

A microscopic image of yellow fever virus particles, which are spherical and covered in surface proteins, set against a purple and white background. The image is framed by a white border with decorative red and yellow wavy borders at the top and bottom.

**GLOBAL HEALTH & UNDERSERVED POPULATIONS
PROGRAM**

YELLOW FEVER

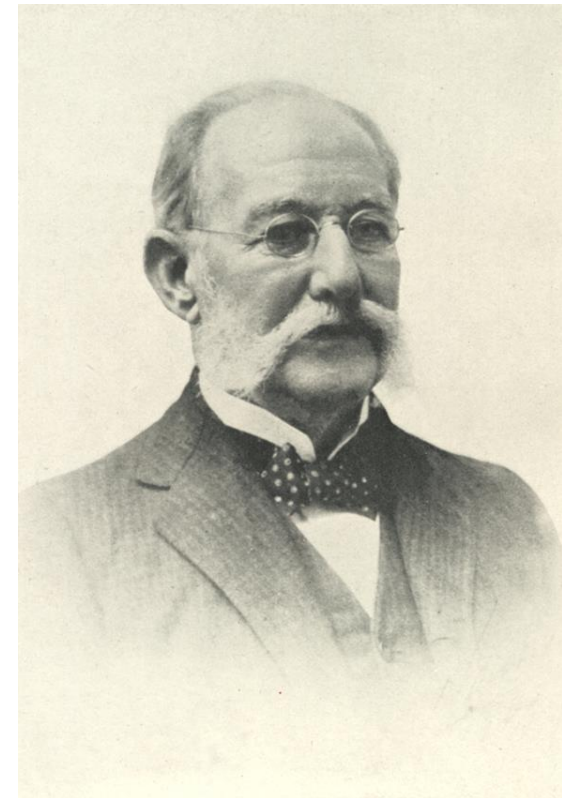
Wednesday, May 25, 2016

Carlos Finlay and Yellow Fever: Triumph over Adversity

Guarantor: Enrique Chaves-Carballo, MD

Contributor: Enrique Chaves-Carballo, MD

The eradication of yellow fever in Havana, Cuba, was achieved by a fruitful collaboration between American and Cuban physicians. Carlos Finlay, a Cuban physician who proposed the mosquito-vector theory in 1881, shared his ideas, his publications, and a sample of mosquito eggs with the U.S. Army Yellow Fever Commission. The commission, headed by MAJ Walter Reed, used human volunteers to confirm Finlay's theory. MAJ William Gorgas adopted mosquito-control measures in his sanitation program and, within 6 months, yellow fever was controlled in Havana for the first time. Finlay held fast to his ideas despite incredulity and ridicule. His tenacity and scientific honesty vindicated his ideas about yellow fever.





THE ETIOLOGY OF YELLOW FEVER.—A PRELIMINARY
NOTE.

By WALTER REED, M. D., SURGEON, U. S. A.;
JAMES CARROLL, M. D.; A. AGRAMONTE, M. D., AND
JESSE W. LAZEAR, M. D.,¹
ACTING ASSISTANT SURGEON, U. S. A.

Yellow fever and Max Theiler: the only Nobel Prize for a virus vaccine

In 1951, Max Theiler of the Rockefeller Foundation received the Nobel Prize in Physiology or Medicine for his discovery of an effective vaccine against yellow fever—a discovery first reported in the *JEM* 70 years ago. This was the first, and so far the only, Nobel Prize given for the development of a virus vaccine. Recently released Nobel archives now reveal how the advances in the yellow fever vaccine field were evaluated more than 50 years ago, and how this led to a prize for Max Theiler.



Max Theiler receives the Nobel Prize in Physiology or Medicine from the hands of His Majesty the King Gustaf Adolf VI on December 10, 1951. Photo provided by the Karolinska Institutet.

Yellow Fever in History



History Timeline Transcript

Table 1. History Timeline

Date	Event
3000 B.C.E.	Yellow fever has had an important role in the history of Africa, the Americas, Europe, and the Caribbean. Scientists believe that yellow fever evolved in Africa around 3,000 years ago.
1600s	Yellow fever was imported into the western hemisphere on slave ships from West Africa.
1648	The first definitive evidence of yellow fever in the Americas was in Mayan manuscripts describing an outbreak of the disease in the Yucatan and Guadeloupe.
1668-1699	Outbreaks were reported on the eastern coast of the United States, including in New York (1668), Boston (1691), and Charleston (1699).
1700s	Yellow fever spread to Europe.
1730	In one of the first epidemics described, 2,200 deaths were reported in Cadiz, Spain. This epidemic was followed by outbreaks in French and British seaports. Over the next century, widespread epidemics were recorded in tropical and subtropical areas of the Americas, including the West Indies, Central America, and the United States.
1800s	Until the mid-1800s, scientists believed yellow fever was spread by direct contact with infected individuals or contaminated objects.
1848-1881	The first suggestions that the vector might be a mosquito were made by the American physician Josiah Clark Nott in 1848 and by Cuban physician Carlos Finlay in 1881.
1839-1860	Annual outbreaks in New Orleans led to more than 26,000 cases of yellow fever.
1898	Yellow fever caused difficulties for the U.S. Army in Cuba during the Spanish-American War; reportedly more soldiers died of the disease than in battle. The ongoing outbreaks prompted military efforts for further research and the formation of the Reed Yellow Fever Commission led by Walter Reed, an American army surgeon.
1900	The Reed Yellow Fever Commission proved that yellow fever infection is transmitted to humans by the <i>Aedes aegypti</i> mosquito.
1905	The last outbreak in the United States occurred in New Orleans.
1906	Following the demonstration that <i>Ae. aegypti</i> mosquitoes are responsible for transmission of the yellow fever virus to humans, intense sanitation programs began in Panama and Havana, Cuba. These efforts led to the eradication of the disease in these areas. Eradication of yellow fever in Panama enabled completion of the Panama Canal in 1906. The previous construction had been hampered severely by yellow fever infection among the workers.
1930	Two yellow fever vaccines were developed, the 17D vaccine and the French neurotropic vaccine.

1940s	Mass campaigns were conducted using the 17D vaccine in South America and the French neurotropic vaccine in French-controlled areas of Africa.
1950	Doctors became concerned with the high rate of postvaccinal encephalitis following administration of the yellow fever vaccine to infants. The range of yellow fever virus transmission in the Americas expanded, and cases were reported in Panama for the first time in 43 years. Before the end of the decade, the disease had spread throughout Central America, finally stopping near the border of Guatemala and Mexico.
1960s	Yellow fever cases occurred in both Africa and the Americas. Thousands of cases were reported in West Africa, where vaccination coverage had waned or was absent, and in Ethiopia where the disease was not reported previously.

Date	Event
1980s	A major increase in the incidence of the disease occurred in Africa. An estimated 120,000 cases and 24,000 deaths were reported in Nigeria alone. Ecological surveillance of jungle mosquitoes and monkeys showed that these expansions occurred because of an amplification of the disease in nonhuman primates. From a public health perspective, however, the fundamental problem was poor or nonexistent vaccine coverage, despite its availability and cost-effectiveness.
1982	Because of high rates of postvaccinal encephalitis, the French neurotropic vaccine was abandoned. The 17D vaccine became the standard for use in immunization for yellow fever worldwide.
2000s	Yellow fever vaccine was incorporated into the routine childhood vaccinations of several South American and African countries. While this strategy decreases the number of persons susceptible to the disease over time, a large portion of the at-risk population is not covered in the short-term. Hundreds of cases of yellow fever from endemic countries in South America and Africa are still reported annually to the World Health Organization (WHO). Two virus substrains are currently used in the production of yellow fever vaccines: 17DD, which is used in Brazil, and 17D-204 in all other vaccines, including the Sanofi Pasteur vaccine, YF-VAX®, which is used in the United States. WHO estimates that thousands of yellow fever cases each year go unreported. Many are not recognized due to asymptomatic infections and lack of effective surveillance systems. The International Health Regulations (IHR) of the WHO permit countries to establish entry requirements for yellow fever vaccination to protect their citizens and prevent the spread of yellow fever within their borders. Many governments now require travelers who enter their countries to show official proof of vaccination against the disease. Due to the possibility of contraindications in specific groups, it is especially important that vaccine providers be knowledgeable and understand the circumstances surrounding administration of the vaccine.

CONTROL DISCOURSES AND POWER RELATIONS OF YELLOW FEVER: PHILADELPHIA IN 1793.

Abstract

1793 Yellow fever in Philadelphia was the most severe epidemics in the late 18th century in the United States. More than 10% of the population in the city died and many people fled to other cities. The cause of yellow fever in the United States had close relationship with slaves and sugar in Philadelphia. Sugarcane plantation had needed many labors to produce sugar and lots of Africans had to move to America as slaves. In this process, *Aedes aegypti*, the vector of yellow fever had migrated to America and the circumstances of ships or cities provided appropriate conditions for its breeding. In this period, the cause of yellow fever could not be established exactly, so suggestions of doctors became entangled in political and intellectual discourses in American society. There was a critical conflict between Jeffersonian Republicanism and Federalism about the origin and treatment of yellow fever. Benjamin Rush, a Jeffersonian Republican, suggested urban sanitation reform and bloodletting. He believed the infectious disease happened because of unsanitary city condition, so he thought the United States could be a healthy nation by improvement of the public health and sanitation. He would like to cope with national crisis and develop American society on the basis of republicanism. While Rush suggested the improvement of public health and sanitation, the city government of Philadelphia suggested isolation of yellow fever patients and quarantine. City government isolated the patients from healthy people and it reconstructed space of hospital. Also, it built orphanages to take care of children who lost their parents during the epidemic and implemented power to control people put in the state of exception. Of course, city government tried to protect the city and nation by quarantine of every ship to Philadelphia. Control policies of yellow fever in 1793 showed different conflicts and interactions. Through the yellow fever, Jeffersonian Republicanism and Federalism had conflicted in politically, but they had interactions for control of the infectious disease. And with these kinds of infectious diseases policies, we can see interactions in local, national and global level.

SUMMARY OF IMPORTANT EVENTS RELATED TO YELLOW FEVER

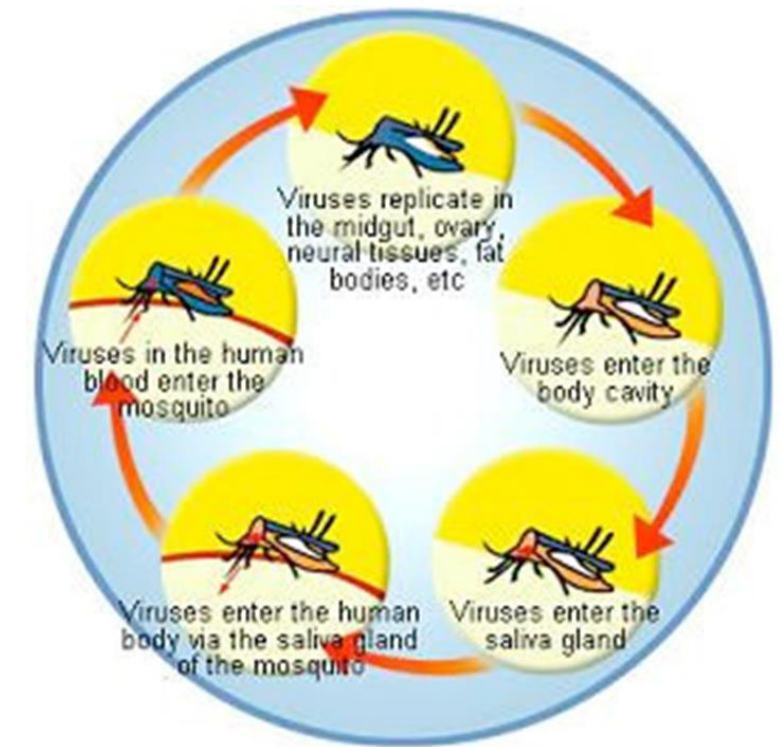
- 1648 - South America outbreak with 280,000 deaths
- 1793 – Most severe epidemic in the US in the 18th century – 5,000 deaths in 4 months – Philadelphia
- 1839-1860- New Orleans outbreaks: 26,000 cases with 7,790 deaths
- 1878- Southern States over 13,000 people died from yellow fever in lower Mississippi Valley
- 1881- Dr. Carlos Finlay proposed the mosquito-vector theory
- 1898- Spanish-American war, Cuba: 400 soldiers died in battle; 2,000 died of yellow fever
- 1900 – Dr. Walter Reed published his studies confirming transmission of yellow fever by mosquitoes
- 1906- Eradication of yellow fever in Panama enabled completion of the Panama Canal in 1906
- 1927- Dr. Mahaffey isolated the virus from a 28 yo survivor in West Africa
- 1930s – Dr. Max Theiler developed the 17D vaccine, another one was developed (French neurotropic vaccine)
- 1940- Mass vaccination campaign in South America and Africa
- 1951- Dr. Max Theiler received the Nobel Prize in Medicine/Physiology for his discovery of yellow fever vaccine

YELLOW FEVER VIRUS

- Yellow Fever Virus is an enveloped, single-stranded RNA virus that belongs to the genus *Flavivirus*.
- It is the virus responsible for Yellow Fever (acute viral hemorrhagic fever)
- Relatively small virus: 40-60 nm
- 7 genotypes have been described: 5 in Africa, 2 in South America
 - West Africa Genotype I (Nigeria, Cameroon and Gabon)
 - West Africa Genotype II (Senegal, Guinea, Ivory Coast and Ghana)
 - East and Central African genotype (Sudan, Ethiopia, DRC and CAR)
 - East African Genotype (Uganda, Kenya)
 - Angola Genotype
 - South American Genotype I (Brazil, Bolivia, Colombia, Ecuador, Panama, Venezuela)
 - South American Genotype II (Peru, Bolivia, Western Brazil)

TRANSMISSION

- Yellow fever virus is transmitted to people primarily through the bite of infected *Aedes* or *Haemagogus* species mosquitoes.
- Mosquitoes acquire the virus by feeding on infected primates (human or non-human) and then can transmit the virus to other primates (human or non-human).
- People infected with yellow fever virus are infectious to mosquitoes shortly before the onset of fever and up to 5 days after onset.
- Yellow fever virus has three transmission cycles:
 - jungle (sylvatic)
 - intermediate (savannah)
 - urban



TRANSMISSION

- **Sylvatic (jungle) cycle:**

- In tropical rainforests, yellow fever virus is endemic among lower primates.
- Infected monkeys pass the virus to mosquitoes that feed on them.
- Persons who subsequently enter the forest (often workers and travelers) are infected with this form of disease.
- In Africa, the principal vector of the jungle cycle is *A africanus*
- In South America, *H janthinomys* is the primary vector for jungle transmission
- Nonhuman primates remain the preferred host in this setting.

TRANSMISSION

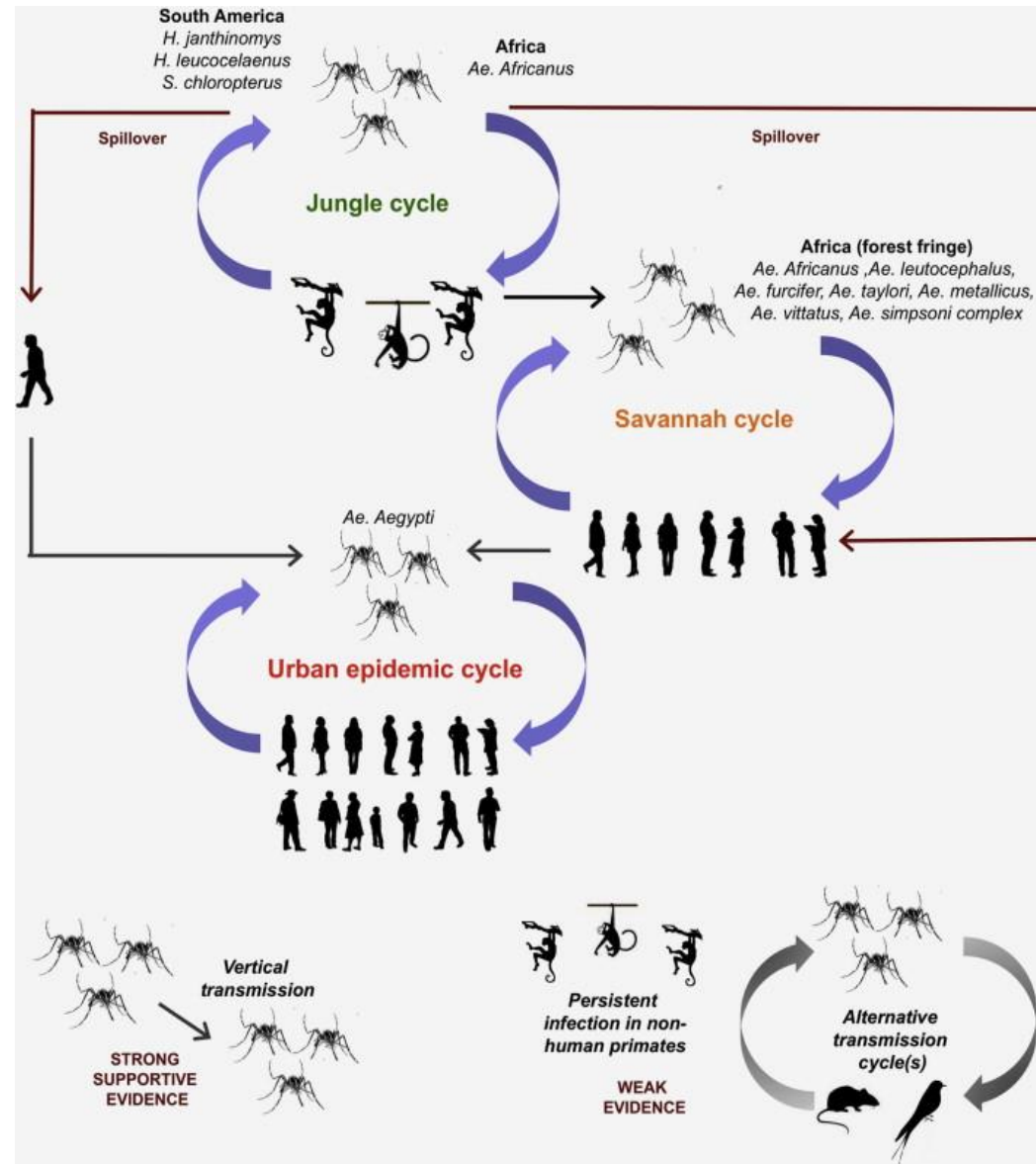
- **Intermediate (savannah) cycle**

- In moist and semi-humid areas of Africa, semi-domestic mosquitoes (which breed in the wild and around households) feed primarily on monkeys but will also feed on humans when the opportunity arises.
- This cycle likely reflects the evolution of yellow fever into an epidemic human disease.
- It is the most common cycle present in Africa and frequently leads to small-scale outbreaks in villages.
- However, transmission can potentially lead to large-scale epidemics if an infected individual carries the disease into an urban region.
- This cycle has not been identified in South America

TRANSMISSION

- **Urban cycle**

- *A aegypti* is responsible for the transmission of urban yellow fever in Africa and South America.
- This mosquito can breed in urban water containers, allowing mosquito transmission of the yellow fever virus from human to human.
- Thus, *A aegypti* can infect large populations of unvaccinated individuals.
- Urban outbreaks are rare in South America, yet they are still occasionally reported in densely populated regions in Africa.

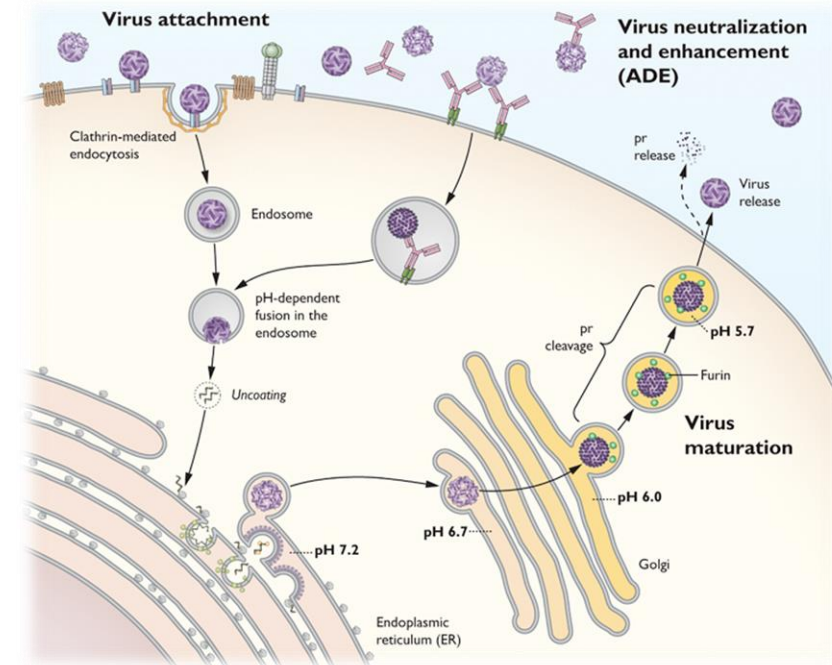


TRANSMISSION/PATHOGENESIS

- The virus is transmitted via the saliva of an infected mosquito.
- An infected female mosquito inoculates approximately 1000 to 100,000 virus particles intradermally during blood feeding.
- Virus replication begins at the site of inoculation, in dendritic cells in the epidermis, and spreads through lymphatic channels to regional lymph nodes.
- Lymphoid cells, particularly macrophages and histiocytes, appear to be the preferred cell types for primary replication.
- The virus reaches other organs via the lymph and then the bloodstream, seeding other tissues.
- Large amounts of virus are produced in the liver and spleen and released into the blood.
- During the viremic phase (days three to six), infection may be transmitted to blood-feeding mosquitoes.

PATHOGENESIS

- The virus gains entrance through receptor-mediated endocytosis.
- RNA synthesis occurs in the cytoplasm and protein synthesis takes place in the ER.
- Virions are released through the cell membrane.
- The viral envelope contains a lipid bilayer taken from the infected cell.
- Virulence factors include the following:
 - Capsid protein C - Facilitates viral binding
 - Membrane protein M - A minor glycoprotein
 - E proteins - Initiate infection and mediate viral entry
 - Nonstructural protein 1 (NS1) - May play a role in RNA replication
 - NS2A protein - Involved in RNA replication and packaging
 - NS2B and NS3 - Form a complex and are involved in polyprotein processing and replication of RNA
 - NS5 - Has a major role in RNA replication



PATHOGENESIS

- After invasion in the host, Kupffer cells (fixed liver macrophages) are infected within 24 hours.
- The infection quickly disseminates to the kidneys, lymph nodes, spleen, and bone marrow.
- Renal failure occurs as renal tubules undergo fatty change and eosinophilic degeneration, likely due to direct viral effect, hypotension, and hepatic involvement.
- The liver is the most important organ affected in yellow fever.
- The disease was labeled "yellow" based on the profound jaundice observed in affected individuals.
- Hepatocellular damage is characterized by lobular steatosis, necrosis, and apoptosis with subsequent formation of Councilman bodies (degenerative eosinophilic hepatocytes).

THE LANCET Infectious Diseases

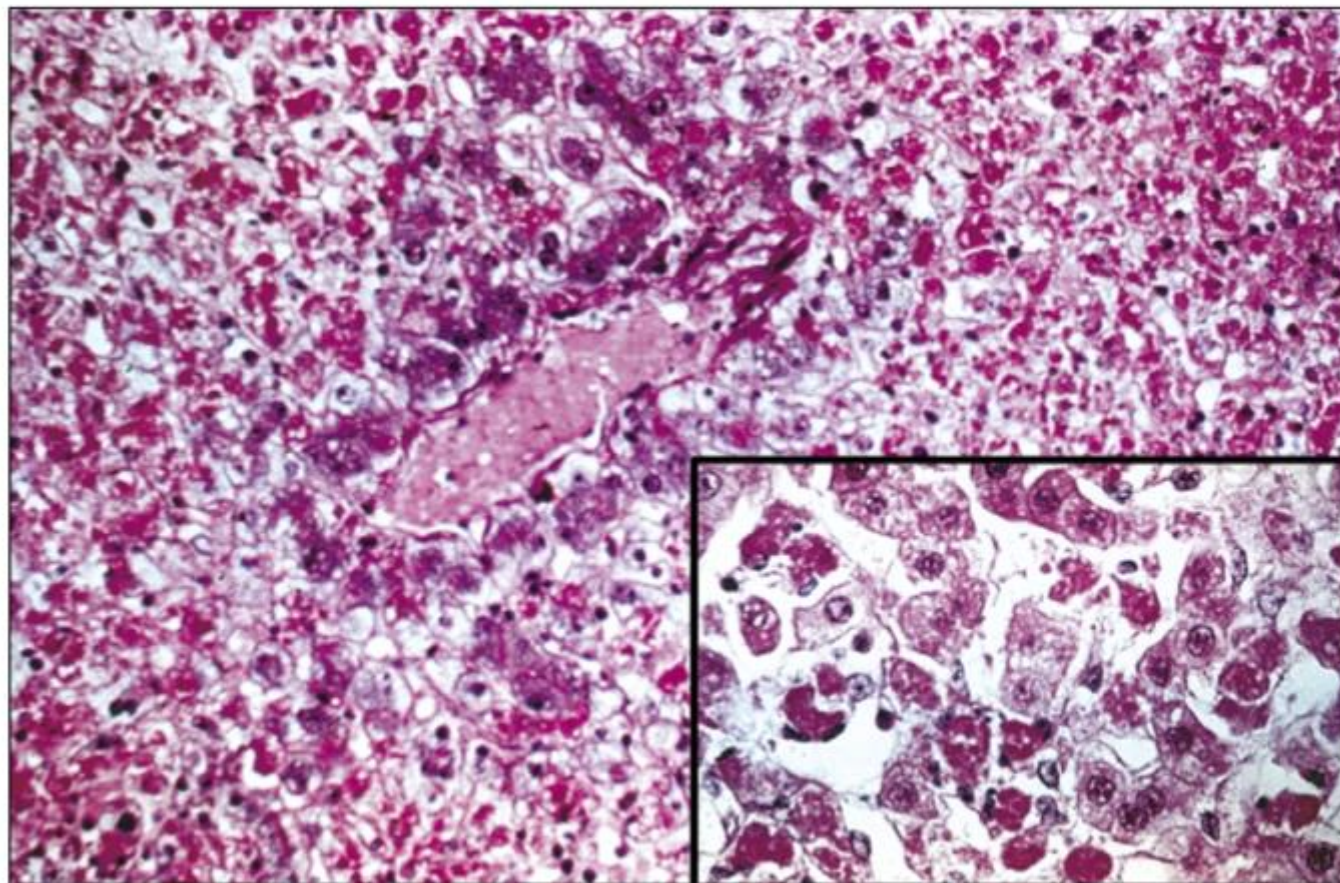


Figure 7. Histopathological features of yellow fever infection of the liver. The lesion is mid-zonal in distribution with sparing of cells around the central vein. There are microvesicular fatty changes but little inflammatory response. Inset: eosinophilic degeneration of hepatocytes (Councilman bodies) reflects apoptotic cell death.

PATHOGENESIS

- The kidneys also undergo significant pathologic changes.
- Albuminuria and renal insufficiency evolve secondary to the pre-renal component of yellow fever; consequently, acute tubular necrosis develops in advanced disease.
- Hemorrhage and erosion of the gastric mucosa lead to hematemesis, popularly known as black vomit.
- Fatty infiltration of the myocardium, including the conduction system, can lead to myocarditis and arrhythmias

PATHOGENESIS

- Central nervous system (CNS) findings can be attributed to cerebral edema and hemorrhages compounded on metabolic disturbances.
- The bleeding diathesis of this disease is secondary to reduced hepatic synthesis of clotting factors, thrombocytopenia, and platelet dysfunction.
- The terminal event of shock can be attributed to a combination of direct parenchymal damage and a systemic inflammatory response.

PATHOGENESIS

- Finally, circulatory shock develops secondary to cytokine storm, with evidence of increased levels of interleukin (IL)-6, IL-1 receptor antagonist, interferon-inducible protein-10, and tumor necrosis factor (TNF)-alpha.
- Viral antigens are found diffusely in kidneys, myocardium, and hepatocytes. In individuals who survive yellow fever, the recovery is complete, with no residual fibrosis.

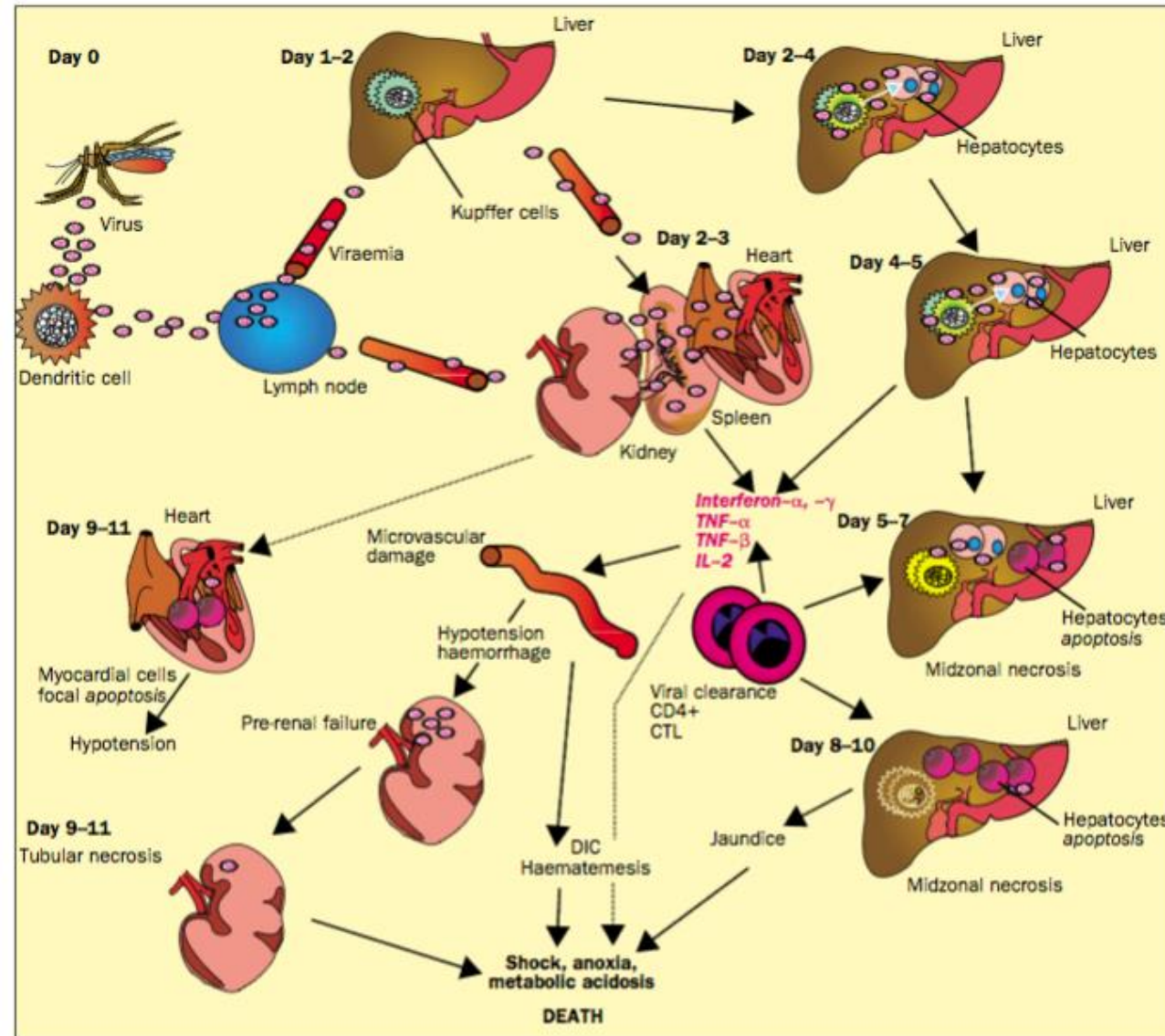


Figure 6. Pathogenesis of yellow fever based on studies in experimentally infected monkeys and human case reports (**bold**). Speculative mechanisms shown in *italics* are drawn from *in-vitro* data or reports on other flavivirus infections. CTL=cytotoxic T lymphocyte, DIC=disseminated intravascular coagulation, IL=interleukin.

CLINICAL PRESENTATION

- The majority of persons infected with yellow fever virus have no illness or only mild illness.
- In persons who develop symptoms, the incubation period (time from infection until illness) is typically 3–6 days.
- The initial symptoms include sudden onset of fever, chills, severe headache, back pain, general body aches, nausea, and vomiting, fatigue, and weakness. Most persons improve after the initial presentation.
- After a brief remission of hours to a day, roughly 15% of cases progress to develop a more severe form of the disease
 - The severe form is characterized by high fever, jaundice, bleeding, and eventually shock and failure of multiple organs
 - Of these patients up to half will die

THE LANCET Infectious Diseases

THE LANCET Infectious Diseases Vol 1 August 2001

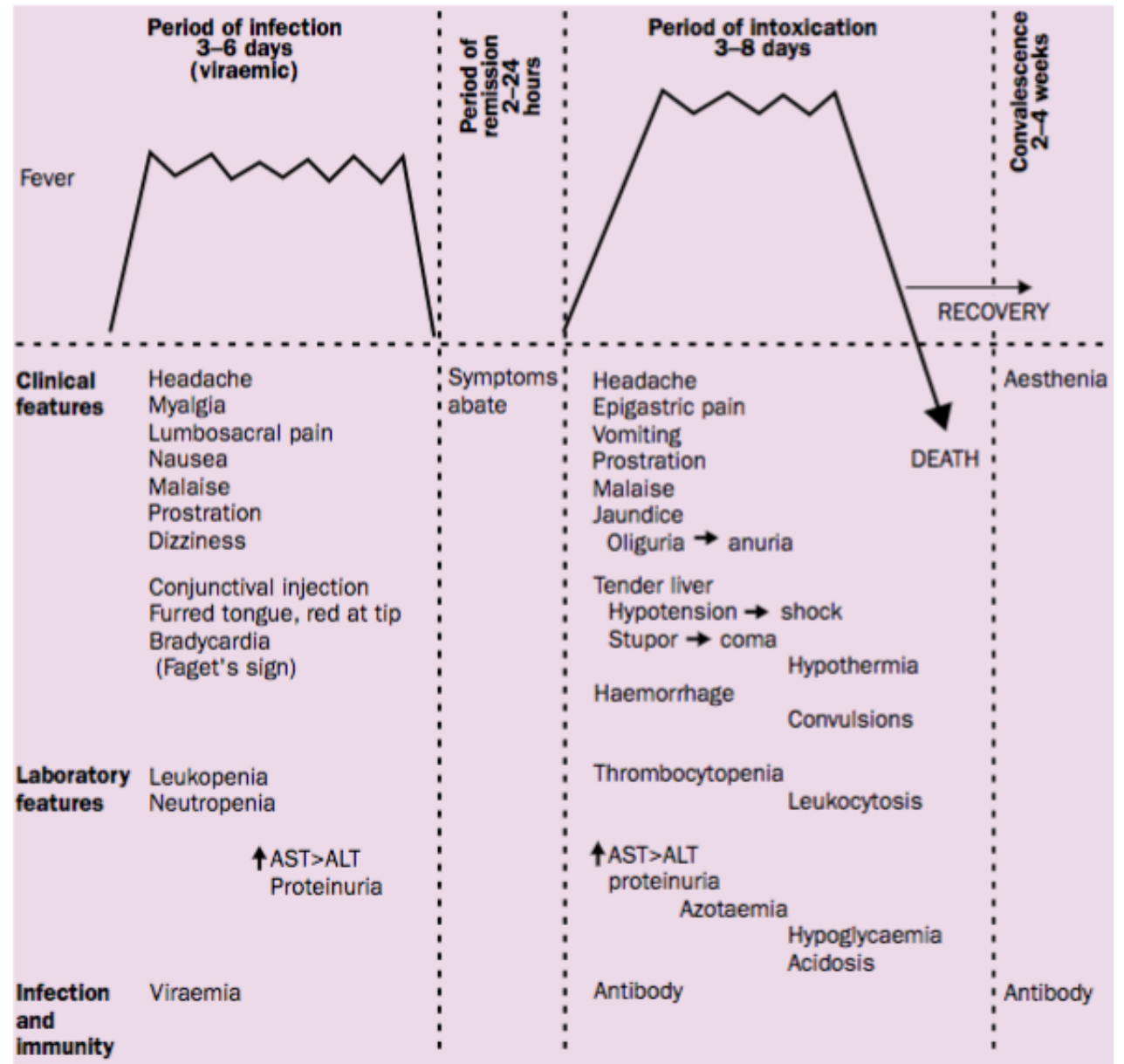


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

EPIDEMIOLOGY

- Forty seven countries in Africa (34) and Central and South America (13) are either endemic for, or have regions that are endemic for, yellow fever.
- A modelling study based on African data sources estimated the burden of yellow fever during 2013 was:
 - 84 000–170 000 severe cases 29 000–60 000 deaths.

NEWS

Yellow fever outbreak: Health officials to weigh declaring global emergency



Yellow fever is transmitted by the *Aedes aegypti* mosquito, which can also carry Zika, the virus linked to birth defects. (U.S. Department of Agriculture) LA Times May 18, 2016.

WHO: Yellow fever outbreak is 'serious and of great concern'

By Debra Goldschmidt, CNN
Updated 3:05 PM ET, Thu May 19, 2016

Yellow Fever Worse Than Zika Virus? Africa Crisis 'Serious Concern,' Says WHO



DHEERAJ RAWAL

Update Date: May 21, 2016 06:00 AM EDT



A city environmental health worker displays literature to be distributed to the public on April 14, 2016 in McAllen, Texas. Health departments, especially in areas along the Texas-Mexico border, are preparing for the expected arrival of the Zika Virus, carried by the aegypti mosquito, which is endemic to the region. The U.S. Centers for Disease Control (CDC), announced this week that Zika is the definitive cause of birth defects seen in Brazil and other countries affected by the outbreak. (Photo by John Moore/Getty Images) (Photo : John Moore/Getty Images News)

Yellow fever outbreak triggers vaccine alarm



The Angolan military administers yellow fever vaccine at a market in Luanda in February.

The disease has since spread far outside the Angolan capital. Science 08 Apr 2016:

Vol. 352, Issue 6282, pp. 128-129



The mosquitoes that changed history

OUTBREAK IN ANGOLA

- The first epidemic of the yellow fever to hit Angola in 30 years was detected in late December 2015
 - Likely introduced following increased viral circulation among forest monkeys
- 2,420 suspected cases of yellow fever (736 laboratory confirmed), with 298 death as of 19 May 2016, largely concentrated in main cities & ports
- Emergency Committee convened by WHO's Director-General
 - The urban yellow fever outbreaks in Angola and DRC are serious public health events that warrant intensified national action & enhanced international support



Map showing countries with Yellow fever reports, April 2016

- **Three countries have reported confirmed yellow fever cases imported from Angola**

- Democratic Republic of The Congo (DRC): 39 cases
- Kenya: 2 cases
- People's Republic of China: 11 cases

→ **Highlights the risk of international spread through non-immunized travelers**

- **Democratic Republic of The Congo: 3 probable and 41 laboratory confirmed cases** as of 11 May

- Yellow fever outbreak officially declared on 23 April
- 39 cases imported from Angola and 2 autochthonous cases
- The possibility of locally acquired infections is under investigation for at least 10 cases in both Kinshasa & Kongo central provinces

- **Uganda (autochthonous): 51 suspected, 7 laboratory confirmed cases** as of 11 May

- Reported from 3 districts: Masaka, Rukungiri & Kalangala.
- According to sequencing results, those clusters are not epidemiologically linked to Angola.

- **The risk of spread**


- The virus in Angola and DRC is largely concentrated in main cities → concern for local transmission to other provinces
- High risk also for potential spread to bordering countries, especially those classified as low risks for yellow fever disease (i.e. Namibia, Zambia) where the population, travelers and foreign workers are not vaccinated against yellow fever

Map Scale (A3) : 1:85,000,000

1 cm = 850 km


Coordinate System: GCS WGS 1984
Datum: WGS 1984
Units: Degree

Data Source:
Data and Admin. Boundaries: World Health Organization
Base Map: GEBCO

 Countries with imported cases (from Angola)

 Countries with autochthonous transmission unrelated to Angola outbreak

 Countries with autochthonous transmission (Angola)

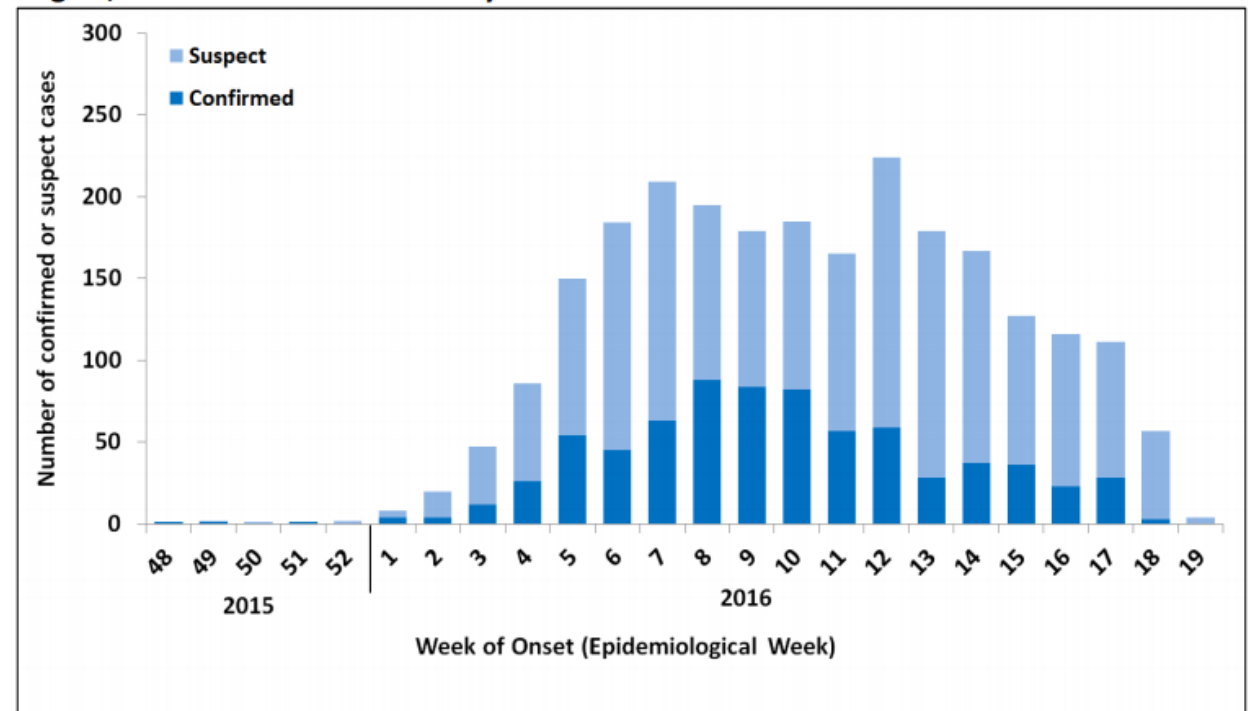
 Disputed Areas

 Disputed Borders

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 and dashed lines on maps represent approximate borders for which there may not yet be full agreement.

- Persistent local transmission reported in 7 highly populated provinces including Luanda, despite the fact that >7 million people have been vaccinated
- High risk of spread to neighboring countries:
 - Confirmed cases have already travelled from Angola to DRC, Kenya and People's Republic of China
 - As the borders are porous with substantial crossborder social and economic activities, further transmission cannot be excluded
 - Viremic patients travelling pose a risk for the establishment of local transmission especially in countries where adequate vectors and susceptible human populations are present
- Inadequate surveillance system capable of identifying new foci or areas of cases emerging

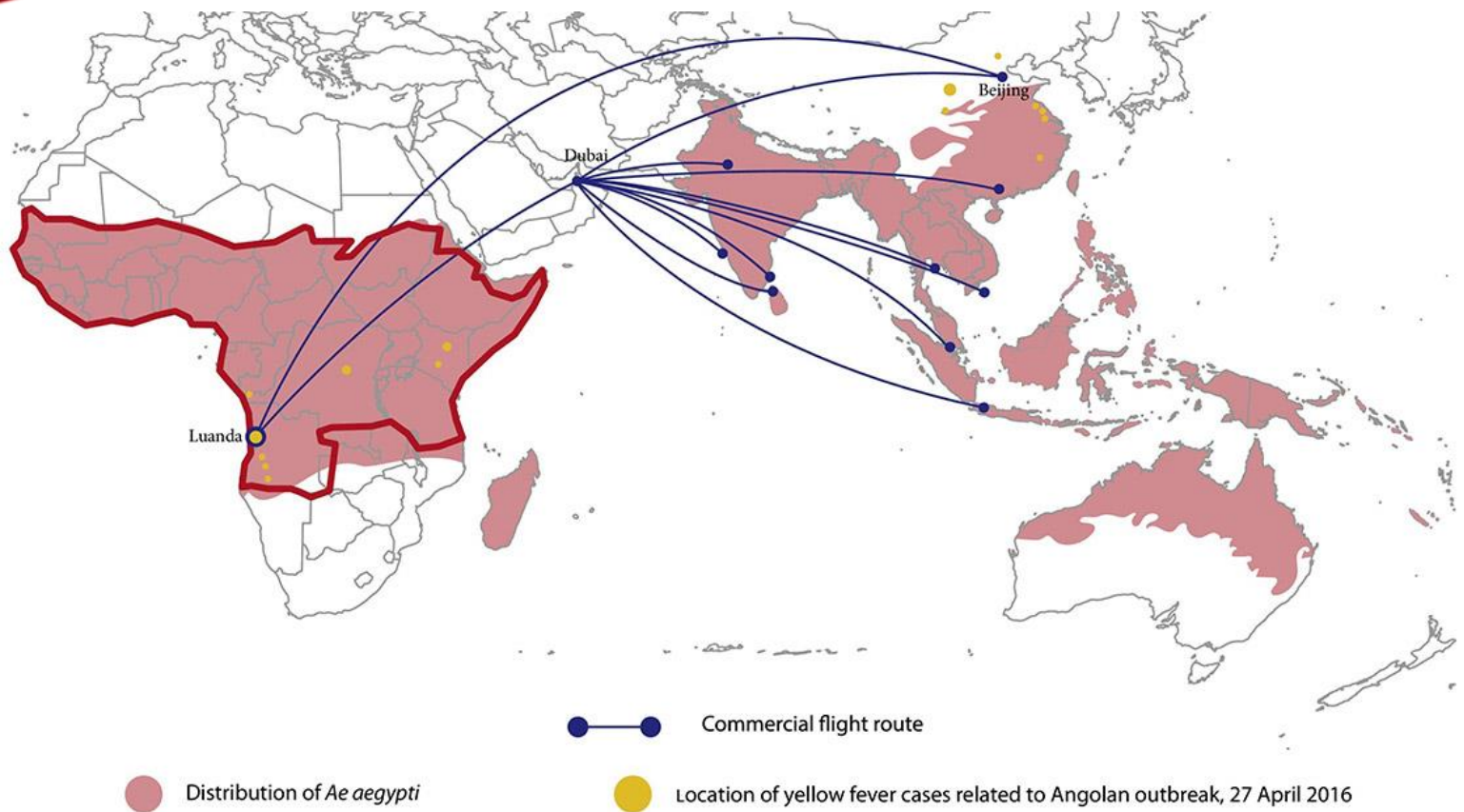
Figure 3. National weekly number of suspected and confirmed yellow fever cases in Angola, 5 December 2015— 15 May 2016



Data provided by Angola yellow fever situation report as of 15 May 2016.² Data for the last two weeks is incomplete due to lags between onset of symptoms and reporting.

NEWS

- Lead author Sean Wasserman, of the University of Cape Town, South Africa, warns:
 - “The current scenario of a yellow fever outbreak in Angola, where there is a large Chinese workforce, most of whom are unvaccinated, coupled with high volumes of air travel to an environment conducive to transmission in Asia, is unprecedented in history. These conditions raise the alarming possibility of a YF epidemic, with a case fatality of up to 50 percent, in a region with a susceptible population of two billion people and where there is extremely limited infrastructure to respond effectively.”



Map showing the distribution of *Aedes aegypti* across Africa and the Asia-Pacific region (areas shaded pink). The red outline delineates yellow fever-endemic regions. Yellow dots represent the location of yellow fever cases related to the Angolan outbreak (source: HealthMap). Commercial flight routes with direct connections between Luanda and Beijing and indirect connections from Luanda to South and Southeast Asia via Dubai (source: FLIRT) are also represented. (This map appears in Wasserman et al: *International Journal of Infectious Diseases*)

Yellow fever epidemic threatens to spread from Angola to China: Action needs to be taken now to avert a global catastrophe, say experts in the *International Journal of Infectious Diseases* – Wasserman S, et.al. Yellow Fever cases in Asia: primed for an epidemic. May 9, 2016.

DIFFERENTIAL DIAGNOSIS

- Clinically, severe YF resembles other viral hemorrhagic fevers occurring in Africa and South America, so laboratory confirmation is required to make the diagnosis
- Early exclusion of other causes with the potential for person-to-person spread is important to prevent nosocomial transmission
- Other forms of viral hepatitis, particularly hepatitis E (which frequently appears in outbreaks), leptospirosis, malaria, typhoid, typhus, relapsing fever, and toxin-related hepatitis are alternative diagnoses

DIAGNOSIS

- Presumptive diagnosis is based on the patient's clinical features, vaccination status, and travel history, including destination, time of year, and activities
- Laboratory diagnosis generally is accomplished by serology: Detection of virus-specific IgM and IgG antibodies in serum
 - RT-PCR can be done early in the illness (first 3-4 days), but by the time overt symptoms are recognized, viral RNA is usually undetectable
 - Obtaining a yellow fever vaccination history is important, as IgM from the yellow fever vaccine can persist for several years
- Healthcare providers should contact their state or local health department and CDC (telephone 1-970-221-6400) for assistance with serologic testing
- Instructions for sending diagnostic specimens to CDC's Arbovirus Diagnostic Laboratory can be found at [CDC's Division of Vector-Borne Diseases Arboviral Specimens submission page](#)



TREATMENT

- Disease is severe with high morbidity and mortality
- Hospitalization in an ICU where the patient can be closely monitored, provided supportive care (for hypotension, metabolic acidosis, hypoglycemia, etc), and sequestered from mosquitoes (screen or bednet) to prevent transmission
 - Exploratory studies in small animal models and nonhuman primates of various compounds (e.g., interferons, ribavirin) have had varied results
 - Currently, no antiviral therapy is available, and specific supportive interventions have not been clinically evaluated
 - Avoid drugs dependent on hepatic metabolism
 - Fresh-frozen plasma and vitamin K have been administered to replenish clotting factors
 - The effect of heparin therapy is unproven

PREVENTION

- Vaccination is considered to be the most important and effective measure against yellow fever
- Protective immunity develops within 30 days for >95 (99%) of people receiving the vaccination
 - A single 0.5-mL subcutaneous dose of attenuated 17D vaccine
- WHO recommendations updated in 2013:
 - For healthy immunocompetent individuals, a single dose is sufficient to confer lifelong protective immunity against yellow fever disease
 - A booster dose every 10 years is not necessary.
 - Subsequently, some countries have adopted this recommendation, whereas others (e.g., Brazil) have not

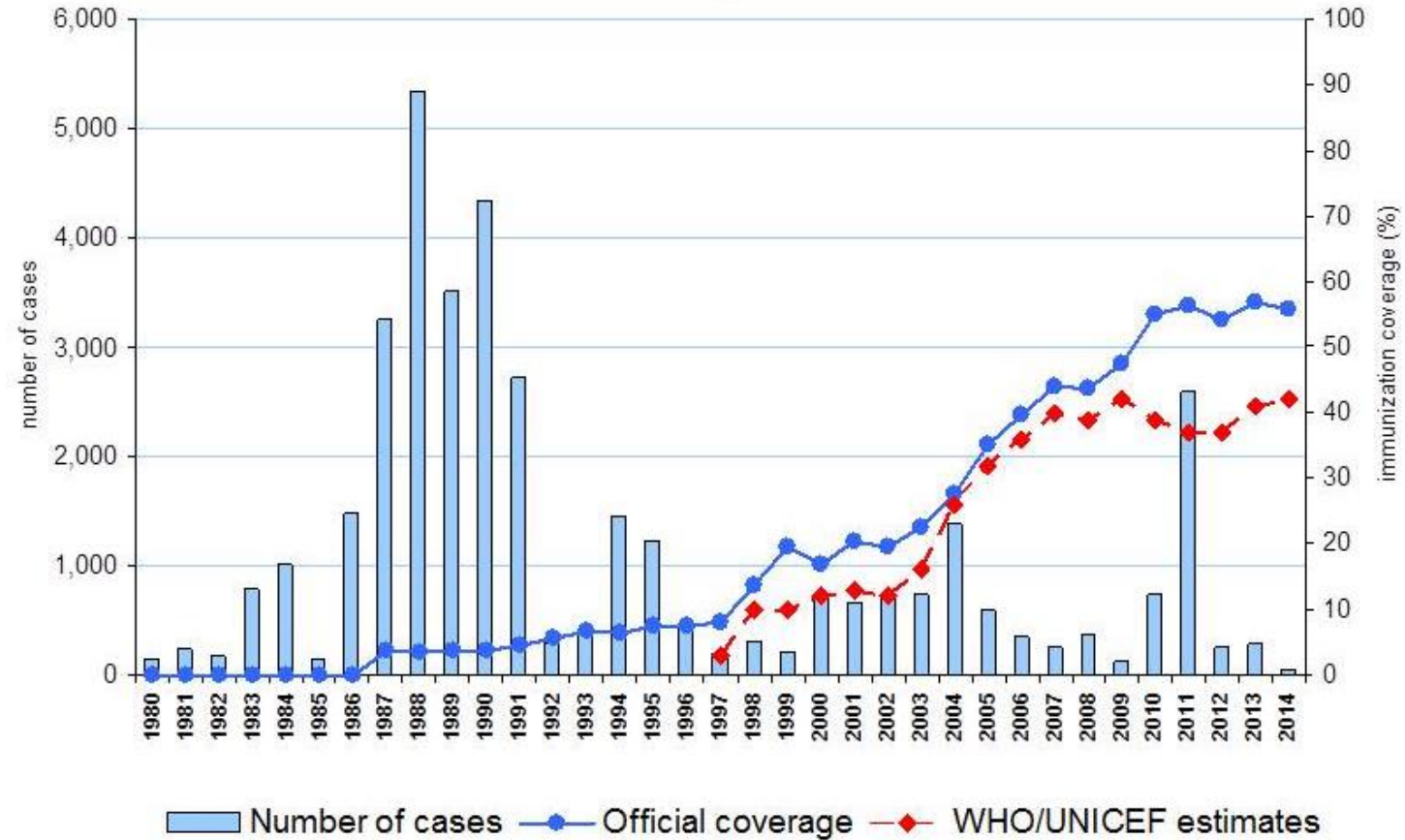
Prophylaxis against: (name of disease or condition)
YELLOW FEVER

in accordance with the International Health Regulations

Vaccine or prophylaxis Vaccin ou agent prophylactique	Date	Signature statu

PREVENTION

Yellow fever global annual reported cases and YFV coverage, 1980-2014




Source: WHO/IVB database, 2015
194 WHO Member States.
Data as of July 2015

Date of slide: 14 July 2015



Table 3-21. Countries with risk of yellow fever virus (YFV) transmission¹

AFRICA			CENTRAL AND SOUTH AMERICA
Angola	Equatorial Guinea	Mauritania ²	Argentina ²
Benin	Ethiopia ²	Niger ²	Bolivia ²
Burkina Faso	Gabon	Nigeria	Brazil ²
Burundi	Gambia, The	Senegal	Colombia ²
Cameroon	Ghana	Sierra Leone	Ecuador ²
Central African Republic	Guinea	South Sudan	French Guiana
Chad ²	Guinea-Bissau	Sudan ²	Guyana
Congo, Republic of the	Kenya ²	Togo	Panama ²
Côte d'Ivoire	Liberia	Uganda	Paraguay
Democratic Republic of the Congo ²	Mali ²		Peru ²
			Suriname
			Trinidad and Tobago ²
			Venezuela ²

¹ Countries or areas where “a risk of YFV transmission is present,” as defined by the World Health Organization, are countries or areas where “yellow fever has been reported currently or in the past, plus vectors and animal reservoirs currently exist” (see the current country list within the *International Travel and Health* publication (Annex 1) at www.who.int/ith/en/index.html ).

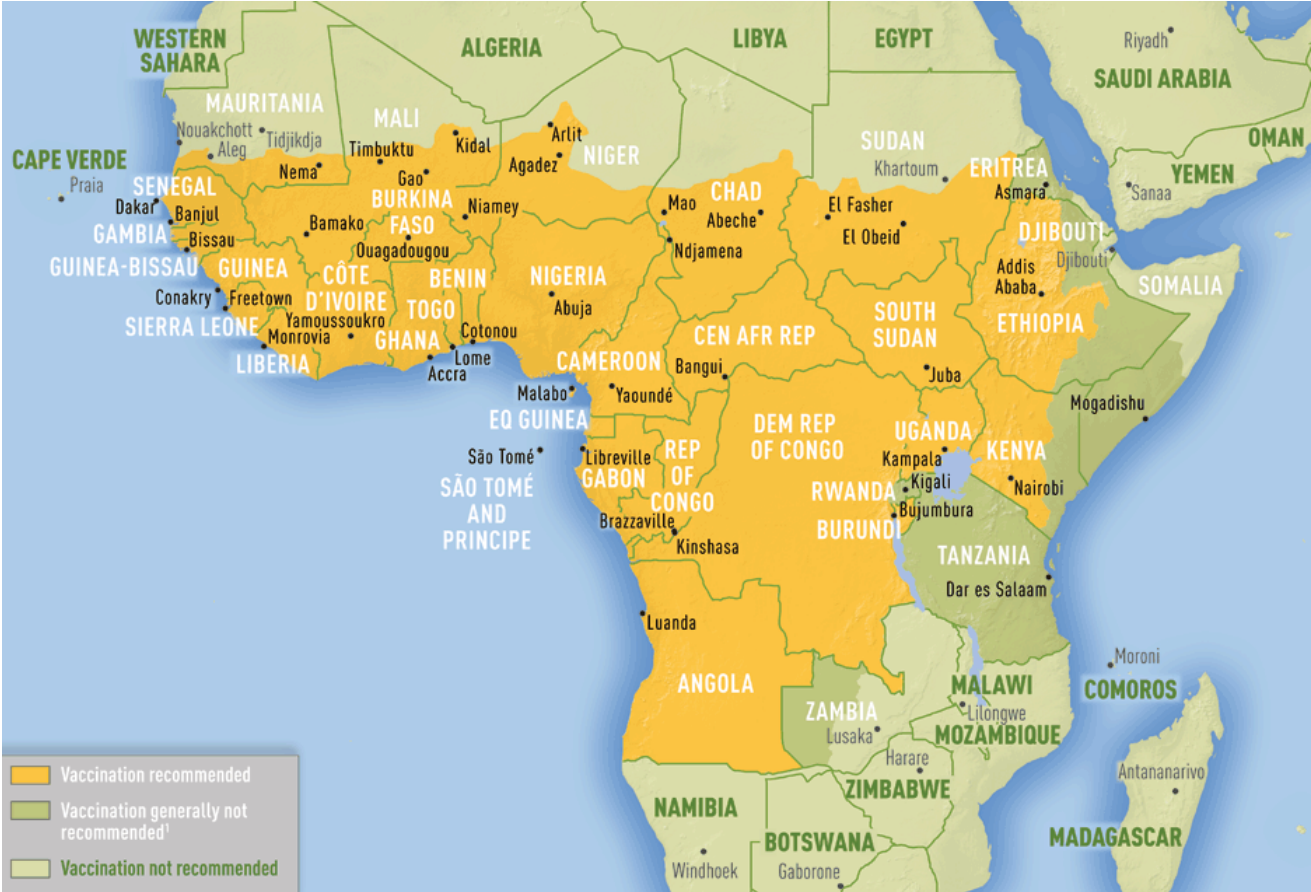
² These countries are not holoendemic (only a portion of the country has risk of yellow fever transmission). See Maps [3-15](#) and [3-16](#) and yellow fever vaccine recommendations ([Yellow Fever & Malaria Information, by Country](#)) for details.



Yellow fever vaccine recommendations in South America & in Africa



As of July 2015



RISK FOR TRAVELERS

- The risk of acquiring yellow fever is difficult to predict
- Influenced by
 - immunization status
 - location of travel
 - season
 - duration of exposure
 - occupational and recreational activities
 - local rate of virus transmission at the time of travel
 - “Epidemiologic silence” ≠ absence of risk
(low level of transmission, high level of immunity in the population, failure of local surveillance systems)



RISK FOR TRAVELERS

- In general, risk is greatest during the rainy season
 - In rural West Africa, usually July–October
 - In South America January–May, with a peak in February and March
- For a 2-week stay, the estimated risks of yellow fever for an unvaccinated traveler visiting an endemic area in
 - West Africa:
 - 50 per 100,000 for illness
 - 10 per 100,000 for death
 - South America:
 - 5 per 100,000 for illness
 - 1 per 100,000 for death



VACCINATION – ADVERSE EFFECTS

- Vaccination has been associated with anaphylaxis in 0.29 of every million doses
 - Vaccine is produced in chick embryos
 - Gelatin, which is added as a vaccine stabilizer, has been implicated in other hypersensitivity events

VACCINATION – ADVERSE EFFECTS

- Yellow fever vaccine–associated neurotropic disease (YEL-AND)
 - Majority of cases are aseptic meningitis, but it can include meningoencephalitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome
 - Since 1989 there have been 113 cases, one fatal
 - HA, fever (>38.6 C, 101.5° F), focal neurologic dysfunction, and AMS occurring 2 to 30 days after immunization, accompanied by CSF pleocytosis or elevated protein
- The rate of YEL-AND
 - In travelers is 2.5 to 8 per 1,000,000 doses
 - In endemic areas: 0.16 to 11 per 1,000,000 doses

VACCINATION – ADVERSE EFFECTS

- Yellow fever vaccine–associated viscerotropic disease (YEL-AVD)
 - Rare, mimics wild-type infection
 - Large quantities of vaccine virus detectable in tissues or blood
 - High fever, arthralgia, myalgia, HA, & vomiting usually within 2 to 5 days after immunization
 - elevated LFTs, thrombocytopenia and lymphocytopenia
 - Fulminant hepatitis, renal failure, coagulation disturbances, shock
 - Case-fatality rate: 63%
 - To date, more than 65 cases of have been reported — all known cases occurred in primary vaccinees
- The rate of YEL-AVD
 - In travelers is 2.5 to 4 per 1,000,000 doses
 - Rates are lower in endemic areas: 0.13 to 3 per 1,000,000 doses
- Host factors are thought to be responsible
 - In patients over age 70, the risk of contracting viscerotropic disease after YF vaccination is estimated to be 2.4 cases/100,000 vaccine doses



VACCINE CONTRAINDICATIONS

Because certain people have an increased risk of developing a serious adverse event if vaccinated with yellow fever vaccine, vaccine is not recommended (i.e., contraindicated) for people with:

- Allergy to a vaccine component
- Age <6 months
- Symptomatic HIV infection or CD4+ T-lymphocytes <200/mm³ (<15% of total in children aged <6 years)
- Thymus disorder associated with abnormal immune function
- Primary immunodeficiencies
- Malignant neoplasms
- Transplantation
- Immunosuppressive and immunomodulatory therapies

Some people may have an increased risk of an adverse event, but they may benefit from receiving the vaccine. Talk to your healthcare provider if you have any of the following:

- Age 6 to 8 months ← except during epidemics when the risk of YFV transmission may be very high
- Age ≥60 years
- Asymptomatic HIV infection and CD4+ T-lymphocytes 200 to 499/mm³ (15-24% of total in children aged <6 years)
- Pregnancy ← pregnant or nursing women may be vaccinated during epidemics or if travel to a country or area at risk of transmission is unavoidable
- Breastfeeding

VACCINATION – ADVERSE EFFECTS

- YF vaccine is contraindicated in infants younger than 6 months of age (well-established risk for vaccine-associated encephalitis in infants)
- The potential risk of administration of vaccine in pregnancy is unclear
 - In one study the vaccine was less immunogenic in pregnant women (39% seroconversion)
 - In another study it was as immunogenic (95% seroconversion) as the general population
 - No adverse events were reported in pregnant women, but there has been a case reported where cord blood IgM viral antibodies were detected, indicating congenital infection but without evidence of birth defects

OTHER ASPECTS OF PREVENTION

- Surveillance of viral activity: Discovery of intensified viral activity → Trigger timely and effective mass immunization
 - Assessing non-human primates in South America
 - Surveys to detect dead monkeys on the forest floor are conducted to monitor viral transmission and risk for its spillover to humans
 - Monitoring viral infection rates in sylvatic mosquitoes has been proposed as an early warning system for West and Central Africa, where outbreaks frequently emerge in a region-wide distribution
 - Limitation — “human landing capture studies are the most appropriate method to obtain adult mosquitoes capable of transmitting YFV”
- Similar to the approach for dengue control: Cover containers of water to eliminate mosquito breeding



WHERE MIGHT YELLOW FEVER GO NEXT?

An ongoing outbreak of yellow fever in Angola has scientists worried that the virus might spread to cities that harbour its urban carrier, the *Aedes aegypti* mosquito.

