Lassa fever: epidemiology, clinical features, and social consequences

J Kay Richmond, Deborah J Baglole

Lassa fever is endemic in west Africa, where it probably kills several thousand people each year. With access to the region improving, the opportunity, and the need, to improve our understanding of this disease are increasing

Lassa fever is a viral haemorrhagic fever transmitted by rats. It has been known since the 1950s, but the virus was not identified until 1969, when two missionary nurses died from it in the town of Lassa in Nigeria. Found predominantly in west Africa,[1] it has the potential to cause tens of thousands of deaths. Even after recovery, the virus remains in body fluids, including semen.[1] The years of civil unrest in Sierra Leone (1991-2002) halted the investigation (through international collaboration) of Lassa fever at a specialist unit in Kenema. Increasing international travel and the possibility of use of the Lassa virus as a biological weapon escalate the potential for harm beyond the local level. Access to the country is improving, so renewed efforts to understand it are feasible.

Summary points

- Lassa fever, a viral haemorrhagic fever transmitted by rats, is endemic in west Africa and may kill tens of thousands of people each year
- Peak incidence was thought to be in the dry season (January to March), but data collected in Sierra Leone shows peaks in the overlap with the wet season (May to November)
- Many infections are subclinical; a high index of suspicion, given the difficulties of clinical diagnosis, is needed when travellers from west Africa present with a fever of unknown origin, with symptoms appearing up to 21 days after leaving the endemic area
- The virus is excreted in semen for three months after infection; we do not know how frequently it may be transmitted through sexual intercourse
- Attempts are being made to produce a vaccine using the yellow fever virus as a vehicle
- The possibility that Lassa virus could be used as a biological weapon has raised the profile of the need for greater understanding of Lassa fever and for more effective control and treatment programmes

Method of review

The information presented comes from a strategic document produced in 2002 for Merlin (Medical Emergency Relief International, a London based non-governmental aid organisation which manages the Lassa unit in Kenema (www.merlin.org.uk)). This document, *'Licking' Lassa fever*,[2] was created through collaboration with experts in infectious disease, community development, clinical management of viral haemorrhagic diseases, and qualitative research. The sources of information were a literature review using Ovid and PubMed (search term "Lassa fever"), case analysis and surveys undertaken in the field, and relevant websites (such as those of the World Health Organization, Centers for Disease Control and Prevention).

Epidemiology

Lassa fever is caused by a single stranded RNA virus and is a disseminated systemic primary viral infection.[3 4] The main feature of fatal illness is impaired or delayed cellular immunity leading to fulminant viraemia.[5] The prevalence of antibodies to the virus in the population is 8-52% in Sierra Leone,[6] 4-55% in Guinea,[7] and 21% in Nigeria.[8] Seropositivity has also been found in the Central African Republic, Democratic Republic of the Congo, Mali, and Senegal (see figure).[1] Staff from the UK Department for International Development, the International Committee of the Red Cross, and the United Nations Mission in Sierra Leone have succumbed. Sporadic cases have occurred in travellers returning to Britain, the Netherlands, and Germany.

The vector

The natural hosts for the virus are multimammate rats (*Mastomys natalensis*), which breed frequently and are distributed widely throughout west, central, and east

24 Llantrisant Rise, Llandaff, Cardiff CF5 2PG
J Kay Richmond
freelance consultant
Merlin, Borough, London SE1 1DB
Deborah J Baglole
health adviser
Correspondence to: J K Richmond Kayrichmondf4h@btinternet.com

BMJ 2003;327:1271–5

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Figs A-C and tables A and B on bmj.com provide details about Lassa fever in Sierra Leone

Distribution of Lassa fever in west Africa. Outbreaks have occurred in the Central African Republic, Guinea, Liberia, Nigeria, and Sierra Leone; serological evidence of human infection has been found in the Democratic Republic of the Congo, Mali, and Senegal

Africa.[3] They are probably the most common rodent in tropical Africa and are found predominantly in rural areas, and in dwellings more often than in surrounding countryside.[6] Members of the genus are infected persistently and shed the virus in their excreta. Humans are infected by contact with the rats or by eating them (they are considered a delicacy and are eaten by up to 90% of people in some areas). Rats found in houses of infected people are seropositive for the virus 10 times more often than those in control houses.[9] Virus antibodies occur after a febrile illness in twice as many people who eat rats as in those who do not, and deafness (an effect of Lassa fever) occurs four times more frequently.[10]

Morbidity and mortality

Presentation of cases used to be highest during the dry season (January to March) and lowest during the wet season (May to November). However, recent data from Kenema (1999-2002) show that admissions were highest during the change from the dry to the wet season (see fig A on bmj.com). This change might be related partly to population movements during the civil unrest in Sierra Leone (see fig B on bmj.com)[11] and overcrowding among refugees. Travel becomes increasingly difficult as the wet season progresses and may help to account for the decrease in numbers of cases later in the season. All the cases reported were diagnosed clinically. Until 1998 laboratory confirmation of diagnosis was available retrospectively and 60-70% of cases were confirmed,[12] but in 2000 over half of a series of 22 cases were wrongly diagnosed. Thus, these recent apparent changes in infection patterns must be interpreted with caution.

People of all ages are susceptible. The disease is mild or has no observable symptoms in about 80% of people infected, but 20% have a severe multisystem disease. The incubation period is 6-21 days. The virus is excreted in urine for three to nine weeks from infection and in semen for three months.[1] The extent of sexual transmission is unknown.

Sensorineural hearing deficit is a feature of the disease: it was found in 29% of confirmed cases compared with none of febrile controls in hospital inpatients.[13] In the general population, 81% of those who experienced sudden deafness had antibodies to Lassa virus versus 19% of matched controls. There is no apparent relation between the severity of viral illness, initial hearing loss, or subsequent recovery.[14]

Lassa fever was responsible for 10-16% of all adult medical admissions in 1987 in two hospitals studied in Sierra Leone and for about 30% of adult deaths.[15] The case fatality rate in Kenema varied from 12% to 23% for the period 1997-2002. A recent case series showed low admission rates and high case fatality rates for people aged less than 18 years (who make up 51% of the total population (United Nations Development Programme)) compared with older people (see table A on bmj.com). During pregnancy, high rates of maternal death (29%) and fetal and neonatal loss (87%) have been recorded (uterine evacuation improves outcome significantly), with 25% of all maternal deaths in Sierra Leone being due to Lassa fever.[16] An estimate of the case fatality rate in the general population is 1-2%, much lower than in hospitalised cases, possibly as a consequence of differences in severity.

Using the figures for rural populations (available from the United Nations Development Programme) and the epidemiology of the disease, we estimate that the "at risk" seronegative population (in Sierra Leone, Guinea, and Nigeria) may be as high as 59 million, with an annual incidence of illness of three million, fatalities up to 67 000, and up to three million reinfections (table 1). Until a complete picture of Lassa fever is known, these are rough estimates. Comparable data are unavailable for the other countries where seropositivity has been recorded.

Peace keepers within Sierra Leone have been affected by Lassa fever.[17] Case records in Kenema for July-September 2002 show 11 admissions from the Sierra Leone army and 10 from the United Nations mission in Sierra Leone, with one death in each group.

Table 1 Estimates of seropositivity and mortality from Lassa fever in Guinea, Nigeria, and Sierra Leone (values are numbers of people unless stated otherwise)

Seropositivity and mortality	Guinea	Nigeria	Sierra Leone	Overall
Estimated rural population*	5 544 720	64 787 478	2 823 605	73 155 803
Seronegativity in general population (%):				
Lowest	45.0	NA	48.0	
Highest	96.0	78.7	92.0	
Population "at risk" (seronegative):				
Lowest	2 495 124	NA	1 355 330	
Highest	5 322 931	50 987 745	2 597 717	58 908 393
Seroconversions per year:				
Lowest (5%)	124 756	NA	67 767	
Highest (22%)	1 171 045	11 217 304	571 498	12 959 847
Seroconversion plus illness per year:				
Lowest (9%)	11 228	NA	6 099	
Highest (26%)	304 472	2 916 499	148 589	3 369 560
Ratio of fatality to infection per year:				
Lowest (1%)	112	NA	61	
Highest (2%)	6 089	58 330	2 972	67 391
Estimated seropositivity (%):				
Lowest	4%	NA	8%	
Highest	55%	21.3%	52%	
Estimated numbers seropositive:				
Lowest	221 789	NA	225 888	
Highest	3 049 596	13 799 733	1 468 275	18 317 604
Estimates of annual reinfection:				
Lowest (1%)	2 218	NA	2 259	
Highest (18%)	548 927	2 483 952	264 289	3 297 168

*Data from United Nations Development Programme.
NA=Not available.

Clinical course

Lassa fever presents with symptoms and signs indistinguishable from those of febrile illnesses such as malaria and other viral haemorrhagic fevers such as Ebola. It is difficult to diagnose clinically but should be suspected in patients with fever (≥38°C) not responding adequately to antimalarial and antibiotic drugs (table 2). The most useful clinical predictors of Lassa fever are fever, pharyngitis, retrosternal pain, and proteinuria for diagnosis; and fever, sore throat, and vomiting for outcome.[15]

Complications include mucosal bleeding (17%), sensorineural hearing deficit (4%), pleural effusion (3%), and pericardial effusion (2%).[15] The outcome is related to the degree of viraemia, not the antibody response, and is worse with high levels of aspartate aminotransferase.[4]

On the basis of a case series of 140 men and 128 women admitted in Kenema during 2001, the duration of illness can vary considerably (table B on bmj.com). The commonest interval between onset of symptoms and discharge was 17 days (half of the patients were in hospital for 10 days) and between onset and death was five days (half died within two days of admission). Delays between onset and admission resulted in most patients not receiving ribavirin within the critical first six days. These data add to the uncertainty surrounding diagnosis and lethality.

Laboratory investigation

At hospital admission, most patients have antibodies to the virus (53% with IgG and 67% with IgM).[4] Together, enzyme linked immunosorbent assays (ELISAs) for Lassa virus antigen and for virus IgM are 88% sensitive and 90% specific for acute infection.[19] Other effects of illness include lymphocytopenia and a moderate thrombocytopenia, which are maximal 10-11 days after the onset of symptoms.[20] The thrombocytopenia is associated with a serum inhibitor and with the occurrence of haemorrhage, depression of platelet aggregation, and the severity of Lassa fever.[21] With reverse transcription polymerase chain reaction, Lassa fever can be diagnosed in all patients by the third day of illness, but immunoflourescence identifies only 52% of the patients.[22]

Clinical management

All suspected cases should be admitted to isolation facilities. Hospital transmission occurs through inadequate infection control measures.[23] Strict isolation of cases and procedures for handling body fluids and excreta must be maintained.[2]

Treatment

Ribavirin and general support are needed.[24] Ribavirin is almost twice as effective when given intravenously as when taken orally, and if given within six days of the start of illness it may reduce deaths by 90%. Dehydration, oedema, hypotension, and poor renal function are common; fluid replacement or the use of blood transfusion requires careful monitoring.

Surveillance and disease control

Surveillance should identify all close contacts of the patients for three weeks after the start of illness, and a search initiated for unreported or undiagnosed cases.[1] Two areas of concern are, firstly, the treatment of undiagnosed cases in hospitals where overcrowding and poor hygiene can spread the disease to other patients, staff, or visitors; and, secondly, traditional burial ceremonies for infected corpses, with the possible risk of spread to many people.

Table 2 Clinical stages of Lassa fever (adapted from McCarthy 2002[18])

Stage	Symptoms
1 (days 1-3)	General weakness and malaise. High fever, >39°C, constant with peaks of 40-41°C
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side, or abdominal pain; conjunctivitis; nausea and vomiting; diarrhoea; productive cough; proteinuria; low blood pressure (systolic <100 mm Hg); anaemia
3 (after 7 days)	Facial oedema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

Vaccine

Production of a combined, single dose vaccine against yellow fever and Lassa fever has been proposed.[25] The cost and logistical problems of delivering it would be huge, particularly since fewer than 20% of districts in the countries studied achieve 80% uptake of childhood vaccination.[2] Use for visitors from the United Nations, non-governmental organisations, and business communities might make it financially viable, even though it is the most expensive of the possible control strategies.

Community perspectives

Civil unrest severs supply and trading links, and people want for basic commodities. Migration disrupts agricultural cycles, reduces farming activities, and encourages looting, killing of livestock, and destruction of property. People are forced into overcrowded camps and public buildings, and spread of communicable diseases is facilitated.

Adverse influences of Lassa fever on socioeconomic wellbeing are mediated through the inability of patients to care for themselves and their dependants, the high death rate in hospital, nosocomial transmission to staff and the subsequent loss of service, and the occurrence of hearing loss through clinical and subclinical infection.

Knowledge, attitude, and practice survey

During 2001, a knowledge, attitude, and practice survey was undertaken in Kenema among 813 men and 867 women in four camps for internally displaced people and eight primary health units. The survey revealed a reasonable knowledge of Lassa fever, its mode of transmission, control measures, and the seriousness of the disease. However, there were some worrying gaps in application of this knowledge, such as inappropriate actions after killing rats (see fig C on bmj.com). This was demonstrated by the occurrence of an outbreak of 823 cases, including 153 deaths (case fatality rate 19%), from January 1996 to April 1997, after an extensive outreach programme.[1] The need for greater understanding of the perceptions and beliefs of the local population became apparent.

Qualitative study

A small pilot study (of 23 people) was undertaken through focus groups and interviews in 2002. The major concerns related to

- Effective rodent control ("We have a rat which happens to be the sweetest meat, and you tell that person not to eat that meat because it creates Lassa fever")
- People understood that Lassa fever can be contracted through contact with an affected person—this leads to patients and their families being isolated and stigmatised ("When my wife was admitted to Lassa ward, well, it was not only an economic depression, it also created social embarrassment, because my children no longer go to other houses, to their relatives")
- Early diagnosis is impeded by the absence of a diagnostic test for use in the community and difficulties reaching health facilities ("No, no, what are you trying to tell me? I don't want you to be guessing in Lassa.… As far as Lassa is concerned, you have to be very much more serious, you don't have to be hypothetical, you have to correct in your diagnosis when you are treating Lassa fever … we need a lab." "In the rainy seasons, the river runs, there is no means of transportation. Others, the location of the health facility is so far away, there is no ambulance service to transport the sick")
- Many people are unlikely to seek medical care if they suspect they have Lassa fever: treatment is expensive and can usually be afforded only by sacrificing necessities such as food and school fees ("There will be lots of gossiping, because there is no money at home and no food at home, you have to go to friends to get you some food, so you can help the children, or to take to the hospital")
- Belief in traditional remedies and mistrust of treatment offered at the hospital were described ("There are certain people in the community we live in, they believe in herbs, in going to the bush to get some tea herbs … they think herbs can mend them" "People don't go to medical facilities … especially when they say they have Lassa fever, they will be given injections to kill them")
- Miscarriage is blamed on the woman, is often attributed to witchcraft, and commonly leads to divorce ("People class you as a witch because you have aborted")
- Deafness was described as a social embarrassment and as having a catastrophic effect on family relationships ("She is now like someone who is crazy, stupid, because she has lost her hearing sense").

Many of these factors lead to social exclusion.

Research needs

The epidemiology of both rat and human populations requires urgent investigation if we are to understand this disease fully. It could be done through developing

- International collaboration over research
- A map of the complete epidemiological and clinical story
- Involvement of the communities affected
- Effective and affordable diagnostic kits and treatment
- Efficient and effective specialist treatment centres
- An effective and affordable vaccine to control the infection in its natural habitat, protect international visitors, and deter the use of the virus as an agent of biological warfare.

The terrorist attack in New York on 11 September 2001 and the subsequent anthrax attacks served to alert governments to the potential of biological agents as weapons. A special report in the *Lancet* signposts increased funding for the National Institute for Allergy and Infectious Disease and its blueprint for research, including Lassa fever.[18] Thus, the need for a greater understanding of Lassa fever and for more effective control and treatment programmes has assumed a higher profile. The time is ripe for a concerted international effort to achieve these ends.

Additional educational resources

Merlin. Lassa fever publications—www.merlin.org.uk/template7.asp?PageID = 178

WHO Information. Fact sheets: Lassa fever—www.who.int/inf-fs/en/fact179.html

WHO Communicable Disease Surveillance and Response (CSR). Lassa fever—www.who.int/csr/disease/lassafever/en/

WHO Communicable Disease Surveillance and Response (CSR). Disease outbreaks: Lassa fever—www.who.int/disease-outbreak-news/disease/A96.2.htm

CDC. Infectious disease information: viral hemorrhagic fever—www.cdc.gov/ncidod/diseases/virlfvr/virlfvr.htm

Health Protection Agency. Viral haemorrhagic fever (VHF)—www.hpa.org.uk/infections/topics_az/VHF/menu.htm

National Institute of Allergy and Infectious Diseases. *NIAID biodefense research agenda for CDC category A agents*. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, 2002 (www.niaid.nih.gov/biodefense/research/biotresearchagenda.pdf).

This article is based on the Merlin document *'Licking' Lassa fever*. We are grateful for comments on drafts from Dr Edward Coyle, director of Wales Centre for Health, Cardiff, and Professor T Cullinan, TB health adviser for Merlin, London.

Funding: *'Licking' Lassa fever* was produced under a grant from the Rockefeller Foundation.

Competing interests: JKR was employed by Merlin in 2002 as country medical coordinator in Sierra Leone and as main author and collator of the paper '*Licking' Lassa fever*. DJB is employed by Merlin as a health adviser with responsibility for Sierra Leone.

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Lesson of the week

Colchicine in acute gout

Ian Morris, George Varughese, Peter Mattingly

We describe three histories of patients with gout who were treated with doses of colchicine as advised by the *British National Formulary* (BNF)—that is, 1 mg initially followed by 500 µg every 2-3 hours until relief of pain is obtained or vomiting or diarrhoea occurs or until a total dose of 6 mg has been reached; the course should not be repeated within three days.[1] All three patients developed nausea or diarrhoea with this regimen. We consider that an alternative low dose schedule should be used to avoid such adverse events.

Case reports

Case 1—A 91 year old woman with a history of ischaemic heart disease and non-insulin dependent diabetes developed an ulcer over the right first metatarsophalangeal joint, which was discharging a white toothpaste-like material containing urate crystals. She was given 1 mg colchicine and then 500 µg every three hours, but she developed diarrhoea, and colchicine was stopped. After three days, the toe was still painful, and the course was repeated. She developed severe diarrhoea again and became dehydrated and unwell. We rehydrated her intravenously and gave her meloxicam. After the first few days we started her on colchicine 500 µg daily. She tolerated this well and it helped with pain relief.

Case 2—An 88 year old woman with a history of ischaemic heart disease, atrial fibrillation, congestive cardiac failure, chronic renal failure, hypertension, and osteoarthritis was admitted with pain in her right knee. Investigations led to a diagnosis of acute gouty monoarthritis (serum urea 27.1 mmol/l, serum creatinine 236 µmol/l, and serum uric acid 920 mmol/l). She was given 1 mg colchicine and then 500 µg every eight hours (a reduced dose because the BNF advises caution with renal and cardiac impairment). Within two days she developed nausea and vomiting. We stopped colchicine for 24 hours and then resumed with 500 µg twice a day. This improved her right knee pain without further nausea.

Case 3—A 56 year old man in general good health with recurrent acute gout found that non-steroidal anti-inflammatory drugs were ineffective and productive of severe indigestion; therefore he was given 1 mg colchicine and 500 µg every three hours for acute attacks. With this regimen, he had diarrhoea and sickness, and the acute attacks of gout continued. We reduced colchicine to 500 µg two or three times a day, which was effective without adverse event.

Discussion

The current BNF recommends a regimen for colchicine which is unchanged since the 1966 edition. The same regimen was also expressed in grains in Hollander's *Textbook of Rheumatology*, 1960. (The BNF is an authoritative guide on drugs and their use. In a recent survey of general medical staff in our hospital, of the 17 respondents, 12 said they would follow the BNF's advice, three gave no indication as to what dose they would use, one suggested an improbably large dose, and one would never use colchicine.)

The BNF states that colchicine is probably at least as effective as a non-steroidal anti-inflammatory drug in an acute attack of gout (although to our knowledge only one double blind placebo controlled study has been done with colchicine in gout,[2] and none has been done for NSAIDs and gout). The BNF also states that colchicine does not induce fluid retention and can therefore be used in heart failure, and it can be given to patients on anticoagulants. Thus the non-specialist is encouraged to use colchicine, especially when other treatments such as non-steroidal anti-inflammatory drugs or sometimes steroids (whether local or systematic) are inappropriate or ineffective. The BNF cautions about gastrointestinal disease, cardiac, hepatic, and renal insufficiency, but the only contraindication noted is pregnancy.

Although non-specialists are likely to prescribe the regimen as given, many rheumatologists have never used such high doses because they were trained to use

In acute gout, lower doses of colchicine are effective yet less toxic than traditional regimens

Department of Rheumatology, Kettering General Hospital, Kettering, Northamptonshire NN16 8UZ
Ian Morris *consultant rheumatologist*
George Varughese *senior house officer*
Peter Mattingly *consultant rheumatologist*
Correspondence to: I Morris ian.morris@kgh.nhs.uk

BMJ 2003;327:1275–6