

Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread

ROY C. BARON,¹ JOSEPH B. MCCORMICK,² & OSMAN A. ZUBEIR³

Between 31 July and 6 October 1979, 34 cases of Ebola virus disease (22 of which were fatal) occurred among five families in a rural district of southern Sudan; the disease was introduced into four of the families from a local hospital. Chains of secondary spread within the family units, accounting for 29 cases resulted from direct physical contact with an infected person. Among all persons with such contact in the family setting, those who provided nursing care had a 5.1-fold increased risk of infection, emphasizing the importance of intimate contact in the spread of this disease. The absence of illness among persons who were exposed to cases in confined spaces, but without physical contact, confirmed previous impressions that there is no risk of airborne transmission. While the ecology of Ebola virus is unknown, the presence of anti-Ebola antibodies in the sera of 18% of persons who were unassociated with the outbreak suggests that the region is an endemic focus of Ebola virus activity.

Ebola virus was first identified in 1976 (1-3) in association with two simultaneous outbreaks of haemorrhagic fever in southern Sudan (4) and north-eastern Zaire (5). The illness included fever, headache, and malaise at onset, with profuse vomiting and diarrhoea developing 2-4 days later (6-9). Altogether, 55% of the cases in Sudan and 88% in Zaire were fatal. Haemorrhagic manifestations were prominent features in patients who died, but were observed less commonly in survivors. The outbreaks were recognized after they had been amplified within hospital settings, and were further perpetuated by secondary household spread. While the use of unsterile needles was implicated as a mode of transmission in the Zaire hospital, much of the person-to-person transmission apparently resulted from close physical contact. In the Sudan outbreak, the first few cases occurred among textile factory workers in the town of Nzara (4, 10, 11). However, no animal reservoir was found during subsequent environmental studies in the factory (12), and the natural host of the virus has remained undetermined.

In late August 1979, epidemic haemorrhagic fever recurred in Nzara and was also seen among persons in Yambio, 25 km away. During emergency efforts to control the outbreak and confirm the etiological

agent, we evaluated the potential role of airborne spread within high-risk family units. We also conducted serological studies to assess whether sub-clinical infection had occurred in these households and to estimate the prevalence of anti-Ebola antibody in unaffected families.

BACKGROUND

Nzara and Yambio are located in the remote savanna of southern Sudan, near the border with Zaire. Approximately 40 000 persons live within a 15-km radius of the two towns, mostly residing on individual family compounds constructed on relatively isolated clearings in the dense grasslands.

In each town there is a small overcrowded hospital staffed by one or two physicians and several nurses. The hospital in Nzara consists of two small concrete structures for 2 patients each, and a larger building with three 8-bed wards. Patients at the Yambio facility are accommodated in several thatched huts. There is no running water in the patient-care areas, and the hospitals have a limited supply of masks, caps, and gowns. The staff do not routinely practise barrier nursing and often do not sterilize needles, syringes, or other instruments used on the wards. Relatives of hospitalized patients provide much of the routine nursing, which includes handling emesis, excreta, and soiled clothing. Family members often choose to care for the severely ill at the family compound.

¹ Medical Epidemiologist, Division of Surveillance and Epidemiologic Studies, Epidemiology Program Office, Centers for Disease Control (CDC), 1600 Clifton Road NE, Atlanta, GA 30333, USA.

² Chief, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases, CDC, Atlanta, GA, USA

³ Medical Epidemiologist, Blue Nile Health Project, Wad Medani, Sudan (Deceased).

On 2 August 1979, a 45-year-old man (later identified as the index patient) was admitted to the Nzara hospital with a history of fever for 3 days and recent onset of vomiting and diarrhoea. He later developed gastrointestinal bleeding and died on 5 August. The hospital staff had not taken precautionary isolation measures, and only several weeks later was it learned that three of this patient's relatives, who had cared for him before admission, had developed haemorrhagic fever and died in the family compound (Fig. 1, family A). An outbreak was first recognized in late August, when several persons from another family (family B) were hospitalized with haemorrhagic fever. In early September, the district was quarantined, and regional surveillance was begun under the direction of one of the authors (O.Z.). A team sponsored by the World Health Organization arrived to give assistance on 22 September, after two hospital nurses in Nzara had died of haemorrhagic fever.

METHODS

Case-finding and serological survey

Between 22 September and 9 October, serial blood specimens were collected from all persons with fever in the two hospitals. Postmortem liver tissue was obtained from two patients by percutaneous needle biopsy. Hospital records were reviewed to identify persons with fever who had died or been discharged between 1 July and 22 September. Teams of local

health workers visited family compounds in the Nzara-Yambio district and reported all febrile illnesses and deaths that had occurred among non-hospitalized persons since 1 July. We obtained clinical and epidemiological information and collected single convalescent-phase blood specimens at the family compound from each survivor of febrile illness not interviewed in the hospital. Family members provided the corresponding information for patients who had died. Ebola virus disease was clinically defined as a febrile illness with haemorrhage, or with vomiting or diarrhoea developing 2-4 days after the onset of fever. We obtained single blood specimens from 160 asymptomatic relatives of suspected infected persons, and took details of their exposure to ill persons. Of this group, 103 had been exposed to one or more cases of Ebola virus disease; the remaining 57, who comprised a comparison group, were members of families in which none of the ill persons investigated were considered to have the disease. Records at the Nzara textile factory were reviewed for absenteeism after 1 July to ascertain whether illnesses similar to Ebola virus disease had occurred among workers there.

Laboratory studies

Sera, separated by hand centrifuge, and liver tissues were stored in liquid nitrogen and later transported on dry ice to the Centers for Disease Control in Atlanta, USA. Isolation of virus from acute-phase sera, diluted 1:4 in 7.5 ml/litre bovine serum albumin

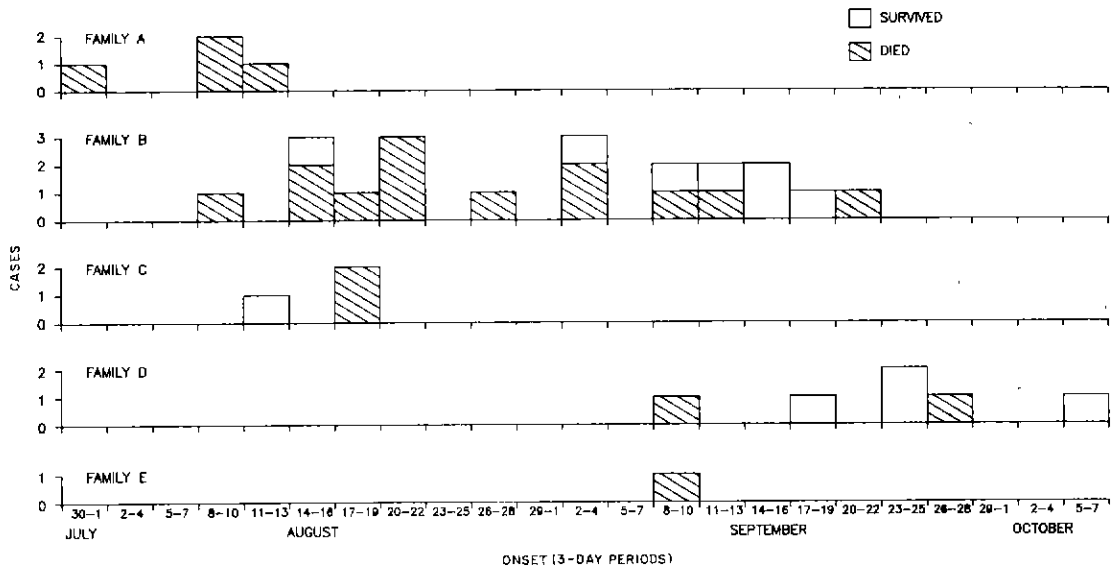


Fig. 1. Onset of Ebola virus disease in five families in Sudan, 30 July-7 October 1979.

phosphate-buffered saline (BAPS), and from post-mortem liver tissues, prepared as 10% suspensions in BAPS, was attempted in Vero (African green monkey kidney) cell cultures or in young guinea pigs (13). Sera were tested for Ebola virus antibody by the indirect immunofluorescent method (14). A test was considered positive if fluorescence was observed at dilutions of 1:16 or higher.

RESULTS

Case finding

Among 69 ill persons investigated, we identified 34 cases of Ebola virus disease. Ebola virus was isolated from the blood or postmortem liver tissue of 6 per-

sons, and anti-Ebola antibody titres were high in 4 others who were examined during the acute phase of illness (Table 1). Four persons not seen until after the acute phase were counted as cases on the basis of clinically compatible histories and positive convalescent-phase sera. An additional 20 cases, including 19 who died before we could interview them and 1 survivor whose serum was not obtainable, were identified by clinical history alone. Among the other 35 ill persons, 29 of 31 who survived had no antibody in convalescent-phase sera. The 2 seropositive survivors and a further 4 persons who died before the investigation began had clinical histories incompatible with Ebola virus disease.

The outbreak involved 5 families and occurred between 31 July and 6 October (Fig. 1). There were 21 female and 13 male patients, comprising 32 adults

Table 1. Results of virus isolation and indirect fluorescent antibody (IFA) studies for Ebola virus infection in 10 cases of haemorrhagic fever, Sudan, 1979.

Patient	Age	Sex	Specimen collection (Day of illness)	Specimen	Virus isolation ^a	Reciprocal IFA titre ^a	Outcome
1	9	M	13	blood	positive	< 8	died
			14	liver	positive	—	
2	42	F	6	blood	positive	< 8	survived
			15	blood	N.T.	128	
3	29	F	4	blood	positive	< 8	survived
			7	blood	N.T.	≥ 256	
4	27	M	4	blood	positive	128	survived
			13	blood	N.T.	N.T.	
5	23	F	5	blood	positive	16	survived
			8	blood	N.T.	64	
			16	blood	N.T.	≥ 256	
6	45	F	4	blood	negative	< 8	died
			5	blood	negative	< 8	
			7	liver	positive	—	
7	40	F	11	blood	negative	64	survived
			20	blood	N.T.	≥ 256	
8	28	F	16	blood	negative	< 8	survived
			19	blood	N.T.	16	
9	28	F	8	blood	negative	16	survived
			13	blood	N.T.	128	
10	58	M	12	blood	negative	64	died
			14	blood	negative	128	

^a N.T. = not tested

between 23 and 60 years of age, one 9-year-old child, and one 10-month-old infant. Twenty-two (65%) patients died. Death occurred between 5 and 15 (median 9) days after the onset of illness and, in the 3 cases we observed, was preceded by hypovolaemic shock. Twenty-one (95%) of the patients who died and 4 (33%) survivors had haemorrhagic manifestations, usually haematemesis (13 persons) or bloody diarrhoea (16 persons), but bleeding from the gingiva (11 persons) and the nasal mucosa (7 persons) was also reported.

Course of the outbreak

Every case, except that of the index patient, could be traced to a human source of infection. The first case in family B was a man who had been hospitalized in the bed adjacent to the index patient, while recovering from a non-febrile gastrointestinal disorder. The two patients were attended by the same nurses, but it was not possible to determine whether they had any direct contact, or whether the recovering patient had received injections with unsterile needles used for the index patient. The man left the hospital feeling well on 6 August; 4 days later he became febrile and died after an episode of haemoptysis on 15 August.

The woman identified as the first case in family C had attended her husband who was convalescing from surgery while the index patient was on the ward. She did not recall any contact with the index patient but developed illness compatible with Ebola virus disease on 13 August. Ebola-specific antibody was later demonstrated in a 1:256 dilution of her convalescent-phase serum.

The first case in family D and the only case in family E occurred in two nurses in the Nzara hospital, who developed fatal haemorrhagic fever after attending patients from family B.

The remaining 29 cases occurred in chains of secondary spread in four families (Fig. 1) after exposure to an ill member of the household. Details of exposure to infection were not available for 2 secondary cases; the other 27 were associated with physical contact. Of these, 24 had provided nursing care to other patients in the family; for the remaining 3 patients (including the 2 children) the history indicated that the physical contact had been less intimate. The association between the risk of disease transmission within the family and physical contact is emphasized by the exposure history of 103 persons who lived in the affected compounds but who did not contract the disease (Table 2). Of these, 43% had no physical contact with cases, and more than half of this group had been exposed to a patient within a small hut or room. Intimate contact associated with nursing care carried a 5.1-fold increased risk of developing

Table 2. Degree of exposure to cases of Ebola virus disease among 29 secondary cases and 103 asymptomatic persons in affected families in Sudan, 1979

Degree of case contact within family	Secondary cases	Asymptomatic family members
Provided nursing care	24	36
Physical contact but no history of nursing care	3	23
Entered same room but no physical contact	0	23
Never entered same room	0	21
Contact history unknown	2	0
Total	29	103

disease, relative to less intense physical contact (estimated by the odds ratio; 95% confidence interval, 1.31-15.48).

Among the 61 asymptomatic family members aged 16 years or over who had been exposed to cases with onset of illness before 10 September, 12 of 38 (32%) who had physical contact were seropositive for antibody against Ebola virus. Antibodies were also present in 3 (13%) of the 23 adult household members who denied any physical contact with cases (difference not significant), and in 8 (18%) of the 45 adults in the unaffected families evaluated for comparison.

By tracing the contacts, we estimated that this outbreak resulted from 7 generations of virus transmission, including the index patient. The mortality rate diminished as the outbreak progressed. There was an 89% fatality rate in the first 4 generations of transmission, compared with a 38% rate in the last 3 generations (Table 3).

The patient identified as the index case had been employed in the Nzara textile factory. Three other factory workers developed Ebola virus disease later in the outbreak, but only after close contact with a case

Table 3. Case-fatality ratio in the outbreak of Ebola virus disease by generation of infection, Sudan, 1979.

	Generation of infection							Total
	1	2	3	4	5	6	7	
No. of cases	1	5	7	5	10	5	1	34
No. of deaths	1	4	6	5	5	1	0	22
Case-fatality ratio (%)	100	80	86	100	50	20	0	65

in their respective families. Among approximately 500 factory workers, there was no other incidence of febrile illness resulting in prolonged absenteeism after 1 July. According to the factory managers, the index case had been the first such illness since 1976. Interviews with relatives of the index case revealed no prior contact with a case of fever and provided no information to suggest an alternative environmental or enzootic source of infection.

DISCUSSION

After three well-documented epidemics of haemorrhagic fever caused by Ebola virus, the basic ecology of this agent remains unknown. Although the index patient in this outbreak was employed in the Nzara textile factory, cited as the source of the first outbreak in Sudan (4, 10, 11), a review of the absentee and illness records failed to incriminate the factory as an active source of infection. The detection of Ebola virus antibody in the sera of 18% of the adults not associated with this outbreak and the recurrence of epidemic haemorrhagic fever in the town where an earlier episode began (4) support the notion that Ebola virus is endemic in this region. It is likely that sporadic infection is more common than can be appreciated from these dramatic outbreaks, which probably represent the extreme of the interaction between man and the virus. Because the cultural and social structure in Sudan tends to limit contact with severely ill persons to a few adults in a relatively secluded compound, sporadic cases of Ebola virus disease may have little impact on the community at large.

In this outbreak, however, the hospital appeared to be the important focal point for dissemination of infection to several family units after the admission of the index patient. Both of the previous outbreaks of Ebola virus disease were similarly amplified in hospital environments. These and notable outbreaks of Lassa fever (15-17), Marburg virus disease (18), and Crimean-Congo haemorrhagic fever (19), which have also resulted from nosocomial spread, underscore the importance of rapid diagnosis and isolation of hospitalized patients with suspected haemorrhagic fever. Unfortunately, recognition of these diseases in endemic zones presents a major challenge since the early signs and symptoms are non-specific and similar to those of more common tropical infections, including typhoid fever and malaria. Furthermore, as in this outbreak, even after a fatal case with haemorrhage, the diagnosis may not be considered until several patients are observed simultaneously. Thus, important preventive measures should include routine maintenance of sterile precautions and isolation of

the suspected patient once identified.

While direct patient contact was probably responsible for the infection of the two nurses in the Nzara hospital, there was insufficient information to determine the circumstances of transmission from the index patient to both a fellow patient and an unassociated visitor to the ward. Because there are multiple opportunities for cross-contamination in crowded open wards, such as contact with bedpans, soiled linen and clothing, and unsterile instruments, the precise mechanism of person-to-person spread, which might include airborne transmission, is not clear.

Study of transmission within family units, however, confirmed a previous report (4), suggesting that Ebola virus is not easily transmitted via the airborne route. Even among persons exposed to cases in the confined space of relatively small and poorly ventilated huts, illness occurred only among those who had direct physical contact with an infected person. Furthermore, among family members who did have physical contact with cases, the risk of acquiring illness was much greater if they provided nursing care. This supports the belief that person-to-person transmission depends on direct contact with the body fluids of infectious persons.

The implications of these data are relevant to hospitals in endemic regions and to others where imported cases might arrive. They suggest that the use of high-efficiency particulate air filtration and complex air circulation systems is less important than adherence to sound isolation practices, which should include precautionary decontamination of bodily fluids with phenol or hypochlorite solution (J. V. Lange & H. Wulff, unpublished data, 1979).

Both the inefficient spread from person to person and the apparent virulence of the organism support the concept that Ebola virus is poorly adapted to sustained transmission among humans. The case-fatality ratio (65%) in this outbreak is comparable to those of the earlier Ebola epidemics. However, the diminished fatality observed in the later phases of the outbreak suggests that the virus was less virulent after several generations of person-to-person passage. This hypothesis, however, has not been convincingly substantiated in the natural setting or by animal studies. Other factors, such as the dose and route of infection, may be important determinants in the outcome of the disease. Alternatively, the reduced mortality recorded in later generations may reflect improved detection of non-fatal cases after the outbreak was recognized and may represent a more accurate assessment of virulence. Finally, although not statistically significant, the higher antibody prevalence noted among asymptomatic family members who had physical contact with cases suggests that infection with this virus may occur in the absence of overt clinical manifestations.

Guidance in the planning of studies to define further the clinical features of Ebola virus disease, its epidemiology, and the ecology of the virus, will require intensive surveillance for sporadic cases. Such

surveillance will, furthermore, sensitize the medical community in endemic regions of Africa to this disease and alert hospital personnel to possible increases in the occurrence of cases.

ACKNOWLEDGEMENTS

The authors are indebted to Mr Abdel Gadhiri El Sid, of the WHO Expanded Programme on Immunization, Khartoum, Sudan, and to Dr Simon von Nievenhowe, Director of the Belgian Assistance Programme Sleeping Sickness Project, Li Rangu, Sudan, for their valuable help with the field investigations. Thanks are also due to Luanne Elliot, Centers for Disease Control (CDC), for her role in isolating the agent and performing the serological studies; to Karl M. Johnson, CDC, for technical consultation; to Dr Paul Brès, Dr Fakhry Assaad, and Dr M. H. Wahdan, WHO, for their support during the operation; and to Dr Stephen B. Thacker, CDC, for reviewing this manuscript.

RÉSUMÉ

MALADIE À VIRUS EBOLA AU SOUDAN MÉRIDIONAL : TRANSMISSION NOSOCOMIALE ET TRANSMISSION INTRAFAMILIALE

Entre le 31 juillet et le 6 octobre 1979, 34 cas de maladie à virus Ebola (dont 22 ont été mortels) se sont produits dans cinq familles d'un district rural du Soudan méridional; dans quatre d'entre elles, l'infection avait pour origine l'hôpital local. Il en est résulté des chaînes de transmission secondaire au sein des cellules familiales, représentant 29 cas, par contact physique direct avec un sujet infecté. Parmi toutes les personnes ayant eu ce genre de contact dans le cadre familial, celles qui ont pris soin des malades ont vu le risque d'infection multiplié par 5,1, ce qui souligne l'importance

d'un contact étroit dans la propagation de cette maladie. La non survenue de la maladie chez des personnes qui étaient exposées à des malades dans un espace réduit mais n'avaient pas de contact physique avec eux confirme, comme on l'avait antérieurement présumé, qu'il n'existe pas de risque de transmission par voie aérienne. L'écologie du virus Ebola n'est pas connue; la présence d'anticorps anti-Ebola dans le sérum de 18% des personnes non concernées par cette flambée n'en donne à pas moins penser que cette région constitue un foyer endémique d'activité du virus Ebola.

REFERENCES

1. JOHNSON, K. M. ET AL. Isolation and partial characterization of a new virus causing acute haemorrhagic fever in Zaire. *Lancet*, 1: 569-571 (1977).
2. BOWEN, E. T. W. ET AL. Viral haemorrhagic fever in southern Sudan and northern Zaire. *Lancet*, 1: 571-573 (1977).
3. PATTYN, S. ET AL. Isolation of Marburg-like virus from a case of haemorrhagic fever in Zaire. *Lancet*, 1: 573-574 (1977).
4. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. *Bulletin of the World Health Organization*, 56: 247-270 (1978).
5. Ebola haemorrhagic fever in Zaire, 1976. Report of an International Commission. *Bulletin of the World Health Organization*, 56: 271-293 (1978).
6. PIOT, P. ET AL. Clinical aspects of Ebola virus infection in Yambuku area, Zaire, 1976. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 7-14.
7. ISAACSON, M. ET AL. Clinical aspects of Ebola virus disease at the Ngaliema Hospital, Kinshasa, Zaire, 1976. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 15-20.
8. SMITH, D. H. ET AL. African haemorrhagic fever in southern Sudan, 1976: The clinical manifestations. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 21-26.
9. EMOND, R. T. D. Isolation, monitoring, and treatment of a case of Ebola virus infection. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 27-32.
10. SMITH, D. H. ET AL. The Nzara outbreak of viral haemorrhagic fever. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 137-141.
11. FRANCIS, D. P. ET AL. Ebola fever in the Sudan, 1976: Epidemiologic aspects of the disease. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 129-135.
12. ARATA, A. A. & JOHNSON, B. Approaches towards studies on potential reservoirs of viral haemorrhagic fever in southern Sudan. In: Pattyn, S. R., ed., *Ebola virus haemorrhagic fever*. Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 191-200.

13. MCCORMICK, J. B. ET AL. Biologic differences between strains of Ebola virus from Zaire and Sudan. *Journal of infectious diseases*, **147**: 264-267 (1983).
 14. WULFF, H. & LANGE, J. V. Indirect immunofluorescence for the diagnosis of Lassa fever infection. *Bulletin of the World Health Organization*, **52**: 429-436 (1975).
 15. FRAME, J. D. ET AL. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *American journal of tropical medicine and hygiene*, **19**: 670-676 (1970).
 16. CAREY, D. E. ET AL. Lassa fever. Epidemiological aspects of the 1970 epidemic, Jos, Nigeria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **66**: 402-408 (1972).
 17. MONATH, T. P. ET AL. A hospital epidemic of Lassa fever in Zorzor, Liberia, March-April 1972. *American journal of tropical medicine and hygiene*, **22**: 773-779 (1973).
 18. SMITH, D. H. ET AL. Marburg virus disease in Kenya. *Lancet*, **1**: 816-820 (1982).
 19. BURNEY, M. T. ET AL. Nosocomial outbreak of viral hemorrhagic fever caused by Crimean hemorrhagic fever-Congo virus in Pakistan, January 1976. *American journal of tropical medicine and hygiene*, **29**: 941-947 (1980).
-

