical Description:

Acute viral infection of short duration and varying severity, characterized by acute onset of fever, chills, headache, backache, generalized muscle pain, prostration, nausea and vomiting. In addition, the pulse may be slow, weak and out of proportion to the elevated temperature (i.e., Faget sign). Most cases improve and recover within 3 - 4 days; however, about 15% enter into a second or toxic phase  $\leq$  1 day of initial recovery. Symptoms of the toxic phase include, fever, jaundice, epistaxis, gingival bleeding, hematemesis (i.e., vomiting of blood, usually coffee-ground or black in color), Melina, and liver and renal failure. Twenty to 50% of jaundiced cases are fatal.

### C. Reservoirs:

In urban areas: humans and *Aedes aegypti* mosquitoes; in forest areas: vertebrates other than humans and forest mosquitoes. Humans do not have a role in transmission of jungle yellow fever or in maintaining the virus, but are the primary amplifying host in the urban cycle.

### D. Mode(s) of Transmission:

Bite of infected mosquitoes. Direct person-to-person spread does not occur.

### E. Incubation Period:

3-6 days.

### F. Period of Communicability:

No person-to-person transmission. Human blood can infect feeding mosquitoes during first 3-5 days of illness. Mosquitoes can transmit virus 9-12 days after feeding and remain infected for life. Mosquitoes can live weeks to months.

### G. Susceptibility and Resistance:

Susceptibility of non-immunized individuals is universal. Individuals 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.

### H. Treatment:

No specific treatments. Supportive care only

**I. Vaccine:**

YF-Vax, the only yellow fever vaccine licensed for use in the United States, is manufactured by Sanofi Pasteur. Studies of various yellow fever vaccines, including those manufactured outside the United States, suggest that there is no significant difference in the reactogenicity or immune response generated by the various vaccines. Thus, people who receive yellow fever vaccines in other countries should be considered protected against yellow fever.

- A single dose provides lifelong protection for most people.
- The vaccine is a live, weakened form of the virus given as a single shot.
- Vaccine is recommended for people aged 9 months or older and who are traveling to or living in areas at risk for yellow fever virus in [Africa](#) and [South America](#).
- Yellow fever vaccine may be required for entry into certain countries.
- Vaccination requirements and recommendations for specific countries are available on the [CDC Travelers' Health page](#).

During shortages of YF-Vax, CDC and the US Food and Drug Administration have worked to make alternative yellow fever vaccine available. This was recently done in 2019 with the use of Stamaril vaccine during a shortage of YF-Vax.

**General Information on Yellow Fever Vaccine in Kansas**

An official yellow fever uniform stamp holder has the authority granted by the State of Kansas to administer yellow fever vaccine to the public.

- An official yellow fever stamp holder authorization is required to order and administer yellow fever vaccine.
- A uniform stamp on the International Certificate of Vaccination or Prophylaxis (ICVP) card is the international verification that an individual has been vaccinated against yellow fever.

Due to the risk of serious adverse events that can occur following yellow fever vaccine administration, providers should only vaccinate persons who:

- 1) are at risk for exposure to yellow fever virus, or
- 2) require proof of vaccination for country entry.

To further minimize the risk of serious adverse events, medical providers should carefully observe the contraindications and consider the precautions to vaccination to administration of yellow fever vaccine.

For more information on **Kansas requirement to become an official Yellow Fever Uniform Stamp Holder**, refer to:

[www.kdheks.gov/immunize/yellow\\_fever.htm](http://www.kdheks.gov/immunize/yellow_fever.htm)

To find an authorized Yellow Fever Vaccine Center visit the [CDC's](#) website.

- <https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search>

## NOTIFICATION TO PUBLIC HEALTH AUTHORITIES

Yellow fever shall be reported reported within 24 hours, except if the reporting period ends on a weekend or state-approved holiday, the report shall be made by 5:00 p.m. on the next business day after the 24-hour period.: \*

1. Health care providers and hospitals: report to the local public health jurisdiction or KDHE-BEPHI (see below)
2. Local public health jurisdiction: report to KDHE-BEPHI (see below)
3. Laboratories: report to KDHE-BEPHI (see below)

**Kansas Department of Health and Environment (KDHE)  
Bureau of Epidemiology and Public Health Informatics (BEPHI)**

**Phone: 1-877-427-7317**

**Fax: 1-877-427-7318**

\* **Immediately** contact the KDHE-BEPHI at (877-427-7317) if a bioterrorism situation is suspected.

### **Further responsibilities of state and local health departments to the CDC:**

*As a nationally notifiable condition, Confirmed and Probable yellow fever cases require an IMMEDIATELY NOTIFIABLE, URGENT report to the Center of Disease Control and Prevention (CDC).*

1. IMMEDIATELY, URGENT reporting requires a KDHE epidemiologist to call the CDC EOC at 770-488-7100 within 24 hours of a case meeting the [confirmed](#) and probable criteria, followed by submission of an electronic case notification in next regularly scheduled electronic transmission.
  - KDHE-BEPHI will notify the CDC immediately by phone of all confirmed measles cases.
  - KDHE-BEPHI will file electronic reports weekly with CDC.
2. **Local public health jurisdiction** will report information requested as soon as possible, completing the electronic form within 7 days of receiving a notification of a measles report.

## INVESTIGATOR RESPONSIBILITIES

- 1) [Report](#) all confirmed, probable and suspect cases to the KDHE-BEPHI.
- 2) Contact medical provider to collect additional information and confirm diagnosis using current [case definition](#).
  - Collect all information requested in [Step 1](#) of case investigation.
  - Establish whether symptoms of yellow fever exist.
  - Ensure that case/proxy is aware of the diagnosis.
- 3) Continue with the [case investigation](#) to identify potential source of infection.
  - Start the case investigation within 3 days of notification.
  - Completed the case investigation within 7 days of notification.
- 4) Conduct [contact investigation](#) to identify additional cases.
- 5) Identify whether the source of infection is major public health concern.
  - *Was there no travel to an active yellow fever endemic area?*
- 6) Initiate [control and prevention](#) measures to prevent spread of disease.
  - Conduct [Case](#) or [Contact Management](#) as needed.
- 7) [Record](#) data, collected during the investigation, in the KS EpiTrax system under the data's associated [\[tab\]](#) in the case morbidity report (CMR).
- 8) As appropriate, use the notification letter(s) and the disease [fact sheet](#) to notify the case, contacts and other individuals or groups.

## STANDARD CASE INVESTIGATION AND CONTROL METHODS

### Case Investigation

- 1) Contact the medical provider who ordered testing of the case and obtain the following information. (This includes medical records for hospitalized patients.)

**Note:** *If the physician submitted samples to CDC, a [CDC submission form \(CDC 50.34\)](#) may already be completed or started – try to obtain a copy.*

  - Collect case's demographic data and contact information (Full name, birth date, county, sex, race/ethnicity, home address, occupation and work address, and phone number(s)) [\[Demographic\]](#)
  - Identify if the patient was ill with symptoms of yellow fever:
    - 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.
    - Record onset date of symptoms. [\[Clinical\]](#)
  - Examine any laboratory testing that was done; if not yet reported:
    - Record date serum specimen(s) and/or tissue (specify) were collected.
    - Record or obtain copies of serology results and virus isolation and PCR tests, if done.
  - Record [hospitalizations](#): location and duration of stay [\[Clinical\]](#)
  - Record outcomes: survived or [date of death](#) [\[Clinical\]](#)
  - Record information about patient's receipt of any yellow fever vaccine. [\[Notes\]](#)

- 2) Interview the case or proxy to determine source and risk factors; focus on incubation period 3-6 days prior to illness onset. [Notes]
  - Travel history:
    - Travel outside of KS; list states visited; dates visited
    - Travel outside of U.S.; list country; date of departure and return to U.S.
  - *Travel to an active yellow fever area is a **crucial** element. With no travel to areas endemic for yellow fever, refer to Managing Special Situations.*
  - Note any exposure to mosquitoes, include dates and places.
  - Exposure to ticks, rodents, primates or livestock of African origin.
  - Inquire about any laboratory exposure, blood donation or receipt, or organ donation or receipt.
  - Household members or visitors with recent travel to endemic areas in the last 3 months.
- 3) Examining the epidemiological information, record where the infection was most likely imported from. (Indigenous or out-of-county, state, or U.S.) [Epidemiologic]
- 4) Collect information from case for the Contact Investigation. (See below).
- 5) Investigate epi-links among cases (clusters, household, co-workers, etc).

### Contact Investigation

- 1) Contacts are those who have exposure. Exposure is defined as:
  - Travel to a yellow fever endemic country or presence at location with ongoing outbreak within previous two weeks of yellow fever-like illness, OR
  - Association in time and place with a confirmed or probable yellow fever case.
- 2) Identify other individuals who may have had contact with the source in the week prior to the case becoming ill to find unreported or undiagnosed cases.
- 3) If a blood transfusion or organ transplant is suspected, coordinate with BEPHI.
- 4) ONLY if a risk of transmission exists, create a line listing of contacts at-risk of developing disease. [Contact]

### Isolation, Work and Daycare Restrictions

- 1) Follow blood and body fluid precautions.
- 2) **Prevent access of mosquitoes to case until fever subsides** and at least 5 days after the onset of symptoms. If mosquitoes can enter the living space, use insect screens, bed nets, and spray with insecticides.

### Case Management

None required.

### Contact Management

- 1) If indicated, recommend yellow fever vaccine.
- 2) Certified Yellow Fever Vaccination Clinics can be found at <https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search>

## Environmental Measures

Mosquito control is important in preventing virus transmission. The *A. aegypti* mosquito, while rare in the U.S., has been found in: Alabama, Arkansas, Delaware, Florida, Georgia, Illinois, Kansas, Kentucky, Louisiana, Maryland, Mississippi, Missouri, New Mexico, New York, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia and Washington, D.C..

The Association of State and Territorial Health Officials [Vector-Borne and Zoonotic Disease Resources](#) may be of assistance for planning.

## Education

- 1) Instruct travelers to endemic areas on the risks and the need for immunizations and to minimize contact with mosquitoes through the use of nets and repellents.
- 2) Information for travelers to endemic areas can be found at the CDC Traveler's Health website. (<http://wwwnc.cdc.gov/travel/>)

## MANAGING SPECIAL SITUATIONS

### A. 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.

### B. No Recent Travel to Endemic Areas:

- A single diagnosed or suspected case of yellow fever with no travel history should be reported and investigated immediately. Contact the on-call epidemiologist (local) and KDHE (1- 877-427-7317) immediately.
- A locally acquired case of yellow fever would be an unusual occurrence in the United States.
- Environmental measures such as investigating local areas visited by the case to locate the source of infection and surveillance of other people for illness may be necessary.

### C. Intentional Contamination

Yellow fever is a potential bioterrorism weapon. If the case has no remarkable travel history, a bioterrorism event should be considered. If a natural etiology cannot be established by a prompt, vigorous investigation; the situation is considered a bioterrorist act until proven otherwise.

If suspected:

- Contact the local Health Officer, the on-call epidemiologist (local) and KDHE (1-877-427-7317) immediately. Notify local law enforcement and state public health officials.
- Implement "[Chain of Custody](#)" procedures for all samples collected, as they will be considered evidence in a criminal investigation.
- Work to define population at risk which is essential to guide response activities. Public health authorities will play the lead role in this effort, but must

consult with law enforcement, emergency response and other professionals in the process. The definition may have to be re-evaluated and redefined at various steps in the investigation and response.

- Once the mechanism and scope of delivery has been defined, the identification of the symptomatic and asymptomatic exposed individuals can be completed and recommendations for the treatment and/or chemoprophylaxis made.
- Establish and maintain a detailed line listing of all cases and contacts with accurate identifying and locating information.

Safety Considerations:

- By the time the first cases are identified the risk of exposure is dependent on the number of infected mosquitoes remaining at the exposure site. Appropriate protective clothing and repellents should be used.

Vaccination:

- Yellow fever vaccine is a live virus vaccine which has been used for several decades. A single dose confers immunity lasting 10 years or more. If a person is at continued risk of yellow fever infection, a booster dose is needed every 10 years. Adults and children over 9 months can take this vaccine.

Treatment:

- No specific therapy. Patients who develop severe illness may require anticonvulsant and supportive care to maintain fluid and electrolyte balance, for ventilation, and to prevent secondary bacterial infections.

Postexposure prophylaxis (PEP):

- No post-exposure prophylaxis is associated with this group of diseases; however, vaccination may be an option for some of the arboviruses.

Environmental decontamination:

- The viruses do not persist in the environment for long periods of time. No environmental decontamination necessary.
- A release in areas populated with appropriate animal host and/or appropriate arthropod vectors could initiate both an epizootic and epidemic trends.
- Integrated pest management at the presumed infected site, including insecticide fogging, may be a reasonable approach.

## DATA MANAGEMENT AND REPORTING TO THE KDHE

- A. Accept the case assigned to the LHD and record the date the LHD investigation was started on the [[Administrative](#)] tab.
- B. Organize and collect data, using appropriate data collection tools including:
  - Investigators can collect and enter all required information directly into EpiTrax [[Investigation](#)], [[Clinical](#)], [[Demographics](#)], [[Epidemiological](#)] and [[Contact](#)] tabs without using the paper forms. Enter all data that collected during the investigation that helps to confirm or classify a case, including:
    - Demographic Tab: All demographic data available or mark ‘unknown’
    - Clinical Tab: **Onset date, Diagnosis date, Patient Outcome**
    - Contacts Tab: **Contact name, Disposition, Disposition Date, Contact Type**
    - Epidemiological Tab: **Occupation, Place of Exposure** (source and/or transmission locations), **Imported from**
    - Note Tab: **Symptoms, Yellow Fever Vaccination History, Exposure Risk Factors**, Progress on investigation, follow-up, and other notes
  - During outbreak investigations, refer to guidance from a KDHE epidemiologist for appropriate collection tools.
- C. Report data collected during the course of the investigation via EpiTrax.
  - Verify that all data requested on the [Step 1](#)) has been recorded on an appropriate EpiTrax [[tab](#)], or that actions are completed for a case lost to follow-up as outlined below.
  - Some data that cannot be reported on an EpiTrax [[tab](#)] may need to be recorded in [[Notes](#)] or scanned and attached to the record.
  - Paper report forms do not need to be sent to KDHE after the information is recorded and/or attached in EpiTrax. The forms should be handled as directed by local administrative practices.
- D. If a case is lost to follow-up, after the appropriate attempts to contact the case have been made:
  - Indicate ‘lost to follow-up’ on the [[Investigation](#)] tab with the number of attempts to contact the case recorded.
  - Record at least the information that was collected from the initial reporter.
  - Record a reason for ‘lost to follow-up in [[Notes](#)].
- E. After completing requirements listed under [Case Investigation](#), record the “Date LHD investigation completed” field located on the [[Administrative](#)] tab.
  - Record the date even if the local investigator’s [Case](#) or [Contact Management](#) for the contact is not “Complete”.
- F. Once the entire investigation is completed, the LHD investigator will click the “Complete” button on the [[Administrative](#)] tab. This will trigger an alert to the LHD Administrator, so they can review the case before sending to the state.
  - The LHD Administrator will then “Approve” or “Reject” the CMR.
  - Once a case is “Approved” by the LHD Administrator, BEPHI staff will review and close the case after ensuring it is complete and that the case is assigned to the correct event, based on the reported symptoms reported.

## **ADDITIONAL INFORMATION / REFERENCES**

- A. Treatment / Differential Diagnosis:** American Academy of Pediatrics. Red Book: Report of the Committee on Infectious Disease, 29th Edition. Illinois, Academy of Pediatrics, 2014.
- B. Epidemiology, Investigation and Control:** Heymann. D., ed., Control of Communicable Diseases Manual, 19th Edition. Washington, DC, American Public Health Association, 2010.
- C. Case Definitions:** CDC Division of Public Health Surveillance and Informatics, Available at: [wwwn.cdc.gov/nndss/](http://wwwn.cdc.gov/nndss/)
- D. Kansas Regulations/Statutes Related to Infectious Disease:** [www.kdheks.gov/epi/regulations.htm](http://www.kdheks.gov/epi/regulations.htm)
- E. Chain of Custody:** KDHE Chain of Custody Standard Operating Guide, [www.kdheks.gov/cphp/operating\\_guides.htm](http://www.kdheks.gov/cphp/operating_guides.htm)
- F. ASTO Mosquito Control Resources:** [www.astho.org/Programs/Environmental-Health/Natural-Environment/Vector-Borne-and-Zoonotic-Diseases/Vector-Borne-and-Zoonotic-Disease-Resources/Main/](http://www.astho.org/Programs/Environmental-Health/Natural-Environment/Vector-Borne-and-Zoonotic-Diseases/Vector-Borne-and-Zoonotic-Disease-Resources/Main/)
- G. Guidelines for Arbovirus Surveillance Programs** in the United States (CDC 1993). Available at: [www.cdc.gov/ncidod/dvbid/Arbor/arboguid.pdf](http://www.cdc.gov/ncidod/dvbid/Arbor/arboguid.pdf)
- H. Additional Information (CDC):** [www.cdc.gov/health/default.htm](http://www.cdc.gov/health/default.htm)
- **CDC Arboviral Specimen Submission Instructions:** [www.cdc.gov/ncezid/dvbd/specimensub/index.html](http://www.cdc.gov/ncezid/dvbd/specimensub/index.html)