Yellow Fever

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Introduction

Yellow fever is a rapidly-evolving acute hemorrhagic disease caused by a single-stranded RNA arbovirus of the family *Flaviviridae*. The virus is spread through the bite of an infected mosquito.

According to historians, the first confirmed epidemic of yellow fever in the Americas was in 1647 in Barbados. However, records of yellow fever outbreaks in the Americas date back at least two centuries before the classic Mayan period. The *Popol-Vuh*, sacred book of the Quiché Mayas, refers to the epidemic of a disease called “*xekik*” (black vomit or bloody vomit) prior to the arrival of the Spaniards, from 1480 to 1485, affecting monkeys and human-beings later on, who developed a yellowish skin color. The book clearly narrates the disease transmission path from monkeys to human-beings: “by a mosquito created by the Gods”.

In 1881, at the end of the 19th century, a Cuban clinician and researcher, Carlos Juan Finlay y Barrés, discovered and described the importance of a biological mosquito vector —*Aedes aegypti* (then known as *Stegomyia fasciata*)— in the transmission of yellow fever. His theory on the transmission of yellow fever through an intermediary agent was not well accepted by the health community. However, he was able to publish it in the New Orleans Medical and Surgical Journal.

Also in 1881, Finlay verified his hypothesis through clinical research conducted on volunteers and discovered that an individual bitten once by an infected mosquito remained protected against future yellow fever outbreaks. He presented his findings to the Havana Academy of Medical Sciences. Shortly afterwards, the Yellow Fever Commission, led by Army physician Walter Reed, documented yellow fever as a viral disease. William Gorgas applied the same principles on vector control as indicated by Finlay and was able to turn around the situation in the Panama Isthmus, future site of the Panama Canal.

It should be noted that the first conference held by the Pan-American Sanitary Bureau (PASB), the oldest international health agency in the world (predecessor to the Pan American Health Organization [PAHO]), was held in Washington, D.C. in November 1902. An important agreement point during the event was the recognition of yellow fever transmission through the bite of an infected mosquito.
The Agent

Yellow fever is caused by a single-stranded RNA arbovirus of the family Togoviridae, of the genus Flavivirus, with only one serotype and five genotypes. This virus is related to the West Nile, the San Louis encephalitis, and the Japanese encephalitis viruses. It replicates in the cytoplasm of affected cells. The virions are 40 nm in diameter and the viral envelope comprises a host-membrane derived lipid bilayer. The E protein on the surface is responsible for the initial phases of the infection in the host cells and it is also the main target for the host immune response.  

Epidemiology and Transmission

Yellow fever is endemic in 10 Latin American countries and more than 30 Sub-Saharan African countries. Based on recent World Health Organization (WHO) reports, globally there are an estimated 130,000 to 200,000 cases of yellow fever yearly, causing 44,000 deaths in endemic African countries, which account for 90% of the cases.  

There are three transmission cycles: 1) the jungle cycle involves non-human primates as the reservoir and Haemagogus as the mosquito vector species; 2) the urban cycle involves human to human transmission and Aedes aegypti is the mosquito vector; and 3) in Africa, the intermediate (savannah) cycle involves transmission of the virus from monkeys to humans and from humans to humans though Aedes simpsoni and Aedes bromeliae mosquitos resulting in small outbreaks in villages.  

Despite its lesser magnitude as compared to the African continent, yellow fever continues to be a public health problem in the Americas, where the risk of yellow fever transmission still prevails. Based on the definition by WHO, these are countries or areas where “yellow fever has been reported currently or in the past, plus vectors and animal reservoirs currently exist.” From 2000 to 2013, more than 1,100 laboratory-confirmed cases were reported. Ninety-five percent of the cases were concentrated in four countries: Peru (54%), Bolivia (18%), Brazil (16%), and Colombia (7%). These countries are not holoendemic. Only some areas of the country are at risk for transmission of yellow fever.  

Risk Factors

The main risk factor is to enter any enzootic region without previous immunization against the yellow fever virus. Individuals from the tree felling sector face a higher risk since after tree cutting mosquitoes descend to the ground level. The disease is often more frequent at the end of the rainy season when vector density is high and individuals cut trees to prepare the land for crops or livestock. This explains why young adults aged 15 to 40 years are the most affected and the impact on men is fourfold higher than in women.  

Factors currently conditioning the urbanization of yellow fever are associated with land-use changes, climate change, and the high degree of infestation by Aedes aegypti in urban areas. A viremic individual who exits the jungle may be bitten by the urban vector and initiate the transmission chain. Migration of populations induced by social, political, and economic conflicts affecting any endemic country determine the emergence of temporary settlements of unvaccinated populations in the jungle.
Climate change and increased rainfall are impacting and will continue to impact, both directly and indirectly, the spread of vector-borne diseases. Since *A. aegypti* is the main urban vector for the transmission of dengue, chikungunya, Zika, and yellow fever, there is widespread interest in the potential impact of climate change on the bionomics and transmission of pathogens by this mosquito. Low temperatures limit vector distribution by killing larvae and mosquito eggs; however, *Aedes (Stegomyia) aegypti* has a broad distribution in tropical and subtropical areas of the Americas. It has been adequately established that warmer water temperatures shorten larva maturation and increases their capacity to produce more offspring during the transmission periods of several vector-borne disease.\(^8\)\(^{10}\)

The extrinsic incubation period of dengue and yellow fever viruses is also dependent on temperature: the warmer the ambient temperature, the shorter the incubation period from the time the mosquito imbibes the infective blood until the mosquito is able to transmit by bite. A warmer temperature would not only imply wider distribution of *Ae. aegypti* and faster mosquito metamorphosis but also dengue and yellow fever viruses as well as other viruses would have a shorter extrinsic incubation period, cycle faster in the mosquito and thus increase the rate of epidemic transmission.\(^9\)

**Recent Yellow Fever Outbreaks in the Americas**

Starting in the 1970’s the area of emergence of jungle yellow fever cases has been restricted to the Northern region of the South-American Hemisphere. From 1985 to December 2007, a total of 3,837 human cases of jungle yellow fever and 2,229 deaths were reported. In 2007 and early 2008, there were intense and widespread jungle yellow fever epizootics in an area comprising six Brazilian states (Goias, Distrito Federal, Mato Grosso do Sul, Minas Gerais, Tocantins, and São Paulo). The epizootics were laboratory confirmed and/or used clinical-epidemiological criteria for confirmation through the state Health Departments. In January and February 2008, human cases were reported in three states (Goias, Mato Grosso do Sul, and Distrito Federal): 26 were confirmed cases with 13 deaths. The affected areas have high vaccination coverage. However, as part of the control measures the health authorities intensified their vaccination activities for previously-unvaccinated individuals aged six months and older, residing or travelling to the affected areas.\(^11\)\(^{12}\)

**Re-Emergence of Urban Yellow Fever in Paraguay, 2008**

In 2008, jungle yellow fever cases were documented in the departments of San Isidro and San Pedro in Paraguay. A few weeks later, 24 cases of yellow fever with 8 deaths were confirmed (several more individuals were assumed to have been infected) in the districts of San Pedro, Caaguazú, Laurelty district, and the metropolitan capital area of Asunció. This marked the first urban outbreak of yellow fever in Paraguay since 1942.\(^13\)

The urban-rural transmission cycle may have been affected by environmental and demographic changes. The presence and transmission of the virus in urban-rural districts were confirmed; entomological studies did not detect *Haemagogus*; human transmission was assumed. The lethality of the outbreak was 33%. As a result of the support provided by PAHO/WHO, 850,000 vaccines were sourced from Brazil, 144,000 from Peru and 2 million doses were shipped by WHO Global Fund. With the support of the Spanish Cooperation Agency for International Development (AECID) and the Office of U.S. Foreign Disaster Assistance at the United States Agency for International Development (OFD/USAID), PAHO/WHO was able to implement emergency projects to escalate epidemiological surveillance, vector control, laboratory diagnosis, communication of risk, and complete vaccination in areas at risk.\(^14\) Upon implementation of vector-control measures and a mass immunization campaign, no more cases were reported.
The Disease: Clinical Presentation

After the virus is acquired and the 3-to-6-day incubation has elapsed, the infection may be in one of two phases: the acute phase or the toxic phase. In the acute phase of the infection, the disease ranges from a non-specific mild febrile state with myalgia, myalgia with intense back pain, migraines, shivers, loss of appetite to nausea or vomiting. It may be misinterpreted as severe malaria, hemorrhagic dengue fever, leptospirosis, or vital hepatitis (in particular the lethal manifestations of hepatitis B and D). Later on, most of the patients improve and symptoms disappear after 3 to 4 days. In the second phase, known as the classic manifestation, 15% of patients enter a more toxic phase within 24 hours of the initial remission. The patient quickly turns jaundiced and complain of abdominal pain with vomits. There may be oral, nasal, ocular, or gastric bleeding with bloody vomit or bloody stools and kidney function is impaired. Half of the patients who enter the toxic phase die within 10 to 14 days, while the rest recover without significant organ damage.15

Pathogenesis and Immunity

Knowledge of the pathogenesis of yellow fever is derived from experimental studies of the disease induced in non-human primates that usually express the viscerotropic infection, including virus replication in lymph nodes, the liver, the spleen, the heart, and the kidneys. Pathological changes in the liver and kidneys with apoptotic changes in Councilman bodies are also present. An increase of TNFα, IL-1 and IL6 has been confirmed in vaccine studies.15

A fast immune response follows infection with the yellow fever virus. During the first week of the disease, IgM antibodies are produced reaching their peak during the second week and decreasing over 1 to 2 months. By the end of the first week, specific neutralizing antibodies are developed as the main mediators of protection and lasting several years. These antibodies bind to proteins in the viral envelope and interfere with the binding and penetration of the yellow fever virus to the host-cell membrane. Some structural proteins (NS1 and NS2) of the virus are associated with the infected host-cell membrane and targeted for elimination through the immune system.6,15

Diagnosis

Diagnosis of yellow fever in tropical areas is challenging and may be misinterpreted as other hemorrhagic fevers (the Bolivian, Argentinean, and Venezuelan hemorrhagic fevers, and other Flaviviruses such as West Nile and Zika viruses), and other diseases. Diagnosis of yellow fever is usually based on clinical data.

Detection of neutralizing antibodies is the only useful test to determine immunity to yellow fever. Blood tests detect specific antibodies against the virus and diagnostic confirmation entails demonstration of a fourfold increase in the neutralizing antibody titers in patients without recent history of yellow fever vaccination, and exclusion of cross-reactions to other Flaviviruses. Otherwise, demonstration of the presence of the yellow fever virus, its antigens, or genome in tissue, blood, or biological fluids is difficult, particularly in the early stages. Other techniques are also used to identify the virus in blood samples or liver tissue obtained from an autopsy. These tests require highly-trained laboratory personnel, specialized material, and equipment.16
Treatment and Prognosis

There is no specific treatment or cure for people infected with the yellow fever virus, which underscores the importance of vaccination. In severe cases, treatment is symptomatic, aimed at reducing symptoms in particular through rehydration and control of potential hypotension. Global mortality is 5% amongst indigenous populations residing in endemic regions despite the fact that, for severe cases, epidemics or other non-indigenous populations, up to 50% of the patients may die. Some cases result in acute kidney failure and dialysis becomes a significant treatment. Severe cases need management at intensive care units. Notwithstanding the severity, once the disease is acquired infected persons gain immunity for life.\textsuperscript{6, 7,15}

Prevention

Yellow fever is a vaccine-preventable disease and vaccination is the most efficient measure against transmission. The vaccine was developed by Max Theiler and colleagues in 1936,\textsuperscript{17} and his contribution afforded him the Nobel Prize in 1950. The vaccine is considered effective and safe and it has been used for more than 70 years for the active immunization of children and adults against the infection caused by the yellow fever virus. From its creation, more than 600 million doses have been administered globally. The live attenuated 17D or 17DD vaccines from chick embryo tissue are safe and confer effective immunity with neutralizing antibodies for 90% of the vaccinated individuals within a 10-day period and for 99% at thirty days with only one dose. One dose provides immunity during ten years as of the tenth day of administration.\textsuperscript{15}

Other preventive measures entail reducing human exposure to mosquito bites and controlling mosquito reproduction. Some measures include: physical control associated with the protection of water reservoirs, elimination of mosquito breeding sites through environmental rearrangement and waste collection, and chemical control (i.e. the application of insecticides and larvicides to control pockets and biological control to focus on larva elimination).
Vaccine Prevention

The vaccine prevention strategy in regions at risk for yellow fever transmission is comprised of two components. The first one is the inclusion of the yellow fever vaccine in the national vaccination schedules at twelve months of age. The vaccine should be administered subcutaneously in one 0.5 mL dose, on the upper arm. Administration may be concomitant with any other vaccine, even with other live injectable vaccines, such as measles, MMR (measles, mumps and rubella), MR (measles, rubella) and chicken pox, provided they are administered with a separate syringe on different injection sites. The only exception is the cholera vaccine, which should not be administered concomitantly with the yellow fever vaccine; or any other attenuated vaccine such as MMR, chicken pox or herpes zoster. These vaccines should be administered with a minimum three-week interval to generate an adequate immune response. If the yellow fever vaccine is NOT administered concomitantly with other injectable live vaccines (measles, MMR, MR, and chicken pox), a four-week interval at least shall be observed in between applications. The vaccine is not recommended for pregnant women, individuals with egg allergies, immunocompromised individuals, or children aged <9 months.6,17,18

The second component of vaccine prevention is the implementation of mass vaccination campaigns to protect vulnerable groups of older adults in at risk areas. Assessment of the risk level may help establish priority areas for mass vaccination campaigns. The vaccine is not recommended for children <9 months and adults >60 years, individuals with egg allergies, pregnant women, breastfeeding women, individuals with primary immunodeficiencies and HIV due to potential adverse events.6,18

Likewise, the introduction of the yellow fever vaccine into the vaccination schedule as part of the National Immunization Program is recommended for countries with enzootic areas. As of 2016, 13 countries in Latin America with enzootic areas have introduced the yellow fever vaccine in their vaccination schedules as part of the Expanded Program on Immunization (EPI) (Figure 1). In Argentina, Brazil, and Suriname, the vaccine is administered exclusively in areas of potential risk. Vaccination coverage for children aged 1 year in yellow fever endemic countries has been close to 70% in the 2007–2011 period, yet it has been significantly impacted by vaccine shortage.
Figure 1. Countries at Risk for Yellow Fever Transmission and the Vaccination Strategies Used in the Region of the Americas, 2013

Source: World Health Organization Yellow Fever Working Group. Available at: http://www.who.int/ith/yellow-fever-risk-mapping/risk_mapping/en/.
Severe Adverse Events Associated with the Yellow Fever Vaccine

The yellow fever vaccine is considered one of the safest attenuated vaccines, with few associated adverse events. Adverse events, such as pain on the administration site, muscle pain or headaches, and potentially a febrile state have been reported. Vasconcelos et al. reported two deaths caused by the administration of the 17D-derived vaccine and recommended a safety review of this vaccine. Such events are extremely rare and need to be further studied as the authors noted “host factors, probably idiosyncratic reactions, might have had a substantial contributed to the unexpected outcome.”

To establish the incidence of adverse events associated with the 17D or 17DD-derived yellow fever vaccine, Thomas et al. conducted a systematic review of six studies on vaccination campaigns with open populations that included 94,500,528 individuals, with data mainly from Brazil (99%) resulting in an estimate of 0.51 Events Supposedly Attributable to Vaccination or Immunization (ESAVIs) /million doses administered.

In five retrospective reviews of the clinical histories of 60,698 individuals, no severe ESAVIs were confirmed. Most of the data (96%) was from the Hospital for Tropical Diseases in London: two studies with 35,723 children; four studies with 138 pregnant women; six studies with 191 HIV-positive individuals and a review of HIV+ patients, without severe ESAVIs reported.

Every country has their own database with different definitions, protocols, and surveillance mechanisms to identify and report cases and adverse events, as well as strategies for the clinical follow-up of cases. Drug monitoring from databases offers three estimates: low estimate for data from Brazil and Argentina; intermediate estimate for the United States Vaccine Adverse Event Reporting System (VAER) data and a high estimate for data from the United Kingdom and Switzerland. Active surveillance estimates are lower (authors suggest they were influenced by data from Brazil) while passive surveillance estimates are lower (and strongly influenced by the data from the London Hospital for Tropical Diseases dating back to 1950).

Neurotropic or Viscerotropic Disease

Severe adverse events include yellow fever vaccine-associated viscerotropic disease and yellow fever vaccine-associated neurotropic disease, known as YF-AVD and YF-AND, respectively. The neurotropic event has been reported in 26 cases (typically with full recovery) and the viscerotropic disease has been reported in 10 cases since 1990 (seven since 1996), with eight deaths (six of them had been vaccinated as a travel requirement to an endemic area and four affected inhabitants of endemic areas). Signs of an immune response elicited by the 17D-vaccine were found in tissue of the deceased individuals. The onset is abrupt at 3 to 5 days post vaccination, with multiple organ failure, and typical pathological findings. No risk factor has been identified. These cases have underscored the importance of guiding vaccination campaigns exclusively for populations exposed to the risk of acquiring the disease and the need to continuously promote the development of new vaccines against yellow fever.
Yellow Fever and International Health Regulations

WHO recommends the administration of the vaccine for travelers beyond urban areas in countries located in areas of Central and South America and parts of South-Saharan Africa. Yellow fever has unique status in the International Health Regulations (IHR, 2005), which outline requirements for proof of vaccination for people who travel to specific countries or enter select countries from an area where yellow fever is endemic.

The International Health Regulations indicate that travelers may be required to produce evidence of yellow fever vaccination as a condition to enter a country that so requires. Travelers without vaccination evidence could have the vaccine administered at the point of entry to the country or could be detained for up to six days to guarantee they are free from the yellow fever infection. The yellow fever vaccine is only administered at designated vaccination clinics where a sealed and signed “international certificate of vaccination or prophylaxis” (yellow card) is provided upon vaccination. This certificate is valid for 10 years after vaccination.

Previously, a booster dose was required every 10 years. In 2014, the WHO World Health Assembly adopted the recommendation to suspend the requirement for application of a booster at ten years of vaccination to persons at risk of exposure to transmission as established in the International Health Regulations as of June 2016.

PAHO/WHO Response Strategies to Outbreaks of Yellow Fever in the Region of the Americas

PAHO/WHO has developed a detailed map of yellow fever risk areas in the Americas (Figure 1) and enables countries to carry out mass preventive vaccination campaigns during inter-epidemic periods. Evidence-based plans have been developed to provide support and technical guidance to all countries facing outbreaks with the purpose of requesting support, including vaccine mobilization through the PAHO Revolving Fund.

Conclusion

Yellow fever is a significant cause of hemorrhagic fever in several African countries with more than 30,000 deaths yearly and, sporadically, in some South-American countries. Given the emergence of other diseases borne by the vector *Aedes aegypti*, such as dengue and, more recently, the Zika virus, there is great interest in the impact global warming may have and also in the risk of re-urbanization for yellow fever not only in tropical areas but also in more temperate areas.

The yellow fever vaccine is the most effective measure to avoid transmission. The WHO recommends the administration of the vaccine for any travel beyond urban areas in enzootic countries located in regions of Central and South America and areas of South-Saharan Africa. Likewise, the introduction of the yellow fever vaccine into the vaccination schedule as part of the Expanded Program on Immunization is recommended in enzootic countries.
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