Surveillance of Lassa fever in missionaries stationed in West Africa

JOHN D. FRAME [1]

To determine the distribution of Lassa virus in West Africa, a serological survey was undertaken. A number of mission hospital supplied sera from patients admitted with a history of fever and specimens were also collected in New York from missionaries who had experienced an unusual febrile illness while working in Africa. More cases of Lassa fever were detected among missionaries than among Africans, possibly because many African patients had left hospital before the complement fixation tests had become positive. Although most adults had fairly high fever and some were prostrated, fever was less severe in the children examined. In general the findings confirm that not all Lassa fever patients have the severe syndrome described in the original reports.

Since 1972 Dr Jordi Casals of the Yale Arbovirus Research Unit (YARU) and I have been conducting a survey to determine the distribution of Lassa virus (LV) in West Africa; this is a report of our findings with some details of the clinical histories of missionary patients.

MATERIALS AND METHODS

183 sera of 123 patients with a history of fever within the previous year were sent us by a number of mission hospitals in West Africa. The specimens were accompanied in most instances by simple clinical information.

134 specimens were obtained from 124 missionaries seen in my New York offices who had lived in any part of Africa and who presented with a history of an unusual febrile illness while in the field.

Specimens were frozen; most thawed at least once on the way from the mission hospitals. They were forwarded from my office to YARU where they were tested by complement fixation (CF). Initial tests were with a small stock of LV antigen previously prepared there; later, antigen supplied by the Center for Disease Control (CDC), Atlanta, GA, was used.

[1] Associate Professor of Tropical Medicine, Division of Tropical Medicine, School of Public Health, Columbia University, 630 West 168 Street, New York, N.Y. 10032; Director, Associated Mission Medical Office, Division of Overseas Ministries, National Council of Churches, 475 Riverside Drive, New York, N.Y. 10027, USA.

RESULTS

Some specimens were anticomplementary or gave nonspecific reactions. Two or more specimens were obtained from some patients. 129 specimens from 94 people sent from the field and 114 sera from 104 missionaries seen in New York were suitable for testing (Table 1).

Antibodies to LV were found in 14 specimens from 13 people. In 3 instances positive specimens were sent by Evangel Hospital in Jos, Nigeria, from Lassa fever patients diagnosed previously, 2 in that hospital and one in south-eastern Nigeria. In all, 11 new cases of LV infection were identified (Table 2).

In 3 instances, antibodies to LV were found in the second of a serum pair, indicating current illness. In 2 other cases, the early sera were not available for

Table 1. Serological specimens tested for antibodies to Lassa virus, by source, 1972-1975

Source	Total tested		Total diagnostic	
	No. sera	No. persons	No. sera	No. persons
JDF[a]	134	124	114	104
Mission hospitals	183	123	129	94
Total	317	247	243	198

[a] Specimens collected by Dr Frame from missionaries on leave

Table 2. Number of patients positive for antibodies to Lassa virus in specimens from residents in Africa, 1972-1975

Source	Persons tested	Positive for Lassa virus [b]	Positive (%)
JDF [a]	104	6	5.8
Mission hospitals	94	5	5.3
Total	198	11	5.6

[a] Specimens collected by Dr Frame from missionaries on leave.
[b] Three other specimens were positive: one a second specimen from one of these patients obtained 10 months after his original infection, one from a medical missionary diagnosed elsewhere as having had Lassa fever in 1974, and the third from a Nigerian medical worker 4 years after his illness in the 1970 Jos outbreak.

testing, but the history suggested current or recent infection. In 6 instances, the history indicated infection at least several weeks prior to the collection of sera (Table 3). Five of the new infections were discovered in the field, 3 in Africans and 2 in missionaries, and 6 among missionaries seen in New York.

Table 3. Patients with CF antibodies to Lassa virus, 1972-1975 survey [a]

Case	Sex	Nationality	Place of residence	CF titre	Date of illness
RHe	M	USA	Ntorosso, Mali (13°9'N, 5°4'W)	1 : 4	June 71
LRo	F	USA	Hayes Gowien Town Mission, Liberia	1 : 4	June 71
DEp	M	Canada	Sokoto, Nigeria (13°4'N, 5°15'E)	1 : 8	June 71
VJo	F	USA	Djema, Central African Rep. (6°3'N, 25°19'E) or Banda, Zaire (4°11'N, 27°22'E)	1 : 8	Jan. 72
JDa	M	Nigeria	Jos, Nigeria (9°55'N, 8°54'E)	1 : 8	Dec. 72
EAn	F	Nigeria	Jos, Nigeria	1 : 8	Jan. 73
WTe	M	Netherlands	Takum, Nigeria (7°16'N, 9°59'E)	1 : 32	Feb. 74
Saf	F	Nigeria	Takum, Nigeria	1 : 32	March 74
MPe	M	Canada	Banfora, Upper Volta (10°38'N, 4°46'W)	1 : 8	? April 74
GBo	M	USA	Beoumi, Ivory Coast (7°40'N, 5°34'W)	1 : 8	Unknown (1970-74)

[a] One further patient reacted with a CF titre of 1 : 8.

The countries of residence were Nigeria, Liberia, Upper Volta, Mali, Ivory Coast, and Central African Republic/Zaire.[a]

Identification of one positive serum specimen from the group seen in New York was uncertain.

COMMENTS

LV infections have been documented on the Jos plateau of Nigeria for every calendar year since 1969, as determined by previous reports, by the current investigation, and by information that is being received at the present time. If outbreaks are defined by the presence of two or more epidemiologically related cases, outbreaks have been identified in every year, including 1975, except for the 1971–1972 season.

Whether Lassa fever is equally common in other parts of Nigeria is unclear. The frequency of the discovery of the disease in the hospitals of the Jos plateau is probably due primarily to the high degree of suspicion of their staffs following their experience in 1970.

We were able to obtain the most detailed information regarding the missionary patients, and I shall confine most of my discussion to their cases (Table 4). The current investigation has added 8 cases of LV infection among missionaries and their children. The 2 children lived in Upper Volta and Ivory Coast. Of the adults, there was one case each from Mali, Liberia, and Central African Republic/Zaire, and 2 from Nigeria.

Including infections documented previously, 17 cases in all have been diagnosed in the Protestant missionary population with which I work.

In some ways, the most useful prior study was the serological survey of 712 missionary sera conducted in 1970 (1). I should like to review the salient features of the cases found in Telekoro, Guinea, at that time (Table 5).

1. None of the Guinea cases had pharyngitis or haemorrhagic symptoms; 2 of them had evidence of 8th cranial nerve involvement.

2. A child positive for antibodies to LV gave no clear history of her illness. Her father had had a

[a] One patient had been resident in both the Central African Republic and Zaire and it was not possible to determine where the disease had been contracted.

Table 4. Clinical data of missionaries with CF antibodies to LV, 1972-1975 survey

Case	Sex	Birth date	Probable date of illness	Date serum obtained	CF titre	Clinical symptoms and course	Remarks
RHe	M	29/6/21	Jun 71	23/7/73	1 : 4	Fever to 103.5°F (39,7°C), aching in back, legs, and chest. Nausea; vomited once. 1 week illness	Also CF 1 : 26 to chikungunya
LRo	F	8/2/28	Jun 71	12/4/72	1 : 4	Chills, fever, rash, severe backache, headache, abdominal pain. Fever dropped in several days, recurrent for 3 months	Colleague ill at same time had negative CF tests. Possibly local outbreak of "flu" with high mortality
DEp	M	(38 years)	15/6/71	31/6/71	1 : 8	Chills, fever, headache, generalized aching. Soreness of neck, dysphagia. On 31/7/71, wbc 25 000. Otitis media	History suggestive of Lassa fever with secondary bacterial pharyngitis and otitis media
VJo	F	12/5/30	1/1/72	25/1/72	1 : 8	Generalized aching, chills, fever. Severe headache. Vomited once. 3-day illness. Fatigue with gradually increasing strength during next 2 weeks	Husband had infectious hepatitis in Oct. 71
WTe	M	(33 years)	20/2/74	4/3/74 21/3/74	0 1 : 32	Malaise, fever 103-104°F (39.4-40°C). Head, back, chest and abdominal pain. Cough. Posterior cervical lymphadenopathy. Wbc: early, 20 000-4 000; later, 6 300; on 8/3/74: 12 800. Some loss of hair and loss of hearing	Hospital administrator. Sister-in-law (nurse-midwife) had "typhoid" previously. African midwife ill at same time (Case Saf, Table 3), CF 1 : 32
MPe	M	30/10/67	Apr. 74	14/7/74	1 : 8	Persistent low grade fever. Previous mild fevers (?malaria)	CF tests for arboviruses and IFA for malaria neg. Mother had severe fever with chest pain 1 week prior to return to USA
GBo	M	26/11/67	Unknown	14/8/74	1 : 8	Occasional mild fevers	Considerable illness in family (see text)
SEv [a]	F	(30y)	24/12/74 to 16/1/75	2/6/75	1 : 32	Pharyngitis 5 days, then chills, high fever, pneumonia, rash. Delivered macerated stillborn fetus. Hospitalized 18 days in all	2 Nigerian nurses hospitalized 21/1/75 after several days of fever, malaise. Both leukopenic. One died 30/1/75 (LV isolated from serum). Second developed pneumonia 5/2/75, discharged for convalescence 10/2/75

[a] Reported in Addendum.

fever unusual enough to be noted in his medical history upon his return to New York. Apparently the child had not been ill at the time of her father's illness, though she had had "measles and scarlet fever together" 3 years previously.

3. No secondary cases were discovered among those who had attended the patients.

4. There were cases in 3 out of 4 consecutive years on that one station, suggesting the endemic nature of the disease in Telekoro, whether human or zoonotic.

These findings helped define our serological survey when we set out to determine the distribution of LV in Africa. We did not emphasize the symptoms of classical Lassa fever (2, 3) but requested mission hospitals to obtain sera from patients with a history of significant fever within the previous year, and to send specimens from children as well, if blood were obtained for diagnostic purposes during hospitalization.

Similiarly, when serum was obtained for diagnosis of fever in missionary children seen in my office, I

Table 5. Summaries of the medical histories of missionaries from Telekoro, Guinea, with neutralizing antibodies to Lassa virus, 1970 survey [a]

Case	Birth date	Sex	Date of onset	Clinical information
CM	6/9/04	F	14/8/65	Insidious onset, fever and malaise, increasing lassitude, euphoria, nausea, hyperaesthesia of feet, loss of hearing, loss of hair. 4 weeks' illness, 2 months' convalescence. 12 pound (5.5-kg) weight loss. Permanent total deafness.
DoL	2/10/28	M	15/1/67	Slight fever, malaise, anorexia, prostration. Sensitivity of muscles, testicles, chest, abdomen. Rapid breathing. 5 weeks' illness, 3 more weeks' convalescence.
DeL	18/10/60	F	Unknown	"Measles and scarlet fever", April 64. Occasional mild fevers (?malaria). Not ill during illness of father (DoL).
PE	31/1/25	M	Feb. 68	Fatigue, dry mouth, fever and chills after 1 week. Headache, vomiting, anorexia. Fever to 38.9°C. Generalized aching and tenderness. Prostration. Tinnitus, impaired hearing. Fever for 2 weeks, 4 weeks' convalescence.

[a] Henderson, B. E. et al. (1).

reserved some for virological tests if any member of the family had had unusual or severe fever. The following "family-as-case" illustrates one such instance:

This family was examined in New York on 14 August 1972, at the end of a 4-year term in Ivory Coast. All members had immunofluorescent antibody (IFA) tests for malaria, as well as CF tests for LV, Congo virus, and a battery of arboviruses.

AB, a 35-year-old white male, had had a severe illness soon after his arrival in Ivory Coast; it was characterized by chills, fever, sweats, vomiting, and general malaise. He was treated for malaria at the time, and on the occasion of several milder episodes of this syndrome subsequently. In November 1969, he was ill with icteric hepatitis. In March 1970, he had an illness diagnosed as viral pneumonia, and in March 1971 a bout of fever with headache and a rash. All serological tests in New York were negative.

BB, a 34-year-old white female, had had one or two bouts of fever ascribed to malaria. In March 1971, she had a high fever with headache and a rash on the third day. Serological tests were negative.

EB, their 5½ year-old adopted son, had about 4 fevers a year while in Africa, generally accompanied by vomiting and lasting a day or two. In the most recent illness in the spring of 1972, his fever rose to 104°F (40°). All serological tests were negative.

GB, their son aged 4 years 8 months, had a history of occasional fevers ascribed to malaria. CF tests were positive for Lassa fever at a titre of 1: 8, for Dengue-2 fever at a titre of 1: 4, and for West Nile fever at a titre of 1: 8, with trace reactions to Zika and Sindbis antigens; Bunyamwera antibodies were present at a titre of 1: 8. CF tests for Congo virus and IFA tests for malaria were negative. Dr Casals interpreted the results as indicating infection with a Group B agent, as well as with Lassa and Bunyamwera viruses.

Because of the known relatively rapid fall in CF titres with the passage of time (Casals, personal communication), one may speculate that haemagglutination-inhibition tests with arbovirus antigens and neutralization tests with LV might have shown positive reactions to a number of agents in other members of the family as well.

Another case is cited to illustrate that if one is to look for LV where it has not been found previously, one must test patients without close reference to the classic symptoms of Lassa fever.

VJ, a 37-year-old white female was seen at the close of her second 3-year term in the Central African Republic and Zaire. About 6 weeks prior to leaving her home in Banda, Zaire, she returned to Djema, Central African Republic to pack household goods left at their previous station, as it was apparent the family would not return there after leave. On 1 January 1972, 10 days after her return to Banda, she developed chilly sensations, fever, and generalized aching. Headache and "bone aches" became severe, she could not eat, and she vomited on the second night. Fever subsided on the third day, but fatigue severe enough to interfere with packing persisted for two weeks. She was seen on 25 January; her serum was positive to LV at a titre of 1: 8, as well as to filariasis by IFA and bentonite flocculation. It was negative to the arbovirus antigens used.

This account also shows the difficulties encountered in determining the likely place of origin of some of the infections.

CONCLUSION

The surveillance of missionaries residing in Africa has added Ivory Coast, Mali, and Central African Republic/Zaire to the area where Lassa fever is known to be present. To date missionary cases have contributed more to the determination of the dis-

tribution of the disease than cases among Africans. This may be due to our ability to obtain late sera from them; many African patients leave the hospital before the beginning of the fourth week of illness, when CF tests may be expected to be positive. The current series of new cases confirms earlier findings that not all patients with Lassa fever present with the severe syndrome originally described. Most of the adults had an illness with a fever of some note, and a few were prostrated. None of the cases among children could be associated with remarkable fever, though a parent did have illness compatible with one of the moderate to severe syndromes we associate with Lassa fever.

Table 6. Surveys for Lassa virus at 2 mission hospitals in Nigeria early in 1975

Source	No. sera	No. persons	No. positive
Evangel Hospital, Jos			
Patients	19	11	—
Staff	29	29	4[a]
Vom Christian Hospital			
Patients	13	13	2[b]

[a] Including 1 case discovered to be CF positive in 1970.

[b] In one additional case from this hospital LV was isolated from serum at the Center for Disease Control, Atlanta, GA.

ADDENDUM

Since this report was completed, another group of sera from 2 mission hospitals in Nigeria has been tested for LV antibodies. The results, uncorrected for anticomplementary or nonspecific reactions, are summarized in Table 6. None of 11 patients in the Evangel Hospital, Jos, gave evidence of LV infection; of 29 staff members tested, 4 Nigerians were positive for LV, including 1 known to be positive since 1970. In the Vom Christian Hospital, 2 of 13 patients were positive: an American missionary physician and a Nigerian nurse. Another Nigerian nurse died of LF during the same outbreak; LV was isolated from her serum by Dr Herta Wulff at the Center for Disease Control, Atlanta, GA.

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RÉSUMÉ

SURVEILLANCE DE LA FIÈVRE DE LASSA CHEZ LES MISSIONNAIRES RÉSIDANT EN AFRIQUE OCCIDENTALE

Depuis 1972, des sérums de sujets ayant présenté en Afrique des épisodes fébriles insolites ont été soumis à des épreuves de recherche des anticorps fixant le complément en présence de toute une série d'antigènes viraux, dont le virus de la fièvre de Lassa. Ces épreuves ont été effectuées à la Yale Arbovirus Research Unit sauf sur certain échantillons qui ne s'y prêtaient pas à cause de réactions anticomplémentaires ou de réactions non spécifiques. Sur 129 échantillons provenant de 94 malades admis dans des hôpitaux de mission en Afrique occidentale, huit contenaient des anticorps dirigés contre le virus de la fièvre de Lassa; cinq, dont deux provenant de missionnaires, correspondaient à des cas nouveaux de fièvre de Lassa. Depuis 1969, des cas de flèvre de Lassa ont été chaque année enregistrés dans les hôpitaux de mission du plateau de Jos en Nigéria, depuis cette même date, on ne compte qu'une seule année où l'on n'ait pas observé de poussées d'au moins deux cas présentant entre eux des liens épidémiologiques.

Parmi 104 missionnaires (114 échantillons de sérum) rentrés récemment d'Afrique, six étaient porteurs d'anticorps dirigés contre le virus de la fièvre de Lassa. Ces missionnaires avaient séjourné au Libéria, au Mali, en Haute-Volta, en Côte-d'Ivoire et au Zaïre (le dernier atteint s'était également trouvé en République Centrafricaine pendant la période d'incubation de la fièvre de Lassa). Deux autres cas étaient des enfants chez qui la maladie avait été bénigne.

A la faveur d'investigations spéciales portant uniquement sur le virus de la fièvre de Lassa dans deux hôpitaux de mission du Nigéria, on n'a trouvé aucun sérum positif parmi 19 échantillons provenant de 13 malades de Jos, mais quatre sérums étaient positifs (dont un provenant d'un sujet déjà connu pour être positif) parmi les échan-

tillons prélevés sur 29 membres du personnel hospitalier. Pour la localité de Vom, deux malades sur 13 étaient porteurs d'anticorps dirigés contre le virus de la fièvre de Lassa; chez un autre malade, qui finalement sucomba, le virus de la fièvre de Lassa a été isolé par le Center for Disease Control à Atlanta, Georgie, dans un échantillon prélevé pendant la phase aiguë de la maladie.

Des cas de fièvre de Lassa sont peut-être passés inaperçus dans certains hôpitaux parce que l'on n'avait pas de spécimens prélevés pendant la phase terminale de la convalescence, ou parmi les missionnaires chez qui les anticorps fixant le complément auraient disparus dans l'intervalle entre la maladie et la date des épreuves.

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DISCUSSION

MONATH: There seems to have been considerable variation in the interval between probable onset of illness and the date the serum was obtained. In a number of cases you obtained a serum very quickly after the onset, and in other cases there was some delay. What kind of surveillance system do you have with regard to missionary personnel? Are you contacting them on a regular basis to inquire about illness? What kind of mechanism exists to obtain specimens?

FRAME: I have the responsibility for the health of about 5000 Protestant missionaries from North America. In any given year I see about 400 or 500 adults and an equal number of children. If they have any history of fever whatsoever, we collect serum from them. In addition, we have notified the mission society headquarters that when anyone has a severe, febrile illness I should be notified. So the mission hospitals and mission personnel are becoming increasingly aware of the possibility of Lassa fever and we receive cables from them from time to time. Generally it is a difficult matter, however, to see that overseas personnel are sufficiently well informed.

HOTCHIN: Do you have any indication that perhaps there might be more danger of catching Lassa fever from another human patient than from the original rodent host. Is there any evidence that it is more virulent after a single passage in man?

FRAME: I do not think we have any hard evidence of that.

MONATH: There is some evidence that after the first generation of cases among people who are exposed to the initial or index case, transmission appears to cease. Only a few well documented instances of tertiary infection have occurred, and most of these are single episodes among people who have had parenteral exposures.