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Yellow fever in Africa:
public health impact and prospects for control
in the 21st century

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In the last two decades, yellow fever re-emerged with vehemence to constitute a major public health problem in Africa. The disease has brought untold hardship and indescribable misery among different populations in Africa. It is one of Africa's stumbling blocks to economic and social development. Despite landmark achievements made in the understanding of the epidemiology of yellow fever disease and the availability of a safe and efficacious vaccine, yellow fever remains a major public health problem in both Africa and America where the disease affects annually an estimated 200,000 persons causing an estimated 30,000 deaths. Africa contributes more than 90% of global yellow fever morbidity and mortality. Apart from the severity in morbidity and mortality, which are grossly under reported, successive outbreaks of yellow fever and control measures have disrupted existing health care delivery services, overstretched scarce internal resources, fatigued donor assistance and resulted in gross wastage of vaccines. Recent epidemics of yellow fever in Africa have affected predominantly children under the age of fifteen years.

Yellow fever disease can be easily controlled. Two examples from Africa suffice to illustrate this point. Between 1939 and 1952, yellow fever virtually disappeared in parts of Africa, where a systematic mass vaccination programme was in place. More recently, following the 1978-1979 yellow fever epidemic in the Gambia, a mass yellow fever vaccination programme was carried out, with a 97% coverage of the population over 6 months of age. Subsequently, yellow fever vaccination was added to the EPI Programme. The Gambia has since then maintained a coverage of over 80%, without a reported case of yellow fever, despite being surrounded by Senegal which experienced yellow fever outbreaks in 1995 and 1996.

The resurgence of yellow fever in Africa and failure to control the disease has resulted from a combination of several factors, including: 1) collapse of health care delivery systems; 2) lack of appreciation of the full impact of yellow fever disease on the social and economic development of the affected communities; 3) insufficient political commitment to yellow fever control by governments of endemic countries; 4) poor or inadequate disease surveillance; 5) inappropriate disease control measures, and 6) preventable poverty coupled with misplaced priorities in resource allocation.

Yellow fever can be controlled in Africa within the next 10 years, if African governments seize the initiative for yellow fever control by declaring an uncompromising resolve to control the disease, the governments back up their resolve with an unrelenting commitment and unwavering political will through adequate budgetary allocations for yellow fever control activities, and international organisations, such as WHO, UNICEF, GAVI, etc., provide support and technical leadership and guidance to yellow fever at risk countries. Over a ten-year period, of stage-by-stage mass yellow fever vaccination campaigns, integrated with successful routine immunisation, Africa can bring yellow fever under control. Subsequently, for yellow fever to cease being a public health problem, Africa must maintain at least an annual 80% yellow fever vaccine coverage of children under the age of 1 year, and sustain a reliable disease surveillance system with a

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responsive disease control programme. This can be achieved at an affordable annual expenditure of less than US$1.00 per person per year, with a reordering of priorities.

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Historical review

Yellow fever (YF) is a disease of antiquity that has been called by as many names as the countries where the disease has been reported. According to Augustin (1909), "no disease under heaven has had more synonyms than yellow fever" (1). Beginning in 1494, when it was generally designated by the name 'contagion', it had by 1907 acquired 152 synonyms including American Pestilence, Barbados Distemper, Continua Putrida Icterioides Caroliniensis, Yellow Jack, etc. However, the term yellow fever, by which the disease is now known was first used by Griffin Hughes in 1750 in his Natural history of Barbadoes (1750)(2). While the origin is subject to much controversy, it is generally agreed that yellow fever disease originated in either of the two areas of the world, Africa and America, where it is currently endemic (3) (figure 1).

The earliest epidemics of YF occurred in Barbados, Cuba, Guadeloupe and Mexico between 1647 and 1649. For the next two centuries, tropical and subtropical America continued to suffer recurrent large urban epidemics of YF which "decimated populations, paralyzed industry and trade and held the people of the region in a state of endless fear of the Yellow Jack" (2). The disease was spread by trade ships to US ports, reaching New York (1668), Boston (1691) and Charleston, North Carolina (1699). As late as 1905, YF accounted for 5,000 cases and 1,000 deaths in port cities of southern United States. During the eighteenth century, the disease appeared in Italy, France and Spain. In 1800, over 60,000 deaths were associated with the Spanish YF epidemic (2).

Yellow fever has often changed the course of history. This was the case of the British attack on Cartagena in 1741 intended to destroy the Spanish power in the Caribbean. Arrayed against the Spanish military forces of 6 ships and 2,700 men were the overwhelming invading forces of the British force of 124 ships and 23,000 men (4). The silent ally of the Spaniards was yellow fever. Soon after their arrival to engage the Spaniards, the 'virgin' British soldiers became victims of the defenders guns as well as yellow fever and many of them started feeling feverish and developed a headache. Nausea and vomiting soon set in, with backache muscle pains. In many cases, the disease progressed to jaundice, with injected conjunctiva, and hemorrhage. At the end, the British not only lost the war, but also 8,400 men, representing approximately 37% of the army, and close to 50% of their men convalescing from the devastation and ravages of disease. On the other hand, the Spaniards, many of whom were not strangers to yellow fever, lost only 600 men, about 22% of their forces. But for YF outbreak of 1741 in Cartagena, today Colombia might have been under the influence of Britain, and the language of expression, English, instead of Spanish.

Epidemics of YF probably occurred in Africa much earlier than the documented outbreak of 1778, which reportedly decimated English troops stationed at Saint Louis, Senegal (1,3). It was, however, not until 1925 that serious investigations of the disease began in West Africa. In 1848, Josiah Nott, first floated the idea that mosquitoes may be serving as agents for the dissemination of both yellow fever and malaria (5). However, the full credit for the theory of mosquitoes as vectors for yellow fever transmission was given to Carlos Finlay of Havana, Cuba, who in 1881, proposed the theory in a paper presented before the Royal Academy at its session in Havana (1,2,6). Reed and colleagues later demonstrated that yellow fever is caused by a filterable agent, and that Aedes aegypti mosquitoes could transmit the disease (7). Following the successful eradication of yellow fever in Havana and Panama at the beginning of
1900s, through anti-mosquito measures (1,2), it was widely believed that A. aegypti mosquito was exclusively responsible for the transmission of yellow fever. It took the studies of Soper and co-workers to correct this widely held opinion (8). Their findings, later confirmed in other parts of the tropics (9,10) resulted in the elucidation of the concept of jungle yellow fever transmission involving wild monkeys and sylvatic mosquito species, and the realization that it would take more than antimosquito measures to control yellow fever. In 1927, Mahaffy and Bauer of the Rockefeller Yellow Fever Commission (RYFC), isolated yellow fever virus by inoculating the blood of a Ghanaian patient into rhesus monkeys (2). This strain, the Asibi strain, was attenuated by passage in chick embryo tissue and the modified (17D) virus later became the source of human YF vaccine (11,12). In other studies (13,14), the staff of RYFC confirmed that: 1) the causative agent of YF was a filterable virus; 2) the infection was easily transmitted from man to monkey or from monkey to monkey, by injection of citrated blood taken early in the disease; 3) that once infected, mosquitoes remained infective for life, which could be as long as 3 months or more, and 4) the bite of a single infected mosquito was sufficient to produce a fatal infection in a monkey. Despite these landmark achievements in the understanding of the epidemiology of YF disease and the availability of a safe and efficacious vaccine, YF remains a major public health problem in both Africa and America where annually, the disease affects an estimated 200,000 persons causing an

Figure 1. Countries at risk for yellow fever and having reported at least one outbreak, 1985 - 1999.

Figure 2. Age distribution of reported yellow fever cases during selected outbreaks, 1981-1991.
Using RNA oligonucleotide mapping, these genotypes have been segregated into three distinct non-overlapping regional topotypes or variants (22). The West African genotype consists of two variants, the Senegal-Gambia and the Cote d'Ivoire-Burkina Faso-Nigeria variants, while there is only one variant representing the Central Africa and East African genotype (22). The variants show considerable genetic stability over time, indicating that epidemics arise from local sources (23). One of the South American genotypes has not been recovered since 1974, suggesting that the virus may have been lost. All other South American strains fall into one major phylogenetic group, which in contrast to the African viruses, do not segregate into discrete geographical topotypes (21) (figure 3).

Yellow fever virus, a small (35 to 45 nm) virus, possesses a single stranded positive polarity genome containing 10,862 nucleotides with a relative molecular mass of 3.75 x 10^6. It encodes for three structural proteins and up to 12 nonstructural proteins, which are synthesized in infected cells (24). The genome is surrounded by an envelope, which contains a single glycoprotein with type and group specific antigenic determinants. Yellow fever virus is inactivated by ether, chloroform, sodium deoxycholate, proteases, lipases, by heat (56 °C for 30 minutes) and by ultraviolet light (25).

Yellow fever virus replicates in a wide variety of primary and continuous cell cultures (18). These include continuous monkey kidney (MA-104, Vero, LLC-MK2), baby hamster kidney (BHK), and porcine kidney cell lines as well as monolayers of primary chick and duck embryo fibroblast. Vaccine strains (17D and French neurotropic viruses) attain higher titers and produce more evident cytopathic effects (CPE), in these cultures. With wild strains, plaque formation is inconsistent and variable from strain to strain. Both 17D and parent Asibi virus grow in cell cultures of human origin, such as Chang liver cells, Henle embryonic intestine, HeLa and KB. Mosquito cell cultures are more sensitive that Vero cells or infant mice for primary isolation (18). While A. pseudoscutellaris (AP-61) cells consistently show CPE following infection with YF virus, infections of cloned A. aegypti and cells

![Figure 3. Distribution of yellow fever topotypes in Africa.](image_url)
can be demonstrated by immunofluorescence and/or subpassage of mice or Vero cells (18). Intrathoracic inoculation of *Toxorhinchites* or *A. aegypti* mosquitoes is another isolation or assay method for YF virus. After a 10-16 day incubation period, inoculated mosquitoes can be examined directly by immunofluorescence or by subpassaging to a susceptible host, e.g., suckling mice (18). Yellow fever virus produces both neurotropic and viscerotropic patterns of infection in a variety of vertebrate hosts. Infant mice are highly susceptible to encephalitis following either intraperitoneal or intracerebral inoculation with YF virus. However, there is considerable variation between strains in their neuropathogenicity for mice. Older mice, as well as guinea pigs, are susceptible by intracerebral route. Monkeys intracerebrally inoculated with wild-type virus develop encephalitis, but die of viscerotropic yellow fever. In man and non-human primates (*Rhesus cynomolgus* macaques, viscerotropism is characteristic of YF virus infection by the peripheral route (18). As reported for other flaviviruses (17,18), viral synthesis and maturation occurs predominantly in the rough endoplasmic reticulum of the host cell, while the site of formation of the envelope surrounding the virion remains unclear. Mature viral particles accumulate within the cisternae of membranous organelles and are released from the cell by exocytosis or by plasma membrane rupture. Host-cell macromolecular synthesis is not seriously affected by the YF infection (18). Treatment of cells with actinomycin D inhibits host cell RNA synthesis but does not affect viral RNA synthesis. Peak viral RNA synthesis occurs when the virus titre in the supernatant reaches a maximum. Three types of viral RNA are observed: the genome-size RNA with a sedimentation coefficient of 40S; the RNase-resistant RNA identified as the replicative intermediate, which is soluble in 2 mol/l HCl and sediments at about 20S; and the partially Rnase-resistant RNA, presumed to be the replicative form and sedimenting at about 28S (18).

### The disease

Yellow fever is an acute infectious disease characterized by a sudden onset with a two-phase development, separated by a short period of remission (17). The clinical spectrum of yellow fever varies from very mild, nonspecific, febrile illness to a fulminating, sometimes fatal disease with pathognomic features. Severe or classical YF, usually recognized during epidemics, begins abruptly, following an incubation period of 3-6 days or longer, after the bite of an infected mosquito. Fever (39-40 °C), chills, intense headache, lumbosacral and generalized muscular pains, nausea and vomiting, conjunctival injection are the signs and symptoms associated with the first phase or period of infection (17). This syndrome lasts 3-5 days. The urine at this stage is dark in color and may not contain albumin. A slow pulse in relation to the fever (Faget's sign) is also typical at this stage. A period of remission lasting 12-24 hours, generally follows. This is characterized by a fall in temperature, disappearance of the headache, and an improvement in the general condition of the patient. The remission phase is followed by the intoxication period or hepatorenal phase, which is marked by a rise in temperature, the reappearance of generalized symptoms, more frequent vomiting, epigastric pain, and prostration (17). Jaundice appears at this stage. Bleeding diathesis, another common feature of this phase, is manifested by coffee grounds hematemesis (vómito negro), melena, metrorrhagia, petechiae, ecchymoses, and diffuse oozing from the mucous membranes. Dehydration results from vomiting and insensible losses. Renal dysfunction is marked by a sudden increase in albuminuria and diminishing urine output. Progressive tachycardia, shock and intractable hiccups are considered ominous and terminal signs. The case fatality rate of severe yellow fever is 50% or higher. Death usually occurs between the seventh and the tenth day after onset. Convalescence, with profound asthenia may last 1-2 weeks.

### Treatment

In the absence of specific therapy, treatment of YF cases is chiefly supportive (17,18). Since most YF cases occur in areas lacking basic hospital facilities, they do not benefit from availability of modern intensive care. In the early stages of the disease, therapy should focus on controlling the fever and vomiting, relieving the headache and abdominal pains, and managing the dehydration.
During the stage of intoxication, suitable therapy based on careful patient monitoring should be administered to control the bleeding, and manifestations associated with hepatorenal damage. Appropriate treatment to control malaria and secondary bacterial infections should be administered where necessary (17,18).

**Diagnosis**

It is clinically difficult to distinguish YF disease from many other tropical conditions, and often impossible when the condition is mild or atypical. The clinical symptoms associated with the early stages of YF infection are indistinguishable from those of malaria, and where the two diseases co-exist, yellow fever should not be ruled out even in the absence of jaundice or the finding of malaria parasites in a blood smear. Other diseases resembling anicteric YF include typhoid fever, rickettsial infections, other arboviral fevers, and influenza. Yellow fever must also be differentiated from other diseases with hepatorenal dysfunction and/or hemorrhagic manifestations such as viral hepatitis, viral hemorrhagic fevers (Lassa fever, Marburg and Ebola virus diseases, Crimean-Congo hemorrhagic fever, Rift Valley fever), leptospirosis, etc. (17,18).

Laboratory diagnosis of YF requires special reagents and techniques as well as expertise in the interpretation of test results. Specific diagnosis depends on histopathologic studies, isolation of the virus, demonstration of viral antigen or a specific antibody response (17,18). For histopathology, liver samples may be obtained from fatal cases by abdominal incision or by the use of viscerotome or a large caliber biopsy needle. Liver samples obtained from a patient dying before the tenth or twelfth day after onset, is also suitable for virus isolation. Specimens should be divided into separate portions for virus isolation and for fixation and histopathology. Specimens for histopathology should be fixed in either Boiun's solution or 10% formalin. An examination of a paraffin section of a typical case of YF reveals an eosinophilic degeneration of the hepatocytes leading to the formation of Councilman's bodies, prominent midzonal necrosis and microvacuolar steatosis. However, histopathology of other infections, such as Lassa fever, Marburg and Ebola virus diseases, Crimean-Congo hemorrhagic fever, viral hepatitis, and leptospirosis, may be easily confused with that of YF. The virus is most readily isolated from acute stage serum obtained during the first 4 days of illness, but may be recovered from serum up to the 14th. day and, as earlier indicated, from the liver tissue at death. Several methods are available for the isolation of yellow fever virus from clinical specimens. These include, inoculation of suckling mice, the intrathoracic inoculation of mosquitoes, or the inoculation of cell cultures. Isolated virus can be identified using a variety of serological tests. An antigen-capture ELISA, which is as sensitive as virus isolation in suckling mouse, is available for rapid detection of virus in serum, blood or liver (18).

For serological diagnosis of YF infection, the following methods are useful: hemagglutination - inhibition (HI), complement fixation (CF), and neutralization (N) tests, single radial hemolysis, ELISA, IFA and RIA (17). The HI, IFA, and N antibodies appear within a week of onset; CF antibodies appear later. The plaque reduction neutralization test has replaced the less sensitive mouse neutralization test. Paired acute and convalescent phase sera are required to confirm diagnosis by demonstrating significant (usually a fourfold) rise in antibody titer. Determination of IgM antibodies either by the indirect IFA or ELISA, may indicate recent infection. The duration of IgM antibodies appears to be quite variable. A presumptive diagnosis of recent YF infection may be made when IgM antibodies are detected by ELISA or IFA or when there is a high specific CF antibody titer in a single sample taken during convalescence. Although IgM antibodies show relative specificity, prior exposures to other flaviviruses may sometimes complicate interpretation of results. In persons without prior flavivirus exposure, yellow fever 17D vaccine induces a neutralizing antibody, seroconversion and low titer (1:10-1:40) HI antibodies, but no detectable IFA or CF. However, persons with preexisting flavivirus antibodies respond to 17D vaccination with marked rises in yellow fever and heterologous HI and CF antibodies (17,18).
The ecology of yellow fever

Virus transmission occurs between man, mosquitoes and monkeys (2,18). The mosquito vector, which may belong to one of several species, becomes infected by feeding on a viremic host (man or monkey) and then transmits the virus to another susceptible man or monkey. Although monkeys and man have been considered as the reservoirs of yellow fever, the true reservoir is the susceptible mosquito species that not only remains infected throughout life, but can also transmit the virus transovarially to a proportion of the descendants through infected eggs. Men and monkeys, on the other hand, play the role of temporary amplifiers of the amount of virus available for mosquito infection. In man high-level viremia, required for mosquito infection, lasts from just before onset of infection until about the fourth day after onset, when specific antibodies begin to appear. Most African monkey species develop an effective viremia lasting several days or more, and produce protective antibodies after the viremia. Unlike some of the American species, African monkeys rarely die from yellow fever infection. American howler monkeys (Alouatta sp.), spider monkey (Ateles sp.), squirrel monkeys (Saimiri sp.) and owl monkeys (Aotus sp.) develop high levels of viremia and commonly die from yellow fever infection (17). On the other hand, capuchin monkeys (Cebus sp.), and wooly monkeys (Lagothrix sp.) develop subclinical yellow fever infections with viremia. The role of other nonhuman vertebrates in yellow fever transmission, such as African bush baby (Galago) and South American edentates, marsupials and rodents, remain undefined and require further studies (18).

Epidemiology of yellow fever

In the Americas, two types of epidemiological cycles are in operation: the jungle and the urban (17). Urban type yellow fever epidemic is transmitted from man to man by A. aegypti mosquitoes, while the jungle type is transmitted by the bite of a yellow fever infected Haemagogus or other forest-breeding mosquitoes. Virus activity is low with sporadic cases and focal outbreaks.

In Africa, three different epidemiological patterns, leading to the same clinical picture, are recognized for yellow fever virus transmission (17). These are the sylvatic or forest cycle, the A. aegypti-mediated urban cycle and an intermediate cycle bridging the sylvatic and urban cycles (figure 4). Transmission is determined by the complexity of the vegetational zones, rainfall patterns, abundance and distribution of vertebrate hosts and mosquito vectors. In the equatorial rain forest which extends from Guinea in the west to Uganda in the east and as far south as northern Angola, there is year round transmission of yellow fever between monkeys and A. africanus mosquitoes, in a manner analogous to jungle yellow fever in South America. Transmission is predominantly monkey to monkey, with sporadic human infection (17,23). The humid and semihumid savanna extend from the African rain forest. However, during the rainy season, with resulting high population densities of hosts and sylvatic vectors (A. fucifer, A. luteocephalus, A. vittatus), these areas of savanna forest mosaic and moist (Guinea) savanna experience repeated and sometimes high rates of yellow fever transmission (17). Periodic yellow fever epizootics occur in monkey populations with interhuman transmission. Virus survival and continuation of epizootics are ensured by vertical transmission in the mosquitoes. With most YF epidemics occurring in this vegetational zone, this is the major area of risk of transmission. This is also known as the intermediate zone of transmission (17). The dry savanna zone is characterized by very low rainfall and a short rainy season. Consequently, the sylvatic vector populations are

![Figure 4. Yellow fever virus transmission cycles.](image)
either too low or active for only a short period to sustain an epizootic. However, yellow fever infection can be introduced into the dry savanna zone and maintained in a cycle of interhuman transmission by the domestic vectors, A. aegypti mosquitoes, following the extension of an epizootic from the intermediate zone, or movement of infected persons into villages. Explosive urban A. aegypti borne epidemics occur when the virus is introduced into urban centers or very dry savanna regions where water is stored in and around homes, and human population lives in association with domestic A. aegypti (17). Under such conditions, the epidemic can spread to distant places and from village to village along the lines of human communication. The extent and speed of virus spread is only limited by the distance an infected person or infected mosquito can move by available means of transportation.

**Prevention and control**

Two live attenuated vaccines have been used for the prevention or control of yellow fever epidemics (26). A yellow fever vaccine, the French Neurotropic Vaccine (FNV) was developed in 1930, and consisted of desiccated brain of mice inoculated with the French neurotropic strain of yellow fever virus (27). Between 1939 and 1953, over 80 million vaccinations were performed by scarification, resulting in the virtual disappearance of yellow fever from French speaking countries of Africa (28). However, severe post-vaccinal reactions were developed by vaccinees (18), including systemic symptoms in approximately 20%, meningeal signs in 3-4%, and post-vaccinal encephalitis in 0.5-1.3%. An attempt to control the 1965 yellow fever outbreak in Senegal, using the neurotropic vaccine resulted in the identification of 248 cases of encephalitis with a 22% case-fatality rate (23). The manufacture of the French neurotropic vaccine was discontinued in 1980 (26). The second vaccine, the 17D vaccine, is a safe and efficacious live attenuated vaccine prepared from infected chicken embryo (12). About 95% of vaccinees develop measurable antibody within 10 days of primary vaccination. For international certification, immunization is valid for 10 years, but immunity may be lifelong, as antibodies have been shown to persist for as long as 30-35 years (18). Adverse reactions to the 17D vaccine include mild headache, myalgia or other mild symptoms in 2-5% of persons receiving the vaccine. Allergic reactions, including skin rash, urticaria and asthma occur in at a very low rate, less than one in a million, predominantly in persons with a history of allergy to eggs. No liver function test abnormalities are associated with 17D vaccination. The risks of encephalitis associated with the use of the 17D vaccine are minimal and it is the only vaccine currently produced (18,26). Promotion of effective immunization strategies, both routine and supplemental, are required for the control YF in endemic countries (16). The four strategies proposed for the prevention and control yellow fever are: 1) routine immunization, 2) surveillance, (including vector monitoring and control), 3) outbreak prevention, and 4) outbreak response (29). All at-risk countries require a continuing and sensitive surveillance system for the early detection of YF cases, as a prerequisite for institution of rapid response to contain a potential outbreak. Laboratories with capability for differential diagnosis are essential because of the difficulties in distinguishing YF from other diseases with similar symptoms such as hepatitis, malaria, typhoid fever and other febrile jaundice. Other preventive measures include vector monitoring and control (29). A vigorous but well coordinated and continuous programme of eliminating the breeding sites (tires, artificial containers, etc.) of domestic vectors of yellow fever (A. aegypti mosquitoes), treatment of potable water with temephos (Abate ®), perifocal spraying with

![Figure 5. Control of yellow fever in Africa: the miracle of 1934-1953.](image)
organophosphorus insecticides, are effective steps in interrupting virus transmission (29).

Impact of yellow fever on development through the ages

At different stages of human development, yellow fever has caused untold hardship, and indescribable misery among different populations in America, Europe and Africa. Hundreds of thousands of people were affected by the disease through the ages, of which tens of thousands died. Yellow fever brought economic disaster in its wake, constituting a stumbling block to development. Along the trade routes between the settlements in North America and the West Indies, yellow fever was brought to New York in 1668 riding on the wings of A. aegypti mosquitoes breeding in water casks of old wooden trading ships. The 1668 outbreak was described as "particularly destructive in the cities of New York and Philadelphia" (2). Between 1668 and 1905, from as far north as Boston to New Orleans and the Mississippi valley, YF returned each succeeding summer, "decimating populations, paralyzing industry and trade, and holding the peoples of these regions in a state of perpetual dread of the Yellow Jack" (1,2). Between 1668 and 1870, New York suffered no less than 15 epidemics. Thirty epidemics were reported in Philadelphia between 1668 and 1867, with the most devastating epidemic being the 1793 outbreak. The epidemic started "soon after the arrival of refugees from Santo Domingo in August, and lasted for 7 weeks" (2). About 4,000 people died as a result of the epidemic. When yellow fever invaded the plains of the US in 1846, "the Mormons (during their march from Nauvoo to Utah) suffered from remittent and yellow fevers. Their track across the desert was marked by the graves of those who perished" (30-32). The most devastating of the eighteen yellow fever epidemics reported in New Orleans, between 1811 and 1878, occurred in 1853 with close to 5,000 cases and 1,000 deaths. The city of Charleston, South Carolina, lost 682 persons to yellow fever during the 1854 epidemic, and suffered at least 15 other major epidemics between 1690 and 1876. In the Mississippi Valley, the YF epidemic of 1878 caused the death of thirteen thousand people, and "by bringing business to a standstill resulted in an economic loss of more than one hundred million dollars" (2). The work of Reed and associates of the Rockefeller Commission (2) pointed clearly to mosquito eradication as the practical method of exterminating yellow fever. This principle was accepted and put to test with dramatic results by the government of Cuba. In February 1901, anti-mosquito measures to rid the city of domestic A. aegypti were started and by September of the same year, yellow fever was completely eradicated. This success was repeated in Panama, El Salvador, Nicaragua, Honduras, Guatemala, Ecuador, México, Perú, Colombia and Brazil. By the end of 1924, urban yellow fever had been eradicated in many locations of Central and South America (2). Although yellow fever has not been reported in North America since the 1905 New Orleans outbreak, much of southern eastern United States has been reinfested with A. aegypti mosquitoes, increasing the possibility for a yellow fever outbreak (23).

Central and South America

Countries of Central and South America were not spared from the devastations of yellow fever (2,30-33). Between 1649 and 1900, over one hundred epidemics were reported in different countries in the region. The earliest reported YF outbreak occurred in 1649 in the West Indies (2). The most severe epidemic reported from the West Indies was the 1795 outbreak among European troops stationed in the West Indies. Approximately 31,000 people died during this epidemic. Other notable epidemics were the French Guiana epidemic of 1762 which raged for three years, the San Juan outbreak of 1804, with mortality described as "inordinate" (34) and the Rio de Janeiro epidemic of 1804, in which mortality was in excess of 95% (35). Colombia and Venezuela (30,31) suffered frequent outbreaks between 1907 and 1929. In 1949, ten countries, most devastated by yellow fever (Brazil, Bolivia, British Guiana, Colombia, Ecuador, French Guiana, Panamá, Perú, Surinam and Venezuela) launched a vigorous eradication campaign against A. aegypti. By 1965, urban breeding grounds of the mosquitoes had been destroyed.
and yellow fever disease eradicated from most urban centers in America (33). However, from 1985 to 1994, sylvatic yellow fever cases were reported in Bolivia, Brazil, Colombia, Ecuador, and Perú. During the decade, a mean of 154 sylvatic yellow fever cases were reported annually (range, 88-237 cases) from South America (23). In 1995, Perú reported a jungle-type yellow fever outbreak, with 440 cases and a case fatality rate of 38%. This was the largest outbreak in South America since the 1950s. Urban yellow fever has not been reported in the Americas since 1954. However, A. aegypti mosquitoes have reinfested many tropical cities of South America, providing the potential for explosive urban outbreaks of yellow fever. Dengue fever, another arbovirus transmitted by A. aegypti, has made a dramatic comeback in the Americas with over 200,000 cases reported from 27 countries in South, Central America and the Carriebean as of November 1995 (3).

Europe

Yellow fever, one of the most dreaded diseases during the seventeenth century slave trade on the Atlantic sea routes, inspired the legend of the Flying Dutchman. This was a vessel fated to haunt the Cape of Good Hope, because yellow fever broke out on the vessel, and no port allowed her to dock, and all the crew perished (33). Between 1649 and 1878, twenty-two outbreaks of yellow fever were reported from Gibraltar to Dublin, in Europe (33). Yellow fever was brought in ships to and from Africa and the West Indies, to Gibraltar in 1649. The 1723 outbreak, probably the first episode of the disease in the heart of Europe, was reported in Lisbon, and eventually spread to London (33). But by far the greatest epidemic in Europe began in September 1730, when 22,000 people died after the arrival of the flotilla of Pintado. The flotilla came in from Cartagena, where many of Pintado's men had died of "el vómito prieto" (30,34). Commenting on the outbreak, Bascome was reported to have said "...it was probably this pestilence which during the seven years 1729-35, raged in Vienna, Pignol Fossano, Nizza, Rivoli, Asti, Larti, Acqui, Basile, Silesia, Thrasburg (Lower Rhine), Trino, Fresneuse (Lower Seine), Vimeux (Seine et Oise), Orleans (Loiret), Plouvierres (Loiret), Meaux, Villeneuve, St. George (Seine et Maine), Bohemia, Denmark, Sweden and Russia (1,35). During the military operation of 1741, over 8,000 people were reported to have died as a result of yellow fever infection in Málaga, Spain. For the next 60 years, there were few reports of yellow fever outbreaks in Europe. At the beginning of the 19th century, yellow fever reappeared in Spain and Portugal. In 1821, no less than 20,000 deaths were reportedly caused by yellow fever disease in Spain, of which 5,000 of the fatalities were in Barcelona alone (1,35). The 1857 outbreak in Oporto and Lisbon, Portugal was described as "awesome in both scale and mortality", and was the last major epidemic in Europe. Other outbreaks of interest, include the 1826 Dublin outbreak, being the most remote location of yellow fever outbreak in Europe, the Gibraltar outbreak of 1828, with over 5,000 cases and more than 1,000 deaths; the 1861 outbreak in Saint Nazaire, France, brought in by "Anne Marie", a small wooden sailing ship from Havana. Before docking in Saint-Nazaire, the ship had already suffered a case fatality of 22% due to yellow fever (1,35).

Africa

As far back as 1494, diseases, similar in signs and symptoms to YF had been reported from islands (Canary, Cape Verde, etc.) off the coast of Africa, and sometimes in coastal countries such as Gambia, and Sierra Leone (1). Since the latter half of the 18th century, outbreaks of yellow fever have occurred at intervals in Africa, with the 1778 outbreak of yellow fever among British soldiers stationed in St. Louis, Senegal, being the first documented episode of the disease (17). The clinical report of this outbreak published in 1782, read like extracts from modern day fiction on emerging and exotic diseases: "... the vomiting continued... It became green, brown, and at last black, and was coagulated in small lumps. A continual diarrhea, with grippings, now took place, by which a great quantity of black and putrid faeces was evacuated. The skin became now full of petechiae” (1,34). Serious investigation of the yellow fever disease commenced in 1925 when the Rockefeller Foundation established Yellow Fever Laboratories in Ghana and Nigeria (2). Before
mass immunization campaigns began in Africa, typical urban YF outbreaks occurred in different centers in West Africa and the Sudan. In addition, YF occurred as sporadic cases of jungle YF mainly in the forested areas. While epidemiological data on these outbreaks are not available, there are reports of YF outbreaks involving thousands of cases and deaths in Nigeria (1925-1928), Ghana (1926-1927, 1937) and the Gambia (1934-1935)(17). Between 1940 and 1953, in francophone West Africa, over 40 million doses of FNV were administered during compulsory mass YF vaccination exercise (figure 2). Consequently, yellow fever virtually disappeared from these areas, but remained as an endemic disease with periodic epidemic outbreaks in other countries where an immunization programme was not in force (16). The decline in the number of reported cases of YF resulted in a loss of interest in the disease and a progressive neglect of surveillance and YF immunization programmes in the latter half of 1950s. Furthermore, the production and use of FNV was stopped with increasing reports of severe and fatal encephalitis in children under the age of 12 years who had received the vaccine (25). Within five years of the cessation of mass YF vaccination campaigns, more countries in Africa began to experience outbreaks of YF. Between 1958 and 1962, Zaire (now the Democratic Republic of Congo), Sudan and Ethiopia reported severe outbreaks of YF. It was estimated that, during the Ethiopian yellow fever epidemic of 1960-62, there were 100,000 cases and 30,000 deaths (17). From 1969 to 1995, epidemics of YF raged in varying proportions in different parts of Africa. The period 1988 to 1990 was an extraordinarily active period for YF. The worldwide total of 8,685 cases and 2,643 deaths for the three years, while gross underestimates of actual situation, still represented the greatest number of YF cases and deaths reported to WHO since 1948. African countries reported over 90% of the number of yellow fever cases and deaths, during this period. In 1992, YF appeared farther east in Kenya, a country that had been free of YF for more than 50 years. Improved laboratory based surveillance in Kenya detected yellow fever cases in 1994 and 1995. In 1996, five African countries, Benin, Burkina Faso, Ghana, Liberia and Nigeria reported a total of 1,132 yellow fever cases. Recent YF epidemics in Africa have primarily affected children younger than 15 years of age (15,16), because many African countries abandoned routine mass YF vaccination campaigns since the 1960s, and opted for post outbreak emergency campaigns (26). Children accounted for 62% of 4,661 YF cases reported in Africa between 1965 and 1991. In Senegal, Burkina Faso and Cameroon, over 80% of YF cases occurred in children. For the first six years of the 1990s, Africa has reported 9,876 cases of yellow fever, which is over 70% of the total number of cases reported for the entire decade of the 1980s. African countries at risk for yellow fever have traditionally used the "fire fighting" vaccination approach in combating recent YF outbreaks, often with disastrous effects. Apart from the great numbers of preventable deaths, this approach has resulted in the disruption of fragile health care delivery systems, enormous wastage of vaccines and has put a great strain on donor and existing national human and material resources. For example, Nigeria suffered a devastating epidemic of YF from 1986-1991 and imported over 30 million doses of YF vaccine to contain the epidemic. The country was unable to rapidly and effectively contain the epidemics because of her capacity and capability to effectively utilize the imported doses of YF vaccines were overwhelmed, leading to a wastage of over 30% of the imported vaccines, health services were diverted to cope with the massive epidemics, and vaccination exercise always lagged behind the outbreaks by at least three to four months. Consequently, the importation of massive doses of YF vaccine had little effect on an epidemic that raged unabated for more than four years and from one part of the country to the other. Enormous resources required to conduct emergency immunization campaigns have been mobilized following reports of YF epidemics in Nigeria, Liberia, Benin and other countries without routine YF immunization programme. It is estimated that attempting to control YF epidemics through emergency vaccination campaigns, at least seven times as costly as introducing YF vaccine in childhood immunizations (36). The true burden of yellow fever disease, during epidemic
and interepidemic periods, has not been accurately determined, due to the insensitive disease surveillance systems in operation in YF endemic countries. Following the 1986 YF epidemic in Nigeria, two of the affected villages were abandoned, as the villagers moved out to settle in nearby villages, unaffected by the epidemic. Four years later, the villages remained desolate as the villagers refused to return. With the resurgence of the disease, especially in Africa, in the last two decades, yellow fever continues to decimate populations, and cause economic stagnation and underdevelopment. Perhaps the most disturbing aspect of recent yellow fever epidemics in Africa, is that it has affected predominantly children under the age of fifteen years (15,16). The non-appreciation, by the government and health authorities, in YF endemic areas of the world, of the real impact of yellow fever on their development, is a modern day tragedy. It is an inexcusable tragedy, knowing that a safe and effective vaccine has been available for over 60 years, especially as the disease was once brought under control following mass vaccination exercises carried out between 1939 and 1953 in African countries under French colonial rule (3,28).

Yellow fever in Asia
As early as 1934, concerns had been expressed about the possibility of yellow fever spreading across from east Africa to Asia (37). Despite the occurrence of yellow fever epidemics in 1940 in Sudan (37), from 1960-62 in Ethiopia (39), and from 1992-93 in Kenya (40,41), Asia has remained free of the disease. Numerous reasons have been advanced for the failure of yellow fever to spread to Asia, including, 1) non introduction of yellow fever into Asia, 2) variation in human susceptibility to yellow fever, 3) variation in vector competence and/or behaviour, 4) flavivirus cross-protection, and 5) absence of maintenance cycle. None of these reasons has provided a satisfactory explanation for the failure of yellow fever to spread to Asia. However, while yellow fever has not yet spread to Asia, it could still occur. Therefore Asian countries should continue to maintain that all visitors from yellow fever endemic or at risk countries should have valid yellow fever vaccination certificate.

Factors responsible for the resurgence of yellow fever disease
Some of the factors responsible for the resurgence of yellow fever and indeed, other diseases, especially in Africa, include (42): collapse of health care delivery systems, poor or inadequate disease surveillance, inappropriate disease control measures, urban poverty with overcrowding and massive population movements, poor environmental management and indiscriminate deforestation.

Epidemics usually begin in rural areas, far removed from urban centers and the seat of national authorities responsible for taking control measures. Delays of two or more months are common between onset and recognition/reporting of epidemics.

Where an outbreak is promptly reported, confirmation of the clinical or presumptive diagnosis is generally impossible, because of the poor state of laboratory diagnostic facilities. Furthermore, when laboratory confirmation is available, responsible authorities are incapable of responding adequately and in a timely manner, with appropriate control measures. In many developing countries, health care delivery systems and infrastructures have suffered years of neglect resulting in shortages of basic equipment and supplies and low staff morale. Under this situation, health care institutions are unable to provide appropriate care for the sick. In the event of an epidemic, the community has sought alternative medical care with the possibility of increased risk of disease spread within the community where the sick are cared for by family members. Two approaches: mass vaccination campaigns and inclusion of yellow fever vaccinations in national EPI programmes, have been proposed for the control of yellow fever. Since the resurgence of yellow fever in Africa, only Gambia, among the African countries at risk for yellow fever (34), has successfully carried out a mass vaccination campaign, attaining a coverage of 95%. Seventeen of the 34 have included yellow fever vaccination as part of the national EPI programme, with widely
varying degree of success. One reason often adduced for the poor state of health in Africa is the state of underdevelopment arising from poverty or vice versa. Indeed poverty coupled with ignorance is responsible for the occurrence and severity of most infectious disease in Africa. Poverty in Africa manifests in different forms resulting in massive population movements to already overcrowded urban centers where environmental sanitation standards are appalling. The search for food and means of livelihood, the shortage and competition for arable farmlands lead to invasion of virgin forests and the extension of YF infected zones through bad environmental management. The 1994 outbreak of YF in Gabon illustrates this point. The outbreak began as a jungle-type outbreak in a remote mining camp, and later spread rapidly to villages outside the forest, where a shift to urban type was indicated by the presence of A. aegypti mosquitoes (2). While there is poverty in the developing world, it needs to be emphasized that this is not often due to a lack of material and human resources, but more from misplaced and misdirected priorities. For example, between 1990-1995, defence and military expenditure in many of the developing countries was between 15 to 273 times more than the expenditure on health and education combined (43).

**Options for control of yellow fever**

What are the options available for control of yellow fever in developing countries? Recently, WHO launched an initiative to combat the dramatic resurgence of YF in Africa, and control YF by the year 2000. The initiative which is to be coordinated with national ministries of health, will integrate the partnership efforts of bilateral agencies, other United Nations bodies and non-governmental organizations (44). The two goals of the yellow fever control initiative are: 1) the introduction, by 1997, of yellow fever vaccine into the childhood immunization programme in all the 34 countries at risk, and 2) the attainment, by the year 2000, of at least 80% coverage with yellow fever vaccine in children under 5 years of age in all the 34 countries. Four strategies are proposed to achieve these objectives (29): immunization, improved disease surveillance, outbreak prevention, and outbreak response. The promotion of effective immunization strategies, both routine and supplemental, is required for the control YF in the 34 African countries at risk for YF epidemics. The joint WHO/UNICEF Technical Group on Immunization in Africa recommended, in 1988, that YF immunization be integrated into the immunization programmes in all 34 countries at risk for YF epidemics (29). National immunization programmes are to implement the necessary strategies to achieve and sustain in each district at least 80% coverage by one year of age for all scheduled childhood vaccines including yellow fever. However, financing YF vaccine has been the major obstacle to its procurement. Although 17 countries have adopted the policy, only 13 (Angola, Burkina Faso, Central African Republic, Chad, Cote d'Ivoire, Gabon, Gambia, Mali, Mauritania, Niger, Senegal, and Togo) were able to obtain funds and procure the vaccine. Immunization coverage has ranged between 87% in the Gambia to 1% in Nigeria, with only 2 countries achieving more than 50% YF vaccine coverage in infants in 1995. The Gambian experience is an example of the success of this strategy. Following the 1978-79 YF epidemic in the Gambia, and the successful YF mass vaccination carried out in 1978/79, in which 95% of the population over 6 months received a dose, YF vaccination was added to the EPI Programme in Gambia. The vaccine was given at the time of the child's visit for measles vaccine. Gambia has since then maintained a coverage of over 80%, without a reported case of YF. This is in the presence of reported YF cases in Senegal, a country which literally envelops the Gambia. In addition to the effective introduction and achievement of high YF immunization coverage in infants, YF can only be brought under control if a concurrent well coordinated mass immunization campaign is embarked upon over a period of 5-10 years. The duration of the campaign and the focus target group will depend on the epidemiology of YF in each of the at risk countries.

All at-risk countries require a continuing and sensitive surveillance system for the early detection of YF cases as a prerequisite for institution of rapid response to contain a potential
outbreak. Laboratories with capability for
differential diagnosis are essential because of the
difficulties in distinguishing YF from other diseases
with similar symptoms such as hepatitis, malaria,
typhoid fever and other febrile jaundice. The WHO
Africa Region is strengthening disease surveillance
to encourage timely and complete reporting of priority
diseases and monitoring of standard performance
indicators. Since 1994, WHO in collaboration with
other partners, has organized training courses on
YF diagnosis and vaccine potency testing, for over
80 technicians and scientists from laboratories in
20 African countries. Trainees return to their
laboratories with supplies and diagnostic reagents.
To further enhance YF diagnosis, training/refresher
courses are planned for pathologists in the region
to improve diagnostic capabilities based on
histopathology.

The prime goal of the new WHO YF control
initiative is to rapidly expand vaccination coverage
for YF in Africa by linking it with mass campaigns
against polio and measles, while integrating YF
vaccination into routine childhood immunization
programmes. The success of mass YF
immunization in west Africa in the 1940's and 1950's
highlights the effectiveness of achieving high
coverage of the population. YF antibodies acquired
through natural infection or vaccination probably
persists for life. Therefore country specific YF mass
campaigns will be required in countries at risk.
Since millions of doses of YF vaccine will be
needed to achieve 80% or greater coverage of
both urban and rural populations, vaccine
manufacturing companies must be encouraged
to increase production.

Measures to rapidly control YF epidemics are
hampered by the late recognition and reporting of
the disease. Countries are being assisted by WHO
to carry out activities that will enhance appropriate
responses to reported YF outbreaks. These activities
include: collection and testing specimens,
epidemic investigation to determine the scope of
the outbreak, entomological investigation and vector
control, and institution of measures to prevent
spread of virus from patients to mosquitoes.
Emergency vaccination of at risk populations is
made possible through a stock of YF vaccine
maintained by WHO, and which can be made
rapidly available for outbreak response.

Conclusion

Why is yellow fever still a significant public health
problem in developing world, and especially,
Africa? Why, despite what we know of the virus,
the availability of a safe efficacious vaccine, the
disease still remains uncontrolled? Why is the
international community that is so ready to flood
Africa with aid (vaccine and logistic support)
during an epidemic so reticent when it comes to
prevention of the disease through support for
childhood immunization and other preventive
activities? Why are governments in developing
countries so unconcerned by the devastations
caused by YF? If YF is to be controlled, answers
must be found urgently to these questions. A
report on the 1748 yellow fever outbreak that
plagued Senegal and the Guinea coast of West
Africa, said in part "... in several towns, among
the negro population, the mortality was so great
that there were no sufficient left to bury the dead"
(3). One hundred and thirty five years later, in
another part of Africa, the chief of a village
decimated by yellow fever welcomed our
investigating team with almost identical words,
"... Had you come four weeks ago, the young and
the able-bodied would have welcomed you at the
gate of our village with traditional hospitality. They
now lie unburied for four days or more, because
only the old are around, and they are too weak in
body and in spirit to bury their young and ... their
future". The tragedy of yellow fever disease in
the developing world and especially in Africa is
non-appreciation of the deleterious impact of YF
on the economic and social development of large
mass of the population by governments and
health officials. In most African countries, a
criminal nonchalance about YF control is shown
by the government and educated elite, who have
gone on to protect their families and friends with
available YF vaccine and neglected the teeming
masses of unvaccinated rural dwellers and
residents of periurban slums. The initiative for
yellow fever control in developing countries lies
to a large extent with national governments and
the people of yellow fever endemic countries. The
human and material resources required to control
yellow fever exist in these countries just as yellow fever is endemic. The failure to control YF in developing countries is not a failure of public health, but it is the failure of improper application of public health strategies. To control yellow fever and minimize its impact not only on the developing countries, but also on the entire world, governments of yellow fever endemic countries must seize the initiative for yellow fever control, reorder their priorities and support disease surveillance and control activities through political commitment and increased funding. International partners also need to reorder their priorities in terms of the scope and mode of support provided for disease control. Only then can look forward with the hope and confidence expressed on yellow fever disease by Major Gorgas in 1902 (1).

References

192


