Yellow Fever

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DISEASE AND VACCINE CHARACTERISTICS

Yellow fever (YF), caused by a Flavivirus, is transmitted by several species of infected mosquitoes (e.g. *Haemogogus* and *Aedes spp.*). The incubation period is usually 4–6 days after an infected mosquito bites the person (Figure 1). The course of infection can be asymptomatic or mild in most infected persons. However, in severe cases, infected persons enter a second, more toxic phase of illness within 24 hours of recovering from initial symptoms. Approximately 15% of infected persons develop this severe form of YF disease, and it is during the toxic phase that the severe signs and symptoms classically associated with yellow fever present, including severe abdominal pain, jaundice and liver failure, renal insufficiency, and hemorrhagic signs such as bleeding from the mouth, nose, eyes, or stomach. Death occurs in 20-50% of people who develop hepatorenal failure *(1)*.
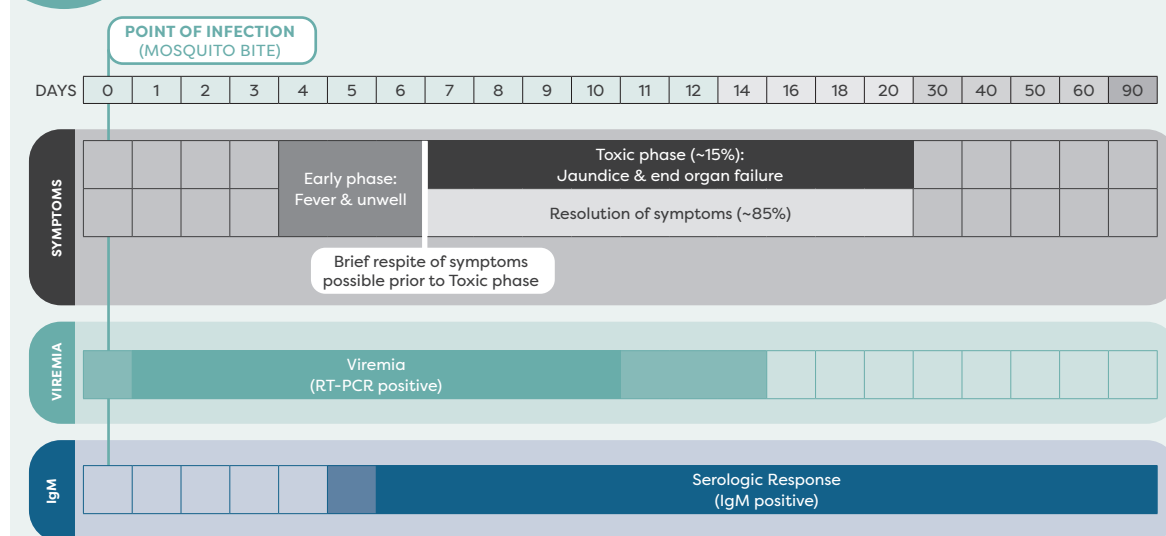
Infected persons are usually viremic for 3-6 days after initial symptom onset (10 days from time of infection). The serological immune response to YF virus involves production of anti-YF virus IgM antibodies. IgM forms rapidly after disease onset, usually within 6 days and typically persists for several years in most persons *(2)*. IgG is not routinely tested, but appears a week after infection, and persists for years, likely providing lifelong protection against repeat infection.

There are three transmission patterns of YF:

1. **sylvatic** – where the animal reservoir (non-human primates in forests or jungle) infect tree-dwelling species of mosquitoes (e.g. *Haemogogus spp.* in the Americas and *Aedes spp.* in Africa), which in turn bite and cause YF infection in humans who have close contact with the forest habitat;

2. **intermediate** – where *Aedes spp.* mosquitoes moving between forest and human settlements are implicated, with humans serving as hosts in the transmission cycle. This cycle is unique to Africa and is observed in small towns or rural villages, sometimes called the emergence zone; or

3. **urban** – where *Aedes aegypti* acts as a primary vector, facilitating rapid human-to-human transmission without reliance on a wildlife reservoir.
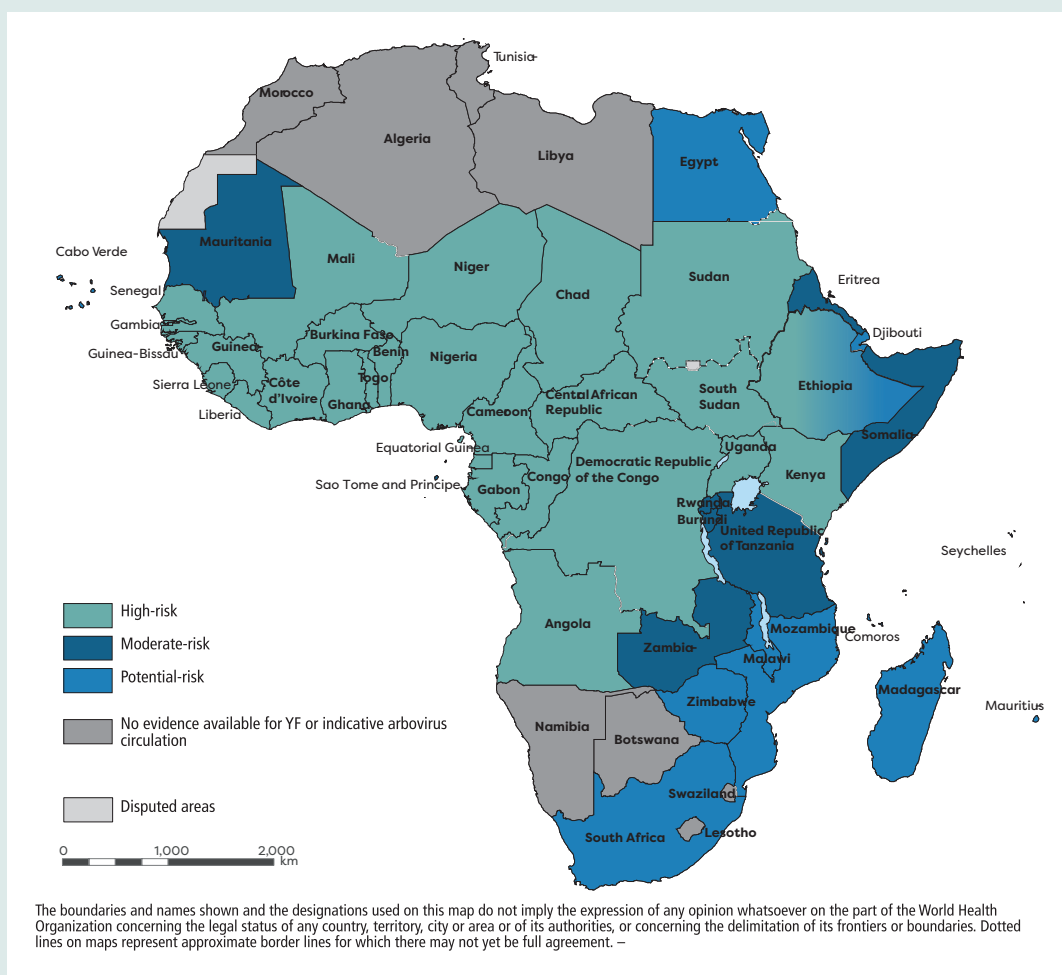

FIGURE 1

Timeline of clinical disease and laboratory diagnostics relative to point of infection

Dark colors indicate where the majority of persons are viremic or IgM positive. Lighter colors signify periods where some persons can be positive, but the diagnostic measure is less reliable.
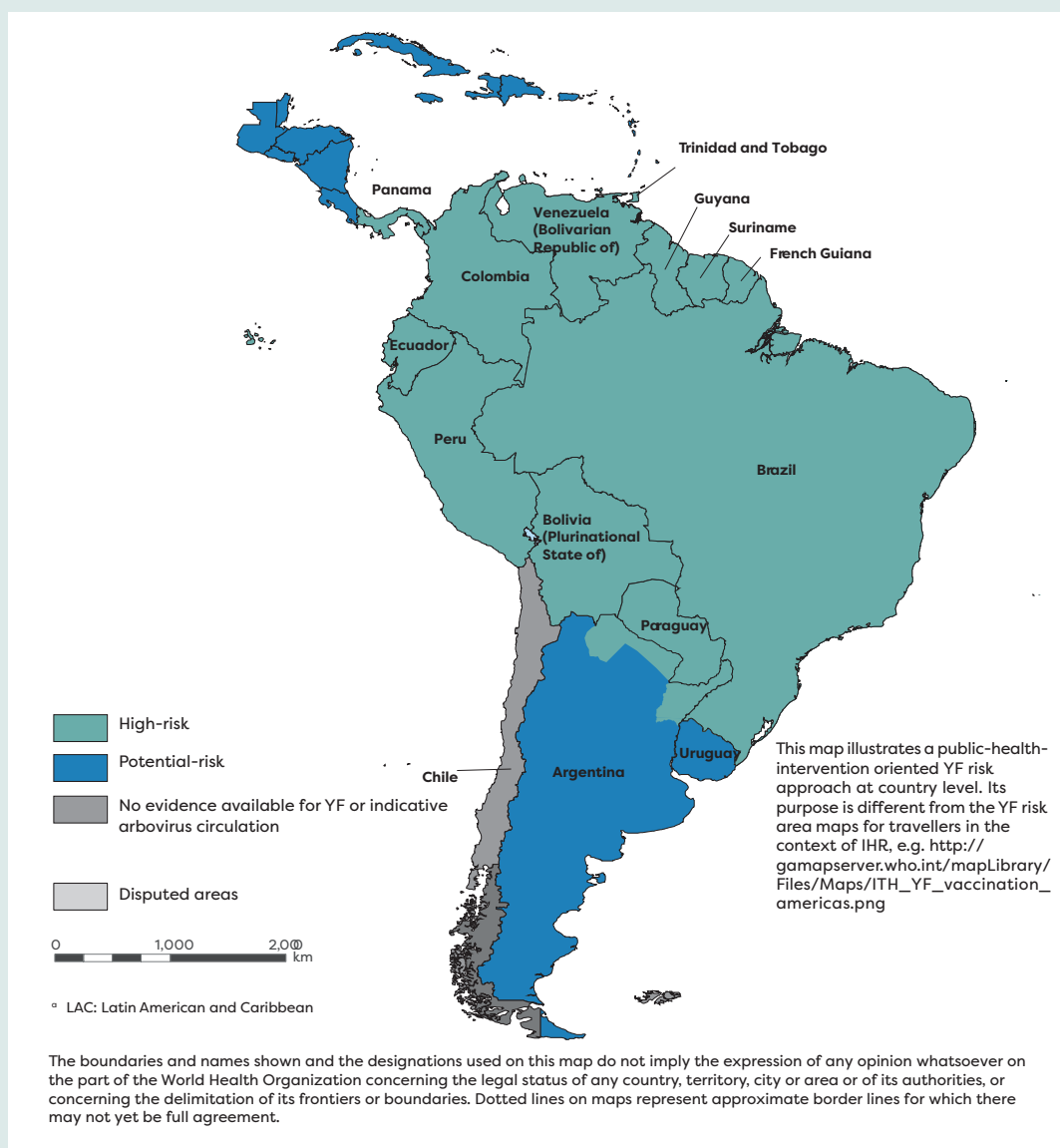
YF risk classification by country in Africa, 2016.

Tunisia
Morocco
Algeria
Libya
Egypt
Cabo Verde
Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Senegal
Djibouti
Gambia
Burkina Faso
Benin
Nigeria
Ethiopia
Guinea-Bissau
Guinea
Sierra Leone
Côte d'Ivoire
Togo
Central African Republic
South Sudan
Somalia
Liberia
Ghana
Cameroon
Uganda
Equatorial Guinea
Democratic Republic of the Congo
Kenya
Sao Tome and Principe
Gabon
Congo
Rwanda
Burundi
Seychelles
United Republic of Tanzania
Angola
Mozambique
Comoros
Zambia
Malawi
Madagascar
Mauritius
Zimbabwe
Namibia
Botswana
Swaziland
South Africa
Lesotho

High-risk

Moderate-risk

Potential-risk

No evidence available for YF or indicative arbovirus circulation

Disputed areas

0   1,000   2,000
km

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. –

40 countries are either endemic for, or have regions that are endemic for, YF.

YF risk classification by country in the Americas, 2016.

Trinidad and Tobago

Panama

Guyana

Venezuela
(Bolivarian
Republic of)

Suriname

French Guiana

Colombia

Ecuador

Peru

Brazil

Bolivia
(Plurinational
State of)

Paraguay

High-risk

Potential-risk

No evidence available for YF or indicative
arbovirus circulation

Disputed areas

Chile

Uruguay

Argentina

This map illustrates a public-health-
intervention oriented YF risk
approach at country level. Its
purpose is different from the YF risk
area maps for travellers in the
context of IHR, e.g. http://
gamapserver.who.int/mapLibrary/
Files/Maps/ITH_YF_vaccination_
americas.png

0   1,000   2,000
km

ᵃ LAC: Latin American and Caribbean

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40 countries are either endemic for, or have regions that are endemic for, YF.

In Africa, urban transmission occurs with large outbreaks and high mortality, particularly among children. In the Americas, transmission is mostly confined to those who live or work in tropical rainforests (sylvatic YF). Local occurrence of diseases caused by other *Aedes*-borne viruses (e.g., dengue, Zika, Japanese encephalitis, Chikungunya) indicate the potential for YF, due to their transmission by the same mosquito vector.

In 2018, it was estimated there were approximately 30,000 YF deaths, mostly in Africa *(3)*.

YF vaccines are live attenuated viral vaccines given as a single dose and probably provide lifelong protection *(4)*. Although YF cannot be eradicated, outbreaks can be eliminated (Box 1) *(5)*.

Multi-pronged approach to elimination of YF epidemics *(5)*

Detection and control of yellow fever hinges on strong surveillance and diagnostics systems, coupled with robust immunization, adherence to International Health Regulations (IHR 2005), and in some circumstances, inclusion of vector control. The Eliminating Yellow fever Epidemics (EYE) strategy is a global and comprehensive strategy aimed to eliminate yellow fever epidemics by 2026, and to minimize the suffering, damage and spread by early and reliable detection with rapid and appropriate response. The EYE was adopted in 2016 by WHO, with three core objectives: i) to ensure all persons at risk are protected through vaccination to achieve protective population immunity, ii) to prevent international spread – supported by International Health Regulations (IHR 2005) and iii) to contain outbreaks through strong surveillance for early detection and rapid response. The strategy can be found here: https://apps.who.int/iris/bitstream/hand le/-9789241513661/272408/10665eng.pdf

RATIONALE AND OBJECTIVES OF SURVEILLANCE

The surveillance system aims to provide reliable detail to support:

➤ Early detection of outbreaks, to support rapid implementation of control measures to help mitigate risk of spread

➤ Identify high-risk areas and vulnerable populations for YF outbreaks and use this data to inform intervention priorities and allocation of resources

➤ Monitor and measure the impact of preventive and control measures.

TYPES OF SURVEILLANCE RECOMMENDED

MINIMAL SURVEILLANCE

YF surveillance is recommended to follow a multi-faceted "One Health" approach, incorporating the elements listed below, as is suitable and feasible in a particular country context.

➤ Case-based surveillance for human cases with syndromic disease.

➤ Mosquito vector surveillance and monitoring of insecticide resistance patterns, with emphasis in urban areas.

➤ Surveillance for non-human primate (NHP) disease, monitoring for sudden die off and testing for YF infection. This is particularly relevant in the New World NHPs, where YF infection is often fatal.

These standards focus on surveillance for human cases. Surveillance for human cases involves the spectrum of activities from epidemiologic investigation including travel and vaccination history, clinical characterization, and timely and complete diagnostic testing including ruling out other possible causes of fever and jaundice.

The minimal surveillance standard is nationwide passive, facility-based, case-based surveillance, with laboratory testing of all suspected cases. YF surveillance for human cases should take place among all age groups. Surveillance in high risk areas should target travellers (both into and out of outbreak areas) and allow for timely reporting as required by IHR. In countries with potential for YF transmission but not currently at risk, it is crucial to have an early warning system in place to detect YF virus introduction.

CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED CASE DEFINITION FOR CASE FINDING

A suspected case is any person with acute onset of fever, with jaundice appearing within 14 days of onset of the first symptoms. The syndromic definition of suspected cases is broad and has many possible differential diagnoses, making it a sensitive but not very specific definition. It is expected that approximately 1-3% of suspected cases will actually have YF. All cases of acute fever and jaundice in high risk areas will ideally include laboratory confirmation to confirm the diagnosis. However, this sensitive definition provides an alert within an early warning system that there might be an outbreak, and it should trigger the activation of an appropriate outbreak response. More details are available in the reference documents *(6)*.

FINAL CASE CLASSIFICATION

Probable case: A suspected case AND at least one of the following:

➤ Presence of YF IgM antibody in the absence of YF immunization within 30 days of illness onset

➤ Epidemiological link to a confirmed case or an outbreak (e.g. household members or persons in close proximity to case through work, residence in past month)

Confirmed case: A probable case AND at least one of the following:

➤ Negatives results of differential neutralization testing with flaviviruses endemic in the area of exposure

➤ Seroconversion in appropriately paired samples tested by YF neutralization testing

AND

➤ Absence of YF immunization within 30 days before onset of illness

OR

➤ A suspected case AND at least one of the following:

  » Detection of YF virus genome in blood or other organs by real-time reverse transcriptase polymerase chain reaction (RT-PCR)

  » Detection of YF antigen in liver, or other organs by immunohistochemistry

  » Isolation of YF virus

AND

  » Absence of YF immunization within 14 days before onset of illness

In the event of complex test results, results must be carefully interpreted by surveillance and laboratory experts with review of relevant clinical and epidemiological details (e.g. if both YF and differential neutralization testing signals).

Discarded case: a person who tests negative for YF antibody testing (with specimen collected > 7 days post onset) or negative immunohistochemistry on tissue samples. *Note: A negative RT-PCR result does not rule out a case.*

CASE INVESTIGATION

Rapid and thorough investigation can facilitate confirmation of YF, better understanding of disease transmission dynamics (urban or intermediate transmission versus isolated sylvatic transmission) and supports risk analysis of ongoing transmission. Differentiating sporadic cases from spill-over sylvatic transmission from epidemic prone outbreaks is critical to informing the response. The extent of follow-up investigation for a case depends on its case classification. All suspected cases are investigated. Once a case is determined to be probable or confirmed, then a deeper investigation must be conducted as outlined below. Other factors, such a local capacity, and outbreak versus non-outbreak settings will also influence the nature of the investigation.

FOR ANY SUSPECTED CASE OF YF

Once a health worker identifies a suspected YF case, they should notify the local public health authorities. Within 48 hours of notification, each case should have a case investigation form completed, along with a blood sample collected for molecular (RT-PCR) and serological (IgM) testing. A sample should be collected

on first contact with the case, not waiting for the ideal window. A case record should be maintained and iteratively updated if the diagnostics indicate a probable or confirmed case, or if the case is discarded. Note that a second sample should be taken for IgM testing if the first sample is IgM negative and was collected ≤ 7 days after symptom onset.

FOR ANY PROBABLE OR CONFIRMED CASE OF YF

If the suspected case turns out to be probable or confirmed, a follow-up detailed investigation should be conducted to understand the most likely location of infection (e.g. local/in the place of residence versus distant/outside the place of residence). Probable and confirmed cases warrant further investigation to understand local epidemiology and risk; this includes understanding the local population context and connectivity, evaluating routine immunization, active case search for other community cases, and possibly conducting an entomological investigation. This is discussed in the outbreak response section below.

SPECIMEN COLLECTION

Ideally, a specimen is collected on every suspected case when there is not an outbreak. Serum is the principal diagnostic sample. At least 5 ml of blood should be collected and put in a serum separator tube or red-top tube. For IgM, blood should be collected at first contact with the case. Serum should be collected within 14 days of onset of symptoms; if the serum is collected ≤ 7 days after symptom onset and serology is negative, a second sample should be collected > 7 days after onset. Fatal cases should have a fresh or fixed tissue sample (in particular liver and kidney) collected for immunohistochemistry.

STORAGE AND TRANSPORT

Whole blood should never be frozen. Avoid hemolysis as it will affect the assay; to reduce hemolysis, serum should be separated at the point of collection. If no separation facilities are available, whole blood may be held at 4-8˚C and sent to the laboratory as soon as possible, no later than 24 hours after collection. Separated serum should be shipped to the laboratory on wet ice within 48 hours or stored at 4-8˚C if there is a delay. If it is expected that transport will take longer, serum should be frozen at -20˚C but for no longer than 7 days. Serum should be kept frozen (-70˚C) if processed after more than a week. Serum can be stored at -70˚C for extended periods of time.

LABORATORY TESTING

Interpretation of YF diagnostics is made based on knowledge of time since symptom onset, vaccination status, and the type of diagnostic tests used.

CONFIRMATION METHODS

Serology. The most commonly used serological test is ELISA. A positive IgM ELISA test indicates presumptive acute YF infection in a suspected case, but interpretation of a positive IgM ELISA should be considered in the epidemiologic context of co-circulation of other flaviviruses and previous vaccination of the individual.

➤ A positive IgM ELISA should be followed up with a differential neutralization testing with flaviviruses endemic to the area of exposure or neutralization testing of an appropriately paired sample set to demonstrate seroconversion performed in a reference laboratory, as this is more specific for YF. IgG ELISA testing for YF is not recommended for surveillance.

➤ Seroconversion. Seroconversion (IgM negative by neutralization testing in the early phase sample and IgM positive result in the later sample, taken 7-14 days after symptom onset) can also confirm an acute YF infection.

➤ Other flaviviruses (e.g., dengue virus, West Nile virus, Zika virus) may give a false positive YF IgM ELISA result so testing for other expected flaviviruses (as determined by local epidemiology) should be performed to rule out these other flavivirus infections.

➤ Current lab tests cannot differentiate between YF virus IgM stimulated by vaccination and that by wild-type YF virus. In people who have received a YF vaccine within 30 days, interpret IgM results with care, on a case-by-case basis considering clinical presentation and epidemiological context. However, sequencing or use of vaccine-specific RT-PCR, can differentiate between infections with wild-type YFV and the vaccine strain.

➤ National or regional YF reference laboratories are often needed to do confirmatory testing. Longer transport times to reference labs can potentially affect the timeliness and quality of the specimens.

RT-PCR. If a serum/whole blood sample is collected ≤ 10 days after symptom onset, RT-PCR can be used to detect YF RNA; detection in samples that have been collected up to 14 days have yielded positive results in some cases so RT-PCR can be attempted on these samples. A positive result confirms the diagnosis. However, a negative result does not rule out YF, and negative results should be referred for IgM testing regardless of the day post-symptom onset on which it was collected. RT-PCR results should be available and reported within 4 days. For fatal cases, RT-PCR should be performed on all available samples, independent of the collection date.

Immunohistochemistry can be performed on fixed tissue specimens from a suspected fatal case.

SPECIAL LABORATORY CONSIDERATIONS

Rapid diagnostic tests and RT-PCR for urine and saliva samples which might allow extending the period for viral genome detection are currently being developed, but they are not currently accepted to confirm YF cases.

➤ **Laboratory Networks:** YF laboratory networks exist in Africa, and Latin America (7). In Latin America and the Caribbean, a regional network of labs is integrated with arbovirus surveillance. Laboratory testing in the Eastern Mediterranean Region is integrated with high threat pathogen testing.

DATA COLLECTION, REPORTING AND USE

RECOMMENDED DATA ELEMENTS FOR ALL SUSPECTED CASES

➤ **Demographic information**

» Name (if confidentiality is a concern, the name can be omitted so long as a unique identifier exists)

» Unique identifier

» Place of residence (city, district, and province)

» Date of birth (or age if date of birth not available)

» Sex

➤ **Reporting information**

» Date of notification

» Date of investigation

➤ **Clinical signs and symptoms**

» Date of fever onset

» Date of jaundice onset

• For severe cases, date of onset of severe or toxic phase of illness (e.g. jaundice, abdominal pain and vomiting, signs of bleeding)

» Description of symptoms with emphasis on any signs of:

• Jaundice

• Bleeding

» Severe complications

» Outcome (patient survived or died)

• Date of death

➤ **Vaccination status**

» Number of doses of yellow fever vaccine

• Dates of all doses of vaccine given (if card available)

➤ **Epidemiologic Data**

» Occupational risk factors (e.g. extraction industries such as mining, or forestry, duties with high contact with sylvatic habitats such as agriculture or road construction)

» Travel within 10 days of illness onset? If yes, where?

» Risk factors related to sociocultural reasons (e.g. case is a member of a marginalized population, barriers to accessing preventive and curative health care)

➤ **Laboratory methods and results**

» Type(s) of specimen(s) collected (serum, whole blood, kidney, liver, etc)

» Date of specimen(s) collected

» Date specimen(s) sent to laboratory

» Date specimen(s) received in laboratory

» Date of results from laboratory

» Results (both YF and other flaviviruses)

• IgM (positive, negative, equivocal, unknown)

• RT-PCR (positive, negative, not tested, unknown)

• IgM seroconversion (positive, negative, not tested, unknown)

• Neutralization testing (positive, negative, not tested, unknown)

• Immunohistochemistry (positive, negative, not tested, unknown)

➤ **Final classification** (Confirmed, Probable, Discarded)

RECOMMENDED DATA ELEMENTS FOR INVESTIGATION OF ALL PROBABLE/ CONFIRMED CASES

➤ **Clinical signs and symptoms:** Review signs/ symptoms and update if new signs/symptoms since initial investigation.

➤ **Epidemiologic data for case:** Review initial answers provided to confirm/add additional information.

➤ **Epidemiologic data of community**

» Setting (urban or rural, climate and seasonal factors, ecological characteristics such as presence of jungle / forest / delta areas, presence of non-human primates).

» Risk factors related to amplification and geographic spread (e.g. presence of infrastructure linkages like roads, or other transit-ways, patterns of formal and informal population movement including displacement or transient populations – whether seasonal or continual)

REPORTING REQUIREMENTS AND RECOMMENDATIONS

To ensure surveillance is ongoing, designated reporting sites at all levels should report at a specified frequency (e.g. weekly or monthly) even if there are zero cases (often referred to as "zero reporting") for case-cased surveillance and include an update on laboratory results for suspected cases. Reporting should be at least weekly during outbreaks. Final case classification should be clearly reported/updated as laboratory results become available.

If routine case-based reporting is not feasible, then at a minimum, monthly reporting of aggregated data on suspected, probable and confirmed cases from the peripheral level to the intermediate and central should be done; in some settings, this can be done via Integrated Disease Surveillance and Response (IDSR) reporting systems.

Reporting of YF cases is a requirement of IHR, and countries should report all cases to WHO within 24 hours of being notified of a confirmed case. Additionally, every WHO Member State uses the Joint Reporting From (JRF) to report confirmed cases of yellow fever. All national laboratories are requested to provide a monthly report of results to WHO.

RECOMMENDED DATA ANALYSES

- Among suspected cases, number and incidence rate by month, year and geographical area

- Among confirmed and probable cases, number and incidence rate by month, year and geographical area

- Confirmed and probable cases by age group, immunization status, geographical area, by month and year

- Age-specific, sex-specific, district-specific incidence rate of confirmed yellow fever cases by month and year

- Case-fatality ratio among confirmed and probable cases

- Epidemic curve for outbreaks, and spot map or other representation of the spatial evolution of the outbreak

USING DATA FOR DECISION-MAKING

- Data from detailed investigations and quality diagnostics are a critical source of information to differentiate sporadic from epidemic cases, to confirm an outbreak, and to inform an appropriate response plan, including emergency immunization activities.

- In the case of outbreak, monitoring the extent and intensity of virus circulation and monitoring ongoing spread will be informed by iterative collection and analysis of all surveillance data, including epidemiology, clinical presentation, and laboratory diagnostic results to provide valuable information about populations at risk and monitor the impact of response activities.

- Data are also used to develop a better understanding of the epidemiology of yellow fever to guide prevention strategies and assess their impact.

SURVEILLANCE PERFORMANCE INDICATORS

YF surveillance should be evaluated routinely at national and subnational/local levels to ensure that the country is able to meet the objectives of surveillance. Strong performance of a surveillance system is measured by timely reporting of suspected cases on a routine basis, with appropriate laboratory testing to confirm the case, and rapid detection of concerning clusters and outbreaks. Below are suggested surveillance performance indicators.

TABLE 1

Recommended Yellow Fever Surveillance Performance Indicators

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)	COMMENTS
COMPLETENESS OF REPORTING	Percentage of designated reporting units reporting suspected YF cases, even in the absence of confirmed cases	≥ 80%	# units reporting YF / # designated reporting units for YF surveillance x 100 (for a given time period)	Measure of all suspected cases reported by each subnational reporting unit is an important indicator for the sensitivity and function of surveillance system.
TIMELINESS OF REPORTING	Percentage of designated reporting units reporting to the national level on time	≥ 80%	# of designated reporting units in the country reporting on YF by the deadline / # of designated reporting units in the country x 100	At each level, reports should be received on or before the requested date.
INVESTIGATION RATE	Percentage of districts reporting and collecting blood samples from at least one suspected case of yellow fever per year	≥ 80%	# districts reporting AND collecting blood samples from at least one suspected case of yellow fever in a year/# districts	
TIMELINESS OF INVESTIGATION	Percentage of all suspected YF cases that have had an investigation initiated within 48 hours of notification	≥ 80%	# of suspected cases of YF for which an investigation was initiated within 48 hours of notification / # of suspected YF cases x 100	
SPECIMEN COLLECTION	Percentage of suspected YF cases with a specimen collected	≥ 80%	# of suspected cases of YF with a specimen collected / # of suspected YF cases x 100	This is a target during non-outbreak periods.
TIMELINESS OF SPECIMEN TRANSPORT	Percentage of specimens received at the laboratory within three days of collection	≥ 80%	# of specimens received within 3 days of collection by laboratory/# of specimens x 100	Indicator only applies to public laboratories.
TIMELINESS OF IGM LABORATORY RESULTS	Percentage of IgM results reported within 4 days of receipt of specimen	≥ 80%	# of IgM results reported within 4 days of specimen receipt / # of specimens received for IgM testing in laboratory*100%	
TIMELINESS OF RT-PCR RESULTS	Percentage of RT-PCR results reported within 4 days of receipt of specimen	≥ 80%	# of RT-PCR results reported within 4 days of specimen receipt / # of specimens received for RT-PCR in laboratory x 100	This date of receipt in the laboratory refers to the date of receipt in the laboratory conducting RT-PCR testing (not receipt in the referring laboratory)
REGIONAL REFERENCE LAB REFERRAL	Percentage of IgM positive samples sent to the regional reference laboratory for confirmatory testing within 7 days of results becoming available	≥ 80%	# of IgM positive samples sent to regional reference laboratory within 7 days of results becoming available / # of positive samples x 100	Positive samples detected from any newly infected district should be sent immediately Not needed once outbreak is confirmed, so can exclude those from the denominator.

CLINICAL CASE MANAGEMENT

High quality, early supportive treatment in hospitals improves survival rates. There are no specific anti-viral drugs for yellow fever, but treatment of dehydration, hepatorenal failure, and fever improves outcomes *(1, 8)*. Associated bacterial infections can be treated with antibiotics. Patients still thought to be in the viremic phase of illness should be sheltered under insecticide treated bed nets to help reduce risk of onward spread. Local protocols for YF treatment should be followed.

CONTACT TRACING AND MANAGEMENT

YF is a vector-borne disease and not transmitted person-to-person directly. As a result, contact tracing and investigations are not required. However, once a probable or confirmed case is identified, active case finding involves looking for other individuals in the community with similar symptoms to see if there is local transmission of the disease (see cluster investigation below).

CLUSTER INVESTIGATION

Clusters of cases in households or close communities should be evaluated. Once a probable or confirmed case is identified, active case search in the household and surrounding community (e.g. perimeter of approximately 500 m) is recommended. This involves looking for other individuals in the community with similar symptoms to see if there is local transmission of the disease.

SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

The approach to outbreak investigation and control is given in detail in *A Global Strategy to Eliminate Yellow Fever Epidemics (EYE), 2017-2026* and in *Managing Yellow Fever Epidemics (5, 9)*.

DEFINITION OF OUTBREAK

A single laboratory confirmed case of YF is sufficient to identify a potential outbreak and should trigger a rapid investigation with potential intervention. Detailed comprehensive investigation of an index case or cluster of cases, including analysis of the results from a complete epidemiological investigation, is crucial to inform the planning of the response.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK

➤ During outbreaks, surveillance should become active and case-based, if it is not already. Active case finding should be done in health facilities near a confirmed case.

➤ Investigations should include 1) determining the vaccine coverage in the affected area (coverage of routine immunization services, recent YF vaccination outbreak responses, and YF preventive campaigns), 2) determining the extent and characteristics of unvaccinated populations in the area, and 3) evaluating the risks of the outbreak spreading in geographic scope and/or the extent of transmission.

➤ Rapid entomological investigations to identify the likely species of mosquito vector(s) and to assess vector density are recommended *(10)*.

➤ The suspected case definition might need to be broadened, to include cases with fever and an epidemiologic link to a confirmed case/outbreak. However, these persons should be tested to confirm if they are true cases.

➤ Laboratory testing algorithms might need to be modified. Ideally every suspected case has a sample collected and tested, though this could over burden the laboratory.

  » In districts where active YF virus circulation has not yet been confirmed, blood samples should be taken from all suspected cases of YF.

  » If the laboratory has reached maximal capacity, priority should be given to testing specimens from those areas where local transmission has not yet been confirmed.

  » It is not essential to perform serology testing to differentiate yellow fever and other flaviviruses on specimens where local transmission of YF has already been confirmed.

PUBLIC HEALTH RESPONSE

The principal aspects of outbreak response include reactive vaccination, vector control, social mobilization, and case investigations.

➤ Reactive vaccination

  » In areas with low vaccination coverage, initiate vaccination in the affected area, such as village, district, town or city or within 10-50 km of the affected area (scale to be determined by several factors, such as population density and vaccination coverage).

  » In areas with good vaccination coverage (from routine coverage among children and/or preventive vaccination campaigns), offer targeted vaccination to susceptible individuals or unvaccinated groups in the immediate area. Large-scale emergency vaccination or revaccination is not justified in these areas.

  » An emergency stockpile of YF vaccines is available for reactive vaccination through the International Coordinating Group on Vaccine Provisions *(11)*.

➤ Vector control

  » In urban outbreaks, emergency vector control is a supplemental strategy to help stop transmission. Vector control strategies begin with identifying the vectors implicated in transmission and the patterns of insecticide resistance. Control efforts need to target both mosquito larvae and adults, and they should be implemented as quickly as possible in neighbourhoods and districts where persons with YF reside.

➤ IHR implementation should be strengthened with emphasis on point of entry requirements for proof of the international certificate of vaccination against yellow fever by all travellers and visitors entering or leaving an outbreak area.

SPECIAL CONSIDERATIONS FOR YF SURVEILLANCE

VECTOR SURVEILLANCE

Vector surveillance is an important adjunct to disease surveillance for YF *(10)*. Targeting *Aedes aegypti* and *Aedes stegomyia* helps to inform the areas risk. Understanding the distribution of these mosquitoes allows a country to prioritize areas to strengthen their human disease surveillance and testing and consider vector control. *Aedes aegypti* indices should be calculated regularly in cities at-risk or with a potential for YF. These measures should be part of broader arbovirus surveillance and readiness in countries at risk for dengue, Zika, and chikungunya.

HUMANITARIAN EMERGENCIES

Humanitarian emergencies can pose increased risk for YF. Natural disasters such as flooding can increase the vector population. Migration of people through endemic areas, such as refugees or internally displaced persons, can lead to YF exportation into areas with low population immunity. The YF immunization status of travelers (e.g., workers) needs to be confirmed upon arrival into and departure from areas at risk for YF to prevent YF exportation to naive populations where the potential for local transmission exists

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