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RE-EMERGENCE OF YELLOW FEVER IN SENEGAL IN 1995

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Abstract. An outbreak of yellow fever (YF) occurred in the central part of Senegal during October 1995. Thirty-one probable cases were detected and 79 cases were confirmed either by IgM ELISA or by virus isolation (30 strains isolated). The case fatality rate was 18.9%. Incidence of the infection was evaluated by a serosurvey in the area. Males 10–29 years old belonging to the Peul ethnic group were more affected. Moreover, 28 YF virus strains were isolated from mosquitoes and larvae pools and vertical transmission of YF virus by *Aedes aegypti* was also demonstrated for the first time in the field. This outbreak occurred after the major amplification of the wild cycle of YF virus in 1993 in West Africa. This epidemic represented a typical example of intermediate transmission of YF: both humans and wild vertebrates are involved in the virus cycle through wild mosquitoes with semidomestic habits, mainly *Ae. furcifer, Ae. luteocephalus,* and domestic vector *Ae. aegypti.* It was controlled by a prompt immunization campaign. The impact of inclusion of YF vaccine in the Expanded Program of Immunization, which has been conducted in Senegal for eight years, is discussed.

Yellow fever (YF) is an acute arboviral disease. Yellow fever virus is transmitted by mosquitoes to humans and monkeys in South America and Africa. This virus is a member of the family Flaviviridae and genus *Flavivirus.*[1] In West Africa, YF epidemiology can be related to the vegetation.[2] In the rain forest, the zoonotic transmission cycle, involving monkeys and wild mosquito vectors, is maintained all year long. Further north in the humid savannah, YF transmission increases during the rainy season with the high density of vectors and the availability of immunologically susceptible vertebrate hosts. Amplification of this enzootic cycle occurs under appropriate ecologic conditions (excessive rainfall, environmental changes) that intensify horizontal transmission and spatial diffusion to the drier savannah along riverine (gallery) forests. This humid or semi-humid savannah, which also supports human activities (settlements and agriculture) is defined as the emergence zone of YF.

Transmission of YF to humans occurs in three different situations: sylvatic, intermediate, or urban.[3] Humans are only incidentally infected in the sylvatic cycle. In urban epidemics, humans are the only vertebrate hosts involved and the vector is *Aedes aegypti.* During intermediate transmission of YF, both humans and monkeys are involved, with a variety of wild mosquitoes, mainly *Ae. luteocephalus, Ae. furcifer,* and a domestic vector (*Ae. aegypti*). Moreover, vertical transmission, (passage of virus from a vector to its progeny) could support virus activity from one rainy season to another in the same area.

In West Africa, YF displays a patterns of recurring epidemics depending on the amplification of the sylvatic cycle and the prophylaxis undertaken by each country. An endemic zone between 15°N and 10°S has been defined, covering 33 African countries, in which populations still remain at risk.[4] Although, a safe and effective vaccine against YF has been available for 60 years, several yellow fever epidemics occurred in the 1990s in Kenya (1992), Ghana (1993), Gabon (1994), Liberia (1995), and regularly in Nigeria. Moreover, YF is vastly underreported (World Health Organization [WHO] estimation is approximately 200,000 cases each year in sub-Saharan Africa).[5]

In Senegal, YF immunization has been included in the Expanded Program of Immunization (EPI) since 1987 in association with measles vaccine given at nine months of age. The overall level of coverage is 45% for the YF vaccine. An active surveillance of the wild cycle of the virus also contributed to the control of YF transmission. Indeed, the last major Senegalese YF epidemic was in 1965 in Djourbel, although four and seven cases were reported in 1978 and 1981, respectively.[6–8]

The occurrence of an unusual number of patients with jaundice and a high fatality rate was reported at the dispensary in Ribo-Escale, Senegal in mid-October 1995. At the request of the Ministry of Public Health, a team from the Pasteur Institute and ORSTOM investigated aspects of this outbreak. On October 30, 1995, a vaccination campaign was started. This report describes the major epidemiologic and entomologic features of the YF outbreak that occurred in October and November 1995 in the district of Koungheul and provides a comprehensive epidemiology of YF in Senegal.

MATERIALS AND METHODS

Study area. Two rural administrative districts, Ribo-Escale (14°20'N, 14°41'W) and Guente-Pate (14°17'N, 14°55'W) near Koungheul town, were affected (Figure 1). This remote area is 45 km north of the main road and the railway linked to the capital of Dakar. The zone is limited to the north by the sparsely populated reserve of Ferlo. The affected area is ecologically characterized by a semi-humid savannah. The fossile Saloum River valley runs from east to west, creating temporary ponds during the rainy season. Heaviest rainfalls occur between June and October and the annual average rainfall is approximately 750 mm.

The population of the two rural districts is approximately 20,000 in an area of 700 km^2. Two ethnic groups, the Peul and the Wolof live in different but nearby villages that vary in population from less than 100 to 1,000 inhabitants. Subsistence agriculture is based on Indian millet and groundnuts. The Peuls are also stock-breeders. Water is obtained from wells and domestic water storage is common. The population structure is typical for Senegal: about half is less than 15

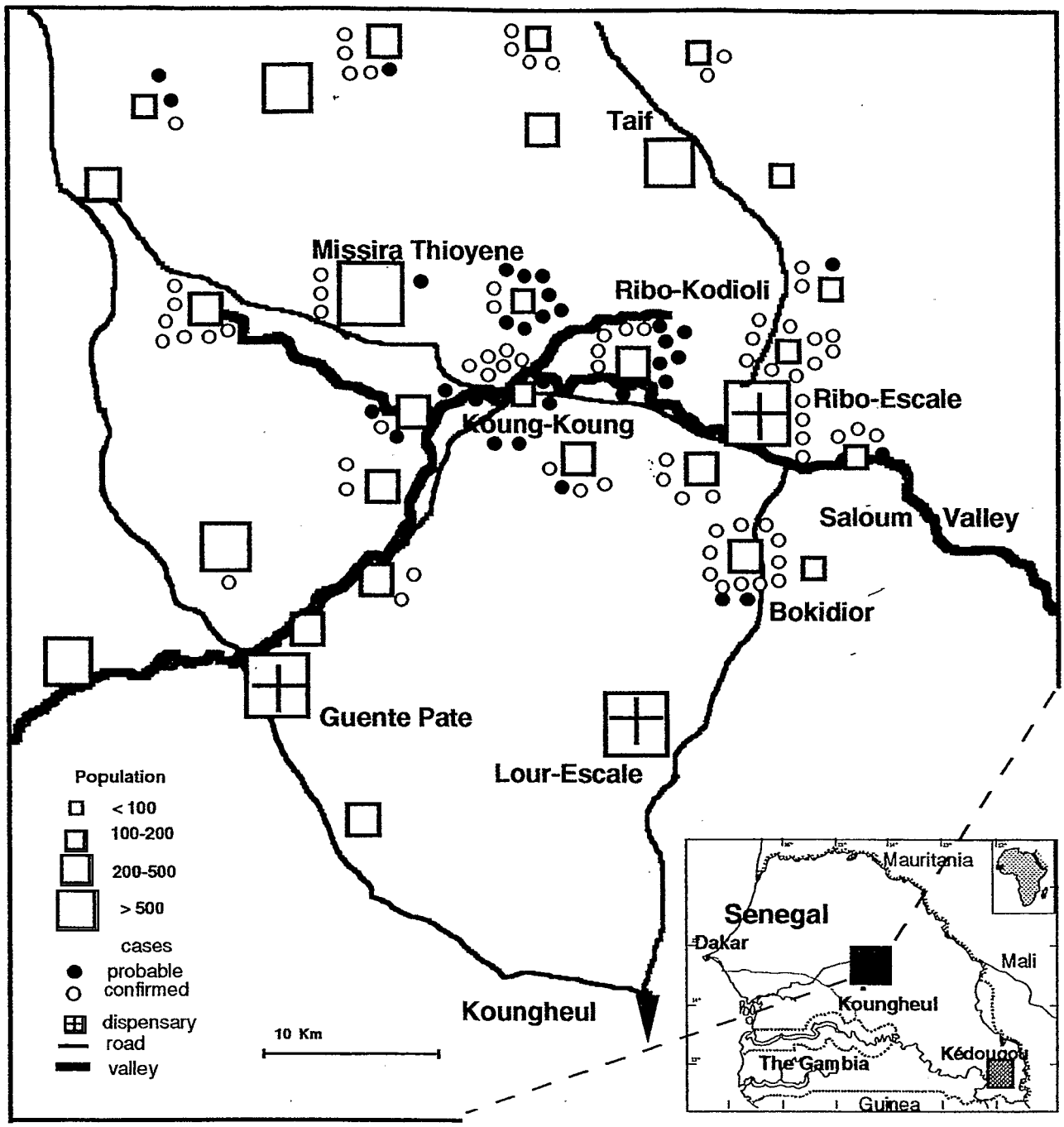

FIGURE 1. **Inset,** map of Senegal showing localities mentioned in the text (n = epidemic area; hatched square = entomologic surveillance area), and a map of the area with location of probable and confirmed cases in Koungheul in 1995. The + symbols indicate dispensaries.

years of age (according to the most recent census in 1988). Health care facilities are limited to two dispensaries.

Epidemiologic studies. *Chronology of the study.* A case detection and a serosurvey were conducted between October 25 and November 11, 1995. Diagnosis of YF was assessed by an IgM antigen-capture ELISA on October 27, 1995. The villages were visited twice for case detection. Adjacent districts and Koungheul town were also investigated to define the affected area. After this date, surveillance was done by local health authorities. This study was conducted under the supervision of the Senegalese Health Authorities according to the recommendations of their *Ad Hoc* Ethical Committee.

Case definition. A probable case of YF was defined as a death occurring after a febrile illness of two-weeks duration or less, with jaundice and/or hemorrhagic signs. A confirmed case of YF was defined as a person with a febrile illness and/or jaundice with a YF IgM positive test result or positive virus isolation.

Search for and surveillance of human cases. With the cooperation of chiefs and rural agents, villagers were ques-

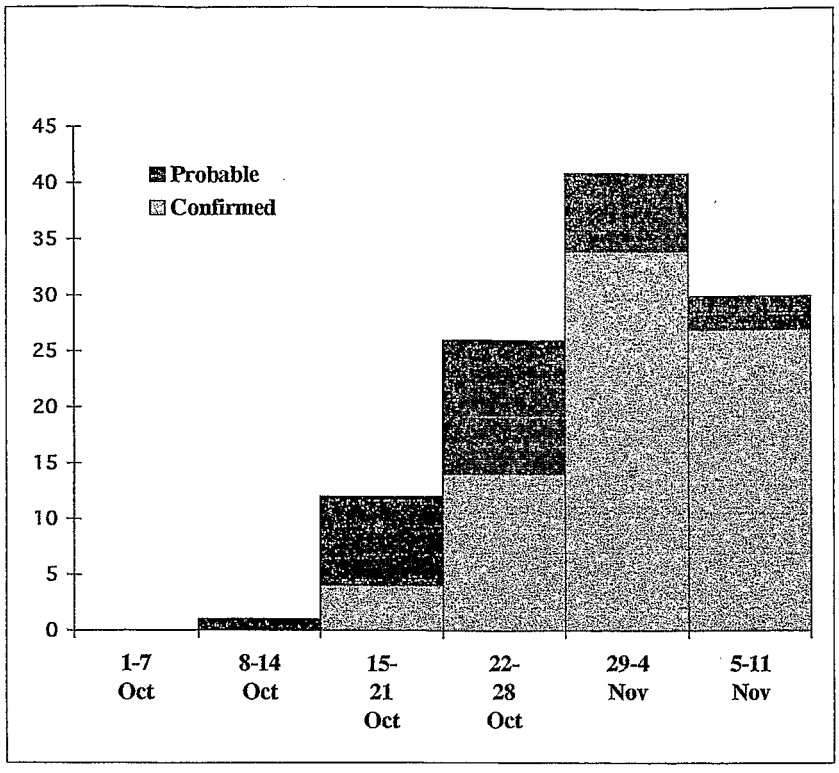

FIGURE 2. Epidemic plot of yellow fever: confirmed and probable cases in Koungheul in 1995.

tioned as to the presence of ill persons, both those meeting the definition of probable case and others with nonspecific febrile illness with one or more of the following symptoms (headache, nausea and vomiting, myalgia, or lumbosacral pain). Inquiries were made concerning deaths and jaundice in the last three months. Individuals who were ill were examined and a case investigation form was filled out. Venous blood samples were obtained from these patients and randomly from healthy persons in villages where probable or confirmed cases were observed.

Virus isolation and identification. Serum samples collected in the field were stored and transported in liquid nitrogen to the Pasteur Institute of Dakar. Only one post-mortem specimen (liver) was obtained from a probable case. Virus isolation attempts on acute phase sera were performed in parallel with intracerebral inoculation of suckling mice and by inoculation of an *Ae. pseudoscutellaris* cell line (AP 61). Cells were examined for a cytopathic effect and by indirect immunofluorescence on the 10th day. Identification was made with a specific hyperimmune mouse ascitic fluid and confirmed with a monoclonal antibody (2D12).[9,10] Mice were observed for 21 days. A 10% brain suspension from animals showing signs of illness was passaged to establish the isolate. Confirmation of passages was obtained by a complement fixation method.[11]

Serologic studies. Sera were tested at 1:100 dilution for IgM antibodies against YF virus by an IgM antigen-capture ELISA as previously described.[12] Neutralization YF antibodies were detected by a plaque-reduction neutralization test carried out in 24-multiwell plates on pig kidney cells.[13]

Entomologic studies. An entomologic survey was conducted between October 28, 1995 and November 11, 1995. Adult mosquitoes were collected between 5:30 PM and 10:00 PM in tubes after landing on immunized human volunteers during a total of 445 person-hr of capture, and also with Centers for Disease Control and Prevention (Atlanta, GA) light traps. They were sorted and pooled by species and sex in the field and stored in liquid nitrogen.

Aedes larval development sites were investigated. Larvae and pupae were collected in clay jars located indoors and outdoors and in 200-liter barrels situated outdoors. The Breteau index (number of containers with larvae of *Ae. aegypti* per 100 houses) and container index (number of containers with larvae of *Ae. aegypti* per 100 water-filled containers) were calculated. Larvae and pupae were reared in the Dakar insectary at 28°C and 80% relative humidity. Specimens from each breeding site were reared separately. Emerged adults were sorted, pooled by species and sex 12–48 hr after emergence, and stored at -70°C until tested for viruses. Blind virus isolation attempts were made. Pools of mosquitoes that are not potential vectors of YF (e.g., *Culex, Anopheles*) were interspersed among *Aedes* pools as a control for contamination.

RESULTS

Epidemiologic results. Two rural districts, Ribo-Escale and Guente-Pate, were investigated between October 30 and November 11, 1995. During this investigation, 79 acute cases of YF were confirmed and 31 probable cases were detected. The epidemic plot with a weekly distribution of all cases is shown in Figure 2. The case that caused the initial concern was detected on October 25. However, the first death occurred on October 12 in Ribo-Kodioli village. The

TABLE 1
Distribution by age of confirmed and probable cases of yellow fever and the attack rate in Koungheul, Senegal in 1995

Age (years)	Population age group distribution (%)	Estimated age group population	No. of confirmed cases	No. of probable cases	Total cases		Attack rate per 1,000
					No.	%	
0–9	38.6	3,358	9	6	15	13.7	4.5
10–19	22.7	1,969	35	8	43	39.1	21.8
20–29	15.2	1,310	20	11	31	28.2	23.6
30–39	9.6	834	8	4	12	10.8	14.3
≥40	13.9	1,207	7	2	9	8.2	7.4
Total	100	8,678	79	31	110	100	12.6

peak was reached between October 29 and November 4. The geographic distribution of confirmed and probable cases of YF is shown in Figure 1, with a major distribution of cases along the Saloum River valley.

As shown in Table 1, the distribution of ages of cases was different from that of the population. The proportion of those 10–29 years of age was 67.3% (74 of 110) of the total cases. The higher attack rates were observed in teenagers and young adults. Males were more affected than females ($P < 0.05$). About 90% of the YF cases occurred in the Peul ethnic group (Table 2). The case fatality rate among the 79 confirmed cases was 18.9% (15 of 79). In fatal cases, the symptoms occurred in the following decreasing order: jaundice (9 of 15), hemorrhagic signs (7 of 15), and neurologic signs (5 of 15).

Four hundred fifty blood samples were collected randomly from persons without illness in villages where cases were observed. The overall population of these 22 villages was estimated to be 8,678. Forty-five individuals with specific IgM antibodies were considered to have had a recent YF virus infection and were considered asymptomatic cases; none were immune to YF virus before the outbreak. The incidence of asymptomatic YF virus infection during the outbreak was estimated to be 10% (95% confidence interval = 7.3–12.7).

The overall attack rate was calculated on the basis of the total number of YF cases (symptomatic and asymptomatic) as a proportion of the overall population. This rate and those for the ethnic groups are shown in Table 3. The average attack rate was 11.2%. This rate was significantly higher for the Peul group (14.1 %) than for the Wolof group (4.9%) ($P < 0.0001$). The clinical expression rate (percentage of symptomatic cases among YF- infected persons) was 11.5% and 9.4% for the Peuls and Wolofs, respectively. The risk of infection by YF virus for a Peul individual was 2.9 times higher than for a Wolof. However, there was no significant statistically significant difference between ethnic groups for the expression of the illness. Among the 46 deaths, 31 occurred before the survey (probable cases) and 15 occurred during the investigation (biologically confirmed). The overall mortality rate was 5.3 per 1,000.

TABLE 2
Cases of yellow fever (YF) related to population characteristics (sex and ethnicity) on the two groups studied in Koungheul, Senegal in 1995

Distribution of YF cases	No. of confirmed cases	No. of probable cases	Total	
			No.	%
Sex				
Male	42	22	64	58.2
Female	37	9	46	41.8
Ethnic group				
Peul	71	27	98	89.1
Wolof	8	4	12	10.9

Prevalence of neutralization antibodies against YF. Table 4 shows the results of the neutralization tests. The average YF immunity rate was 61.3%, with a significantly higher prevalence of YF antibodies in the Wolof ethnic group than in the Peuls ($P < 0.002$). The prevalence increased significantly with age and the Wolof ethnic group was overall more protected. The 10–19-year-old age group had the lower prevalence. Among children 0–9 years of age, 45.6% were immunized against YF.

Entomologic results. Table 5 shows the list of species, the number of mosquitoes inoculated according to the method of capture, and the number of strains isolated. One hundred sixty-eight pools representing 1,125 mosquitoes belonging to 21 species were inoculated. Most of the female were unfed. Moreover, a few pools were interspersed with fed and unfed females. *Aedes aegypti* was the most commonly captured mosquito. Twenty-eight strains were isolated from *Ae. aegypti* females (19) and males (5), including newly emerged specimens and from wild vectors: *Ae. furcifer, Ae. metallicus,* and *Ae. luteocephalus.* Despite the attempt to inoculate females of the genera *Culex, Anopheles,* and *Mansonia,* YF virus was isolated only from already known vectors from the genus *Aedes.*

A total of 293 containers with water, potential larval development sites for *Ae. aegypti,* were examined in 13 villages. The average Breteau index was 35 (range = 0–135). The container index ranged from 0 to 63 (average = 29.7).

Virologic results. Fifty-eight strains of YF virus were isolated. Thirty strains were isolated from human samples (29 sera and one liver specimen) and 28 were isolated from entomologic samples using both detection systems (newborn mice and the AP 61 cell line). The sensitivity of the isolation procedure depended on the origin of the samples. In the case of human specimens, AP 61 cells and newborn mice were equally efficient for virus isolation. However, for entomologic products, AP 61 cells were significantly more efficient. Only two of 28 strains isolated from AP 61 cells from mosquito samples were found in newborn mice (paired $\chi^2 = 26$, $P < 0.001$).

DISCUSSION

This epidemic represents a typical example of intermediate transmission of YF virus as described by Cornet and

TABLE 3

Estimated number of asymptomatic cases, attack rates, clinical expression rates, and mortality rates for the ethnic groups during the yellow fever epidemic in Koungheul, Senegal in 1995

Population		Asymptomatic cases (IgM+)		Estimated no. of cases			Attack rate (%)	Clinical expression rate* (%)	Mortality rate per 1,000	
Ethnic group	No.	%	No.	Asymptomatic	Symptomatic	Total			%	(No.)†
Peul	6,036	12.5	(39/313)	751	98	849	14.1	11.5	6.7	(41)
Wolof	2,642	4.4	(6/137)	116	12	128	4.9	9.4	1.9	(5)
Total	8,678	10‡	(45/450)	867	110	977	11.2	11.2	5.3	(46)

* Clinical expression rate based on the number of symptomatic cases/total cases.
† No. = number of deaths.
‡ 95% confidence interval = 7.3–12.7.

others[14] and Cordellier.[15] Transmission in the area probably began with sylvatic vectors (*Ae. furcifer, Ae. metallicus,* and *Ae. luteocephalus),* which disappeared after the rainy season. Transmission then continued with *Ae. aegypti,* the major domestic vector species remaining after the rainy season. *Aedes aegypti* were abundant in the villages and continued human-to-human transmission. According to the WHO, there is a risk of a YF outbreak when Breteau and container indexes are both > 5.[16] These indexes were generally higher in the epidemic area. To our knowledge, YF virus was isolated for the first time from four different vector species during the same outbreak. The implication of *Ae. metallicus* as a vector of YF virus was observed only once before during the 1983 epidemic in Burkina-Faso.[17] Although *Ae. aegypti* was the major vector during intermediate and urban epidemics, vertical transmission to its progeny was observed in the laboratory but never in nature.[18] Yellow fever virus was isolated from *Ae. aegypti* males that were either captured on humans or from adults reared from larvae in the insectary. This demonstrated for the first time natural vertical transmission in *Ae. aegypti.*[19]

This vertical transmission has two epidemiologic implications. First, the virus can be transmitted a few days after the emergence of the *Ae. aegypti* females without completing its extrinsic cycle. This could accelerate and increase horizontal transmission to humans. Second, the YF virus can persist until the next rainy season inside dried, infected eggs laid in domestic breeding sites such as used tires, earthenware pots and cans.

In Africa, YF epidemics usually last several months before being detected, especially in remote areas. In this study, the time between initial cases and biologic diagnosis is particularly short (15 days). Intermediate epidemics generally have a dynamic process that is different from urban epidemics: they are plurifocal (involving certain villages and not others) with a lower case fatality rate. In this intermediate outbreak, the case fatality rate was 18.9%. The methods of case detection based on immunocapture of IgM and virus isolation allowed the detection of severe as well as milder cases. If YF viremia is short, YF IgM antibodies persist about two months.[20] In countries without YF immunization programs, children are more affected than the other age groups during YF epidemics that involve domestic vectors with human-to-human transmission. In Africa, the prevalence of the antibodies against YF virus increases with age and protects older persons.[21] Here, the classic distribution of the outbreak was modified: children less than 10 years of age were relatively protected by the EPI-included YF vaccine. Those 10–29 years of age were more affected because they were not old enough to acquire the level of protection observed in persons more than 30 years of age. Although they are less protected than the older individuals, they are as equally exposed to wild mosquito bites as the older individuals during agricultural work, especially at the beginning of an outbreak. Moreover, our investigations took place almost until the peak of the outbreak. Therefore, during an amplification of the wild cycle of YF virus, the virus spreads through the rural areas. An overall YF antibody prevalence of 60.3% in an area is not enough to prevent an outbreak of YF. Higher attack rates were generally related to small Peul rural areas located along the Saloum Valley than to more populated areas (Figure 1). For example, in Bokidior Peul and Bokidior Wolof, two villages located 1 km apart, the Peul village was infected and the Wolof population was uninfected at the time of the investigation.

Since 1972, ORSTOM and the Pasteur Institute of Dakar have conducted a surveillance program in the area of Kedougou (12°33'N, 12°11'W) a more humid and bushy savannah 200 km southeast of Koungheul. Wild strains of YF virus have been regularly isolated from mosquito samples from the Kedougou area and serologic evidence of YF virus infection has been obtained from monkeys. An amplification of the wild cycle of YF is possible when the immunity rate in the monkey population is low. The last increase in the sylvatic cycle occurred in 1993 and lasted until 1994.[22] The increased viral activity in the wild cycle could correspond

TABLE 4

Yellow fever antibody prevalence by plaque-reduction neutralization test by age and ethnic groups in Koungheul, Senegal in 1995

	Age group (years)											
	0–9		10–19		20–29		30–39		≥40		Total	
Ethnic group	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Peul	59	42.4	87	36.8	83	60.2	43	76.7	41	90.2	313	55.9
Wolof	20	55	32	51.3	32	75	20	80	33	93.9	137	72.2
Total	79	45.6	119	41.2	115	64.3	63	79.3	74	91.9	450	61.3

TABLE 5

Number of mosquitoes captured by each method (number of yellow fever [YF] strains isolated on the AP61 cell line) in Koungheul, Senegal in 1995

Species	Captured on humans (445 person-hr)		Light traps	Newly emerged adults		Total	Number of YF strains
Aedes aegypti females	312	(17)	0	165	(2)	477	19
Ae. aegypti males	33	(4)	0	189	(1)	222	5
Ae. furcifer females	19	(2)	0	0		19	2
Ae. furcifer males	2		0	0		2	0
Ae. metallicus	1	(1)	0	0		1	1
Ae. luteocephalus	1	(1)	0	0		1	1
Ae. vittatus males	5		0	0		5	0
Other *Aedes*	0		5	0		5	0
Aedeomyia sp.	0		1	0		1	0
Anopheles sp.	22		31	0		53	0
Culex sp.	119		162	34		315	0
Mansonia sp.	9		15	0		24	0
Total	523	(25)	214	388	(3)	1,125	28

to outbreaks of human YF in surrounding West African countries.[23] Furthermore, disorganized human settlements in rural areas or towns with household breeding sites infested with *Ae. aegypti* could relay and trigger YF transmission.[24] This epidemic could have corresponded to a spread of this YF amplification to the north of the emergence area. The virus via vectors infected nonimmunized persons in this area, mainly young Peul individuals exposed during agricultural activities, who served as viremic hosts in the epidemic cycle. Social factors such as water storage could have magnified transmission, as well as social events (e.g., funerals, weddings, and family gatherings). These factors unite the members of the same community and could then have increased transmission in other Peul villages when the inhabitants returned.

Previous studies analyzing different parts of the YF virus genome demonstrated that wild African strains of this virus can be divided into two major genotypes: a Central African genotype and a West African genotype.[25,26] Further work analyzing the sequences of the strains from Kedougou 1993 and Koungheul 1995 will be necessary to confirm the hypothesis of the spread of the YF virus to the north of the emergence area.

A rapid immunization campaign extended to two neighboring rural districts (noninfected), stopped the epidemic, and was accompanied by passive actions such as draining and cleaning containers. However, the immunization was not extended to the total administrative region.

The latest WHO initiative for YF is to expand vaccination coverage in Africa, perhaps by linking YF immunization to mass campaigns against polio and measles. The epidemic in Koungheul is a demonstration that a failure in the rural YF immunization coverage is sufficient to start an outbreak during or after amplification of the wild cycle. Without strengthened YF surveillance and competent laboratories, the lapse of time between the onset of the epidemic and its recognition would have been sufficient for extension of the epidemic to cities.

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