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Yellow fever outbreak in Kaffrine, Senegal 1996: epidemiological and entomological findings

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Summary In November 1996 a yellow fever (YF) outbreak occurred near Kaffrine in the central part of Senegal. Thirty-six deaths were notified, all children under 15 years of age. The YF diagnosis was confirmed by MAC-ELISA or by virus isolation. The immune status against YF virus of a sample population of 449 individuals was determined, and 31 confirmed cases and 69 asymptomatic cases were reported. Distribution of YF cases and incidence rate decreased with age, while the attack rate was stable in all age groups. Larva indices were high and *Aedes aegypti* was common in all villages, causing man-to-man transmission. The greatest risk of YF disease was lack of immunity, especially in individuals <20 years of age. The outbreak was rapidly controlled by an emergency immunization campaign. YF epidemics occurred in Senegal over two consecutive years. The last outbreak reached the main road to Dakar and the risk of spread to urban areas has increased.

keywords yellow fever, epidemic, Senegal, West Africa correspondence

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Introduction

A safe and efficient vaccine against yellow fever (YF) virus has been available for 60 years. But due to the collapse of health care delivery systems in Africa, there has been a dramatic resurgence of YF epidemics over the last 10 years (Robertson *et al.* 1996). Based on adjustments for under-reporting, WHO estimates that some 200 000 yellow fever cases occur every year, mostly in subsaharan Africa. YF displays a pattern of recurring epidemics depending on the amplification of the sylvatic cycle and the prophylaxis undertaken in each country. YF virus circulation could relate to the distribution of vegetation in West Africa, as proposed by Cordellier (1991): the *area of endemicity* is the region of enzootic sylvatic circulation of YF virus, from rainforest to semihumid savannah, the *area of epidemicity*, where the virus does not circulate unless introduced by man, consists of dry and sahelian savannahs and between both lies the proposed *zone of emergence*, which varies depending on annual rainfall patterns.

Thus, three epidemic patterns are described. Sylvatic epidemics involve only wild vertebrates and sylvatic vectors. Urban epidemics result from man-to-man transmission by the domestic vector *Aedes aegypti* and occur within the epidemic area. The intermediate epidemic, the most common in rural areas, consists of two successive phases: transmission by wild mosquitoes (*Aedes furcifer, Aedes taylori, Aedes luteocephalus*) and relay by a domestic vector: *Aedes aegypti* (Cornet *et al.* 1977). In the area of emergence, resurgent outbreaks depend on mosquito density and human immune patterns. In Senegal, a country which has included YF vaccine in the Expanded Programme of Immunization (EPI) for 9 years, YF epidemics occurred in 1995 (Anonymous 1996) and in 1996.

This report describes the epidemiological and entomological features of the 1996 outbreak. Investigations were conducted from November 16th to 23rd by a three-party team including epidemiologists and virologists from the Institut Pasteur of Dakar, entomologists from ORSTOM and members of the national health authorities. Specific topics addressed are risk factors (primarily the possible lack of immunity), infection spread from this area and investigations based on serological studies.

Materials and methods

Study area

The epidemic area has a 20-km radius centred on Kaffrine, which is situated on the main road 300 km from Dakar

(Figure 1). Kaffrine is the economical and administrative centre of this agricultural district characterized by Guinean savannah vegetation and comprising the fossil Saloum River valley crossing from east to west. Rainfall is approximately 750 mm/year, with the heaviest precipitation between June and November. Water is widely stored in large clay pots and metal drums. The total population of the district is about 160 000 inhabitants (census 1988, increase rate:1.029), and 50% of the population is under the age of 15.

Chronology of the study

On November 16th 1996 presentation of unusual numbers of patients with jaundice and a high mortality rate was noted at Kaffrine hospital. The Institut Pasteur de Dakar diagnosed them as YF by IgM immunocapture on November 18th, launching entomological and virological investigations as well as active case detection conducted until November 23th in villages where the hospitalized cases originated. Active case detection was then extended first to neighbouring villages and later to villages of the whole district to further define the affected area. Village chiefs, administrative agents and especially sanitary agents were required to report ill individuals either meeting the case definition or with apparently unrelated febrile illnesses. All investigations were done one day before vaccine immunization of the population. Data on the emergency immunization campaign are not reported here.

Case definition

A probable YF case was defined as a death occurring after a febrile illness lasting two weeks or less, with jaundice and/or haemorrhagic signs. A confirmed YF case was defined as a person with a febrile illness and/or jaundice with YF IgM-positive test or virus isolation. An asymptomatic YF case was one without illness positive for YF IgM. A person supposed immune before the outbreak was defined as without YF IgM and YF virus isolation but positive for YF IgG. Sampling was

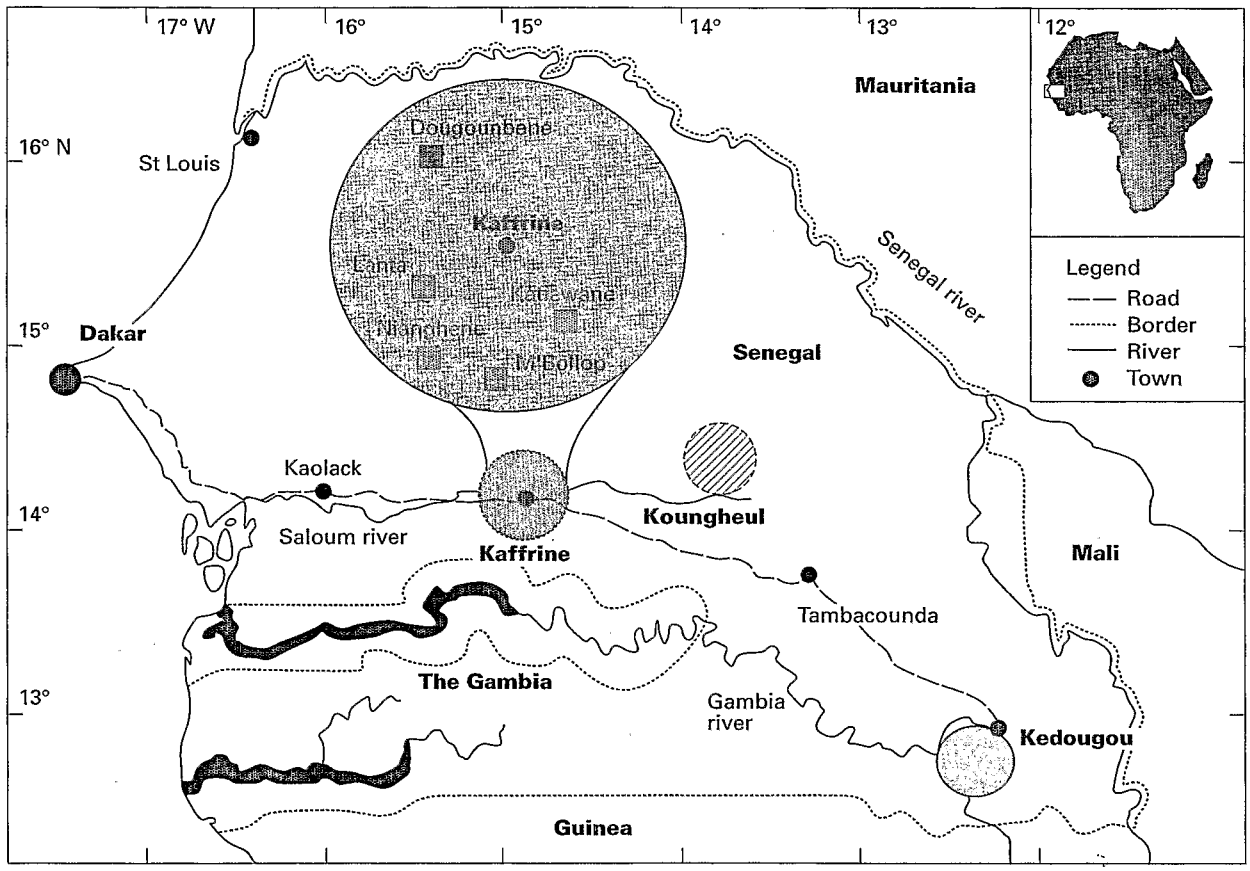

Figure 1 Map of Senegal, with the entomological survey area (Kedougou), the outbreak areas: Koungheul 1995 and Kaffrine 1996 with sites of epidemic villages.

Table 1 Distribution of YF cases according to definitions in Kaffrine hospital and in the investigated villages

Sites	Population	Samples	Confirmed cases	Asymptomatic cases	Total*	Probable cases	Total**
Kaffrine hospital	—	12	9	0	9	5	14
Dougounbene	234	167	16	21	37	4	41
Katiawane	597	78	4	12	16	9	25
Lanta	312	67	1	8	9	1	10
M'Bollop	608	42	1	9	10	9	19
Nianghene	415	83	0	19	19	0	19
Total	2166	449	31	69	100	28	128

*confirmed + asymptomatic cases; **confirmed + asymptomatic + probable cases

based on randomization of compounds: Every person of a sorted compound was asked to give blood and to fill in a case investigation form (identification, symptoms, etc.). We never met with refusal.

Laboratory procedures

Sera samples collected in the field were stored and transported in liquid nitrogen to the Institut Pasteur of Dakar. Tests for virus isolation on acute phase sera were performed in parallel with intracerebral inoculation of suckling mice and by inoculation on C6–36 mosquito cell line (Digoutte *et al.* 1992). Briefly, cells were examined by indirect immuno-fluorescence on day 10. Identification was made with a specific hyper immune mouse ascitic fluid and confirmed with a monoclonal antibody (2D12) (Schlessinger *et al.* 1983). Mice were observed for 21 days. A 10% brain suspension from animals showing signs of illness was passaged to establish the isolate. Confirmation on passages was obtained by complement fixation method (LBCM) (Casey 1969). Antibodies against YF virus were performed on sera diluted 1/100: IgM were detected by MAC-ELISA as previously described (Lhuillier & Sarthou 1983) and IgG were detected by indirect ELISA. The specificity and sensivity of the neutralization test and IgG ELISA cut-off were compared previously (J. Thonnon, unpublished observation).

Entomological studies

Mosquitoes were captured when landing for biting on immunized human volunteers between 1730 and 2100 h. Alternatively, they were collected after indoor insecticide spraying or use of outdoor CDC light traps. Adult mosquitoes were locally sorted and pooled by species and sex and stored in liquid nitrogen until virus isolation was attempted as for sera samples. *Aedes* larval development sites were investigated and larval indices were calculated as recommended by WHO (1986).

Results

Kaffrine hospital cases

The only hospital in the district had 14 YF cases: 5 probable and 9 confirmed (Table 1), 13 of whom were under 15. Clinical manifestations by decreasing order of frequence were: fever (100%), jaundice (93%) and haemorrhagic signs (64%). Twelve children (86%) died. All patients came from villages immediately surrounding Kaffrine (Figure 1).

Village investigations

During this YF outbreak, 36 fatalities were reported of which 24 occurred in villages. Table 1 gives the overall population, number of samples and distribution of cases according to the proposed case definition for each village investigated. Twenty-eight probable YF patients died before being investigated, only five of whom were hospitalized. All were under the age of 19. A total of 449 people were examined and tested for immunity to YF virus: 31 were confirmed cases and 69 asymptomatic. All had recently been infected with YF virus (incidence rate: 22.3%, 95% CI:18.5–24.5) and consequently were not immune before the outbreak (Table 2). Conversely, persons who had YF IgG without YF IgM were considered protected against YF by prior infection or immunization. The overall immunity rate before the outbreak was 60.4% (95% CI: 55.7–64.9).

As shown in Table 3, the distribution of cases was age-related. The incidence rate and attack rate were calculated on the basis of serologically defined cases related to sampled people and nonimmune people, respectively. The incidence rate decreased with age: about 30% in the youngest age groups and dropping significantly to 5.8% from the age of 20 years onward ($\chi^2 = 53.2$; $P < 0.0001$) and the attack rates were comparable in all age groups (average rate: 56.2%,

Table 2 Distribution of the YF immunity before the outbreak and incidence rate by villages

Sites	Samples (*n*)	Cases (*n*)	Incidence rate %	Immune before the outbreak (*n*)	Immune before the outbreak %
Kaffrine hospital	12	9	*	3	*
Dougounbene	167	37	22.2	100	59.8
Katiawane	78	16	20.5	50	64.1
Lanta	67	9	13.4	40	59.7
M'Bollop	42	10	23.8	27	64.2
Nianghene	83	19	22.9	51	61.4
Total	449	100	22.3	271	60.4

*non appreciated

Table 3 Kaffrine 1996, YF cases, incidence rate and attack rate by age.

Age (years)	Samples *n*	Non immune before the outbreak *n*	YF cases *n*	Incidence rate %	Incidence rate CI 95%	Attack rate %	Attack rate CI 95%
0–9	143	101	53	37.1	29.1–45.5	52.5	42.3–62.5
10–19	115	61	36	31.3	23.0–40.6	59.0	45.7–71.4
≥20	191	16	11	5.8	2.9–10.1	68.8	41.3–89.0
Total	449	178	100	22.3	18.5–26.4	56.2	48.6–63.6

$\chi^2 = 1.79$; $P < 0.41$). Conversely, YF immunity before the outbreak increased significantly with age, ranking from 29.3% for the 0–9 years age group to 47% for the 10–19 years age group and 91.6% for the oldest (Table 4). Virus isolation attempts were successful in 8 human sera.

Entomological results

A total of 485 adult mosquitoes belonging to 12 species was collected. *Aedes aegypti* was the commonest mosquito (47.2%) with a average of 0.7 bites per man per hour. The highest bite rate was observed in Dougounbene village, where 2.6 bites per man per hour were recorded inside a house. Two other mosquito species, captured once each, were also potentially capable of transmitting YF virus: *Aedes luteocephalus* and *Aedes metallicus*. Attempts to isolate YF virus on C6/36 cell culture succeeded once with *Aedes aegypti*, captured in Dougounbene. In all 240 households examined, Breteau and container indices exceeded levels associated with a risk of virus transmission in all villages and in Kaffrine (Table 5).

Table 4 YF immunity before the outbreak by age, Kaffrine 1996

Age	Samples (*n*)	Immune before the outbreak %	Immune before the outbreak CI 95%
0–9	143	29.4	21.9–36.9
10–19	115	47	37.9–56.1
≥20	191	91.6	87.6–95.5
Total	449	60.4	100

Table 5 Entomological surveys in villages and the town of Kaffrine with larval indices, Kaffrine 1996

Sites	Compounds units inspected N°	Breteau index	Container index %
Dougounbene	39	72	58
Katiawane	24	79	53
Lanta	22	36	32
M'Bollop	17	94	59
Nianghene	59	31	26
Kaffrine	79	28	27
Total	240	46	39

Discussion

This outbreak was the second occurring in Senegal in two years; the first one happened in Koungheul, in October 1995. The two epidemic areas were 150 km apart and both situated in the fossil Saloum River basin. The outbreak in Kaffrine was rapidly recognized without delay in diagnosis. Twenty-eight people died before investigations began and only 5 patients were hospitalized at Kaffrine although all villages are less than one hour away from the town. A social explanation was proposed by some village chiefs: YF jaundice was confused with other types of hepatitis which are usually considered mild and curable (e.g. endemic viral hepatitis A, malaria). As a consequence, only 14 patients from villages were hospitalized, all with severe symptoms. The case-fatality rate (CFR) of hospitalized cases was 86% (12/14). Another estimate of CFR based on all reported cases for the 2166 persons investigated is about 28.1% (36 deaths/128 cases) with a mortality rate of 1.3%. This CFR could be overestimated because our definition of probable cases was restrictive. The CFR in the previous Senegalese epidemic of Koungheul in 1995 was 18.9%.

Immunity against YF virus before the outbreak reported here was similar in all villages, with an overall rate of 60.4%. This high rate was not sufficient, however, to protect the populations from an epidemic. The incidence rates decreased significantly with age. On the contrary, the attack rate, in nonimmune persons, was remarkably stable in all groups (56.2%) (Table 3). There was no significant difference between sexes, either for incidence or attack rate. The highest age-related YF immunity rate (91.6%) occurred in the >20 age group and the lowest in the 0–9 years age group (29.4%), which was also significantly different from the intermediate group aged 10–19 years (47%) (Table 4). Immunity for the youngest would thus be attributable to the EPI conducted since 1987 in Senegal; at best, one third of the children area appear to be protected against YF virus, which is a lower score than the official overall vaccine coverage of Senegalese children (46% in 1994). On the contrary, the high level of protection shown in the older age group could be related to the neighbouring Gambia epidemics in 1979 (Monath *et al.* 1980), to mass campaigns of immunization along the border with the Gambia or to unreported natural infections.

In villages the density of the *Aedes aegypti* vector as assessed by high larval indices and land biting collections suggested a close association to humans. *Aedes aegypti* was found in adult and larval stages in all units visited. High larval indices in all villages favour man-to-man transmission by *Aedes aegypti* in this rural area. This domestic vector ensured YF virus transmission despite its low vector competence reported by Miller *et al.* (1988). It was also involved in natural vertical transmission during the outbreak of Koungheul (Fontenille *et al.* 1997). Other potential vectors such as *Aedes furcifer* and *Aedes metallicus* were very rare and did not transmit YF in the present epidemic. Thus this outbreak should be ascribed to an intermediate epidemic as defined by Cordellier and Cornet, investigated during the second phase, when *Aedes aegypti* transmission predominated. Kaffrine, which was inhabited by about one third of the district population, was surrounded by infected villages (Figure 1) and had high larval indices (Table 5). These factors were determinant in the decision to extend the emergency immunization campaign, first to surrounding villages, then to Kaffrine and lastly to the entire district.

Two hypotheses could be proposed for the sparing of Kaffrine (no urban cases were hospitalized) although larvae indices there were high: Firstly, transmission started in surrounding villages and did not reach the town at the time the outbreak was recognized; secondly, background immunity was higher in the urban population (though not estimated).

According to the *Aedes aegypti* transmission in a village, the only factor that determined the risk of YF disease was the YF-specific immune status as suggested by the constant attack rate (Table 3). Unprotected children are at greatest risk of YF infection in Africa. The excess of cases among children has motivated WHO to improve vaccine coverage within the context of EPI (Tomori 1997).

Re-emergence of YF in Senegal followed two different stages: the 1993–94 amplification of the wild cycle detected in the Kedougou area with sylvatic transmission vectors (Traore-Lamizana *et al.* 1996); then the 1995–96 outbreaks, first in Koungheul – a remote area (Thonnon *et al.* 1998) – and then around Kaffrine. A preventive mass campaign after the 1993 wild cycle amplification would probably have avoided the occurrence of outbreaks. Since it presently reaches one of the major roads in Senegal, the risk of spread to major towns infested by *Aedes aegypti* must be reevaluated. In the last two outbreaks, the delay between the first YF cases and biological confirmation was particularly short (15 days) due to local capability of distinguishing between YF and other viruses, and of establishing differential diagnoses. The serosurveys were based on IgM immunocapture (MAC-ELISA and IgM take 2–3 months) (Saluzzo *et al.* 1986). This biological procedure could be applied to active case detection during the season of high YF virus transmission (September-December). To improve the practicability, the test could be done on confetti. For each patient with jaundice, a drop of blood would be spotted on paper (confetti) and mailed to adapted laboratories for MAC-ELISA testing. Finally, improved vaccine coverage is the obvious manner to stop YF in endemic areas and to prevent its worldwide spread via travel. Two possibilities for YF control are available: preventive YF vaccination vs. emergency mass vaccination campaign for epidemic control. Cost-effectiveness varies according to the

scenario used in the model (Monath & Nasidi 1993). For small outbreaks, EPI doubles the price per prevented case/death compared to emergency mass campaign. Moreover, until EPI-induced immunity prevalence in all areas reaches at least 60%, YF epidemics will remain a topical question.

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