

Yellow fever

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Yellow fever is an acute viral disease.^[3] In most cases, symptoms include fever, chills, loss of appetite, nausea, muscle pains particularly in the back, and headaches.^[3] Symptoms typically improve within five days.^[3] In some people within a day of improving, the fever comes back, abdominal pain occurs, and liver damage begins causing yellow skin.^[3] If this occurs, the risk of bleeding and kidney problems is also increased.^[3]

The disease is caused by the yellow fever virus and is spread by the bite of an infected female mosquito.^[3] It infects only humans, other primates, and several species of mosquitoes.^[3] In cities, it is spread primarily by mosquitoes of the *Aedes aegypti* type.^[3] The virus is an RNA virus of the genus *Flavivirus*.^[4] The disease may be difficult to tell apart from other illnesses, especially in the early stages.^[3] To confirm a suspected case, blood sample testing with polymerase chain reaction is required.^[5]

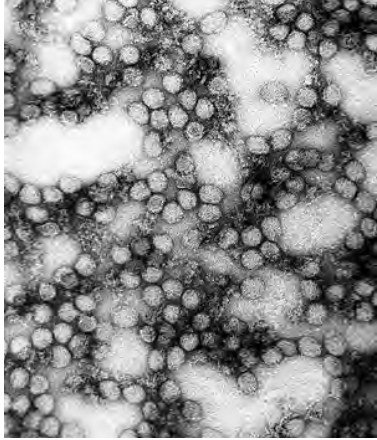
A safe and effective vaccine against yellow fever exists and some countries require vaccinations for travelers.^[3] Other efforts to prevent infection include reducing the population of the transmitting mosquito.^[3] In areas where yellow fever is common and vaccination is uncommon, early diagnosis of cases and immunization of large parts of the population is important to prevent outbreaks.^[3] Once infected, management is symptomatic with no specific measures effective against the virus.^[3] The second and more severe phase results in death in up to half of people without treatment.^{[3][6]}

Yellow fever causes 200,000 infections and 30,000 deaths every year,^[3] with nearly 90% of these occurring in Africa.^[5] Nearly a billion people live in an area of the world where the disease is common.^[3] It is common in tropical areas of South America and Africa, but not in Asia.^{[3][7]} Since the 1980s, the number of cases of yellow fever has been increasing.^{[3][8]} This is believed to be due to fewer people being immune, more people living in cities, people moving frequently, and changing climate.^[3] The disease originated in Africa, from where it spread to South America through the slave trade in the 17th century.^[1] Since the 17th century, several major outbreaks of the disease have occurred in the Americas, Africa, and Europe.^[1] In the 18th and 19th centuries, yellow fever was seen as one of the most dangerous infectious diseases.^[1] In 1927 yellow fever virus became the first human virus to be isolated.^{[4][9]}

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Synonyms yellow jack, yellow plague,^[1] bronze john^[2]



A TEM micrograph of the yellow fever virus (234,000X magnification)

Classification and external resources

Specialty	Infectious disease
ICD-10	A95 (http://apps.who.int/classifications/icd10/browse/2016/en#/A95)
ICD-9-CM	060 (http://www.icd9data.com/getICD9Code.aspx?icd9=060)
DiseasesDB	14203 (http://www.diseasesdatabase.com/ddb14203.htm)
MedlinePlus	001365 (https://medlineplus.gov/ency/article/001365.htm)
eMedicine	med/2432 (http://www.emedicine.com/med/topic2432.htm) emerg/645 (http://www.emedicine.com/emerg/topic645.htm#)
MeSH	D015004 (https://www.nlm.nih.gov/cgi/mesh/2017/MB_cgi?field=uid&term=D015004)

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Signs and symptoms

Yellow fever begins after an incubation period of three to six days.^[10] Most cases only cause a mild infection with fever, headache, chills, back pain, fatigue, loss of appetite, muscle pain, nausea, and vomiting.^[11] In these cases, the infection lasts only three to four days.

In 15 percent of cases, however, people enter a second, toxic phase of the disease with recurring fever, this time accompanied by jaundice due to liver damage, as well as abdominal pain.^[12] Bleeding in the mouth, the eyes, and the gastrointestinal tract will cause vomit containing blood, hence the Spanish name for yellow fever, *vomito negro* ("black vomit").^[13] There may also be kidney failure, hiccups, and delirium.^{[14][15]}

The toxic phase is fatal in about 20 to 50 percent of cases, making the overall fatality rate for the disease about 3.0 to 7.5 percent.^{[16][17]} However, the fatality rate of those with the toxic phase of the disease may exceed 50%.^[18]

Surviving the infection provides lifelong immunity,^[19] and normally there is no permanent organ damage.^[20]

Cause

Yellow fever is caused by the yellow fever virus, a 40- to 50-nm-wide enveloped RNA virus, the type species and namesake of the family Flaviviridae.^[4] It was the first illness shown to be transmissible by filtered human serum and transmitted by mosquitoes, by Walter Reed around 1900.^[21] The positive-sense, single-stranded RNA is around 11,000 nucleotides long and has a single open reading frame encoding a polyprotein. Host proteases cut this polyprotein into three structural (C, prM, E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5); the enumeration corresponds to the arrangement of the protein coding genes in the genome.^[22] Minimal yellow fever virus (YFV) 3'UTR region is required for stalling of the host 5'-3' exonuclease XRN1. The UTR contains PKS3 pseudoknot structure which serves as a molecular signal to stall the exonuclease and is the only viral requirement for subgenomic flavivirus RNA (sfRNA) production. The sfRNAs are a result of incomplete degradation of the viral genome by the exonuclease and are important for viral pathogenicity.^[23] Yellow fever belongs to the group of hemorrhagic fevers.

<i>Yellow fever virus</i>
Virus classification
Group: Group IV (+)(ssRNA)
Order: <i>Unassigned</i>
Family: <i>Flaviviridae</i>
Genus: <i>Flavivirus</i>
Species: <i>Yellow fever virus</i>

The viruses infect, amongst others, monocytes, macrophages, and dendritic cells. They attach to the cell surface via specific receptors and are taken up by an endosomal vesicle. Inside the endosome, the decreased pH induces the fusion of the endosomal membrane with the virus envelope. The capsid enters the cytosol, decays, and releases the genome. Receptor binding, as well as membrane fusion, are catalyzed by the protein E, which changes its conformation at low pH, causing a rearrangement of the 90 homodimers to 60 homotrimers.^[22]

After entering the host cell, the viral genome is replicated in the rough endoplasmic reticulum (ER) and in the so-called vesicle packets. At first, an immature form of the virus particle is produced inside the ER, whose M-protein is not yet cleaved to its mature form and is therefore denoted as prM (precursor M) and forms a complex with protein E. The immature particles are processed in the Golgi apparatus by the host protein furin, which cleaves prM to M. This releases E from the complex which can now take its place in the mature, infectious virion.^[22]

Transmission

Yellow fever virus is mainly transmitted through the bite of the yellow fever mosquito *Aedes aegypti*, but other mostly *Aedes* mosquitoes such as the tiger mosquito (*Aedes albopictus*) can also serve as a vector for this virus. Like other arboviruses which are transmitted by mosquitoes, the yellow fever virus is taken up by a female mosquito when it ingests the blood of an infected human or other primate. Viruses reach the stomach of the mosquito, and if the virus concentration is high enough, the virions can infect epithelial cells and replicate there. From there, they reach the haemocoel (the blood system of mosquitoes) and from there the salivary glands. When the mosquito next sucks blood, it injects its saliva into the wound, and the virus reaches the bloodstream of the bitten person. Transovarial and transstadial transmission of the yellow fever virus within *A. aegypti*, that is, the transmission from a female mosquito to her eggs and then larvae, are indicated. This infection of vectors without a previous blood meal seems to play a role in single, sudden outbreaks of the disease.^[24]

Three epidemiologically different infectious cycles occur,^[8] in which the virus is transmitted from mosquitoes to humans or other primates.^[25] In the "urban cycle", only the yellow fever mosquito *A. aegypti* is involved. It is well adapted to urban areas and can also transmit other diseases, including Zika fever, dengue fever and chikungunya. The urban cycle is responsible for the major outbreaks of yellow fever that occur in Africa. Except in an outbreak in 1999 in Bolivia, this urban cycle no longer exists in South America.

Besides the urban cycle, both in Africa and South America, a sylvatic cycle (forest cycle or jungle cycle) is present, where *Aedes africanus* (in Africa) or mosquitoes of the genus *Haemagogus* and *Sabethes* (in South America) serve as vectors. In the jungle, the mosquitoes infect mainly non-human primates; the disease is mostly asymptomatic in African primates. In South America, the sylvatic cycle is currently the only way humans can become infected, which explains the low incidence of yellow fever cases on the continent. People who become infected in the jungle can carry the virus to urban areas, where *A. aegypti* acts as a vector. Because of this sylvatic cycle, the yellow fever cannot be eradicated.^[8]

In Africa, a third infectious cycle known as "savannah cycle" or intermediate cycle, occurs between the jungle and urban cycles. Different mosquitoes of the genus *Aedes* are involved. In recent years, this has been the most common form of transmission of yellow fever in Africa.^[26]

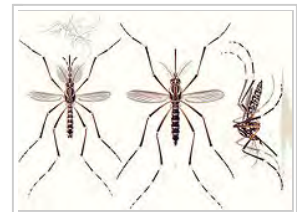
There is concern about yellow fever spreading to southeast Asia, where its vector *Aedes aegypti* already occurs.^[27]

Pathogenesis

After transmission from a mosquito, the viruses replicate in the lymph nodes and infect dendritic cells in particular. From there, they reach the liver and infect hepatocytes (probably indirectly via Kupffer cells), which leads to eosinophilic degradation of these cells and to the release of cytokines. Apoptotic masses known as Councilman bodies appear in the cytoplasm of hepatocytes.^{[28][29]}



Aedes aegypti feeding



Adults of the yellow fever mosquito *A. aegypti*: The male is on the left, females are on the right. Only the female mosquito bites humans to transmit the disease.

Fatality may occur when cytokine storm, shock, and multiple organ failure follow.^[16]

Diagnosis

Yellow fever is most frequently a clinical diagnosis, made on the basis of symptoms and the diseased person's whereabouts prior to becoming ill. Mild courses of the disease can only be confirmed virologically. Since mild courses of yellow fever can also contribute significantly to regional outbreaks, every suspected case of yellow fever (involving symptoms of fever, pain, nausea and vomiting six to 10 days after leaving the affected area) is treated seriously.

If yellow fever is suspected, the virus cannot be confirmed until six to 10 days after the illness. A direct confirmation can be obtained by reverse transcription polymerase chain reaction where the genome of the virus is amplified.^[5] Another direct approach is the isolation of the virus and its growth in cell culture using blood plasma; this can take one to four weeks.

Serologically, an enzyme linked immunosorbent assay during the acute phase of the disease using specific IgM against yellow fever or an increase in specific IgG-titer (compared to an earlier sample) can confirm yellow fever. Together with clinical symptoms, the detection of IgM or a fourfold increase in IgG-titer is considered sufficient indication for yellow fever. Since these tests can cross-react with other flaviviruses, like dengue virus, these indirect methods cannot conclusively prove yellow fever infection.

Liver biopsy can verify inflammation and necrosis of hepatocytes and detect viral antigens. Because of the bleeding tendency of yellow fever patients, a biopsy is only advisable *post mortem* to confirm the cause of death.

In a differential diagnosis, infections with yellow fever must be distinguished from other feverish illnesses like malaria. Other viral hemorrhagic fevers, such as Ebola virus, Lassa virus, Marburg virus, and Junin virus, must be excluded as cause.

Prevention

Personal prevention of yellow fever includes vaccination, as well as avoidance of mosquito bites in areas where yellow fever is endemic. Institutional measures for prevention of yellow fever include vaccination programmes and measures of controlling mosquitoes. Programmes for distribution of mosquito nets for use in homes are providing reductions in cases of both malaria and yellow fever. Usage of EPA-registered insect repellent is recommended when outdoors. A short duration of time is enough exposure for a potential mosquito bite. Long sleeved clothing, long pants, and socks are useful for prevention. The awareness of peak mosquito exposure is from dusk to dawn. The application of larvicides to water storage containers can help eliminate potential mosquito breeding sites. Adult mosquitos can be killed through insecticide spray usage, which decreases the transmission of yellow fever.^[30]

- Use insect repellent when outdoors such as those containing DEET, picaridin, IR3535, or oil of lemon eucalyptus on exposed skin.
- Wear proper clothing to reduce mosquito bites. When weather permits, wear long-sleeves, long pants and socks when outdoors. Mosquitoes may bite through thin clothing, so spraying clothes with repellent containing permethrin or another EPA-registered repellent will give extra protection. Clothing pre-treated with permethrin is commercially available. Mosquito repellents containing permethrin are not approved for application directly to skin.
- The peak biting times for many mosquito species is dusk to dawn. However, & ;*Aedes aegypti*, one of the mosquitoes that transmits yellow fever virus, feeds during the daytime. Staying in accommodations with screened or air-conditioned rooms, particularly during peak biting times, will also reduce risk of mosquito bites.

Vaccination

Vaccination is recommended for those traveling to affected areas, because non-native people tend to suffer more severe illness when infected. Protection begins by the 10th day after vaccine administration in 95% of people,^[31] and lasts for at least 10 years. About 81% of people are still immune after 30 years. The attenuated live vaccine stem 17D was developed in 1937 by Max Theiler.^[31] The World Health Organization (WHO) recommends routine vaccinations for people living in affected areas between the ninth and 12th month after birth.^[5] Up to one in four people experience fever, aches, and local soreness and redness at the site of injection.^[32]

In rare cases (less than one in 200,000 to 300,000^[31]), the vaccination can cause yellow fever vaccine-associated viscerotropic disease, which is fatal in 60% of cases. It is probably due to the genetic morphology of the immune system. Another possible side effect is an infection of the nervous system, which occurs in one in 200,000 to 300,000 cases, causing yellow fever vaccine-associated neurotropic disease, which can lead to meningoencephalitis and is fatal in less than 5%^[31] of cases.^{[5][16]}

In 2009, the largest mass vaccination against yellow fever began in West Africa, specifically Benin, Liberia, and Sierra Leone.^{[33][34]} When it is completed in 2015, more than 12 million people will have been vaccinated against the disease.^[33] According to the WHO, the mass vaccination cannot eliminate yellow fever because of the vast number of infected mosquitoes in urban areas of the target countries, but it will significantly reduce the number of people infected.^[33] The WHO plans to continue the vaccination campaign in another five African countries — the Central African Republic, Ghana, Guinea, Ivory Coast, and Nigeria — and stated that about 160 million people in the continent could be at risk unless the organization acquires additional funding to support widespread vaccinations.^[35]

In 2013, the WHO stated, "a single dose of vaccination is sufficient to confer life-long immunity against yellow fever disease."^[36]

Compulsory vaccination

Some countries in Asia are theoretically in danger of yellow fever epidemics (mosquitoes with the capability to transmit yellow fever and susceptible monkeys are present), although the disease does not yet occur there. To prevent introduction of the virus, some countries demand previous vaccination of foreign visitors if they have passed through yellow fever areas. Vaccination has to be proven in a vaccination certificate which is valid 10 days after the vaccination and lasts for 10 years. Although the WHO on 17 May 2013 advised that subsequent booster vaccinations are unnecessary, an older (than 10 years) certificate may not be acceptable at all border posts in all affected countries. A list of the countries that require yellow fever vaccination is published by the WHO.^[37] If the vaccination cannot be conducted for some reasons, dispensation may be possible. In this case, an exemption certificate issued by a WHO-approved vaccination center is required. Although 32 of 44 countries where yellow fever occurs endemically do have vaccination programmes, in many of these countries, less than 50% of their population is vaccinated.^[5]

Vector control



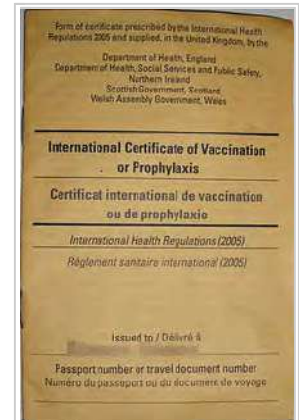
Information campaign for prevention of dengue and yellow fever in Paraguay

Control of the yellow fever mosquito *A. aegypti* is of major importance, especially because the same mosquito can also transmit dengue fever and chikungunya disease. *A. aegypti* breeds preferentially in water, for example in installations by inhabitants of areas with precarious drinking water supply, or in domestic waste; especially tires, cans, and plastic bottles. These conditions are common in urban areas in developing countries.

Two main strategies are employed to reduce mosquito populations. One approach is to kill the developing larvae. Measures are taken to reduce the water accumulations in which the larva develops. Larvicides are used, as well as larvae-eating fish and copepods, which reduce the number of larvae. For many years, copepods of the genus *Mesocyclops* have been used in

Vietnam for preventing dengue fever. It eradicated the mosquito vector in several areas. Similar efforts may be effective against yellow fever. Pyriproxyfen is recommended as a chemical larvicide, mainly because it is safe for humans and effective even in small doses.^[5]

The second strategy is to reduce populations of the adult yellow fever mosquito. Lethal ovitraps can reduce *Aedes* populations, but with a decreased amount of pesticide because it targets the mosquitoes directly. Curtains and lids of water tanks can be sprayed with insecticides, but application inside houses is not recommended by the WHO. Insecticide-treated mosquito nets are effective, just as they are against the *Anopheles* mosquito that carries malaria.^[5]



The cover of a certificate that confirms the holder has been vaccinated against yellow fever

Treatment

As for other flavivirus infections, no cure is known for yellow fever. Hospitalization is advisable and intensive care may be necessary because of rapid deterioration in some cases. Different methods for acute treatment of the disease have been shown to not be very successful; passive immunisation after emergence of symptoms is probably without effect. Ribavirin and other antiviral drugs, as well as treatment with interferons, do not have a positive effect in patients.^[16] A symptomatic treatment includes rehydration and pain relief with drugs such as paracetamol (acetaminophen in the United States). Acetylsalicylic acid (aspirin) should not be given because of its anticoagulant effect, which can be devastating in the case of internal bleeding that can occur with yellow fever.

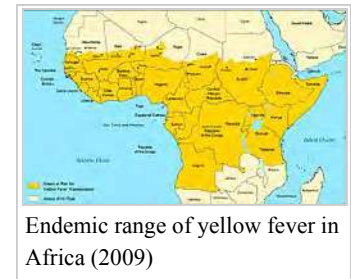
Epidemiology

Yellow fever is common in tropical and subtropical areas of South America and Africa. Worldwide, about 600 million people live in endemic areas. The WHO estimates 200,000 cases of disease and 30,000 deaths a year occur; the number of officially reported cases is far lower.

Africa

An estimated 90% of the infections occur on the African continent.^[5] In 2008, the largest number of recorded cases were in Togo.

In March 2016, the Chinese government confirmed the first imported case in a 32-year-old man who had been in Angola, the site of an ongoing outbreak of yellow fever.^[38] On 28 March 2016, ProMED-mail issued a warning that the yellow fever outbreak in Angola might spread further and that countries where dengue and the mosquito vector of dengue and yellow fever are present are at risk of a potential outbreak of yellow fever.^[39] Authorities are warning that a spread to Asia could be serious since vaccine stockpiles are insufficient.^[40]



Phylogenetic analysis identified seven genotypes of yellow fever viruses, and they are assumed to be differently adapted to humans and to the vector *A. aegypti*. Five genotypes (Angola, Central/East Africa, East Africa, West Africa I, and West Africa II) occur only in Africa. West Africa genotype I is found in Nigeria and the surrounding areas.^[41] This appears to be especially virulent or infectious, as this type is often associated with major outbreaks. The three genotypes in East and Central Africa occur in areas where outbreaks are rare. Two recent outbreaks in Kenya (1992–1993) and Sudan (2003 and 2005) involved the East African genotype, which had remained unknown until these outbreaks occurred.^[42]

South America

In South America, two genotypes have been identified (South American genotypes I and II).^[8] Based on phylogenetic analysis these two genotypes appear to have originated in West Africa^[43] and were first introduced into Brazil.^[44] The date of introduction into South America appears to be 1822 (95% confidence interval 1701 to 1911).^[44] The historical record shows an outbreak of yellow fever occurred in Recife, Brazil, between 1685 and 1690. The disease seems to have disappeared, with the next outbreak occurring in 1849. It was likely introduced with the importation of slaves through the slave trade from Africa. Genotype I has been divided into five subclades, A through E.^[45]

Asia

Though the main vector (*A. aegypti*) also occurs in tropical and subtropical regions of Asia, the Pacific and Australia, yellow fever does not occur in these parts of the globe. Proposed explanations include the idea that the strains of the mosquito in the East are less able to transmit the yellow fever virus, that immunity is present in the populations because of other diseases caused by related viruses (for example, dengue), and that the disease was never introduced because the shipping trade was

insufficient, but none are considered satisfactory.^{[46][47]} Another proposal is the absence of a slave trade to Asia on the scale of that to the Americas.^[48] The trans-Atlantic slave trade was probably the means of introduction into the Western hemisphere from Africa.^[49]

History



Carlos Finlay

The evolutionary origins of yellow fever most likely lie in Africa, with transmission of the disease from non-human primates to humans.^{[50][51]} The virus is thought to have originated in East or Central Africa and spread from there to West Africa. As it was endemic in Africa, the natives had developed some immunity to it. When an outbreak of yellow fever would occur in an African village where colonists resided, most Europeans died, while the native population usually suffered nonlethal symptoms resembling influenza.^[52] This phenomenon, in which certain populations develop immunity to yellow fever due to prolonged exposure in their childhood, is known as acquired immunity.^[53] The virus, as well as the vector *A. aegypti*, were probably transferred to North and South America with the importation of slaves from Africa, part of the Columbian Exchange following European exploration and colonization.



Walter Reed

The first definitive outbreak of yellow fever in the New World was in 1647 on the island of Barbados.^[54] An outbreak was recorded by Spanish colonists in 1648 in the Yucatán Peninsula, where the indigenous Mayan people called the illness *xekik* ("blood vomit"). In 1685, Brazil suffered its first epidemic, in Recife. The first mention of the disease by the name "yellow fever" occurred in 1744.^[55] McNeill argues that the environmental and ecological disruption caused by the introduction of sugar plantations created the conditions for mosquito and viral reproduction, and subsequent outbreaks of

yellow fever.^[56] Deforestation reduced insectivorous bird populations and other creatures that fed on mosquitoes and their eggs.

Although yellow fever is most prevalent in tropical-like climates, the northern United States were not exempted from the fever. The first outbreak in English-speaking North America occurred in New York in 1668, and a serious one afflicted Philadelphia in 1793.^[57] English colonists in Philadelphia and the French in the Mississippi River Valley recorded major outbreaks in 1669, as well as those occurring later in the 18th and 19th centuries.

The southern city of New Orleans was plagued with major epidemics during the 19th century, most notably in 1833 and 1853. At least 25 major outbreaks took place in the Americas during the 18th and 19th centuries, including particularly serious ones in Cartagena in 1741, Cuba in 1762 and 1900, Santo Domingo in 1803, and Memphis in 1878.^[58] There has been considerable debate over whether the number of deaths caused by disease in the Haitian Revolution of the 1780s was exaggerated.^[59]

Major outbreaks have also occurred in southern Europe. Gibraltar lost many to outbreaks in 1804, in 1814, and again in 1828.^[60] Barcelona suffered the loss of several thousand citizens during an outbreak in 1821. Urban epidemics continued in the United States until 1905, with the last outbreak affecting New Orleans.^[61]

In Colonial times and during the Napoleonic Wars, the West Indies were known as a particularly dangerous posting for soldiers due to the presence of yellow fever. The mortality rate in British garrisons in Jamaica was seven times that of garrisons in Canada, mostly because of yellow fever and other tropical disease like malaria.^[62] Both English and French forces posted there were seriously affected by the "yellow jack." Wanting to regain control of the lucrative sugar trade in Saint-Domingue (Hispaniola), and with an eye on regaining France's New World empire, Napoleon sent an army under the command of his brother-in-law to Saint-Domingue to seize control after a slave revolt. The historian J. R. McNeill asserts that yellow



Endemic range of yellow fever in South America (2009)



Sugar curing house, 1762. Sugar pots and jars on sugar plantations served as breeding place for larvae of *A. aegypti*, the vector of yellow fever.

fever accounted for about 35,000 to 45,000 casualties of these forces during the fighting.^[63] Only one-third of the French troops survived for withdrawal and return to France. Napoleon gave up on the island, and in 1804 Haiti proclaimed its independence as the second republic in the Western Hemisphere.

The yellow fever epidemic of 1793 in Philadelphia, which was then the capital of the United States, resulted in the deaths of several thousand people, more than 9% of the population. The national government fled the city, including President George Washington.^[64] Additional yellow fever epidemics struck Philadelphia, Baltimore, and New York in the 18th and 19th centuries, and traveled along steamboat routes from New Orleans. They caused some 100,000–150,000 deaths in total.^[65]

In 1853, Cloutierville, Louisiana, had a late summer outbreak of yellow fever that quickly killed 68 of the 91 inhabitants. A local doctor concluded that some unspecified infectious agent had arrived in a package from New Orleans.^{[66][67]} In 1858, St. Matthew's German Evangelical Lutheran Church in Charleston, South Carolina, suffered 308 yellow fever deaths, reducing the congregation by half.^[68] A ship carrying persons infected with the virus arrived in Hampton Roads in southeastern Virginia in June 1855.^[69] The disease spread quickly through the community, eventually killing over 3,000 people, mostly residents of Norfolk and Portsmouth. In 1873, Shreveport, Louisiana, lost almost a quarter of its population to yellow fever. In 1878, about 20,000 people died in a widespread epidemic in the Mississippi River Valley.^[70] That year, Memphis had an unusually large amount of rain, which led to an increase in the mosquito population. The result was a huge epidemic of yellow fever.^[71] The steamship *John D. Porter* took people fleeing Memphis northward in hopes of escaping the disease, but passengers were not allowed to disembark due to concerns of spreading yellow fever. The ship roamed the Mississippi River for the next two months before unloading her passengers.^[72] The last major U.S. outbreak was in 1905 in New Orleans.^{[8][73]}

Ezekiel Stone Wiggins, known as the Ottawa Prophet, proposed that the cause of a yellow fever epidemic in Jacksonville, Florida, in 1888, was astronomical.

The planets were in the same line as the sun and earth and this produced, besides Cyclones, Earthquakes, etc., a denser atmosphere holding more carbon and creating microbes. Mars had an uncommonly dense atmosphere, but its inhabitants were probably protected from the fever by their newly discovered canals, which were perhaps made to absorb carbon and prevent the disease.^[74]

In 1848 Josiah C. Nott suggested that yellow fever was spread by insects such as moths or mosquitoes, basing his ideas on the pattern of transmission of the disease.^[75] Carlos Finlay, a Cuban doctor and scientist, proposed in 1881 that yellow fever might be transmitted by mosquitoes rather than direct human contact.^{[76][77]} Since the losses from yellow fever in the Spanish–American War in the 1890s were extremely high, Army doctors began research experiments with a team led by Walter Reed, composed of doctors James Carroll, Aristides Agramonte, and Jesse William Lazear. They successfully proved Finlay's "mosquito hypothesis". Yellow fever was the first virus shown to be transmitted by mosquitoes. The physician William Gorgas applied these insights and eradicated yellow fever from Havana. He also campaigned against yellow fever during the construction of the Panama Canal, after a previous effort on the part of the French failed (in part due to mortality from the high incidence of yellow fever and malaria, which killed many workers).^[8]

Although Dr. Reed has received much of the credit in United States history books for "beating" yellow fever, he had fully credited Dr. Finlay with the discovery of the yellow fever vector, and how it might be controlled. Reed often cited Finlay's papers in his own articles, and also gave him credit for the discovery in his personal correspondence.^[78] The acceptance of Finlay's work was one of the most important and far-reaching effects of the Walter Reed Commission of 1900.^[79] Applying methods first suggested by Finlay, the United States government and Army eradicated yellow fever in Cuba and later in Panama, allowing completion of the Panama Canal. While Reed built on the research of Carlos Finlay, historian François Delaporte notes that yellow fever research was a contentious issue. Scientists, including Finlay and Reed, became



Yellow Fever Epidemic of 1878 can still be found in New Orleans' cemeteries.



Yellow fever in Buenos Aires, 1871

successful by building on the work of less prominent scientists, without always giving them the credit they were due.^[80] Reed's research was essential in the fight against yellow fever. He should also receive full credit for his use of the first type of medical consent form during his experiments in Cuba, an attempt to ensure that participants knew they were taking a risk by being part of testing.^[81]



Max Theiler

During 1920–23, the Rockefeller Foundation's International Health Board (IHB) undertook an expensive and successful yellow fever eradication campaign in Mexico. The IHB gained the respect of Mexico's federal government because of the success. The eradication of yellow fever strengthened the relationship between the US and Mexico, which had not been very good in the past. The eradication of yellow fever was also a major step toward better global health.^[82]

In 1927, scientists isolated the yellow fever virus in West Africa.^[83] Following this, two vaccines were developed in the 1930s. The vaccine 17D was developed by the South African microbiologist Max Theiler at the Rockefeller Institute in New York City. This vaccine was widely used by the U.S. Army during World War II.^[54] Following the work of Ernest Goodpasture, Theiler used chicken eggs to culture the virus and won a Nobel Prize in 1951 for this achievement. A French team developed the French neurotropic vaccine (FNV), which was extracted from mouse brain tissue. Since this vaccine was associated with a higher incidence of encephalitis, FNV was not recommended after 1961. 17D is still in use and more than 400 million doses have been distributed. Little research has been done to develop new vaccines. Some researchers worry that the 60-year-old technology for vaccine production may be too slow to stop a major new yellow fever epidemic. Newer vaccines, based on vero cells, are in development and should replace 17D at some point.^[5]

Using vector control and strict vaccination programs, the urban cycle of yellow fever was nearly eradicated from South America. Since 1943, only a single urban outbreak in Santa Cruz de la Sierra, Bolivia, has occurred. But, since the 1980s, the number of yellow fever cases has been increasing again, and *A. aegypti* has returned to the urban centers of South America. This is partly due to limitations on available insecticides, as well as habitat dislocations caused by climate change. It is also because the vector control program was abandoned. Although no new urban cycle has yet been established, scientists believe this could happen again at any point. An outbreak in Paraguay in 2008 was thought to be urban in nature, but this ultimately proved not to be the case.^[5]

In Africa, virus eradication programs have mostly relied upon vaccination. These programs have largely been unsuccessful because they were unable to break the sylvatic cycle involving wild primates. With few countries establishing regular vaccination programs, measures to fight yellow fever have been neglected, making the future spread of the virus more likely.^[5]

Research

In the hamster model of yellow fever, early administration of the antiviral ribavirin is an effective early treatment of many pathological features of the disease.^[84] Ribavirin treatment during the first five days after virus infection improved survival rates, reduced tissue damage in the liver and spleen, prevented hepatocellular steatosis, and normalised levels of alanine aminotransferase, a liver damage marker. The mechanism of action of ribavirin in reducing liver pathology in yellow fever virus infection may be similar to its activity in treatment of hepatitis C, a related virus.^[84] Because ribavirin had failed to improve survival in a virulent rhesus model of yellow fever infection, it had been previously discounted as a possible therapy.^[85] Infection was reduced in mosquitoes with the wMel strain of *Wolbachia*.^[86]

In the past, yellow fever has been researched by several countries as a potential biological weapon.^[87]

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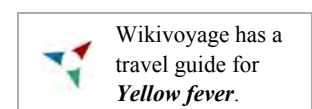
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- Yellow fever



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