Ebola Hemorrhagic Fever, Kikwit, Democratic Republic of the Congo, 1995: Risk Factors for Patients without a Reported Exposure

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In 1995, 316 people became ill with Ebola hemorrhagic fever (EHF) in Kikwit, Democratic Republic of the Congo. The exposure source was not reported for 55 patients (17%) at the start of this investigation, and it remained unknown for 12 patients after extensive epidemiologic evaluation. Both admission to a hospital and visiting a person with fever and bleeding were risk factors associated with infection. Nineteen patients appeared to have been exposed while visiting someone with suspected EHF, although they did not provide care. Fourteen of the 19 reported touching the patient with suspected EHF; 5 reported that they had no physical contact. Although close contact while caring for an infected person was probably the major route of transmission in this and previous EHF outbreaks, the virus may have been transmitted by touch, droplet, airborne particle, or fomite; thus, expansion of the use of barrier techniques to include casual contacts might prevent or mitigate future epidemics.

In 1995, 316 people became ill with Ebola (EBO) hemorrhagic fever (EHF) in Kikwit, Democratic Republic of the Congo (DRC). Prior to this, only three major outbreaks of EHF had been reported to the international medical community. The first two outbreaks occurred in 1976, when concurrent epidemics caused by 2 distinct virus subtypes [1–4] were reported in northern DRC (318 cases; case-fatality rate, 88%) [5] and the southern Sudanese towns of Maridi and Nzara (284 cases; case-fatality rate, 53%) [6]. In 1979, a smaller (n = 34) EHF outbreak recurred in Nzara [7]. Isolated reports of EHF were subsequently noted in DRC (1977, 4 cases) and Côte d'Ivoire (1994, 1 case) [8, 9]. In these outbreaks, provision of nursing care by health workers and household members was a risk factor for infection, as were working in a specific cotton factory, admission to a hospital, receipt of an injection, and assistance during birth by an infected woman [10].

Epidemiologists identified primary cases (the person who introduced the disease into the family or group under study [11]) in all of the outbreaks noted above. However, the source of infection (reservoir), mode of transmission, and risk factors associated with infection in patients with primary cases could not be determined. In all but the 1976 Nazara outbreak, field studies of patients with secondary cases established either evidence of contact with an EHF-infected person or another risk factor for infection in patients without such contacts. The likely spread of infection in the community could therefore be traced, and the entire epidemic attributed to the patient with the primary case. In the 1976 Nzara outbreak, investigators were unable to document contact with an infected person or any other previously identified risk factor for 14 patients (21%) [6]. Similarly, in Kikwit, 55 (17%) of the 316 persons with likely EHF had no reported contact with another infected person during an initial assessment. These 55 individuals were the focus of a detailed epidemiologic investigation conducted to determine if a source of exposure could be found when systematic investigation procedures were followed; if social customs, occupational activities, or dietary habits might explain infection in patients for whom no source of infection was identified; and if specific risk factors for transmission existed among patients for whom an exposure source was identified.

Methods

During the 1995 Kikwit outbreak of EHF, surveillance to identify cases included the following passive and active components [12]: centralized death registry, retrospective and prospective review of clinic and hospital records, door-to-door case finding, and rumor registry (i.e., hearsay evidence of persons who had symptoms compatible with EHF).

All cases identified via these methods were initially investigated by interviewers using a short, standard questionnaire that catego-

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rized cases into those with or without a reported source of exposure as determined by a history of physical contact with an infected person.

A probable case of EHF was defined as an illness characterized by the following signs and symptoms in a resident of or visitor to the Bandundu region of DRC between January and August 1995: fever and unexplained hemorrhage (e.g., gingival bleeding, subconjunctival bleeding, petechia, purpura, melena, and hematemesis); or fever and previous contact with another EHF infected person; or fever accompanied by (any three) headache, nausea, vomiting, anorexia, intense fatigue, abdominal pain, myalgia, arthralgia, dysphagia, dyspnea, or hiccups.

A confirmed case of EHF was defined by the detection of EBO antigen or antibody, using ELISA, or the detection of viral RNA, using reverse transcription–polymerase chain reaction in a person who had signs or symptoms suggestive of EHF [13, 14].

These surveillance case definitions were used to screen eligible participants for this study; only those patients without a reported source of exposure were included. If a patient was deceased, a household member or a close relative was interviewed about the patient. These surrogates were chosen using a hierarchical preference system. The first surrogates chosen were individuals residing in the same household (i.e., sharing the same cooking fire) and who knew the patient well (e.g., the deceased patient's spouse or oldest child). Next, individuals from a different household who knew the patient well (e.g., the deceased patient's parents or grandparents) were chosen. The last surrogates chosen were individuals residing on the same parcel of land as the patient (e.g., the deceased patient's landlord or closest neighbor).

After each patient (or surrogate) interview, sex- and age-matched ($\pm$10 years) control subjects were sought, using a systematic selection process. Three control subjects were selected for each patient enrolled in the study: 1 family control and 2 neighborhood controls. A family control was defined as a person who resided in the same household as the patient and had not had signs or symptoms suggestive of EHF between 1 January 1995 and the interview date. Because some families had many members who had died during the epidemic, it was not always possible to designate an individual of the same sex and age group to serve as the household control. Therefore, we developed a hierarchical system of identifying family controls. First, we looked for an individual of the same sex and within 10 years of the patient's age. If there were no family members that fit those criteria, we looked for an individual of the opposite sex and within 10 years of the patient's age. If that failed, we looked for an individual of the same sex and $>$10 years older or younger than the patient, and last, we looked for an individual of the opposite sex and $>$10 years older or younger than the patient.

Neighborhood controls were selected from among those persons who resided at least 5 houses away from patients to ensure that neighbors were from the same area but did not share the same cooking fire as the patient. In an effort to exclude control subjects who may have been infected with EHF between 1 January 1995 and the time of the interview, all potential control participants were screened using a structured questionnaire; those with signs and symptoms suggestive of EHF during this period were offered serologic testing to confirm or exclude the diagnosis, but they were not enrolled in the study.

Interviews of patients and control subjects were identical in format, order, and content. In addition to demographic information, the survey included questions regarding potential risk factors for infection, dietary habits, social customs, and occupational activities during the 3 weeks before onset of illness in patients and the same 3-week interval for matched control subjects. The potential risk factors for transmission of EHF that were evaluated in the interview included admission to a hospital for a preceding illness, receipt of an injection, working in a health care facility, attending a funeral, preparing a body for burial, visiting a friend with fever and bleeding, and physical contact outside the home (e.g., market, workplace) with a person who had fever and bleeding.

Univariate crude conditional maximum likelihood estimates of odds ratios (OR) and exact 95% confidence intervals (CI) were determined for each potential risk factor, using Epi Info software (version 6.02; USD, Stone Mountain, GA). For the multivariate analyses in this matched case-control study, exact conditional logistic regression (LogXact; Cytel Software, Cambridge, MA) was used. A multivariate model was constructed, which included univariate analysis risk factors with a significance level of $P \leq .05$. Interactions between variables were explored; the effect measures were not significant. The backwards stepwise elimination procedure was applied.

Results

On the basis of a review of all initial surveillance information, 55 of 316 patients had no reported source of exposure at the beginning of the investigation. Interviews were conducted with 44 (80%) of the 55 eligible patients (8 patients could not be located, and 3 refused to participate). Four patients had survived the illness and were able to participate in the survey. Surrogates provided information for the remaining 40 patients (91%). Serum specimens were obtained from 11 patients (25%); all were positive for EBO virus. The mean ages of the 44 patients and 132 control subjects was 37 years. Eighteen patients (41%) and 72 control subjects (55%) were female ($P = .2$).

In-depth interviews identified potential risk factors for 32 (73%) of the 44 patients. Seven risk factors were statistically significant by univariate matched analysis (table 1). After we applied a multivariate logistic regression, two risk factors remained statistically significant in the final model: hospitalization for an unrelated illness before onset of EHF and visiting a person with fever and bleeding.

Fifteen (35%) of 43 patients (1/43 did not provide a response) reported admission to a health care center for an unrelated illness during the 3 weeks preceding onset of EHF; 7 (5%) of 132 control subjects reported hospital admission during the same time period (matched OR = 12; 95% CI = 2.7–76.8). At least 7 of the 15 patients had been admitted to Kikwit General Hospital (the major community hospital) for the previous illness, the first on 28 April 1995. The diagnoses at the time of hospital admission included malaria, tuberculosis, gastrointestinal disorders, and pregnancy-related complications.

Table 1. Matched odds ratios (crude) of univariate analysis of a matched case-control (1:3) study comparing risk factors for infection in 44 patients without reported source of exposure to Ebola virus at the start of this investigation and 132 controls during the Ebola hemorrhagic fever (EHF) outbreak (Kikwit, Democratic Republic of the Congo, 1995).

Risk factor for infection	No. of patients with risk factor	No. of control subjects with risk factor	Matched odds ratio (crude)	95% confidence interval
Admission to hospital	15	7	9.9	3.1–41
Receipt of injection*	10	1	30.0	4.3–1302
Visit to ill friend†	23	11	10.6	3.8–36.3
Attended a funeral	17	25	3.0	1.2–7.6
Prepared a cadaver for burial	5	2	13.1	1.4–631
Physical contact with ill person at work or market†	8	1	24.0	3.2–1065
Health care worker	6	2	9.0	1.6–91.2

NOTE. All risk factors pertain to 3-week interval before onset of EHF in patients and same period for matched controls.

* 9 received injection during hospitalization; 1 as outpatient.

† Ill with fever and bleeding.

Nine patients (60%) were reported to have received an injection during their hospitalization.

The second independent risk factor for infection was visiting a person with fever and bleeding during the 3-week period before onset of EHF. Twenty-three (58%) of 40 patients and 11 (8%) of 131 control subjects were reported to have visited a friend or relative with fever and bleeding during the 3 weeks preceding onset of EHF (matched OR = 10; 95% CI = 3.2–38.9); information was not available for 4 patients and 1 control. The matched design of the study precluded analysis of other potential risk factors related to the visit (the few [11] control subjects who reported visiting a sick friend were not matched to patients who reported similar visits).

The probable source of exposure was identified for 32 (73%) of the 44 patients. Seventeen had visited an ill friend or relative with symptoms suggestive of EHF, 9 had been admitted to a health center in the 3 weeks preceding onset of EHF symptoms, and 6 had both risk factors. Of the 23 who had visited an ill friend or relative with symptoms suggestive of EHF, 4 (17%) resided in the same household as the ill patient and were their caregivers, 14 reported touching the ill patient, and 5 visited without touching the patient.

Information regarding the 12 patients who did not have a reported source of exposure and their matched controls was used to explore the role of social customs, occupational activities, and dietary habits in the acquisition of EHF infection (table 2). The univariate analysis did not identify any specific custom, occupation, or dietary factor that significantly increased the risk of infection. Although these 12 patients lacked serologic confirmation of EBO infection, their median age and duration of illness prior to death did not differ substantially from those of patients who had virologically confirmed EHF (table 3), and their high mortality rate was consistent with rates reported in previous outbreaks of infection with the Zaire subtype of EBO.

Figure 1 (epidemic curve) depicts the epidemic by week of onset for the 273 patients for whom date of onset and information on exposure source was available. Dates of illness onset were available for 11 of the 12 patients who had an unknown source of exposure; no clustering was observed.

Discussion

The 1995 Kikwit epidemic was the fourth major outbreak of EHF reported and the first to occur in a large population center. At the start of this investigation, 55 patients did not have a reported source of exposure to EHF; at the end, only 12 patients had no reported source. Among these 12 patients, no behavioral, occupational, or dietary activity was associated with illness. Transmission via inanimate objects (e.g., patient clothing, food utensils) was not implicated in this epidemic and has never been proven in previous investigations.

Admission to a health care center for an illness during the 3 weeks preceding onset of EHF was a statistically significant risk factor for infection during the outbreak. It was not possible to identify individual risk factors during hospitalization or determine the exact mode of transmission within Kikwit hospitals, primarily because of the numerous opportunities for disease transmission in open, crowded wards and outpatient clinics (e.g., direct or indirect contact with other sick patients or nursing staff, bedpans, soiled linen or clothing, and contaminated equipment). Although indirect transmission of EBO virus via reuse of nonsterile needles and syringes was a major route of transmission during the EHF outbreak in DRC in 1976 [5], this study did not identify receipt of an injection as an independent risk factor.

Table 2. Results of a matched case-control (1:3) study comparing social customs, occupational activities, and dietary habits in 12 patients without identified source of exposure to Ebola hemorrhagic fever (EHF) at study completion and their matched controls (Kikwit, Democratic Republic of the Congo, 1995).

Activity	Patients who took part in activity	Control subjects who took part in activity	Matched odds ratio (crude)	95% confidence interval
Social custom				
Attending special rituals	5	19	0.8	0.2–3.2
Traveling outside Kikwit	2	2	3.0	0.2–41.4
Taking medication	7	14	2.0	0.5–9.8
Frequenting markets	6	17	1.1	0.3–4.5
Occupational activity				
Working in forest	6	14	1.3	0.4–6.0
Fishing	1	1	3.0	0.04–235
Collecting insects	1	0	—*	†
Making charcoal	1	0	—*	†
Dietary habit				
Eating insects	9	25	1.4	0.3–6.7
Eating raw eggs	0	3	—*	†
Eating monkey meat	0	1	—*	†
Drinking special beverages	5	17	0.8	0.2–3.1

NOTE. All variables pertain to 3-week interval before onset of EHF in patients and same period for matched controls. Only partial list of social customs, occupational activities, and dietary habits is shown.

* Matched odds ratio undefined.

† $P > .05$.

The main transmission route of EBO virus is believed to be direct or indirect inoculation of mucous membranes. In Kikwit, as in previous outbreaks, it was customary for a close family member or friend to serve as a caregiver, that is, to clean, feed, and assist the patient both at home and in the hospital. Before recognition of EBO virus as the cause of this outbreak, care was administered without precautions to prevent exposure to infected blood, vomitus, urine, or stool. Almost inevitably, caregivers, particularly spouses of patients, became infected with the virus [15].

Of the 23 patients in our study who were subsequently determined to have had previous exposure to a case of EHF, 19 had merely visited another patient with EHF and were not involved in patient care. None reportedly had any contact with patient blood, feces, vomitus, urine, or saliva, although 14 reported touching a patient with EHF. Recent immunohistochemical examination of skin biopsy specimens from patients with EHF has demonstrated viral antigens in skin and sweat glands [16], supporting the hypothesis that EHF may have been transmitted to these individuals in Kikwit (and others in previous outbreaks) by brief, unnoticed, superficial contact with EHF-infected persons.

Table 3. Characteristics of 74 patients with virologically confirmed infection with Ebola hemorrhagic fever (EHF) and 12 patients without identified source for exposure to EHF at study completion (Kikwit, Democratic Republic of the Congo, 1995).

Characteristic	Virologically confirmed cases ($n = 74$)	Patients without a reported source ($n = 12$)
Laboratory confirmed infection	74	0
Median age, years	39	41
Median duration, days, between onset of symptoms and death (range)	10 (3–21)	8 (4–15)
Mortality (%)	37 (54)*	10 (83)
Male (%)	34 (46)	9 (75)
Health care worker (%)	24 (32)	0

* Outcome was unknown for 5 patients.

The transmission mode in the 5 patients who became infected without any physical contact remains enigmatic. However, animal experiments have documented transmission of EBO virus via noncontact routes. For example, both guinea pigs and monkeys have been infected experimentally with EBO virus by direct installation of drops into the eye and throat [17]. Transmission of EBO virus from experimentally infected monkeys to control monkeys in separate cages has also been documented [18]. Furthermore, airborne spread was suggested during the EBO epizootic outbreak in Reston, Virginia [19, 20, 21]. In a review, Peters et al. [22] concluded that although the major mode of interhuman transmission of hemorrhagic fevers is direct contact, transmission via large droplets, aerosolized particles, or fomites cannot be excluded. This may explain the mode of transmission in the 5 patients without reported physical contact.

Our investigation had several limitations. First, the team frequently had to rely on surrogates to provide answers for patients who had died. Responses by surrogates describing the

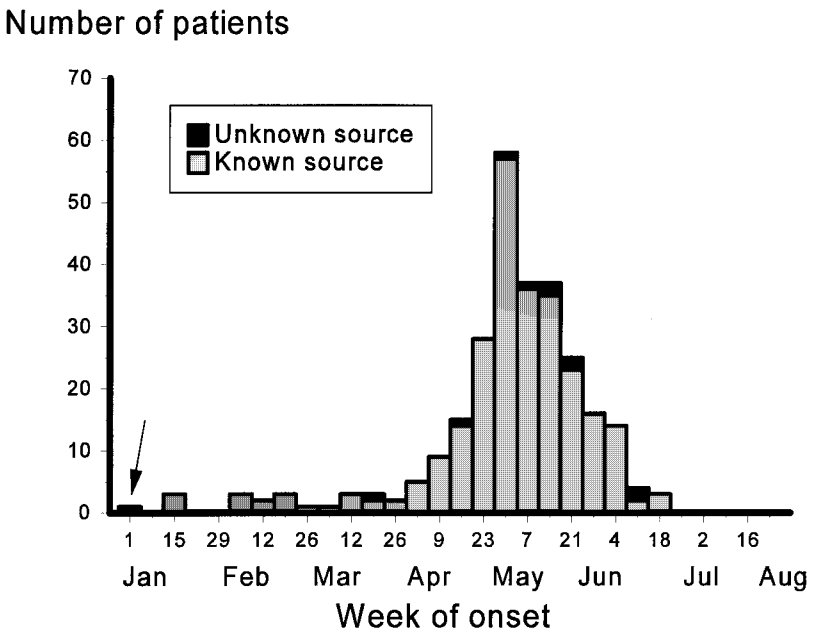

Figure 1. Onset date of Ebola hemorrhagic fever in 273 patients, by known source of exposure to infection (Kikwit, Democratic Republic of the Congo, 1995). Onset date was missing for 32 patients, and source was not assessed for 11 (3 refused to participate, 8 could not be located).

type of contact between deceased patients and ill persons visited by the patient may have been inaccurate, particularly if the surrogate had not accompanied the patient. Second, the interviewers may have been more aggressive in attempting to establish potential contacts or risk factors for patients than for control subjects. Third, although serologic confirmation of all cases would have been preferable, only 11 of 44 cases provided sera for confirmation. Fourth, the interval between the period of interest and the date of the interview was long and may have resulted in inaccuracies. Fifth, our matched design made it impossible to identify specific risk factors during hospitalization or during a visit to a sick person.

In conclusion, we identified an exposure source for 32 of 44 patients for whom no source was originally reported. Of the 12 patients who did not have an identified exposure source, no sociologic, occupational, or dietary risk factors for illness were found. Direct person-to-person contact was the likely mode of transmission for most EHF cases during this outbreak. However, our findings suggest that other EHF transmission modes cannot be excluded and may account for infection in those individuals for whom no previously recognized mode of transmission could be documented.

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