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CD Alert

National Centre for Disease Control,
Directorate General of Health Services, Government of India

November, 2023

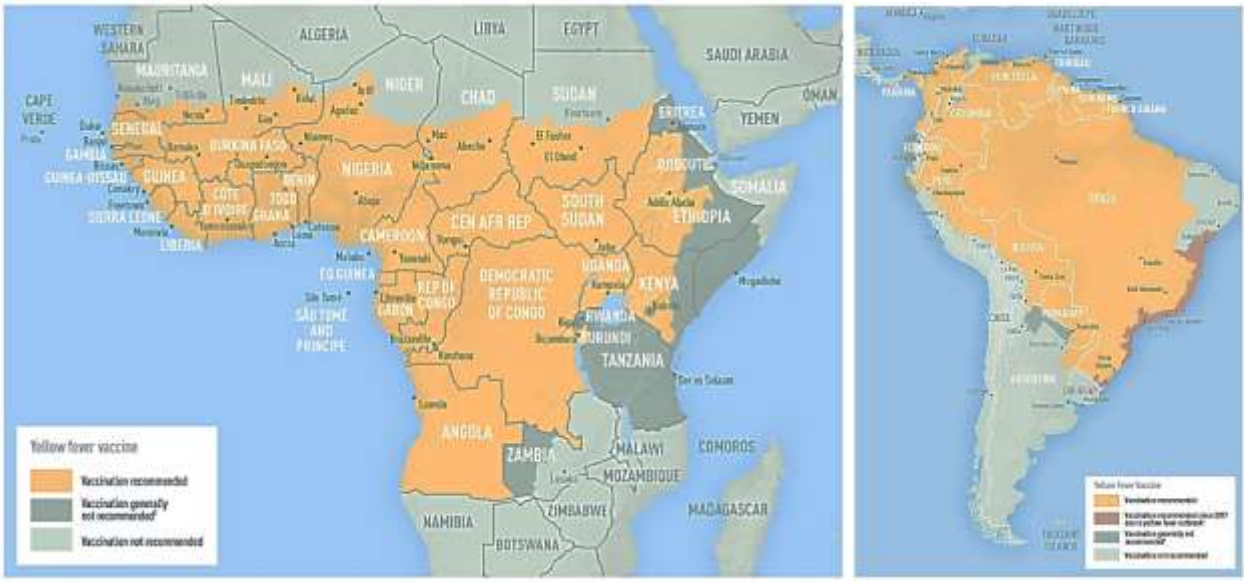
Yellow Fever

INTRODUCTION

Yellow fever is an acute viral hemorrhagic disease endemic in tropical areas of Africa and Latin America. Travelers visiting these places are at risk for infection. Cases may be difficult to distinguish from other viral hemorrhagic fevers such as arenavirus, hantavirus or dengue, especially during early stages. Yellow fever presents with a myriad of clinical symptoms/signs and varied outcomes ranging from mild to severe, fatal cases. The virus is spread by the bite of an infected mosquito. Illness ranges from a fever with aches and pains to severe liver disease with bleeding and jaundice. Yellow fever infection is diagnosed based on travel history, symptoms and a positive laboratory diagnosis, a person's symptoms, and travel history. There is no specific medicine to cure infection. Treatment is symptomatic, aimed at managing symptoms to make the patient comfortable. Preventive measures include prevention of mosquito bites, wearing fully covered clothes, and getting vaccinated with an effective vaccine which provides immunity within 10 days with an efficacy ranging from 80-100%.

GEOGRAPHIC DISTRIBUTION

The Yellow fever virus is found in tropical and subtropical areas of Africa and South America. Urban outbreaks are often reported in Africa. particularly West Africa. In South America. urban outbreaks are uncommon although one occurred in 2008 in Asuncion, Paraguay. According to WHO, yellow fever is endemic in 45 Countries, (32 in Africa and 13 in Central and South America). Most frequently in sub-Saharan West Africa, outbreaks have occurred in Central and East African countries (Central African Republic, Democratic Republic of



Yellow fever prevalent countries of Africa and South America (Source: CDC)

Congo, Chad, Ethiopia, Sudan Darfur and Uganda. From 2007-2009 human epizootic disease due to yellow fever virus has been seen in many areas of South America that had not seen activity for several decades (Argentina, Southern Brazil, Paraguay, and Trinidad and Tobago). Yellow fever disease and transmission was documented previously in Europe and North America, but no recent cases have been identified. There is no evidence of Yellow fever being present in Asia.

EPIDEMIOLOGY

THE CAUSATIVE AGENT: Yellow fever virus (family Flaviviridae and genus Flavivirus) is related to West Nile, Zika, dengue and Japanese encephalitis viruses.

Reservoir-

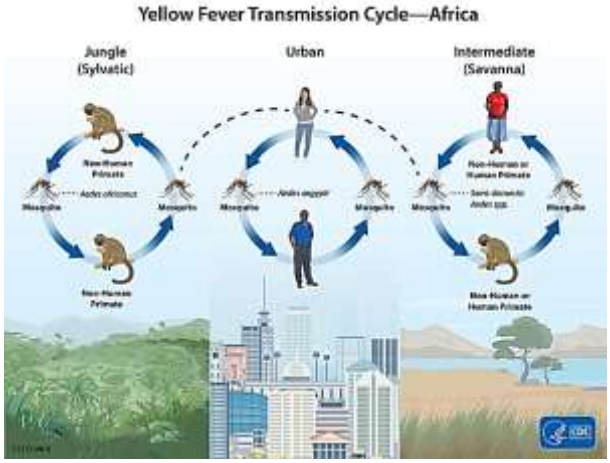
- In urban areas, humans and Aedes mosquitoes;
- In forest areas, vertebrates other than humans, mainly nonhuman primates and possibly marsupials and forest mosquitoes.
- Transovarian transmission of the infection in mosquitoes has been documented, but its contribution to maintenance of infection is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

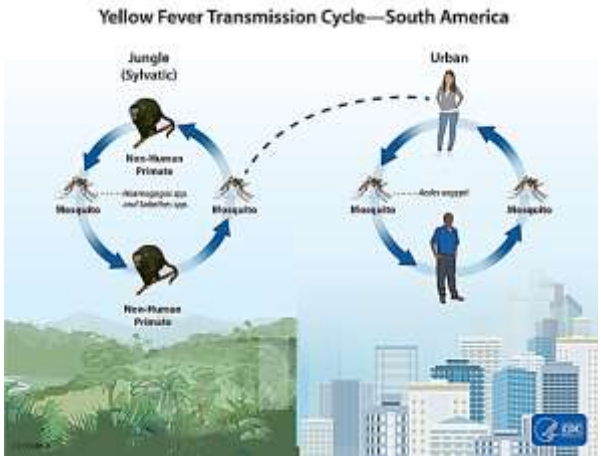
Route of transmission

Yellow fever virus is transmitted to humans primarily through the bite of infected Aedes or any other Haemagogus species mosquitoes. Mosquitoes acquire the virus by feeding on infected primates (human or non-human). People infected with yellow fever virus are infectious to mosquitoes (referred to as being "viremic") shortly before onset of fever and up to 5 days after onset of fever. However, the virus has been found in the blood up to 17 days after onset of illness.

Yellow fever virus has three transmission cycles: jungle (sylvatic), inter-mediate (savannah), and urban.

- **Jungle (sylvatic) cycle** involves transmission of the virus between non-human primates (e.g., monkeys) and mosquito species found in the forest canopy. The virus is transmitted to humans when they visit or work in the jungles.
- In Africa, an **intermediate (savannah) cycle** exists that involves transmission of virus from mosquitoes to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from primates to humans and vice versa.
- **Urban cycle** involves trans-mission of the virus between humans and urban mosquitoes, primarily Aedes aegypti. The virus is brought into urban setting by a viremic human infected in jungle or savannah cycles.





Incubation period: 3-6 days

The extrinsic incubation period in A. aegpti is 9-12 days at usual tropical temperatures. Once infected, mosquitoes remain so for life. The disease is not communicated through contact secretions or fomites. Since yellow fever vaccine virus has been documented to be transmitted through breastfeeding and blood transfusions, it is likely that natural yellow fever virus may be transmitted through breastfeeding or exposure to infected blood or organs.

Risk groups - Risk groups include unvaccinated travelers to endemic areas, forest workers in endemic areas, and those living near forest areas or in A. aegypti-infested areas who have not been vaccinated against yellow fever. The disease is highly communicable where many susceptible people and abundant vector mosquitoes coexist. Transient passive immunity in infants born to immune mothers may persist for up to 6 months.

Case Fatality Rate (CFR): Reported CFR values for Yellow Fever vary, offering wide ranges. Through a systematic literature review and meta-analysis, the estimated CFR is 39 % (95 % CI: 31 %, 47 %). Stratifying by continent showed that South America observed a higher CFR than Africa. The case-fatality rate for severe yellow fever is 30%–60%. (https://ndc.services.cdc.gov/case-definitions/yellow-fever-2019/)

CASE DEFINITION

Suspected case:

Any person with acute onset of fever, with jaundice appearing within 14 days of onset of the first symptoms.

Probable case:

A suspected case; **and** one of the following:

- presence of yellow fever IgM antibody in the absence of yellow fever immunization within 30 days before onset of illness; **or**
- positive post-mortem liver histopathology; **or**
- epidemiological link to a confirmed case or an outbreak.

Confirmed case:

1. A probable case; **and**
   Absence of yellow fever immunization within 30 days before onset of illness; **and** one of the following:
   - detection of yellow fever-specific IgM; **or**
   - detection of fourfold increase in yellow fever IgM, or IgG antibody titers between acute **and** convalescent serum samples, or both; **or**
   - detection of yellow fever-specific neutralizing antibodies.

   or
2. Absence of yellow fever immunization within 14 days before onset of illness; **and** one of the following:
   - detection of yellow fever virus genome in blood or other organs by polymerase chain reaction (PCR); **or**
   - detection of yellow fever antigen in blood, liver or other organs by immunoassay; **or**
   - isolation of yellow fever virus.

Surveillance Strategies

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

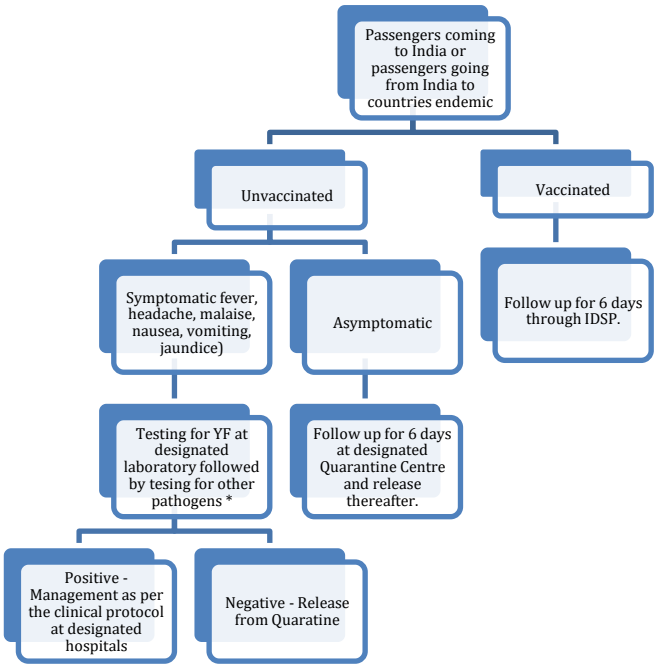
The minimal surveillance standard is nationwide passive, facility-based, case-based surveillance, with laboratory testing of all suspected cases. YF surveillance for human cases should take place among all age groups. Surveillance in high-risk areas should target travelers (both into and out of outbreak 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.

- **Quarantine facilities**

- **Bengaluru**- Rajiv Gandhi Hospital
- **Delhi-**
  1) APHO
  2) Safdarjung Hospital
  3) Lady Harding Medical College
  4) Rural Health & Training Center
- **Mumbai**

- As cases have not been reported from India, so the surveillance strategies should be more focused at the point of entry in the country (PoE).
- Adequate measures shall be instituted at Points of Entry (PoEs) to make operating airlines and travelers aware of the signs & symptoms of YF for self-reporting.
- Any person coming from YF affected areas or having contact with suspected or confirmed MVD and develops symptoms within 6 days, starting from day of leaving the YF endemic country should immediately report to the designated health care facility.
- The isolation of infected patients combined with appropriate infection prevention and control measures is one of the important public health surveillance activities.
- 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, which involves looking for other individuals in the community with similar symptoms to see if there is local transmission of disease, can be carried out

Guidelines to identify Suspected Cases



*Malaria, Dengue, Rift valley fever, West Nile fever and others as per clinical guidance

- ❖ Vector Surveillance at Airports/Quarantine Centre
- ❖ Risk Communication-regarding need for Yellow fever vaccination/ Quarantine period (in case unvaccinated), Full sleeve clothes, Mosquito Repellent, Use of bed nets.

CLINICAL FEATURES

Most people infected with yellow fever virus will either have no symptoms or mild symptoms and completely recover. For people who develop symptoms, the time from infection until illness is typically 3 to 6 days.

- Initial symptoms can include sudden onset of fever, chills, severe headache, back pain, general body aches, nausea, vomiting, fatigue (feeling tired), weakness.
  - Most people who develop symptoms improve within one week.
  - For some people who recover, weakness and fatigue (feeling tired) might last several months.
- A few people will develop a more severe form of the disease.
  - For 1 out of 7 people who have the initial symptoms, there will be a brief remission that may last only a few hours or for a day, followed by a more severe form of the disease.

Severe symptoms include high fever, yellow skin or eyes (jaundice), bleeding (from the mouth, nose, eyes or stomach), shock, and organ failure.

DIAGNOSIS

In acute disease, laboratory diagnosis often can be made through:

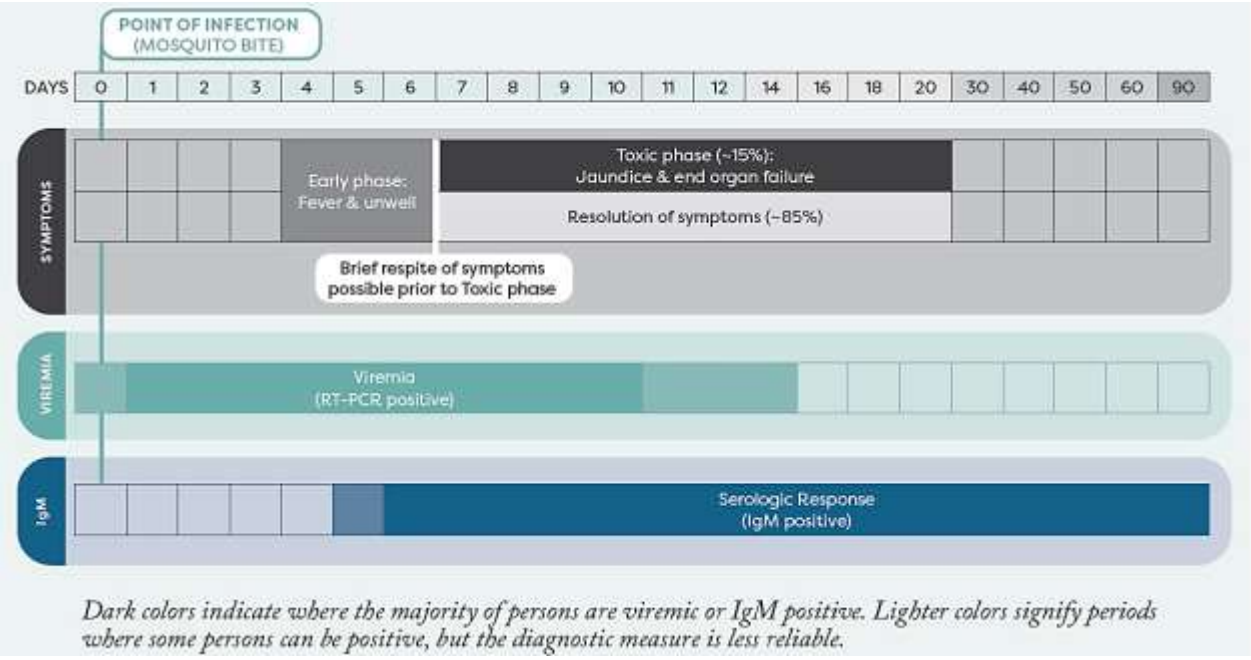
(a) isolation of virus from blood by inoculation into suckling mice, mosquitoes, or cell cultures;

(b) demonstration of viral antigen in tissues, especially liver, by use of labelled specific antibodies; or

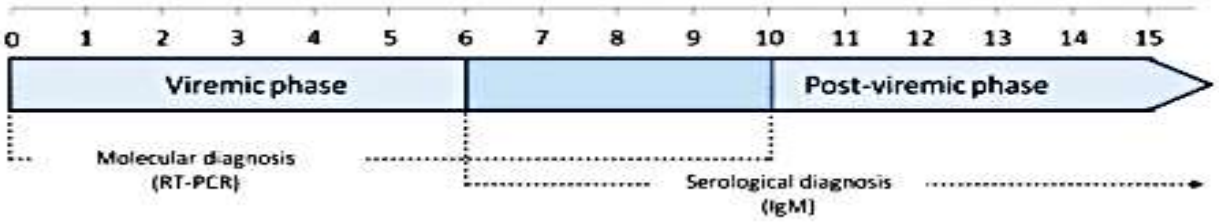
(c) demonstration of viral ribonucleic acid (RNA) in blood or tissue by reverse transcription polymerase chain reaction (RTPCR).

RTPCR can also be used to distinguish acute infections with yellow fever virus from recent vaccination. Serological diagnosis includes demonstrating virus-specific IgM in early sera or a 4-fold or greater rise in titer of virus-

Recovery from yellow fever results in life-long immunity.



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

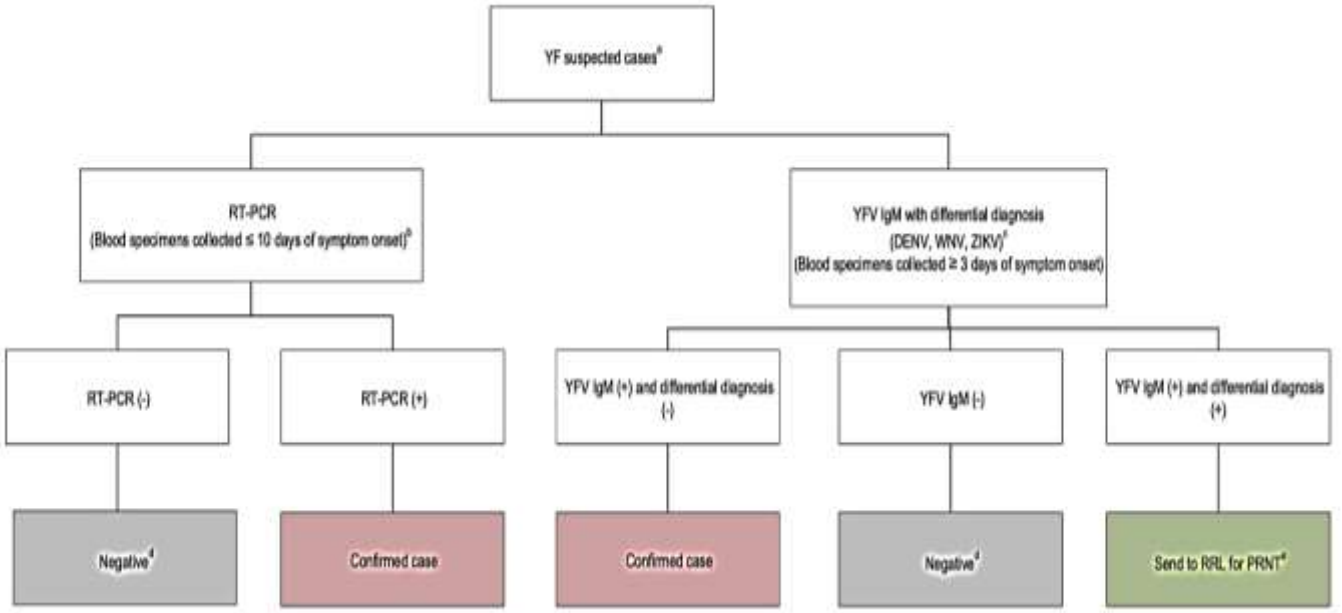


specific antibodies in paired acute and convalescent sera. Serological cross-reactions occur with other flaviviruses. In natural infections, antibodies appear in blood within the first week.

Significant cross-reactivity of yellow fever IgM assays with other flaviviruses has been described, in particular in secondary flavivirus infections. Thus, in areas where other flaviviruses co-circulate (especially dengue and Zika viruses), the probability of cross-reactivity is high. Moreover, as with any IgM test, a positive result in a single sample is only presumptive of a recent infection. Laboratory confirmation requires demonstration of seroconversion in paired serum samples (acute and convalescent with at least 1 week of difference) and no seroconversion to other relevant flavivirus. https://www.who.int/publications/i/item/laboratory-diagnosis-of-yellow-fever-virus-infection

All biological samples (whole blood, serum or fresh tissue) should be considered as potentially infectious. Furthermore, it is recommended to carry out all procedures in certified class II biosafety cabinets and to take all necessary precautions to avoid percutaneous exposure.

Laboratory Testing Guidelines of Suspected Cases



YF = yellow fever; YFV = yellow fever virus; DENV = dengue virus; WNV = West Nile virus; ZIKV = Zika virus; RRL = regional reference laboratory; PRNT = plaque reduction neutralization test

[a] Any person with acute onset of fever, with jaundice appearing within 14 days of onset of first symptoms[1]

[b] If RT-PCR is conducted immediately after onset of symptom (< 3 days), negative cases should be retested 3 days after the onset of symptoms. In people with severe clinical symptom, RT-PCR may be positive for more than 10 days after the onset of symptoms. Urine testing is planned for the future but is not yet validated. When this is introduced it is important to know that when urine is tested by RT-PCR, the period of time after onset of symptoms during which the result may be positive, might exceed 10 days.

[c] Dengue virus, West Nile virus and Zika virus should be considered potential causative agents of symptoms and may test positive for YFV IgM. Depending on the local epidemiological situation, testing for other flaviviruses (ELISA) may need to be performed.

[d] When blood from people with suspected yellow fever is negative on both RT-PCR and YFV IgM testing, they are considered negative for YF. However, a negative result for only one of these tests does not rule out yellow fever infection.

[e] Plaque reduction neutralization test.

Laboratories for testing YF:

1) National Centre for Disease Control, New Delhi
2) ICMR-National Institute of Virology, Pune
3) ICMR-National Institute of Cholera and Enteric Diseases (NICED), Kolkata, West Bengal
4) All India Institute of Medical Sciences (AIIMS), Bhopal, MP
5) Sawai Man Singh (SMS) Medical College, Jaipur, Rajasthan
6) King George's Medical University (KGMU), Lucknow, UP
7) King Institute of Preventive Medicine & Research (KIPMR), Chennai, Tamil Nadu
8) Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry
9) Regional Medical Research Centre (RMRC), Dibrugarh, Assam
10) Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir
11) BJ Medical College, Ahmedabad, Gujarat
12) Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh
13) ICMR-National Institute of Virology, Bangalore Unit
14) ICMR- National Institute of Virology Kerala Unit

TREATMENT

No specific antiviral therapies available; treatment is supportive. Good and early supportive treatment in hospitals improves survival rates. Specific care to treat dehydration, liver and kidney failure, and fever improves outcomes. Associated bacterial infections can be treated with antibiotics. Blood and body fluid precautions should be used. Prevent access of mosquitoes to the patient for at least 5 days after onset by screening the sick room, spraying quarters with residual insecticide, and using insecticide treated bed nets. The homes of patients and all houses in the vicinity should he sprayed promptly with an effective insecticide.

PREVENTIVE MEASURES

1. Vaccination

The Government of India reserves the right to consider the whole territory of a country as infected with yellow fever whenever yellow fever has been notified under Article 6 and other relevant articles in this regard of International Health regulations (IHR 2005). The Government of India reserves the right to continue to regard an area as infected with yellow fever until there is definite evidence that yellow-fever infection has been completely eradicated from that area.

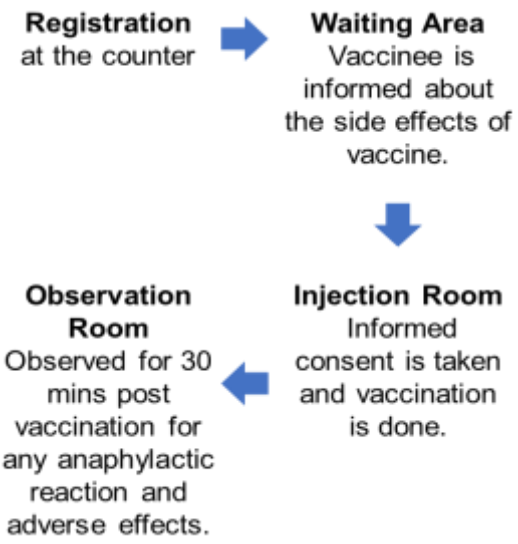
Yellow fever disease is considered as a disease of public health emergency of international concern and all health measures being applied presently like disinfection of conveyances, vaccination requirements and quarantine of passengers and crew (as may be required) will be administered.

- All passengers coming to India or passengers going from India to countries endemic for Yellow Fever should have a valid International Vaccination Card for yellow fever from a designated yellow fever vaccination center (List of designated centers for vaccination in India can be accessed at https://ihpoe.mohfw.gov.in/yfvc.php.
- The Yellow fever certificate of vaccination or prophylaxis should be in the proper format as specified by the WHO. All the columns in the vaccination certificate should be filled correctly and the official seal of the vaccination center should be affixed to it.
- Any passenger arriving in India from any yellow fever endemic country without a valid yellow fever vaccination prophylaxis certificate in original, will be

treated as suspects of carrying the yellow fever Virus in their body and are quarantined.

- The period of quarantine is limited to 6 days and the period is counted from the time of departure of the passenger from the Airport in the endemic country or till the time YF vaccination becomes valid (whichever is less).
- Exemption from taking YF vaccine on medical grounds/ pregnancy/ sickness etc. does not give immunity for person from quarantine.
- Any illness in the quarantined passengers during the period of their quarantine will be treated by the designated specialist doctors under the supervision of the APHO.

Vaccination Procedure: -



Contraindications for Vaccination

1) Anyone with allergy to eggs, chicken proteins, or gelatin, who had a severe allergic reaction to a previous dose of yellow fever vaccine
2) Pregnant, Children younger than 09 months of age, HIV/AIDS patient.
3) Immune system is weakened because of cancer or other medical conditions, a transplant, or radiation or drug treatment (such as steroids or cortisone, cancer chemotherapy, or other drugs that affect immune cell function).
4) Persons with acute/moderate illness (with or without a fever) should postpone receiving this vaccine until they are well.
5) Patients with thymus disorder, such as myasthenia gravis, DiGeorge syndrome, or thymoma or Thymus removed.
6) Patients with major liver or kidney disease.

Please note:

1) Nursing mothers should avoid or postpone travel to an area where there is risk of yellow fever.
2) Adults 60 years of age and older might be at increased risk for severe problems following vaccination.

Side Effects of Vaccination

1) Fever with aches, soreness, redness or swelling where the shot was given. These problems occur in up to 1 out of 4 persons. They usually begin soon after the shot and can last up to a week.
2) Immediate hypersensitivity – rash, itching faint or asthma.
3) Severe allergic reaction to a vaccine component.
4) Severe nervous system reaction.
5) Life-threatening severe illness with organ failure.
6) Inflammation of multiple organs e.g. lungs, kidney, liver, spleen, encephalitis, etc.

In case of severe reaction

1) Look for any unusual condition, such as a high fever, behavior changes, or flu-like symptoms and signs of an allergic reaction can include difficulty in breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heartbeat, or dizziness within a few minutes to a few hours after the shot.
2) Inform the doctor from the vaccination center.

Vaccine Specifications:

Type of Vaccine	**Attenuated, live-virus preparation of the 17D strain of yellow fever virus grown in leucosis-free chick embryos**
Number of doses	One dose of 0.5 ml subcutaneously
Route of Administration	Sub-cutaneous
Storage temperature	+2 to +8 degrees centigrade
Validity	Yellow fever Vaccination Certificate becomes valid only after 10 days of vaccination.

2. Vector control

The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites, including by applying larvicides to water storage containers and other places where standing water collects.

Both vector surveillance and control are components of the prevention and control of vector-borne diseases, especially for transmission control in epidemic situations. For yellow fever, vector surveillance targeting *Aedes aegypti* and other *Aedes* species will help inform where there is a risk of an urban outbreak.

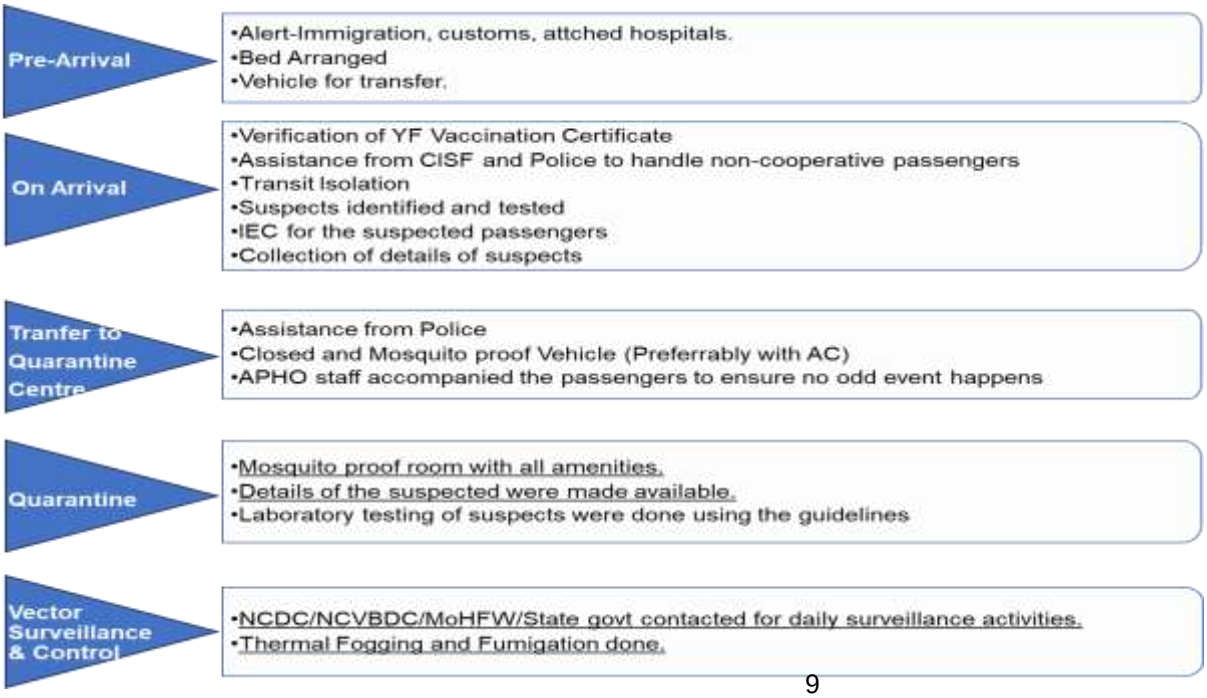
Understanding the distribution of these mosquitoes within a country can allow a country to prioritize areas to strengthen their human disease surveillance and testing, and to consider vector control activities.

Personal preventive measures such as clothing minimizing skin exposure and repellents are recommended to avoid mosquito bites. The use of insecticide-treated bed nets is limited by the fact that *Aedes* mosquitos bite during the daytime.

3. Epidemic preparedness and response

Prompt detection of yellow fever and rapid response through emergency vaccination campaigns are essential for controlling outbreaks. However, underreporting is a concern. WHO recommends that every at-risk country have at least one national laboratory where basic yellow fever blood tests can be performed. A confirmed case of yellow fever in an unvaccinated population is considered an outbreak. A confirmed case in any context must be fully investigated. RRTs must assess and respond to the outbreak with both emergency measures and longer-term immunization plans.

4. IHR (2005) and Yellow fever: IHR (2005)-India's reservation- Even a single case would be termed as an outbreak. Yellow Fever



does not occur in India therefore the focus for prevention of disease spread is at the Point of Entries (POEs). The conditions for transmission of yellow fever are very conducive in India due to the presence of mosquito vectors in abundance and susceptible population.

Operation Kaveri

Operation Kaveri was an operation conducted by the Indian Armed Forces to evacuate Indian citizens and foreign nationals from Sudan during the 2023 Sudan conflict. The evacuation was conducted by air and sea, in Port Sudan where most of the evacuations were done by Indian Navy through INS Sumedha. (Refer chart above)

CONCLUSION

Yellow fever is an acute viral hemorrhagic disease transmitted by infected mosquitoes which is endemic in tropical areas of Africa and Latin America. Travelers going to these places are at risk for infection with the virus. There is no evidence that yellow fever has ever been present in Asia, but disease is considered as a disease of public health emergency of international concern and even a single case would be termed as an outbreak. Large epidemics of yellow fever occur when infected people introduce the virus into heavily populated areas with high mosquito density and where most people have little or no immunity, due to lack of vaccination. In these conditions, infected mosquitoes of the Aedes aegypti species transmit the virus from person to person, therefore all health measures like disinfection of conveyances, vaccination requirements and quarantine of passengers and crew are to be applied. In India, the conditions fortransmission of yellow fever are very conducive due to the presence of mosquito vectors in abundance and susceptible population, therefore there is a greater need for vigilance and the focus for prevention of disease spread is at the Point of Entries (POEs). Yellow fever is prevented by an extremely effective vaccine, which is safe and affordable. A single dose of yellow fever vaccine is enough to grant sustained immunity and life-long protection against yellow fever disease. A booster dose of the vaccine is not needed. The vaccine provides effective immunity within 10 days for 80-100% of people vaccinated. All passengers coming to India or passengers going from India to countries endemic for Yellow Fever should have a valid International Vaccination Card for Yellow Fever from a designated yellow fever vaccination center. There is currently no specific anti-viral drug for yellow fever, so for those getting infected, good supportive treatment in hospitals improves survival rates.

….about CD Alert

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