

Lassa Fever in Travelers from West Africa, 1969–2016

Aaron Kofman, Mary J. Choi, Pierre E. Rollin

Lassa virus is a rodentborne arenavirus responsible for human cases of Lassa fever, a viral hemorrhagic fever, in West Africa and in travelers arriving to non-Lassa-endemic countries from West Africa. We describe a retrospective review performed through literature search of clinical and epidemiologic characteristics of all imported Lassa fever cases worldwide during 1969–2016. Our findings demonstrate that approximately half of imported cases had distinctive clinical features (defined as fever and ≥ 1 of the following: pharyngitis, sore throat, tonsillitis, conjunctivitis, oropharyngeal ulcers, or proteinuria). Delays in clinical suspicion of this diagnosis were common. In addition, no secondary transmission of Lassa fever to contacts of patients with low-risk exposures occurred, and infection of high-risk contacts was rare. Future public health investigations of such cases should focus on timely recognition of distinctive clinical features, earlier treatment of patients, and targeted public health responses focused on high-risk contacts.

Originally discovered in 1969, Lassa fever is a rodentborne viral hemorrhagic fever endemic to West Africa and caused by Lassa virus (1). The clinical course of Lassa fever is either not recognized or mild in 80% of patients; however, $\approx 20\%$ of patients might experience severe disease, including facial swelling, hepatic and renal abnormalities, pulmonary edema, and hemorrhage. Although overall case-fatality rates for patients with Lassa fever is $\approx 1\%$, rates among hospitalized case-patients are $\geq 15\%$ (2). Intravenous administration of the antiviral drug ribavirin has become the standard of care for treatment of Lassa fever, but data on the efficacy of intravenous ribavirin are limited. The original study among Lassa fever patients in Sierra Leone found survival to be significantly higher ($p = 0.0002$) among those who obtained ribavirin within the first 6 days of illness (55%) compared with those who never received the drug (5%) (3). In the United States, intravenous ribavirin use is still considered investigational and may only be obtained through Emergency Investigational New Drug application to the US Food and Drug Administration (4).

Author affiliation: Centers for Disease Control and Prevention, Atlanta, Georgia, USA

DOI: <https://doi.org/10.3201/eid2502.180836>

Diagnosis of Lassa fever in patients arriving from West Africa might be challenging for healthcare providers unfamiliar with the spectrum of its clinical presentation, a challenge that is also common to the consideration of other viral hemorrhagic fevers in returning travelers (5–7). Additionally, although Lassa virus is not transmitted through casual contact, contact-tracing investigations of returning case-patients have often been large in scale (8). To quantify the frequency of case-patients having distinctive clinical features, time from patient presentation to clinical suspicion of a Lassa fever diagnosis, and the risk for secondary Lassa virus transmission, we performed a retrospective review of all 33 reported cases of Lassa fever imported from West Africa during 1969–2016.

Methods

We searched PubMed for publications using the terms “Lassa” and “Lassa fever.” We identified additional articles by reviewing references in retrieved reports (9) and official correspondence by public health officials involved in these cases. We selected 74 publications discussing clinical or epidemiologic aspects of the 33 imported Lassa fever cases for review and collected information pertaining to case demographics, distinctive clinical features suggestive of Lassa fever, time from patient seeking care to clinical suspicion of Lassa fever, and number of contacts traced. We defined distinctive clinical features as fever and ≥ 1 of the following: sore throat or pharyngitis, retrosternal chest pain, or proteinuria. We selected these features on the basis of the cumulative positive predictive value for fever, sore throat, retrosternal chest pain, and proteinuria for Lassa fever of 0.81 in a case-control study among 441 hospitalized patients in Sierra Leone (10). Although precise definitions varied between investigations, high-risk contacts were typically defined as contacts with substantial direct contact with patients or their body fluids.

Findings

During 1969–2016, a total of 33 patients traveling from 7 West Africa countries to 9 other countries were diagnosed with Lassa fever (Appendix Table 1, <https://wwwnc.cdc.gov/EID/article/25/2/18-0836-App1.pdf>). The median age of these patients was 45 years (range 18–72 years). Potential sources of Lassa fever exposures varied. Eleven

patients were healthcare workers working in West Africa with either known or suspected exposures to Lassa fever patients; 4 patients had known exposure to rodents or history of travel to rural areas in West Africa. The only known risk factor for 18 patients was living in or traveling to West Africa. Twenty patients had illness onset during the West Africa dry season (November–April), and 10 patients had onset during the wet season (May–October); time of year for disease onset was not specified for 3 patients.

Twenty patients traveled to their destination on a commercial airliner; of these, 12 were symptomatic during flight. Ten patients were medically evacuated, 6 of whom had a known or suspected exposure to Lassa fever at the time of evacuation. Information on method of travel was not available for 3 patients. At the time patients sought care, medical providers were aware of travel history to West Africa for 26 (87%) of 30 patients; ascertainment of travel histories by medical providers was not described for 3 cases.

Of the 29 patients for whom clinical information was available (Appendix Table 2), 17 (59%) had fever and ≥ 1 distinctive clinical features of Lassa fever. Time from patients seeking medical care to clinical suspicion of Lassa fever by clinical providers in their destination country ranged from 1 to 22 days (median 5 days). The time from when patients sought care to patient isolation ranged from 1 to 25 days (median 7 days). We found no reports of Lassa virus PCR testing performed on any patient before 2000; however, 9 of 16 patients (56%) in 2000 and later years had a positive Lassa virus PCR test within 1–2 days of hospital admission. Of the 32 patients for whom information on isolation procedures were described, 24 patients were isolated at some point during their hospitalizations in their destination countries. Of these, 11 (34%) patients were placed in a form of isolation immediately after they sought medical care; 3 patients were transferred to biocontainment units, and the remaining 8 patients were isolated with techniques ranging from standard precautions to a combination of contact, droplet, and airborne precautions. Of the 13 patients who were isolated later in their hospital stay, 2 patients were isolated with contact and airborne precautions, and 11 were subsequently transferred to specialized hospitals with infection control capacity designed for the care of patients with highly infectious diseases. Time to isolation ranged from 3 to 15 days after hospital admission (11). The last 2 patients who sought care in the United States were admitted to dedicated Ebola treatment units established during the 2014–2015 West Africa Ebola epidemic. Of the 31 patients for whom outcomes were described, 12 patients died, yielding a case-fatality rate of 39%.

Treatment regimens were described for 23 patients. Twelve (52%) patients initially received antimalarial medications or antimicrobial drugs because of clinical suspicion of malaria or another infectious disease during

their treatment course. In total, intravenous ribavirin was ordered for 7 (30%) patients. Four patients received intravenous ribavirin; 2 received a full course, and the other 2 died during treatment. Three patients had intravenous ribavirin ordered but died before receiving the medication.

Contact tracing investigations were either not performed or not described in the literature for 16 (48%) patients. For the remaining 17 (52%) patients, a total of 3,420 contacts were followed; the number of contacts followed per investigation ranged from 3 to 552 (median 173). Eleven contact investigations stratified contacts into high-risk and low-risk contacts, with some further separating high-risk contacts into first-line or second-line contacts (12). High-risk contacts were defined as having substantial exposure to patients or their body fluids, such as through direct unprotected exposure to blood or other body fluids from a case-patient. By these criteria, 139 total contacts were defined as being high-risk across 11 investigations. In 9 investigations, high-risk contacts accounted for 2%–8% of total contacts; in 2 investigations, they accounted for 40%–60% of total contacts.

Only 2 cases of secondary transmission of Lassa virus occurred, both in Germany. Neither of the source case-patients for these 2 patients was isolated. The first instance of transmission occurred to a physician who performed a physical examination, obtained intravenous access, and obtained blood samples from a Lassa fever patient without wearing any personal protective equipment (13). Because of the physician's high-risk exposure, ribavirin prophylaxis was initiated and completed. Serologic testing was performed and yielded IgG titers of 1:320 specific to the strain of Lassa virus from the case-patient, indicating probable seroconversion in the physician. However, the physician remained asymptomatic.

The second instance of secondary transmission, reported in 2016, occurred in a mortician who handled the body of a healthcare worker who was evacuated from Togo to Germany and diagnosed with Lassa fever retrospectively. The mortician reported wearing 2 pairs of gloves when handling the corpse but did not wear an apron or a facial mask. The mortician reported mild upper respiratory tract symptoms before contact with the deceased patient. However, 4 days after handling the corpse, his symptoms worsened. Six days after handling the corpse, the mortician tested positive for Lassa virus by real-time reverse transcription PCR. The mortician's clinical course was notable for fever, upper respiratory tract symptoms, and pharyngeal erythema with exudates, myalgias, and arthralgias. He received intravenous ribavirin for 10 days and oral favipiravir for 4 days, with gradual resolution of his symptoms and clinical recovery (14,15). Contacts of this secondary case-patient were followed but did not indicate any evidence of further transmission.

Discussion

The 33 cases of imported Lassa fever that occurred during 1969–2016 posed a similar set of challenges: timely diagnosis of a rare infectious disease not endemic to the patient's destination country, timely treatment, and prevention of Lassa virus transmission to contacts. Among patients who were not medically evacuated, the median number of days from patient presentation to clinical suspicion of Lassa fever by clinicians in the destination country was 5 days. Several factors might have contributed to this delay in diagnosis. First, patients were seen by providers in countries where Lassa fever is not endemic, requiring consideration of a travel-associated illness infrequently encountered outside of West Africa. Second, in many cases, the patients' travel to West Africa was not known at the time they initially sought care. Third, the clinical findings of Lassa fever are variable, ranging from nonspecific symptoms, such as fever, nausea, and myalgias in the early phase, to more distinctive features later, including pharyngitis, sore throat, tonsillitis, oropharyngeal ulcers, facial and neck swelling, conjunctival injection, and proteinuria. Hemorrhage is usually seen only in a minority of cases. Although fever and ≥ 1 distinctive clinical features can be suggestive of the diagnosis, they were only present in 59% of patients. In addition, of patients with a known travel history to West Africa, 12 (48%) did not demonstrate distinctive clinical features of Lassa fever. As such, providers encountering patients who have a nonspecific febrile illness after travel to West Africa should elicit a travel history and consider Lassa fever early in the differential diagnosis. Suspicion should be especially high for those patients with fever and ≥ 1 of the distinctive features we have described. Although most returning travelers from West Africa with Lassa fever in 2000 or later had viremia confirmed through a positive Lassa virus test obtained within 1–2 days of admission, some patients did not have their illness diagnosed until weeks into their illness. Samples of patients with suspected Lassa fever should be obtained as early as possible and tested by Lassa virus PCR at a reference laboratory; most reference laboratories in Europe and elsewhere have demonstrated proficiency in performing Lassa virus molecular diagnostics (16,17).

Treatment of Lassa fever comprises effective supportive care and use of intravenous ribavirin. Although timely treatment with intravenous ribavirin depends on successful procurement of the drug, it also rests on early consideration of the diagnosis, and might even be administered before laboratory confirmation of Lassa fever diagnosis in patients with severe illness. The relative minority of case-patients who received intravenous ribavirin in our review highlights the importance of early consideration of Lassa fever in the differential diagnosis for appropriate patients.

Infection control was another challenge encountered by medical providers and healthcare systems caring for

Lassa fever patients. The lack of appropriate use of isolation or barrier precautions in the 2 instances of secondary transmission speaks to the importance of adhering to standard precautions when caring for all patients, regardless of their diagnosis or presumed infectious status. In addition, the case of secondary transmission to the mortician in Germany illustrates the importance of maintenance of standard precautions during autopsy. Early consideration of Lassa fever as a diagnosis might also enable early institution of isolation and prevention of secondary transmission. Among those case-patients for whom a specific form of isolation was specified, most were admitted to high-security containment facilities or negative-pressure rooms with airborne precautions. Although these forms of isolation can prevent secondary transmission of Lassa virus, simple barrier or contact precautions have also been demonstrated to be safe and are less expensive and labor-intensive (5,18).

Contact tracing investigations frequently involved hundreds of contacts and a substantial investment of time and labor on the part of public health teams. One investigation noted that "active surveillance of contacts by public health teams was impracticable and required enormous resources, involving over 3,000 communications" (6). Most investigations were similarly comprehensive, involving identification and longitudinal follow-up of case-patients' friends, family, and casual contacts, including airplane passengers, as well as numerous healthcare staff. Contacts were often separated into 2 categories: high-risk (i.e., having substantial exposure to case-patients) and low-risk (i.e., having only casual contact or proximity to case-patients). However, body temperature monitoring, home visits, and serologic testing were frequently coordinated for contacts in both high- and low-risk categories. To minimize the burden on public health systems and maximize the likelihood of successful secondary case identification, future responses should consider focusing on investigating high-risk contacts exclusively.

Our review had several limitations. Information on historic cases, particularly those before 1985, was incomplete and limited. In some cases, reports provided scant or no information on the physical examination or laboratory studies of patients upon admission. Reports on contact tracing provided different degrees of detail, and levels of risk assessment were variable between investigations.

With the ease and frequency of international travel, Lassa fever will continue to be encountered by healthcare providers in countries where Lassa fever is not endemic. Strict maintenance of standard infection control precautions in healthcare is critical for all patients and will help prevent secondary transmission of Lassa virus. Timely recognition of distinctive clinical features, earlier treatment of patients, and targeted public health responses focused on high-risk contacts will also be important components of future responses to imported cases of Lassa fever.

About the Author

Dr. Kofman is an Epidemic Intelligence Service Officer in the Viral Special Pathogens Branch, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC. His research interests are viral hemorrhagic fevers, including Lassa fever and Ebola virus disease.

References

1. Frame JD, Baldwin JM Jr, Gocke DJ, Troup JM. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *Am J Trop Med Hyg.* 1970;19:670–6. <http://dx.doi.org/10.4269/ajtmh.1970.19.670>
2. World Health Organization. Lassa fever fact sheet [cited 2018 May 15]. <http://www.who.int/mediacentre/factsheets/fs179>
3. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever. Effective therapy with ribavirin. *N Engl J Med.* 1986;314:20–6. <http://dx.doi.org/10.1056/NEJM198601023140104>
4. Riner A, Chan-Tack KM, Murray JS. Original research: Intravenous ribavirin—review of the FDA’s Emergency Investigational New Drug Database (1997–2008) and literature review. *Postgrad Med.* 2009;121:139–46. <http://dx.doi.org/10.3810/pgm.2009.05.2014>
5. Fisher-Hoch SP, Price ME, Craven RB, Price FM, Forthall DN, Sasso DR, et al. Safe intensive-care management of a severe case of Lassa fever with simple barrier nursing techniques. *Lancet.* 1985;2:1227–9. [http://dx.doi.org/10.1016/S0140-6736\(85\)90752-4](http://dx.doi.org/10.1016/S0140-6736(85)90752-4)
6. Crowcroft NS, Meltzer M, Evans M, Shetty N, Maguire H, Bahl M, et al. The public health response to a case of Lassa fever in London in 2000. *J Infect.* 2004;48:221–8. <http://dx.doi.org/10.1016/j.jinf.2003.11.009>
7. Beeching NJ, Fletcher TE, Hill DR, Thomson GL. Travellers and viral haemorrhagic fevers: what are the risks? *Int J Antimicrob Agents.* 2010;36(Suppl 1):S26–35. <http://dx.doi.org/10.1016/j.ijantimicag.2010.06.017>
8. Galbraith NS, Berrie JRH, Forbes P, Young S. Public health aspects of viral haemorrhagic fevers in Britain. *R Soc Health J.* 1978; 98:152–60. <http://dx.doi.org/10.1177/146642407809800407>
9. Macher AM, Wolfe MS. Historical Lassa fever reports and 30-year clinical update. *Emerg Infect Dis.* 2006;12:835–7. <http://dx.doi.org/10.3201/eid1205.050052>
10. McCormick JB, King IJ, Webb PA, Johnson KM, O’Sullivan R, Smith ES, et al. A case-control study of the clinical diagnosis and course of Lassa fever. *J Infect Dis.* 1987;155:445–55. <http://dx.doi.org/10.1093/infdis/155.3.445>
11. Smith PW, Anderson AO, Christopher GW, Cieslak TJ, Devreede GJ, Fosdick GA, et al. Designing a biocontainment unit to care for patients with serious communicable diseases: a consensus statement. *Biosecur Bioterror.* 2006;4:351–65. <http://dx.doi.org/10.1089/bsp.2006.4.351>
12. Cooper CB, Gransden WR, Webster M, King M, O’Mahony M, Young S, et al. A case of Lassa fever: experience at St Thomas’s Hospital. *Br Med J (Clin Res Ed).* 1982;285:1003–5. <http://dx.doi.org/10.1136/bmj.285.6347.1003>
13. Haas WH, Breuer T, Pfaff G, Schmitz H, Köhler P, Asper M, et al. Imported Lassa fever in Germany: surveillance and management of contact persons. *Clin Infect Dis.* 2003;36:1254–8. <http://dx.doi.org/10.1086/374853>
14. Raabe VN, Kann G, Ribner BS, Morales A, Varkey JB, Mehta AK, et al.; Emory Serious Communicable Diseases Unit. Favipiravir and Ribavirin Treatment of Epidemiologically Linked Cases of Lassa Fever. *Clin Infect Dis.* 2017;65:855–9. <http://dx.doi.org/10.1093/cid/cix406>
15. Ehlkes L, George M, Samsosny G, Burckhardt F, Vogt M, Bent S, et al. Management of a Lassa fever outbreak, Rhineland-Palatinate, Germany, 2016. *Euro Surveill.* 2017;22:1–8. <http://dx.doi.org/10.2807/1560-7917.ES.2017.22.39.16-00728>
16. Nikisins S, Rieger T, Patel P, Müller R, Günther S, Niedrig M. International external quality assessment study for molecular detection of Lassa virus. *PLoS Negl Trop Dis.* 2015;9:e0003793. <http://dx.doi.org/10.1371/journal.pntd.0003793>
17. Trombley AR, Wachter L, Garrison J, Buckley-Beason VA, Jahrling J, Hensley LE, et al. Comprehensive panel of real-time TaqMan polymerase chain reaction assays for detection and absolute quantification of filoviruses, arenaviruses, and New World hantaviruses. *Am J Trop Med Hyg.* 2010;82:954–60. <http://dx.doi.org/10.4269/ajtmh.2010.09-0636>
18. Helmick CG, Webb PA, Scribner CL, Krebs JW, McCormick JB. No evidence for increased risk of Lassa fever infection in hospital staff. *Lancet.* 1986;2:1202–5. [http://dx.doi.org/10.1016/S0140-6736\(86\)92206-3](http://dx.doi.org/10.1016/S0140-6736(86)92206-3)

Address for correspondence: Aaron Kofman, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30329-4027, USA; email: yct7@cdc.gov

Lassa Fever in Travelers from West Africa, 1969–2016

Appendix

Appendix Table 1. Demographic and travel-related characteristics of imported Lassa fever (LF) cases, 1969–2016

Case no.	Year	Origin country	Destination country	Age, y	Sex	Suspected route of exposure
1 (1–5)	1969	Nigeria	United States (NY)	52	F	Nurse in Nigeria caring for LF patients
2 (6)	1971	Sierra Leone	United Kingdom	?	F	Nurse in Nigeria caring for LF patients
3 (6)	1971	Sierra Leone	United Kingdom	?	M	Doctor in Sierra Leone likely caring for LF patients
4 (7)	1972	Sierra Leone	United Kingdom	35	F	Nurse in Sierra Leone, needle-stick from patient with unknown illness who later died
5 (8–10)	1974	Nigeria	Germany	?	M	Doctor in Nigeria caring for physician with LF
6 (11,12)	1975	Nigeria	United Kingdom	39	M	Doctor in Nigeria
7 (13–17)	1976	Sierra Leone	United States (DC)	42	F	Lived in Sierra Leone in house with rodents
8 (18)	1976	Nigeria	United Kingdom	33	M	Working in Nigeria
9 (19–22)	1980	Burkina Faso	Netherlands	34	M	Working in Burkina Faso, manure seen near house
10 (23–25)	1981	Nigeria	United Kingdom	18	F	Lived/worked in Nigeria
11 (26)	1982	Nigeria	United Kingdom	21	F	Lived in Nigeria
12 (27,28)	1984	Sierra Leone	United Kingdom	47	M	Rodent exposure while camping in Sierra Leone
13 (29–31)	1985	Sierra Leone	United Kingdom	27	F	Midwife in Sierra Leone caring for LF patients
14 (32)	1987	Sierra Leone, Liberia	Israel	47	M	Travel to rural Sierra Leone and Liberia
15 (33)	1987	Sierra Leone	Japan	48	M	Worked in Sierra Leone
16 (34)	1989	Nigeria	Canada	38	M	Worked in Nigeria in agriculture
17 (35,36)	1989	Nigeria	United States (IL)	43	M	Attended funeral of relative in Nigeria who died from febrile illness diagnosed as malaria
18 (37–41)	2000	Cote d'Ivoire, Burkina Faso, Ghana	Germany	22	F	Travel to Cote d'Ivoire, Burkina Faso, Ghana
19 (37,42–45)	2000	Sierra Leone	United Kingdom	50	M	Aid worker in eastern Sierra Leone
20 (46–49)	2000	Nigeria	Germany	56	M	Unknown
21 (50–55)	2000	Sierra Leone	Netherlands	48	M	Surgeon working at hospital with LF patients
22 (56)	2003	Sierra Leone	United Kingdom	?	?	Work as soldier in rural Sierra Leone
23 (57)	2004	Sierra Leone, Liberia	United States (NJ)	38	M	Travel to farms in Sierra Leone and Liberia
24 (58,59)	2006	Sierra Leone	Germany	68	M	Travel to Sierra Leone
25 (60)	2007	Nigeria	South Africa	46	?	Public health physician from Nigeria
26 (61)	2009	Nigeria	United Kingdom	66	M	Travel to Nigeria
27 (62)	2009	Mali	United Kingdom	20s	M	Worked in rural Mali
28 (63)	2010	Liberia	United States (PA)	47	M	Travel to Liberia, sleeping in dwelling infested by living and dead rats
29 (64,65)	2014	Liberia	United States (MN)	46	M	Travel to Liberia
30 (66–68)	2015	Liberia	United States (NJ)	55	M	Work in Liberia, contact with rodents/excreta
31 (69)	2016	Togo	Germany	40s	M	Nurse in Togo
32 (70)	2016	Togo	United States (GA)	33	M	Nurse in Togo, cared for patient with LF
33 (71,72)	2016	Liberia	Sweden	72	F	Travel to rural Liberia, possible exposure to rodent excreta and acquaintances with LF

Appendix Table 2. Clinical and epidemiologic characteristics of imported Lassa fever cases, 1969–2016*

Case no.	Year	Initial clinical symptoms	Physical exam/basic lab findings	Positive LASV PCR test within 1-2 days of admission (N/A = not available)	Treatment (s)	Outcome	High-risk contacts/total contacts (% high-risk/total)†	Secondary cases
1 (1–5)	1969	Fever, sore throat, malaise, headache, nausea	Oropharyngeal ulcer, epigastric tenderness, lymphadenopathy, tremor, nystagmus, dizziness, scalp hair loss, muscle tenderness; leukopenia (neutrophil-predominant), anemia, elevated ESR, proteinuria	N/A	Hydroxychloroquine, procaine and crystalline penicillin, supportive treatment	Survived	Unknown	0
2 (6)	1971	Fever, iridocyclitis, nausea/vomiting, anorexia	Abdominal tenderness	N/A	Chloramphenicol, ampicillin, hydrocortisone, prednisone, cloxacillin	Survived	Unknown	0
3 (6)	1971	Fever, malaise, anorexia, headache, joint pains, pleuritic and shoulder pain	Leukocytosis; mild thrombocytopenia, elevated ESR	N/A	None	Survived	Unknown	0
4 (7)	1972	Fever, headache, prostration, nausea/vomiting, limb and back pain	Hypotension; anemia, elevated ESR, microscopic hematuria	N/A	Chloroquine	Survived	Unknown	0
5 (8–10)	1974	Fever, malaise, pharyngitis, nausea/vomiting, subconjunctival hemorrhage, myalgias	Pharyngitis, soft palate ulceration, cervical adenopathy	N/A	Chloroquine, ampicillin, chloramphenicol, convalescent serum	Survived	3	0
6 (11,12)	1975	Fever, joint pains	Unknown	N/A	Unknown	Died	361	0
7 (13–17)	1976	Headache, vomiting, diarrhea, neck/back pain, headache, vertigo	Leukopenia	N/A	Unknown	Survived	29/552 (5%)	0
8 (18)	1976	Unknown	Unknown	N/A	Unknown	Survived	300	0
9 (19–22)	1980	Abdominal pressure, poor appetite, fever, rash, face and feet swelling	Conjunctival erythema, skin peeling at fingertips; elevated ESR	N/A	Chloroquine	Survived	Unknown	0
10 (23–25)	1981	Fever, abdominal pain, bilious vomiting, retro-orbital pain, facial edema, urinary frequency	Abdominal tenderness; leukocytosis, hyponatremia, microscopic hematuria and proteinuria, transaminitis, thrombocytopenia, coagulation abnormalities	N/A	Chloramphenicol, convalescent serum, supportive treatment	Survived	5/173 (3%)	0
11 (26)	1982	Fever, headache, fatigue	Leukocytosis, elevated bilirubin	N/A	Chloroquine, quinine, sulfadoxine/pyrimethamine	Survived	Unknown	0
12 (27,28)	1984	Fever	Unknown	N/A	Unknown	Survived	Unknown	0
13 (29–31)	1985	Fever, diarrhea, exudative pharyngitis,	Unknown	N/A	Chloroquine, quinine, chloramphenicol, oral ribavirin,	Survived	20/50 (40%)	0

Case no.	Year	Initial clinical symptoms	Physical exam/basic lab findings	Positive LASV PCR test within 1-2 days of admission (N/A = not available)	Treatment (s)	Outcome	High-risk contacts/total contacts (% high-risk/total)†	Secondary cases
		conjunctivitis, generalized tender lymphadenopathy			IV ribavirin, prostacyclin analogue, plasma, dexamethasone, mannitol			
14 (32)	1987	Fever, headaches	Exudative pharyngitis, hypotension, neurological signs/myelitis; leukopenia, thrombocytopenia, transaminitis	N/A	Supportive treatment	Survived	Unknown	0
15 (33)	1987	Fever, sore throat, malaise, diarrhea, epigastric pain	Facial edema, pharyngitis, axillary lymphadenopathy, papular rash on neck and chest, distended abdomen with ascites, hepatomegaly; transaminitis, proteinuria, ketonuria, elevated LDH, CPK, ESR, CRP	N/A	Supportive treatment	Survived	Unknown	0
16 (34)	1989	Fever, headache, malaise, nausea, chills, sore throat, dry cough, pleuritic chest pain	Inflamed conjunctiva and pharynx; leukopenia, albuminuria, elevated AST	N/A	Chloroquine, sulfadoxine/pyrimethamine, trimethoprim/sulfamethoxazole, chloramphenicol	Survived	Unknown	0
17 (35,36)	1989	Fever, shaking chills, sore throat, myalgia, persistent severe headaches	Transaminitis	N/A	Penicillin VK, cefaclor; ribavirin requested but not received prior to patient dying	Died	7/102 (7%)	0
18 (37-41)	2000	Fever, flu-like symptoms, tonsillitis	Pharyngitis, ulcerative tonsillitis; transaminitis, renal failure, thrombocytopenia, elevated LDH	Yes	Artesunate, ciprofloxacin, IV ribavirin	Died	Unknown	0
19 (37,42-45)	2000	Fever, malaise, diarrhea	Unknown	Yes	Unknown	Died	125	0
20 (46-49)	2000	Fever, diarrhea, one episode of generalized seizures	Transaminitis, elevated CSF protein, decreased glucose	Yes	Unknown	Died	18/232 (8%)	1
21 (50-55)	2000	Fever, malaise, nausea, diarrhea, myalgias, arthralgias	Rash on trunk; thrombocytosis, transaminitis, renal injury	No (diagnosis considered on day 6, PCR returned positive day 8)	Artesunate, cefmandol, netilmicin, doxycycline, IV ribavirin	Died	132	0
22 (56)	2003	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	0
23 (57)	2004	Fever, chills, severe sore throat, diarrhea, back pain	Unknown	No	Antimalarial, antibiotic therapy; IV ribavirin requested but not received prior to patient dying	Died	5/188 (3%)	0
24 (58,59)	2006	Fever, worsening of pre-existing neurological symptoms	Unknown	No (first sample was sent on day 10 and tested positive)	Unknown	Unknown	Unknown	0
25 (60)	2007	Unknown	Unknown	Yes	Unknown	Died	Unknown	0
26 (61)	2009	Fever, malaise, loss of appetite, abdominal	Unknown	Yes	IV ribavirin requested but not received prior to patient dying	Died	0/328 (0%)	0

Case no.	Year	Initial clinical symptoms	Physical exam/basic lab findings	Positive LASV PCR test within 1-2 days of admission (N/A = not available)	Treatment (s)	Outcome	High-risk contacts/total contacts (% high-risk/total)†	Secondary cases
		pain, confusion, lethargy, mild diarrhea						
27 (62)	2009	Unknown	Unknown	Yes	Antimalarial therapy	Died	7/125 (6%)	0
28 (63)	2010	Fever, chills, knee/ankle pain, anorexia, sore throat, skin tenderness, shortness of breath	Parotid enlargement, tonsillar exudates, posterior cervical lymphadenopathy, splenomegaly; leukopenia, thrombocytopenia, transaminitis	No (diagnosis considered on day 3, first sample was sent on day 5 and tested positive)	None	Survived	0/140 (0%)	0
29 (64,65)	2014	Fever, nausea, vomiting, diarrhea	Confusion, generalized abdominal pain, proteinuria	Yes	Dialysis, methylprednisolone	Survived	6/255	0
30 (66–68)	2015	Fever, chills, myalgias, sore throat	Pharyngeal erythema and exudates, tender cervical lymphadenopathy; transaminitis, renal injury	Yes	Broad-spectrum antibiotics; IV ribavirin requested but not received prior to patient dying	Died	15/177 (8%)	0
31 (69)	2016	Fever, malaise, sore throat	Unknown	No (diagnosed postmortem)	Anti-malarials, broad-spectrum antibiotics	Died	33/55 (60%)	1
32 (70)	2016	Fevers, sore throat, retro-orbital headache, diminished hearing, diarrhea, malaise, weakness	Conjunctival pallor, oral thrush, systolic murmur, bladder distention with suprapubic tenderness; leukopenia, thrombocytopenia, renal injury, transaminitis	Yes	IV ribavirin, oral favipiravir	Survived	Unknown	0
33 (71,72)	2016	Fever, nausea, arthralgia, loose stools, headache	Atrial fibrillation; elevated CRP, renal injury, transaminitis, proteinuria	No (diagnosis considered on day 22, first sample was sent on day 24 of sample from day 15 which tested positive)	None	Survived	122	0

*AST, aspartate aminotransferase; IV, intravenous; CPK, creatine phosphokinase; CRP, C-reactive protein ; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; LASV, Lassa virus LDH, lactate dehydrogenase; N/A, not available.

†For those investigations that did not specify number of high-risk contacts, number refers to total contacts.

References

1. Frame JD, Baldwin JM Jr, Gocke DJ, Troup JM. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *Am J Trop Med Hyg.* 1970;19:670–6. [PubMed http://dx.doi.org/10.4269/ajtmh.1970.19.670](http://dx.doi.org/10.4269/ajtmh.1970.19.670)
2. Leifer E, Gocke DJ, Bourne H. Lassa fever, a new virus disease of man from West Africa. II. Report of a laboratory-acquired infection treated with plasma from a person recently recovered from the disease. *Am J Trop Med Hyg.* 1970;19:677–9. [PubMed http://dx.doi.org/10.4269/ajtmh.1970.19.677](http://dx.doi.org/10.4269/ajtmh.1970.19.677)

3. Buckley SM, Casals J. Lassa fever, a new virus disease of man from West Africa. 3. Isolation and characterization of the virus. *Am J Trop Med Hyg.* 1970;19:680–91. [PubMed http://dx.doi.org/10.4269/ajtmh.1970.19.680](http://dx.doi.org/10.4269/ajtmh.1970.19.680)
4. Speir RW, Wood O, Liebhaber H, Buckley SM. Lassa fever, a new virus disease of man from West Africa. IV. Electron microscopy of Vero cell cultures infected with Lassa virus. *Am J Trop Med Hyg.* 1970;19:692–4. [PubMed http://dx.doi.org/10.4269/ajtmh.1970.19.692](http://dx.doi.org/10.4269/ajtmh.1970.19.692)
5. Casals J, Buckley S, Frame JD, Leifer E. Isolation and characterization of “Lassa” virus—Connecticut and New York. *MMWR Morb Mortal Wkly Rep.* 1969;18:293–4.
6. Gilles HM, Kent JC. Lassa fever: retrospective diagnosis of two patients seen in Great Britain in 1971. *BMJ.* 1976;2:1173. [PubMed http://dx.doi.org/10.1136/bmj.2.6045.1173](http://dx.doi.org/10.1136/bmj.2.6045.1173)
7. Woodruff AW, Monath TP, Mahmoud AAF, Pain AK, Morris CA. Lassa fever in Britain: an imported case. *BMJ.* 1973;3:616–7. [PubMed http://dx.doi.org/10.1136/bmj.3.5881.616](http://dx.doi.org/10.1136/bmj.3.5881.616)
8. Corey L. Suspect outbreak of Lassa fever in Onitsha, Nigeria. Unpublished investigation report; 1974.
9. Reinhardt. Outbreak suspect Lassa fever. Unpublished investigation report; 1974.
10. Hutchins D. Evaluation of Lassa fever. Unpublished investigation report; 1974.
11. Vella EE. Lassa fever. *Trans R Soc Trop Med Hyg.* 1975;69:430–1.
12. Lassa fever. *Wkly Epidemiol Rec.* 1975;3.
13. Zweighaft RM, Fraser DW, Hattwick MAW, Winkler WG, Jordan WC, Alter M, et al. Lassa fever: response to an imported case. *N Engl J Med.* 1977;297:803–7. [PubMed http://dx.doi.org/10.1056/NEJM197710132971504](http://dx.doi.org/10.1056/NEJM197710132971504)
14. Sheagrin JN, Oner VO, Pate JR, Wolfe M. Possible Lassa fever—Washington, D.C. *MMWR Morb Mortal Wkly Rep.* 1976;25:64.
15. Pate JR. Follow-up on Lassa fever—Washington, D.C. *MMWR Morb Mortal Wkly Rep.* 1976;25:68.
16. Wolfe M, Oner VO, Pate JR. Follow-up on Lassa fever—Washington, D.C. *MMWR Morb Mortal Wkly Rep.* 1976;25:83.

17. Lassa fever. *Wkly Epidemiol Rec.* 1976;15:119.
18. Suspect case of Lassa fever. *Wkly Epidemiol Rec.* 1976;33:264.
19. Clayton AJ. Lassa fever, Marburg and Ebola virus diseases and other exotic diseases: is there a risk to Canada? *Can Med Assoc J.* 1979;120:146–55. [PubMed](#)
20. Van der Heide RM. Een patient met Lassakoorts uit Opper-Volta, herkend in Nederland. *Ned Tijdschr Geneesk.* 1982;314:20–2.
21. Unexpected diagnosis of Lassa fever. *Commun Dis Rep CDR Wkly.* 1980;80:4.
22. Lassa fever surveillance. *Wkly Epidemiol Rec.* 1981;6:48.
23. Cooper CB, Gransden WR, Webster M, King M, O’Mahony M, Young S, et al. A case of Lassa fever: experience at St Thomas’s Hospital. *Br Med J (Clin Res Ed).* 1982;285:1003–5. [PubMed](#) <http://dx.doi.org/10.1136/bmj.285.6347.1003>
24. Emond RT, Bannister B, Lloyd G, Southee TJ, Bowen ETW. A case of Lassa fever: clinical and virological findings. *Br Med J (Clin Res Ed).* 1982;285:1001–2. [PubMed](#) <http://dx.doi.org/10.1136/bmj.285.6347.1001>
25. Banatvala JE. A case of Lassa fever. *Br Med J (Clin Res Ed).* 1982;285:1653. [PubMed](#) <http://dx.doi.org/10.1136/bmj.285.6355.1653>
26. Bowen ETW, Emond RTD. A case of Lassa fever. *Commun Dis Rep CDR Wkly.* 1982;82:3.
27. Emond RTD, Weir WRC, Bowen ETW, Lloyd G, Southee T. Managing Lassa fever. *Lancet.* 1984;2:926. [PubMed](#) [http://dx.doi.org/10.1016/S0140-6736\(84\)90679-2](http://dx.doi.org/10.1016/S0140-6736(84)90679-2)
28. Lassa fever: Ex Sierra Leone. *Commun Dis Rep CDR Wkly.* 1984;84:1.
29. Fisher-Hoch SP, Price ME, Craven RB, Price FM, Forthall DN, Sasso DR, et al. Safe intensive-care management of a severe case of Lassa fever with simple barrier nursing techniques. *Lancet.* 1985;2:1227–9. [PubMed](#) [http://dx.doi.org/10.1016/S0140-6736\(85\)90752-4](http://dx.doi.org/10.1016/S0140-6736(85)90752-4)
30. Glover SC, Fisher-Hoch SP. Management of Lassa fever. *Lancet.* 1985;2:1359. [PubMed](#) [http://dx.doi.org/10.1016/S0140-6736\(85\)92651-0](http://dx.doi.org/10.1016/S0140-6736(85)92651-0)
31. “Mission Midwife.” *Midwives Chron Nurs Notes.* 1389(98):138.

32. Schlaeffer F, Bar-Lavie Y, Sikuler E, Alkan M, Keynan A. Evidence against high contagiousness of Lassa fever. *Trans R Soc Trop Med Hyg.* 1988;82:311. [PubMed http://dx.doi.org/10.1016/0035-9203\(88\)90458-0](http://dx.doi.org/10.1016/0035-9203(88)90458-0)
33. Hirabayashi Y, Oka S, Goto H, Shimada K, Kurata T, Fisher-Hoch SP, et al. An imported case of Lassa fever with late appearance of polyserositis. *J Infect Dis.* 1988;158:872–5. [PubMed http://dx.doi.org/10.1093/infdis/158.4.872](http://dx.doi.org/10.1093/infdis/158.4.872)
34. Mahdy MS, Chiang W, McLaughlin B, Derksen K, Truxton BH, Neg K. Lassa fever: the first confirmed case imported into Canada. *Can Dis Wkly Rep.* 1989;15:193–8. [PubMed](http://dx.doi.org/10.1093/cdis/w15n193)
35. Holmes GP, McCormick JB, Trock SC, Chase RA, Lewis SM, Mason CA, et al. Lassa fever in the United States. Investigation of a case and new guidelines for management. *N Engl J Med.* 1990;323:1120–3. [PubMed http://dx.doi.org/10.1056/NEJM199010183231607](http://dx.doi.org/10.1056/NEJM199010183231607)
36. Conrad JL, Mahy BWJ. Investigation of a Confirmed Lassa Case. Unpublished investigation report; 1989.
37. Haas WH, Breuer T, Pfaff G, Schmitz H, Köhler P, Asper M, et al. Imported Lassa fever in Germany: surveillance and management of contact persons. *Clin Infect Dis.* 2003;36:1254–8. [PubMed http://dx.doi.org/10.1086/374853](http://dx.doi.org/10.1086/374853)
38. World Health Organization. Imported case of Lassa fever in Germany—update [cited 2017 Aug 23]. http://www.who.int/csr/don/2000_01_18a
39. World Health Organization. Lassa fever in Germany [cited 2017 Aug 23]. http://www.who.int/csr/don/2000_01_13
40. Günther S, Emmerich P, Laue T, Kühle O, Asper M, Jung A, et al. Imported lassa fever in Germany: molecular characterization of a new lassa virus strain. *Emerg Infect Dis.* 2000;6:466–76. [PubMed http://dx.doi.org/10.3201/eid0605.000504](http://dx.doi.org/10.3201/eid0605.000504)
41. Robert Koch Institute. Anmerkungen zu einem importierten Lassa-Fieber-Erkrankungsfall. *Epid Bull.* 2000;3:23–4.
42. Crowcroft NS, Meltzer M, Evans M, Shetty N, Maguire H, Bahl M, et al. The public health response to a case of Lassa fever in London in 2000. *J Infect.* 2004;48:221–8. [PubMed http://dx.doi.org/10.1016/j.jinf.2003.11.009](http://dx.doi.org/10.1016/j.jinf.2003.11.009)
43. World Health Organization. Suspected Lassa fever, UK [cited 2017 Aug 23]. http://www.who.int/csr/don/2000_03_13
44. World Health Organization. Suspected Lassa fever, UK—confirmation [cited 2017 Aug 23]. http://www.who.int/csr/don/2000_03_14

45. Jones J. Lassa fever imported to England. *Euro Surveill.* 2000;4.
46. Günther S, Weisner B, Roth A, Grewing T, Asper M, Drosten C, et al. Lassa fever encephalopathy: Lassa virus in cerebrospinal fluid but not in serum. *J Infect Dis.* 2001;184:345–9. [PubMed http://dx.doi.org/10.1086/322033](http://dx.doi.org/10.1086/322033)
47. Kiehl W, Haas W. A case of Lassa fever imported into Wiesbaden, Germany. *Euro Surveill.* 2000;4.
48. World Health Organization. Imported case of Lassa fever in Germany [cited 2017 Aug 23]. http://www.who.int/csr/don/2000_04_04
49. Fock R, Wirtz A, Finke E-J, Koch U, Scholz D, Niedrig M, et al. Management und Kontrolle lebensbedrohender hochkontagioser Infektionskrankheiten. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.* 1999;5:389–401. <http://dx.doi.org/10.1007/s001030050124>
50. Swaan CM, van den Broek PJ, Wijnands S, van Steenberghe JE. Management of viral haemorrhagic fever in the Netherlands. *Euro Surveill.* 2002;7:48–50. [PubMed http://dx.doi.org/10.2807/esm.07.03.00338-en](http://dx.doi.org/10.2807/esm.07.03.00338-en)
51. Wijnands S, van Steenberghe J. Public health management of fatal case of Lassa fever in the Netherlands. *Euro Surveill.* 2000;4.
52. World Health Organization. Imported case of Lassa fever in the Netherlands—update [cited 2017 Aug 23]. http://www.who.int/csr/don/2000_07_26
53. Swaan CM, van den Broek PJ, Kampert E, Berbée GAM, Schippers EF, Beersma MFC, et al. Management of a patient with Lassa fever to prevent transmission. *J Hosp Infect.* 2003;55:234–5. [PubMed http://dx.doi.org/10.1016/j.jhin.2003.08.002](http://dx.doi.org/10.1016/j.jhin.2003.08.002)
54. Schmitz H, Köhler B, Laue T, Drosten C, Veldkamp PJ, Günther S, et al. Monitoring of clinical and laboratory data in two cases of imported Lassa fever. *Microbes Infect.* 2002;4:43–50. [PubMed http://dx.doi.org/10.1016/S1286-4579\(01\)01508-8](http://dx.doi.org/10.1016/S1286-4579(01)01508-8)
55. Imported case of Lassa fever in the Netherlands. *Euro Surveill.* 2000;4.
56. World Health Organization. Imported case of Lassa fever in United Kingdom [cited 2018 May 15]. http://www.who.int/csr/don/2003_02_10a
57. Aufiero P, Karabulut N, Rumowitz D, Shah S, Nsubuga J, Piepszak B, et al.; Centers for Disease Control and Prevention (CDC). Imported Lassa fever—New Jersey, 2004. *MMWR Morb Mortal Wkly Rep.* 2004;53:894–7. [PubMed http://dx.doi.org/10.1093/mmwr/5311a1](http://dx.doi.org/10.1093/mmwr/5311a1)

58. E-alert 24 July: Case of Lassa fever imported into Germany from Sierra Leone. *Euro Surveill.* 2006;11:E060727.1. [PubMed](#)
59. World Health Organization. Imported case of Lassa fever in Germany [cited 2017 Aug 23]. http://www.who.int/csr/don/2006_07_25
60. Archer B, Blumberg L, Jansen van Vuren P, Kemp A, Leman P, Le Roux C, et al. Viral haemorrhagic fever outbreaks in South Africa, 2007–2009. *NICD Commun Dis Surveill Bull.* 2010;8:15–6.
61. Kitching A, Addiman S, Cathcart S, Bishop L, Krahe D, Nicholas M, et al. A fatal case of Lassa fever in London, January 2009. *Euro Surveill.* 2009;14:14. [PubMed](#)
62. Atkin S, Anaraki S, Gothard P, Walsh A, Brown D, Gopal R, et al. The first case of Lassa fever imported from Mali to the United Kingdom, February 2009. *Euro Surveill.* 2009;14:14. [PubMed](#)
63. Amorosa V, MacNeil A, McConnell R, Patel A, Dillon KE, Hamilton K, et al. Imported Lassa fever, Pennsylvania, USA, 2010. *Emerg Infect Dis.* 2010;16:1598–600. [PubMed](#) <http://dx.doi.org/10.3201/eid1610.100774>
64. Centers for Disease Control and Prevention. Lassa fever reported in U.S. traveler returning from West Africa [cited 2017 Aug 16]. <https://www.cdc.gov/media/releases/2014/p0404-lassa-fever.html>
65. Choi MJ, Worku S, Knust B, Vang A, Lynfield R, Mount MR, et al. A case of Lassa fever diagnosed at a community hospital—Minnesota 2014. *Open Forum Infect Dis.* 2018;5:ofy131. [PubMed](#) <http://dx.doi.org/10.1093/ofid/ofy131>
66. Kulkarni PA, Chew D, Youssef-Bessler M, Hamdi HA, Montoya LA, Cervantes KB, et al. Case report: imported case of Lassa fever—New Jersey, May 2015. *Am J Trop Med Hyg.* 2018;99:1062–5. [PubMed](#) <http://dx.doi.org/10.4269/ajtmh.17-0316>
67. World Health Organization. Lassa fever—United States of America [cited 2017 Aug 16]. <http://www.who.int/csr/don/28-may-2015-lassa-fever-usa-en>
68. Lehmann C, Kochanek M, Abdulla D, Becker S, Böll B, Bunte A, et al. Control measures following a case of imported Lassa fever from Togo, North Rhine Westphalia, Germany, 2016. *Euro Surveill.* 2017;22:22. [PubMed](#) <http://dx.doi.org/10.2807/1560-7917.ES.2017.22.39.17-00088>

69. World Health Organization. Lassa fever—Germany [cited 2017 Aug 16]. <http://www.who.int/csr/don/23-march-2016-lassa-fever-germany/en>
70. Raabe VN, Kann G, Ribner BS, Morales A, Varkey JB, Mehta AK, et al.; Emory Serious Communicable Diseases Unit. Favipiravir and Ribavirin Treatment of Epidemiologically Linked Cases of Lassa Fever. *Clin Infect Dis*. 2017;65:855–9. [PubMed](#)
<http://dx.doi.org/10.1093/cid/cix406>
71. Grahn A, Bråve A, Lagging M, Dotevall L, Ekqvist D, Hammarström H, et al. Imported case of Lassa fever in Sweden with encephalopathy and sensorineural hearing deficit. *Open Forum Infect Dis*. 2016;3:ofw198. [PubMed](#) <http://dx.doi.org/10.1093/ofid/ofw198>
72. World Health Organization. Lassa fever—Sweden [cited 2017 Aug 23]. <http://www.who.int/csr/don/8-april-2016-lassa-fever-sweden>