

37561

WHO/EPI/GEN/91.6

DISTR: GENERAL

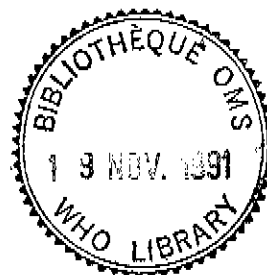
ORIGINAL: ENGLISH

EXPANDED
PROGRAMME
ON IMMUNIZATION



Yellow Fever Vaccine

James M. Meegan, PhD
MIM/CDS



WORLD
HEALTH
ORGANIZATION

INTRODUCTION AND BACKGROUND

Yellow fever (YF) virus is a member of the *Flaviviridae* family of viruses. This family contains over 70 related but distinct viruses, of which most are arthropod-borne. Other major pathogens in this classification include dengue viruses, which are present in most tropical areas and periodically cause large epidemics with severe disease in Southeast Asia, and Central and South America, and Japanese encephalitis virus, which is endemic in much of Southeast Asia and causes epidemics with high mortality.

The disease YF was first distinguished from other tropical febrile diseases during the 1647-49 epidemics in the Americas. Since then it has raged as periodic epidemics in the Americas and Africa. In the 20th century, the disease has circulated in an endemic, sylvatic cycle in the Americas usually infecting up to 500 unimmunized forest workers per year. In contrast, YF in Africa periodically explodes out of its endemic cycle to infect large numbers during major epidemics.

Yellow fever: number of cases notified to WHO, 1948-1988

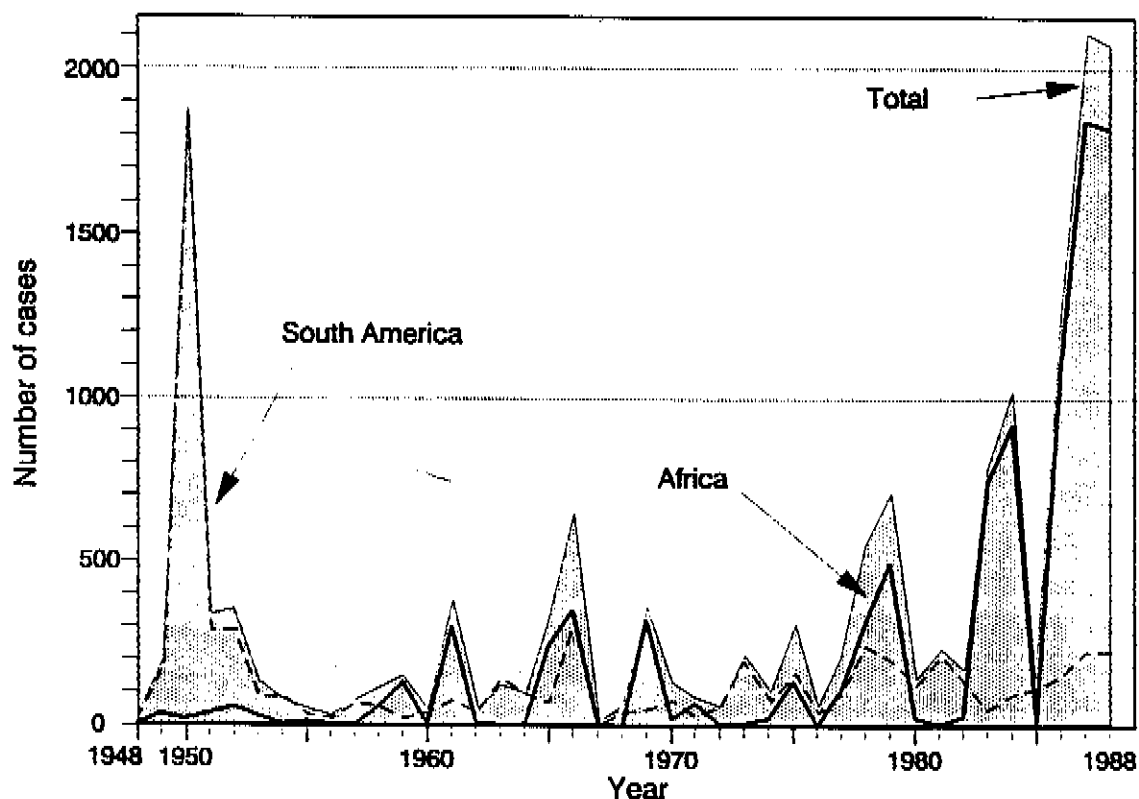


Figure 1 Yellow fever activity 1948-1988

Clinically, this disease starts with the sudden onset of acute fever followed by a second phase of hepato-renal dysfunction and haemorrhage. Mortality rates vary widely, from 20 to 80 percent of the cases.

THE CURRENT MAGNITUDE OF THE YELLOW FEVER PROBLEM

Recent yellow fever activity worldwide

The 3 year period 1986-1988 represented an extraordinarily active period of YF. The worldwide total of 5395 cases and 3172 deaths [case fatality rate (CFR) 58.8%] represents the greatest amount of YF activity reported to WHO for any 3 year period since reporting began in 1948 (Figure 1). Of this 3 year total, the number of reported cases in Africa was 4772, with 2470 deaths (CFR 51.8%). This represents the highest number of African cases in any 3 year period since 1948. The 629 cases and 540 deaths (CFR 85.9%) officially reported from South America represents the largest number reported during any 3 year period since 1952. Ironically, 1988 marked the 50th anniversary of the development of the live-attenuated YF vaccine. There now has been a safe and efficacious YF vaccine since 1937-8.

In 1988 alone, both Africa and South America reported substantial amounts of yellow fever (YF) activity [2058 cases, 1709 deaths, CFR 83.0%].

South America-1988. For the third consecutive year, the majority (83%) of the total of 235 YF cases and 198 deaths (CFR 84.3%) in South America were reported from Peru. As in the past 2 years, the remaining YF cases were reported from three other countries: Bolivia, Brazil, and Colombia.

Peru itself reported the second largest number of cases (195 cases with 166 deaths) recorded by any individual South American nation since 1948. A constant increase in YF cases has been seen in Peru since 1982 (Figure 2). During peak YF activity in the first 4 months of 1988, at least one YF death was reported each day.

Africa-1988. Since 1980, 11 African countries have reported YF activity. However, in 1988, only two African countries reported YF activity which totalled 1823 cases with 1511 deaths (CFR 82.9%). The total number of cases during the three years 1986-1988 in Africa was 4772, with 2470 deaths (CFR 51.8%). This represents the largest number of cases in any three year period since 1965.

The vast majority of 1988 African cases were reported as part of a major epidemic in Nigeria, which followed the 1987 epidemic of urban yellow fever in southwestern Nigeria (Oyo State), and the 1986 outbreak of sylvatic YF in southeastern Nigeria (Benue and Cross-River States).

In Nigeria, the majority of 1988 cases (1067) were reported from Kano State on the northern border of Nigeria, but significant YF activity also was reported from the north-central States of Kaduna (375 cases) and Bauchi (150 cases). Preliminary reports indicate that the epidemic continued through 1989, with many YF cases observed in the central and south-central portions of Nigeria.

Revised official figures of YF activity in Nigeria over the last 5 years are as follows: 1984, 898 cases, five deaths; 1985, six cases, no deaths; 1986, 1102 cases, 374 deaths; 1987, 1510 cases, 599 deaths; and 1988, 1786 cases, 1497 deaths. As

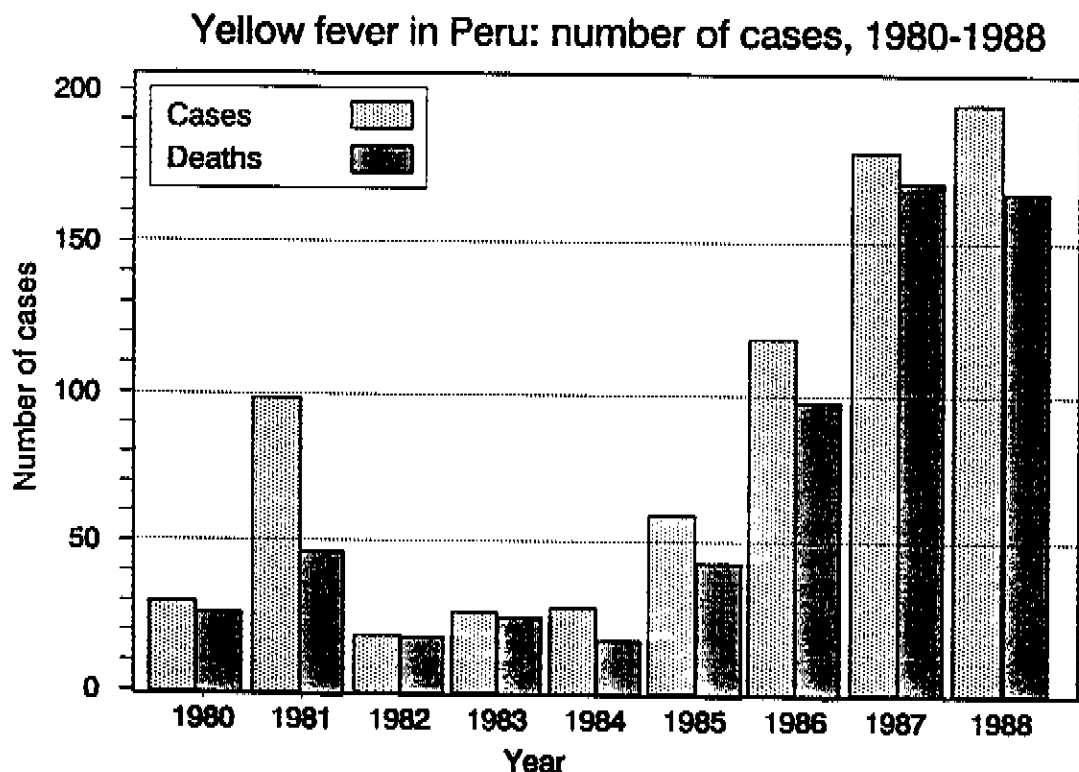


Figure 2 Yellow fever in Peru since 1980

in Peru, the trend over the last 8 years has been a substantial increase in YF (Figure 3). Not only have the total cases and deaths risen during this period, but the case fatality rate appears to be rising. This could be an artifact of reporting, since active case surveillance efforts in 1986-87 were switched to a more passive surveillance system in 1988. Other possibilities are that the occurrence of clinically similar diseases might be confusing the reporting of YF, or that a more virulent virus strain has emerged.

The actual extent of the yellow fever problem in Africa

In regard to Africa, numerous studies have shown that only a small percentage of African YF cases are reported, and only if village-based serological studies are undertaken does the true extent of the disease become known. This is due to a number of reasons including: the often remote epidemic sites, lack of diagnostic facilities, difficulties in clinical recognition of the disease by peripheral health workers, delays in recognition of the epidemic, and sparse communication of reports to a central reporting system. In seven epidemiological studies undertaken during YF outbreaks over the last 25 years in Africa, morbidity and mortality were consistently under-reported by 10 to 500 times.

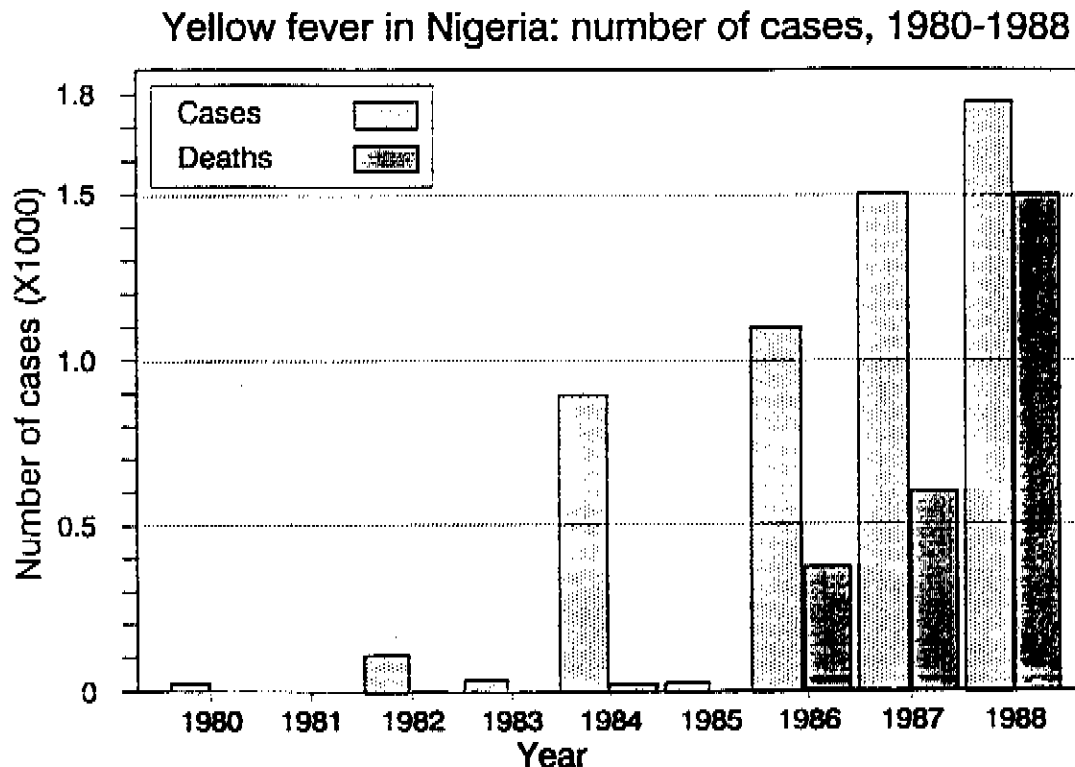


Figure 3 Yellow fever in Nigeria since 1980

In an attempt to determine the extent of the YF outbreaks in Nigeria, the Nigerian Ministry of Health and WHO supported two separate epidemiological studies during 1986 and 1987.

In 1986, surveys in treatment centers 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%. Oju in Benue State was one of two major epicenters in the 1986 sylvatic YF epidemic, the other was in Cross-River State. The at-risk population was 200000 in Oju, and thus the study suggested that 9800 cases with 5600 deaths occurred in Oju. Official 1986 figures reported to the Ministry of Health indicated 559 cases with 200 deaths for the entire Benue State. Thus, in 1986 under-reporting for cases and deaths was at least 17 and 28 times respectively for Benue State.

In 1987, surveys were undertaken in 17 hospitals and three villages in Oyo State. Of the 60000 village residents, 3.6% were interviewed, and results indicated an attack rate of 2.9% and a mortality rate of 0.6%. The 1987 outbreak was in a heavily populated area (198 inhabitants/sq.km), and was an urban type of YF epidemic spread by *Aedes aegypti*. The at-risk population was estimated at 4 million, and the study estimated that 116000 cases with 24000 deaths occurred in Oyo State. Official 1987

The recent pattern of YF epidemics shows predominantly children infected

One apparent problem has developed as a result of many African countries switching from the preventive YF immunization programmes of the 1940-50 period, to a post-outbreak, emergency immunization approach to YF control. 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 1977-80, the epidemic involved mainly children under 15 years of age. These children were too young to have been immunized in 1969, and consequently 67% of the cases and 82% of the deaths in 1977-80 occurred in this age group (Figure 5).

The same phenomenon was observed in 1987 in the YF epidemic in Mali, where 71% of the cases occurred in children (Figure 5). Indeed, the age distribution of cases in many recent outbreaks, this epidemiological pattern of epidemics in children is repeated in several African countries (Figure 5).

AGE DISTRIBUTION OF YELLOW FEVER CASES DURING RECENT EPIDEMICS

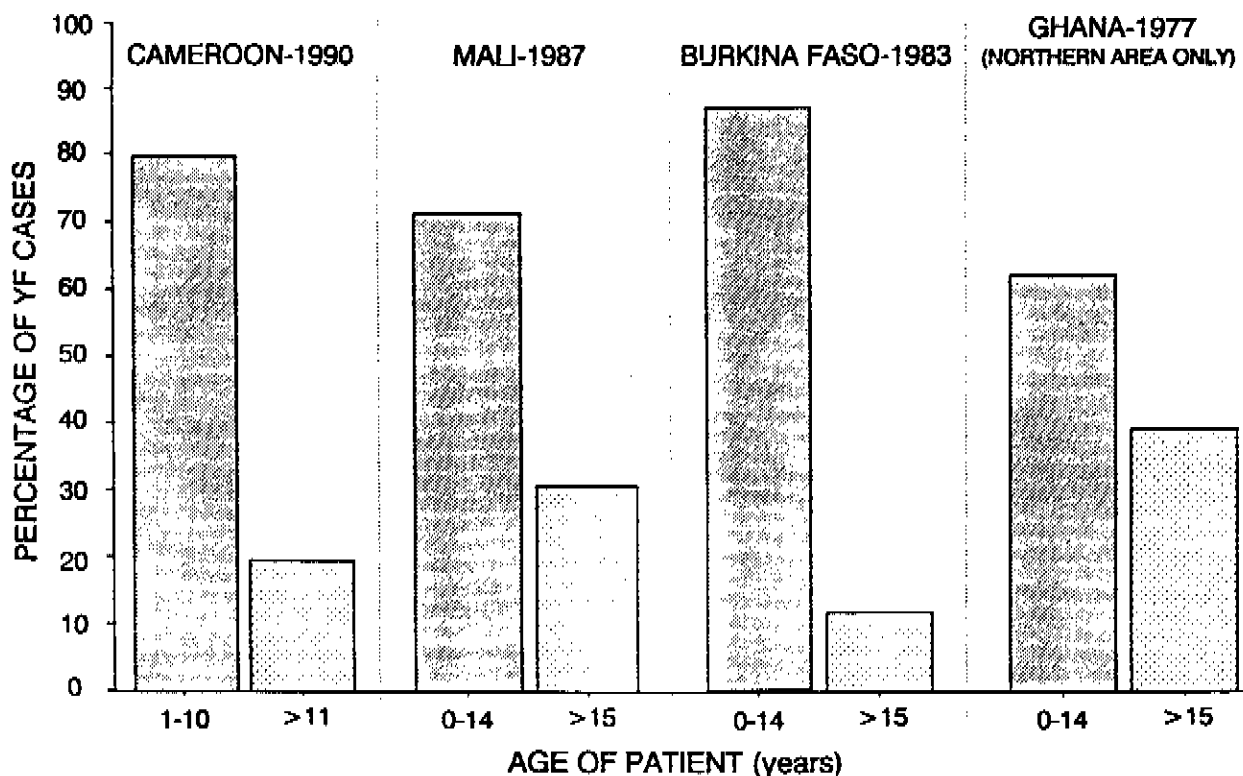


Figure 5 Pattern of age distribution of cases in some recent YF epidemics

VACCINE ISSUES FACING EPI

The live-attenuated YF vaccine was one of the earliest viral vaccines to be developed, and it has proved safe and efficacious. The 50th anniversary of the development of the YF vaccine was in 1988. There now has been a safe, efficacious vaccine against YF for half a century.

The YF vaccine is a live-attenuated vaccine produced in eggs. After one shot, the vaccine protects for a period of at least 10 years. Indeed, protection is probably life-long since neutralizing antibodies have been detected in individuals 40 years after immunization.

Until recently, the vaccine was thermal labile, but the development of new protective additives have increased its thermostability. 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. The half-life of reconstituted vaccine is 2-10 hours. However, a 1986 study of vaccine thermostability showed that further work on stabilizing YF vaccine is needed since only five vaccine preparations from a total of 12 manufacturers met both WHO criteria for vaccine thermostability (Figure 6).

THERMOSTABILITY OF YELLOW FEVER VACCINE AT 37°C

CRITERION A - MUST RETAIN 10^3 MLD₅₀/HUMAN DOSE FOR 14 DAYS

CRITERION B - MUST NOT LOSE MORE THAN 1 LOG TITER AFTER 14 DAYS

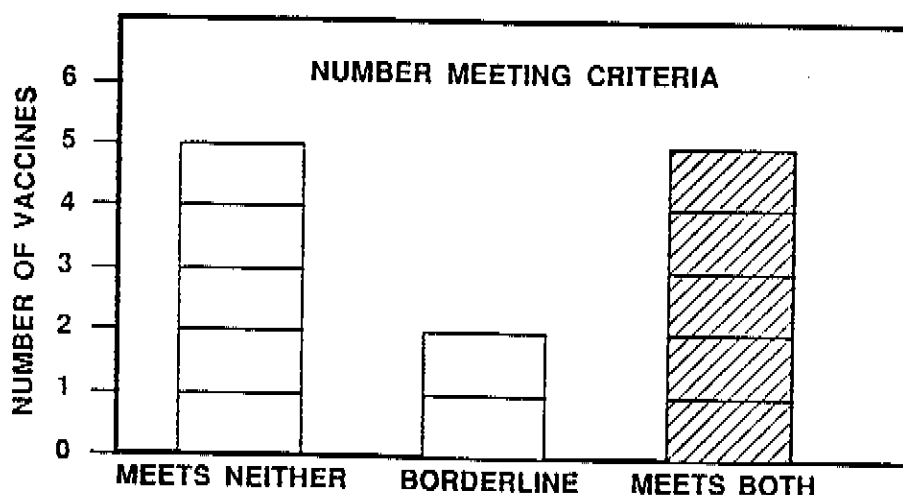


Figure 6 Studies of YF vaccine preparations from 12 manufacturers to determine if they meet WHO thermostability criteria

The vaccine is one of the safest viral vaccines ever produced. From 1945 through 1989, only 17 cases (one fatal in a 3 year old) of encephalitis temporally associated with YF immunization have been reported worldwide. Since all but three of these occurred in children immunized at 4 months of age or younger, a review by a panel of experts recommended that YF vaccine not be given before 6 months of age.

Being a disease recognized for many years, numerous studies, articles, and books describe YF control strategies, and all include well-formulated sections detailing the role of international, regional, and national organizations in the control of YF. However, YF continues to infect and kill unimmunized people. Two control strategies have been attempted in Africa in the last 40 years. The first is a routine immunization programme, and the second is a post-outbreak, emergency control programme.

A mass, immunization programme was begun in the early 1940's in French West Africa, and 25 million people were immunized in 4 year cycles. The recurring pattern of epidemics in West Africa was interrupted, and through the 1950's this preventive immunization strategy controlled YF in West Africa.

This strategy was abandoned in the 1960's, and replaced by a post-outbreak, emergency response immunization and control strategy. Since then, there has been a series of epidemics of various severity. In the case of the Nigerian outbreak, attempts to control it with a post-outbreak, "fire-fighting" type of programme severely strained the resources of local and international agencies. It is now being argued among international experts that there has been excessive confidence in instantaneous, emergency control procedures.

One basic principle is well-documented, that if the at-risk populations are immunized with YF vaccine, YF epidemics can be prevented. Therefore, any future strategy to control YF will have as its main action point immunization of larger numbers of the at-risk population.

In 1988, the joint UNICEF/WHO Technical Group on Immunization for the African Region reviewed the situation on YF. This group urged YF endemic countries to consider incorporating YF vaccine into their EPI schedules on a routine basis.

Also in 1988, the EPI Global Advisory Group reviewed the situation on YF. It recommended that countries at-risk for YF should incorporate YF vaccine into the routine activities of the national immunization programme. It suggested that YF vaccine may be given at 6 months of age or with measles at 9 months of age.

In 1990, the EPI Global Advisory Group again considered YF and made the following recommendation:

"Yellow fever endemic countries of the African and Eastern Mediterranean Regions should incorporate yellow fever (YF) vaccine in their routine immunization programmes. YF vaccine is recommended for use from 6 months of age and can be administered at the same time as measles, polio (OPV or IPV), DPT, BCG, and/or hepatitis B vaccines. Inclusion of older children may be appropriate in areas where yellow fever epidemics are occurring or considered a high risk. Countries that include YF vaccine in their immunization programmes should monitor immunization coverage and disease incidence.

YF vaccines should meet WHO requirements and WHO should exercise its special powers mandated by the World Health Assembly to monitor YF vaccine quality."

Coverage with measles and yellow fever vaccines,
by coverage survey, children 12-23 months
4 African countries, 1979-1990

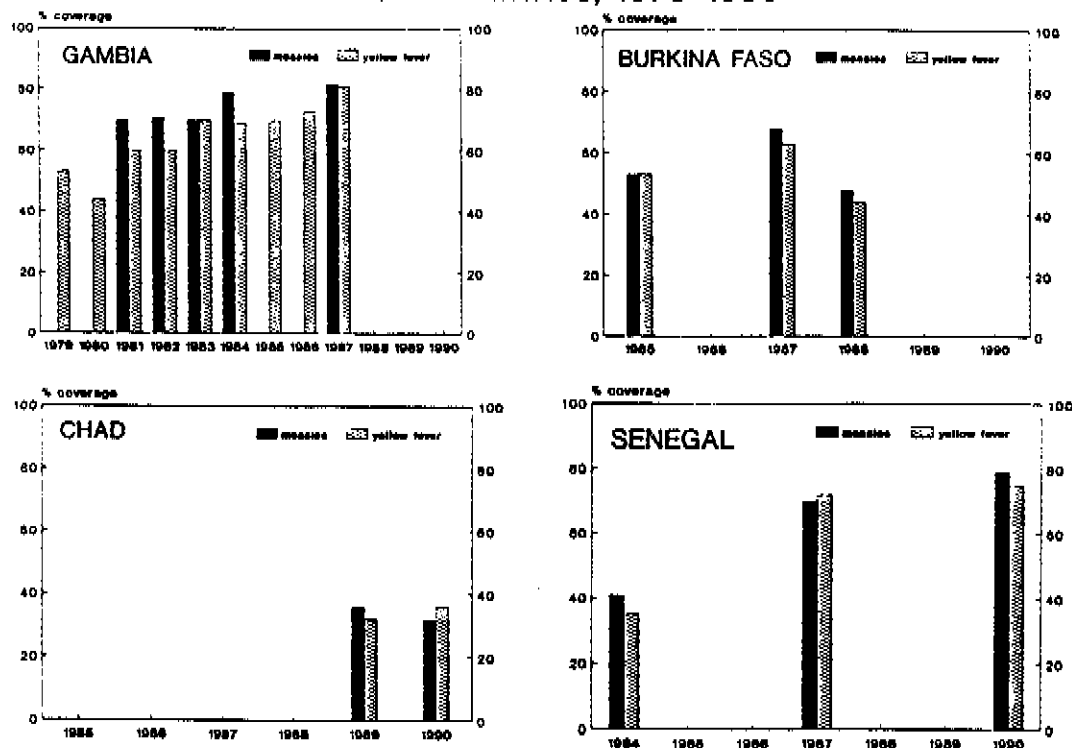


Figure 7 YF vaccine coverage in four African countries

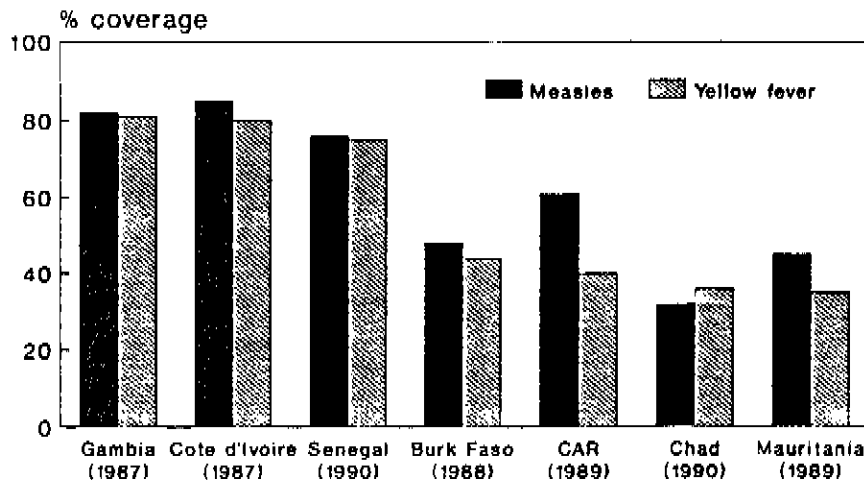
THE CURRENT STATUS OF YF VACCINE WITHIN EPI IN AFRICA

Data available from coverage surveys has recently been reviewed, and information on YF vaccine coverage within the EPI in several African countries is summarized in Figures 7 and 8. It is important to note that systematic collection of data on YF immunization has not been a major emphasis in the past, and thus the data are limited.

It appears that the following countries have at least partially incorporated YF vaccine into their EPI in some recent years: Angola, Burkina Faso, Central African Republic (CAR), Chad, Cote d'Ivoire, Gabon, Gambia, Ghana, Mauritania, Niger, Nigeria, and Senegal. Most give YF vaccine with measles vaccine at 9 months of age (the simultaneous administration of these two vaccines has been shown acceptable in limited studies). Simultaneous immunization explains the generally good agreement between immunization coverage for measles and YF (Figure 8).

Obviously, one major future goal must be to improve the reporting of coverage with YF vaccine.

National coverage* with measles and
yellow fever vaccines, 7 countries,
African Region, 1987-1990



* Coverage surveys, children 12-23 mo., nationwide weighted averages, data reported to WHO/EPI as of December 1990.

Figure 8 Measles and YF vaccine coverage in seven African countries 1987-90

DISCUSSION

New tactics are available to control YF. Modern biotechnology has provided new, improved diagnostic and surveillance techniques which could improve YF control. The EPI represents a new opportunity to more effectively deliver YF vaccine to a wider population at a reduced cost. Alone, the EPI will not reach older children and adults, and further programmes to immunize these populations must be considered.

The availability of vaccine has been a problem in the past. The number of surviving infants in 1990 in the countries where YF is a potential risk (Figure 4) will be approximately 18 million. Vaccine is made in a number of developing countries, including Senegal and Nigeria in Africa. About 6-10 million doses are produced yearly in Africa. However, newer technology will help partially solve the problem of vaccine availability. The thermostability of the vaccine has been increased, renovated vaccine production facilities (along with a longer shelf life) have increased vaccine supply, and the cost of the vaccine has been somewhat reduced. The most recent cost of YF vaccine (for WHO) is in the range of \$0.12 to \$0.25 (US\$) per dose. Ongoing development of a cell-culture produced vaccine might allow increased vaccine production and further improve vaccine supply.

The basic principles of YF control remain as they have been for years. These include: efficient surveillance to establish at-risk areas and an early-warning system; a reliable source of thermostable vaccine; efficient delivery of vaccine to all ages at risk; optimum patient management programmes; a well-maintained vector control programme; and the social, political, and economic commitment to support and maintain YF control efforts.

History clearly documents that a YF immunization programmes can prevent YF epidemics. However, at this juncture, we are still challenged by the dream of controlling YF. In one way, considering the last decade of YF disease activity, YF can be viewed as a "re-emerging" virus. A renewed effort is needed to combat this often-forgotten disease.