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The Immunological Basis for Immunization Series

Module 8:

Yellow fever

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
EXPANDED PROGRAMME ON IMMUNIZATION

World Health Organization
Geneva

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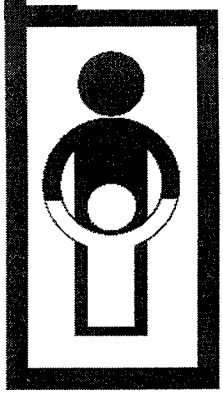

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
EXPANDED PROGRAMME ON IMMUNIZATION

World Health Organization
Geneva

*Dr Robertson's current title is Medical Officer, Vaccine Research and Development, GPV.

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The Immunological Basis for Immunization **series is available in English and French (from the address below). It has also been translated by national health authorities into a number of other languages for local use: Chinese, Italian, Persian, Russian, Turkish, Ukranian and Vietnamese. The series comprises eight independent modules:**

Module 1: General Immunology
Module 2: Diphtheria
Module 3: Tetanus
Module 4: Pertussis
Module 5: Tuberculosis
Module 6: Poliomyelitis
Module 7: Measles
Module 8: Yellow fever

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Contents

Preface

This series of modules on the immunological basis for immunization has grown out of the experience of persons working with the WHO Expanded Programme on Immunization (EPI). The EPI was established in 1974 with the objective of expanding immunization services beyond smallpox, with emphasis on providing these services for children in developing countries.

Six vaccine-preventable diseases have been included within the EPI since its beginning: diphtheria, measles, pertussis, polio, tetanus, and tuberculosis. To protect newborns against neonatal tetanus, tetanus toxoid is administered to the mother either during her pregnancy or prior to pregnancy during the childbearing years.

Two more vaccine preventable-diseases will be addressed by the EPI during the 1990s. The World Health Assembly has set the target of including yellow fever vaccine in the EPI by 1993 in countries where this disease poses a risk. Hepatitis B vaccine is being added gradually, with the target date of 1997 for incorporation of this vaccine in the immunization programme in all countries.

Titles of the nine modules in this series are listed inside the front cover of this module. They are intended to provide information on the immunological basis for WHO-recommended immunization schedules and policies. They have been prepared for the following main audiences:

- immunization programme managers, whose questions and concerns caused this series to be written,
- consultants and advisers on immunization activities,
- teachers of courses on immunization at the university level and facilitators of workshops,
- medical and nursing students as part of the basic curriculum,
- laboratory scientists providing diagnostic or research services for vaccine-preventable diseases, and
- scientists involved in basic research aimed at improving the delivery of vaccines or providing improved vaccines.

Other modules in this series and additional materials on the EPI are available from the Expanded Programme on Immunization, World Health Organization, 1211 Geneva 27, Switzerland.

Yellow Fever

1. The Virus and the Disease

Yellow fever is a viral hemorrhagic fever which strikes an estimated 200 000 persons worldwide each year and causes an estimated 30 000 deaths *(Expanded Programme on Immunization 1992).* The case fatality rate may reach 20% to 80%; however, these figures are based on the most severe cases that are hospitalized and the overall case fatality rate is lower.

Yellow fever virus is classified in genus *Flavivirus* which is in the family *Flaviviridae.* Previously flaviviruses were classified as a genus of the family *Togaviridae;* however, based on structure, replication, and morphogenesis, a new family, *Flaviviridae,* was approved by the International Committee on Taxonomy of Viruses in 1984 *(Rehle 1989).* The family *Flaviviridae* contains over 70 related but distinct viruses, most of which are arthropod-borne. Other major pathogens in this classification include dengue viruses and Japanese encephalitis virus.

The yellow fever virus is small (35 to 45 nm) and consists of a core containing single-stranded RNA surrounded by a lipid envelope. The genome has been completely sequenced and found to contain 10 862 nucleotides *(Rice et al. 1985).* The envelope contains a single glycoprotein with type and group-specific antigenic determinants. Yellow fever virus can be inactivated with lipid solvents (ether, chloroform), heat (56°C for 30 minutes), and ultraviolet light *(Monath 1990).*

Antigenic differences have been shown between strains of yellow fever virus. Antibody-absorption techniques can distinguish between strains from South America and Africa *(Clarke 1960).* Strains can also be differentiated on the basis of virulence characteristics for mice *(Fitzgeorge □□Bradish 1980).* RNA oligonucleotide mapping has shown three genetically distinct geographical variants in Africa: Senegal-Gambia; Ivory Coast-Burkina Faso-Nigeria; Central and East Africa *(Deubel et al. 1986).*

The disease yellow fever was first distinguished from malaria, dengue, and other tropical diseases during the 1647 to 1649 epidemics in Barbados, Cuba, Guadeloupe and Mexico *(Bres 1986).* Since then, it has raged as periodic epidemics in the Americas and Africa. In 1900, a commission headed by Walter Reed confirmed that the disease was transmitted from human to human by the mosquito *Aedes aegypti,* a finding earlier theorized by the Cuban physician Carlos Finlay in 1881. This information led to efforts at mosquito control in the Americas, with excellent results in eliminating the disease from many areas.

There are two epidemiologic patterns of yellow fever virus transmission: the urban cycle and the forest cycle (also known as the jungle or sylvatic cycle). The two epidemiologic patterns lead to clinically identical disease, since they are produced by the same virus. In some instances, spread from forest to urban cycles has been documented. Today, the yellow fever virus circulates in an endemic, forest cycle in the Americas, resulting in up to 500 reports of infections of unimmunized forest workers per year. In Africa, yellow fever virus circulates in both urban and forest cycles, and the disease periodically explodes out of its endemic pattern to infect large number of unimmunized persons during major epidemics.

Yellow fever does not occur in the Middle East, Asia, or the Pacific, despite the fact that a mosquito vector, A. *aegypti,* is widespread in these regions. Experimentally, *A. aegypti* mosquitos collected in different parts of Asia have been able to transmit the virus to monkeys or newborn mice with variable success *(Bres 1986).* However, the reason for lack of spread of yellow fever outside Africa and the Americas is not known.

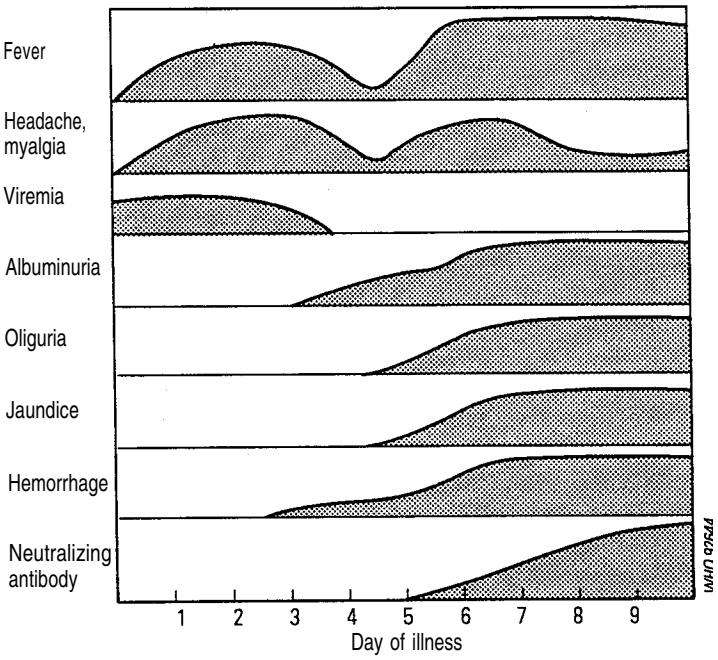
In the urban pattern, the virus is transmitted by mosquito from infected humans to susceptible humans. For the urban cycle, the mosquito vector is usually A. *aegypti,* a domestic mosquito that breeds near houses, with the female preferring to lay eggs in water collected in water jars, old tires, gutters, or discarded tin or plastic containers. In 1978, it was found that A. *aegypti* females could transmit yellow fever virus transovarially to a small proportion of their offspring and these eggs can thus maintain the virus during the dry season *(Aitken et al. 1979).* The urban pattern is found in cities and in villages in Africa. In the Americas, the last documented A. *aegypti*-borne urban yellow fever outbreak occurred in Trinidad in 1954 *(ACIP 1990).*

In the forest pattern of yellow fever, the main host is the monkey; man is an accidental host. The forest cycle of transmission among monkeys was not discovered until the 1930s in South America and the 1940s in Africa *(Bres 1986).* The vectors are mosquitos of the genus *Haemagogus* in South America and *Aedes africanus* and several other mosquito species in Africa; most of these mosquitos live at the tops of trees in the forest.

The virus multiplies in the mosquito vector. About 12 to 21 days after biting an infected person or monkey the mosquito becomes infective and it remains infective for the rest of its life.

The disease in humans is characterized by sudden onset of fever, headache, backache, general muscle pain, nausea, and vomiting. As the disease continues, albuminuria, oliguria (even anuria), and jaundice occur. Hemorrhagic symptoms may include epistaxis, hematemesis, and melena (Figure 1).

Figure 1. Time course of clinical features of yellow fever and the neutralizing antibody response to natural infection.



2. The Nature of Immunity to Yellow Fever

Passive immunization experiments in animals show that neutralizing antibodies provide the most efficient protection against challenge *(Brandriss et al. 1986).*

There is antigenic cross-reactivity between yellow fever virus and many other flaviviruses. Cross reactions in antibody tests complicate survey and diagnostic serology and must be considered in assessing immunogenicity of yellow fever vaccines. For this reason, it is useful to categorize persons as previously exposed to flaviviruses and not previously exposed to flaviviruses.

Previous exposure to one or more flaviviruses appears-to modify the degree of clinical illness in individuals infected by wild yellow fever virus. This has been studied indirectly, by assessing the ratio of inapparent to apparent yellow fever infection among various groups of individuals in The Gambia, following an extensive outbreak in 1978 to 1979. For individuals (mainly children) who experienced a primary yellow fever infection, the ratio of inapparent to clinical yellow fever infection was 2:1. In contrast, for individuals with serological patterns indicating that they had sustained yellow fever infection on a background of prior exposure to one or more flaviviruses (most were Zika viruses), the ratio of inapparent to clinical yellow fever infection was 22:1 *(Monath 1980).* Experimental evidence in monkeys also indicates that prior infection with certain flaviviruses (Zika, Wesselbron, dengue) can modify the response to challenge with yellow fever virus.

There is presently no evidence to suggest that prior flaviviral infection could "sensitize" the host to subsequent more severe yellow fever infection, as has been postulated to occur in dengue hemorrhagic fever-shock syndrome *(Monath 1990).* The presence of neutralizing antibody to yellow fever does not induce cross-protection against dengue viruses, but increases the antibody response to dengue. Scott et al. *(1983)* described small-scale experiments where volunteers with or without neutralizing antibody to yellow fever viruses were inoculated with an attenuated dengue type 2 candidate vaccine. The volunteers with pre-existing yellow fever antibody all seroconverted; in contrast, no relation between virus dose and seroconversion was detected in volunteers who had no pre-existing antibody to yellow fever virus.

3. Techniques to Measure Antibody Response

Serologic methods used in studying antibody response to yellow fever include neutralization, hemagglutination inhibition (HI), complement fixation (CF), enzyme linked immunosorbent assay (ELISA), and the indirect fluorescent antibody test (IFA). Neutralizing, HI, and IFA antibodies appear within a week of onset; CF antibodies appear later.

3.1 Neutralization tests

The neutralization test is the most specific. Neutralizing antibodies appear during the first week

after onset and last for many years, probably for life (Figure 1). Techniques for the measurement of neutralizing antibody include the plaque reduction assay in cell culture and the mouse protection test. In 1930, Theiler found that yellow fever immune serum mixed with the virus and inoculated intracerebrally had neutralizing activity that prevented infection in mice; this was the basis for the mouse protection test *(Smithburn et al. 1956).* Because of its widespread use in early studies, it should be noted that the mouse protection test was never fully standardized and many factors were reported to cause variability of results, including different sensitivity of mice to yellow fever virus depending on the age of the mouse, the route of virus introduction, the type of animal sera used, and the method of rehydrating lypophilized virus *(Smithburn et al. 1956).*

The plaque reduction method for detecting neutralizing antibody is the standard for assessing response to yellow fever vaccine today *(Spector & Tauraso 1968 and 1969, DeMadrid & Porterfield 1974).* This method is more sensitive in detecting neutralizing antibody that the mouse protection test *(Poland et al. 1981).*

3.2 Hemagglutination inhibition and complement fixation tests

The hemagglutination inhibition (HI) test detects antibodies that usually appear early, within the first week after onset, and this method is widely used for the diagnosis of natural infection *(Clarke & Casals 1958).* The HI test is not a good way to assess response to yellow fever vaccine and is often negative in persons demonstrating seroconversion by the neutralization test.

The complement fixation (CF) test is more specific than the HI test. Complement fixing antibodies appear later (during the second week after onset) and may decline relatively rapidly to low levels 6 to 12 months after infection *(WHO 1986).* Thus the presence of CF antibodies usually indicates a recent infection. However, in some studies CF antibodies have been shown to persist at moderate to high titers for prolonged periods (at least 2 years).

3.3 ELISA and indirect fluorescent antibody tests

Determination of IgM antibodies by ELISA is the most useful method indicating recent infection and for diagnosis in cases demonstrating extensive flavivirus cross-reactions by standard tests *(Monath 1990).* The duration of IgM antibodies is uncertain and appears to be quite variable. In persons vaccinated with 17D virus, detectable IgM neutralizing antibodies are present as long as 18 months after immunization.

The ELISA for IgG antibodies, using a viral antigen specific for the yellow fever virus, is more sensitive and more specific than the CF and HI tests. The results of the ELISA test correlate well with those obtained by neutralization *(Deubel et al. 1983, Barry et al. 1991).* ELISA is being increasingly used by laboratories, since it is less time-consuming than the plaque reduction neutralization test *(R. Shope, personal communication).*

The indirect fluorescent antibody (IFA) tests, using cells infected with yellow fever virus, can detect both IgG and IgM antibodies in serum specimens *(WHO 1986).* In primary infection, IgG antibodies are regularly found and the specificity of the IFA test is comparable to that obtained in the CF and neutralization tests. IgM antibodies are highly specific, but not always present by this technique due to interference by IgG antibodies *(Monath 1990).*

3.4 Assessing exposure to other flaviviruses

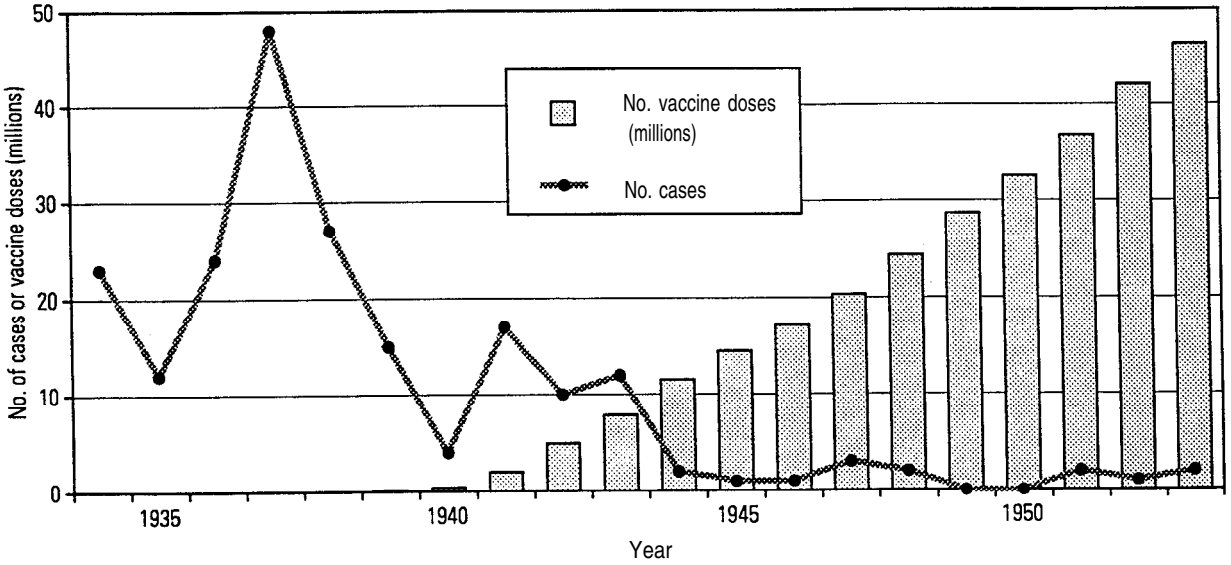
Primary yellow fever infection is followed by the appearance of specific antibody responses by most test methods. In contrast, individuals with prior flavivirus experience develop a rapid and cross-reactive response. Measurement of IgM antibodies by IFA or ELISA provides a specific diagnosis in a high proportion of cases with cross-reactive patterns in tests on whole sera *(Monath 1990).* Alternatively, it may be necessary to use parallel tests with flaviviruses closely related to yellow fever virus to eliminate their role as a causative agent.

4. Response to Natural Infection

Following natural infection, neutralizing, HI, and IgM antibodies appear about 5 to 7 days after the onset of disease (Figure 1). Neutralizing antibodies are responsible for elimination of the virus. It is not unusual to find both infectious virus and antibody in serum, but the role of immune complexes in the pathogenesis of the disease remains uncertain *(Institute of Medicine 1986).* CF antibodies appear in the second week after onset. Neutralizing and HI antibodies persist for long period, but CF antibodies disappear after about 6 to 12 months.

Inapparent, abortive, or clinically mild infections with yellow fever are frequent. In endemic areas of West Africa subject to yearly wet season recrudescence and amplification of yellow fever, the annual incidence of infection may be as high as 1% to 5%; the prevalence of immunity in young adults in such areas is 50% to 90% *(Monath 1990).*

Figure 2. Doses of French neurotropic yellow fever vaccine (FNV) given (by scarification) and cases of yellow fever reported in French West Africa, 1934 to 1953.



5. Response to Immunization

5.1 Vaccines

Two live attenuated yellow fever vaccines were developed in the 1930s: the French neurotropic vaccine (FNV) from human virus passaged in mouse brain and the 17D vaccine from human virus passaged in embryonated chicken eggs.

FNV was a successful vaccine. Between 1939 and 1952 over 38 million doses of FNV were administered (mostly by scarification along with smallpox vaccine) in Francophone countries of West Africa *(Durieux 1956).* Yellow fever cases declined dramatically in these countries (Figure 2). However, FNV was associated with a high incidence of encephalitic reactions in children *(Rey et al. 1966).* The FNV stopped being recommended for children under 10 years in 1961 and manufacture of this vaccine strain was discontinued in 1980.

Today, 17D is the only type of yellow fever vaccine produced. The 17D vaccine was developed by Theiler and Smith in 1937. The virus was passed 53 times in monkeys, 18 times in mouse embryo tissue culture, 58 times in chick embryo tissue culture, and an additional 160 times in chick embryo culture which contained no brain or spinal cord tissue *(Freestone 1988).*

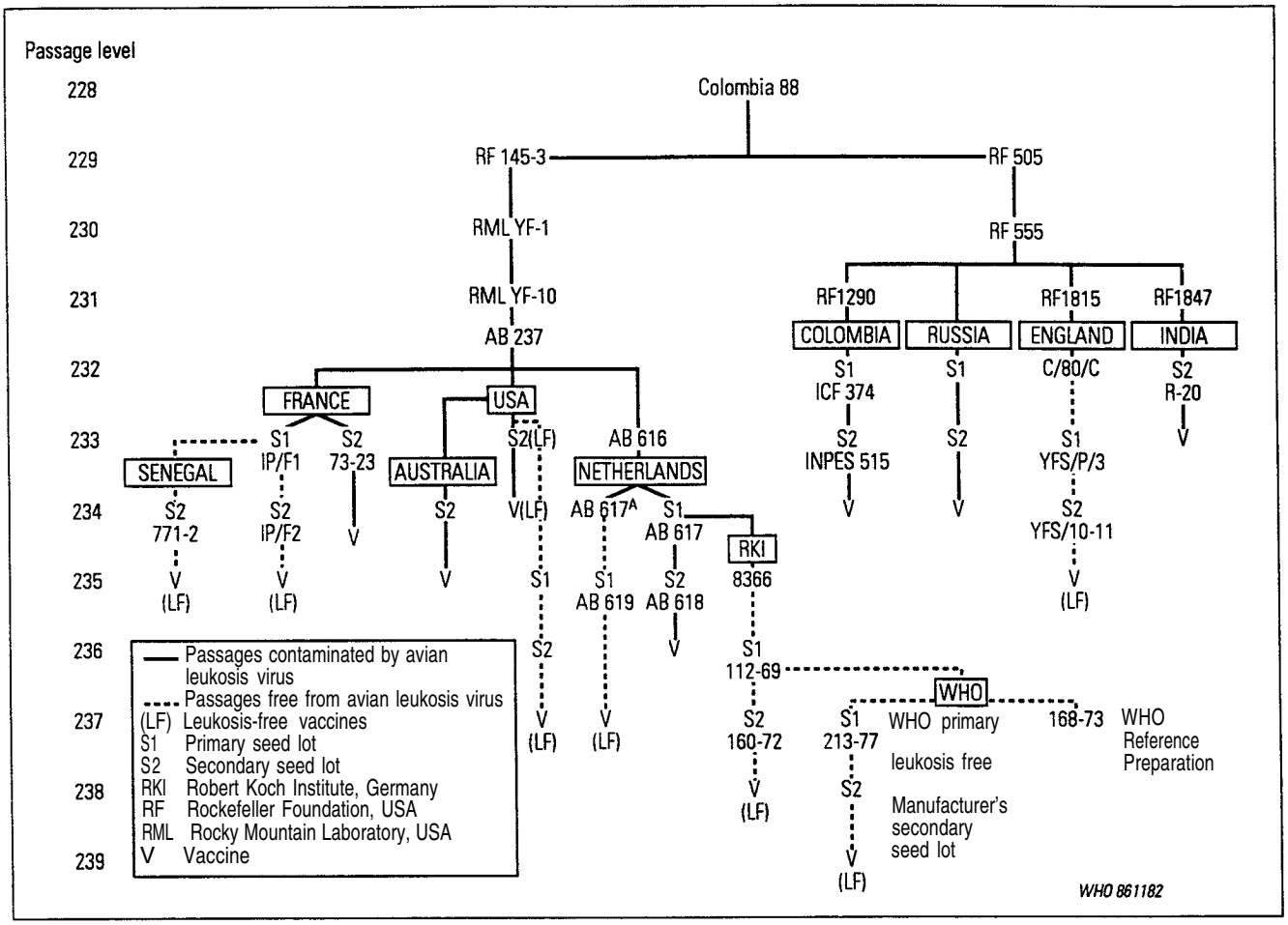
Initially, there were problems with the 17D vaccine becoming over-attenuated or under-attenuated. These problems were resolved by the establishment of a virus seed lot system in 1945; WHO requirements are that no vaccine shall be manufactured that is more than one passage level from a seed lot that has passed ail safety tests *(WHO Expert Committee 1976).* The various strains used today for manufacture of 17D vaccine are shown in Figure 3. A detailed study of genetic and antigenic variation among these different 17D virus vaccines using oligonucleotide mapping and monoclonal antibody analysis found a high degree of genetic and antigenic similarity among them *(Monath et al. 1983).* The study showed an RNA sequence homology of 98% to 100% among these vaccines, providing experimental confirmation of the usefulness of the virus seed lot system.

5.2 Thermal stability of 17D vaccine

Until recently, 17D yellow fever vaccine was thermolabile, but the development of new protective additives has increased its thermal stability. Research in a number of laboratories revealed that stabilizing media such as lactose, sorbitol, histidine, and alanine considerably improve the heat stability of lyophilized 17D vaccine *(Barme & Bronnert 1984, Barme et al. 1987).* The development of a more stable formulation of yellow fever vaccine has provided a product whose shelf life at a temperature of -20°C or 4°C is prolonged to 2 years.

However, lyophized 17D vaccines presently available differ considerably in their stability *(Galazka 1989, Ishak & Howard 1990).* A collaborative study undertaken with the cooperation of 12 manufacturers of 17D yellow fever vaccine showed a very wide range of stability among vaccines stored at 37°C for 32 days *(WHO 1987).* The study found that some vaccines contained at least 1000 PFU after 14 days exposure, while other vaccines lost most of their activity after 1 to 5 days exposure. As a result of this study, WHO established a heat stability requirement for yellow fever vaccine. The vaccine should retain 1000 mouse LD_{50}, or its equivalent in plaque forming

Figure 3. The derivation of the currently available 17D yellow fever vaccines.



units per human dose and the mean loss in titer should be less than 1 log after being heated for two weeks at 37°C *(WHO Expert Committee 1988).*

If the lyophilized, stabilized 17D vaccine is reconstituted with refrigerator-temperature diluent and then kept in an ice-bath, it will maintain potency for up to 3 hours. However, if the lyophilized, stablized 17D vaccine is reconstituted with diluent at 37°C, the vaccine loses all potency within one hour *(de Souza Lopes et al. 1988).*

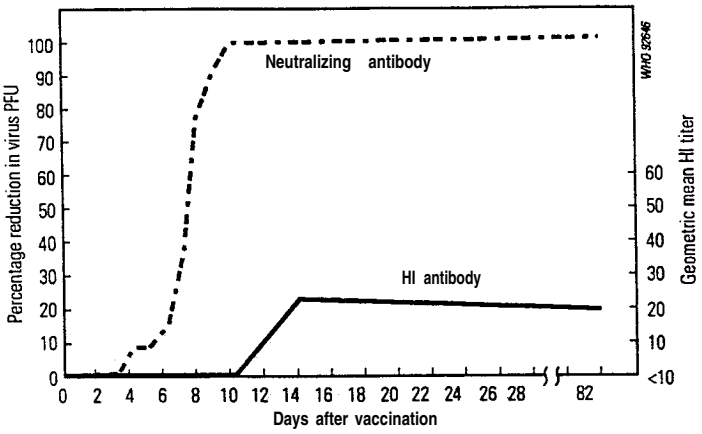
5.3 Immunity induced by 17D vaccine

Initial studies on the 17D strain vaccine involved nearly 60 000 persons in Brazil *(Smith et al. 1938).* Neutralizing antibodies developed between the 7th and 21st day after immunization and 95% of recipients developed antibody. The vaccine was well tolerated, and any reactions were mild and limited to headache and low grade fever, usually on the 6th or 7th day after vaccination. Virus was recovered from the blood of vaccinees most readily on the 5th, 6th, and 7th days after vaccination.

A detailed study of the kinetics of the serum antibody response to a 0.5 ml dose of 17D vaccine given subcutaneously to persons previously unimmunized and not exposed to flaviviruses showed that they developed neutralizing antibody by the 8th day *(Monath 1971)* (Figure 4). HI antibodies started to be seen about day 12; low titers (1:10 to 1:40) of HI antibodies were found at about 14 days after vaccination; after day 14 they remained stable or declined slightly. IgM antibodies first appeared by day 8 to 9, rose to high titers on days 14 to 17 and then declined gradually thereafter. In the first 4 to 6 weeks after vaccination, IgM antibody titers were 16 to 256 times higher than IgG antibody titers. IgG antibodies appeared between 10 to 17 days after vaccination and tended to remain stable or rise slightly. IgA appeared about the same time as IgG, but generally disappeared by 80 days after immunization.

Most early studies on 17D vaccine were conducted in adults and many of these studies used methods which were not fully standardized, specifically the mouse protection test. Studies of the immunogenicity of the 17D vaccine in children are summarized in Table 1. These studies confirm rates of seroresponse to 17D vaccine of higher than 90% in children, based on the plaque reduction neutralization test.

Figure 4. Antibody response to 17D yellow fever vaccine (Monath 1971).

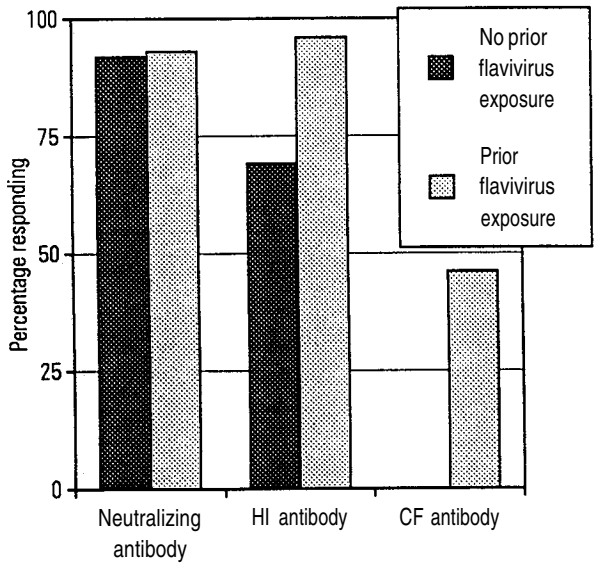


Several studies have examined the response to yellow fever vaccine in persons with previous flavivirus exposure. These studies were conducted in adults; no equivalent studies are reported in children. In one study among 13 persons with no prior antibodies to flaviviruses or to yellow fever virus, 92% showed a neutralizing antibody response (4-fold or greater), 69% showed an HI antibody response, and none developed CF antibody following receipt of a dose of yellow fever vaccine *(Monath 1980)* (Figure 5). By contrast, among 28 persons with antibody to flaviviruses, 93% showed a neutralizing antibody response, 96% showed an HI antibody response, and 46% a CF antibody response.

5.4 Duration of vaccine-induced immunity

After a single subcutaneous injection, 17D yellow fever vaccine protects for many years. Neutralizing antibodies have been detected in some individuals up to 35 years after immunization.

Figure 5. Percentage of persons with antibody response (at least a 4-fold rise) to 17D yellow fever vaccine depending on their prior flavivirus exposure *(Monath 1980).*



One group conducted a careful prospective study in Brazil *(Groot and Ribeiro 1962).* In 1940 to 1941, 17D yellow fever vaccine was administered to 5172 persons in the Brazilian highlands, an area where yellow fever is not endemic. One month after immunization, 918 persons were tested and all were found to have yellow fever neutralizing antibody. Seventeen years after vaccination, 108 persons from the study were bled again. Using the mouse protection neutralizing antibody test, 82 (76%) were found to be strongly positive, 23 (21%) weakly positive, and only 3 (3%) negative. In a control group of 78 unimmunized persons from the same area, only one had neutralizing antibody, indicating that natural flavivirus infection had not contributed to the high rate of long-lasting seropositivity in vaccinees.

In another study, sera were obtained from a group of 41 individuals with well documented written histories of receipt of a single dose of 17D yellow fever vaccine 0 to 19 years previously ***(Rosenzweig et al.*** 2963). All 41 persons (including 24 who had received vaccine 16 to 19 years previously) were found to have neutralizing antibody, as measured by the mouse protection test. HI antibody titers of 20 or higher were found in all individuals who received yellow fever vaccine 0 to 16 years previously and in 22 of 24 individuals who received yellow fever vaccine 16 to 19 years previously. There was a small decline in HI antibodies with time since vaccination; however, this trend was not significant.

In 1975 to 1976, investigators obtained serum from US veterans of World War II, who had been vaccinated from 1940 to 1945 with 17D vaccine administered as a 0.5 ml dose subcutaneously *(Poland et al. 1981).* Immunization records were not available; persons were considered "vaccinated" if they had served in areas and at times when immunization with yellow fever vaccine was mandatory for US military personnel. None of the individuals had traveled to a yellow fever endemic area since 1948. By the plaque neutralization test 81% of veterans who had been presumably vaccinated showed antibody persistence for 30 or more years. Among those with neutralizing antibody by plaque reduction, 88% also had neutralizing antibody by the mouse protection test.

5.5 Simultaneous immunization with other antigens

There is good evidence that any or all of the other EPI antigens can be given simultaneously with yellow fever vaccine with subsequent good take rates.

An early study suggested that a mixture of yellow fever vaccine, smallpox vaccine, and measles vaccine

administered by jet injector to African children aged 5 to 54 months led to lower responses to yellow fever vaccine (85% by the mouse protection test) than when yellow fever vaccine was administered alone (97%) *(Meyer et al. 1964).* However; this study delivered the vaccines intradermally, rather than subcutaneously, as is usually recommended. Other investigators found no interference in the response to yellow fever vaccine administered simultaneously with smallpox vaccine or with tetanus toxoid, smallpox, measles, and BCG vaccines *(Gateff et al. 1973).* Results of a study in Nigeria showed high (>95%) rates of yellow fever antibody when yellow fever vaccine was administered simultaneously (at different sites) with smallpox, measles, and DPT vaccines *(Ruben et al. 1973)* (Table 1).

Recent studies conducted in the Ivory Coast and Cameroon showed that yellow fever vaccine mixed with measles vaccine immediately before injection produced similar seroconversion rates as when the vaccines were given separately *(Lhuillier et al. 1989, Mouchon et al. 1990)* (Table 1). Another study in Mali used a combined vaccine in which 17D yellow fever vaccine and Schwarz measles vaccine had been lyophilized together *(Soula et al. 1991)* (Table 1). However, in these three studies, the investigators were careful to administer the reconstituted mixture within one hour, not after several hours, as would occur in a routine immunization clinic. There is presently insufficient data available on the stability of yellow fever vaccine mixed with measles vaccine and maintained for several hours *(Galazka 1990).*

In Senegalese children, yellow fever seroconversion was comparable in those receiving yellow fever vaccine (simultaneously with measles and a quadruple vaccine containing DPT and inactivated polio vac-

Table 1. Serological response by plaque reduction neutralization test of children aged 4 to 59 months in 5 African countries to a 0.5 ml dose of 17D yellow fever vaccine administered subcutaneously.

Country	Age (months)	Neutralization test positive proportion (%)	Vaccine(s)	Reference
Cameroon	6 to 10	63/68 (93%)	Pasteur (France) 17D (stabilized)	Mouchon et al. 1990
	6 to 10	68/71 (96%)	Pasteur (France) 17D (stabilized) • mixed with measles (Schwarz)	
Central African Republic	12 to 59	198/209 (94%)	Pasteur (France) 17D (stabilized)	Georges et al. 1985
Cote d'Ivoire	5 to 10	103/108 (95%)	Pasteur (France) 17D (stablized)	Lhuillier et al. 1989
Mali	4 to 8	50/52 (96%)	Pasteur (France) 17D (stablized)	Soula et al. 1991
	12 to 24	18/19 (95%)		
	4 to 8	51/55 (93%)	Pasteur (France) 17D • with measles (Schwarz)	
	12 to 24	39/41 (95%)	• combined lyophilized vaccine	
Nigeria	6 to 23	85/88 (97%)	National Drug Co (USA) 17D • by jet injector • with smallpox, measles • simultaneous, different sites	Ruben et al. 1973
	6 to 23	73/77 (95%)	National Drug Co (USA) 17D • by jet injector • with smallpox, measles, DPT • simultaneous, different sites	
Senegal	9 to 35	97/105 (92%)	Pasteur (Senegal) 17D • with measles, DPT-IPV* hepatitis B • simultaneous, different sites	Yvonnet et al. 1986
	9 to 35	73/78 (94%)	Pasteur (Senegal) 17D • with measles, DPT-IPV* • simultaneous, different sites	

** DPT-IPV — quadruple vaccine with diphtheria, pertursis, tetanus and inactivated polio vaccine.*

cine) and those receiving yellow fever vaccine (simultaneously with measles and the quadruple vaccine) and a booster dose of hepatitis B vaccine *(Yvonnet et al. 1986)* (Table 1).

5.6 Other factors related to immunogenicity

Limited data are available on other factors which may be related to the immunogenicity of yellow fever vaccine, including nutritional status, HIV positivity, and treatment with chloroquine.

A single small study has examined the effect of nutritional status on the response of children to yellow fever vaccine *(Brown & Katz 1966).* That study compared the response to a dose of 17D yellow fever vaccine in 8 seronegative 2 year old children with kwashiorkor and 6 seronegative children with normal nutritional status; sera were obtained at 13 days post immunization, too early to adequately judge serological response to the vaccine. None of the children with kwashiorkor developed antibodies, compared with 4 of the 6 children with normal nutritional status. Larger studies regarding the effect of nutritional status of infants on response to yellow fever vaccine would be useful.

Based on information reported to WHO as of December 1992, no specific information is available on complications of 17D yellow fever vaccine in HIV-positive individuals.

Malaria remains a serious problem in the countries where yellow fever poses a risk and prophylaxis or treatment with chloroquine is common. Experimental data indicate that chloroquine may inhibit yellow fever virus in vitro *(Brandriss & Schlesinger 1984).* However, two studies (both conducted in American adults) have shown no effect on serological response to 17D yellow fever vaccine in persons receiving oral chloroquine prophylaxis for malaria *(Tsai et al. 1986, Barry et al. 1991).* Further data based on studies of children in developing countries would be of interest.

Table 2. Cases of encephalitis in children reported to WHO as temporally associated with receipt of 17D yellow fever vaccine, by age at onset, based on information reported as of December 1992.

Case no.	Age	Incubation* (days)	Outcome	Country	Reference
1	1 mo	11	recovered	France	Stuart 1956
2	1 mo	12	recovered	France	Stuart 1956
3	1 mo	9	recovered	UK	Smith 1954
4	1 mo	21	recovered	S. Africa	Swift 1955
5	1 mo	13	recovered	France	Louis et al. 1981
6	2 mo	14	recovered	Nigeria	Scott 1954
7	2 mo	17	recovered	UK	Thomson 1955
8	2 mo	12	recovered	USA	Feitel et al. 1960
9	3 mo	11	recovered	UK	Haas 1954
10	3 mo	11	recovered	UK	Beet 1955
11	3 mo	8	recovered	France	Lartigaut & Lartigaut 1954
12	4 mo	8	recovered	France	Lartigaut & Couteau 1954
13	4 mo	12	recovered	France	Stuart 1956
14	4 mo	10	recovered	France	Stuart 1956
15	7 mo	19	recovered	France	Stuart 1956
16	3 yr	6	died	USA	Anon 1966
17	6 yr	8	recovered	UK	Dick 1952
18	13 yr	7	recovered	S. Africa	Schoub et al. 1990

**Number of days from receipt of vaccine to onset of symptoms.*

5.7 Adverse reactions to 17D vaccine

After vaccination with 17D yellow fever vaccine, 2% to 5% of persons experience mild headache, myalgia, or other mild symptoms. Allergic reactions, including skin rash, urticaria, and asthma, occur at a very low rate (less than one in a million), predominantly in persons with a history of allergy to eggs *(ACIP 1990).* No abnormalities in liver function tests are associated with 17D vaccination *(Freestone et al. 1977).*

Neurological reactions are extremely uncommon with 17D yellow fever vaccine. A single fatal case of encephalitis is reported in a 3-year-old child *(Anon 1966).* Only 17 other cases of encephalitis temporally associated with the 17D vaccine (within 8 to 19 days post-immunization) have been reported in children following over 200 million doses delivered since 1945 (Table 2). Since all but four of these occurred in children immunized at 4 months of age or younger, a review by a panel of experts recommended that yellow fever vaccine not be given routinely before six months of age *(Meegan 1991).*

Several clusters of severe and fatal reactions following administration of 17D vaccine have been reported in West Africa between 1974 and 1987 *(WHO 1986, T. Monath, unpublished data).* These episodes involved 6 to 39 patients with case fatality rates of 20% to 33%. Although the etiological agents and cause of these outbreaks have not been established, some if not all may have been due to improper handling and bacterial contamination of the vaccine.

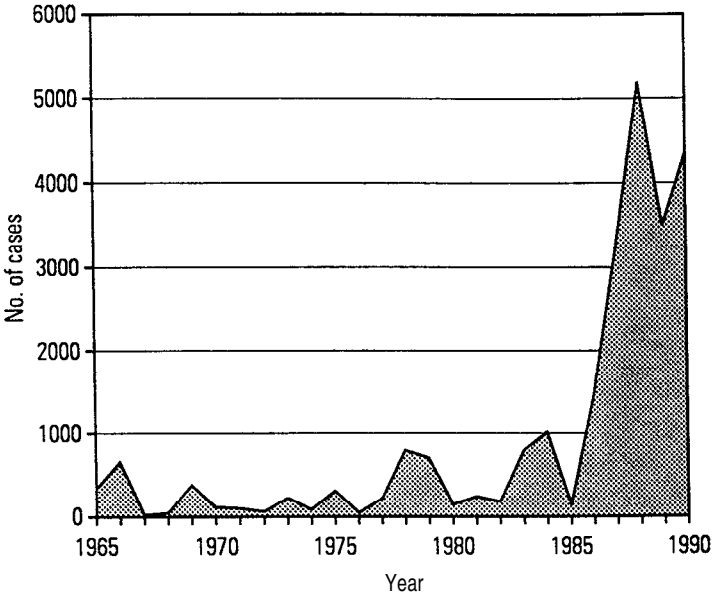
6. Re-emergence of Disease

For the 5 year period 1986 to 1990, the worldwide total of 17 728 cases represents the greatest amount of yellow fever activity reported to WHO for any 5 year period since reporting began in 1948 *(WHO 1992)* (Figure 6). Of this total, 16 782 cases were reported from Africa and 946 from South America. However, under-reporting is a serious problem and the true number of yellow fever cases worldwide probably exceeded one million during 1986 to 1990.

6.1 Predomimance of cases in children in Africa

Since the 1960s, a number of countries in Africa have switched from administering yellow fever vaccine through routine immunization services to post-outbreak emergency immunization. As a result, recent epidemics have primarily affected children younger than 15 years of age. In other African countries where populations were not previously immunized, yellow fever epidemics have also affected

Figure 6. Yellow fever cases reported to WHO, worldwide, 1965-1990.



children. In these countries, the lower incidence in older unimmunized populations may be due to the protective effect of antibodies to other flaviviruses; however, this remains to be proved.

African outbreaks affecting predominantly children are summarized below.

Senegal, 1965 *(Chambon et al. 1967, Rey et al. 1966, Bres 1986).* This epidemic came as a surprise, as the entire population of Senegal had been carefully vaccinated from 1940 to 1960. There were 230 cases detected, mainly by active case finding; it is estimated that a total of 2000 to 20 000 cases occurred. Ninety percent of the cases were in unvaccinated children younger than 12 years of age.

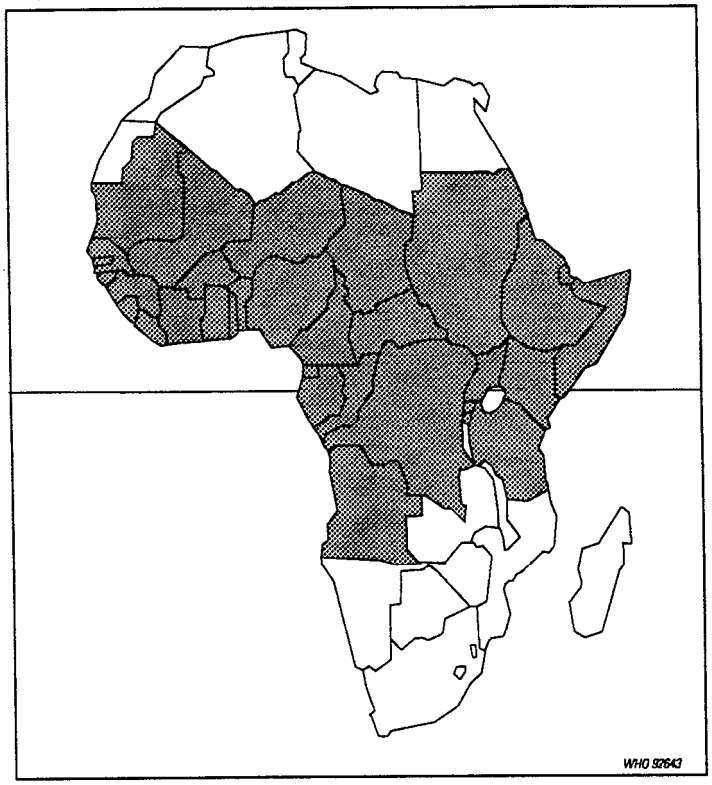
Burkina Faso, 1969 *(Bres 1986).* Although 87 cases and 44 deaths were notified, it is estimated that about 3000 cases with 100 deaths occurred. Ninety percent of the cases were in young children.

Gambia, 1978 to 1979 *(Monath 1980).* Of a total of 80 cases confirmed by serology, 34 (43%) were younger than 10 years, 12 (15%) were 10 to 19 years. The highest attack rate (6.7%) was found in children 0 to 9 years of age.

Ghana, 1977 to 1980 *(Addy et al. 1986).* In 1969, the population in the Northern Area of Ghana was immunized in a large campaign conducted in response to an outbreak of yellow fever. When the disease recurred in the same areas in 1977 to 1980, the epidemic involved mainly children under 10 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 to 1980 occurred in this age group.

Burkina Faso, 1983 *(WHO 1984).* Of a total of 356 reported cases, nearly 80% occurred in children under 14 years of age. Additional epidemiological

Figure 7. The 33 African countries at risk from yellow fever.



Note: This map does not imply official endorsement or acceptance by WHO of the status or boundaries of listed areas

studies showed that between 6300 and 7600 persons had been infected, although it is not known what proportion of these persons had clinical symptoms. The IgM seropositivity rate (indicating recent infection) was 49% in children 0 to 10 years, 39% in children 11 to 14 years, and 24% in persons 15 years and older. The population affected (the Peul, a seminomadic tribe) had not been immunized previously.

Ghana, 1983 *(WHO 1984).* Of a total of 372 yellow fever cases in the Northern Region (East Gonja and Nalerigu Districts), 81% were under 14 years and 48% under 4 years of age. The case fatality rate was 53%. These two districts escaped two preceding epidemics in Ghana and had not been covered by previous vaccination campaigns.

Nigeria, 1986 to 1990 *(Nasidi et al. 1989, WHO 1992).* For the S-year period 1986 to 1990, Nigeria reported 16 230 cases of yellow fever during widespread outbreak which affected 19 of the country's 22 states. Epidemiological investigations suggested that the actual number of cases was 4 to 90 times higher than reported figures. In Oyo State, hospital record surveys revealed that 71% of the cases were in children and teenagers, a significantly higher proportion than expected based on the age distribution of the population. Case fatality rates were highest (80% or more) in children under 10 years of age.

Mali, 1987 *(WHO 1989).* Of a total of 305 suspected yellow fever cases, 70% were under 15 years of age. The low proportion of adults affected (only 17% of patients were over 20 years of age) may be accounted for by the fact that this population had been reached by mass vaccinations conducted in the area in 1969 during the previous epidemic. The case fatality rate varied from 36% to 80% depending on the district. It was significantly higher in patients under 15 years (63%) than in older patients (46%).

Cameroon, 1990 *(WHO 1991).* The 1990 epidemic was the largest ever experienced by Cameroon. In all, 173 cases with 118 deaths were reported (case fatality rate 68%). Fifty-one percent of cases occurred in children less than 5 years of age, while 28% were in children 6 to 10 years of age.

6.2 Potential for re-emergence based on spread of the mosquito vector in South America

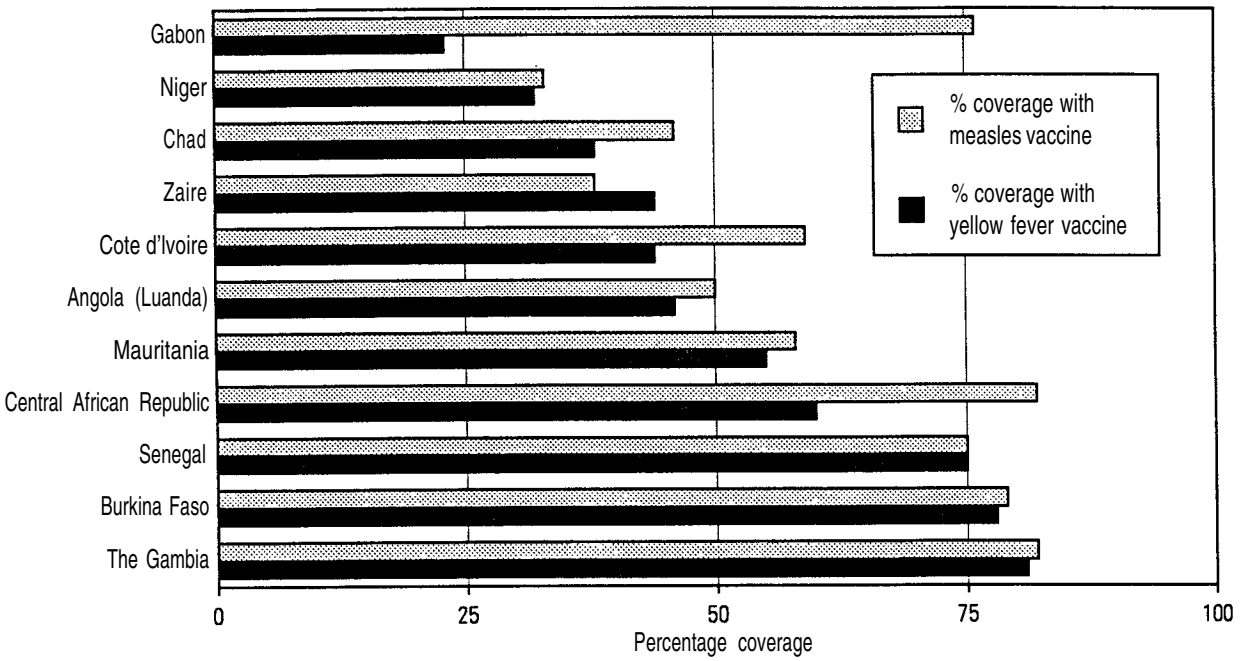
There is also the potential for re-emergence of yellow fever in South America. An A. *aegypti* eradication campaign was launched in the Americas in 1947. This campaign was at first a remarkable success but it has been compromised by reinfestations which began to appear in 1965. The reestablishment of A. *aegypti* populations in extensive areas of South America, including rural areas where jungle yellow fever is endemic, poses the threat of urbanization of yellow fever. In 1981, yellow fever cases were reported near Santa Cruz, Bolivia, a city infested with A. *aegyptae.* In 1985, yellow fever cases were reported near Presidence Prudente, Brazil, another mosquito infested city; in response, mass immunization was carried out with yellow fever vaccine *(WHO 1986).* Reports of yellow fever cases near several cities in Brazil in 1991 led public health officials in a limited number of areas to include yellow fever vaccine in a measles immunization campaign in May 1992 *(P. Evans, personal communication).*

7. Implications for EPI Managers

Attempts to control outbreaks with emergency immunization have severely strained the resources of local and international agencies. It is now argued that there has been excessive confidence in the ability to contain outbreaks and that it would be prudent to include yellow fever vaccine routinely within the EPI rather than wait for the disease to strike in an epidemic.

There are 33 countries at risk in Africa (Figure 7). Already, 16 of these countries routinely include yellow fever vaccine in the EM. Most countries give yellow fever vaccine at the same time as measles vaccine at 9 months of age. This explains the gener-

Figure 8. Coverage with yellow fever vaccine and measles vaccine in children aged 12 to 23 months, based on coverage surveys reported to WHO as of April 1992, 11 African countries.



ally good agreement between coverage with measles vaccine and yellow fever vaccine (Figure 8). Simultaneous administration makes good sense. "Simultaneous" means the vaccines are administered in the same immunization session at different injection sites on the child's body. Neither the vaccines nor diluent are mixed in the same syringe. This strategy results in no additional visit for the administration of yellow fever vaccine.

In 1988, the joint UNICEF/WHO Technical Group on Immunization (TGI) for the African Region reviewed the situation on yellow fever Countries where yellow fever is endemic were urged to consider incorporating the vaccine into their EPI schedules on a routine basis *(TGI 1988).* In the same year, this recommendation was repeated by the EPI Global Advisory Group *(Expanded Programme on Immunization 1989).* In 1990, the EPI Global Advisory Group again considered yellow fever and made the following recommendations *(Expanded Programme on Immunization 1991):*

- Countries in Africa at risk for yellow fever should incorporate yellow fever vaccine in their routine immunization programmes.
- Yellow fever vaccine is recommended for use from 6 months of age and is most easily integrated into the EPI by administering it at the same time as measles vaccine (at 9 months of age).
- Countries that include yellow fever vaccine in their immunization programmes should monitor yellow fever immunization coverage and yellow fever disease incidence. (As of April 1992, 11 countries have provided yellow fever vaccine coverage data to WHO, Figure 8).

  In areas where yellow fever epidemics are occurring or considered a high risk, inclusion of older children may be appropriate as a special "catch up" programme.

In support of these recommendations, UNICEF has agreed to purchase yellow fever vaccine in the same way as other EPI vaccines.

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Abbreviations

BCG	Bacille Calmette-Guérin. vaccine against tuberculosis
CF	complement fixati
CFR	case fatality rate
DPT	diphtheria-pertussis-tetanus vaccine
ELISA	enzyme-linked immunosorbent assay
FNV	French neurotropic yellow fever vaccine
HI	hemagglutination-inhibition
IFA	indirect fluorescent antibody

IPV	inactivated polio vaccine
LD_{50}	lethal dose for 50% of animals tested
OPV	oral polio vaccine
PFU	plaque forming unit

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