The Reemergence of Ebola Hemorrhagic Fever, Democratic Republic of the Congo, 1995

Ali S. Khan, F. Kweteminga Tshioko, David L. Heymann, Bernard Le Guenno, Pierre Nabeth, Barbara Kerstiëns, Yon Fleerackers, Peter H. Kilmarx, Guenael R. Rodier, Okumi Nkuku, Pierre E. Rollin, Anthony Sanchez, Sherif R. Zaki, Robert Swanepoel, Oyewale Tomori, Stuart T. Nichol, C. J. Peters, J. J. Muyembe-Tamfum, and Thomas G. Ksiazek, for the Commission de Lutte contre les Epidémies à Kikwit

Special Pathogens Branch and Infectious Disease Pathology Activity, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, and Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia; Ministry of Health, Kinshasa, Democratic Republic of the Congo; World Health Organization, Geneva, Switzerland; Institut Pasteur, and Epicentre, Paris, France; Médecins sans Frontières, Brussels, and Institute of Tropical Medicine, Antwerp, Belgium; Special Pathogens Unit, National Institute for Virology, Department of Health, Sandringham, South Africa

In May 1995, an international team characterized and contained an outbreak of Ebola hemorrhagic fever (EHF) in Kikwit, Democratic Republic of the Congo. Active surveillance was instituted using several methods, including house-to-house search, review of hospital and dispensary logs, interview of health care personnel, retrospective contact tracing, and direct follow-up of suspect cases. In the field, a clinical case was defined as fever and hemorrhagic signs, fever plus contact with a case-patient, or fever plus at least 3 of 10 symptoms. A total of 315 cases of EHF, with an 81% case fatality, were identified, excluding 10 clinical cases with negative laboratory results. The earliest documented case-patient had onset on 6 January, and the last case-patient died on 16 July. Eighty cases (25%) occurred among health care workers. Two individuals may have been the source of infection for >50 cases. The outbreak was terminated by the initiation of barrier-nursing techniques, health education efforts, and rapid identification of cases.

No pestilence had ever been so fatal, or so hideous.
Edgar Allan Poe, *The Masque of the Red Death,* 1842

Ebola (EBO) hemorrhagic fever (EHF) is a lethal viral hemorrhagic fever with person-to-person transmission and the potential to cause major epidemics. It was first recognized during the course of parallel outbreaks in Equateur region in northern Democratic Republic of the Congo (DRC) and in adjacent southern Sudan in 1976 [1, 2]. The outbreak in northern DRC was centered around the town of Yambuku near the banks of the Ebola River and was characterized by extensive nosocomial transmission in a mission hospital (mainly from needle reuse), with 318 documented cases and 280 deaths (88% case fatality) over a 2-month period. The southern Sudan outbreak appeared to originate among workers at a cotton factory in Nzara and subsequently spread to Maridi, where disease was amplified in a large, active hospital. A total of 284 cases, with 151 deaths (53% case fatality), were documented over a 5-month period. Despite the geographic and temporal coincidence of these outbreaks, the implicated viruses were genetically related but distinct subtypes [3]. The necessity for the highest level of biologic containment for these agents was rapidly established after a laboratory infection occurred in England [4].

Reprints or correspondence: Dr. Ali S. Khan, Special Pathogens Branch, CDC, MS A26, 1600 Clifton Rd., N.E., Atlanta, GA 30333.

The Journal of Infectious Diseases 1999; 179(Suppl 1):S76–86

0022–1899/99/79S1–0014$02.00

In 1977, a fatal case of EHF was recognized in a child from Tandala, DRC, 325 km from Yambuku [5]. Investigation of this case led to the retrospective identification of a case in 1972 and suggested that EHF was endemic but sporadic in northern DRC. In 1979, a 34-person cluster of cases with a 65% case fatality was noted in southern Sudan; the cases had direct links to an index patient employed in the same textile factory that was implicated in the 1976 outbreak [6]. In Côte d'Ivoire in 1994, the isolation of a new strain of EBO from an ethologist who had necropsied a chimpanzee not only extended the geographic distribution of known cases and strains but also provided another tantalizing clue about a possible role for nonhuman primates as a link for these viruses in human outbreaks [7]; imported cynomolgus monkeys *(Macaca fascicularis)* from the Philippines had been associated with the Reston subtype of EBO virus in the United States in 1989 and 1990 [8–10]. Also in 1994, an outbreak of EHF occurred north of Makoukou, the provincial capital of Ogooué-Ivindo, Gabon; there were 44 cases and 28 deaths (64% case fatality). This outbreak was originally misdiagnosed as yellow fever and subsequently was ascribed to the Zaire subtype of EBO virus [11]. Although key epidemiologic and control measures were elucidated during these investigations, a reservoir for these virus subtypes remains unknown.

In May 1995, the Centers for Disease Control and Prevention (CDC) was notified of an outbreak of viral hemorrhagic fever in Kikwit, DRC. The outbreak was of unknown magnitude but had caused the death of at least 2 Italian nuns and other members of a surgical team and their subsequent contacts. Specimens sent to Belgium were forwarded to CDC for diagnostic

testing, and the presence of acute or recent EBO virus infection was confirmed for all 14 persons tested. Within 48 h of diagnostic confirmation, a multinational contingent led by the World Health Organization (WHO), composed of physicians, epidemiologists, sanitarians, health educators, and logistic support personnel from WHO, CDC, Institut Pasteur, Epicentre, Médecins sans Frontières, Institute of Tropical Medicine, and the International Red Cross were dispatched to assist DRC authorities in controlling and characterizing the outbreak [12–15]. This report describes the surveillance methodologies and key epidemiologic characteristics of this outbreak.

Background

Kikwit (population ~200,000), the former regional capital of Bandundu region, is located on the banks of the Kwilu River, ~475 km east of Kinshasa, the capital of DRC. The economy of the area is based on agriculture, hunting, and fishing, with the majority of the populace commuting to the surrounding secondary forest for subsistence. As in the rest of DRC, a declining public sector has recently had devastating effects on the community's health care, education, transportation, and communication facilities. The two major hospitals are Kikwit General Hospital (350 beds) and Kikwit II Maternity Hospital (100 beds). Reportedly, a small nosocomial cluster of EBO cases among the nursing staff at Kikwit II Maternity Hospital was first recognized but misdiagnosed as epidemic dysentery in early April 1995.

Toward the end of April, a similar nosocomial cluster was identified at Kikwit General Hospital among the operating room staff who participated in a surgical procedure on a laboratory technician employed at Kikwit II Maternity Hospital; the patient had been transferred on 10 April to Kikwit General Hospital for a laparotomy to treat a suspected typhoid-associated abdominal perforation. No perforation was noted intraoperatively, and the patient underwent an appendectomy during the exploration. The next day, the patient had increased abdominal pain and distention, with a diagnostic bloody abdominocentesis. A repeat laparotomy was done to exclude bleeding around the appendix suture site; it revealed diffusely bleeding abdominal contents. The patient died 2 days later. Within several days of his death, physicians and nursing personnel, including 2 Italian missionary nurses involved in his care, became ill with a febrile disorder suggestive of a viral hemorrhagic fever. The unusual nature of these cases was recognized independently at Kikwit II Maternity and Kikwit General Hospitals and two other regional health facilities that managed these patients and their subsequent contacts.

An ad hoc committee was locally established on 1 May 1995 to examine the presumptive epidemic dysentery deaths. In consultation with the physicians at Kikwit General Hospital, J. J. Muyembe-Tamfum, Ministry of Health, DRC, who had participated in the follow-up of the 1976 EHF outbreak, suggested that these deaths were due to viral hemorrhagic fever. Specimens were obtained on 4 May and sent to the Institute of Tropical Medicine. The specimens were forwarded and subsequently arrived at CDC on 9 May, where testing confirmed EBO virus as the etiologic agent for the disease in all 14 patients. From that point on, the original ad hoc committee evolved into an international commission to manage the outbreak. The various activities of this commission, such as patient management, community education, transportation of cadavers, and research activities, are described elsewhere in this supplement.

Not unexpectedly, surveillance activities proved extremely difficult. Initial case counts were based on nonsystematic reports from various hospitals, clinics, and private individuals. Reports of cases and deaths often conflicted from day to day. Because no public health surveillance system existed within Kikwit or its environs, one had to be constructed de novo by using a patchwork of paid and unpaid volunteers with various levels of skill, experience, background, and tenure. The foreign members of the international commission were just as diverse, and the problem was compounded by language and cultural differences. Surveillance was hindered by many logistic difficulties, including the lack of transportation and telephones. It was also hampered by confounding societal forces that led to concealment and denial of cases to avoid the social stigmata that rapidly became attached to those with the disease and to the contradictory reporting of noncases in the belief that this could lead to some tangible benefit for the afflicted family or village or reporter. Retrospective surveillance was also initially limited by the early impression that all febrile hemorrhagic deaths prior to that of the laboratory technician from Kikwit II hospital were due to epidemic dysentery.

The commission's health education campaigns proved challenging because of the lack of mass media, closure of all schools, unpaid health care workers in hospitals and many health centers, and an estimated literacy rate of 55%–61%. Education of the populace was conducted using leaflets, posters, and banners strung across the main roads. The Kikwit Diocese of the Catholic Church helped to disseminate accurate educational material at church gatherings. In addition, educational messages were broadcast by megaphone through the streets of Kikwit and by word of mouth from commission members to the populace. Health care providers at the local hospitals received individual instruction on the use of protective clothing and equipment, diagnostic features of the disease, case definitions, and patient management. Training for ~60 health care workers from the Kikwit sentinel health clinics and 30 regional physicians was conducted in 2 separate sessions on 12 and 14 May, respectively. Individual training sessions for other local and regional health care workers and facilities were conducted as needed, and protective equipment was provided.

Methods

Case Definitions

The field-case definition was modified during the course of the outbreak investigation. The initial field-case definition required

that cases have contact with another case-patient and that they meet clinical illness criteria, and the definition categorized suspected cases into either probable or clinical (''clinque'') cases on the basis of the presence of hemorrhage. Since education of suspected cases and their family members was our major intervention strategy, this case definition was modified on 13 May to be highly sensitive and identify individuals who may not have recalled or have had an obtainable history of contact with a case-patient. A probable case was defined as someone who had (1) an unexplained fever and contact with another case-patient; (2) unexplained fever plus $\geq$3 of 10 symptoms (abdominal pain, anorexia, asthenia, simple [nonbloody] diarrhea, dysphagia, dyspnea, headache, hiccups, myalgia or arthralgias, and nausea or vomiting); or (3) unexplained acute hemorrhagic signs or symptoms, such as melena, hematemesis, petechiae, or epistaxis. In an effort to completely ascertain the geographic and temporal nature of this outbreak, this case definition was not restricted to any region of DRC or to a time frame. Operationally, however, case-finding occurred in the Bandundu region from 13 May to 1 July 1995 for cases with onset dates after 1 January 1995 (prior to the onset date of the first identified case). A case-report form was completed on all such probable case-patients in addition to all unexplained deaths for whom additional information was garnered to determine if they otherwise met the case definition. This field-case definition was the basis for all case counts reported during the course of the outbreak after the arrival of the international team.

For the purpose of this report, with the availability of the final laboratory results, the case definition was revised as follows: (1) individuals with negative laboratory results who otherwise met the field-case definition were excluded and (2) acutely ill individuals for whom clinical information was insufficient to meet the field-case definition but who otherwise had laboratory data confirming an acute or recent EBO virus infection (i.e., presence of detectable antigen or IgM antibodies) were included as case-patients. Healthy individuals with no recent disease history and from whom blood specimens were drawn for antibody surveys were not included as case-patients if EBO antibodies were detected.

Surveillance and Case-Finding

Surveillance was conducted separately for the city of Kikwit and the surrounding areas of Bandundu region, but the data were coordinated through a central data registry and epidemiologic subcommittee. After 1 July 1995, reports of probable cases were no longer being systematically collected and were not recorded in the central database, although DCR officials continued to monitor the families of some of these individuals.

Surveillance in Kikwit and Surrounding Area

City of Kikwit surveillance and case-finding during the acute phase of the outbreak was divided into four separate components as follows.

Rumor surveillance for suspect cases. Any persons suspected of having viral hemorrhagic fever could be reported by the public to 2 sites in Kikwit for appropriate follow-up and intervention. These activities were supplemented by the secourists (Red Cross first aid workers) and others who went from door to door in neighborhoods to identify probable cases.

Hospital and sentinel health clinic surveillance. A 2- or 3-member team was assigned to review the patient logs at Kikwit General Hospital and the 11 main functioning mission and public (i.e., sentinel) health clinics at which staff had initially been trained, and they provided protective equipment. Case-report forms were completed for all patients who met the surveillance case definition and forwarded to the central registry for completion or for inclusion as case reports and for follow-up.

Death registry. By 13 May 1995, most of the corpses for fatal cases of suspected EHF and those for persons with unexplained deaths were collected by the secourists, who forwarded case-report forms to the central registry for completion.

Active surveillance and family follow-up. A temporally variable group of 22–44 second- and third-year medical students from the Bandundu Medical School, Kikwit, were paired into teams to follow up on all suspected cases to complete case-report forms and to determine if the individuals met the surveillance case definition. If persons who met the case definition were still residing in the household, they were instructed to seek medical evaluation and possible hospitalization at Kikwit General Hospital to clinically verify the diagnosis and prevent spread to household members. Family members of probable case-patients were educated on how to reduce their risk of infection if the ill individual continued to reside in the household. These family members were revisited at least 3 times a week for 3 weeks following their last contact with the probable case-patient prior to death or convalescence to ascertain if secondary transmission had occurred. Nurses previously trained in the sentinel clinics also visited the household of probable case-patients to distribute basic protective material (e.g., a pair of gloves, soap, and wash basin) as needed and to reinforce the educational messages about risks of transmission and symptoms suggesting disease in subsequent family members.

Regional Surveillance

Bandundu regional surveillance and case-finding was divided into two separate components maintained by the regional surveillance team, which was responsible for appropriate follow-up and interventions. Efforts were markedly hampered by the scarcity of motor vehicles and an almost nonexistent communication system.

Rumor surveillance for suspect cases. Similar to the system within the city of Kikwit, suspected cases from within Bandundu region were reported to the commission. Cases from outside Bandundu region were reported to the National Committee on Hemorrhagic Fevers in Kinshasa.

Mission radio network surveillance. Voice contact by shortwave radio system (''phonies'') was made each morning with all 23 Catholic missions functioning in the Diocese of Kikwit, an area comprising several health zones (''zones de santé'') around the city, to inquire about possible case-patients and obtain follow-up information on villages with known cases within the last 3 weeks. In addition, individuals from Protestant churches and from the public with radios were contacted as needed.

All suspected case-patients were visited by members of the regional surveillance team from Kikwit or by local health care workers who had been trained in Kikwit. Probable case-patients were

confined in their households, instructions for care were given, and basic protective equipment was provided to the primary care givers. Family members and other villagers were educated about the disease and monitored for secondary cases once or twice weekly for 3 weeks after the last contact with the probable case-patient.

Additional Surveillance

Retrospective case-finding was conducted to identify chains of EHF transmission. Several retrospective cases were found by examining the reported source of infection in addition to interviewing health care workers and affected families. Surveillance activities were maintained by testing postmortem skin snips [16] and liver biopsy specimens from deceased possible case-patients after 20 June 1995, the presumptive date of onset of the presumed last identified case. This individual was discharged from isolation on 14 July 1995, which was the referent date to declare the end of the outbreak 6 weeks later [17]. However, the case definition for selecting patients with onset dates after 30 June became highly variable and erratic without central organization; therefore, these cases, except for a single laboratory-confirmed case, are not included in the final case counts.

Data Collection and Analysis

Information in our report was obtained from surveillance case-report forms that were used to solicit basic demographic data and selected clinical and exposure information. Case-report forms were completed as soon as EHF was suspected or after the fact from retrospectively identified case-patients. Although detailed chart reviews were available for a minority of patients, this information was used only to supplement the demographic data from the case-report forms. The clinical descriptions from these other data sources are presented by Bwaka et al. elsewhere in this supplement. Data collection was not uniform for all suspected cases because of the evolution of the surveillance system and inherent difficulties in collecting information about deceased persons, but similar variables were analyzed in this study.

The date of disease onset was unavailable for ~10% of suspected cases, and for the rest, it was often disputable. However, the date of death was invariably available and rarely in dispute. For certain representation purposes, the month of onset has been calculated as either the difference of the mean onset to hospitalization from the date of hospitalization or the difference of the mean onset to death from the date of death. Comparisons between deceased patients and survivors were made using the χ^2 or Fisher's exact (2-tailed) tests, as appropriate. The Wilcoxon rank sum test was used to compare age, phase of the outbreak, and various durations [18].

Results

Index Patient and Initial Cluster of Cases

The first identified case-patient was GM, a 42-year-old male charcoal worker and farmer who became ill on 6 January 1995 and died of a febrile hemorrhagic disease at Kikwit General Hospital on 13 January 1995. He directly infected at least 3 members of his family, all of whom died, and an additional 10 secondary cases (all fatal) occurred among members of his extended family over the next 9 weeks in an area encompassing Kikwit and 3 surrounding villages. This case-patient had no known identifiable contact with another EHF case-patient and is presumed to have been infected from the natural reservoir at his charcoal pit or farm in Mwembe, 15 km from his residence in Kikwit. Ill persons from this family and secondary and tertiary cases in other families that provided nursing care and participated in the burial rituals of family members of this family were traced through the community and into Kikwit II Maternity Hospital, where a small nosocomial outbreak among 9 hospital employees started in the middle of March. The retrospective identification of GM and other individuals strongly supports our belief that many ''sporadic'' cases diagnosed as ''diarrhée rouge'' (bloody diarrhea or dysentery) before the recognition of the outbreak were actually EHF and part of a chain of transmission going back to the presumed primary case for the outbreak.

Besides the initial family cluster and other associated cases, EHF was already well established in Kikwit II maternity and Kikwit General Hospitals before the large nosocomial outbreak in Kikwit General Hospital. In fact, the main focus of the nosocomial outbreak in Kikwit General Hospital was patient WB, who was initially thought to have been infected by the transferred laboratory worker; however, WB appears to have been infected from a prior independent contact with an obstetric patient who had a febrile hemorrhagic disease. Similarly, an obstetric nurse at Kikwit General Hospital was initially thought to have been infected by the transferred laboratory worker; however, she had no contact with the technician and apparently contracted EHF from a nosocomially infected patient who had undergone a cesarean section at Kikwit II hospital and was subsequently admitted to Kikwit General Hospital.

Amplification and Time Course of the Epidemic

At least four generations of cases were traced through the hospital and into the community from the initial nosocomial cases in Kikwit General Hospital (figure 1). This periodicity of deaths has not been previously noted. The epidemic was interrupted coincident with the arrival of protective equipment and intensive training and education efforts. The beneficial effect of initiating barrier-nursing precautions in Kikwit General Hospital, the site designated for management of all suspect cases, was clearly evident: Only 1 health care worker developed disease after institution of preventive measures (8 days later; figure 2). All health care workers, except the 1 who became sick after institution of the extended personal protective measures, had previously provided care without these precautions and had become ill within an incubation period of their last unprotected contact with case-patients. The final infected health care provider had laboratory-confirmed infection 15 days after

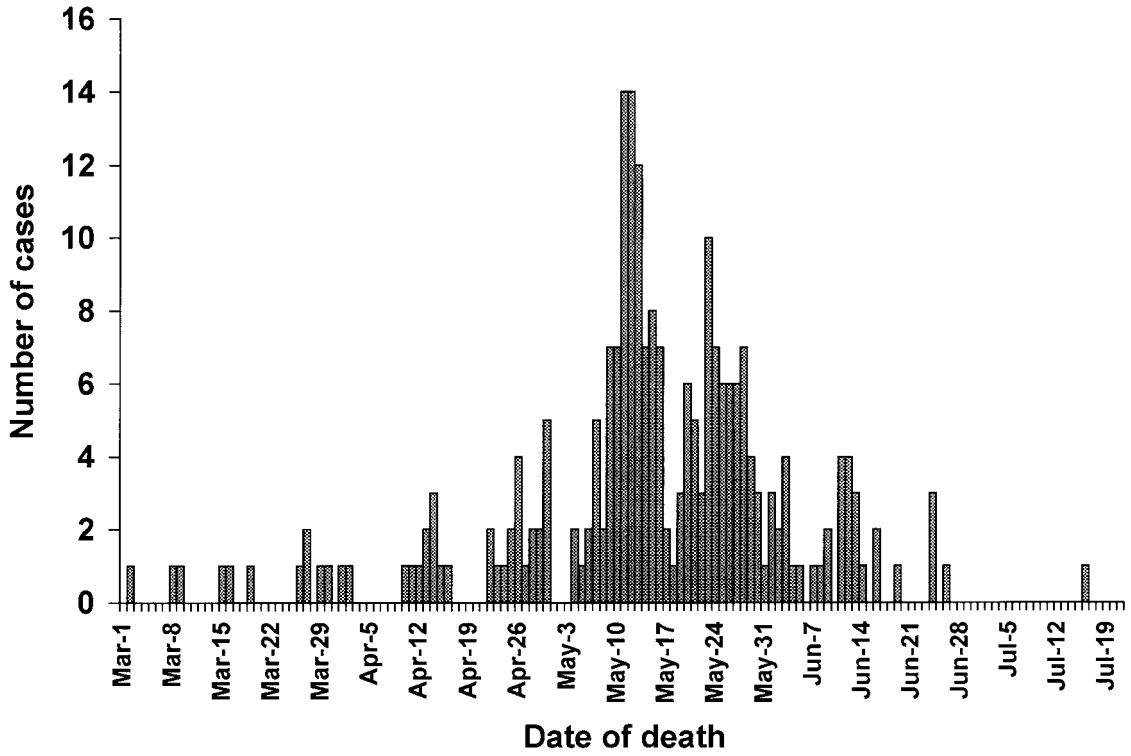

Figure 1. Fatal Ebola hemorrhagic fever cases by date of death, Bandundu region, Democratic Republic of the Congo, 1 March to 21 July 1995. Mar = March, Apr = April, Jun = June, Jul = July.

institution of these precautions. This provider tended 2 case-patients in a separate 2-room building and wore a disposable HEPA filter mask and eye protection in addition to gloves, gowns, and boots; however, she claimed to have inadvertently rubbed her eyes with soiled gloves. In addition, we could not exclude the possibility of an occult needle stick or otherwise assess adherence to all other infection-control precautions.

The last identified case was a 27-year-old housewife from Nzinda, Kikwit. She died at home on 16 July 1995, shortly after discharge from Kikwit II hospital, where she was hospitalized for management of a septic abortion. Her cadaver was brought to Kikwit II hospital on the day she died and was transferred to the morgue, where a postmortem biopsy specimen was obtained the next day and transported to CDC with other such samples on 27 August 1995. Her surveillance case-report form indicated that she had contact with a case-patient, and she had fever, headache, vomiting, anorexia, diarrhea, asthenia, abdominal pain, dyspnea, and melena. Additional history was unavailable at that time, but the diagnosis of EHF or septic shock was indicated on the form by the medical director of Kikwit II hospital. The postmortem sample was not flagged in any way to indicate that it was obtained from a patient with a highly suspicious clinical illness and was collected as part of the nonsystematic process by which access to corpses was provided after the presumptive last case. However, 13 family members of this individual were monitored for 21 days without subsequent disease as part of the follow-up surveillance for suspect deaths. EBO antigens were detected in this patient's tissue specimen by immunohistochemistry on 8 September 1995.

Case-Finding and Characteristics of Case-Patients

A total of 315 case-patients met the revised case definition for EHF; 314 had onset dates between 6 January and 20 June 1995, and the case-patient who died on 16 July (mentioned above) was retrospectively added to the final case count (figure 3). All case-patients for whom information was available resided within 3 administrative subregions of Bandundu region: Kikwit (262 cases), Kwilu (45 cases), and Kwango (1 case) (figure 4). This area represented 10 of 39 health zones encompassing ~30 affected villages, although 268 (87%) of the cases came from Kikwit, and 17 (6%) came from Mosango. These two towns were the principal foci of infection and source of secondary case-patients, some of whom went back to their villages and died without subsequent disease transmission. A major hospital located in Mosango (80 km west of Kikwit) admitted patients and was a site for subsequent nosocomial transmission of disease. All affected villages were within a 150-km radius of Kikwit. A single case-patient, who was infected in Kikwit, was hospitalized in Kinshasa, but no secondary transmission occurred despite the initial lack of barrier-nursing pre-

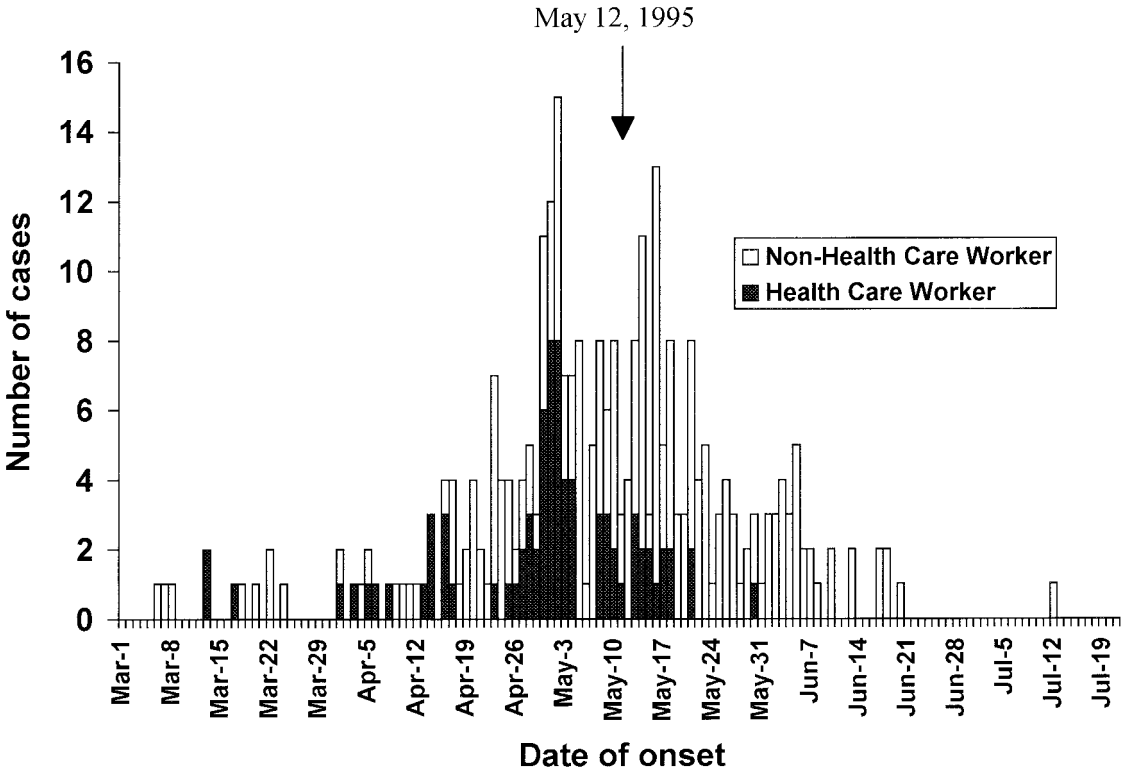

Figure 2. Ebola hemorrhagic fever cases by date of symptom onset and occupation, Bandundu region, Democratic Republic of the Congo, 1 March to 21 July 1995. Arrow indicates date of initiation of upgraded infection control practices. Mar = March, Apr = April, Jun = June, Jul = July.

cautions. No case-patient associated with this outbreak was identified outside DRC.

Of 310 case-patients for whom information was recorded, 165 (53%) were female. The average age of case-patients was 37.4 years (median, 37; range, 2 months to 71 years). Twenty-two case-patients (7.5%) were children or adolescents (≤16 years). Eighty (25%) of the 315 case-patients were health care workers. The overall case fatality was 81% (250/310). A linear decrease in mortality was noted from January (100%) to June (62%) (χ^2 for linear trend by month, $P < .0001$). A significant

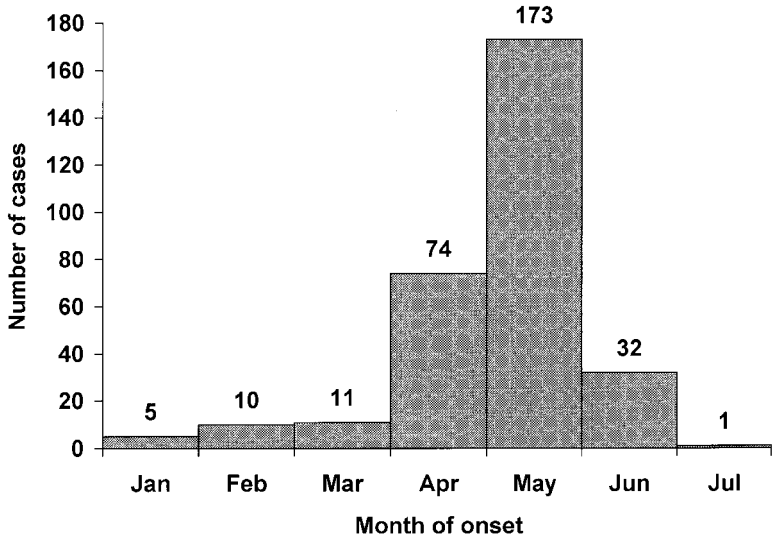

Figure 3. Ebola hemorrhagic fever cases by month of onset, Bandundu region, Democratic Republic of the Congo, January to July 1995. Month of onset could not be calculated for 9 case-patients. Jan = January, Feb = February, Mar = March, Apr = April, Jun = June, Jul = July.

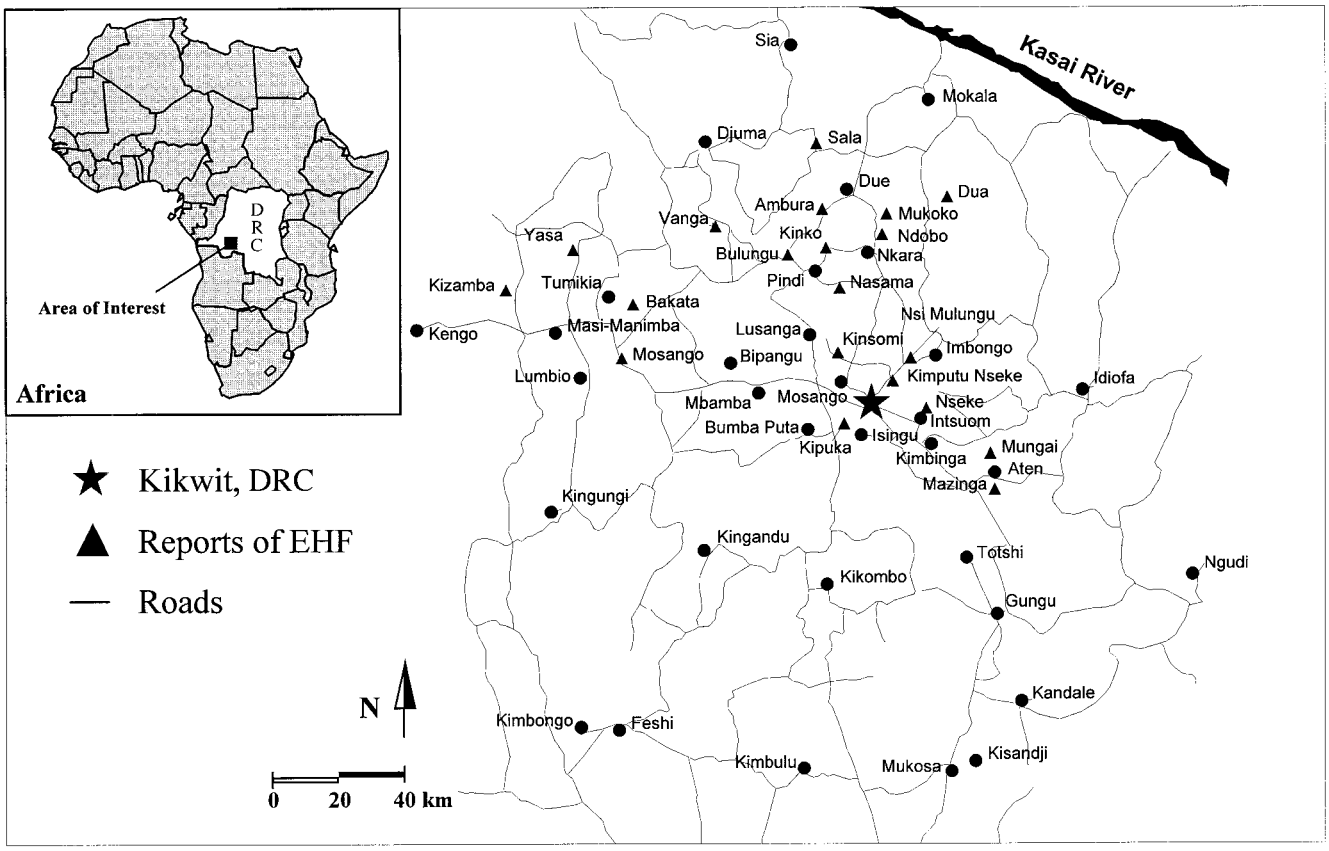

Figure 4. Geographic distribution of Ebola hemorrhagic fever cases, Bandundu region, Democratic Republic of the Congo (DRC), 1995. EHF = Ebola hemorrhagic fever.

difference in age was noted among survivors compared with nonsurvivors (32.8 vs. 38.5 years, respectively; $P \leq .01$). A crude onset-to-onset period based on an estimation in the mean difference in onset dates between a case-patient and the implicated source of infection was 14 days.

Hospitalization was noted for 80% (247/310) of case-patients. The mean number of days from onset to hospitalization for 219 patients was 5 days (median, 4; range, 0–19). There was a mean of 4.6 days (median, 4; range, 0–20) from hospitalization to death for 185 nonsurvivors for whom data were available. The mean number of days from hospitalization to discharge for 34 survivors for whom data were available was 17 (median, 14; range, 0–56), and the mean number of days from symptom onset to death for 224 patients was 9.6 (median, 9; range, 0–34). Reported signs and symptoms up to the time when the case-report form was completed (often on admission to the hospital but frequently covering the whole course of illness for retrospectively identified case-patients) are listed in table 1. Some form of frank hemorrhage (gingivorrhagia, melena, hematemesis, or petechiae) was reported for 37% (82/219) of case-patients; subconjunctival hemorrhage was excluded because this sign was often confused with conjunctivitis. Eight abortions were reported, 4 of which were concomitant with maternal fatality; however, these data were not collected systematically.

The field case definition was met by 318 persons, 92 of whom had samples collected for diagnostic testing. Laboratory testing was positive for EBO virus infection for 82 case-patients and negative for 10. Only 315 cases met the revised case definition because the 10 individuals with negative laboratory results were replaced by 7 case-patients, as indicated in the Methods section, with positive laboratory results and for whom clinical information was not available. The positive predictive value of the field-case definition was 89%. The high positive predictive value of the case definition used in the field is based mainly on laboratory confirmation during the second half of the outbreak because only 1 person with disease onset prior to 14 May 1995 had laboratory-confirmed infection. Moreover, because specimens were obtained mainly from survivors, we cannot exclude that this estimate may include a selection bias because of the large number of missing laboratory confirmations for case-patients who died; all the case-patients with laboratory-negative results were alive.

Prior contact with a suspected case-patient was reported by 93.5% (159/170) of case-patients for whom data were available. Eleven case-patients reported receiving an injection within 3

Table 1. Signs and symptoms recorded for 219 Ebola hemorrhagic fever case-patients, surveillance data, Democratic Republic of the Congo, 1995.

Sign or symptom	No. (%) with	No. without	Not recorded	Comment
Headache	160 (73)	57	2	
Nausea/vomiting	154 (70)	60	5	Not differentiated
Anorexia	159 (73)	57	3	
Diarrhea	162 (74)	53	4	
Asthenia	170 (78)	46	3	Severe weakness
Abdominal pain	123 (56)	89	7	
Myalgia/arthralgias	111 (51)	95	13	
Dysphagia	89 (41)	120	10	
Dyspnea	55 (25)	154	10	
Hiccups	32 (14)	95	92	
Gingival hemorrhage	46 (21)	162	11	
Conjunctival inflammation/hemorrhage	75 (34)	135	9	Not differentiated
Petechiae	33 (15)	175	11	Difficult to assess
Melena	30 (14)	178	11	
Hematemesis	28 (13)	182	9	

weeks of onset of symptoms (mean, 3 days; range, 1–6). An unexpected observation during this outbreak was the identification of 2 persons as a potential source of infection for ~20% of all the case-patients (figure 5). The first individual, designated as identification number (IDNUM) 3 (patient WB), was a 29-year-old man associated with 38 secondary cases, although 10 of these also reported other potential sources of infection. He was a popular anesthetist at Kikwit General Hospital who died with fulminant hemorrhagic disease at the end of April and had many visitors during his 8-day hospitalization. The second person, IDNUM 2260, was a 45-year-old woman who died of hemorrhagic disease at Kikwit II Maternity Hospital at the end of May with 21 case-patients among her contacts, none of whom reported other sources of infection. Conflicting details of her case history suggest that she was misdiagnosed with dysentery before her cadaver was turned over to the family. Although the disease was well recognized in the community, details to explain the large number of cases among her contacts are obscure; however, it appeared that most contacts occurred postmortem during her traditional funeral, which included washing and touching of the cadaver.

Discussion

The magnitude of this EHF outbreak in DRC after an 18-year hiatus dramatically confirms the potential of EBO virus to cause large outbreaks associated with high fatality. This was the first outbreak in a large population center in proximate location to the even larger population of Kinshasa, with its established intra- and intercontinental transportation links. The newly described waves of death in the Kikwit community may be a reflection of the density of this large population. The 3-month latency between occurrence of the first case in Kikwit, in January 1995, and recognition of the outbreak despite the presence of classic disease with clear chains of transmission, multiple hospitalizations, and a very high case fatality rate is disturbing. Equally disturbing was the initial misdiagnosis of dysentery, resulting in an additional 4- to 6-week delay before the correct diagnosis was considered and confirmed. This outbreak demonstrated once again the propensity for this disease to affect health care workers when proper barrier-nursing procedures are absent (25% of all cases were among health care providers), and it demonstrated the potential for this disease to be amplified in health care settings, even with little or no needle reuse. Moreover, we reaffirmed that education and the use of personal protective equipment can rapidly interrupt ongoing disease transmission. These features emphasize the necessity of rudimentary public health surveillance coupled with adherence to barrier-nursing precautions and infection-control practices, such as elimination of needle and syringe reuse or proper sterilization of these items between uses.

Experimental studies of nonhuman primates have been helpful in assessing the potential routes of transmission of EBO virus. Late in infection in monkeys, there are large amounts of virus in saliva, feces, and urine, and ultrastructural and immune electron microscopy examination of tissue from the respiratory tract of monkeys has shown virus replication in type 1 pneumocytes, with abundant, apparently infectious, virions in alveoli and bronchi [19–21]. EBO virus requires only 1–2 pfu of EBO virus must be retained in the alveoli to initiate a lethal infection in the African green monkey *(Cercopithecus aethiops),* and filoviruses are moderately stable in aerosol [19, 22]. Thus, it is not surprising that intercage transmission, suggesting mediation by small-particle aerosols, has been reported [23]. However, direct application of EBO virus onto conjunctiva and ingestion has resulted in fatal monkey disease; therefore, large-droplet dissemination may well be another mechanism for this observed intercage transmission [24].

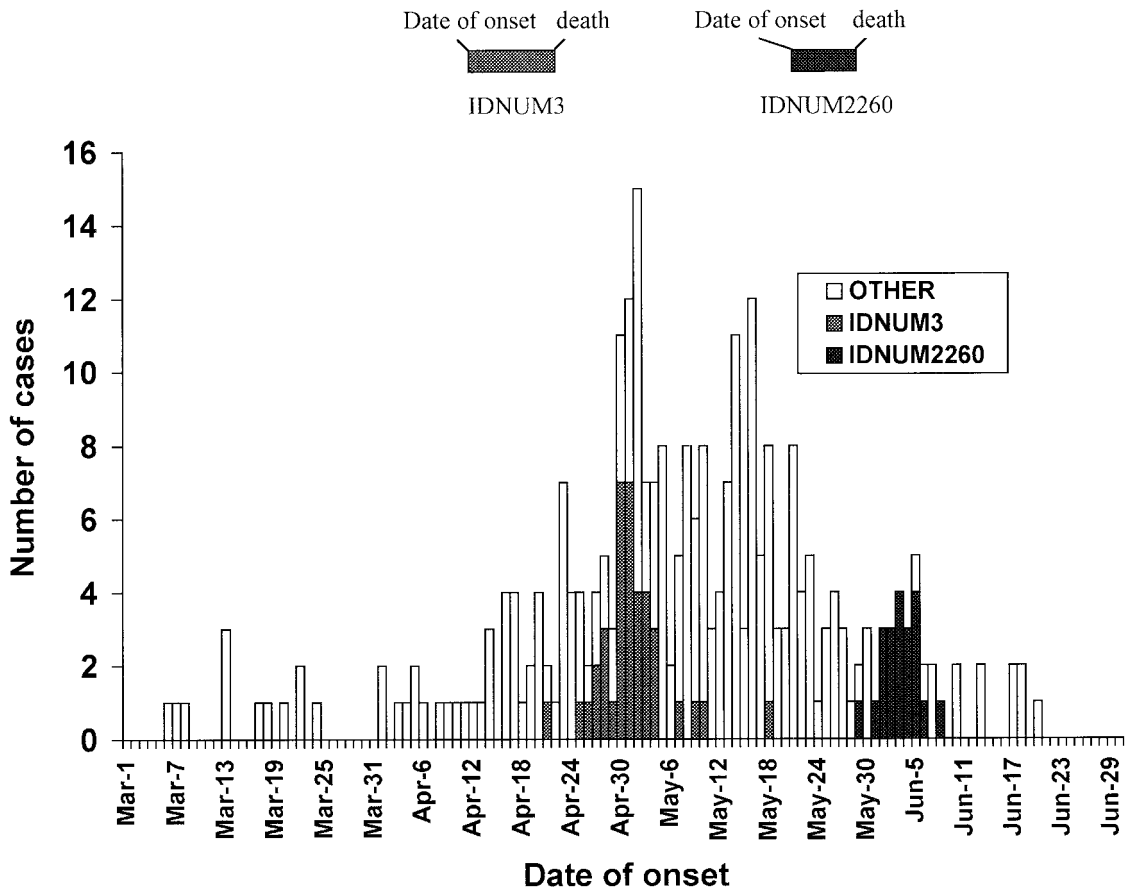

Figure 5. Ebola hemorrhagic fever cases by date of symptom onset and source of infection (patient IDNUM3 [identification no. 3], IDNUM2260, or other), Bandundu region, Democratic Republic of the Congo, 1 March to 30 June 1995. Shaded and black columns indicate period of illness, from onset to death, for IDNUM3 and IDNUM2260 and those infected by them. Mar = March, Apr = April, Jun = June.

The observed environmental stability of EBO virus (Swanepoel R, unpublished data, 1995) raises the possibility of fomites as a source of infection [22]. Recent evidence of a copious amount of viral antigen in skin and sometimes within the lumen of sweat glands, although its viability is unknown, suggests a potential mechanism for direct disease transmission through abraded skin or inoculation onto mucous membranes [16]. However, the barrier presented by intact skin is unknown. Direct observations in deceased EHF patients show the same abundant alveolar particles [17], but we have no way of knowing if this material is aerosolized, is stable in the aqueous milieu in which it is suspended [22], or is an equivalent infection for humans; thus, we must rely on field epidemiology to assess the influence of these multiple potential sources of transmission.

Field epidemiologic studies have found no human correlate for aerosol infection, and airborne transmission has not appeared to play a role in human-to-human transmission, except for possibly in a rare subset of patients. The preponderance of evidence during this outbreak suggests that EBO virus was once again transmitted between humans via direct contact or direct projection (droplet spread) of droplets onto mucous membranes and indirectly via fomites and body fluids. The periodicity of deaths implies that direct contact due to burial rituals, which included washing and touching the cadaver, may have played a role in disease transmission. The pattern of transmission of EHF from the infected person to the primary care provider and from that person to their primary care provider, without affecting household members who did not share nursing duties but who may have slept in the same room, further suggests that airborne transmission was an unlikely route of transmission and is consistent with similar observations during the 1976 EHF outbreaks [1, 2, 25].

A large number of case-patients identified 2 case-patients as their contacts, both of whom had gastrointestinal hemorrhaging. Although the number of contacts may have been biased by the reporting of an individual who was known to be a suspected case-patient and some reported secondary contacts, the sheer magnitude of the effect suggests that it is not artifactual. The concept of a ''super-spreader'' or ''high-frequency transmitter'' is novel for this viral hemorrhagic fever, and the mechanism for this high-frequency transmission is unknown. The large number of cases may simply have been a matter of

a larger number of contacts of these case-patients or some inherent differences in the virus-host relationship. These differences could include a more virulent virus strain or high levels of viral shedding; unfortunately, no samples are available from these case-patients. Enhanced transmission via a respiratory route (either small-particle aerosols or large droplets) is a remote possibility that is supported by the experimental data and evidence that a portion of experimentally inoculated animals are more likely to have alveolar disease. However, the onset dates of these secondary cases suggest that most of the contacts occurred during the course of a traditional funeral, when aerosols are unlikely to be generated. A similar increased risk for transmission of viral hemorrhagic fevers in a hospital setting has been reported for Lassa fever and Bolivian hemorrhagic fever [26, 27]. An analogous super-spreader concept has been recognized for rubella and group A streptococci in addition to others [28, 29].

Key determinants for secondary transmission of infection remain unknown. Although the paucity of children with this disease may be explained by shielding from contact with an ill family member, the lack of such secondary transmission in certain settings is inexplicable [30].

A large number of case-patients returned to their villages, yet no subsequent transmission was recorded in these settings. Similarly, many of the initial case-patients, including the primary case-patient for the outbreak, were hospitalized without evident nosocomial transmission. This was also true for the case-patient hospitalized in Kinshasa who had active mucosal bleeding and was admitted with little or no barrier-nursing precautions. This unexplained lack of secondary transmission is in contrast to the many family clusters of disease, in which 2–3 generations of secondary cases were documented. However, it further establishes that sporadic cases of unrecognized EHF may not be uncommon.

Since this outbreak, EHF has continued to be identified in Africa, including a case from Liberia that was not confirmed by virus isolation [31, 32]. A recent outbreak of EHF in the village of Mayibout 2, Makokou Health District, Ogooué-Ivindo region, near the site of the 1994 outbreak [33, 34], was linked to the butchering, transport, and preparation for consumption of a chimpanzee found dead in the forest on 22 January 1996. The total number of cases was 37 (20 males, 17 females), the mean age was 27 years (range, 7 months to 70 years), and the case fatality rate was 57%. Two generations of secondary cases were documented, and the outbreak terminated over a 7-week period. Most recently, there was a 7-month outbreak due to EBO (subtype Zaire) in Booué, Ogooué-Ivindo Province, Gabon, involving 60 cases (case fatality rate, 75%) associated with 8 generations of secondary cases and with secondary cases in the capital of Libreville [35–40]. In Johannesburg, South Africa, the death of a nurse who was nosocomially infected by a physician who was transferred for medical treatment from Libreville with unsuspected EHF was also linked to this outbreak [36]. These outbreaks continue to highlight the vulnerability of human populations to these infections, and they highlight the potential for further large outbreaks and the lack of information regarding the natural reservoir.

Although investigation of previous cases has helped to refine control measures, public health authorities remain unprepared to anticipate and prevent future large outbreaks. Prevention requires better definition of the epidemiologic features of these diseases by clarifying their geographic distribution, the spectrum of illness, and risk factors for both disease acquisition and transmission. Targeted serologic surveys using newly developed diagnostic assays that circumvent the specificity problems of older assays should also be done to define these issues. While recognizing that the general lack of facilities and infrastructure remains the paramount problem in dealing with this disease, we also need to provide ''field-friendly'' mechanisms prepositioned at regional sites for rapid identification of infected individuals to anticipate outbreaks. However, even with simpler diagnostic technology, it will never be possible to make a rapid field diagnosis in all locations, given the challenges imposed by a huge geographic area with spotty communication and transportation links to urban centers.

A feasible approach would be to continue uncoupling the use of local prevention activities from the occurrence of laboratory-confirmed diagnoses. All patients with suspected viral hemorrhagic fever should be considered to be sentinel events and managed according to generic accepted guidelines [41]. A kit comprising personal protective equipment assigned specifically for such patients and materials to collect specimens, with a set of guidelines on preventing disease transmission, can be distributed to remote locations [41]. Integration of this kit into national health care surveillance protocols (governmental and nongovernmental) should help prevent additional disease associated with suspected EBO patients, allow for laboratory confirmation of remote cases, and help anticipate ''hot spots'' on the basis of geographic or temporal clustering of confirmed cases.

Acknowledgments

This work is not a reflection of the relatively few individuals chosen to write the report nor the many other members of Commission de Lutte contre les Epidémies à Kikwit who were actively involved in characterizing and controlling this epidemic. It is a reflection of the hard work and dedication of the medical students, local officials, military personnel, Red Cross, Catholic Relief Services, Kikwit Diocese, and other concerned citizenry who educated the populace and helped gather the information that has been presented. We thank Ramses Sadek for assistance with statistics, Kent Wagoner for assistance with graphics, and John O'Connor and Claudia Chesley for editorial review of this manuscript.

References

1. International Commission. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ **1978**;56:271–93.

2. WHO/International Study Team. Ebola haemorrhagic fever in Sudan, 1976. Bull World Health Organ **1978**;56:247–70.
3. Sanchez A, Trappier SG, Mahy BWJ, Peters CJ, Nichol ST. The virion glycoproteins of Ebola viruses are encoded in two reading frames and are expressed through transcriptional editing. Proc Natl Acad Sci USA **1996**;93:3602–7.
4. Emond RTD, Evans B, Bowen ETW, Lloyd G. A case of Ebola virus infection. Br Med J **1977**;2:541–4.
5. Heymann DL, Weisfeld JS, Webb PA, et al. Ebola hemorrhagic fever: Tandala, Zaire, 1977–1978. J Infect Dis **1980**;142:372–6.
6. Baron RC, McCormick JB, Zubeir OA. Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread. Bull World Health Organ **1983**;61:997–1003.
7. Le Guenno B, Formenty P, Wyers M, Gounon P, Walker F, Boesch C. Isolation and partial characterization of a new strain of Ebola virus. Lancet **1995**;345:1271–4.
8. CDC. Ebola virus infection in imported primates—Virginia, 1989. MMWR Morb Mortal Wkly Rep **1989**;38:831–2, 837–8.
9. Dalgard DW, Hardy RJ, Pearson SL, et al. Combined simian hemorrhagic fever and Ebola virus infection in cynomolgus monkeys. Lab Animal Sci **1992**;42:152–7.
10. Jahrling PB, Geisbert TW, Dalgard DW, et al. Preliminary report: isolation of Ebola virus from monkeys imported to USA. Lancet **1990**;335:502–5.
11. Amblard J, Obiang P, Edzang S, Prehaud C, Bouloy M, LeGuenno B. Identification of the Ebola virus in Gabon in 1994 [letter]. Lancet **1997**;349:181–2.
12. CDC. Outbreak of Ebola hemorrhagic fever—Zaire, 1995. MMWR Morb Mortal Wkly Rep **1995**;44:381–2.
13. CDC. Update: outbreak of Ebola hemorrhagic fever—Zaire, 1995. MMWR Morb Mortal Wkly Rep **1995**;44:399.
14. CDC. Update: outbreak of Ebola hemorrhagic fever—Zaire, 1995. MMWR Morb Mortal Wkly Rep **1995**;44:468–9, 475.
15. Muyembe T, Kipasa M, International Scientific and Technical Committee, WHO Collaborating Centre for Haemorrhagic Fevers. Ebola haemorrhagic fever in Kikwit, Zaire [letter]. Lancet **1995**;345:1448.
16. Zaki SR, Shieh WJ, Greer P, et. al. A novel immunohistochemical assay for detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. J Infect Dis **1999**;179(suppl 1):S36–47.
17. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1995**;70:241–2.
18. Lehmann EL. Nonparametrics: statistical methods based on ranks. San Francisco: Holden-Day, **1975**.
19. Bazhutin NB, Belanov EF, Spiridonov VA, et al. The effects of the methods for producing an experimental Marburg virus infection on the characteristics of the course of illness in green monkeys. Vopr Virusol **1992**;37:153–6.
20. Jahrling PB, Geisbert TW, Jaax NK, Hanes MA, Ksiazek TG, Peters CJ. Experimental infection of cynomolgus macaques with Ebola-Reston filoviruses from the 1989–1990 US epizootic. Arch Virol **1996**;11(suppl):115–34.
21. Johnson E, Jaax N, White J, Jahrling P. Lethal experimental infections of rhesus monkeys by aerosolized Ebola virus. Int J Exp Pathol **1995**;76:227–36.
22. Cheprunov AA, Chuev YP, P'yankov OV, Efimova IV. Effects of some physical and chemical factors of inactivation of Ebola virus. Vopr Virusol **1995**;2:74–6.
23. Jaax N, Jahrling P, Geisbert T, et al. Transmission of Ebola virus (Zaire strain) to uninfected control monkeys in a biocontainment laboratory. Lancet **1995**;346:1669–71.
24. Jaax NK, Davis KJ, Geisbert TJ, et al. Lethal experimental infection of rhesus monkeys with Ebola-Zaire (Mayinga) virus by the oral and conjunctival route of exposure. Arch Pathol Lab Med **1996**;120:140–55.
25. Dowell SF, Mukunu R, Ksiazek TG, et al. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis **1999**;179(suppl 1)S87–91.
26. Carey DE, Kemp GE, White HA, et al. Lassa fever. Epidemiologic aspects of the 1970 epidemic, Jos, Nigeria. Trans R Soc Trop Med Hyg **1972**;66:402–8.
27. Peters CJ, Kuehne RW, Mercado RR, Le Bow RH, Spertzel RO, Webb PA. Hemorrhagic fever in Cochabamba, Bolivia, 1971. Am J Epidemiol **1974**;99:425–33.
28. Hattis RP, Halstead SB, Hermann KL, Witte JJ. Rubella in an immunized island population. JAMA **1973**;223:1010–21.
29. Hamburger M Jr, Green MJ, Hamburger VG. The problem of the ''dangerous carrier'' of hemolytic streptococci. II. Spread of infection by individuals with strongly positive nose cultures who expelled large numbers of hemolytic streptococci. J Infect Dis **1945**;77:96–108.
30. Dowell S. Ebola hemorrhagic fever: why were children spared? Pediatr Infect Dis J **1996**;15:189–91.
31. WHO. Ebola haemorrhagic fever—confirmed case in Côte d'Ivoire and suspect cases in Liberia. Wkly Epidemiol Rec **1995**;70:359.
32. Georges-Courbot MC, Sanchez A, Lu CY, et al. Isolation and phylogenetic characterization of Ebola viruses causing different outbreaks in Gabon. Emerg Infect Dis **1997**;1:59–62.
33. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1996**;71:71.
34. WHO. Outbreak of haemorrhagic fever in Gabon officially declared over. Wkly Epidemiol Rec **1996**;71:125–6.
35. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1996**;71:320.
36. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1996**;71:359.
37. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1996**;71:366.
38. WHO. Ebola haemorrhagic fever—a summary of the outbreak in Gabon. Wkly Epidemiol Rec **1997**;72:7–8.
39. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1997**;72:23–4.
40. WHO. Ebola haemorrhagic fever. Wkly Epidemiol Rec **1997**;72:71.
41. Lloyd ES, Zaki SR, Rollin PE, et al. Long-term disease surveillance in Bandundu region, Democratic Republic of the Congo: a model for early detection and prevention of Ebola hemorrhagic fever. J Infect Dis **1999**;179(suppl 1)S275–80.