Transmission of Ebola Hemorrhagic Fever: A Study of Risk Factors in Family Members, Kikwit, Democratic Republic of the Congo, 1995

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The surviving members of 27 households in which someone had been infected with Ebola virus were interviewed in order to define the modes of transmission of Ebola hemorrhagic fever (EHF). Of 173 household contacts of the primary cases, 28 (16%) developed EHF. All secondary cases had direct physical contact with the ill person (rate ratio [RR], undefined; $P < .001$), and among those with direct contact, exposure to body fluids conferred additional risk (RR, 3.6; 95% confidence interval [CI], 1.9–6.8). After adjusting for direct contact and exposure to body fluids, adult family members, those who touched the cadaver, and those who were exposed during the late hospital phase were at additional risk. None of the 78 household members who had no physical contact with the case during the clinical illness were infected (upper 95% CI, 4%). EHF is transmitted principally by direct physical contact with an ill person or their body fluids during the later stages of illness.

Ebola (EBO) and Marburg viruses make up the family Filoviridae, which are named for their string-like appearance, which is visible by use of electron microscopy [1]. EBO virus was first discovered in 1976 during concurrent outbreaks in the Democratic Republic of the Congo (DRC) and Sudan; the outbreaks involved >550 persons and resulted in 430 deaths [2, 3]. EBO reappeared in 1979 in Sudan, with 34 cases and 22 deaths [4]. Since then, there have been only a handful of human cases, although there have been several outbreaks among monkeys kept in animal facilities [5]. After an incubation period of ~7 days, the early clinical features of infection with the Zaire subtype of EBO (EBO-Z) appear, including fever, headache, sore throat, diarrhea, and myalgias, followed by vomiting, worsening diarrhea, oliguria, shock, and death after 7–14 days [3].

Investigation of these few outbreaks permitted general conclusions about the modes of transmission, but it was not possible to quantify the risks associated with specific activities, such as sharing meals, patient care, physical contact, contact with body fluids, funeral practices, exposures to fomites, or airborne spread. In the 1976 outbreak in Yambuku, DRC, much of the transmission was attributed to the reuse of contaminated needles, and the closure of Yambuku Mission Hospital was believed to be the most important event leading to control of the outbreak [3]. Person-to-person transmission certainly occurred in the outbreaks in Sudan and DRC, with secondary attack rates among household contacts of 10%–20% [2–4], and spouses and those who provided nursing care were noted to be at higher risk [3, 4].

Whether EBO virus can be transmitted by airborne routes has been an important concern. In a 1989 outbreak in a monkey facility in Reston, Virginia, animals in nonadjoining cages and previously uninvolved rooms were infected with EBO, subtype Reston, lending some empiric support to the theoretical possibility of aerosol transmission, at least for this subtype [6, 7]. However, there were few cases in DRC or Sudan without direct exposure to another case; therefore, airborne spread likely played a minor role, if any, in these outbreaks [4].

The three human outbreaks terminated abruptly, coincident with implementation of barrier control measures, such as wearing gloves during patient contact and careful disposal of cadavers.

On 11 May 1995, an international team responded to a request from the government of DRC for assistance in the investigation of an outbreak of viral hemorrhagic fever in the town of Kikwit. The death of a laboratory technician at Kikwit General Hospital after a febrile illness with hemorrhagic signs, was followed by the illness and deaths of dozens of other hospital workers and their family members [8]. Retrospectively, it became apparent that transmission of EBO had been occurring in Kikwit since January 1995. Specimens from 14 patients were tested at the Centers for Disease Control and Prevention (Atlanta) and were confirmed positive for EBO-Z on May 9. Within days of the arrival of the international team, strict barrier precautions were being instituted in the hospital and community to prevent further spread of the virus. This investigation focuses on modes of transmission in those families with a member whose illness occurred prior to the institution of these barrier precautions.

Methods

Description of the town and hospital. Kikwit is a sprawling inland town of 200,000 people, which is served by several

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health facilities, including two hospitals. Kikwit General Hospital is the largest, with 350 beds in six free-standing wards. As in much of Africa, the families of inpatients are responsible for providing food and many other aspects of patient care, such as cleaning bedpans and washing soiled clothing and linens. Often, family members arrange to sleep on the hospital ward to ensure continued care through the night.

Study design and definitions. The study had a cross-sectional design, in which all households whose primary case died or was discharged from the hospital between 1 January and 7 May 1995 were eligible. Households with a primary case were identified through contacts of known cases, hospital record review, and intensive active surveillance throughout the town of Kikwit and the surrounding region. Interviews of remaining family members were conducted between 17 May and 3 June 1995. These household members were interviewed about exposures to family members who met the EBO hemorrhagic fever (EHF) case definition, and the proportion with secondary infection was compared among those with and without various risk factors.

The household was defined as all those who shared the same cooking fire at the onset of illness in the primary household case. A primary case was the first household member who met the EHF case definition. Secondary household cases were all those who subsequently met the EHF case definition. EHF was defined as new onset of fever after 1 January 1995 accompanied by either hemorrhagic signs (hematemesis, hematochezia, epistaxis, hematuria, or purpura) or three or more of the following signs or symptoms: severe weakness, nausea or vomiting, diarrhea, abdominal pain, myalgias or arthralgias, dysphagia, dyspnea, or hiccup. Contact with body fluids included touching or washing any clothes or linens visibly soiled with blood, urine, or stool.

Households were excluded if there was the possibility of ongoing transmission (considered possible if a household member had died or been discharged from hospital with EHF within the 14 days prior to the interview).

Interviews. All available remaining household members were interviewed at home by 1 interviewing team using a standardized questionnaire. Questions were read in French by 1 of the investigators (S.F.D. or R.M.) and translated into the local language, Kikongo. After the name of each household member was recorded along with their relationship to the primary household case and whether they had experienced an illness that met the EHF definition, the group as a whole was questioned about details of exposure for each household member; answers were often established by consensus.

The questionnaire included a section on general characteristics of the household, as well as clinical features of the primary household case and any secondary household cases. Details of the exposures of each household member to the ill persons were requested in turn. These detailed exposure questions were repeated for four distinct time periods of exposure: the incubation period, the early clinical phase, the late clinical phase, and after the death. (For example, ''did you touch [name the ill person] while she was in the hospital?'') The incubation period was defined as the 7 days preceding onset of fever in the ill person(s). To optimize accurate reporting, the early clinical phase was arbitrarily defined as the period when the ill person remained at home. Similarly, the late clinical phase was defined as the period of hospitalization. Finally, details about any exposures to the cadaver were requested.

Laboratory testing. Serum samples were requested from each remaining family member to test for IgG antibodies to EBO virus, using ELISA [9]. Infection with EBO virus in those who met the case definition and who had a specimen available was confirmed by detection of EBO antigen, antibody, viral RNA, or virus isolation [9].

Statistical analysis. Crude prevalence rate ratios (RR) associated with each risk factor were calculated by comparing the proportion developing EHF among the household members with and without each risk factor. Prevalence RR are calculated in cross-sectional studies (in which disease and exposure are ascertained simultaneously for all members of a defined group) as the ratio of disease in exposed persons to disease in unexposed persons, analogous to the relative risk calculated from prospective studies. Multiple exposures were common; therefore, adjusted RR were calculated by using Mantel-Haenszel stratification and logistic regression. Adjustment for various risk factors was done sequentially, with priority given to those with a high RR on crude analysis and those believed to be important on the basis of previous investigations. Stepwise logistic regression was used as a confirmatory test. Because the methods and the potential confounders involved are more straightforward to interpret, the RR and probabilities presented are based on stratified Mantel-Haenszel χ^2 tests.

Results

As of 17 May 1995, 33 households were identified as having a primary case. Two of the households had possible ongoing transmission, four could not be located because of incorrect addresses, and interviews were completed on the remaining 27. In addition to the 27 primary cases, these households included an additional 173 members; 28 (16%) had experienced an illness that met the case definition, and 145 remained well. Of the 55 persons who met the case definition, 52 (95%) died. One primary and 2 secondary case-patients survived.

Because this study was designed to investigate transmission of EBO virus among persons who were ill prior to the arrival of the international team, few specimens were available from these subjects for laboratory confirmation of infection with EBO virus. Sera were obtained from the 3 survivors, and all had EBO-specific IgG antibodies. In addition, sera obtained from 32 household contacts from 12 families who did not meet the case definition were all antibody negative.

Among the 27 primary household cases, the median duration of the early phase of illness at home was 4 days (range, 0–9).

The median duration of the late (hospital) phase of illness, from admission to death or discharge, was 6 days (range, 2–13). The minimum incubation period, defined as the median duration of the interval from the death of the primary case to the onset of fever in the first secondary household case, was 7 days (range, 1–15). The maximum incubation period, defined as the median duration of the interval from the onset of fever in the primary case to the onset of fever in the first secondary case, was 17 days (range, 9–25). The median duration of illness, defined as the time from onset of fever to death, was 10 days.

Percutaneous exposures were uncommon. Only 2 of 27 primary cases and none of 28 secondary cases reported any injections or surgeries in the 2 weeks prior to illness.

Overall, 15 (56%) of the 27 households had at least 1 secondary case; of those, 7 (26%) had >1 secondary case. No characteristics of the household studied increased the likelihood of multiple secondary cases. For example, the likelihood of secondary spread was not increased for larger households. No characteristic of the primary case, such as the presence of visible hemorrhage (seen in 26% of cases), cough (19%), or hiccup (30%), predicted secondary spread, either to a single secondary case or to multiple cases.

Crude risks for secondary transmission to individual household members according to their demographic characteristics and the nature of their exposures to other ill family members were calculated first (table 1). Many of the risk factors are correlated with each other. For example, spouses of primary cases were also likely to have direct physical contact during the illness, to have contact with body fluids, such as blood, stool, or vomitus, and to share a hospital bed with the ill person. Nevertheless, a pattern of increasing risk with exposures to patients in the later phases of illness was apparent.

The exposure that was most strongly predictive of risk for secondary transmission was direct physical contact with an ill family member, either at home in the early phase of illness or during the hospitalization. Of 95 family members who had such contact, 28 became infected, whereas none of 78 family members who did not touch an infected person during the period of clinical illness were infected (RR, undefined; $P < .001$). Nevertheless, the 78 family members who did not report direct physical contact with an ill person during the clinical phase of illness participated in a variety of activities that would have exposed them to fomite or airborne routes of spread. During the incubation period, all 78 shared meals with their ill family member, 26 reported direct physical contact, 15 shared their bedroom, and 6 shared their bed. In the early phase of illness, 62 slept in the same house and 42 shared meals. During the late phase of illness, 24 visited the hospital and 18 spoke with their ill family member.

After controlling for direct physical contact, by considering only those 95 persons who reported this risk factor, several other risk factors remained that were strongly predictive of secondary infection, including reported contact with the body fluids of an ill person (RR, 3.6; 95% confidence interval [CI], 1.9–6.8), being an adult family member (RR, 4.6; 95% CI, 2.0–10.3), and sharing the hospital bed (RR, 3.4; 95% CI, 1.8–6.2). For the remainder of the analysis, we chose to control for contact with body fluids of an ill person, because this was a consistently strong predictor of risk in all models and because this risk factor was more clearly implicated in previous investigations than were the other two. When the analysis was rerun by controlling for either of the other two strongly predictive risk factors rather than contact with body fluids, the conclusions remained substantially the same. Logistic regression produced substantially similar conclusions to the stratified analysis presented here; therefore, the results are not presented separately.

The risks associated with various exposures, after adjusting for direct physical contact with an ill person and contact with their body fluids, were substantially different from the crude risks described above. No exposure during the incubation period was associated with additional increased risk, and there was no increased risk for conversing, sharing a meal, or sharing a bed with a sick person during the early phase of illness (table 2). There was an independent risk associated with several

Table 1. Crude risks of developing Ebola hemorrhagic fever (EHF) among 173 household contacts of 27 patients with EHF.

Risk factor	% developing EHF		RR
	With risk factor	Without risk factor	
Female sex	21	10	2.1
Spouse of index case	45	12	3.8
Age >18 years	30	4	6.8
Exposures during incubation period			
Sharing a meal	16	—	—
Conversation	16	11	1.5
Sharing a bed	32	11	2.9
Touching	22	7	2.9
Exposures during early illness			
Sharing a meal	20	8	2.5
Conversation	19	6	3.3
Sharing a bed	37	10	3.8
Touching	31	3	12.5
Contact with body fluids	63	10	6.1
Exposures during late illness			
Sharing a meal	68	10	7.0
Conversation	33	3	10.6
Sharing a bed	53	7	7.4
Touching	43	3	12.5
Contact with body fluids	50	8	5.9
Exposure to cadaver			
Viewed	21	4	4.8
Touched	37	7	4.9
Prepared	—	—	—

NOTE. RR = prevalence rate ratio. By definition, all household members shared meals with primary household case at time of onset of illness. Risk factors are not mutually exclusive (e.g., household member might have had no conversation with case-patient during incubation period but had conversation during late illness).

Table 2. Risks of household transmission of Ebola hemorrhagic fever (EHF) among 173 household contacts of 27 EHF patients, after adjusting for direct physical contact during illness and contact with the patient's body fluids.

Risk factor	Adjusted RR	95% CI	*P*
Female sex	1.0	0.5–2.1	NS
Spouse of index case	1.3	0.7–2.5	NS
Age >18 years	3.6	1.3–10.1	.02
Exposures during incubation period			
Conversation	0.7	0.2–3.0	NS
Sharing a bed	1.4	0.8–2.4	NS
Touching	0.8	0.4–1.8	NS
Exposures during early illness			
Sharing a meal	1.2	0.5–2.7	NS
Conversation	0.7	0.3–2.0	NS
Sharing a bed	1.3	0.7–2.5	NS
Exposures during late illness			
Sharing a meal	2.2	1.2–4.0	.009
Conversation	3.9	1.2–12.2	.02
Sharing a bed	2.2	1.2–4.2	.009
Exposure to cadaver			
Viewed	1.6	0.5–4.9	NS
Touched	2.1	1.1–4.2	.03

NOTE. RR = prevalence rate ratio; 95% CI = 95% confidence interval; NS = not significant ($P > .2$). Risk factors are not mutually exclusive (e.g., household member might have had no conversation with case-patient during incubation period but had conversation during late illness).

different exposures in the late phase of illness, as there was with being an adult family member and with touching the cadaver. For 4 of the 28 secondary cases, the only known exposure to ill persons was during the prehospital phase of illness, a minimum of 2–11 days prior to death.

Discussion

This investigation confirmed several earlier theories about the important modes of transmission of EBO virus [2–4], and it allowed for some estimation of the magnitude of risk associated with specific exposures. Direct physical contact with an infected person during the phase of clinically apparent illness was the most important risk factor for secondary household transmission, but contact with the body fluids of the ill person and a variety of exposures during the late phase of clinical illness conferred additional risk. Careful comparison with the control group and the use of stratified analysis was necessary to identify these underlying risk factors. Other apparent risk factors, such as being a spouse or female family member, were confounded by strong associations with physical contact with ill family members because spouses and females were often the caregivers.

Direct physical contact with a clinically ill patient was necessary, though not sufficient, for secondary transmission. All 28 secondary cases touched the ill person, while none of the 78 household members who reported no physical contact during the period of clinical illness became infected. It is clear from previous investigations that EBO can be transmitted by means other than direct person-to-person spread, such as percutaneous exposure through unsterilized needles, as in the Yambuku outbreak [3] or laboratory accidents [10], but in large community outbreaks such as this one, where person-to-person spread is predominant, direct physical contact with ill persons may account for the majority of transmission episodes. One intriguing explanation for the role of direct physical contact in transmission is that the virus is excreted in sweat. In support of this hypothesis, skin biopsies obtained during the Kikwit outbreak have shown evidence of EBO virus antigen in various cutaneous structures, including sweat glands [11]. However, direct physical contact is required for the efficient transmission of many other infectious agents, including common respiratory viruses and enteric pathogens, without implication of infected sweat glands.

Among those household members who reported direct physical contact with the ill person, reported contact with their blood, stool, or vomitus was one of several factors that conferred additional risk. Experience with other infectious agents certainly lends biologic plausibility to this potential mode of transmission, by analogy with either fecal-oral pathogens, such as *Shigella dysenteriae* or hepatitis A virus, or with bloodborne pathogens, such as hepatitis B virus. Most patients had diarrhea or vomiting as part of their clinical course, and family members were responsible for handling these fluids in the hospital as well as at home. EBO virus has been recovered in high titers from urine and blood of nonhuman primates [12], and therefore would be expected to be present in bloody stools and vomitus as well. Finally, the strong empiric evidence of the efficacy of barrier precautions in terminating this as well as previous EBO outbreaks argues for the role of infected body fluids and direct physical contact in maintaining transmission, at least in the hospital setting [2–4, 13].

After controlling for contact with the ill person and exposure to body fluids, there was additional risk associated with a variety of exposures to patients in the terminal stages of illness, such as sharing a hospital bed or hospital meals and touching the cadaver. As these exposures were often overlapping, independent risk from each exposure in the terminal phase (such as conversation) cannot be assured. This supports earlier findings of a 5-fold increased risk for family members who provided nursing care to the ill person [4]. Viremia in experimental EBO virus infection of rhesus monkeys rises dramatically in the late stages of illness, peaking at titers of 10^6–10^7 particles/mL of blood [12]. This high virus load in terminally ill persons, along with their increasing obtundation and high output of diarrhea, vomitus, and blood, probably explains the increased risk for those family members exposed in the late stages of illness.

It is also important that 4 family members who were exposed only in the prehospital phase were infected. Thus, the risk from

exposure to a patient in the early stages of illness cannot be completely discounted. This fact is important for public health control measures, since even mildly ill persons may pose some risk, for example, to fellow passengers on an airplane.

As in the previous outbreaks in human populations [2–4], we found no clear evidence of small-particle aerosol transmission, although it is not possible to conclusively rule out the possibility of such transmission in rare circumstances. However, since none of the 78 household members without direct physical contact were infected, this fact may be helpful in providing an estimate of the risk for such transmission (upper limit of 95% CI on a rate of 0/78 is 4%). Given the biologic differences between the 4 known subtypes of EBO [1] and the ability to experimentally transmit EBO by small-particle aerosol to rhesus monkeys [14], such calculations should be applied with caution to future EBO virus outbreaks.

Children were relatively spared in this outbreak, as has been typical for the previous EBO outbreaks and for certain other viral hemorrhagic fevers [2–4, 15, 16]. Only 27 (9%) of the 315 persons in Kikwit who developed EHF were <17 years of age [17], and in this study, adult household contacts were at considerably increased risk compared with children. Much of this risk was related to more frequent exposure of the adults to ill family members and their body fluids, but elevated risk for adults remained even after adjusting for their increased exposures. Thus it remains possible that in addition to being less likely to be exposed to EBO, children are less susceptible to infection or severe disease. This question requires further study.

This study was designed to assess risks for transmission prior to the institution of strict barrier precautions and other public health measures. It is likely that these risks decreased after such measures were implemented. In fact, the termination of the outbreak coincident with the implementation of these measures is evidence that transmission decreased dramatically. In other outbreak settings, such as in a more developed country or in a hospital where universal precautions are carefully observed, the quantification of risks and the predominant modes of transmission would likely be different than those found here.

These findings imply that the use of barrier precautions by household members and standard universal precautions in hospitals would have prevented the majority of infections and deaths from EHF in Kikwit.

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