Yellow Fever

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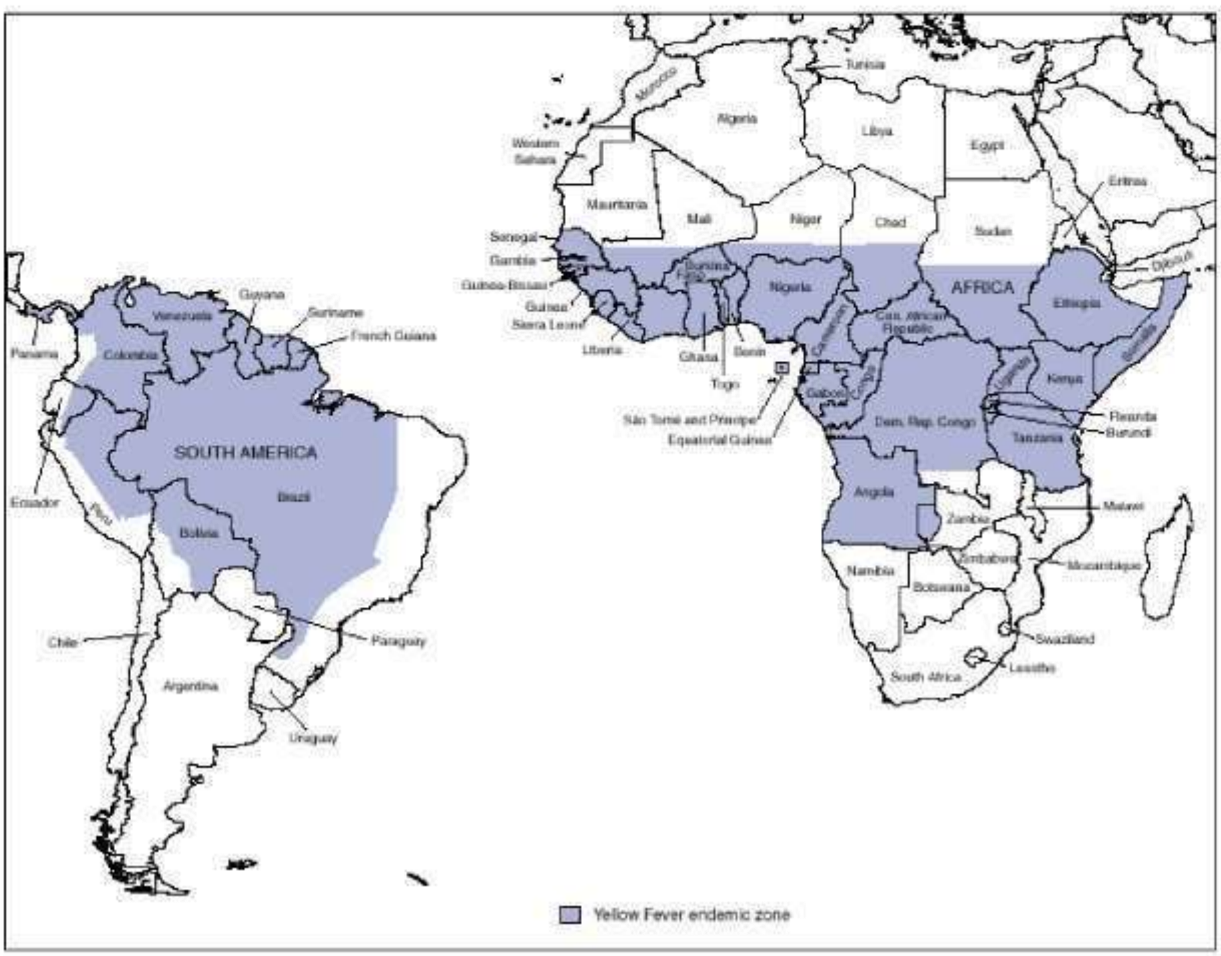
Introduction

Yellow fever is a viral disease that has caused large epidemics in Africa and the Americas. It can be recognized from historic texts stretching back 400 years. Infection causes a wide spectrum of disease, from mild symptoms to severe illness and death. The "yellow" in the name is explained by the jaundice that affects some patients. Although an effective vaccine has been available for 60 years, the number of people infected over the last two decades has increased and yellow fever is now a serious public health issue again.

FIGURE 1. Yellow Fever endemic zones



The disease is caused by the yellow fever virus, which belongs to the *flavivirus* group. In Africa there are two distinct genetic types (called topotypes) associated with East and West Africa. South America has two different types, but since 1974 only one has been identified as the cause of disease outbreaks.

Symptoms

The virus remains silent in the body during an incubation period of three to six days. There are then two disease phases. While some infections have no symptoms whatsoever, the first, "acute", phase is normally characterized by fever, muscle pain (with prominent backache), headache, shivers, loss of appetite, nausea and/or vomiting. Often, the high fever is paradoxically associated with a slow pulse. After three to four days most patients improve and their symptoms disappear.

However, 15% enter a "toxic phase" within 24 hours. Fever reappears and several body systems are affected. The patient rapidly develops jaundice and complains of abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes and/or stomach. Once this happens, blood appears in the vomit and feces. Kidney function deteriorates; this can range from abnormal protein levels in the urine (albumin) to complete kidney failure with no urine production (anuria). Half of the patients in the "toxic phase" die within 10-14 days. The remainder recover without significant organ damage.

Yellow fever is difficult to recognize, especially during the early stages. It can easily be confused with malaria, typhoid, rickettsial diseases, haemorrhagic viral fevers (e.g. Lassa), arboviral infections (e.g. dengue), leptospirosis, viral hepatitis and poisoning (e.g. carbon tetrachloride). A laboratory analysis is required to confirm a suspect case. Blood tests (serology assays) can detect yellow fever antibodies that are produced in response to the infection. Several other techniques are used to identify the virus itself in blood specimens or liver tissue collected after death. These tests require highly trained laboratory staff using specialized equipment and materials.

Regions Affected

The virus is constantly present with low levels of infection (i.e. endemic) in some tropical areas of Africa and the Americas. This viral presence can amplify into regular epidemics. Until the start of this century, yellow fever outbreaks also occurred in Europe, the Caribbean islands and Central and North America. Even though the virus is not felt to be present in these areas now, they must still be considered at risk for yellow fever epidemics.

Thirty-three countries, with a combined population of 508 million, are at risk in Africa. These lie within a band from 15°N to 10°S of the equator. In the Americas, yellow fever is endemic in nine South American countries and in several Caribbean islands. Bolivia, Brazil, Colombia, Ecuador and Peru are considered at greatest risk.

There are 200,000 estimated cases of yellow fever (with 30,000 deaths) per year. However, due to underreporting, only a small percentage of these cases are identified. Small numbers of imported cases also occur in countries free of yellow fever. Although yellow fever has never been reported from Asia, this region is at risk because the appropriate primates and mosquitoes are present.

Risk for Travelers

A traveler's risk of acquiring yellow fever is determined by various factors, including immunization status, location of travel, season, duration of exposure, occupational and recreational activities while traveling, and the local rate of virus transmission at the time of travel. Although reported cases of human disease are the principal indicator of disease risk, case reports may be absent because of a high level of immunity in the population (e.g., due to vaccination campaigns), or because cases are not detected by local surveillance systems. Only a small proportion of yellow fever cases is recognized and officially reported because the involved areas are often remote and lack specific diagnostic capabilities.

During interepidemic periods, low-level transmission may not be detected by public health surveillance. Such interepidemic conditions may last years or even decades in certain countries or regions. This "epidemiologic silence" does not equate to absence of risk and should not lead to travel without the protection provided by vaccination. Surveys in rural West Africa during "silent" periods have estimated an annual incidence of yellow fever of 1.1-2.4 cases per 1,000 persons and 0.2-0.5 deaths per 1,000 persons. YFV transmission in rural West Africa is seasonal, with elevated risk during the 2-4 months that the rainy season ends and the dry season begins (usually July-October); therefore, the annual incidence reflects incidence during a transmission season of 2-4 months.

The incidence of yellow fever in South America is lower than that in Africa because the mosquitoes that transmit the virus between monkeys in the forest canopy do not often come in contact with humans and because immunity in the indigenous human population is high. Urban epidemic transmission has not occurred in South America for many years, although the risk of introduction of the virus into towns and cities is ever present. For travelers, the risks of illness and death due to yellow fever are probably 10 times greater in rural West Africa than in South America; the risk varies greatly according to specific location and season. In West Africa, virus transmission is highest during the late rainy and early dry seasons

(July-October). In Brazil, the risk of infection is highest during the rainy season (January-March).

The low incidence of yellow fever in South America, generally a few hundred reported cases per year, could lead to complacency among travelers. However, it is important to note that four of the six cases of yellow fever reported among travelers from the United States and Europe in 1996-2002 acquired yellow fever in South America. All six cases were fatal and occurred among unvaccinated travelers. An increase in enzootic and epizootic yellow fever transmission in South America during the 1990s and the potential for epidemiologic change in the Americas remains a concern.

The risk of acquiring yellow fever is difficult to predict because of variations in ecologic determinants of virus transmission. As a rough guideline, the risks of illness and death due to yellow fever in an unvaccinated traveler in endemic areas in West Africa during the highest risk season from July to October have been estimated at 100 per 100,000 and 20 per 100,000 per month, respectively; for a 2- week stay, the estimated risks of illness and death were 50 per 100,000 and 10 per 100,000, respectively. The risks of illness and death in South America are probably 10 times lower (5 per 100,000 and 1 per 100,000, respectively for a 2-week trip). These estimates are based on risk to indigenous populations and may not accurately reflect the true risk to travelers, who may have a different immunity profile, take precautions against getting bitten by mosquitoes, and have less outdoor exposure. Based on data for U.S. travelers during 1996-2004, the overall risk for serious illness and death due to yellow fever in travelers has been roughly estimated to be 0.05 -0.5 per 100,000 travelers to yellow fever-endemic areas. This range reflects an unvaccinated population of 10-90% and assumes that all travelers visiting holo-endemic countries are at risk and 10% of travelers to non holo- endemic countries are visiting risk areas.

Transmission

Humans and monkeys are the principal animals to be infected. The virus is carried from one animal to another (horizontal transmission) by a biting mosquito (the vector). The mosquito can also pass the virus via infected eggs to its offspring (vertical transmission). The eggs produced are resistant to drying and lie dormant through dry conditions, hatching when the rainy season begins. Therefore, the mosquito is the true reservoir of the virus, ensuring transmission from one year to the next.

Several different species of the *Aedes* and *Haemogogus* (S. America only) mosquitoes transmit the yellow fever virus. These mosquitoes are either domestic (i.e. they breed around houses), wild (they breed in the jungle) or semi-domestic types (they display a mixture of habits). Any region populated with these mosquitoes can potentially harbor the disease. Control programs successfully eradicated mosquito habitats in the past, especially in South America. However, these programs have lapsed over the last 30 years and mosquito populations have increased. This favors epidemics of yellow fever.

Infection in Humans

There are three types of transmission cycle for yellow fever: sylvatic, intermediate and urban. All three cycles exist in Africa, but in South America, only sylvatic and urban yellow fever occur.

- *Sylvatic (or jungle) yellow fever*: In tropical rainforests, yellow fever occurs in monkeys that are infected by wild mosquitoes. The infected monkeys can then pass the virus onto other mosquitoes that feed on them. These infected wild mosquitoes bite humans entering the forest resulting in sporadic cases of yellow fever. The majority of cases are young men working in the forest (logging, etc).

On occasion, the virus spreads beyond the affected individual.

- *Intermediate yellow fever*: In humid or semi-humid savannahs of Africa, small-scale epidemics occur. These behave differently from urban epidemics; many separate villages in an area suffer cases simultaneously, but fewer people die from infection. Semi-domestic mosquitoes infect both monkey and human hosts. This area is often called the "zone of emergence", where increased contact between man and infected mosquito leads to disease. This is the most common type of outbreak seen in recent decades in Africa. It can shift to a more severe urban-type epidemic if the infection is carried into a suitable environment (with the presence of domestic mosquitoes and unvaccinated humans).

- *Urban yellow fever*: Large epidemics can occur when migrants introduce the virus into areas with high human population density. Domestic mosquitoes (of one species, Aedes aegypti) carry the virus from person to person; no monkeys are involved in transmission. These outbreaks tend to spread outwards from one source to cover a wide area.

Treatment

There is no specific treatment for yellow fever. Dehydration and fever can be corrected with oral rehydration salts and paracetamol. Any superimposed bacterial infection should be treated with an appropriate antibiotic. Intensive supportive care may improve the outcome for seriously ill patients, but is rarely available in poorer, developing countries.

Prevention

Vaccination is the single most important measure for preventing yellow fever. In populations where vaccination coverage is low, vigilant surveillance is critical for prompt recognition and rapid control of outbreaks. Mosquito control measures can be used to prevent virus transmission until vaccination has taken effect.

Vaccination

Yellow fever vaccine is safe and highly effective. The protective effect (immunity) occurs within one week in 95% of people vaccinated. A single dose of vaccine provides protection for 10 years and probably for life. Over 300 million doses have been given and serious side effects are extremely rare. However, recently a few serious adverse outcomes, including deaths, have been reported in Brazil, Australia and the United States. Scientists are investigating the cause of these adverse events, and monitoring to ensure detection of any similar incidents.

The risk to life from yellow fever is far greater than the risk from the vaccine, so those who may be exposed to yellow fever should be protected by immunization. If there is no risk of exposure, for example, if a person will not be visiting an endemic area, there is no necessity to receive the vaccine. Since most of the other known side effects have occurred in children less than six months old, vaccine is not administered to this age group. The vaccine should only be given to pregnant women during vaccination campaigns in the midst of an epidemic.

Vaccination can be part of a routine preventive immunization program or can be done in mass "catch-up" campaigns to increase vaccination coverage in areas where it is low. The World Health Organization (WHO) strongly recommends routine childhood vaccination. The vaccine can be administered at age nine months, at the same time as the measles vaccine. Eighteen African nations have agreed to incorporate yellow fever vaccine into their routine national vaccination programs. This is more cost effective and prevents more cases (and deaths) than when emergency vaccination campaigns are performed to control an epidemic.

Past experience shows the success of this strategy. Between 1939 and 1952 yellow fever cases almost vanished from French West Africa after intensive vaccination campaigns. Similarly, Gambia instituted mass routine vaccination after its 1979/1980 epidemic and later incorporated yellow fever vaccine into its childhood immunization program. Gambia reported 85% vaccine coverage in 2000. No cases have been reported since 1980, yet the virus remains present in the environment.

To prevent an epidemic in a country, at least 80% of the population must have immunity to yellow fever. This can only be achieved through the effective incorporation of yellow fever into childhood immunization programs and the implementation of mass catch-up campaigns. The latter is the only way to ensure that coverage of all susceptible age groups is achieved and will prevent outbreaks from spreading. Very few countries in Africa have achieved this level to date.

Vaccination is highly recommended for travelers to high-risk areas. A vaccination certificate is required for entry to many countries, particularly for travelers arriving in Asia from Africa or South America. Fatal cases in unvaccinated tourists have been reported.

Surveillance

Because vaccination coverage in many areas is not optimal, prompt detection of yellow fever cases and rapid response (emergency vaccination campaigns) are essential for controlling disease outbreaks. Improvement in yellow fever surveillance is needed as evidenced by the gross underreporting of cases (estimates as to the true number of cases vary widely and have put the underreporting factor between three- and 250-fold). A surveillance system must be sensitive enough to detect and appropriately investigate suspect cases. This is facilitated by a standardized definition of possible yellow fever cases, that is "acute fever followed by jaundice within two weeks of onset of symptoms, or with bleeding symptoms or with death within three weeks of onset". Suspect cases are reported to health authorities on a standardized case investigation form.

Ready access to laboratory testing is essential for confirming cases of yellow fever, as many other diseases have similar symptoms. WHO has recently recommended that every at-risk country have at least one national laboratory where basic yellow fever blood tests can be performed. Training programs are being conducted and test materials are provided by WHO.

Given the likelihood that other cases have occurred (but have not been detected), one confirmed case of yellow fever is considered to be an outbreak. An investigation team should subsequently explore and define the outbreak. This produces data for analysis, which guides the epidemic control committee in preparing the appropriate outbreak response (e.g. emergency vaccination programs, mosquito control activities). This committee should also plan for the long term by implementing or strengthening routine childhood yellow fever vaccination.

Mosquito Control

In general, eliminating potential mosquito breeding sites is an important and effective means for controlling mosquito-transmitted diseases. For prevention and control of yellow fever, priority is placed on vaccination programs. For example, mosquito control programs against wild mosquitoes in forested areas are not practical or cost-effective for preventing sylvatic infections. Spraying to kill adult mosquitoes during epidemics may have value by interrupting virus transmission. This "buys time" for immunity to develop after an emergency vaccination campaign.

Summary

Over the last 20 years the number of yellow fever epidemics has risen and more countries are reporting cases. Mosquito numbers and habitats are increasing. In both Africa and the Americas, there is a large susceptible, unvaccinated population. Changes in the world's environment, such as deforestation and urbanization, have increased contact with the mosquito/virus. Widespread international travel could play a role in spreading the disease. The priorities are vaccination of exposed populations, improved surveillance and epidemic preparedness.

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