Yellow fever

**Written by:
Dr Jari Vainio and Dr Felicity Cutts,
London School of Hygiene and Tropical Medicine**

**DIVISION OF EMERGING AND OTHER COMMUNICABLE
DISEASES SURVEILLANCE AND CONTROL**

**GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
EXPANDED PROGRAMME ON IMMUNIZATION**

*World Health Organization
Geneva
1998*

This documents is available on the Internet at:
http://www.who.ch/gpv-documents/

Copies may be requested from:
World Health Organization
Global Programme for Vaccines and Immunization
CH-1211 Geneva 27, Switzerland
• *Fax:* +22 791 4193/4192 • *E-mail:* gpv@who.ch •

Contents

Maps and figures

Tables

Glossary

Endemic disease: The constant presence of a disease or infectious agent within a given geographic area or population group.

Enzootic: The constant presence of a disease within a given animal population

Epidemic: An outbreak of disease in human population

Epizootic: An outbreak of disease in animal population

Information bias: Systematic error due to differences in accuracy or completeness of recall of prior events or experience

Reservoir: Any person, animal, arthropod, plant , soil, or substance, or a combination of these, in which an infectious agent lives and multiplies and where it reproduces itself in such a manner that it can be transmitted to a susceptible host.

Selection bias: Error due to systematic differences in characteristics between those who are selected for study and those who are not

Strain: A clone of organisms that differs in one or more inheritable characteristics from other organisms assigned to the same species.

Topotype: Genetically distinct geographical variant of yellow fever virus[2]

Trophic: Pertaining to an insect's preference for the species to feed on:-

- **anthropophilic:**   Preference for feeding on humans
- **primatophilic:**   Preference for feeding on primates
- **simiophilic:**   Preference for feeding on monkeys
- **zoophilic:**   Preference for feeding on animals even when human hosts are available

Vector: An insect that transports an infectious agent from an infected individual to a susceptible individual

Zoonosis: An infection or infectious disease transmissible under natural conditions from vertebrate animals to man. May be enzootic or epizootic

List of abbreviations

AFRO	WHO Regional Office for Africa
CFT	complement fixation text
CIGN	country in greatest need
CRF	case fatality rate
DHF	dengue haemorrhagic fever
DMO	district medical officer
DTP	diphtheria-tetanus-pertussis vaccine
ELISA	enzyme-linked immunosorbent assay
EMC	Division of Emerging and other Communicable Diseases Surveillance and Control
EPI	WHO Expanded Programme on Immunization
GPV	WHO Global Programme for Vaccines and Immunization
HI	haemagglutination inhibition (test)
HIV	human immunodeficiency virus
HRC	human resources coordinate
KEMRI	Kenya Medical Research Institute
Ksh	Kenyan shillings
MOH	ministry of health
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PMO	provincial medical officer
RT-PCR	reverse transcription / polymerase chain reaction
UNICEF	United Nations Children's Fund
YF	yellow fever

Preface

This is a draft background document for the Yellow Fever Technical Meeting, Geneva, March 1998 organized jointly by the WHO Division of Emerging and other Communicable Diseases Surveillance and Control and the Global Programme on Vaccines and Immunization's Expanded Programme on Immunization.

We thank Dr T.P. Monath for extensive and detailed comments on an earlier draft.

Summary

Yellow fever is a viral haemorrhagic fever which strikes an estimated 200 000 persons world-wide each year and causes an estimated 30 000 deaths.[3] Yellow fever virus is the prototype of the family *Flaviviridae*, which currently contains over 70 viruses, of which most are arthropod-borne, including the dengue viruses.[4, 5] There are three different epidemiological patterns of yellow fever virus transmission: the **sylvatic** or **forest pattern**; the ***Aedes aegypti*-borne urban cycle**;[6] and an intermediate cycle that bridges these two patterns. The different epidemiological patterns of transmission lead to the same clinical disease.[7]

The main vector of yellow fever within village and urban settlements is female *Aedes (Stegomyia) aegypti* (only females feed on blood to obtain protein for egg production). The virus is transmitted when a mosquito bites an infected human and then, after an extrinsic (in the mosquito) incubation period of 12-21 days, bites a susceptible human. *Ae. aegypti* breeds readily in all types of domestic and peridomestic collections of fresh water, including flower vases, water drums, tin cans, broken coconut shells, old tyres and gutters.[4, 5, 7-9] In the forest pattern of yellow fever monkeys are the primary host, and man is an accidental host (in South America yellow fever is an occupational disease of people cutting down the forest[9]). Humans become infected with yellow fever virus when bitten by the primary mosquito vector, *Ae. africanus*, *Ae. bromeliae* or one of several other mosquito species. Most of these mosquitos breed and live in holes and cracks in the upper part of the trees in the forest.[4, 7-9] Intermediate epidemics are a mixture of man-to-man and monkey-to-man transmission, and are often characterised by focal outbreaks separated by areas without human cases.[10] In some surveys, it has been possible to estimate an annual incidence of infection of susceptible humans of at least 1%, so that, by adulthood, immunity rates of 50% or more are not unusual.[11] An attack of yellow fever is followed by a solid, long-lasting immunity against reinfection.[12]

The incubation period in humans is generally three to six days after the bite of an infected mosquito. The patient is only infectious to mosquitos for the first three to four days after onset of symptoms.[7] The disease is characterised by a sudden onset of fever, headache, backache, general muscle pain, nausea, and vomiting.[13] Milder cases of yellow fever may not present with jaundice.[7] There is a characteristic bradycardia in relation to the temperature (Faget's sign).[6, 14] About 15% of those infected develop a serious illness with several phases: an acute phase of about three days with sudden onset of fever, headache, myalgia, nausea, and vomiting; remission for up to 24 hours (characteristic "saddle-back" fever);[14] and a toxic phase with jaundice and vomiting (black vomitus), in which haemorrhagic signs (bleeding of gums, nose and haematuria), albuminuria, and oliguria (reduction of urine production) may occur. The patient may suffer from hiccups, diarrhoea, progressive tachycardia, and shock. Examination

of the abdomen reveals intense epigastric tenderness.[7, 15] At least half of the individuals who reach the toxic phase do not survive.[7, 9, 10] Death usually occurs between the seventh and tenth day after onset.[7, 16]

The possibility of yellow fever should not be dismissed in the absence of jaundice or of albuminuria. Malaria and yellow fever may coexist in a region,[17] and malaria usually shows clinical symptoms almost identical with those of the early stages of yellow fever: sudden onset, headache, generalised aches, and vomiting.[7] Even with the finding of malaria parasites in a blood smear, the possibility of yellow fever is not ruled out.[18] In the beginning of an infection, there is little to distinguish the illness from a number of other febrile conditions. Typhoid fever, rickettsial infections, influenza, leptospirosis, viral hepatitis, infectious mononucleosis, and other arboviral fevers like dengue, Lassa fever and chikungunya may all resemble anicteric yellow fever.[6, 7, 17]

Later in the course of disease the following conditions must be taken into consideration: the hepatitides, Weil's disease, carbon tetrachloride poisoning, dengue haemorrhagic fever, tick-borne relapsing fever, malaria or blackwater fever in addition to several virus diseases with haemorrhagic manifestations (Argentine haemorrhagic fever, Bolivian haemorrhagic fever, Crimean-Congo haemorrhagic fever, dengue, Ebola fever, Kyasanur forest disease, Lassa fever, Marburg disease and Rift Valley fever).[17]

The definitive diagnosis of yellow fever is made by serology or virus isolation, which requires special reagents and techniques as well as expertise in the interpretation of the test results. But prior to this, it is important that staff of the health facility are alert to the possibility of yellow fever and have the means to collect appropriate clinical specimens from suspected patients.[7] Liver samples may be obtained from fatal cases by the use of a viscerotome. The histopathological diagnosis is based on eosinophilic degeneration of the hepatocytes leading to the formation of Councilman bodies.[10] In the 1930s, a viscerotomy program was instituted in South America. All individuals who died after a short-term febrile illness had a liver punch specimen taken by health officials and sent to specially trained pathologists.[19] Liver biopsies are not done in living patients because of the risk of severe haemorrhage. A viscerotomy service has not been instituted in Africa.[17]

Yellow fever is endemic in 34 countries of Africa with a combined population of 468 million. Yellow fever vaccine, one of the earliest viral vaccines to be developed, has proved safe and efficacious.[5] The vaccine is transported and stored frozen.[7] The development of new protective additives have increased the thermostability of the vaccine. The shelf life at -20° or 4°C is now up to two years, and the estimated half life at room temperature is 10 months.[5] However, once a vial is opened, the vial must be kept cold and used within one immunization session and it must be discarded after then (in this case, one imunization session is considered to be six hours).[133] One dose of yellow fever vaccine provides protection for at least 10 years and possibly life-long.[2, 20] A single dose will confer immunity in 95% of persons vaccinated.[7]

Four strategies have the potential to bring yellow fever fully under control in Africa: epidemic control, mass immunization, routine childhood immunization and surveillance.[7, 21] In Africa, epidemic control often suffers from delays of two months or more between the onset of epidemics and their recognition, partly due to the

occurrence of the first cases in remote areas with few medical services and the unfamiliarity of medical personnel with the disease. Responses to a possible outbreak include collection and testing of specimens, epidemic investigation, emergency vaccination, entomological investigation and vector control.[7, 21] Emergency vaccination takes place as soon as an outbreak has been confirmed, in an attempt to limit the spread of infection by immunizing all persons in the focus, regardless of their former immune status. Good surveillance is essential in all at-risk countries for the early detection of cases which will allow fast action to control an outbreak. It has often proved difficult to identify early, isolated cases before they trigger an epidemic because of the difficulties of distinguishing yellow fever from diseases with similar symptoms (e.g. malaria).[20] Other potential problems with emergency campaigns include difficulty in obtaining the large supply of vaccine, syringes and needles, and sudden deployment at short notice of large numbers of health workers. Another disadvantage is that immunity does not appear until seven days after immunization.[10] It should also be noted that several operational difficulties in responding quickly to outbreaks have been extensively documented for measles and meningitis, and this strategy needs discussion.

One study estimated that including yellow fever vaccine in the routine EPI is more cost-effective than conducting emergency campaigns in response to yellow fever epidemics. That study was based on data from Nigeria, which is one of the countries worse-affected by yellow fever, and it is possible that the costs and benefits of the different strategies would be different in countries which have less frequent yellow fever epidemics. No published studies have compared costs and benefits of preventive mass YF vaccine campaigns (e.g. periodic vaccination of a wide age range) with those of routine YF vaccination of infants. Nonetheless, in countries which have recently experienced YF epidemics, there is likely to be a high level of natural immunity in older persons, and it makes sense to concentrate efforts on implementing routine YF vaccination of infants.

A potential scheme for prioritising countries in need of support specifically for yellow fever control is presented for discussion and debate. Although the absence of reported YF activity in a country in the "YF" zone does not mean that there is no risk of a resurgence, it makes sense to focus activities first on those countries that have evidence of recent YF activity and which have either not yet introduced YF vaccine into their EPI or which have low coverage of YF vaccine. However, the prioritization of countries and of areas within countries will need thorough discussion. Although in most countries, nationwide YF vaccination is needed, countries such as Kenya, Angola, and perhaps Mali have focal areas of YF activity, and can consider whether vaccination can be concentrated in the districts at greatest risk. All countries in the YF zone need better information on trends in the epidemiology of YF, and efforts to improve YF surveillance should be intensified. The YF laboratory network needs to be strengthened, and peripheral health workers need training in the use of the YF clinical case definition.

I. Introduction

In 1988, the EPI Global Advisory Group reviewed the situation on yellow fever and noted a relatively high incidence in children. It recommended that countries at-risk for yellow fever (Map 1) should incorporate yellow fever vaccine into the routine activities of the national immunization programme, and this was endorsed by a joint WHO and the United Nations Children's Fund (UNICEF) Technical Group on Immunization in Africa.[7] Due to a small risk of adverse reactions, yellow fever vaccine should not be administered to children less than six months of age, so it is usually administered at the time of the measles vaccination at nine months of age. Older children should also be vaccinated routinely in areas at high risk for yellow fever epidemics.[2, 20, 22]

Since the late 1980s, there has been a dramatic resurgence of yellow fever (chart 1). Vaccination activities in many of the countries at risk, which include the poorest in the world, are generally weak. Only five of 34 African countries at risk reported yellow fever vaccine coverage data in 1996. Outbreaks were reported in several countries in West Africa in 1994-1995, and in 1995, Peru experienced the largest yellow fever outbreak reported from any country in the Americas since 1950.

The WHO therefore commissioned a literature review of yellow fever to provide background material for assessment of the current strategies, focusing on the following:

- the epidemiology of yellow fever, particularly in Africa;
- a review of yellow fever surveillance systems and their effectiveness;
- a review of studies examining the cost-effectiveness of preventive yellow fever vaccination programmes versus emergency vaccination programmes.

A *Medline* literature search was conducted, and further articles were obtained from the bibliographies of papers reviewed. Published information on the surveillance of yellow fever was complemented by a review of the Kenyan sentinel surveillance programme conducted by Jari Vainio in July-August 1997 as part of his MSc programme at the London School of Hygiene and Tropical Medicine.

In chapter II, "History of yellow fever", the history of yellow fever and YF vaccines is reviewed, focussing on the major epidemics which extended even to Europe and North America that remind us the capability of yellow fever to spread to these continents.

In chapter III, "Epidemiology of yellow fever", recent YF epidemiology is reviewed with emphasis on data from the African region. The situation in the Americas is briefly summarized, and the possibility of spread of YF to Asia discussed.

In chapter IV, "Cost-effectiveness of yellow fever", the small literature on this topic is reviewed, and the factors that are likely to affect costs of yellow fever vaccination are discussed.

In chapter V "Surveillance", the advantages and disadvantages of different methods of yellow fever surveillance are discussed. A more detailed description of the unique Latin American surveillance based on viscerotomy is given, and a summary of key findings in the review of the Kenyan sentinel surveillance programme is presented. The published results of mosquito and monkey surveys, which often only serve to provide lists of names of vectors and primates, are summarised in Appendices III, IV and V.

Finally, in the "Conclusion and recommendations" chapter, potential activities are prioritized according to practical criteria, with the aim of stimulating further critical discussion and comments.

Chart 1: Resurgence of yellow fever, Africa & Latin America, 1980-95

□ Africa   ■ Latin America

Number of reported cases

6 000
5 000
4 000
3 000
2 000
1 000
0

1980   1985   1990   19

Year

GPV/EPI

Estimated 200 000 cases annually!
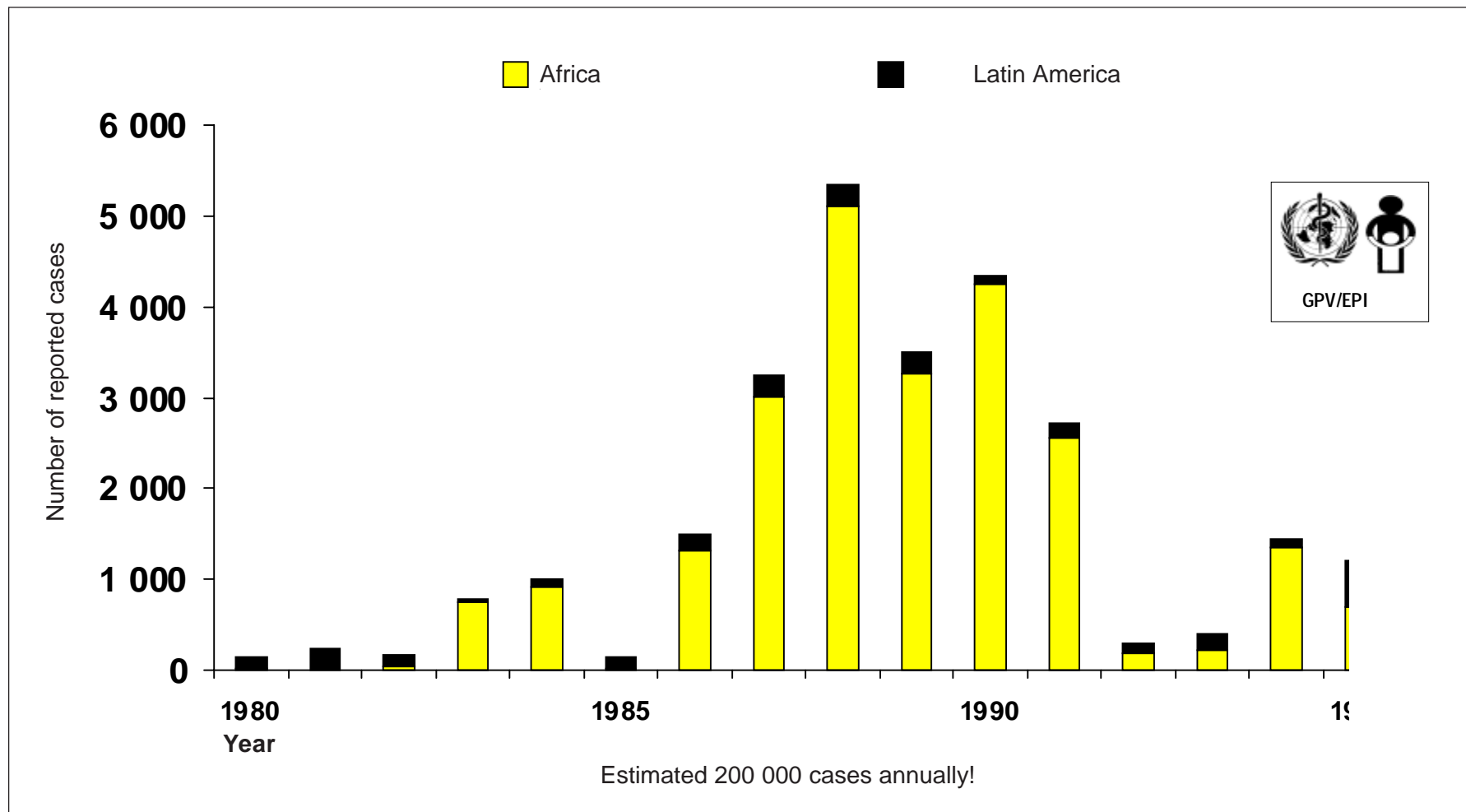
Map 1: Countries at risk for yellow fever and having reported at least one outbreak, 1985-1998

Countries at risk

Reported outbreak

GPV/EPI

The designation employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not be full agreement.

II. Historical review

II.1. Pre-vaccination epidemiology 1700-1930

The first account of a sickness that can definitely be recognised as yellow fever occurred in Guadeloupe and in Yukatan in 1648.[23, 24]

Slave trade in the seventeenth century formed an intimate bond between West Africa and Spanish-Portuguese America. "Yellow Jack" was one of the most dreaded of the diseases of the Atlantic trade routes; the legend of the "Flying Dutchman", a vessel doomed to haunt the seas around the Cape of Good Hope because yellow fever broke out and no port would give her harbourage and all the crew perished, as described by Sir Walter Scott, was inspired by stories of this disease.[23]

Lind's account (1792) of fever aboard the vessel off the coast of Senegal in 1768 is usually accepted as the first in which we can definitely recognise yellow fever in Africa. No clinical description of the fever was given, but the evidence for its being yellow fever was its occurrence first in men who had been ashore, and its apparent propagation aboard ship. The first clinical report on yellow fever was published by Schotte in 1782 on the "Synochus Atrabiliosa" in Senegal in 1778: "...the vomiting continued...It became green, brown, and at last black, and was coagulated in small lumps...A continual diarrhoea, with gripings, now took place, by which a great quantity of black and putrid faeces were evacuated... The skin became now full of petechiae..." [24]

For more than two hundred years the tropical and subtropical Americas were subject to devastating epidemics, while serious outbreaks occurred as far north as Boston and as far away from the endemic centres as Spain, France, England, and Italy.[12] Epidemics swept repeatedly over the West Indies, Central America, and the southern United States decimating populations and paralysing industry and trade.[12] In the course of history Philadelphia suffered from 20 epidemics, New York 15, Boston 8, and Baltimore 7.[12]

In 1848 Josiah Clark Nott (1804-1973) was the first to suggest that yellow fever was spread by mosquitos: "We can well understand how Insects wafted by the winds (as happens with musquitoes, flying ants, many of the Aphides, etc.,) should haul up on the first tree, house, or other object in their course, offering a resting place; but no one can imagine how a gas or emanation, entangled or not with aqueous vapor, while sweeping along on the wings of the wind, could be caught in this way..." [25]

But it was Cuban physician C. J. Finlay (1833-1915) who published in 1881 the first really serious theory of the mosquito transmission of yellow fever:

"1. The existence of a yellow fever patient into whose capillaries the mosquito is able to drive its sting and to impregnate it with the virulent particles, at an appropriate stage of the disease.

" 2. That the life of the mosquito be spared after its bite upon the patient until it has a chance of biting the person in whom the disease is to be reproduced.

"3. The coincidence that some of the persons whom the same mosquito happens to bite thereafter shall be susceptible of contracting the disease" [26].

Because of the considerable difficulties caused by yellow fever for the American army in Cuba during the Spanish-American war, the American authorities appointed a Yellow Fever Commission with Walter Reed (1851-1902), an army surgeon, as its head. In September 1900 the work of the Reed Commission proved conclusively that

a)   the mosquito was the vector of yellow fever;

b)   there was an interval of about twelve days between the time that the mosquito took an infectious blood meal and the time it could convey the infection to another human being;

c)   yellow fever could be produced experimentally by the subcutaneous injection of blood taken from the general circulation of a yellow fever patient during the 1st and 2nd days of his illness; and

d)   yellow fever was not conveyed by fomites.[12, 27]

Reed and his co-workers suggested that the spread of yellow fever could be most efficiently controlled by antimosquito measures and the protection of the sick from the bites of mosquitos.[27] The Commission also demonstrated for the first time that a filterable virus caused a specific human disease.[12] The conclusions of the Reed Commission were confirmed in practice by Gorgas, who eradicated yellow fever in Havana and Panama in early 1900 by depriving the mosquito of its breeding places.[25]

Laboratory work on yellow fever was very much handicapped by the lack of an experimental animal. In 1927 Dr A. F. Mahaffy and Bauer of the Commission's laboratory staff managed to transmit yellow fever to an animal other than man using blood from a yellow fever patient (a 28 year-old West African man named Asibi) into a rhesus monkey.[12] Propagation of the now famous Asibi strain of yellow fever virus also began with this experiment.[28]

The same workers confirmed that[12, 28, 29]:

a)   the causative agent of yellow fever was a filterable virus;

b)   the infection was easily transmitted from monkey to monkey, or from man to monkey, by injection of citrated blood taken from early in the disease;

c)   that it was transmitted from monkey to monkey by *Aedes aegypti* mosquitos;

d)   that once infected, mosquitos remained infective for the entire period of their lives, which in some instances exceeded three months; and

e)   that the bite of a single infected mosquito was sufficient to produce a fatal infection in a monkey.

Dr Max Theiler described in 1931 the use of mice in testing sera for protective substances against yellow fever virus. This mouse protection test became one of the principal tools in yellow fever research and epidemiological investigations[30, 31]. Serological surveys helped to delineate the areas in Africa in which yellow fever had occurred.

Map 2: Limits on endemic and epidemic areas of yellow fever

▨	Western topotype
▨	Eastern topotype
▬	Limit of potential epidemics
▬	Limit of endemic area

GPV/EPI
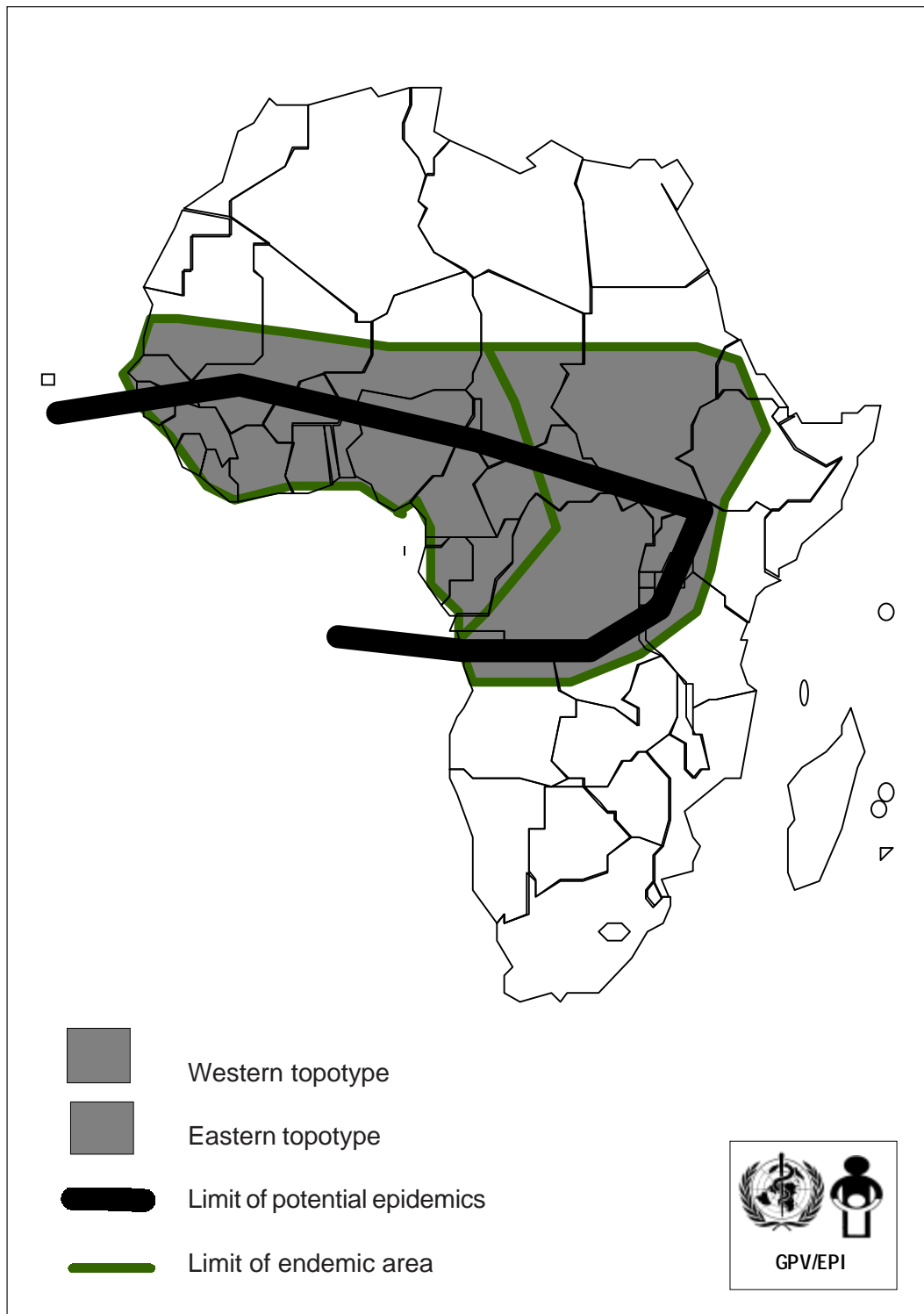
II.2. Pre-vaccination epidemiology in Africa

From 1906-1922 cases of yellow fever were apparently rare in former French Africa. From 1922 to 1927 very numerous small outbreaks without apparent inter-connection were reported in West Africa. In all these small outbreaks the infected area was extremely localised.[32]

From 1927 to 1931, disease incidence decreased markedly and seemed to disappear from one colony after another. In 1931, however, yellow fever reappeared. The almost simultaneous reappearance of cases of yellow fever, with no connection between them, in a large number of places scattered over West Africa and in countries where the disease had not been reported at all for several years, was explained by the persistence of latent yellow fever foci in these countries. In the epidemic periods, it was the Europeans in particular who were affected as they had not gained protection through a previous attack.[33]

The number of serological studies increased considerably after Theiler's discovery enabled mice to be used, instead of monkey *Macacus rhesus*, for protection tests.[34] The results of these tests were often positive in Sierra Leone and Southern Nigeria, and fairly frequently positive in Northern Nigeria. The prospecting mission of Stefanopoulo in 1931-32 in former French West Africa discovered a good number of positive sera in the west and south of Senegal, and along the upper course of the Senegal River, in the Macina area (former French Sudan) and the former Upper Volta Territory.[34] Tests also gave positive results in the parts of former Togoland under French Mandate. On the other hand, the tests gave negative results in almost all the places studied in Guinea and the Ivory Coast (except Grand Bassam).

W.A. Sawyer's researches showed high percentages of sero-positivity in Anglo-Egyptian Sudan, and in the west of Uganda. The exceptional positive results obtained in Kenya, Tanganyika and Northern Rhodesia were not considered as sufficient proof that yellow fever had existed in these countries, since serology was not 100% specific for yellow fever[34].

In places where the disease was endemic, the proportion of positive immunity tests increased fairly regularly with age, whilst in places where the disease appeared sporadically the immunity curve according to age was irregular. Negative results for tests among children indicated the absence of yellow fever during recent years from the area or place in question. In the same way, the ages of children giving a positive reaction to the test fixed the epidemic years.[35] Van Campenhout's report for the former Belgian Congo showed that in the Matadi area, where yellow fever was prevalent in 1928, both children and adults gave positive reactions in equal proportions. On the contrary, above Leopoldville, where yellow fever was not notified during the previous years, the sera from children were negative, whereas, in the case of adults, the older the subjects, the more often were the results positive.[33]

The disease appeared in June 1934 for the first time farther east, at Wau, in Bahr-el-Ghazal Province in former Anglo-Egyptian Sudan. Sero-protection tests reported by Sawyer in 1931 had revealed one third of individuals (7/27) immune to the disease.[36]

The information on the geographical distribution of the disease was more useful than the number of cases recorded, since the number of typical recognised cases was infinitely small compared with the benign atypical cases and subclinical infection in the affected areas. The figures published in 1930s related almost exclusively to Europeans, and often only one or two cases were reported from each affected locality. Thus reports only served to show the presence of yellow fever and not its true burden.[36]

Certain epidemiological features were noted by 1928[32]:

1. Yellow fever followed the trade routes such as rivers, roads and railways.

2. The disease was pre-eminently urban.

3. Nonetheless, outbreaks often occurred in isolated spots in the jungle.

4. Almost inevitably, outbreaks followed the arrival of large numbers of non-immunes, or the incursion of susceptible troops in infected territory, or other mass population movements.

5. Newcomers to endemic foci suffered disease almost exclusively, with high attack rates in non-immunes, while the indigenous population enjoying a relatively very high degree of immunity.

6. Attack rates were higher when infected localities were visited at night.

II.3. Development of vaccines

Two live attenuated YF vaccines were developed in the 1930s; the French neurotropic vaccine from human virus passaged in mouse brain and the 17D vaccine from human virus passaged in embryonated chicken eggs.

Milestones in the development and use of French neurotropic vaccine are summarized in the box. Between 1939 and 1952 over 38 million doses were administered (mostly by scarification along with smallpox vaccine) in Francophone countries of West Africa, and incidence declined dramatically (Table 1). However, a high incidence of encephalitic reactions in children led to its use in children under 10 years being stopped in 1961, and manufacture of the vaccine was discontinued in 1980.

II.3.1. Milestones in the use of French neurotropic vaccine[2, 9, 37, 38]

> **1927:** One of the first strains of yellow fever virus was isolated at the Institut Pasteur at Dakar.
>
> **1928:** The virulent organs from an infected monkey were transported to Europe and America, where they were placed at the disposal of various laboratories under the name of "French strain".
>
> **1931:** The first trials on humans by simultaneous injection of a suspension of the French strain and a certain quantity of human immune serum (the serum was added to limit the potential virulence of the vaccine strain).

1932: A method involving the subcutaneous inoculation of the modified French strain alone, without immune serum, was introduced.

1941: A departmental order made yellow fever vaccination by scarification compulsory for the whole civilian and military population of French West Africa. Yellow fever virtually disappeared from colonial French West and Equatorial Africa by virtue of a programme of compulsory immunization initiated in 1942 (Table 1). The same period was marked by major epidemics in the British colonies of Gold Coast and Nigeria, which had not implemented a policy of preventive immunization.

1951-1952: During the epidemics in Panama, Honduras, and Costa Rica, and again in eastern Nigeria, when the French neurotropic vaccine was used, cases of post vaccinal encephalitis were seen. Encephalitis was reported to occur in Nigeria at a rate of 3-4/1000 vaccinations, mainly in children, with a case-fatalty rate of 38%.

1961: The French neurotropic vaccine stopped being recommended for children under 10 years, because of the noted association with a high incidence of encephalitis reactions in children.

1980: The manufacture of the French neurotropic vaccine was discontinued.

Today, 17D is the only type of YF vaccine produced. Its development and use is summarised in box II.3.2. The immunological basis for its use has been reported elsewhere.

II.3.2. Milestones in the use of 17D vaccine[2, 9, 12, 15, 39, 40, 41]

1936: The Asibi strain of yellow fever was successfully established in a culture medium containing embryonic mouse tissue and 10% normal monkey serum in Tyrode's solution. After cultivation through 18 subcultures in this medium, cultivation of the virus was initiated in a medium containing minced whole chick embryo. After 58 subcultures in the latter medium, the tissue component of the medium was modified by removing the brain and spinal cord from the chick embryo before mincing. The virus was later maintained continuously in this medium for over 160 subcultures. The resultant strain was designated as 17D.

1937: Theiler and Smith reported on the use of the 17D strain for human immunization.

1938: After a year's experience in the production and application of yellow fever vaccine made from the cultured 17D virus strain, Smith, Penna, and Paoliello reported that there was available a practicable safe method of large-scale immunization against yellow fever. Vaccination of 59 000 persons in Brazil showed a) that mild reactions occurred five to eight days after vaccination in 10-15% of the persons vaccinated, with more intense reactions in only 1-2%, and b) that the vaccine was harmless even for children and for women at any stage of pregnancy. Laboratory studies indicated that about 95% of the vaccinated had acquired immunity as measured by specific antibodies.

1940: The first cases of jaundice and encephalitis as side-effects of 17D vaccinations in Brazil were recorded. In August of 1940, the practice of adding 10% normal human serum (necessary for the filtration of the virus) to the vaccine was given up. However, serum was used in preparing vaccine in the US, resulting in a major outbreak of hepatitis in the military in 1942. The practice had resulted in the transmission of the virus of infectious hepatitis, which for many years contaminated yellow fever vaccine.

1945: A 17D virus seed lot system was established to resolve the problem of over-attenuation or under-attenuation of 17D vaccine.

1950-1953: Violent outbreaks of yellow fever occurred in southern Brazil. During this period of intensive campaigns against epidemics about 12 000 000 people were vaccinated with 17D vaccine.

1951-1952: The occurrence of postvaccinal encephalitis in 15 infants from UK, US and France formed the basis for a recommendation that excluded use of 17D vaccine in infants under six months of age.

1958: The 17D vaccine was shown to induce very long-lasting immunity, providing the basis for new recommendations regarding reimmunization of travellers at 10-year intervals.

1966: Initiation of 17D manufacture in Dakar, Senegal in response to encephalitis during the FNV vaccination campaign in 1965.

1976: WHO: no vaccine shall be manufactured that is more than one passage level from a seed lot that has passed all safety tests.

1988: The Joint WHO/UNICEF Technical Group on Immunization in Africa recommended incorporation of yellow fever vaccine in routine child immunization programmes of countries at risk for yellow fever.

1997: There are 34 African countries at risk for yellow fever: 17 of these countries have a policy to include yellow fever vaccine in the EPI.

II.4. Early post-vaccination epidemiology 1940 - 1980

The first experiments in large-scale vaccination against yellow fever were conducted in French Africa south of the Sahara. During 1934 and 1935, 5699 persons were given three successive subcutaneous inoculations with the French neurotropic vaccine.[37, 38]

Before mass immunization campaigns were started in Africa, typical urban outbreaks occurred in Lagos, Nigeria, in 1925-1926, in Accra, Ghana in 1926-1927 and again in 1937, and in Banjul , the Gambia, in 1934-1935.[10] In 1940, mass immunization was initiated in French-speaking countries in West and Equatorial Africa where 25 million people were immunized about every four years (Table 1). As a consequence, yellow fever disappeared gradually in these countries, while epidemic and endemic activity continued in countries without immunization programmes.[37, 38]

Table 1: Yellow fever vaccinations with French neurotropic vaccine and cases of yellow fever in Africa, 1934-1953

Year	Number of yellow fever vaccinations by scarification in French West Africa and Togoland	Cases of yellow fever notified*		
		French West Africa and Togoland	Other African territories	Total for Africa
1934		23	41	64
1935		12	16	28
1936		24	19	43
1937		48	122	170
1938		27	49	76
1939	101 633	15	43	58
1940	372 632	4	4	8
1941	2 018 954	17	19	36
1942	4 932 068	10	6	16
1943	7 890 417	12	20	32
1944	11 577 269	2	11	13
1945	14 563 092	1	17	18
1946	17 179 812	1	51	52
1947	20 289 249	3	1	4
1948	24 293 762	2	4	6
1949	28 662 214	0	37	37
1950	32 530 124	0	17	17
1951	36 789 119	2	39	41
1952	42 095 954	1	53	54
1953	46 391 582	2	28	30

[38]* Cases occurring during the 1940 epidemic of yellow fever in the Anglo-Egyptian Sudan are not included.

The largest yellow fever epidemic ever recorded was in Ethiopia in 1960-1962, affecting 10% of the 1 000 000 residents of south-western Ethiopia, a population without a background immunity. The epidemic caused about 30 000 deaths. There had been some yellow fever activity west of Ethiopia in the end of 1950s: in former Belgian Congo, Sudan and Uganda. A curiosity was the appearance of many fatal cases with a fulminating, two to three-day course without hepatic or renal signs.

Entomological investigation implicated *Aedes africanus* in monkey-to-monkey and low-level monkey-to-human transmission, with in addition, intense interhuman spread by *Aedes simpsoni*. In 1964, an isolated human case in Uganda was thoroughly investigated; the evidence also implicated *A. africanus* in monkey-to-human transmission, and was supported by observations that this species descends to feed at ground level during the day.[9]

In 1961, immunization of children under 10 years old was suspended in Francophone West Africa. In 1965, yellow fever appeared explosively in a dry savannah region of Senegal, affecting children born since the last cycle of routine vaccinations. Although only 243 cases were officially documented, the true incidence may have been 20 000 cases, with a case-fatality rate of 10%. Efforts to control the epidemic resulted in a tragic, iatrogenic outbreak of postvaccinal encephalitis. A mass campaign with neurotropic vaccine was undertaken; 248 cases of encephalitis were identified, with a case-fatality rate of 22%. The manufacture of the French neurotropic vaccine was suspended in 1982.[9]

Epidemic activity continued in the 70s, but at a lower level than in the preceding or succeeding decades. A small outbreak in Okwoga District, Nigeria in 1970 provided the first evidence that *A. africanus*, the classic enzootic vector, was responsible for interhuman epidemic transmission.[9]

The decreasing number of cases resulted in a lack of interest in yellow fever and surveillance and immunization were progressively neglected after the early 1960s.

In 1971, yellow fever appeared in Angola for the first time in 99 years. The official incidence understates the true impact of the epidemic, and a serosurvey indicated that at least 13% of the urban population had been infected.[9]

Between 1977 and 1979, Ghana experienced a series of epidemics. As in other epidemics in anglophone countries that had not practised preventive immunization, there was a high attack rate in adults.[9]

The subsequent epidemiology will be discussed by region in later sections. Major milestones in the history of yellow fever are summarized in Table 2.

Table 2: Milestones in the history of yellow fever

Year	Milestones	Comments
- 1700	- epidemics with uncertain YF diagnosis in San Domingo, West Africa, Cuba, West Indies and Barbados in 1600s. - the first generally accepted description of YF in Guadeloupe, the other French Antilles and in Yucatan in 1648. - YF reached New York in 1668, Boston in 1691 and Charleston in 1699 by ship.	- discovery of "The New World" - slave trade from West Africa to Spanish-Portuguese America
1700s	- first generally accepted epidemic of YF in Europe. - first descriptions of YF in Africa.	- in 1730 an epidemic in Cadiz, Spain with 2200 deaths in September and October - Lind's account on YF in 1768 was based on epidemiological evidence in Senegal, while Schotte's publication in 1782 is the first clinical YF report from Africa
1800s	- YF was believed to be caused by poisonous "miasmata" from swamps, "effluvia" from the filthy docks of the port, "breath of other people" or divine displeasure. - ships arrived at European ports with YF on board - theories of the mosquito transmission of YF by Nott (1848) and Finlay (1881)	- devastating epidemics in the tropical and subtropical Americas decimated populations and paralysed industry and trade - YF epidemics in Europe: Brest in 1802, 1839, 1856, St. Nazaire in 1865, Swansea in 1843, 1851, 1864 and 1865, Southampton in 1852, 1866 and 1867
1900 US Reed Board proved that YF is transmitted by mosquito A*edes aegypti*		
1900-1930	- causative agent of YF was isolated. - experimental laboratory animal is found: first monkey in 1927 and later mouse in 1930. - urban outbreaks in Africa. - entomological and ecological knowledge increased.	- *Aedes aegypti* was found to transmit YF from monkey to monkey in 1927, *A. luteocephalus*, *A. apicoannularis* and *Eretmapodites chrysogaster* in 1928, *A. vittatus*, *A. africanus*, *A.simpsoni*-group, *A. scapularis* and *A.albopictus* in 1929, and *Taeniorhynchus africanus* in 1930
1930-1960	- serological surveys in Africa helped to delineate the boundaries of the area in which the disease had occurred (see Map 2). - the first YF vaccine in 1931. - 17D and French neurotropic vaccines were developed concurrently in 1930s. - mass immunization campaigns began in Brazil in 1938 and French-speaking countries in West Africa in 1940.	- mass immunization for YF was continued
1960-1985	- the decreasing number of cases of YF resulted in lack of interest in YF, and surveillance and immunization were progressively neglected.	- severe epidemics in Ethiopia in 1960-1962 and West Africa in 1969-1970
1986-	- 1986-1991 was an extremely active period for YF. - YF vaccination (17D) was recommended to be incorporated in routine child immunization programmes of countries at risk for YF in 1988	- 17 of 34 at risk countries in Africa have a policy to include YF vaccine in the EPI

III. Epidemiology

III.1. Vector reservoir, vertebrate maintainer and amplifier

Yellow fever occurs in tropical areas of South America and Africa. *Aedes aegypti*-infested areas of Central America, the Caribbean, North America, and Europe were subject to introduction and spread of the disease up to the early part of this century and must still be considered receptive areas.[4]

The **reservoir** of yellow fever virus is the susceptible **vector** mosquito species that remains infected throughout its life and can transmit the virus transovarially.[10] Yellow fever can persist as a zoonosis in tropical areas of Africa and America, with nonhuman primates responsible for **maintaining** the infection.[10] Man and monkey play the role of **amplifiers** of the amount of virus available for the infection of mosquitos.[10]

III.2. Yellow fever virus

The causative agent of yellow fever is an arthropod-borne virus from *Flavivirus* genus of the family Flaviviridae. The virus possesses a single-stranded, positive-polarity RNA genome. Viral particles are 43 nm in size; they are made up of a ribonucleoprotein core and a lipoprotein envelope.[10]

Considerable heterogeneity between isolates from Africa and South America has been observed among yellow fever strains.[43] However, there is very little empirical evidence for differences in virulence between wild strains of YF virus.

The prevailing view is that there are only two genotypes of YF in Africa and one or possibly two in South America, found by sequencing wild-type yellow fever virus strains of different geographic origin. The data base includes the entire genome sequences of the Asibi and French viscerotropic viruses (Ghana and Senegal, 1927) and partial sequences of the E gene, the 5' and 3' termini, and of the NS4a-NS4b region of multiple isolates from South America and Africa isolated over a 60 year period. Yellow fever strains in Africa fall into only two genotypes, one represented by West African viruses and the other by Central and East African strains.[44] South American viruses fall into one major phylogenetic group with respect to the E gene sequence. In contrast to the situation in Africa, the two South American genotypes do not segregate into discrete geographic distributions, but one genotype has not been recovered since 1974, suggesting that this virus may have been lost.

III.3. Transmission cycles and factors that affect them

III.3.1. Vertical, passive transmission in mosquitos by passage of virus from a vector to its progeny

In 1981, the vertical transmission of yellow fever virus in *Haemagogus equinus* was demonstrated.[45] This followed Cornet's 1979 recovery of YFV from male *Ae. furcifer-taylori* in Senegal and Aitken's experimental work showing vertical transmission in *Ae. aegypti*.[46] An explanation was now at hand for yellow fever virus to survive in nature without the need to postulate alternate vectors, prolonged survival, retarded transmission by long-lived, drought-resistant, adult female mosquitos, persistent infections of vertebrates, or reintroduction of virus from distant enzootic foci.[9] Recently, natural YF virus vertical transmission has been demonstrated in *Ae. aegypti*, its epidemic vector, in Senegal. It was thought that vertical transmission played a major role in the spread of the epidemic.[47]

The role of vertical transmission in nature has been proved by the isolation of several strains of virus from wild-caught males of vector species.[48] Its efficiency could be increased by the possibility of venereal infection of females by males.[49] By vertical transmission, the vector can keep the virus for very long periods and is thus the true reservoir.[50] The occurrence of vertical transmission has two important epidemiological implicatons. The first is that the virus can be transmitted only a few days after the emergence of *Ae. aegypti* females, theoretically at the first blood meal, without being delayed until the viral extrinsic cycle is completed 8 to 12 days later. Transmission in the human population will be more frequent than if there were only horizontal transmission. The second implication is that the YF virus can persist in the area until the next rainy season inside infected eggs laid in peridomestic breeding sites which dry up, such as used tyres and old pots.[47]

III.3.2. Horizontal, active transmission between vertebrates by passage of virus from one vertebrate host to another through a vector in which the virus replicates

This may occur in one of two ways depending on ecological factors which affect the degree of contact with susceptible hosts [49]:

1) **Maintenance cycles**, with a relatively stable prevalence of infection: vector-vertebrate contact is loose and yellow fever will appear in enzootic or endemic form.

2) **Amplification cycles**, with an increase of the amount of circulating virus: vector-vertebrate contact is close and yellow fever will appear in epizootic or epidemic form.

A number of ecological factors may affect horizontal transmission. The degree of contact between vectors and susceptible vertebrate hosts, and thus the mode of transmission depends on the amount of virus, the abundance of vectors and vertebrates. The infection of the vector depends on the specific *intrinsic* relations between the virus and its invertebrate host (e.g. dissemination of the virus in the invertebrate host: crossing the gut barrier, invading different tissues), but also the *extrinsic* factors which are independent of the virus: the vector must become infected

after a blood meal on an infected vertebrate host, the virus must replicate in the tissues of the invertebrate host and after, the virus must be inoculated with saliva into another vertebrate host. The invertebrate host must thus live long enough for the virus development inside its body. The mosquito must have trophic preferences for primates to act as a vector in nature.

III.4. Distribution, ecological zones and types of transmission in Africa

III.4.1. Vegetation

The distribution of yellow fever in Africa is best understood in terms of vegetational zones which reflect rainfall patterns and determine the abundance and distribution of mosquito vectors and vertebrate hosts (Table 4).

III.4.1.1. Equatorial rain forest (Enzootic; mainly sylvatic)

The great **equatorial rain forest** zone extending from Guinea in the west to Uganda in the east and south to Equatorial Guinea and northern Angola is the zone of year-round enzootic yellow fever transmission between monkeys and *A. africanus*. The virus activity is generally at a low level and sporadic cases or focal outbreaks are the rule, in a manner analogous to jungle yellow fever in South America. Transmission is predominantly monkey-to-monkey, and human infection is sporadic (Figure 1).

III.4.1.2. Humid/semihumid savannah (emergency zone; cyclic epizootics and epidemics; either monkey-to-monkey or monkey-to-man transmission; major area of risk)

Extending outwards from the rain forest zone, with decreasing rainfall, are found in sequence **savannah-forest mosaic and moist (Guinea) savannah**. During the rainy seasons these regions are prone to repeated emergence of yellow fever activity, which may occur at a high rate of transmission due to the presence of vector and host populations. Sylvatic *Aedes* (e.g., *A. furcifer, A. luteocephalus, A. vittatus*) reach very high densities during the rainy season, and are responsible for cyclic epizootics in monkey populations and epidemics with interhuman transmission.[51] This zone is also known as the intermediate zone of transmission (fig 1). Vertical transmission in these mosquitos assures virus survival and continuation of epizootic waves. It is in this vegetational zone that most epidemics of yellow fever have occurred. There may be focal outbreaks separated by areas without human cases.

III.4.1.3. Dry savannah (mainly man-man transmission; potential for epidemics)

In the **dry savannah zones** the rainfall is very low and the rainy season abbreviated. The sylvatic vector populations are too low or active for too short a period to sustain an epizootic. The virus may nonetheless be introduced into a cycle of interhuman transmission by *Aedes aegypti*, either if an epizootic extends from the humid savannah, or if infected individuals move to villages with the domestic vector in the dry savannah. If the virus is introduced into urban or very dry savannah regions where the human population stores water and lives in association with domestic *A. aegypti*, explosive outbreaks of *A. aegypti*-borne yellow fever (urban-type transmission, fig 1) may ensue.[9] Usually the outbreak spreads from village to village following the lines of communication used by humans. When the epidemic has started, the virus can be transported to distant places either by infected persons or by infected mosquitos.

Table 3: Transmission cycles, vegetational zones and vectors[9, 49]

Rainforest	Moist savannahs	Dry savannahs / urban areas
Enzootic area	Zone of emergence -cyclic epizootics & epidemics-	Epidemic zone
Endemic area	**Potential epidemic area**	
Jungle yellow fever	**Intermediate**	**Urban yellow fever**
monkey-mosquito-monkey (human infection is sporadic and often unrecognised)	monkey-sylvatic *Aedes*-human (both humans and wild vertebrates are involved in the virus cycle)	human-mosquito-human
Aedes africanus	*Aedes furcifer*	*Aedes aegypti*
	Aedes luteocephalus	
	Aedes metallicus	
	Aedes neoafricanus	
	Aedes opok	
	Aedes simpsoni group*	
	Aedes taylori	
	Aedes vittatus	

*   Probably *Aedes bromeliae.*

III.4.2. The vectors in Africa

The main vectors of yellow fever in Africa are mosquitos of the genus *Aedes*, subgenera *Stegomyia* and *Diceromyia*. Seven species are thought to play an important role in nature: *Aedes (Stegomyia) aegypti, A. (Stegomyia) africanus, A. (Stegomyia) opok, A. (Stegomyia) luteocephalus, A. (Stegomyia) simpsoni group, A. (Diceromyia) furcifer,* and *A. Diceromyia) taylori.*[49]

The eggs of the vectors are resistant to desiccation; they remain quiescent during the dry season and hatch only when rain fills the breeding places. In savannah areas there are no adults during the dry season and transmission is discontinuous.

Aedes-vectors can be classified into three categories according to their contact with humans:

a)   domestic (i.e. around the household) - mainly *A. aegypti*

b)   wild - all other species

c)   semi-domestic - wild vectors which can acquire domestic habits - *A. furcifer, A. africanus, A. luteocephalus.*

Figure 1: Cycles of yellow fever transmission

South America

Yfcycles

Haemagogus

Aedes aegypti

Monkey

Monkey
Human

Human

Haemagogus

Aedes aegypti

Jungle yellow fever

Urban yellow fever

Africa

Aedes africanus

Sylvan *Aedes spp**

Aedes aegypti

Monkey

?

Monkey
Human

Human

Human

Aedes africanus

Sylvan *Aedes spp**

Aedes aegypti

Jungle yellow fever

Sylvatic yellow fever

Urban yellow fever

Rainforest zone

**Moist savannas
Forest savanna
ecotone**

**Dry savannas and
urban areas**

* West Africa: *Ae. furcifer, taylori, Ae. luteocephalus, Ae. africanus, Ae. opok, Ae. vittatus, Ae. metallicus*
East Arica: *Ae. bromeliae, Ae. africanus,* others

III.4.3. Animal vertebrate hosts in Africa

In 1928 Stokes described the susceptibility of an Asiatic monkey, *Macacus rhesus,*[28] which became the first laboratory animal. In Africa, almost all zoological groups have been studied, but only primates are implicated in the natural transmission cycles of yellow fever virus, because other animals have low viraemia and/or lack of contact with known vectors.

Monkeys remain the main vertebrate hosts involved in the circulation of yellow fever virus in Africa; galagoes (bush babies) may also play an important role. The viraemia developed by monkeys is always short, two to five days, with a maximum of nine days.[52] After infection they have life-long immunity, so they cannot be virus reservoirs.[49] Those monkeys which stay in the canopy (top of the forest trees) will be the main vertebrate hosts in the wild cycle (e.g. *Cercopithecus mitis*), while those which come to ground level (*Cercocebus*) or leave the forest to enter plantations (*Cercopithecus aethiops*) will be the link between the wild cycle and humans. In savannah areas, monkeys usually live at ground level, but sleep in trees where they are exposed to mosquito bites. There, monkeys such as patas or baboons easily disseminate virus because their territory is very large.[49]

III.5. Recent epidemiology in Africa

The period 1986-1991 was an extraordinarily active period for yellow fever in Africa. The world wide total of 20 424 reported cases and 5447 deaths represented the greatest yellow fever activity reported to WHO since reporting began in 1948 (Table 5 / Map 3).[53, 54, 55]

The largest number of cases was reported from Nigeria, where a resurgence of yellow fever has been noted since 1984. In 1986 and 1987, the Nigerian Ministry of Health and WHO supported two epidemiological studies to try to determine the extent of YF outbreaks. One was in Oju, one of two major epicentres in the 1986 sylvatic YF epidemic, the other being in Cross-River state. In 1986, surveys in treatment centres and nine villages in the Oju area of Benue state established an overall attack rate of 4.9% and a mortality rate of 2.8%. The population at risk in Oju was 200 000, thus the study suggested that 9800 cases and 5600 deaths occurred in Oju. Official 1986 figures indicated 559 reported cases and 200 reported deaths for all of Benue state, thus under-reporting in the state was at least 17 and 28 times respectively.

In 1987, during surveys in 17 hospitals and three villages in Oyo state, 3.6% of the 60 000 village residents were interviewed. Results indicated an attack rate of 2.9% and a mortality rate of 0.6%. The 1987 outbreak was in a densely populated area, and was an urban type spread by Aedes aegypti. The population at risk was estimated at four million, thus 116 000 cases and 24 000 deaths were estimated to have occurred in Oyo state; 130 and 50 times respectively those reported.

From 1984 to 1993, Nigeria reported over 20 000 cases and 4000 deaths. Because of under-reporting, YF is estimated to have affected at least one million people in Nigeria over this resurgence. In 1994, another outbreak in Imo State, Nigeria, spread to neighbouring districts of Cameroon.

The first epidemic of YF in Cameroon occurred in 1990, during the second half of the rainy season. There were 180 known cases, of which 125 died. The affected area was in the yellow fever belt, situated around latitude 11 degrees North and 14 degrees East. This is a mountainous area of scattered villages. A serosurvey in 11 villages found 20% YF-IgM-positive individuals among 107 tested; most were aged under-10 years. IgM assays for other flaviviruses were negative, while there was substantial cross-reactivity in IgG. It was estimated that less than 4% of cases had been reported and that the real number of cases could have been between 5000 and 20 000 with 500-1000 deaths.[56]

The years 1992 and 1993 were relatively mild in terms of the total numbers of cases of yellow fever, but the first outbreak ever recorded in Kenya was documented. The outbreak was the jungle type (monkey-man transmission), and affected predominantly young men, but concerns that the disease could spread to cities, where Aedes aegypti was present, led to mass vaccination of almost one million persons in affected districts. This represented the first report of YF from East Africa for almost 50 years. The incidence of yellow fever increased slightly in 1994 and 1995, compared with the previous two years, yet remained lower than incidences reported before 1992.[21]

From November 1994 through January 1995, Gabon reported its first outbreak ever. The outbreak started as jungle-type YF in a remote mining camp in the forest, but spread rapidly to villages outside the forest where A. aegypti mosquitos were present, indicating a shift to person-person transmission. This epidemic was identified as Y.F. according to first serological and reverse transcription/polymerase chain reaction (RT-PCR) results, but no virus was isolated. Subsequently sera were obtained from 37 people who lived in the same region and presented symptoms compatible with YF. In ten, YF virus RNA was obtained by RT-PCR. Nucleotide sequence of two regions of the RNA in three sera differed from that of the Asibi strain of YF, and the presence of a new topotype was hypothesized.[57]

In late 1995, an outbreak was detected in Liberia. The first case was in a Nigerian soldier of the West African Peace Keeping Force stationed in Buchanan. By the end of 1995, 360 cases and 9 deaths were reported, and a yellow fever case had been confirmed in Sierra Leone. Mass immunization campaigns delivered nearly one million YF vaccine doses in response to this outbreak.

In Senegal, an outbreak of intermediate-type YF occurred in 1995, killing at least 46 humans among an estimated exposed population of 9000. It was quickly stopped, following a prompt immunization campaign (quoted in Fontenille).

All the outbreaks occurred in the vicinity of the emergence zone in the moist savannah, or in the dry savannah, along the genuine "yellow fever belt" stretching from Senegal to Ethiopia and Kenya. The rural populations were the most affected, and the vector in the initial phases was frequently an anthropophilic wild mosquito (A. africanus, A. bromeliae, A. furcifer). The towns, however, were not spared (e.g. Luanda, Angola 1971, several cities of south-west Nigeria 1987, Buchanan, Liberia 1995).

In many countries, only part of the countries concerned is exposed to the risk of severe outbreaks. However, experience in Ghana 1977-1979 and Nigeria 1986-1987 shows that yellow fever can be transported from an epidemic focus to a distant area with different climate and environment, and there produce a secondary epidemic if the conditions are favourable.

Despite the clear indication of the potential risk from YF, it is not widely recognised as an endemic problem in Africa. For the most part, only case clusters and outbreaks are recorded. This reflects the insensitivity of reporting, as endemic virus transmission must certainly occur. Nonetheless, the actual disease burden from this endemic infection is difficult to estimate - see section V.

Table 4. Epidemics reported 1984-1996 [21] [53] [54] [55] [58]

Country	Year	Cases	Age	Sex	Place	Time	Occupation	Other comments
Angola	1988	37			Luanda (urban)			- 85% of population of Luanda was vaccinated in response
Benin	1996	124			Atakora-Borgou	July-		
Burkina faso the	1984-1985	24			South-east			- cases notified on the basis of clinical data alone; they occurred at same time as an outbreak of hepatitis.
Cameroon	1990	173	51% <5, 79% <10		Northern		children	
Cameroon	1994	10			Adamaoua Prov.	Nov. - Dec.		- outbreak limited due to its occurrence within the dry period
Gabon	1994-1995	44	4% <15	Majority male	north-eastern mine area	Nov. - Jan.	forest workers	- heavy rains preceded
Ghana	1993-1994	118		Male 67%	Upper West: Jiripa Dist.	Oct. - May		
Ghana	1996	27			Upper East			
Guinea	1987	5			Siguiri (border)			- connected to Malian epidemic
Kenya	1992-1993	54	33% <19	Male 65%	Kerio Valley	Sept. - March	young male	- first epidemic reported from Kenya
Liberia	1995	360			Buchanan	November		- vaccination coverage in Buchanan reached 80% in response
Mali	1987	305	70% <15	Male 62%	near Bamako	Sept. - Nov.	children	- 1969 mass immunization protected adults - urban risk: infected *Aedes aegypti* was found in Bamako
Mauritania	1987	21			south-west	Oct. -Dec.		- connected to Malian epidemic, but coinceded with an epidemic of Rift Valley Fever
Nigeria abscence	1986-1992	18 940	50% adults in 1987, 46% in 1991	Male 58% in 1987, 52% in 1991	Oju, Oyo, Kano, Kaduna, Bauchi, Ipetu-Iyesa			- the population as a whole was susceptible (because of the of regular vaccination, and long time from the last epidemic).
Nigeria	1993-1994	152	9% <5 18% <15	Male 57%	Imo State	Oct. - Jan.		
Nigeria	1994	1227			Imo State	Sept. - Dec.		
Niger	1990							- spread from epidemic in Nigeria. First outbreak ever in that country
Senegal	1995	79		Male 53%	Kounglel Dist.	Oct. - Nov.		- 8000 people exposed. Prompt immunization campaign conducted
Sierra leone	1995	33			Eastern Prov.	Nov. - Dec.		- a single case of YF was serologically confirmed within weeks of the YF outbreak in the bordering area of Buchanan, Liberia (suspected cases 33).

III.6. Risk factors

The distribution of cases by age depends on the immune status of the population at the time of the outbreak. When the entire population is devoid of natural or vaccination-induced immunity, the distribution of cases parallels the demographic distribution (e.g. Nigeria 1987). On the other hand, when the population has been subjected to an epidemic and/or a mass vaccination campaign several years earlier, the adults still have some protection and are relatively less affected by the epidemic. For example, in 1969, the population in the northern area of Ghana was immunized in a large campaign conducted in response to an outbreak of YF. When YF recurred in the same area in 1977-1980, the epidemic involved mainly children under 15 years of age, who were too young to have been immunized in 1969. Thus 67% of cases and 82% of deaths in 1977-1980 occurred in this age group. Similar phenomena occurred in several African countries including Burkina Faso 1983; Mali 1987; Cameroon 1990, where over 70% of cases were in children under 15 years of age. This led to the EPI recommendation that YF vaccine be included in the routine EPI in countries at risk for yellow fever.

Climatic conditions affect both the abundance of the vector and the incubation period (the time between the infecting blood meal and the time of the first transmission) which is shorter with higher temperatures. Human activities can also influence transmission by action on host abundance, either negative (hunting monkeys and thus reducing the number of hosts; mosquito control), or positive (creating artificial breeding places; overpopulation). Forestry practices such as felling trees may increase transmission by bringing the treetop-dwelling mosquitos down closer to human contact (Table 5).

Table 5: Ecological factors affecting yellow fever transmission

Virus	- amount of virus in the beginning of amplification cycle - virulence
Vector	- abundance - longevity - trophic preferences - number of blood meals/day - length of incubation of YF virus in the vector - vector competence
Vertebrate Host	- abundance - immunity rates - susceptibility (duration, height of viraemia)
Climate	- temperature - humidity - duration of rainy season
Human behaviour	- hunting monkeys - creating artificial breeding places for vectors (pots, tyres, etc.) - forestry practices - population growth - urbanization - migration - political unrest

III.7. Epidemiology in the Americas

Two types of epidemiological cycles have operated in South America: jungle and urban. The last urban-type epidemic was in 1928-1929 in Rio de Janeiro (the last case of urban yellow fever was notified in 1942). The two forms differ in that the urban form is transmitted by *A. aegypti* while the jungle yellow fever is transmitted by the bite of a *Haemagogus* or other forest-breeding mosquito that was previously infected by feeding on an infected vertebrate host.[49] In 1949, the ten countries most afflicted by urban yellow fever (Brazil, Bolivia, British Guyana, Colombia, Ecuador, French Guyana, Panama, Peru, Surinam and Venezuela) unleashed a vast campaign against *A. aegypti*, destroying its urban breeding grounds, that by 1965 had eradicated the mosquito and the disease from most urban areas in the continent. [59] But *A. aegypti* has now reinfested most of Central and South America, and occupies habitats adjacent to the areas where endemic yellow fever transmission occurs.[53]

The endemic zone corresponds to rain forests drained by the great river systems, where the yellow fever virus is circulating "silently" among the monkeys, but the emergence of human cases is rare.[60] Epizootic waves exhaust susceptible nonhuman primate populations, and five to 10 years may elapse before a sufficiently large non-immune population of slow-breeding primates is reconstituted to permit recurrent virus transmission.

Over the last 25 years, a mean of 115 cases have been reported annually from Latin America. In 1990s, five American countries have reported yellow fever: Brazil, Bolivia, Colombia, Ecuador and Peru. Bolivia and Peru has accounted for 82% of the human cases (PAHO, 1998. Personal communication). In 1995, Peru reported a jungle-type outbreak with 440 cases and a case fatality rate of 38%. This was the largest outbreak in the region since the 1950s. Yellow fever affects mainly unvaccinated people who enter the forest for hunting, fishing, or wood cutting and become infected within the sylvatic cycle - about 80% of cases are reported in young adult male forest workers. Thus yellow fever in South America can be considered an occupational disease.[15]

Table 6: Age and sex distribution of yellow fever cases in South America

Country	Year	0-1 years old	1-15 years old	More than 15	Male: female ratio
Bolivia	1997	0	13	87	2.9 : 1
Brazil	1996-97	0	16	84	2.4 : 1
Peru	1997	0	10	90	3.2 : 1
Total		0	15	85	

The apparently low virus circulation for a long period in the Americas may have been due to massive campaigns of vaccination and to vector control. The situation can suddenly reverse as observed in the past with yellow fever.[61] *Aedes aegypti* is present in urban areas in the Americas (including southern parts of the USA).[15] *Aedes albopictus*, which was discovered in the Americas in mid-1980s, and was probably imported from Asia in used car tyres[62], and which seems to have a great adaptive capacity, is now in an intermediate position between the forest galleries and the urban areas infested with *Aedes aegypti,*[60] and thus increases the risk for introduction of yellow fever to the urban environment.[62]

Concerns about the potential for YF epidemics to increase in Latin America were highlighted in two recent reports from Brazil. Yellow fever virus transmission was very active in the rainy season in Maranhao State in Brazil in 1993 and 1994.[63] In 1993, of 932 people examined from Maranhao, 70 were positive for YF serologically, histopathologically, and/or by virus isolation, and another four cases were diagnosed clinically and epidemiologically. In Mirador (17 565 inhabitants), the incidence was 3.5 per 1000 people while in a rural yellow fever risk area (14 659 inhabitants), the incidence was 4.2/1000; 45.2% of 62 infections were asymptomatic. In 1994, 49 serum samples were obtained and 16 infections were confirmed (two by virus isolation, two by seroconversion, and 12 by serology). The investigation suggested that this was the most extensive outbreak of yellow fever in the last 20 years in Brazil, and was related to lack of vaccination.

Aedes aegypti, after having been eradicated in 1954, reappeared definitively in 1976-1977. A second Flavivirus vector, Aedes albopictus has been present in Brazil for about 10 years in some States, including Sao Paulo. Analysis of the distribution of YF cases between 1972 and 1994 showed two epidemiologic regions.[64] In the first region, the endemic area, the YF virus circulates "silently" among monkeys, and the emergence of human cases is rare. In the second region, the epidemic area, some epizootics occur in a more or less cyclic way, and human cases can be numerous. Nevertheless, these outbreaks are considered "sylvatic" epidemics, since as Ae. aegypti is not involved. From the Amazonian region, the virus moves forward along the forest galleries of the Amazone tributaries, from North to South. Dengue epidemics appear in all States, and reflect the geographical distribution of Ae. aegypti. Recently, Ae. aegypti was found in the southern part of the Para State, in the Carajas region considered to be the source of the main YF epidemics. Furthermore, Ae. albopictus is now increasing its distribution area, specially in the suburban zones. This potential vector has an intermediate position between the forest galleries, where the YF virus circulates, and the urban agglomerations infested with Ae. aegypti. Thus, the importance of intensified surveillance of the epidemiological situation of YF in Brazil was stressed.

III.8. Yellow fever and Asia

In 1934 Dudley was already concerned about the possibility of yellow fever to spread from its endemic home in West Africa to the coast of East Africa and from there to Asia.[65] Since then there have been epidemics in Sudan in 1940,[66] Ethiopia in 1960-62[67] and Kenya in 1992-93,[68, 69] but yellow fever never spread to Asia. The following reasons have been postulated but none provides a completely satisfactory explanation: 1) yellow fever was never introduced to Asia, 2) humans vary in susceptibility, 3) there is cross-protection between flaviviruses, 4) the maintenance cycle is absent, or 5) there is variation in vector competence and/or behaviour (C. Leake, 1997, personal communication).

III.8.1. Yellow fever was never introduced in Asia?

There have been multiple opportunities for the introduction and spread of yellow fever to Asia. The opening of the Panama Canal in 1914 brought Asiatic ports into more direct contact with the old endemic homes of the disease.[32] The chances for yellow fever to be introduced in Asia increased with the marked increase in air travel since the 1960s. An average of about 200 000 passengers a year disembarked at Calcutta airport in 1982-1988, and with about 25% of the passengers it was not noted whether they possessed a valid yellow fever vaccination certificate or not.[70]

III.8.2. Humans vary in susceptibility?

There is no convincing evidence of innate differences in susceptibility to YF. The apparently lower susceptibility to YF of the Indian population appears to reflect cross-protection from other flaviviruses. Out of 876 specimens of human sera collected from Australia, Ceylon, China, Java, India, the Malay States, The Philippine Islands, and Syria in 1937, only two gave protection against yellow fever. Both of them came from India, and as far as could be learned neither of the donors had ever been exposed to yellow fever.[71]

In the 10th Regiment of Infantry during the Napoleonic wars, out of 408 officers who contracted yellow fever in Gibraltar in 1815 after service in India, only four died, in contrast to 21 deaths in 55 men who had not been to India (case-fatality rates respectively 1% and 38%).[72] Following slave emancipation in the British West Indian colonies in 1838, hundreds of thousands of workers were brought from India for the sugar plantations. These Indian immigrants were little affected by the outbreaks of yellow fever which occurred among new arrivals from Europe.[73]

The issue of genetic or racial differences in susceptibility deserves further analysis. Genetic determinants are known to affect the pathogenesis of flavivirus infections, and resistance to yellow fever virus in mice is determined by an autosomal dominant allele (*Flv).* Genetic background has been shown also to influence the immune responses to flaviviruses in mice. The role of genetic factors in human responses to yellow fever infection is uncertain. The older literature makes repeated reference to racial differences in the lethality of yellow fever, rates being lower in blacks than whites during outbreaks in West Africa, tropical Africa and the US.[74, 75] It is uncertain whether the apparent increased resistance of blacks reflects acquired immunity or is due to genetic factors. In the case of dengue, whites had a higher incidence of dengue haemorrhagic fever than blacks during the 1981 epidemic in Cuba, a finding that

could not be explained on the basis of a racial difference in the background of immunity. An association between HLA haplotype and disease severity also was found in patients with DHF. The question of racial differences in susceptibility to yellow fever will be resolved only by well-controlled epidemiological and serological studies in the setting of an outbreak affecting both races. (Monath, T.P. Written communication, 1998)

III.8.3. Flavivirus cross-protection?

Serologic cross-reactions between flaviviruses lead to difficulties in laboratory diagnosis and cross-immunity to other flaviviruses has been observed to influence susceptibility to other flavivirus infections. Some measure of protection may be associated with antibodies to epitopes shared by distantly related flaviviruses.[76]

A small study of response to YF vaccination of Malay soldiers around 1960 found that most soldiers had antibody prior to vaccination that cross-reacted with YF antibody assays. Response rates after vaccination were equal in those with or without prior antibody, but the antibody levels achieved were lower in the former.[77]

It has been thought possible that dengue immunity protects against clinical yellow fever, or by reducing viraemia, decreases the possibility of secondary spread following a chance introduction.[4] However, the mouse-protection test gave no support to the suggestion that an attack of dengue protects against yellow fever, since it was found that the blood-serum from a recovered case of dengue contained no immune body to yellow fever.[78] However, cross-protection may be dependent on the specific virus causing primary infection, the interval between primary and secondary infection, and on quantitative and qualitative aspects of the heterologous immune response, including the cellular immune response.

III.8.4. Maintenance cycle absent?

The jungle, intermediate and urban cycles of yellow fever need different vectors. A missing link can cause the cycles to break and an epidemic to die out. The environment is divisible into "niches" which are occupied by one or more species of organism. A species is so closely adapted to its niche in the local environment that it is unlikely to be replaced by an alien emigrant race.[65] In the East African emergence zone the strains of *Aedes bromeliae* were found to be virtually non-man biting. Thus the link between the forest maintenance cycle and establishment of an urban *Aedes aegypti*-man cycle was broken[79]. On the other hand, as early as 1929, Dinger and his team reported the transmission of yellow fever in Java with *Aedes (Stegomyia) albopictus*,[12] which has the potential of bridging the gap between jungle and urban yellow fever cycles.[80] *A. albopictus* is found from Madagascar eastward through Asia to Japan, Korea, and northern China. [81] Furthermore, there is an abundant monkey population, *Macacus rhesus*, which is extremely susceptible to the virus, in the plain of the Indus and Ganges. *M. sinicus* is also susceptible, on the Deccan (south of the Godavari River).[12] Thus, there is no definitive reason for failure of maintenance cycles in Asia.

III.8.5. Variation in vector competence and behaviour?

Asian strains of *A. aegypti* may be less efficient vectors of yellow fever virus than African or American populations.[4] Hindle's experiments in 1929 showed that the one Indian strain of *A. aegypti* was a less effective vector than the African strains of mosquitos for the one strain of the virus in question.[82] But the studies by Aitken and Tabachnick showed Asian populations of *A.aegypti* to be better vectors than West African populations.[83] It was also shown by Miller et al, that in the presence of high population density an incompetent mosquito vector can initiate and maintain virus transmission resulting in an epidemic.[84] Vector incompetence thus becomes less tenable as an explanation for the absence of yellow fever in Asia.

In summary, it is not known why yellow fever never spread to Asia, but there is no evidence to show that this could not occur. All South- East Asia countries should ensure that persons arriving from the Latin American and African countries at risk for yellow fever have a valid yellow fever vaccination certificates.

IV. Cost effectiveness of yellow fever vaccination

Vaccinations provided through the EPI are believed to be one of the most cost-effective child survival interventions at a cost between $10 and $15 per child.[85] The Joint WHO/UNICEF Technical Group on Immunization in Africa recommended in 1988 incorporation of yellow fever vaccine in routine child immunization programmes of countries at risk for yellow fever, and the World Bank's 1993 World Development Report also strongly endorsed adding yellow fever vaccine to the EPI of the at-risk countries.[15]

YF vaccine previously suffered from poor thermo-stability. Improved stabilisers have provided a product whose shelf life is up to two years at a temperature of -20°C or +4°C. In 1995, of the eleven vaccine manufacturers approved by WHO, seven were producing vaccines that met stability standards.[86] An update on this situation will be discussed at the workshop.

There is only one published cost-effectiveness analysis of preventive yellow fever vaccination versus emergency mass vaccination campaigns, conducted by Monath and Nasidi (1993). This analysis was done for Nigeria under conservative assumptions of vaccine coverage and efficacy. The models used are explained in detail in the publication "Should yellow fever vaccine be included in the Expanded Programme of Immunization in Africa? A cost-effectiveness analysis for Nigeria".[87] Using assumptions based on data from other African countries, the cost of adding yellow fever vaccine to the existing EPI was estimated as US$ 0,65 per fully immunized child, whereas the cost of emergency vaccination was estimated as US$ 7,84/person. For an epidemic of moderate size the cost-effectiveness of emergency mass immunization for control of hypothetical yellow fever epidemics was two-fold higher than that of the EPI. However, the efficiency of the EPI was seven-fold greater in terms of cases and deaths prevented.[87]

In the Gambia, yellow fever vaccine was added to the EPI in 1979 following a successful mass campaign in which 97% of the population over six months of age received a dose. There have been no subsequent reports of yellow fever from the Gambia. Adding yellow fever vaccine did not significantly increase the per dose cost of immunization delivered in the EPI. According to the estimated cost of EPI with and without yellow fever vaccination, the average total cost per yellow fever vaccine dose had a difference of only US$ 0,01 (adding the cost of YF vaccine to the total cost of the EPI and averaging this over all vaccine doses given).[88] However, the average cost per CHILD obviously increased with the addition of another vaccine.

Concerns have been raised over the affordability of national immunization programmes and the need for continued donor support, identification of other financing mechanisms, or reconsideration of policies aimed toward accelerating and maintaining immunization coverage has been highlighted.[85] Integration of YF vaccine into the EPI needs to be done in the context of strengthening the immunization programmes in general in many of the affected countries, where current infrastructure for the routine programme is weak.

The cost of preventive immunization campaigns (as opposed to reactive campaigns in the face of an outbreak) is unknown. The increasing promotion of measles vaccine campaigns raises the question as to the integration of YF vaccine in such campaigns. It is of note that most campaigns conducted in the first decades of YF immunization programmes used either scarification or jet injector equipment. Such methods are no longer recommended; in particular WHO does not recommend the use of jet injectors because it is difficult to guarantee that they are free from risk of transmission of bloodborne infection. Mass campaigns using autodestruct needles and syringes are likely to be more costly, and perhaps require more human resources. If YF vaccine is included with measles campaigns, questions would also arise about repeat vaccination. For measles control/elmination, follow-up campaigns would be needed every five years or so (or even more frequently, depending on coverage in the routine programme). YF vaccination need not be repeated, although data on any potential adverse events are lacking.

Immunization campaigns in the lowest income countries tend to involve a substantial importation of cold chain equipment, supplies, vehicles, and technical assistance from developed countries in order to attain coverage goals within a short period of time. These country programmes are vulnerable to breakdowns of equipment and vehicles and limited access to financial resources needed to cover recurrent costs of operating at this level of activity. Rapid increases in coverage rates are sometimes followed by periods of low immunization activity in some countries, demonstrating the need for sustainable immunization strategies in the future.[85] Mass immunizations require a well-co-ordinated and planned effort on the part of national authorities, intensive social promotion, and strong management.[89]

The cost of adding YF to immunization programmes (routine vaccination of infants and/or preventive campaigns in high-risk areas) relates mainly to the cost of the vaccine (12 to 25 cents per dose) and to safe injection and disposal equipment (around 13 cents per injection). In 1995, it was estimated that to provide YF vaccine to the (then) 31 countries at risk, with a combined population of around 18 million infants, would cost some four to five million US dollars per year (S.Robertson, unpublished trip report 1995). Because YF vaccine can be given simultaneously with the EPI vaccines, its delivery should not involve an extra visit to a health facility, which greatly reduces total costs. In practice, however, health workers in many countries are reluctant to administer YF vaccine as a separate injection to children who are already receiving two injections (eg those who come late for DTP and hence are due for DTP and measles on the same day). Mothers are then requested to return on another occasion for YF vaccine, increasing the programme costs as well as reducing coverage because many mothers fail to return.

As discussed in section 6 and Table 9, current coverage with YF vaccine in most of the countries that use it is inadequate to prevent an epidemic. The 1995 outbreak in Senegal occurred when reported coverage was 46% (quoted in [47]); and in the same country in 1967, an epidemic occurred despite prior immunity levels of 57% in children under 10 years.[102] The prevalence of immunity in humans required to prevent an epidemic has been estimated between 60 and 90% depending on vector biting rate and vector competence.[87]

A strategy which allows administration of YF vaccine using the same syringe as measles vaccine would not only reduce costs (the cost of safe injection equipment more or less doubles the cost of each dose of measles or YF vaccine); it would also be likely to increase coverage. A study in Mali used a combined vaccine in which 17D YF vaccine and Schwarz measles vaccine had been lyophilized together[91], and seroconversion to both components was high. A combined preparation of measles and YF vaccine would facilitate the achievement of high coverage, but the fact that the market would be restricted to countries at risk for YF may make its production unattractive to manufacturers. Its distribution could also be complicated in countries where only part of the country is at risk for YF, so that health facilities in some areas would get single-antigen measles vaccine while others would need the combined preparation.

Studies in Cote d'Ivoire and Cameroon showed that YF vaccine mixed with measles vaccine immediately before injection produced similar seroconversion rates as when the vaccines were given separately[92,93]. However, in these studies the investigators administered the reconstituted mixture of vaccine within one hour, not after several hours, as would occur in a routine immunization clinic. There is insufficient data available on the stability of YF vaccine mixed with measles vaccine and maintained for several hours[94]. YF vaccine once reconstituted retains potency for up to three hours if kept in ice, but loses potency much more quickly if it is kept at room temperature. Thus it would be essential to keep vaccine on ice. Strict precautions would also be needed to prevent bacterial contamination. Also we lack data on possible Adverse reactions caused by mixing vaccines from different manufacturers. The EPI/WHO policy does not recommend mixing different vaccines in one syringe before injection.[134]

Cost-effectiveness analyses should also consider factors affecting efficacy and safety of the vaccine. For theoretical reasons, YF vaccine is not recommended for pregnant women, though benefits outweigh the risks in an outbreak setting. A study from Nigeria showed reduced seroconversion to YF vaccine in pregnant women.[87] Yellow fever vaccine is not recommended for symptomatic HIV infected persons or other immuno-suppressed Individuals.[69] A recent study showed poor response to YF vaccine in HIV-infected children aged 7-14 months in Cote d'Ivoire. Only 17% of 18 HIV-infected children sero-responded adequately compared with 74% of 54 HIV-uninfected children[133]. The implications of HIV infection for mass YF vaccine use in areas of high HIV-prevalenceneeds to be assessed.

V. Surveillance

V.1. Definition of surveillance

Surveillance and rapid response to identified disease threats are at the core of preventive medicine. A well-designed and well-implemented infectious disease surveillance programme can provide a means to detect unusual clusters of disease, document the geographic and demographic spread of an outbreak, estimate the magnitude of the problem, describe the natural history of the disease, identify factors responsible for emergence, facilitate laboratory and epidemiological research, and assess the success of specific intervention efforts. The effectiveness of surveillance depends on the speed of reporting and analysing the results.[10]

Monitoring of factors such as population growth and migration, vector abundance (e.g. the effect of the spread of potential yellow fever vector *Aedes albopictus* in Americas, including USA), development projects that disturb the environment (e.g. forest cutting in Brazil), and natural environmental factors (temperature and rainfall: e.g. global warming and the effects of "El Nino") is an essential component of surveillance. These factors can influence both the spread of yellow fever and the effectiveness of efforts to control them.

Official reports do not give an accurate picture of incidence or distribution of yellow fever. Evidence for activity obtained by serological surveys is also largely incomplete or out of date.[4] Cases reported to WHO show only the presence of the virus, and greatly underestimate the real number of cases.[49] In seven epidemiological studies, undertaken during yellow fever outbreaks over the last 25 years in Africa, morbidity and mortality were constantly under-reported by 10 to 500 times.[61] The majority of the mild infections are undetected, which explains the high case fatality rates calculated from these reports.[49]

Only limited attempts have been made to define the incidence of endemic yellow fever infection. In Nigeria (1970-71), a laboratory diagnosis of yellow fever was made in two (1%) of 205 patients hospitalized with jaundice in areas without epidemic activity.[95] Using data from serological surveys in Nigeria and an estimated 7:1 infection : illness ratio, the annual incidence of overt infection was estimated to be between 1.1 and 2.4 per 1000 population, and yellow fever death between 0.2 and 0.5 per 1000.[87] While indicating that endemic yellow fever may be a 'silent' cause of significant morbidity, the incidence levels are 25 to 50-fold lower than those occurring during epidemics, and are thus below the threshold of detection by existing passive surveillance systems. The continued activity of YF in Kenya after the 1993 epidemic detected by active surveillance further supports this view. It is likely that endemic yellow fever activity is geographically focal and that it varies considerably from

year to year, but that it causes thousands of unrecorded deaths annually in West Africa. This provides a strong rationale for preventive immunization, but lacks supporting data from surveillance or serological surveys. {Monath, T.P. Written communication, 1998}

Surveillance can take many forms, each having advantages and disadvantages (Table 6). Although most infections with YF do not cause jaundice, this sign is the easiest on which to base case-reporting. Most countries have a system for reporting cases of hepatitis, or jaundice, which can be adapted to provide information about the occurrence of suspected yellow fever. An unusually high case-fatality rate among cases of jaundice might indicate the possibility of an outbreak of yellow fever.

For effective YF surveillance, the following measures are essential: identification of suspected patients; prompt investigation of each suspected case with collection of appropriate clinical specimens; transport of specimens from the field to the laboratory in cold boxes; reliable completion of laboratory tests; forwarding specimens, as appropriate, to higher-level laboratories should additional tests be indicated, and rapid feedback to the district and national levels so that disease control measures, including mass immunization campaigns, can be instituted.[15] Some of the practical difficulties faced in implementing these measures are described in the review of the Kenyan sentinel surveillance system, below.

Active surveillance takes the form of regular contacts by surveillance officers with health-facility staff, and/or periodic house-to-house surveys, which can provide more complete information on YF incidence and risk factors for YF. Active surveillance may be particularly indicated in the ecological zone of emergence (moist savannah). Annual serologic surveys of young children can also provide important information on the circulation of YF virus (since most infections are subclinical). Surveys conducted during the dry season can detect any increase in seropositivity since the previous rainy season, to help predict a danger of further increase in the following year. Surveys of YF antibodies in monkeys can also provide evidence of YF circulation.[10] (Appendices III, IV and V). Because of an association between increased YF isolates from mosquito vectors and outbreaks of YF in West Africa, vectors have been monitored by Institut Pasteur in Senegal and Ivory Coast.

To improve surveillance, WHO AFRO has developed a training workshop and field guide for district level staff on EPI target disease surveillance, which focuses on poliomyelitis, measles, neonatal tetanus, and yellow fever. A series of laboratory workshops on YF diagnosis have been held in the African region in the 1990s, for Anglophone and Francophone countries (Dr S. Robertson, unpublished trip report Sept 1995). Actions to strengthen the laboratory network for YF have followed on from the success of the WHO polio laboratory network programme. WHO is currently revising its reference materials for surveillance, and has developed suggested case definitions, types of surveillance, minimum data elements and data analysis, and case investigation forms (Appendix).

Since one of the main aims of YF surveillance is the early detection of outbreaks, appropriate training and provision of resources for outbreak preparedness and response is an essential complement to surveillance. Outbreak response consists of mass immunization locally, with possible extension to surrounding areas. Data on age-specific attack rates help in deciding the age group to include in mass vaccination. WHO maintains an emergency stock of vaccine which can be made available rapidly when there is an outbreak. A vector control specialist should also be consulted to determine if specific mosquito control measures are indicated.

In addition to disease surveillance, monitoring immunization coverage also needs improving. Data on YF incidence and vaccine coverage have been included in the WHO EPI computerized monitoring system since 1991. Comparison of YF with measles vaccine coverage can show missed immunization opportunities that may be caused by vaccine supply problems, and/or concern about administering multiple injections on one day.

In South America, routine yellow fever surveillance has been augmented by histopathological review of liver specimens collected post mortem from patients who died following an acute febrile illness.[15] The "viscerotome" was invented by Rickard in 1930[35] to permit the rapid and convenient removal of liver specimens by laymen.[96] From 1500 liver specimens secured in 1931 and 13 733 obtained in 1932, this programme was expanded by 1940 to more than 30 000 viscerotomies per year in Brazil alone. By 1949 more than 400 000 liver samples had been collected and examined. This viscerotomy service was soon extended to Bolivia and Colombia. Pathological examinations confirmed the sero-protection tests, but while positive sero-protection tests revealed past or potential foci,[35] the advantage of liver examination is that it reveals active foci of YF. Surveillance of YF continues to be based on viscerotomy in South America. But even with post mortem surveillance, it is estimated that only a small proportion of yellow fever cases are detected.[10] The countries of Americas notified 2238 cases to the Pan American Health Organization (PAHO) between 1965 and 1984. This figure which is based for the most part on viscerotomy results, gives only an incomplete idea of the real incidence of the disease.[97]

WHO has not emphasised histopathological surveillance in Africa because patients are more likely to die at home, and families are reluctant to provide consent for an autopsy.[12]

In the African Region, until recently, the approach to YF diagnosis was by serology (CFT, HI and NT (in mice or cell cultures). In addition, work was done on virus isolation, again in mice and cell cultures. These tests were tedious and fraught with problems of cross reactions with numerous flaviviruses in Africa. Currently, technicians are being taught to use the IgM test, which is faster, quite sensitive and specific, even in the presence of other flaviviruses. It was used test in 1995 during the Liberian outbreak. Although several laboratories have the capacity to conduct the IgM ELISA test, they have not been fully utilized. As the Kenya experience has shown, laboratory-driven surveillance is limited in scope, and not as cost-effective as a well organised disease/epidemiological surveillance including laboratory diagnosis. The potential of laboratory diagnosis is only realized when it is integrated with a reliable and dependable clinical-epidemiological surveillance system (Tomori O, personal communication 1998).

Table 7: Methods of surveillance for yellow fever

Method	Advantages	Disadvantages	Examples
Case reporting (routine, passive surveillance)	- indicates the presence of virus and yellow fever activity in the area - if high reporting completeness can be achieved, potentially most sensitive method of clinical surveillance	- under-reported; passive systems underestimate the true incidence of disease 10- to 250-fold and the incidence of infection by 20- to 5000-fold - delayed an average of two months in Africa - difficult clinical diagnosis	- 34 countries presently at risk: see annex II.
Monitoring vaccination coverage	- gives an idea of immunization programme performance - low coverage alerts to the risk of a potential epidemic - monitor missed opportunities	- good and reliable reporting system essential - only 31% of countries reported YF immunization coverage in 1995	WHO provides a yearly EPI global summary.
Sentinel surveillance	- can get better quality data - if YF is focal in a country, can concentrate resources on affected areas	- costly - laboratories essential - is not easy to integrate to existing governmental Public Health activities - location of YF activity may be unpredictable	Kenya, 1993 - (Kerio Valley)
Hospital record review	- gives an idea of hospital incidence and geographical distribution of yellow fever	- not all patients are hospitalised - selection bias	Nigeria 1994
House-to-house survey	- gives an estimation of incidence, age and sex proportions	- "verbal autopsy": difficulties of distinguishing YF from disease with similar symptoms - information bias	Nigeria (Obibi village), 1994
Serological survey	- reveal past or potential foci - gives an idea about the population's immunity status and yellow fever circulation in an area. - use of IgM tsst may reveal recent YF activity	- cross-reactions with other flaviviruses confuse the results	Africa 1931-1935 (helped to delineate the boundaries of endemic yellow fever)
Viscerotomy	- pathological examinations confirm the sero-protection tests - detects unconfirmed and atypical yellow fever cases - reveal active foci	- not very sensitive - mostly fatal cases are reported: - not successfully applied in Africa, where death registrations and burial practices are poorly controlled.	- South America from 1930 to today - the countries of Americas notified 2238 cases between 1965 and 1984.
Entomological survey	- confirms virus transmission in mosquitos - limited to research efforts in enzootic foci - YF virus isolations from vectors correlate with outbreaks of YF in humans; can warn of increased risk	- need high level of effort to collect adequate number of adult mosquitos - may not help PH officials to improve control activities, especially in rural and jungle areas	- Ivory Coast, 1982 - Senegal, 1993 routinely monitored in the Kedougou area, Senegal since 1976 - Burkina Faso 1983-86
Monkey survey	- determines the presence of yellow fever and provides a quantitative index of the rate of virus transmission - epizootic can precede an epidemic	- not practical on a large scale - ecological grounds: monkeys need to be shot and killed	- Colombia 1936, 1942 Sentinel monkeys have been used to detect sylvatic yellow fever activity in Uganda - Trinidad 1988-1989 - Senegal 1993

V.2. Yellow fever sentinel surveillance in Kenya[98]

Although periodic outbreaks of yellow fever have been reported in East Africa since 1940, the first yellow fever outbreak reported in Kenya began in September 1992 and continued through March 1993. Sentinel surveillance was established after this outbreak, initially involving 13 health facilities in the Rift Valley, and expanding to its current number of 43. An epidemiological support unit was established at the Kenya Medical Research Institute (KEMRI) laboratory to provide the link between possible disease occurrences in the field and the diagnostic facilities at the distant laboratory.[99]

Surveillance teams usually consist of locally recruited staff trained on the spot and supervised by one or more epidemiologists. Their task is to collect the specimens that are to be sent to laboratories to confirm a suspected diagnosis. Adequate transport facilities and a means of rapid communication are essential for the investigation and control of outbreaks. In July-August 1997 a review of the system was conducted;[98] salient findings are summarised here.

V.2.1. Objective of sentinel surveillance in Kenya

To improve the ability to detect, diagnose, and prevent yellow fever outbreaks in Kenya (and the East Africa Region) through training and education programmes which increase awareness of the disease, improve detection by pathological examination, promote rapid response and planning and stimulate the initiation of isolation precautions for suspect cases, through

- improving knowledge and increasing awareness of yellow fever within the Kenyan medical community and public health facility practitioners.

- implementing a series of sentinel stations equipped to collect samples to send to appropriate laboratories for analysis by pathological examination and immunohistochemistry techniques,

- improving diagnostic capabilities at the KEMRI for viral haemorrhagic fevers and other viral diseases.

V.2.2. Yellow fever case definition for surveillance:[7]

Patients presenting with at least two of the following five symptoms or signs should be reported as suspected yellow fever and a case investigation should be carried out:

1. Fever: >38ºC or 100.4ºF

2. Jaundice: yellow eyes, elevated serum bilirubin, bilirubin in urine

3. Haemorrhages: vomiting blood or coffee-grounds like matter, persistent nose bleeds, bleeding gums, or melaena

4. Encephalopathy: confusion, disorientation, extreme drowsiness, convulsions

5. Renal problem: decreased urine output, proteinuria, blood in urine

V.2.3 Summary of Kenyan guidelines

According to the Ministry of Health of Kenya published booklet "Field Guide for Yellow Fever Surveillance" the health facility chosen as a sentinel surveillance centre collects a blood sample from patients who meet the surveillance case definition. The serum is separated, stored frozen, and transported to KEMRI (according to the guidelines, it is to be kept frozen even during transport) - either through courier services or personal delivery. All positive cases are later followed and if the patient is still alive, a convalescent sample is taken. " A Yellow Fever Case Investigation Form" is completed and sent together with the serum sample.[7]

Any case of suspected yellow fever should be reported to the District Medical Officer (DMO) within 24 hours. The DMO's office should assist the health facility to transport the blood specimen to KEMRI, follow-up the case, search for other cases in the affected area, and report the case to the Provincial Medical Officer (PMO).[7]

The Provincial Medical Office provides support and supervision to the district as necessary, including transporting specimens and helping with investigations of outbreaks. The Central Ministry of Health provides periodic analyses and feedback regarding cases nation-wide, follows up on the outcome of cases, and provides laboratory results to the PMO and DMO. The Virus Research Centre in KEMRI processes specimens for virus isolation and detection of antibodies, and provides results to central MoH and feedback to the health facility that submitted the specimen.[7] All serum samples are to be re-tested and confirmed at the Division of Vector-Borne Infectious Diseases, Fort Collins, USA.

V.3.4. Findings from the review

The blood is collected by the sentinel health facilities from some patients (an unknown proportion of those meeting the clinical case definition), and the serum samples are kept frozen in the laboratories. Because of difficulties in establishing a reverse cold chain the surveillance team from KEMRI, equipped with dry ice or liquid nitrogen, collects the samples (the delay between collection and transport can be months).

The surveillance system is mainly the responsibility of KEMRI, which follows up the positive samples, searches for other cases in affected areas and reports to health facilities and Central Ministry of Health. The surveillance team, which normally consists of an epidemiologist and a driver, but sometimes also a laboratory technologist, also refills the "yellow fever kits" (equipment for specimen collection) during its irregular visits.

Between 1993-1995 only an average of five samples monthly were obtained and in 1996 only two samples were collected for the whole year. The cost was about Ksh. 20 000 (roughly about Ksh. 4000 , about US$ 80, per sample collected), which is very costly.

Table 8: Attributes of yellow fever surveillance system in Kenya

Attribute	Comment	
Usefulness	Capacity to contribute to the prevention and control of YF	-
Simplicity	Refers to both structure and ease of operation; considers flow of information and lines of response	+
Flexibility	Ability to adapt to changing information needs or operating conditions with little additional cost, time, staff	+
Acceptability	Reflects willingness of individuals and institutions to participate	+
Positive value predictive	Proportion of persons identified as cases who actually do have the condition under surveillance	-
Representativeness	Ability to accurately describe the occurrence of YF over time and its distribution in the population, and thus of the ability to generalise findings from surveillance data	-
Timeliness	Reflects the speed or delay between steps in a surveillance system	-

(+= Good; - = Needs improvement)

Results of interviews with health professionals in the sentinel sites in August 1997 showed that:

1) The yellow fever surveillance is perceived to be important because of the high case-fatality of the disease. It is potentially useful but because of the variable participation and delays in the system the surveillance cannot lead to quick implementation of prevention and control measures.

2) The system is otherwise simple and flexible, but needs cold-chain transportation for the samples and depends on laboratory confirmation. The fact that the system is not integrated with other MoH services makes it harder to keep staff motivated. However, for some techniques such as antigen detection, ELISA, PCR and serologic samples, cold chain requirements are much reduced.

3) The staff are interested in the subject, find yellow fever surveillance important, but need more training in the recognition of suspected cases of YF and in the use of the field guide.

4) The Predictive Value Positive of the case definition is low, because of its broadness and the similarity of symptoms with many other common infectious diseases in the area.

5) The representativeness is poor, because of the few samples collected, but also because only a minority of health facilities report regularly.

6) Presently the system is too slow to provide information useful for control activities.

Based on the review of sentinel surveillance in Kenya, a series of recommendations were made for improvement.

An important aspect of the clinical diagnosis is case-definition. For effective surveillance the broadest possible case-definition should be used. The case definition for yellow fever surveillance in Kenya is too complex and needs to be changed to a broader form - for yellow fever it could consist of the three major symptoms: fever, jaundice and haemorrhages.

The guidebook and the case investigation forms should be simple enough to be understood easily by different groups of medical staff with different educational backgrounds.

Continuous training is needed to improve on-the-job performance. Every District Health Office has a "Human Resources Co-ordinator" (HRC) whose responsibility is to co-ordinate all in-service training and who could act as a facilitator for workshops. The surveillance team should spend more time with the field staff with supervision and training on the spot. If communication between the field and KEMRI could be improved (through telephone, letters), a special staff meeting could be easily organised with the surveillance team and the health facility staff. The health facilities need prompt feedback of results to motivate the work.

Laboratory workers in health facilities were better trained than the other staff, but they don't have the mandate to prescribe laboratory investigations - a job clearly for the clinicians. The workload of most Medical Officers in Kenyan hospitals mainly consists of administration and surgery, and the work in medical wards and out-patient clinics is done either by Clinical Officers or nurses. The clinicians (including nurses) need more training on yellow fever and surveillance, because they are in a key position to prescribe an investigation. Also Public Health Officers and Technicians should be involved, because they have been trained to survey diseases in their areas.

The Public Health Department could be the missing link between the specialised yellow fever surveillance programme and the government for co-operation and integration, because the Public Health Officers/Technicians are trained for surveillance and are used to follow-up not only cases but also outbreaks of other infectious diseases. They have motorcycles, which can carry an additional person (e.g. a laboratory technician if samples are needed). The PMO of Rift Valley Province Dr. K. Chebet in an interview on the 24 th of July, 1997 requested KEMRI for logistical support to his staff to participate in surveillance and regular - maybe quarterly - meetings in order to strengthen the link between his office and KEMRI. The surveillance should be seen as a MoH initiative for the sake of sustainability.

The present yellow fever surveillance system can be improved by reducing the number of sentinel sites (it is better to concentrate on few, but well-chosen and well-supervised sentinel sites, than many badly-supervised ones), training more staff locally (especially the staff of public health department), and organising regular and reliable communication between the sentinel sites and KEMRI. The yellow fever surveillance should be integrated gradually with the MoH activities. Any other arboviral research could be carried out in a few well-chosen sentinels for scientific interest and "virological trends" only.

VI. Comments and suggestions

Historically yellow fever has caused devastating epidemics in Africa, South, Central and North America and Europe. Yellow fever has not spread to Asia for unknown reasons. Recently there have been some reported cases of imported yellow fever both in Europe and in the USA. It is of great importance to inform all the international vaccination centres about the dangers of yellow fever.

Yellow fever resurged in the 1990s: 1989-1991 was an especially active period in Africa, where 34 countries are at risk for yellow fever: 17 have a policy to include yellow fever vaccine in the EPI, but 14 have poor immunization programme performance and 14 out of 34 belong to the countries in greatest economical need.

It is very difficult to try to prioritise the 34 African at-risk countries in order of highest to lowest risk, because the resurgence of yellow fever is unpredictable, but certain criteria could be used: the reported epidemics during the past years categorised under the different topotypes; reported cases over the past 15 years; immunization coverage and performance including the reported measles immunization coverage.

1) **Recent epidemics:** According to Map 3, Nigeria, which has reported far more cases than any other country during the past 15 years, seems to have been a centre for epidemics, and needs a lot of support for controlling yellow fever, as does Mali (which may have been the centre of epidemics in 1987) and Liberia. Other countries in West Africa (including Burkina Faso, Ivory Coast, Ghana, Togo, Benin, Nigeria, Niger and Cameroon) also need extensive vaccination coverage. Some countries seem to need only partial yellow fever coverage in the country (especially in East and Central Africa).

2) **The reported cases during the past 15 years** are from Angola, Benin, Burkina Faso, Cameroon, Gabon, Ghana. Guinea, Kenya, Liberia, Mali, Mauritania, Nigeria, Senegal, Sierra Leone and Togo. Out of them Angola, Burkina Faso, Gabon, Ghana, Mauritania, Nigeria and Senegal already have a policy to include yellow fever vaccination to the EPI. Of these countries the **immunization programme performance is poor (<50%)** in Angola, Burkina Faso, Cameroon, Kenya, Mali, Mauritania and Nigeria: Burkina Faso, Mali and Mauritania are also included in the **countries of the greatest economical need**. Only part of some countries is exposed to the risk of severe outbreaks, e.g. in Angola, Mali and Kenya only some districts need to be included in yellow fever vaccination programme. By now because of the extensive epidemics from 1984-1994, much of the population of Nigeria has been vaccinated through mass vaccination programmes or has gained natural immunity - it is important now to emphasise the immunization of the new susceptible population - infants.

Reporting, in general, is poor and slow, and needs to be standardised. E.g. most reports on yellow fever in *Weekly Epidemiological Record* lack the information about sex-ratios and occupational data, and categories of ages can vary enormously making it difficult to make cross-comparisons. The main use of (under-)reported numbers of cases and deaths is only to indicate yellow fever activity in an area, and the Case Fatality Rates, varying from 20 to 80% depending whether the samples are collected from alive or dead persons (e.g. the high CFRs in South America because of the practise of viscerotomy), are not very useful.

Map 4 shows yellow fever vaccine coverage in countries at risk from outbreaks. Table 8 compares different African countries with vaccination performance, immunization coverage, reported cases and epidemics, and economical status. In Tables 11, 12, 13 and 14, the countries have been categorised into four recommended priority groups from highest to lowest priority. **This does NOT mean that the "lowest" priority countries should be neglected, but that the emphasis of work, especially for yellow fever, should initially be in the highest priority countries**. Concurrently, all these countries need readiness for mass vaccination campaigns.

The importance of surveillance should not be forgotten, especially taking the experiences of the surveillance in Kenya into consideration. E.g. Gambia has had a successful immunization programme with combined strategy (mass immunization covered 95% of the population in 1978-1979 followed by preventive vaccination in the EPI which has reached 87% of infants). The last Gambian epidemic was reported in 1979, but a sensitive surveillance system is still needed to improve the detection, diagnosis and prevention of yellow fever outbreaks and monitor yellow fever coverage including details of vaccinations by age group given in response to outbreaks.

Immunizations given through the EPI are one of the most cost-effective child survival interventions. Only one study has been done comparing the cost-effectiveness of preventive yellow fever vaccination and emergency mass vaccination campaigns - the efficiency of the EPI was found greater in terms of cases and deaths prevented. The mass immunization campaigns are also effective, and reasonably cost-effective, and they secure the additional (donated) funding needed. There are no studies about the cost-effectiveness of combined preventive vaccination through EPI and surveillance versus mass vaccination campaigns; such studies should be encouraged. However, in countries that have recently experienced widespread epidemics, most "preventive" campaigns are probably not indicated.

The cost of using YF vaccine could be greatly reduced if the vaccine can be administered in the same syringe as measles vaccine. Laboratory tests to determine the stability of YF and measles vaccines mixed after dilution and kept for up to four hours (as would occur in most routine immunization sessions) would be easy to perform and should be done using measles vaccines from the range of manufacturers, as the effect of mixing could vary depending on vaccine source. Should laboratory experiments be encouraging, a field study of seroresponse to such vaccine mixed prior to vaccination could be done relatively quickly and inexpensively. Concurrently, the potential interest of vaccine manufacturers in producing a combined vaccine should be explored, but the practical implications of distributing this vaccine to only certain countries, or regions within a country, should be assessed.

All Asian countries should make an effort to check that all persons arriving from yellow fever endemic countries have a valid yellow fever vaccination certificate.

In South America yellow fever is a disease of forest workers, but there is a danger that *Aedes aegypti* -mosquito, which has reinfested all over South and Central America, could transmit yellow fever in an urban cycle. The urban epidemics were prevented in the early 1900s just by depriving the mosquitos of their breeding places - this could be also enough today to prevent urban yellow fever in South American towns, combined with yellow fever vaccinations as part of "occupational" health care for forest workers.

Map 3: Reported yellow fever immunization coverage in countries at risk for outbreaks, 1993-1995

Not considered at risk

61 to 100%

41 to 60%

21 to 40%

0 to 20%

No report received since 1993

GPV/EPI

The designation employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not be full agreement.

Data as of 22 July 1997.

Summary of recommendations

The combined strategy of surveillance, outbreak response and prevention is still needed to combat yellow fever.

The group "highest priority" needs yellow fever vaccine to be included in the EPI urgently (either the whole country or only parts of it), but also efforts to improve the immunization performance in general, followed by improved surveillance systems. Practical problems will be caused by political unstability and weak infrastructure in some of these countries.

The group "high priority" needs yellow fever vaccine to be included in the EPI (most already have), but need support to improve the immunization performance in general, together with an improved surveillance system.

Most of the countries in group "medium priority" have already included yellow fever vaccine in the EPI and relatively low YF activity. However, many of these countries are politically unstable and/or in great economic need, and their immunization programmes and surveillance systems for all the EPI diseases need to be strengthened. Reasons for differences between coverage of YF and measles vaccine should be investigated locally. Some of these countries have had little YF activity for decades, but surveillance needs to be continued and strengthened, as resurgence has been documented after long intervals in other countries. The priority to give to introducing YF vaccine into the countries in this group which have no YF vaccination (Congo, Eq. Guinea, Ethiopia, Sierra Leone, Sudan, Uganda and Zaire) needs discussion.

The "lowest priority" countries (excluding Gambia) have not reported yellow fever cases. Surveillance and possible outbreak response is enough at this stage. Gambia has already a good existing immunization programme, which naturally needs support to continue.

Large countries like Mali, Mauritania, Niger, Chad and Sudan could make a decision to immunize below, perhaps, 15° N based on ecological considerations, and similarly Angola could prioritize the region above, perhaps, 12°. However, it needs to be reiterated that such priority schemes are problematic where Ae. aegypti exists outside the 'zone of emergence', creating a 'receptive' area within national boundaries. Moreover, the problem of migration and movement of nonimmune persons into the endemic region both in normal commerce and during political unrest is substantial. These are precisely the issues now in South America, and there is a risk of recreating them in Africa. Guidelines on targetting vaccination need to be developed.

Table 9: Yellow fever outbreaks, immunization coverage & performance in African countries at risk for yellow fever outbreaks.

Country	Total reported cases 1982-1996	last time cases reported	Reported at least one outbreak 1982-1996	immunization programme performance poor (<50% immunization coverage)*	YF vaccine included in the EPI (even partially)	YF immunization coverage (year)	measles immunization coverage (1995)
Angola	37	1988	+	+	+	34 (1994)	32
Benin	124	1996	+				81
Burkina Faso	280	1985	+	+	+	55 (1995)	55
Burundi							44
Cameroon	184	1994	+	+			51
Cape Verde Is.							66
CAR				+	+	52 (1995)	70
Chad				+	+	28 (1994)	
Congo		1961					39
Eq. Guinea		1970					
Eritrea				+			
Ethiopia		1966		+			38
Gabon	44	1995	+		+	23 (1991)	
Gambia		1979			+	68 (1994)	
Ghana	523	1996	+		+	24 (1995)	54
Guinea	5	1987	+				
Guinea Bissau							
Ivory Coast	25	1982		+	+	43 (1995)	57
Kenya	64	1995	+	+			35
Liberia	360	1997	+				
Mali	305	1987	+	+		3 (1994)	49
Mauritania	21	1987	+	+	+	32 (1990)	
Niger		1939		+	+	27 (1995)	38
Nigeria	20 337	1994	+	+	+	1 (1993)	
Rwanda							
Sao Tome						2 (1994)	
Senegal	79	1995	+		+	46 (1994)	80
Sierra Leone	33	1995	+				
Somalia							
Sudan		1942					77
Tanzania							75
Togo	7	1987	+			14 (1993)	65
Uganda		1971					
Zaire		1972		+		8 (1992)	41

* Designated as in greatest need of improved programme performance and enhanced financial support (EPI Information System, 1997)

Table 10: Prioritising 34 African countries at risk for yellow fever for support; highest priority

Highest priority			
Country	Arguments	Comments	Recommendations
Nigeria	- huge epidemics during recent years: highest number of reported cases in Africa - centre of other epidemics in topotype II area	- has already included YF in the EPI, but coverage only 1%	- yellow fever vaccination together with measles at the age > 6 months - the whole country should be included - improve surveillance
Cameroon	- neighbouring Nigeria - two epidemics in 1990s	- 214 000 doses of YF vaccine given in 1990	- as Nigeria
Kenya	- topotype III in Kerio Valley - has established sentinel surveillance for yellow fever - endemic area close to big highly populated urban centres	- mass vaccinations in 1992-1993 covered one million people	- yellow fever vaccination needs to be included into the EPI in Kerio Valley, also all immigrants should be vaccinated. - existing surveillance system needs to be improved
Liberia	- CIGN*** - most recent epidemic reported in Africa (1997)	- mass vaccinations covered one million people in 1995	- yellow fever vaccination together with measles at the age > 6 months - improve surveillance
Mali	- CIGN*** - centres the topotype I area - reported one epidemic in 1987; 70% < 15 years old	- mass vaccination campaign in 1969, and three million were vaccinated in 1987	- EPI activities need support - YF vaccination should be included in EPI in high risk areas - improve surveillance

**   No reports to WHO for the last three to five years.

***   Country in greatest need: EPI has identified 21 countries in greatest need of improved vaccination programme performance and enhanced financial support.[100]

**Table 11: Prioritising 34 African countries at risk for
yellow fever for support; high priority**

High priority countries			
Country	Arguments	Comments	Recommendations
Angola	- reported an epidemic in 1988	- has already included YF in the EPI	- only part of the country needs YF vaccinations, but the overall EPI programme needs to be improved - support surveillance
Burkina Faso	- CIGN - reported an epidemic in 1985	- has already included YF in the EPI	- support EPI activities - support surveillance
Gabon	- reported an epidemic in 1995	- has already included YF in the EPI	- YF immunization coverage poor, surveillance system needed
Mauritania	- CIGN - reported one epidemic in 1987 - but connected with Malian epidemic	- has already included YF in the EPI	- only part of the country needs YF vaccinations
Senegal	- reported an epidemic in 1995 - high risk: historically many epidemics	- has already included YF in the EPI - measles immunization coverage 80%, but YF immunization Coverage <50%	- support EPI and surveillance to sustain good control - monitor YF vaccination coverage and missed opportunities
Togo	- reported an epidemic in 1987	- Difficult to assess degree of risk	- Introduce yellow fever vaccination together with measles at the age > 6 months

Table 12: Prioritising 34 African countries at risk for yellow fever for support; medium priority

Medium priority countries			
Country	**Arguments**	**Comments**	**Recommendations**
Benin	- reported an epidemic in 1996 - historically many epidemics	- measles immunization coverage good	- training needed to add YF vaccinations to EPI
CAR	- CIGN*** - no reported epidemics for tens of years	- has already included YF in the EPI	- support EPI activities - support surveillance
Chad	- CIGN*** - no reported epidemics for tens of years	- has already included YF in the EPI	- support EPI activities - support surveillance
Congo	- last epidemic in 1961		- support EPI activities - support surveillance
Eq. Guinea	- CIGN*** - last cases in 1970		- support surveillance
Ethiopia	- CIGN*** - last epidemic in 1966		- support EPI activities - support surveillance
Ghana	- reported the second highest number of cases during the past 15 years	- has already included YF in the EPI - YF coverage > 50%	- support surveillance
Guinea	- last cases in 1987		- support EPI activities - support surveillance
Ivory Coast	- last epidemic in 1982	- has already included YF in the EPI	- support surveillance and EPI activities
Niger	- CIGN*** - last epidemic in 1939	- has already included YF in the EPI	- support surveillance and EPI activities
Sierra Leone	- CIGN*** - reported an epidemic in 1995		- include yellow fever in the EPI
Sudan	- last epidemic in 1942	- Part of country at risk	- include yellow fever in the EPI, but only partially
Uganda	- last reported cases from 1971		- support surveillance
Former Zaire	- CIGN*** - last epidemic in 1972		- support surveillance and EPI activities

**   No reports to WHO for the last three to five years.

***   Country in greatest need: EPI has identified 21 countries in greatest need of improved vaccination programme performance and enhanced financial support.[100]

Table 13: Prioritising 34 African countries at risk for yellow fever for support; lowest priority

	Lowest priority countries		
Country	Arguments	Comments	Recommendations
Burundi	- CIGN*** - no reported epidemics		- surveillance and outbreak response
Cape Verde Is.	- no reported epidemics		- surveillance and outbreak response
Eritrea	- CIGN*** - no reported epidemics		- surveillance and outbreak response
Gambia	- good immunization performance: no reported epidemics since 1979	- has already included YF in the EPI	- support surveillance
Guinea Bissau	- no reported cases since 1951		- surveillance and outbreak response
Rwanda	- no reported epidemics		- surveillance and outbreak response
Sao Tome & Principe	- no reported epidemics		- surveillance and outbreak response
Somalia	- CIGN*** - no reported epidemics		- surveillance and outbreak response
Tanzania	- no reported epidemics (even historical)		- surveillance and outbreak response

Appendix I:
Examples of historical yellow fever epidemics[12 23 24 25 27 101 102-106]

South and Central America

Year	Place	Cases	Deaths	Comments
164-	West Indies			Epidemics: 1649, 1652, 1656, 1664, 1671, 1686, 1690, 1691, 1694, 1695, 1703, 1705, 1715, 1723, 1664, 1729,
1664	St.Lucia		94% died of 1500	1731, 1734, 1735, 1740, 1741, 1743, 1750, 1751, 1754, 1756, 1761, 1762, 1765, 1767, 1769, 1500, 1770, 1779, 1780, 1781, 1791, 1793, 1795, 1796, 1800, 1801, 1802, 1803, 1804, 1807, 1813, 1816, 1780, 3500, 1817, 1818,
1780	Jamaica		3500	1819, 1820, 1821, 1822, 1823, 1824, 1825, 1826, 1827, 1828, 1829, 1830, 1837, 1838, 1839, 1841, 1842, 1843, 1847, 1850, 1852, 1853, 1854, 1855, 1856, 1858, 1860, 1861, 1862, 1864, 1865, 1866, 1867, 1868, 1869, 1877, 1881, 1887, 1889, 1891, 1894, 1895, 1901, 1907, 1908
1699	Mexico			Vera Cruz attacked: thought to be the first epidemic here
1725	Mexico			At Vera Cruz: reported in Clavigero's *Histoire de la Mexique*
1760	Dutch Guiana: Surinam			Said by Fermin in his "*Traite des Maladies les plus frequentes a Surinam*" to be the first epidemic of yellow fever there
1762	French Guiana			At Cayenne where the outbreak continued for three years, another epidemic in 1791
1793	Venezuela			Caracas attacked in October
1793	British Guiana			Outbreak in Demerara
1795	West Indies		31 000	Among European troops
180-	Central- and South America			Venezuela in 1802, 1869, British Guiana in 1800, 1820, 1821, 1825, 1837, 1838, 1840, 1841, 1881, Colombia in 1830, 1861, 1883, 1886, 1887, 1888, 1889, Dutch Guiana in 1800, 1835, 1837, 1841, 1854, Peru in 1842, 1852, 1854, 1869, Mexico in 1846, 1863, 1865, 1868, 1875, 1878, Rio De Janeiro in 1850, 1894, French Guiana in 1802, 1850, 1855-1858, 1877, Honduras in 1860, San Salvador in 1868, Nicaragua in 1868,
1804	San Juan Puerto Rico			Mortality was "inordinate"
1898	Rio de Janeiro			Mortality 95,5% ???
1900	Colombia			Aedes aegypti was very scarce and the cases may have been of the rural type.
190-	Dutch Guiana			Both epidemics in 1902 and 1908 coincided with the advent of a large number of non-immunes
19—	Colombia			Outbreaks in 1907, 1910, 1912, 1915, 1920, 1929,
19—	Venezuela			Outbreaks in 1908, 1912, 1914, 1917, 1918, 1928-1929.

North America

Year	Place	Cases	Deaths	Comments
1668	North America			Particularly destructive in the cities of New York and Philadelphia. Intercommunication between settlements in North America and corresponding settlements in the West Indies was frequent and the old wooden ships would harbour mosquitos
169-	North America			1690 in Charleston, 1691 in Boston, 1693 in Philadelphia, Charleston and Boston, 1694 in Boston, New York and Philadelphia, 1699 in Charleston and Philadelphia.
169-	Philadelphia			Epidemics: 1699, 1741, 1762, 1780, 1794, 1795, 1796, 1797, 1798, 1799, 1800, 1803, 1804, 1805. The worst one was in 1793.
17—	North America			1702 in New York, 1703 in Charleston, 1728 in Charleston, 1732 in Charleston, 1734 in New York, Boston, Charleston, Philadelphia and Albany, 1737 in Virginia, 1739 in Charleston, 1741 in Virginia, 1743 in New York and Virginia, 1745 in New York and Charleston, 1747 in New Haven, 1748 in Charleston, 1751 in New York and Philadelphia, 1778 in Philadelphia, 1783 in Baltimore, 1791 in New York and Philadelphia, 1792 in Charleston, 1793 in Philadelphia.
1793	Philadelphia		4000	After the arrival of refugees from San Domingo in August, "bilinous fever" started in September and lasted for seven weeks.
180- 1829,	North America			Norfolk in 1801, New York in 1801, 1819, 1821, 1822, 1870, Massachusetts in 1801, Philadelphia in 1802, 1803, 1805, 1819, 1820, 1821, 1867, Boston in 1803, 1821, Charleston in 1807, 1817, 1819, 1821, 1824, 1839, 1843, 1854, 1856, New Orleans in 1811, 1817, 1819, 1820, 1821, 1822, 1824, 1827, 1828, 1837, 1841, 1847, 1854, 1856, 1867, 1873, 1878, Florida in 1811, New Jersey in 1811, Baltimore in 1817, 1819, 1821, Alabama in 1821, 1854, 1873, banks of Mississippi in 1821, 1843, 1855, 1873 Key West in 1823, 1829, 1841, 1867, Natchez in 1825, 1829, 1837, 1847, Washington in 1825, Mobile in 1825, 1827, 1829, 1837, 1839, 1843, 1847, 1854, 1867, Memphis in 1828, 1873, 1879, Galveston in 1839, 1843, 1867,
1839	Galveston, Texas		About 100	Epidemic described in detail by Dr Ashbel Smith
1846	The Plains of US			*"The Mormons, during their march from Nanvoo to Utah, suffered from remittent and yellow fevers. Their track across the desert was marked by the graves of those who perished."* (Walford).
185-	Charleston, South Carolina			Several major epidemics: the most notable in 1852, 1854, 1856 and 1858. 682 deaths were reported in 1854
1853	New Orleans		4858	
1870	New York			The last recorded outbreak of yellow fever in New York
1876	Charleston			The final yellow fever epidemic in Charleston
1877	Port Royal, South Carolina			The last yellow fever epidemic in South Carolina
1878	Mississippi Valley	100 000	20 000	An economic loss of more than 100 million dollars
1905	New Orleans	5000	1000	

Europe

Year	Place	Cases	Deaths	Comments
1649	Gibraltar, Spain			Brought by ships en route to the West Indies from Africa, or returning
1700	Cadiz			According to Hirsch the first record of yellow fever in Cadiz
1723	Lisbon, Portugal, London ???			Report on local epidemic by Pedro Francisco da Costa Alvarenga - yellow fever appeared first time in Europe? The disease is said to have appeared in London, being transmitted from Lisbon.
1724	Spain and Portugal			The disease was attributed to the "eating of fruit and drinking snow-water."
172-	Spain			Gibraltar in 1727, Cadiz in 1730, 1736, 1764, Malaga and Cartagena in 1741
1730	Europe			During September and October 22 000 deaths took place after the arrival of the flotilla of Pintado from Carthagena, where many of his men had died of *'el vomito prieto'*. Bascome writing of this outbreak adds: *"It was probably this pestilence which during the seven years 1729-35 raged in Vienna, Pignerol Fossano, Nizza, Rivoli, Asti, Larti, Acqui, Basle, Silesia, Thrasburg (Lower Rhine), Trino, Fresneuse (Lower Seine), Vimeux (Seine et Oise), Orleans (Loiret), Plouviers (Loiret), Meaux, Villeneuve, St.George (Seine et Maine), Bohemia, Denmark, Sweden and Russia."*
1740	Cartagena			Due to neglecting the precaution of anchoring some distance from the shore resulted an epidemic in the British Navy
1741	Malaga, Spain		8431	During a military operation
180-	Bres, Brittany			Small outbreaks in 1802 and 1856
1802	Cadiz, Spain			Spread by 1804 to Cordoba, Grenada, Valencia, Catalonia and Gibraltar was seriously attacked
1804	Livorno, Italy	2000	650	
181-	Spain			Outbreaks recorded in Barcelona, Cadiz, Cartagena, Malaga in 1810, in Gibraltar in 1813,
1821	Barcelona, Spain		5000-20 000	French and English observers started to recognise that yellow fever might move further and northward within Europe
1823	Portugal			Outbreak at Lisbon
1826	Dublin			The most remote reported epidemic of yellow fever in Europe, according to Fannim, 1848.
1828	Gibraltar	53 83	1183	"Atmospheric causation"
1852	Southampton			Small outbreak
1857	Oporto, Lisbon Portugal			"Awesome in both scale and mortality" - the last major European epidemic
1861	Saint-Nazaire, France	40	26	"Anne Marie", a small wooden sailing ship from Havanna had already at sea a case-fatality of 22% because of yellow fever.
1865	Swansea, Wales	27	17	During a spell of extraordinary hot weather a small number of infected mosquitos from a cargo of copper ore from Cuba established an epidemic in town
1870	Barcelona			
1878	Madrid			

Africa

Year	Place	Cases	Deaths	Comments
1751	West Africa: Guinea Coast, Senegal			Lind: *"In several towns, among the negro population the mortality was so great that there were no sufficient left to bury the dead..."*
181-	West Africa			Senegal in 1814, 1816, 1828, 1830, 1837, 1840-41, 1844, 1852, 1858, 1863, 1866, 1872, Sierra Leone in 1816, 1823, 1859, 1862, 1865, 1866, the Congo Coast in 1816, 1862, 1865, Fernando Po in 1839, 1862, the Gold Coast in 1852, 1862, Senegambia in 1858, 1859, 1866, Gambia in 1860, Angola in 1860, the Benin Coast in 1862, Canary Islands in 1810, 1862, 1888, Lagos in 1864,
1900	West Africa			Started in Senegal and spread along the railway from Kayes to Dioubeba in the French Sudan, 1901. Dakar was almost decimated.
1923-27	West Africa			Yellow fever became active in the Gold Coast, Nigeria, Senegal, French Sudan, the Ivory Coast, Dahomey, Togoland, the Upper Volta, and the Belgian Congo.

Appendix II:
Yellow fever cases reported in Africa, 1900-1996

1900	-00	-01	-02	-03	-04	-05	-06	-07	-08	-09	-10	-11	-12	-13	-14	-15	-16	-17	-18	-19	-20	-21	-22	-23	-24	-25	-26	-27	-28
Angola	X																												
Belgian Congo																												9	45
Dahomey						11		12				2	16									6			14		2	4	6
French Sudan		20						36			5												few				6	5	
French Togo																												8	
Gambia																												1	5
Gold Coast																									8	7	27	107	4
Guinea		1																											
Ivory Coast			15								X				X								7		3		3	3	3
Liberia																										5		5	
Niger																												1	
Nigeria																									1	21	11	3	
Port. Guinea																												X	
Senegal		5				1		2				15															27	116	
Upper Volta																												2	

X = cases reported

	-29	-30	-31	-32	-33	-34	-35	-36	-37	-38	-39	-40	-41	-42	-43	-44	-45	-46	-47	-48	-49	-50	-51	-52	-53	-54	-55	-56	-57
Anglo-Eg. Sudan						1						15,641		1															
Belgian Congo					*	*				14		2	3		7	3				2	3	2	1	5	6	1	3	4	3
British Cameroon			8																										
British Togo				1																									
Dahomey				1		2	4	7	1	1			2									1							
French Cameroon										1	1	2																	
French Eq. Africa						2			7	1	3	5	2		2						1						1		
French Guinea			9	4	1		1					3		7															
French Sudan			8	17			1	7	3	9		1	8	1				3	1										
French Togo			3		4		3				1	1		1															
Gabon						3						8																	
Gambia						3	3																						
Gold Coast (Ghana)		2	20	4	6	5	5	6	77	15	2		4	1	2	1	5			2	27	13	25	6		1	7		
Guinea																										1			
Ivory Coast			16		3	28	101	1	10	24	11	2	4	8	1	2	2	1		1									
Kenya															1	1													
Liberia	22																												
Mauritania			1																										
Niger			2		5	8	1	1		1	3																		
Nigeria		1	4	1	1	7	1	5	26	11	8	3		2		1	1	46			3	1**	13**	42**	18		1		2
Northern Rhodesia																									3				
Port. Guinea				46	7										8	2	2												
Senegal			3	15	22	4		10	24	2	1			1	3										2				
Sierra Leone						3	1							3							3	1			1	3	2		
Uganda													1												1				
Upper Volta			10	1																									

*   Febrile jaundice, which was not confirmed serologically as yellow fever

**   A series of several outbreaks among indigenous population of Nigeria with at least 12 000 cases not reported officially

	-58	-59	-60	-61	-62	-63	-64	-65	-66	-67	-68	-69	-70	-71	-72	-73	-74	-75	-76	-77	-78	-79	-80	-81	-82	-83	-84	-85
Angola														65														
Cameroon													1		2	1	1	2	1				7				1	
Congo	60	11	7	4																								
Eq.Guinea													4															
Ethiopia				***	10				350																			
Gambia																						30 x	x					
Ghana		2				3						5	12	3	5	5	1	2	2	110	213	494	8	4	6	372		
Ivory Coast																									25			
Mali												21																
Nigeria												208 x	4 x			2 x	25					11	1				12	6
Senegal								243#														1		3				
Sierra Leone																		130										
Swaziland																					1							
Togo												1	2														1	
Uganda		1					1							106				14										
Upper Volta (Burkina Faso)												87														356 x	17	7

x =   Estimated cases in Gambia 8,400 and in Nigeria about 100 000 in 1969 and 1000 in 1973 and 3000 in Burkina Faso in 1983.

=   Estimated cases 20 000.

***   100 000 cases in Ethiopia.

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Angola			37								
Benin											124
Cameroon					173				10		
Gabon									28	16	
Ghana								39	79		27
Guinea		5									
Kenya							27	27	7	3	
Liberia										360	
Mali		305 x									
Mauritania		21									
Nigeria	1289 x	2676 x	4920 x	3270	4075	2561	149	152	1227		
Senegal										79	
Sierra Leone										33	
Togo		6									

x = Estimated morbidity 1525 in Mali in 1987, and in Nigeria 9800 in 1986, 120 000 in 1987 and > 1000 in 1988.

Appendix III:
African vectors[49, 51, 79, 83, 107-115]

Mosquito	Breeding / living	Biting habit	Comments
Aedes (Stegomyia) aegypti			
a) *domestic form (aegypti)*	- breeds in artificial containers (containers for water storage, old cans, tins, used tyres, etc.)	- antropophilic - bites inside & outside during day time, especially late afternoon - all the year around - including dry season	- its distribution correlates with human behaviour - major & often the only vector involved in man-to-man transmission
b) *wild form (formosus)*	- breeds in natural water collections (tree-holes, rock-holes, fruit-shells, crab-holes, etc.)	- zoophilic - found during the rainy season & the beginning of the dry season	- little role in yellow fever transmission (life span is short, it has little contact with monkeys).
Aedes (Stegomyia) africanus	- found in forested areas from the rain forest to the dry savannahs	- primatophilic - after dusk in the canopy, but may bite at any time during the day when a convenient host is introduced in its activity area (intrusion effect)	- main vector in the rain forest and as an important vector in forest galleries
Aedes (Stegomyia) opok	- known from savannah areas	- less primatophilic than *A. africanus*	- virus often isolated from *A. opok* in Central African Republic and in Ivory Coast - considered as an important vector
Aedes (Stegomyia) neoafricanus	- known only from forest galleries of eastern Senegal		- it is never very abundant but can act as an effective local vector (infectious rate is high)
Aedes (Stegomyia) luteo-cephalus	- in savannah areas, extending to the Sahelian zone, common in forested areas - breeds in tree-holes	- primatophilic - bites monkeys after dusk in the canopy of forest/mangrove galleries	- incriminated in 1969 during the Jos Plateau epidemic in Nigeria - main vector in savannah areas in West Africa
Aedes (Stegomyia) simpsoni group			- at least three species - isolated in Uganda in 1942 and many times during the Ethiopian epidemic 1960-62. - in West Africa human-biting species of the Simpsoni group were recorded only in Nigeria

Mosquito	Breeding / living	Biting habit	Comments
a) *A. simpsoni*			- found in South Africa only
b) *A. lilii*		- non-primatophilic	- found in East Africa - is not considered as a yellow fever vector
c) *A. brome-liae* the	- vegetal breeding places (leaf axils of banana trees), tree-holes	- day-biter	- most probably the vector incriminated by Mahaffy or Haddow under name *A. simpsoni*
***Aedes (Diceromyia) furcifer-taylori* group**	- savannah dwellers	- take two blood meals during a single gonotrophic cycle	- species of this group first incriminated during the Nuba Mountains epidemic in Sudan in 1940 - 58 yellow fever virus strains were isolated from male and female wild-caught mosquitos during an epizootic in Senegal in 1977
a) *A. taylori*	- in the canopy of forest galleries	- more simiophilic than anthropophilic	- main vector from monkey to monkey in the canopy of forest galleries
b) *A. furcifer*	- in open savannahs and in villages	- anthropophilic - bites indoors and outdoors	- monkey-to-monkey transmission, but also human infections - main vector in intermediate epidemics: Gambia in 1978 Burkina Faso in 1969 and 1983, Mali in 1987
Other mosquitos			- were found infected in nature, but none is efficient vector
a) *A. metallicus* b) *A. vittatus* c) *A. dentatus* d) *A. stokesi* e) *Eretmapo-dites*		- have no strict trophic preferences, or do not bite primates	- never play an important role in dissemination or amplification of the virus
f) *Mansonia* g) *Culex*			- never play an important role in dissemination or amplification of the virus, because the virus has too long incubation period
Ticks			
Amblyomma veriegatum	- in nature of Central African Republic		- yellow fever virus was twice isolated from ticks (once from males and once from eggs) - more important role in maintenance of the virus since the virus can be vertically transmitted

Appendix IV:
African vertebrate
hosts[35, 115, 73, 107, 116-124]

Name	Environment	Comments
Simioidea (monkeys)		- all African monkeys susceptible to yellow fever virus, developing a viraemia followed by neutralising antibodies, but have only a mild, unnoticeable disease
a) *Colobus abyssinicus*	- East and central Africa	- viraemia is long (five to nine days) - antibodies appear after the eighth day - one strain of virus isolated during the Ethiopia epidemic in 1960-62
b) *Colobus polykomos* c) *Colobus badius*	- West Africa	- found serologically positive in Ghana in 1965, Sierra Leone in 1937 and Senegal in 1936
d) *Cercopithecus*	- East Africa: *C. mitis*: transmit the virus in the forest, *C. aethiops* and *C. nictitans* feed in plantations and area source of infection of anthropophilic mosquitos - West Africa: *C. diana* and *C. mona* dwell in forest and *C. aethiops* in savannah areas	- best studied genus
e) *Cercocebus* (mangabeys)	- forest monkeys which often come to the ground level to feed	- in Uganda, *C.albigena* had high antibody prevalence rates, but its viraemia is short-lived and of low level
f) *Erythrocebus patas* (red monkey or patas)	- common in savannahs	- travels long distances and often feed in plantations - often serologically positive
g) *Papio papio* h) *Papio anubis* (baboons)	- savannah dwellers - live in large groups attractive for primatophilic mosquitos	- seropositivity rate in East and West Africa high
i) *Pan troglodytes* (chimpanzee)	- East, West and central Africa	- not very common, so it has not an important role

Name	Environment	Comments
Lemurioidea (pottos and galagoes)		
a) pottos	- nocturnal, tree-dwellers of the rain forest	- too rare species to play an important epidemiological role
b) galagoes *(Galago senegalensis, Galago crassicaudatus)*	- live in forests and savannahs, active at night	- in nature, serological surveys did not show any evidence of their participation in the circulation of virus in West Africa, but in East Africa galagoes were found positive in Kenya and in Uganda
Other vertebrates	- Sudanese *(Atelerix pruneri)* and European hedgehogs *(A. erinaceus)* - bat *(Epomophorus sp.)* - laboratory mice - Guinea pigs (after intracerebral inoculation) - *Steatomys opimus* - carnivora usually resistant, except *Genetta tigrina* and *Nandinia binotata* - *Artiodactyla* (camels, sheep, goats, cattle, pigs etc.) found serologically positive, but often in countries where yellow fever virus has never occurred	- several found susceptible, but their role can be limited because of their lack of contact with known vectors - cross-reactions possible; many positive responses are probably caused by antibodies induced by other flaviviruses

Appendix V:
South American vectors and vertebrate hosts[17,35, 49, 125, 126, 73, 107, 127-131]

Mosquito	Breeding / living	Biting habit	Comments
Aedes (Stegomyia) aegypti	- peridomestic		- imported from West Africa
Haemagogus	- rests in tree-holes & bamboo stems	- simiophilic, but bites occasionally humans	
a) H. (Haemagogus) janthinomys	- abundant in the humid tropical forest canopy of Colombia and the Atlantic coast of Panama		- the principal vector in South America - if the forest is cut, this vector will survive at ground level of plantations
b) Hg. (Haemagogus) equinus	- shares a similar ecology with H. janthinomys		- principal vector in Guatemala
c) Hg. (Haemagogus) mesodentatus			- principal veector in Guatemala in 1956
d) Hg. (Haemagogus) lucifer			
e) Hg. (Haemagogus) iridicolor			
f) Hg. (Haemagogus) capricornii			- major sylvatic vector found infected in nature: taxonomically confused with Hg. janthinomys???
g) Hg. (Haemagogus) albomaculatus		- at ground level bites man both indoors and outdoors	
h) Hg. (Conopostegus) leucocelaenus	- lives in forests	- anthropophilic	
Sabethes (Sabethoides) chloropterus	- rests in tree-holes & bamboo stems	- simiophilic, but bites occasionally humans - active all year long	- highly tolerant of arid conditions: it may play an important role in the maintenance of the virus in areas with long dry seasons
Aedes albopictus			- imported from Asia - potential role???

South American vertebrate hosts

Name	Environment	Comments
Alouatta *(howler monkeys)*	- live in groups in the crowns of trees	- very susceptible to yellow fever
Ateles *(spider monkeys)*	- live in tree tops	- very susceptible
Callithrix *(marmosets)*		- very susceptible
Cebus *(capuchin monkeys)*		- relatively resistant
Saimiri *(squirrel monkeys)*	- live in groups	- play a role in "wandering" epizootic" concept

Bibliography

1.   Last JM. *A Dictionary of Epidemiology*. New York: Oxford Press, 1988.

2.   Robertson S. Yellow Fever; The Immunological Basis for Immunization 8. WHO/EPI/GEN/93.18. Geneva, Switzerland, WHO, 1993.

3.   Division of Epidemiological Surveilance and Health Situation and Trend Assessment. Global Health Situation and Projections: Estimates. Geneva, Switzerland, WHO, 1992.

4.   Monath T. Yellow Fever. In: Monath T, editor. *The Arboviruses; Epidemiology and Ecology*. Boca Raton, Florida: CRC Press, 1988; 139-231.

5.   Meegan JM. Yellow fever vaccine. WHO/EPI/GEN/91.06. Geneva, Switzerland, WHO, 1991.

6.   Simpson DIH. Arbovirus infections. In: Cook GC, editor. *Manson's Tropical Diseases*. Bath, UK: Saunders, 1996; 637-42.

7.   Ministry of Health, Government of Kenya. *Field Guide for Yellow Fever Surveillance*. Nairobi, Kenya, 1996.

8.   Reiter P, Cordellier R, Ouma JO, McLean RG, Cropp CB, Savage HM, Sanders EJ, Marfin AA, Tukei PM, Agata NN, Gubler DJ. First Recorded Outbreak of Yellow Fever in Kenya, 1992-1993. II. Entomological Investigations. Not published.

9.   Monath TP. Yellow Fever: Victor, Victoria? Conqueror, Conquest? Epidemics and Research in the Last Forty Years and Prospects for the Future. *Am. J. Trop. Med. Hyg*: 1991; 45(1):1-43.

10.   WHO. Prevention and Control of Yellow Fever in Africa. Geneva, Switzerland, WHO, 1986.

11.   Monath TP, Lee VH, Wilson DC, Fagbami A, Tomori O. Arbovirus Studies in Nupeko Forest, a Possible Natural Focus of Yellow Fever Virus in Nigeria. *Trans. R. Trop. Med. Hyg*. 1974; 68: 30-38.

12. Strode GK, Bugher JC, Austin-Kerr J, Smith HH, Smithburn KC, Taylor RM, Theiler M, Warren AJ, Whitman L, editors. *Yellow Fever.* New York, McGraw-Hill Book Company, Inc. 1951.

13. Mims CA, Playfair JH, Roitt IM, Wakelin D, Williams R, Anderson RM. *Medical Microbiology.* London, UK: Mosby, 1995: 30.2.

14. Peters W, Gilles HM. *Color Atlas of Tropical Medicine and Parasitology.* London, UK: Mosby-Wolfe, 1995; 4-9.

15. Robertson SE, Hull BP, Tomori O, Bele O, LeDuc J, Esteves K. Yellow Fever. A Decade of Re-emergence. *JAMA,* 1996; 276(14): 1157-62.

16. NasidiA, Monath TP, DeCock K, Tomori O, Cordellier R, Otaleye OD, Harry TO, Adeniyi A, Sorungbe AO, Ajose-Coker AO, van Der Laan G, Oyediran AB. Urban Yellow Fever Epidemic in Western Nigeria. *Trans. R. Soc. Trop. Med. Hyg.* 1989;83: 401-06.

17. Downs WG, Shope RE. Yellow Fever. In: Gear JHS, editor. *CRC Handbook of Viral and Rickettsial Hemorrhagic Fevers.* Florida, USA: CRC Press, 1984; 73-79.

18. Downs WG. Malaria, the Great Umbrella. *Bull. New York Ac. Med.* 1975; 51: 984.

19. Rickard ER. Organization of Viscerotome Service of Brazilian Cooperative Yellow Fever Service. *Am. J. Trop.Med.* 1937; 17: 163.

20. WHO. Inclusion of Yellow Fever Vaccine in the EPI, Gambia. *Wkly Epidemiol. Rec.* 1996; 71: 181-85.

21. WHO. Yellow Fever. *Wkly Epidemiol. Rec.* 1996; 71(42): 313-18.

22. WHO. Field Guide for District Level Staff on Priority Communicable Disease Surveillance. Brazzaville, Congo: WHO Regional Office for Africa, 1994.

23. Hobson W. *World Health and History.* Bristol: Wright, 1963.

24. Carter HR. *Yellow Fever: an Epidemiological and Historical Study of its Place of Origin.* Baltimore: The Williams & Wilkins Company, 1931.

25. Smith A. *Yellow Fever in Galveston, Republic of Texas, 1839.* Austin, Texas: University of Texas Press, 1951.

26. Finlay CJ. *Trabajos Selectos.* Habana, Cuba, 1912.

27. Kelly HA. *Walter Reed and Yellow Fever.* New York, McClune, Phillips and Co, 1907.

28.   Stokes A, Bauer JH, Hudson NP. Transmission of Yellow Fever to Macacus Rhesus: Preliminary Note. *JAMA*, 1928; 90: 253-54.

29.   Stokes A, Bauer JH, Hudson NP. Experimental Transmission of Yellow Fever to Laboratory Animals. *JAMA*, 1928;8: 103-64.

30.   Theiler M. The Development of Vaccines Against Yellow Fever - Les Prix Nobel de 1951. Collected papers by members of the staff of the divisionof medicine and public health of the Rockerfeller Foundation. New York: Division of Medicine and Public Health of the Rockerfeller Foundation, 1952.

31.   Sawyer WA, Lloyd W. Use of Mice in Tests of Immunity Against Yellow Fever. *J. Exp. Med.* 1931; 54: 533-55.

32.   League of Nations. Yellow Fever. *League of Nations Monthly Epidemic Report*, 1928; 7(111): 57-69.

33.   League of Nations. Yellow Fever since the Beginning of 1931. *League of Nations Monthly Epidemic Report*, 1932;11(160): 79-82.

34.   League of Nations. Yellow Fever in 1932-33. *League of Nations Monthly Epidemic Report*, 1933; 12(169): 226-9.

35.   Biraud Y. Present-day Problems of Yellow Fever Epidemiology. *League of Nations Monthly Epidemic Report*, 1935; 14(179): 103-173.

36.   League of Nations. Yellow Fever in 1933-4. *League of Nations Monthly Epidemic Report*, 1934; 13(175): 207-9.

37.   Durieux C. *Preparation of Yellow Fever Vaccine at Institut Pasteur, Dakar.* In: Smithburn KC, Duriex C, Koerber R, Penna HA, Dick GWA, Courtois G, de Sousa Manso C, Stuart G, Bonnel PH. YF Vaccination. Monograph Series No 30. Geneva: WHO, 1956: 31-32.

38.   Durieux C. *Mass Yellow Fever Vaccination in French Africa South of Sahara.* In: Smithburn KC, Duriex C, Koerber R, Penna HA, Dick GWA, Courtois G, de Sousa Manso C, Stuart G, Bonnel PH. YF Vaccination. Monograph Series No 30. Geneva: WHO, 1956: 115-121.

39.   de Sousa Manso C. *Mass Vaccination against Yellow Fever in Brazil.* In: Smithburn KC, Duriex C, Koerber R, Penna HA, Dick GWA, Courtois G, de Sousa Manso C, Stuart G, Bonnel PH. YF Vaccination. Monograph Series No 30. Geneva: WHO, 1956: 123-139.

40.   Penna MD. Production of 17D *Yellow Fever Vaccine.* In: Smithburn KC, Duriex C, Koerber R, Penna HA, Dick GWA, Courtois G, de Sousa Manso C, Stuart G, Bonnel PH. YF Vaccination. Monograph Series No 30. Geneva: WHO, 1956: 67-68.

41. Groot H, Ribeiro RB. Neutralizing and haemagglutination-inhibiting antibodies to YF 17 years after vaccination with 17D vaccine. *Bull.World Health Organ.* 1962; 27: 699-707.

42. WHO. Yellow Fever in 1979. *Wkly Epidemiol. Rec.* 1980; 55(45): 345-51.

43. Deubel V, Pailliez JP, Cornet M, Schlesinger JJ, Diop M, Diop A, Digoutte JP, Girard M. Homogeneity among Senegalese Strains of YF virus. *Am.J.Trop.Med.Hyg.* 1985; 34(5): 976-83.

44. Chang GJ, Cropp CB, Kinney RM, Trent DW, Gubler DJ. Nucleotide sequence variation of the envelope protein gene identifies two distinct genotypes of yellow fever virus. *J. Virol.* 1995; 69(9): 5773-80.

45. Dutary BE, Petersen JL, Peralta PH, Tesh RB. Transovarial Transmission of Gamboa Virus in a Tropical Mosquito, Aedeomyia *squamipennis. Am. J. Torp. Med. Hyg.* 1989; 40(1): 108-13.

46. Beaty BJ, Tesh RB, Aitken THG. Transovarial Transmission of YF Virus in Stegomyia Mosquitoes. *Am J Trop Med Hyg.* 1980; 29(1): 125-32.

47. Fontenille D, Diallo M, Mondo M, Ndiaye M, Thonnon J. First Evidence of Natural Vertical Transmission of Yellow Fever Virus in Aedes Aegypti, Its Epidemic Vector. *Trans. R. Soc. Trop. Med. Hyg.* 1997; 91: 533-35.

48. Cornet M, Robin Y, Heme G, Valade M. Isolement au Senegal Oriental d'une Souche de Virus Amaril a Partir d'un Lot d'Aedes du Sous-genre Diceromyia. C.R.Acad.Sci. *Hebd. Seances Acad. Sci. D.* 1978; 287(16): 1449-51.

49. Digouette J-P, Cornet M, Deubel V, Downs WG. Yellow Fever. In: Porterfield JS, editor. *Exotic Viral Infections.* London: Chapman & Hall, 1995; 67-102.

50. Germain M, Saluzzo JF, Cornet JP, Herve JP, Suleau P, Camicas JL, Robin Y, Salaun JJ, Heme G. Isolation of the Yellow Fever Virus from an Egg-cluster of the Larvae of the Tick Amblyomma Variegatum. *C.R.Seanus.Acad.Sci.D.* 1979: 289 (8): 635-7.

51. Germain M, Francy DB, Monath TP, Ferrera L, Bryan J, Salaun JJ, et al. YF in the Gambia, 1979-1979: Entomological Aspects and Epidemiological Correlations. *Am.J. Trop.Med.Hyg.* 1980 29(5): 929-40.

52. Smithburn KC. Rift Valley Fever : Neurotropic Adaptation of Virus and Experimental Use of this Modified Virus as Vaccine. *Brit. J. Exp. Path.* 1949; 30 : 1-16.

53. WHO. Yellow Fever in 1989 and 1990. *Wkly Epidemiol. Rec.* 1992; 67(33): 245-51.

54.   WHO. Yellow Fever in 1987. *Wkly Epidemiol. Rec.* 1989; 64(6): 37-43.

55.   WHO. Yellow Fever in 1992 and 1993. *Wkly Epidemiol. Rec.* 1995; 70(10): 65-71.

56.   Vicens R, Robert V, Pignon D, Zeller H, Ghipponi PM, Digoutte JP. Yellow Fever Epidemic in the Extreme North of Cameroon in 1990: First Yellow Fever Virus Isolation in Cameroon. *Bull. WHO* 1993; 71: 173-76.

57.   Pisano MR, Durand JP, Tolou H. Partial Genomic Sequence Determination of Yellow Fever Virus Strain Associated with a Recent Epidemic in Gabon. *Acta Virol.* 1996; 40: 103-05.

58.   WHO. Yellow Fever in 1985. *Wkly Epidemiol. Rec.* 1986; 61(49): 377-80.

59.   Maurice J. Yellow Fever Makes Comeback. *Suomen Laakarilehti* 1993; 48: 3057-61.

60.   Mondet B, da Rosa AP, Vasconcelos PF. The Risk of Urban Yellow Fever Outbreaks in Brazil by Dengue Vectors, Aedes ASegypti and Aedes Albopictus. *Bulletin de la Societe de Pathologie Exotique* 1996; 89(2): 107-13.

61.   Chippaux A, Deubel V, Moreau JP, Reynes JM. Current Situation of Yellow Fever in Latin America. *Bulletin de la Societe de Pathologie Exotique* 1993; 86(5): 460-64.

62.   PAHO. PAHO Advisory: Aedes Albopictus in the Caribbean. *Epid. Bull PAHO* 1993; 14(3): 15-16.

63.   Vasconcelos PF, Rodrigues SG, Degallier N, Moraes MA, Travassos-Da-Rosa JF, Travassos-Da-Rosa ES, et al. An Epidemic of Sylvatic Yellow Fever in the Southeast Region of Maranhao State, Brazil, 1993-1994: Epidemiological and Entomological Findings. *Am. J. Trop. Med. Hyg.* 1997; 57: 132-37.

64.   Traore-Lamizana M, Fontenille D, Zeller HG, Mondo M, Diallo M, Adam F, et al. Surveillance for Yellow Fever Virus in eastern Senegal during 1993. *J. Med. Entomol.* 1996; 33(5): 760-65.

65.   Dudley SF. Can Yellow Fever Spread into Asia? An Essey on the Ecology of Mosquito-borne Disease. *J. Trop Med. Hyg.* 1934; 37(18): 273-78.

66.   Mahaffy AF, Hughes TP, Smithburn KC, Kirk R. Isolation of Yellow Fever Virus in Anglo-Egyptian Sudan. *Annals of Tropical Medicine and Parasitology*, 1941; 35: 141-48.

67.   WHO. Annual Epidemiological and Vital Statistics. Geneva, WHO, 1964.

68.   WHO. Yellow Fever. *Wkly Epidemiol. Rec.* 1995; 70(24): 175-6.

69.   WHO. Yellow Fever. *Wkly Epidemiol. Rec.* 1996; 71(13): 103.

70.   Sinha MK, Majumder NM. Will the Present Health Check-up System Invite Yellow Fever in India? *Indian Journal of Public Health*, 1990; 34(2): 119-21.

71.   Sawyer WA, Bauer JH, Whitman L. Distribution of Yellow Fever Immunity in North America, Central America, West Indies, Europe, Asia and Australia with Special Reference to Specificity of Protection Test. *Am. J. Trop. Med* 1937; 17: 137-61.

72.   Pym W. *Observations upon the Bulam Fever which has of Late Years Prevailed in the West Indies, on the Coast of America, at Gibraltar and Other Parts of Spain.* London; J. Callow, 1815.

73.   Wallbridge M, Downs WG. The Communicability of Yellow Fever. Br. Guiana *Med. Ann.* 1891; 3: 7-18.

74.   Elton NW. Sylvan Yellow Fever in Central America. *Publ Health Rep.* 1952; 67(5): 426-32.

75.   Matas R. Nursing in Yellow Fever and the Duties of Trained Nurses in Epidemics. *Trained Nurse Hosp Rev* 1905; Oct. -Dec. 1905: 3-24.

76.   Tsai T, Mitchell C. St. Louis Encephalitis. In: Monath TP, editor. *The Arboviruses: epidemiology and ecology.* Boca Raton, Florida: CRC Press, 1988.

77.   Gordon-Smith CE, Turner LH, Armitage P. Yellow Fever Vaccination in Malaya by Subcutaneous Injection and Multiple Puncture. *Bull. WHO*, 1962; 27: 717-27.

78.   Theiler M, Anderson CR. The Relative Resistance of Dengue-immune Monkeys to YF Virus. *Am J Trop Med Hyg*;1975 24: 115.

79.   Huang Y-M. Aedes (Stegomyia) Bromeliae (Diptera: Culicidae), the Yellow Fever Virus Vector in East Africa. *J. Med. Entomol.* 1986; 23(2): 196-200.

80.   Mitchell CJ, Miller BR, Gubler DJ. Vector Competence of Aedes Albopictus from Houston, Texas, for Dengue Serotypes 1 to 4, Yellow Fever and Ross River Viruses. *JAMA*, 1987;3(3): 460-65.

81.   Moore CG, Francy DB, Eliason DA, Monath TP. Aedes Albopictus in the United States: Rapid Spread of a Potential Disease Vector. *Journal of the American Mosquito Control Association*, 1988; 4 (3): 356-61.

82. Hindle E. An Experimental Study of Yellow Fever. Trans. *R. Soc. Trop. Med. Hyg.* 1929; 22: 405.

83. Tabachnick WJ, Wallis GP, Aitken THG, Miller BR, Amato GD, Lorenz L, Powell JR, Beaty BJ. Oral Infection of Aedes Aegypti with YF Virus; Geographic Variation and Genetic Considerations. *Am J Trop Med Hyg.*1985 34(6): 1219-24.

84. Miller BR, Mitchell CJ, Ballinger ME. Replication, Tissue Trophisms, and Transmission of Yellow Fever Virus in Aedes Albopictus. *Trans. R. Soc. Trop. Med. Hyg.* 1989; 83: 252-55.

85. Brenzel L, Claquin P. *Immunization Programs and Their Cost. Social Science and Medicine 1994*; 39(4): 527-36.

86. Monath TP. Stability of Yellow FeverVaccine. In: Brown F, editor. *New Approaches to Stabilisation of Vaccines Potency*: WHO Headquarters, Geneva, May, 29-31, 1995. Basel, Karger, 1996: 219-25.

87. Monath TP, Nasidi A. Should YF vaccine be included in the expanded program of immunization in Africa? A cost-effectiveness analysis for Nigeria. *Am.J.Trop.Med.Hyg.* 1993;48(2): 274-299.

88. Robertson RL, Foster SO, Hull HF, Williams PJ. Cost-effectiveness of immunization in the Gambia. Am.J.Trop.Med.Hyg. 1985;88(6):343-51.

89. Dietz V, Cutts F. The Use of Mass Campaigns in the Expanded Programme on Immunization: Advantages and Disadvantages. *Internal Journal of Health Services* 1997; 27(4): 767-90.

90. Chambon L, Wone I, Bres P, Cornet M, Cire L, Michel A, et al. Une Epidemie de fievre jaune au Senegal en 1965. *Bull. WHO*, 1967; 36: 113-50.

91. Soula G, Sylla A, Pichard E, Kodio B, Bentejac MC, Teulieres L, Saliou P.. Etude d'un nouveau vaccine combine contre le fievre jaune et la rougeole chez les enfants ages 6 a 24 mois au Mali. *Bull. Soc. Path. Exper.* 1991; 84: 885-97.

92. Lhuillier M, Mazzariol MJ, Zadi S, Le-Cam N, Bentejac MC, Adamowiez L, MarieFN, Fritzell B. Study of Combined Vaccination against Yellow Fever and Measles in Infants from Six to Nine Months. *J. Biol. Stand.* 1989; 17: 9-15.

93. Mouchon D, Pignon D, Vicens R, Tu-Ha-Thanh, Tekaia F, Teulieres L, Garrigue G.. Etude de la Vaccination Combine Rougeole-Fievre Jaune chez l'Infant Africain Age de 6 Mois a 10 Mois. *Bull Soc. Path. Exper.* 1990: 83: 537-51.

94. Galazka A. Stability of Vaccines. WHO/EPI/GEN 89.8:1990.

95.   Monath TP. Surveillance of Yellow Fever in Nigeria, 1970-71. *Nigerian Med. J.* 1972; 2(4):179.

96.   Rickard ER. Organization of Viscerotome Service of Brazilian Cooperative Yellow Fever Service. *Am.J.Trop.Med.* 1937;17: 163-83.

97.   PAHO. Yellow Fever in the Americas. *PAHO Bull.* 1985; 19(2): 209-12.

98.   Vainio JJ. Evaluation of Yellow Fever Surveillance in Kenya (MSc Control of Infectious Diseases). University of London, 1997.

99.   Sanders EJ, Borus P, Ademba G, Kuria G, Tukei PM, LeDuc JW. Sentinel Surveillance for Yellow Fever in Kenya, 1993 to 1995. Emerging Infectious Diseases, 1996; 2(3): 236-238.

100.   EPI. EPI Information System: Global Summary. Geneva: Expanded Programme on Immunization, Global Programme for Vaccines and Immunization, WHO, 1996.

101.   Busvine JR. *Disease Transmission by Insects: Its Discovery and 90 Years of Effort to Prevent It.* New York: Springer-Verlag, 1993.

102.   Leger M. Epidemiology of Yellow Fever in the French West African Colonies. *League of Nations Monthly Epidemic Report,* 1925; 4(83): 472-80.

103.   Scott HH. *A History of Tropical Medicine.* London; Edward Arnold & Co, 1942.

104.   Moe CE. Yellow Fever and Mosquito Control. Public Admin. Series: Bibliography # P 479, 1979.

105.   Coleman W. *Yellow Fever in the North - the Methods of Early Epidemiology.* Madison, Wisconsin: The University of Wisconsin Press, 1987.

106.   Newsom EY. Unto the Least of These : the Howard Association and Yellow Fever. *Southern Med. J.* 1992; 85(6): 632-37.

107.   Monath TP. Chapter 71: Yellow Fever. IN: Warren KS, Mahmoud AAF, editors. *Tropical and Geographic Medicine.* 2nd ed. New York: McGraw-Hill, Inc. 1990: 661-74.

108.   Mahaffy AF, Smithborn KC, Jacobs HR, Gillett JD. Yellow Fever in Western Uganda. *Trans.R.Trop.Med.Hyg.* 1942; 36: 9.

109.   Serie C, Lindrec A, Poirier A, Andral L, Neri P. Etudes sur la Fievre Jaune en Ethiopie.I. Introduction - symptomatologie clinique amarile. *Bull. WHO* 1968; 38(6): 835-41.

110. Haddow AJ. Yellow Fever in Central Uganda, 1964, part I. *Trans.R.Soc.Trop.Med.Hyg.* 1965;59: 436.

111. Haddow AJ. Mosquitoes of Bwamba County, Uganda III. *Bull. Entomol. Research* 1945; 36: 297-304.

112. Deubel V, Digoutte JP. Morphogenesis of Yellow Fever Virus in Aedes Aegypti Cultured Cells. I. Isolation of Different Cellular Clones and the Study of Their Susceptibility to Infection with the Virus. *Am. J. Trop. Med Hyg.* 1981; 30(5): 1060-70.

113. Deubel V, Digoutte JP, Mattei X, Pandare D. Morphogenesis of Yellow Fever Virus in Aedes Aegypti Cultured Cells. II. An Ultrastructural Study. *Am. J. Trop. Med. Hyg.* 1981; 30(5): 1071-77.

114. Gilpin ME, McClelland GA. Systems Analysis of the Yellow Fever Mosquito *Aedes aegypti.* Fortsch. *Zool.* 1979; 25(2-3): 355-88.

115. Lumsden WHR. Probable Insect Vectors of YF Virus from Monkey to Man, in Bwamba County, Uganda. *Bull Entomol Res.* 1951; 42: 317.

116. Dick GWA. Further Studies on the Susceptibility of African Wild Mammals to YF. *Trans R Soc Trop Med Hyg.* 1952; 46: 47-58.

117. Durieux C, Boiron H, Koerber R. Sur l'Existence d'un Reservoir de Virus Amaril Animal en Afrique. *Bull. Soc. Pathol. Exot.* 1947; 40: 111-18.

118. Findlay GM. The Infectivity of Neurotropic Yellow Fever Virus for Animals. *J. Path. Bact.* 1934; 38: 1-6.

119. Findlay GM, Mahaffy AF. Susceptibility of Nigerian Hedgehogs to YF. *Trans R Soc Trop Med Hyg.* 1936; 29: 417-18.

120. Findlay GM, Stephanopoulo GJ, Davey TH, Mahaffy AF. Yellow Fever Immune Bodies in Blood of African Animals. Preliminary Observations. *Trans. R. Soc. Trop. Med. Hyg.* 1936; 29: 419-24.

121. Haddow AJ, Dick GWA, Lumsden WHR, Smithburn KD. Monkeys in Relation to the Epidemiology of YF in Uganda. *Trans R Soc Trop Med Hyg.* 1951; 45: 189-224.

122. Haddow AJ, Smithburn KC, Mahaffy AF, Bugher JC. Monkeys in Relation to Yellow Fever in Bwamba County, Uganda. *Trans. R. Soc. Trop. Med. Hyg.* 1947; 40: 677-700.

123. Monath TP, Kemp GE. Importance of Non-human Primates in YF Epidemiology in Nigeria. *Tropical and geographical medicine,* 1973; 25: 28.

124. Smithburn KC. The Susceptibility of African Wild Animals to Yellow Fever. III. Pottos and Galagos. *Am. J. Trop. Med.* 1949; 29: 411-23.

125. Kumm HW, Cerqueira NL. The Role of Aedes Leucocelaneus in the Epidemiology of Jungle Yellow Fever in Brazil. *Bull. Entomol. Research*, 1951; 42(1): 195-99.

126. Schliessmann DJ. Progress Report of the Aedes Aegypti Eradication Program in the United States for 1965. *Mosq News* 1965; 26: 484-89.

127. Gillette HPS. YF in Trinidad. A Brief Review. *Mosq News*, 1956; 16: 121-25.

128. Boshell MJ, Osorno Mesa E. Observations on Epidemiology of Jungle YF in Santander and Boyaca, Colombia, September, 1941 to April, 1942. *Am J Hyg.* 1944; 40: 170-81.

129. Yellow Fever in the Americas, 1981 and 1982. *Morbidity and Mortality Weekly Report* 1983; 32: 202.

130. Laemmert HW, de Castro Ferreira L, Taylor RM. An Epidemiological Study of Jungle Yellow Fever in an Endemic Area in Brazil; Part II - Investigation of Vertebrare Hosts and Arthropod Vectors. *Am. J. Trop. Med.* Supp. 1946; 26: 23-69.

131. Bugher JC, Boshell MJ, Roca Garcia M, Osorno ME. Epidemiology of Jungle YF in Eastern Colombia. *Am J Hyg.* 1944; 39: 16-51.

132. Miller BR, Ballinger ME. Aedes Albopictus Mosquitoes Introduced into Brazil: Vector Competence for Yellow Fever and Dengue Viruses. *Trans. R. Soc. Trop. Med. Hyg.* 1988; 82: 476-77.

133. WHO. Galazka A, Milstien J, Zaffran M. Thermostability of vaccines. EPI. Advance draft. WHO/EPI/GEN/97. Rev.1, 1997.

134. WHO. Immunization policy. WHO/EPI/GEN/95.03. 1995.