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FIRST RECORDED OUTBREAK OF YELLOW FEVER IN KENYA, 1992–1993. I. EPIDEMIOLOGIC INVESTIGATIONS

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Abstract. Outbreaks of yellow fever (YF) have never been recorded in Kenya. However, in September 1992, cases of hemorrhagic fever (HF) were reported in the Kerio Valley to the Kenya Ministry of Health. Early in 1993, the disease was confirmed as YF and a mass vaccination campaign was initiated. Cases of suspected YF were identified through medical record review and hospital-based disease surveillance by using a clinical case definition. Case-patients were confirmed serologically and virologically. We documented 55 persons with HF from three districts of the Rift Valley Province in the period of September 10, 1992 through March 11, 1993 (attack rate = 27.4/100,000 population). Twenty-six (47%) of the 55 persons had serologic evidence of recent YF infection, and three of these persons were also confirmed by YF virus isolation. No serum was available from the other 29 HF cases. In addition, YF virus was isolated from a person from the epidemic area who had a nonspecific febrile illness but did not meet the case definition. Five patients with confirmed cases of YF died, a case-fatality rate of 19%. Women with confirmed cases of YF were 10.9 times more likely to die than men ($P = 0.010$, by Fisher's exact test). Of the 26 patients with serologic or virologic evidence of YF, and for whom definite age was known, 21 (81%) were between 10 and 39 years of age, and 19 (73%) were males. All patients with confirmed YF infection lived in rural areas. There was only one instance of multiple cases within a single family, and this was associated with bush-clearing activity. This was the first documented outbreak of YF in Kenya, a classic example of a sylvatic transmission cycle. Surveillance in rural and urban areas outside the vaccination area should be intensified.

Periodic outbreaks of yellow fever (YF) have been reported in East Africa since 1940.[1–5] The largest occurred from 1960 to 1962 in Ethiopia, with an estimated 100,000 cases.[5] Despite an estimated seroprevalence of antibody to YF up to 14% in northern Kenya,[6,7] no outbreaks of YF have been reported and only one case of YF has ever been confirmed.[8]

Clusters of cases of hemorrhagic fever (HF) were first reported in September 1992 from the southern parts of the Keiyo (Kerio Valley), Baringo, and Koibatek Districts (former Elgeyo-Marakwet and Baringo Districts) in the Rift Valley Province of northwest Kenya. Subsequent serologic testing at the Kenya Medical Research Institute (KEMRI) and the Division of Vector-Borne Infectious Diseases (DVBID), of the Centers for Disease Control and Prevention (CDC) in Fort Collins, Colorado showed that some of these persons had recently been infected with YF virus.[9,10] Review of the detailed medical record of the first confirmed YF case documented that the man, who survived, was originally admitted with a mysterious illness which had affected and proved fatal for a large number of inhabitants from his residential area. Confirmed cases of YF (HF-YF) and cases of HF had onset of illness to March 1993. The last fatal case of HF was reported to the Kenya Ministry of Health one month after a mass vaccination campaign had been initiated in these two districts.[11,12] We report here on the epidemiologic investigations of the outbreak, carried out by members of the Kenya Ministry of Health, KEMRI, the World Health Organization, and CDC. An account of the entomologic investigations, conducted at the same time, is published in an accompanying article.[13]

DESCRIPTION OF THE AREA

The epidemic area combines the southern part of the Kerio Valley (approximately 0°7′N to 0°35′N; 35°34′E to 35°48′E), in the Keiyo District, and adjacent parts of the Baringo and Koibatek Districts (Figure 1). The first cases were reported from the southern part of the valley. Vegetation in this region is semi-arid with thorny brush land and discontinuous gallery woodland. Numerous small streams drain from the higher altitudes into the Kerio River. Roads are unpaved and communications are poor. Most of the population lives from minimal subsistence agriculture, growing groundnuts, finger millet, and sorghum. Small numbers of cattle, sheep, and goats are reared. Health-care facilities are limited. The population of the southern part of the valley is approximately 66,000.[14]

The adjacent eastern slopes of the Amasha Hills (south of the Kabarnet, Baringo, and Koibatek Districts), where subsequent cases of HF occurred, are less arid and more developed, with some paved roads and better communications. The area is characterized by discontinuous woodland and various human settlements. Health-care facilities are more accessible: there are two government district hospitals and one mission hospital. The population of the affected area in the Baringo and Koibatek Districts is approximately 135,000. There are two rainy seasons, the first from April to June (long rains), and the second from October to November (short rains). The population of the region had never been vaccinated against YF.

MATERIALS AND METHODS

Human case finding. The investigation was conducted in accordance with human research subjects guidelines of the

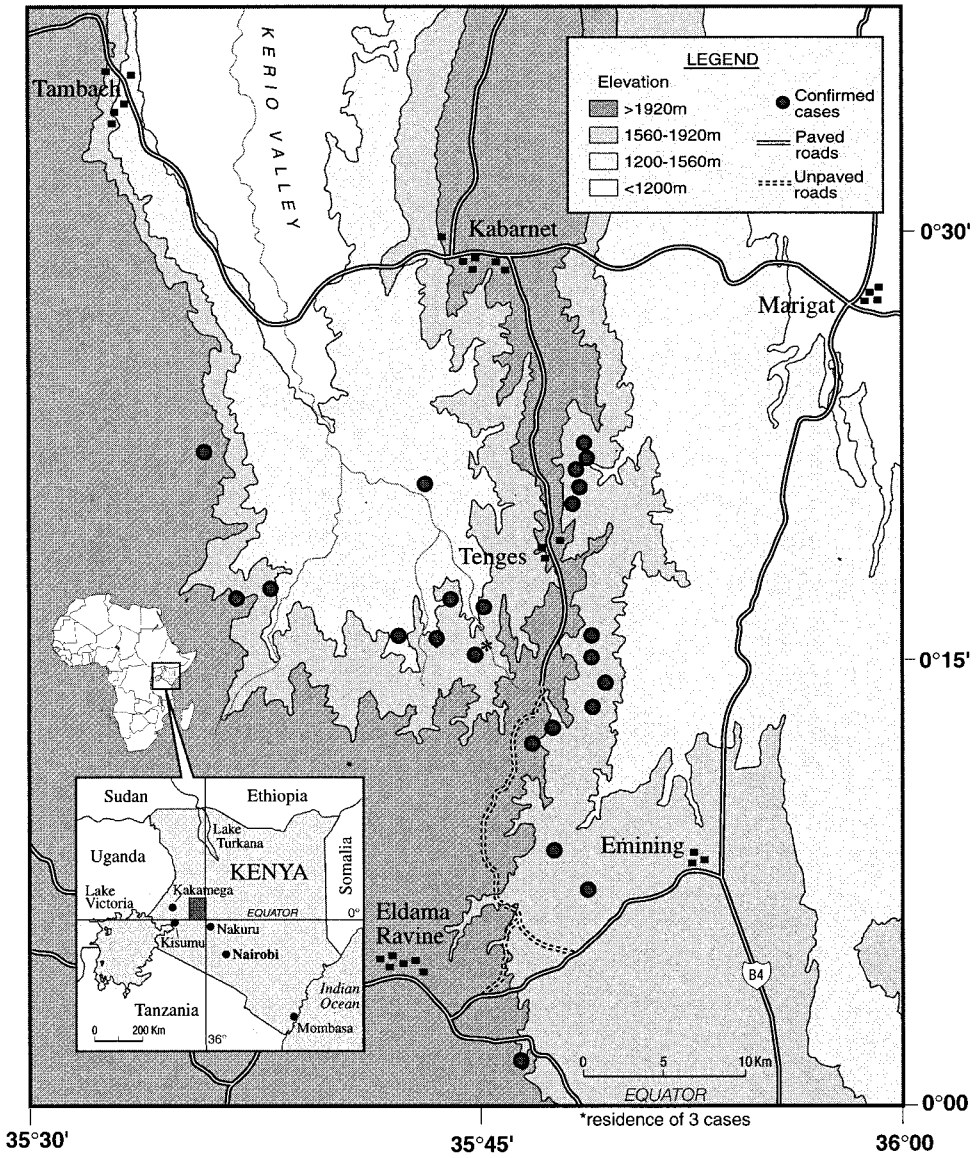

FIGURE 1. Map of the yellow fever outbreak area, Rift Valley Province, Kenya, 1992–1993. Black dots depict residences.

Kenyan Ministry of Health and with guidelines of CDC for studies conducted in rapid response to public health emergencies.

In January 1993, prospective surveillance for cases of HF was initiated in five hospitals in the Uasin Gishu, Baringo, and Koibatek Districts. Persons with suspected HF were identified by medical and nursing staff and interviewed by a member of the investigation team. In addition, staff at these five hospitals were asked to recall patients with symptoms suggestive of HF who had presented from September 1992 through December 1992. Medical records of persons identified, either prospectively or retrospectively, were reviewed by members of the investigation team to determine if HF was present. Clinical samples were sought, but not always obtained, for persons identified prospectively. A case of HF was defined as a person with three of the following five signs and symptoms: jaundice, hemorrhage, encephalitis, renal failure/anuria, or a temperature $\geq$ 38°C. Encephalitis was defined as confusion, disorientation, delirium, coma, or seizures. To confirm a diagnosis of YF, serum samples were collected from persons with HF and liver samples were collected from recently deceased persons with HF. Members of the investigation team visited many of the homes of persons with HF-YF.[13] During home visits, additional clinical and epidemiologic information and a convalescent serum sample were obtained. When the case-patient was unavailable, additional information was obtained from family members.

Laboratory testing. Liver samples and serum were stored in liquid nitrogen or in freezers at -20°C until they could be transported for serologic and virologic testing at KEMRI (Nairobi, Kenya) and the DVBID at CDC (Fort Collins, CO). Serum samples were tested for YF antibodies with an IgM-capture ELISA (MAC-ELISA),[15,16] the hemagglutination-inhibition (HI) test adapted to microtiter,[17] and the plaque-reduction neutralization test.[18] Acute and convalescent serum

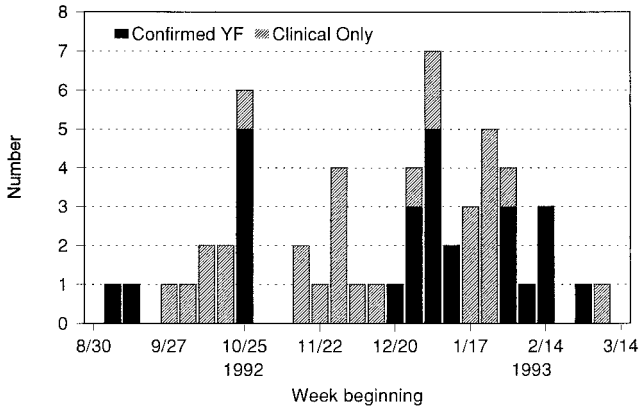

FIGURE 2. Number of cases of hemorrhagic fever, by week, in the Keiyo, Baringo, and Koibatek districts, Kenya, 1992–1993. YF = yellow fever.

samples from the same patient were always tested together by using each assay.

A presumptive diagnosis of YF was made if YF-specific IgM antibody was present in acute or convalescent serum samples by MAC-ELISA and the HI antibody titer was greater than or equal to 1:1,280, and YF etiology was confirmed if there was a four-fold or greater increase in HI antibody titer or YF virus was isolated from the acute serum or from a tissue sample. To confirm the specificity of the antibody response, serum was tested for neutralizing antibody by the plaque-reduction neutralization test for several flaviviruses (Dengue, West Nile, Uganda S, Banzi, Zika, and YF). A specific neutralizing antibody response representing YF infection was defined as a four-fold or greater titer to YF than to the other flavivirus antigens.

For virus isolation, acute serum samples and liver samples were inoculated into three cell culture systems: *Aedes pseudoscutellaris* (AP61), *Ae. albopictus* (C6/36), and Vero cell cultures. Ten to 14 days after inoculation, all cell cultures were harvested and spotted onto teflon-coated slides. After air-drying, slides were fixed for 10 min in cold acetone, air-dried again, and screened for the presence of flavivirus antigen with a direct immunofluorescent antibody assay that used a conjugate prepared from pooled human serum with high-titered (> 5,120) flavivirus antibody.[19] In addition, these same samples were injected into the brains of 1–3-day-old mice. During a period of observation up to 21 days, ill mice were killed and the brains were removed. A 10% mouse brain suspension was inoculated into AP61 cells and processed as noted for primary cell culture virus isolation.[20] The YF isolates were identified by indirect immunofluorescent assay using YF-specific monoclonal antibodies.[19,21] To distinguish between 17 D vaccine virus strain and wild-type YF, the isolates were screened by indirect inununofluorescent assay using specific monoclonal antibodies that differentiate between the two strains.[21]

RESULTS

Case investigation. From September 1992 through March 1993, 55 persons with HF were identified from the Keiyo, Baringo, and Koibatek Districts, resulting in a minimum HF attack rate of 27.4 per 100,000 population. Of 55 patients with HF, serum samples or tissue were not available or were not obtained for 29 (53%). The earliest recorded onset of these 29 HF cases was September 28, 1992 and the latest onset was March 11, 1993 (Figure 2). Twelve (41%) of 29 HF patients were identified prospectively. All 29 died. Of these 29 persons, 11 (38%) were female, and 28 (97%) resided in the Baringo and Koibatek Districts (Table 1). Age was known for 26 of 29; 21 (72%) were less than 40 years of age (mean = 31.0 years, range = 12–65 years).

TABLE 1

Persons with hemorrhagic fever caused by yellow fever infection (HF-YF case), hemorrhagic fever-clinical case (HF case), and total cases (total HF-YF/HF), 1992–1993, Kenya

Characteristic	HF-YF case	HF case	Total HF-YF/HF
Number	26	29	55
Sex			
Male	19 (73%)	18 (62%)	37 (67%)
Female	7 (27%)	11 (38%)	18 (33%)
Age (years)			
10–19	11 (42%)	6 (21%)	17 (31%)
20–39	10 (38%)	15 (52%)	25 (45%)
≥40	4 (15%)	5 (17%)	9 (16%)
Unspecified adults	1 (4%)	3 (10%)	4 (7%)
Fatal cases			
Total	5 (19%)	29 (100%)	34 (62%)
Male	1 (4%)	18 (62%)	19 (35%)
Female	4 (15%)	11 (38%)	15 (27%)
Resident district			
Koibatek or Baringo	22 (85%)	28 (97%)	50 (91%)
Other district	4 (15%)	1 (3%)	5 (9%)
Case finding method			
Retrospective	10 (38%)	17 (59%)	27 (49%)
Prospective	16 (62%)	12 (41%)	28 (51%)

The remaining 26 (47%) persons with HF had serologic evidence of recent YF infection (HF-YF) and YF virus was isolated from the serum of three of the 26 patients. In one fatal case, YF virus was also isolated from the liver samples. Of the 26 persons with HF-YF, five (19%) died and seven (27%) were female (Table 1). Of these seven females, four (57%) died compared with only one of 19 males with HF-YF (relative risk of death for females = 10.9 [95% confidence interval = 1.5–81.3, $P = 0.01$]). Age was known for 25 of 26; 21 (81%) were less than 40 years of age (mean = 27.2 years, range = 10–70 years). For the HF-YF cases, the earliest onset was September 10, 1992 and the latest was March 3, 1993. Sixteen (62%) of the patients with HF-YF were identified prospectively. Of these 26 persons, 22 (85 %) resided in the Baringo and Koibatek Districts, resulting in a minimum attack rate of 16.3 per 100.000 in these two districts. The other four (15%) persons with HF-YF resided in the Keiyo District, resulting in a minimum attack rate of 6.1 per 100.000. The majority (24, 92%) of HF-YF cases were admitted to only two of the five hospitals (12 cases each), where intensified surveillance was implemented.

Clinical findings of hemorrhage were found in every person with HF-YF infection. In addition, of 26 persons with HF-YF, 24 (92%) had fever > 38°C, 24 (92%) were jaun-

diced, 17 (65%) had clinical findings of encephalitis, and 8 (31%) had renal failure or anuria.

Serum samples were also obtained from five adolescent girls, residents of the outbreak area, who were admitted with febrile illness prior to the establishment of the case definition. Three of these five had serologic evidence of recent YF infection but did not have a clinical presentation consistent with HF and were not included above. In one of these persons, a 12-year-old girl with a nonspecific febrile illness, YF virus was isolated from the serum. In addition, an eight-year-old girl with HF who died did not have serologic evidence of YF infection and virus could not be isolated from samples of her serum or liver. This case was previously reported but is not included in this analysis.[12]

Home investigation of persons with YF. Of the 22 homes of persons with HF-YF that were visited, 20 (91%) were located at elevations between 1,200 and 1,900 meters.[13] Except for one patient, none of these 22 persons traveled outside of their home location (approximate radius of home location $<$ 20 km) during the two-week period prior to their illness. One person, whose home was 50 km northeast of Emining (residence is not depicted in Figure 1), had no travel history through any of the affected areas. This case was not previously reported and his residence is located in a division that was not recognized during the outbreak investigation.[12] The majority of persons with HF-YF had outdoor occupations (or walked significant distances) that brought them into regular contact with the dense brush areas. Of 26 persons, 13 (50%) were farmers, herdsmen, or hunters, and nine (35%) were students.

DISCUSSION

This was the first documented outbreak of YF in Kenya. Peridomestic mosquito species were absent, but a number of classic sylvatic species were found throughout the outbreak area.[13] Yellow fever virus was isolated from two species: *Ae. (Stegomyia) africanus* and *Ae. (S.) keniensis.* The entomologic evidence, combined with the lack of multiple cases within families (except for three brothers who had been clearing bush together), confirms that this was a classic sylvatic outbreak in which human infections were acquired by contact with the epizootic vectors.

In most epidemics of YF, the officially reported number of cases is a small proportion of the actual total.[22] Reasons for under reporting include the often remote epidemic sites; difficulties in clinical recognition of the disease by peripheral health workers, resulting in delays or failures to recognize epidemics; lack of information on events outside hospitals; lack of diagnostic facilities; and selected collection of data. Our report concurs with these observations; 40% of the patients with HF-YF and 60% of the patients with HF were identified retrospectively; 92% of the patients with HF-YF were identified through intensified surveillance in two of five hospitals. Although the attack rate for the Baringo and Koibatek Districts appears to be nearly three times higher than for the Keiyo District, it is likely that cases from the latter district were underestimated. Unfortunately, the mission hospital that serves the southern part of the Kerio Valley in the Keiyo district was not included in the surveillance system. It later appeared that six fatal case-patients with onset in August 1992 who met the HF case definition were documented by the medical officer in charge at that hospital, but were not reported (Mettau J, unpublished data). In addition, medical staff who were asked to recall cases of HF may have more readily recognized cases from the Tenges Division of the Baringo District because they remembered persons with Tenges disease, the name given to the unknown illness affecting the area.

Although only 26 (47%) of 55 HF cases were confirmed recent YF infections, several findings suggest that more HF-YF infections and illnesses occurred. First, the dates of onset of illness, age distribution, sex ratio, and home district of persons with HF were very similar to persons with HF-YF. It is likely that many of these HF cases were truly due to YF. Second, six fatal cases from the Keiyo District who met the HF case definition were not reported. Third, persons with mild, nonspecific fevers were confirmed to be infected with YF both by virus isolation and serology. These three findings strongly suggest that our reported cases underestimate the extent of the morbidity and mortality associated with this YF epidemic. Given that 3% of the YF cases present with jaundice, YF illness in this outbreak may have attacked at least 800 persons (24 HF-YF cases with jaundice $\times$ 100/3).[23] Unfortunately, no serosurvey data are available to determine the actual rate of YF infection in this population.

Case fatality from YF infection varies considerably depending on the case definition of YF illness.[23] During this outbreak, we only included the most severely ill and hospitalized persons with YF. The male:female ratio was 2.6:1. One interesting finding was the significant difference in the sex-specific case-fatality ratio among persons with HF-YF. Women with confirmed YF were nearly 11 times more likely to die than men. There is no reason to assume that a sex bias towards obtaining serum samples occurred, or that women were more likely to be bled in the final stage of their illness, when a fatal outcome was evident. The most likely explanation is that in rural Africa, a woman is known to have many domestic responsibilities that may have prevented an earlier presentation to the hospital, especially in the event of a hitherto unknown disease. Underlying chronic liver infection and pregnancy have also been suggested as host factors that worsen fatality from YF. The greatest sex difference was observed in the 1969 YF epidemic in Nigeria, when the male:female ratio was 4:1 for hospitalized patients (morbidity figure). Although the case-fatality rate of 38% (116 of 307) was not specified for sex, no sex difference was documented in antibody prevalence or in disease incidence in nonhospitalized patients.[24] The explanation that males in Nigeria make greater use of hospital care also seems likely to hold for the Kenya epidemic. Recent documentation of 10 patients with confirmed YF from the same area shows an equal sex distribution, suggesting greater awareness of the disease.[25]

In virgin soil YF epidemics, such as that in the 1960–1962 epidemic in Ethiopia, the disease affected all age-groups, with a male:female ratio of 1.6:1.[5] The incidence was slightly higher in adults than in children. In contrast, 81% of the patients with HF-YF in Kenya were less than 40 years of age, and no cases were recorded in individuals less than 10 years of age. Young male adults were at highest risk in this outbreak. Exposure included activities that increased

the time spent in areas of heavy vegetation, including clearing land for cultivation, walking to school, tending animals, and hunting, predominantly male activities. Females spent more time close to home, but collecting water and walking to market were probably significant risk factors.

Only one of 22 persons with HF-YF whose travel history was confirmed had traveled outside the home location. However, less ill viremic persons may have traveled between this region and the cities, as do many of the districts' residents. Since YF vaccination certificates are not required for travel within Kenya, unvaccinated persons visiting the YF-endemic area and returning to the cities increase the risk for an urban outbreak.[26] This potential risk was underscored by the recognition of YF cases outside of the area affected by the 1992–1993 outbreak. Surveillance through 1995 has identified four persons with confirmed YF infection who live south of the Eldama Ravine along the borders with the Kericho and Nakuru Districts, districts that were not targeted by the YF vaccination effort in 1993.[27,28] These findings may be due to the establishment of surveillance and the increased awareness of YF but also may support the existence of other sylvatic cycles and recurrent wandering epizootics, which are believed to maintain YF transmission.[29]

Yellow fever vaccination is the only effective public health intervention for preventing epidemics in enzootic/endemic areas. Information on YF in Kenya has remained fragmentary five years following the emergence of the first recorded YF epidemic. Are there other areas in Kenya experiencing YF transmission, what is the public health threat of an epidemic in areas relatively near the endemic area? The key element to address these questions is the implementation of a country-wide, laboratory-based, active surveillance program.[30] Further studies to identify other areas with recent or ongoing YF transmission in Kenya are necessary. Based on the possible southward expansion of the endemic area in Kenya and the increasing chances of an urban epidemic, we recommend an ongoing selective YF vaccination program for children six months of age and older in the YF-endemic districts and the districts immediately adjacent to the endemic area (Uasin Gishu, Kericho, Nandi, and Nakuru). Inhabitants of and travelers to the enzootic/endemic area of Keiyo, Baringo, and Koibatek should be covered by YF vaccination. In addition, we recommend expanding the existing surveillance for YF/HF to adjacent areas. Consideration should be given to include patients with nonspecific febrile illness.

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