Prevention and control of yellow fever in Africa

WORLD HEALTH ORGANIZATION GENEVA

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Preface

Yellow fever is prevalent in the tropical zones of Africa and the Americas. Although the same virus—with minor antigenic differences—is responsible, the epidemiology and the public health impact of the disease are very different in these two regions.

Until the 1940s, yellow fever was known in Africa only as an epidemic, devastating disease. At that time, workers at the East African Virus Research Institute, Entebbe, Uganda, described a sylvatic cycle of transmission, involving monkeys and the mosquito *Aedes africanus* in the forest canopy; in banana plantations close to the forest, another mosquito, *A. simpsoni*, acted as the vector between monkeys and man.

During the last decade, entomologists and virologists in West and Central Africa have found other transmission cycles between monkeys, mosquitos and man. It is now possible, therefore, to present a complete picture of the transmission of yellow fever in Africa.

This publication provides practical guidance for diagnosis, surveillance, management of cases and epidemics, and prevention of the disease. The information presented represents the consensus of a group of experienced workers in this field who met in Dakar, Senegal, from 30 May to 3 June 1983 (see Annex 1 for a list of participants).

Contents

1. Historical Review

Outbreaks of yellow fever have occurred at intervals in Africa for many years. In 1925, a major investigation into the disease was begun in West Africa, and in 1927 the causative agent was isolated and confirmed to be a virus.

Serological surveys carried out in practically all parts of Africa since 1932 have delineated with reasonable accuracy the boundaries of the area in which the disease has occurred. The endemic zone in Africa lies between parallels of latitude 15°N and 10°S (*1*), extending from the southern borders of the Sahara to Angola, and from the west to the east coast. Fig. 1 shows the yellow fever endemic zone, determined in the 1940s by immunity surveys for the purpose of the International Sanitary Regulations. These limits may be considered to be still valid.

Yellow fever has occurred in Africa either as sporadic cases of jungle yellow fever, mainly in the forest area, or as outbreaks, mainly in savanna areas. It has been found that, in addition to *Aedes aegypti,* at least 13 species of mosquito are able to transmit yellow fever and some of these potential vectors have been captured in large numbers during epidemics (*2*). Yellow fever in tropical Africa is enzootic in monkeys in forested areas. Monkeys may not be the actual reservoir, but they are at least responsible for enhancing the circulation of the virus (*3*). The mosquito vectors responsible for transmission vary in different regions of Africa.

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 (Bathurst), the Gambia, in 1934–1935. A severe epidemic occurred in Sudan in 1940, when 15 641 cases and 1627 deaths were reported among 230 000 inhabitants. Estimations made on the basis of serological evidence produced the figure of approximately 40 000 infections and a death rate of about 10% (*4*).

In 1940, a mass immunization campaign was initiated in French-speaking countries in West Africa (Benin, Burkina Faso (Upper Volta), Côte d'Ivoire (Ivory Coast), Guinea, Senegal, Togo) and Equatorial Africa (Cameroon, Chad, Congo, Gabon), where 25 million people were immunized about every 4 years. As a consequence, yellow fever disappeared gradually in these countries, while epidemic and endemic activity continued in countries without immunization programmes (*5*). The decreasing number of cases

Fig. 1. Yellow fever endemic zone in Africa

NOTE: Although the yellow fever endemic zones are no longer included in the International Health Regulations, a number of countries consider these zones as infective areas and require an international certificate of vaccination against yellow fever from travellers arriving from those areas.

resulted in a lack of interest in yellow fever, and surveillance and immunization were progressively neglected in the early 1960s.

In 1958, there was a period of virus activity in Central and East Africa with an outbreak in what are now the Equateur and Haut-Zaïre Provinces of Zaire. The following year the virus appeared in Sudan. The most severe outbreak occurred in Ethiopia in 1960–62, when a dramatic epidemic affected the south-west of the country and 3000 deaths were notified. It was estimated that as many as 100 000

cases and 30 000 deaths occurred in this area where the population numbered one million (*6*). According to previous serological surveys, yellow fever had never penetrated this area before, which explains the large number of victims.

During the past 25 years several outbreaks of the disease have occurred. The most important of these are listed in Table 1.

Table 1. Yellow fever outbreaks in Africa, 1958–82 showing numbers of cases and deaths, and suspected principal vectors

Country	Date	No. of cases	No. of deaths or % fatality rate	Suspected principal vectors
Zaire	1958	60	23	?
Sudan	1959	120	88	*A. vittatus, A. furcifer-taylori*
Ethiopia	1960–62	100 000 (estimated)	30 000 (estimated)	*A. simpsoni, A. africanus*
Guinea	1964	6	6	?
Senegal	1965	2 000 to 20 000 (estimated)	up to 44%	*A. aegypti*
Ethiopia	1966	?	350 (estimated)	?
Ghana	1969	250 (estimated)	73 (estimated)	multiple vectors
Mali	1969	21	12	multiple vectors
Burkina Faso	1969	3 000 (estimated)	100 (estimated)	multiple vectors
Nigeria	1969	100 000 (estimated)	up to 40%	*A. luteocephalus*
Nigeria	1970	786 (estimated)	15–40 (estimated)	*A. africanus*
Angola	1971	65	42	*A. aegypti*
Sierra Leone	1975	130	36	*A. aegypti*
Ghana	1977–79	434	120	(suspected multiple vectors)
Gambia	1978–79	8 400 (estimated)	1 600 (estimated)	*A. furcifer-taylori, A. aegypti*
Senegal	1981	2	0	*A. furcifer-taylori, A. aegypti*
Côte d'Ivoire	1982	25	25	*A. aegypti*

2. The Public Health Problem

Yellow fever continues to be a major threat in endemic zones of Africa where the virus reappears even after long periods of quiescence. Undoubtedly, from the historical perspective, yellow fever potentially has serious consequences in relation to morbidity and mortality. In some severe epidemics, it has been estimated that hundreds of thousands of people have been affected, with thousands of deaths (*6*).

The exact prevalence and incidence of yellow fever in Africa are not known since many cases are not recognized and thus are not reported. The main reasons for this include: (*a*) occurrence of the disease in relatively remote areas with few medical services; (*b*) unfamiliarity of medical personnel with the disease and a "low index of suspicion"; (*c*) confusion with other endemic diseases, e.g., viral hepatitis and malaria, especially early in the outbreak when the high death rate is not yet apparent; (*d*) lack of access to specific diagnostic laboratory tests and histopathological services; (*e*) inefficient disease reporting and difficult communications; (*f*) popular beliefs that discount the ability of western medicine to treat jaundice, with the result that severely ill patients are often removed from hospital.

Although the reporting of yellow fever cases is obligatory for WHO Member States, the statistical data available largely underestimate the true incidence of the disease. Only a small percentage of cases that actually occur in Africa are seen or recognized and it is only when immunity surveys are carried out that the true extent and distribution of the disease is realized. In Table 2 a comparison is made between the number of cases officially reported during various epidemics and the number of cases estimated from epidemiological investigations; these data indicate that epidemic morbidity and mortality are underestimated by a factor of 10–1000 times. Perhaps more important than the problem of underreporting is the late recognition and investigation of outbreaks, since this delays the initiation of control efforts. A delay of 2 months or more has often occurred between the onset of an epidemic and its recognition (Table 3).

No study has been made of the economic cost of yellow fever epidemics. This aspect deserves attention in the future, since cost-benefit considerations would be extremely useful to health authorities in planning prevention and control strategies. The 1969 outbreaks, which involved many countries in West Africa, must have been extremely expensive, in terms of both direct costs of vaccine, vaccine

Table 2. Discrepancies between the numbers of officially notified yellow fever cases and deaths, and estimates of morbidity and mortality rates from direct investigations of epidemics[a]

Country	Year(s)	Number of cases (deaths in parentheses)	
		Officially notified	Determined by epidemiological investigation
Ethiopia	1960–1962	–[b] (3 000)	100 000 (30 000)
Senegal	1965	243 (216)	2 000–20 000 (200–2 000)
Burkina Faso (Upper Volta)	1969	87 (44)	3 000 (100)
Nigeria	1969	208 (60)	100 000 (–[b])
Nigeria	1970	4 (1)	786 (15–40)
Gambia	1978–1979	30 (3)	5 000–8 000 (1 000–1 700)
Senegal	1981	2 (0)	(several hundreds)

[a] Reproduced, by permission, from: MONATH, T. P. Yellow fever. In: Warren, K. S. & Mahmoud, A. A. F., ed. *Tropical and geographical medicine*. New York, McGraw-Hill, 1984, p. 657.
[b] No estimate available.

Table 3. Interval between onset of yellow fever epidemics and date of first recognition

Locality	Year	Epidemic onset	First recognition
Sudan	1959	August	late October
Senegal	1965	? July	October
Nigeria	1969	July	September
Gambia	1978	August	November
Senegal	1981	August	September

delivery, and medical services, and indirect costs, such as the impact on economic production and the losses of human life. Such epidemics put strains on the resources of African countries. Another factor that must be considered is the harmful impact of epidemics on tourism.

Although no urban yellow fever transmitted by *Aedes aegypti* has occurred during recent decades in large African towns, such an outbreak is always possible.

3. The Virus

The causative agent of yellow fever is an arthropod-borne virus from the *Flavivirus* genus of the family Flaviviridae. This virus shares group-specific antigens with other members of the genus (former group B viruses—e.g., in Africa: Zika, West Nile, Wesselsbron, dengue, Spondweni, Banzi).

Yellow fever and other flaviviruses possess 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. The virus is inactivated by deoxycholate, ether, proteases, and lipases. The envelope contains a single glycoprotein with type- and group-specific antigens.

The morphogenesis of yellow fever virus is similar to that observed for other flaviviruses, i.e., viral synthesis and maturation appear to occur predominantly in the rough endoplasmic reticulum of the host cell. The site of formation of the surrounding envelope of the virion remains unclear. Mature virus particles accumulate within the cisternae of membranous organelles and are released from the cell by exocytosis or by plasma membrane rupture.

The virus is pathogenic in adult mice following intracerebral inoculation, and in suckling mice following intracerebral, subcutaneous, or intraperitoneal inoculation. The rhesus monkey is highly susceptible to yellow fever virus and this animal may be used as a model for the study of the pathogenesis of the disease.

Yellow fever virus replicates in cell cultures of different origin, but these cultures vary in their sensitivity. Cell lines of mosquito, monkey kidney, and hamster kidney are useful for propagation and assay. Wild strains of yellow fever virus vary in their pathogenicity for a host, but the molecular basis for virulence is poorly understood and host factors, including genetic and immunological parameters, must also be considered.

Yellow fever virus replication appears to be analogous to that of other flaviviruses, such as West Nile, Japanese encephalitis, and dengue viruses. Host-cell macromolecular synthesis is not seriously affected by the yellow fever virus infection. Treatment of cells with actinomycin D inhibits host-cell RNA synthesis but does not affect viral RNA synthesis. Peak viral RNA synthesis occurs when the virus titre in the supernatant reaches a maximum. Three types of viral RNA are observed: the genomic-size RNA with a sedimentation coefficient of 40S; the RNase-resistant RNA identified as the

replicative intermediate, which is soluble in 2 mol/litre HCl and sediments at about 20S; and the partially RNase-resistant RNA, sedimenting at about 28S, which is presumed to be the replicative form.

The RNA genome is 10 862 nucleotides in length and has a relative molecular mass of 3.75×10^6. It encodes for three structural proteins and up to 12 nonstructural proteins which are synthesized in infected cells (*64*). The translation of the nucleotide sequence initiates with the capside protein C (relative molecular mass, 13 500), which forms complexes with the RNA, followed by the small membrane nonglycosylated protein M (relative molecular mass, 8500), and the glycosylated or nonglycosylated E protein of the envelope (relative molecular mass 51 000). These structural proteins of the yellow fever virus are virtually indistinguishable from the other mosquito-borne flaviviruses by polyacrylamide gel electrophoresis and differ only slightly from tick-borne flaviviruses in the migration of the small membrane protein. Among the nonstructural proteins, NS 1, which is glycosylated and present in the membrane of infected cells, can induce immunity in mice and monkeys without stimulating antibodies to virion components. Monoclonal antibodies against NS 1 can mediate the complement-dependent lysis of infected cells. These findings could lead to the development of new vaccines and possibly the use of the 17D strain as a vector of other arboviral genes (*65*).

4. Diagnosis of Yellow Fever

4.1 Clinical Diagnosis

Yellow fever is an acute infectious disease. Typically, the disease is characterized by a sudden onset with a two-phase development, the phases being separated by a short period of remission. Viraemia occurs during the first phase, which is clinically undifferentiated, while the second phase is characterized by hepatorenal dysfunction and haemorrhage.

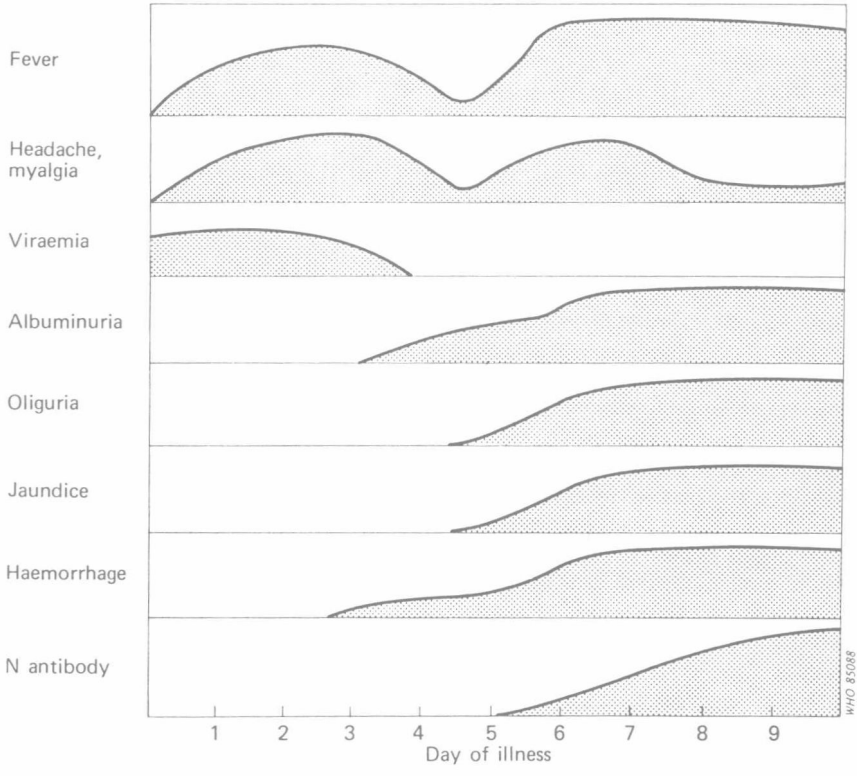
So-called "classical" yellow fever is usually recognized during epidemics, when the disease is observed in many individuals and is relatively easy to diagnose clinically. The incubation period is generally 3–6 days after the bite of an infected mosquito, but may be longer. The disease onset is sudden and marked by a temperature of 39–40 °C, chills, intense headache, lumbosacral and generalized muscular pains, nausea and vomiting, conjunctival injection, and a flushed face. The urine at this stage is dark in colour and may not contain albumin. Faget's sign (slow pulse in relation to the fever) is typical.

Generally, on the third or fourth day after onset, a remission occurs, which is characterized by a fall in temperature, disappearance of the headache, and an improvement in the general condition of the patient. However, this remission is short-lived, lasting only a few hours, and is followed by the period of intoxication, the hepatorenal phase, which is characterized by a rise in temperature, the reappearance of generalized symptoms, jaundice, vomiting—the vomitus may contain digested blood (black vomitus)—other haemorrhagic signs (bleeding of the gums, ecchymoses, menorrhagia, and haematuria), albuminuria, and oliguria. Progressive tachycardia, shock, and intractable hiccups are considered ominous signs. The case-fatality rate of severe yellow fever is 50 %. Death usually occurs between the seventh and tenth day after onset. The chronology of clinical events in the patient with yellow fever is given in Fig. 2.

Yellow fever infection may vary in intensity from a preliminary illness unaccompanied by any classical signs and symptoms with death following in 2–3 days, to very mild or subclinical forms.

The clinical diagnosis of yellow fever may be difficult even during epidemics, and is often impossible in mild or atypical cases. The disease can be definitely diagnosed only by serology or virus isolation. Malaria, which is endemic in Africa, usually shows clinical symptoms

Fig. 2. Time course of the main clinical features of yellow fever



almost identical with those of the early stages of yellow fever: sudden onset, headache, generalized aches, and vomiting. Other diseases resembling anicteric yellow fever include: typhoid fever, rickettsial infections, other arboviral fevers, and influenza. It is particularly important to differentiate between yellow fever and other diseases with hepatorenal dysfunction and/or haemorrhagic manifestations, such as viral hepatitis, malaria, viral haemorrhagic fevers (Lassa fever, Marburg and Ebola virus diseases, Crimean-Congo haemorrhagic fever, Rift Valley fever), leptospirosis, infectious mononucleosis with jaundice, and surgical or toxic causes of jaundice.

4.2. Laboratory Diagnosis

4.2.1 *General considerations*

Laboratory and hospital staff must have been immunized at least 10 days before handling possibly infected necropsy tissue or other pathological, virological, haematological, or biochemical specimens.

The laboratory diagnosis of yellow fever requires special reagents and techniques as well as expertise in the interpretation of test results. Individual histopathologists, especially those with some experience of yellow fever, are often called upon for the diagnosis, although a number of national laboratories in Africa can provide specific serological diagnostic services; some of these can also perform virus isolation.

A list of WHO Collaborating Centres that provide reference services and reagents is given in Annex 2. These centres are a back-up resource for laboratories in the region.

Specimens for the laboratory diagnosis of yellow fever should be accompanied by certain information, and the use of an information form when submitting specimens is helpful. The following information is essential: name, age, sex, residence, date of onset of symptoms, and date of collection of specimens. The following information should be provided if available: occupation, data on presumed location where the infection was acquired, history of recent travel, history of immunization, symptomatology, and results of any clinical laboratory tests (e.g., leukocyte count, albuminuria, liver enzymes).

The virus may be isolated from, or antigen detected in, serum specimens taken as early as possible in the illness as well as from liver specimens taken at autopsy, and stored in the cold to preserve the viability of the virus. For serological diagnosis of yellow fever, appropriately timed paired samples are required. The acute-phase serum should be collected as early as possible in the illness, and if the patient survives, a convalescent sample should be taken during the second or third week after onset.

To facilitate the rapid processing of specimens from suspected cases of yellow fever, it is advisable, whenever possible, to inform the laboratory before sending diagnostic samples. The period of time required for laboratory diagnosis depends on the tests used (summarized in Table 4).

4.2.2 *Histopathological diagnosis*

Liver biopsy is absolutely contraindicated in the living patient, because of the danger of haemorrhage.

Liver samples may be obtained from fatal cases by abdominal incision or by the use of a viscerotome (*1*) or a large-calibre biopsy needle. As large a specimen as possible should be obtained to facilitate histopathological interpretation. It is often possible to isolate yellow fever virus from the liver, if the patient died before the tenth or twelfth day after onset of the disease. Liver specimens should