WASHOE COUNTY HEALTH DISTRICT
ENHANCING QUALITY OF LIFE

January 26, 2022, Vol. 42, No. 02
(Page 1 of 3)

EPI-NEWS

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IN THIS ISSUE: YELLOW FEVER

Yellow Fever Vaccine, Testing, & Diagnosis

Introduction

Yellow fever has historically been a source of major deadly outbreaks in North America and Europe.[1,2] Most notably, in the United States, it swept through the major city of Philadelphia in 1793, killing 10% of the population.[2] However, in the 20th and 21st centuries, the disease has primarily been circulating in Africa and Latin America, causing hundreds of thousands of cases and significant death tolls.[3]

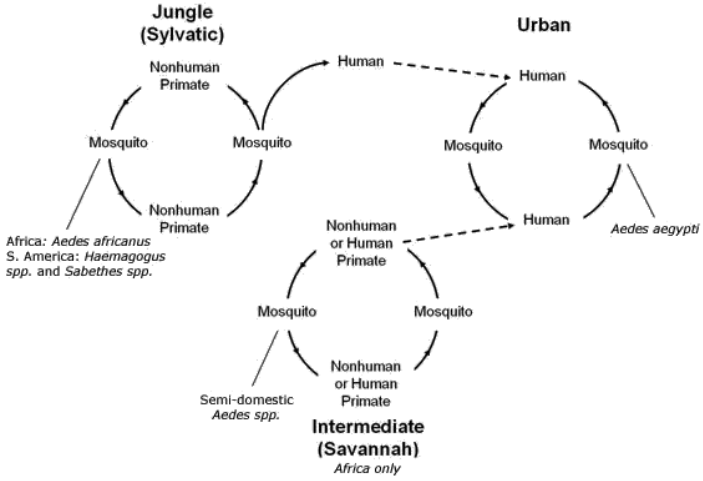
Yellow fever is a disease characterized by jaundice and hemorrhage in severe cases, but the majority of infections are either mild or asymptomatic.[4] Yellow fever can be difficult to diagnose and identify due to testing challenges and misidentification with other diseases.[3] This is a vaccine-preventable disease, which is not endemic to the United States and therefore rarely reported nationally. This is a disease of those traveling to certain endemic areas that providers should be aware of in the case they see patients who have traveled to those areas.[5]

Epidemiology

Yellow fever is an acute, viral hemorrhagic disease caused by the yellow fever virus, an RNA arbovirus of the *Flavivirus* genus and related to West Nile, St. Louis encephalitis, and Japanese encephalitis viruses.[1,5] It is transmitted by *Aedes* and *Haemogogus* mosquitoes, which can live in different habitats: domestically in homes, wild in jungles, and semi-domestic in either type of habitat.[1,5] People (and non-human primates) infected with yellow fever become a reservoir for the virus and are transmissible to mosquitos one day prior to onset of symptoms and up to five days after symptom onset.[5]

There are three primary transmission types of yellow fever (Figure 1).[1,5] First, sylvatic (jungle) yellow fever is where non-human primates, like monkeys, in tropical rainforests are the main reservoir but infected mosquitos can occasionally infect humans traveling the forest. Second, intermediate (savannah) yellow fever is where semi-domestic mosquitos can infect both monkeys and people, typical of villages in Africa. Third, urban yellow fever is where infected mosquitos transmit the virus person to person in heavily populated areas where there are large numbers of *Aedes aegypti* mosquitoes (a viremic person introduces the virus to the mosquito population in this case).

Figure 1: Transmission of Yellow Fever



Source: https://www.cdc.gov/yellowfever/transmission/index.html

Globally, there are approximately 200,000 cases of yellow fever with 30,000 deaths, annually.[3] The true number of cases is estimated to be 10 to 250 times what is reported or, as one study found, likely between one and seventy asymptomatic or mild infections can be estimated for every one severe case identified.[1,4] Yellow fever is considered endemic in tropical areas of Africa (34 countries) and Central and South America (13 countries) (Figures 2 & 3).[1] The following link provides an overview of yellow fever spread in endemic countries: https://www.cdc.gov/yellowfever/maps/index.html

Figure 2: Areas of Risk for Yellow Fever, Africa

Source: https://www.cdc.gov/yellowfever/maps/africa.html

Figure 3: Areas of Risk for Yellow Fever, South America

Source: https://www.cdc.gov/yellowfever/maps/south_america.html

Reported cases of yellow fever in the U.S. were found to have been infected while traveling in endemic countries. The last reported U.S. case recorded and accessible publicly was in 2016 in New York.[7] In Nevada, there has not been a reported case since at least 2005, when data started being collected.[6]

Prevention

Vector Control

Prevention of yellow fever can involve eliminating mosquito breeding sites in urban areas by use of larvicides in areas where there is standing water.[1] However, the number of safe and cost-effective insecticides that can be used against adult vectors is limited where yellow fever is endemic.[1] This is further complicated by the growing resistance of major vectors to common insecticides.[1] For example, most of Central and South America had successful mosquito control campaigns in the past, but resistant mosquitos have recolonized in those areas. In addition, mosquito control is not practical for jungle areas.[1]

Personal preventive measures against vectors are encouraged, such as minimizing exposed skin and use of personal repellents (e.g., DEET) for mosquitos.[1,5] As *Aedes* mosquitos bite during the daytime, the use of treated bed nets has limited preventive effect and extra care must be taken during daytime hours to prevent bites.[1]

More detailed prevention tips for travelers can be found here: https://www.cdc.gov/yellowfever/prevention/index.html

Vaccination

Vaccination is the primary prevention measure for yellow fever.[1] Vaccination has been available for over 80 years and is a single dose of a live, weakened form of the virus, which provides life-long protection at 99% efficacy after 30 days from vaccination.[1,5]

Several strategies are used worldwide, including routine infant immunization, mass vaccination campaigns, and vaccination of persons travelling to endemic locations.[1] While boosters are generally not recommended, some countries may require it and if a traveler is intending to go to an endemic area and it's been at least 10 years since they were last vaccinated, a booster can be administered.[5] Those excluded from vaccination include infants <9 months old, pregnant women (except during outbreaks), people with allergies to eggs, and those with severe immunodeficiency conditions.[1,5]

Vaccination requirements and recommendations for specific countries can be found here: https://wwwnc.cdc.gov/travel/destinations/list

Yellow fever vaccination clinics can be found here: https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search

Infected Travelers

As people are able to be viremic with yellow fever, travelers returning from an endemic area with symptoms of yellow fever should refrain from the risk of being bitten by mosquitos locally for up to five days after their symptoms have begun to prevent introduction of the yellow fever virus into the local mosquito population.[5]

Signs & Symptoms

The incubation period for yellow fever is usually between three to six days.[1,5] Most cases are asymptomatic or mild, but symptoms tend to present as a sudden onset of fever and/or headache, followed

by fatigue, malaise, muscle pain, back pain, body aches, loss of appetite, nausea and vomiting.[1,5] A provider may observe an acutely ill patient with bradycardia and elevated body temperature (Faget's sign), hyperbilirubinemia (day 3-7), leukopenia (1st week), bleeding dyscrasias, elevated prothrombin and partial thromboplastin times, decreased platelet count, and presence of fibrin-split products.[5] Symptoms last typically three to six days, but weakness and fatigue can persist for months.[1,5]

About 15% of infected cases may enter a second phase after recovery (a seeming remission of a few hours to two days).[1,5] This presents as a high fever with burden to multiple systems, sometimes leading to organ failure.[1,5] This is the phase where the classic jaundice appears (the basis of the "yellow" in yellow fever).[1] Other symptoms include abdominal pain, vomiting, dark urine, bleeding from mouth, nose, eyes, or stomach.[1,5] Providers may also observe leukocytosis (2nd week) and elevations of serum transaminase (up to 2 months).[5] Of those who go through this second phase, 30%-60% die within 7-10 days.[1,5] With recovery from infection, asymptomatic or severe, the individual is protected from future infections.[5]

Diagnosis & Testing

Yellow fever is rare in the United States, so travel history is the most important epidemiologic criteria for testing those who present with clinically compatible symptoms.[5] However, yellow fever is difficult to diagnose as early signs and symptoms tends to be ambiguous and later, more severe symptoms can be confused with other severe infections (e.g., malaria).[1]

Laboratory tests performed include testing serum to detect virus-specific IgM and IgG antibodies, but IgM antibodies can persist for years following vaccination.[5] Also, cross reactions with other flaviviruses can also occur, so more specific tests should be performed for confirmatory testing.[5] Polymerase chain reaction (PCR) testing in blood and urine can sometimes detect the virus in early stages of the disease, but in later stages, testing to identify antibodies is needed (e.g., ELISA).[1]

Testing by Stage:[5]

Early Stage: Day 3-4 of infection, yellow fever virus RNA can be detected in serum by virus isolation and RT-PCR testing.

Severe Stage: Viral RNA is undetectable, so RT-PCR may show false negative. Immunohistochemical staining of formalin-fixed material can detect yellow fever virus antigen in histopathologic specimens. Laboratory tests for antibodies can also be performed.

Fatal Cases: Nucleic acid amplification, histopathology with immunohistochemistry, and virus culture of biopsy or autopsy tissues may show positive results.

As only a few state laboratories or other specialized laboratories are able to conduct some of these tests, providers should contact Washoe County Health District for assistance with testing. More information can be found here: https://www.cdc.gov/yellowfever/healthcareproviders/healthcareproviders-diagnostic.html

Treatment

There is no specific anti-viral drug or treatment for yellow fever.[1,5] Early, supportive treatments to care for dehydration, liver and kidney failure is critical.[1] Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs is important as they may increase the risk of bleeding.[5] Hospitalization is required for any care of a severe case.[5]

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