PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Clinical characterization of Lassa fever: A systematic review of clinical reports and research to inform clinical trial design

Laura Merson[1,2], Josephine Bourner[1]*, Sulaiman Jalloh[3], Astrid Erber[1,4], Alex Paddy Salam[1], Antoine Flahault[2], Piero L. Olliaro[1]

1 Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom, **2** Institute of Global Health, Faculty of Medicine, University of Geneva, Geneva, Switzerland, **3** Ola During Children's Hospital, Freetown, Sierra Leone, **4** Department of Epidemiology, Center for Public Health, Medical University of Vienna, Vienna, Austria

* josephine.bourner@ndm.ox.ac.uk

Citation: Merson L, Bourner J, Jalloh S, Erber A, Salam AP, Flahault A, et al. (2021) Clinical characterization of Lassa fever: A systematic review of clinical reports and research to inform clinical trial design. PLoS Negl Trop Dis 15(9): e0009788. https://doi.org/10.1371/journal.pntd.0009788

Editor: Manuel Schibler, University of Geneva Hospitals, SWITZERLAND

Received: June 3, 2021

Accepted: September 3, 2021

Published: September 21, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pntd.0009788

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Background

Research is urgently needed to reduce the morbidity and mortality of Lassa fever (LF), including clinical trials to test new therapies and to verify the efficacy and safety of the only current treatment recommendation, ribavirin, which has a weak clinical evidence base. To help establish a basis for the development of an adaptable, standardised clinical trial methodology, we conducted a systematic review to identify the clinical characteristics and outcomes of LF and describe how LF has historically been defined and assessed in the scientific literature.

Methodology

Primary clinical studies and reports of patients with suspected and confirmed diagnosis of LF published in the peer-reviewed literature before 15 April 2021 were included. Publications were selected following a two-stage screening of abstracts, then full-texts, by two independent reviewers at each stage. Data were extracted, verified, and summarised using descriptive statistics.

Results

147 publications were included, primarily case reports (36%), case series (28%), and cohort studies (20%); only 2 quasi-randomised studies (1%) were found. Data are mostly from Nigeria (52% of individuals, 41% of publications) and Sierra Leone (42% of individuals, 31% of publications).

The results corroborate the World Health Organisation characterisation of LF presentation. However, a broader spectrum of presenting symptoms is evident, such as gastrointestinal illness and other nervous system and musculoskeletal disorders that are not commonly included as indicators of LF.

Funding: This work was supported by the UK Foreign, Commonwealth and Development Office and Wellcome [215091/Z/18/Z] (PO, JB) and the Bill & Melinda Gates Foundation [OPP1209135] (PO, JB). This project is part of the EDCTP2 programme supported by the European Union [RIA2016E-1612 - African coaLition for Epidemic Research, Response and Training (ALERRT)] (LM, SJ). For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

The overall case fatality ratio was 30% in laboratory-confirmed cases (1896/6373 reported in 109 publications).

Conclusion

Systematic review is an important tool in the clinical characterisation of diseases with limited publications. The results herein provide a more complete understanding of the spectrum of disease which is relevant to clinical trial design. This review demonstrates the need for coordination across the LF research community to generate harmonised research methods that can contribute to building a strong evidence base for new treatments and foster confidence in their integration into clinical care.

Author summary

Clinical research in difficult-to-study infectious diseases such as Lassa fever is challenging. Only one controlled clinical trial has been conducted to assess the safety and efficacy of therapeutic interventions for Lassa fever (LF). Further research to test new and repurposed therapies is needed and should be supported by a methodological framework in which clinical trials can be consistently conducted for LF. To establish a basis for a standardised clinical trial methodology, we carried out a systematic review to identify the clinical characteristics and outcomes of LF and describe how LF has historically been defined and assessed in the scientific literature. Our data corroborates the current characterisation of LF, and also highlights a broader range of other general symptoms that characterise the onset of LF, such as gastrointestinal illness and other nervous system and musculoskeletal disorders that are not commonly included as indicators of LF. These findings, however, should be tempered by the lack of systematic assessment and reporting of presenting signs and symptoms, their evolution following treatment, and outcomes at discharge in the historic literature. It is therefore evident that a standardised set of data variables and outcome measures should be developed and incorporated into future trials and reported to accelerate collective knowledge.

Introduction

Lassa Fever (LF) is an acute viral haemorrhagic disease caused by the Lassa virus, which is endemic to parts of West Africa, including Nigeria, Sierra Leone, Guinea and Liberia. Transmission to humans usually occurs through contact with excreta of infected rodents (primarily the Mastomys rat), [1,2] consumption or handling of contaminated food or household items (mostly involving women and children), or through direct contact with the bodily fluid of an infected person (typically healthcare workers) [1,3].

LF is a seasonal disease that is estimated to cause 100,000 to 300,000 new cases and 5,000 deaths each year. [4] The reported case fatality rate (CFR) is approximately 30% in patients who present to health care settings [5]–although this figure is lower (12%) in the most recent large cohort study taking place in a research setting. [6] During the peak season it is possible for large outbreaks to occur. Nigeria has experienced increases of confirmed cases and deaths every year since 2017, although this may be attributed to heightened clinical awareness and improvements in diagnostic capacity. [7–10]

Healthcare workers and pregnant women are considered to be at significant risk of severe Lassa fever outcomes. [11] High prevalence of LF has been identified in healthcare workers [5] which is thought to be a result of low levels of clinical suspicion of LF and an inadequate supply of quality protective equipment, making adherence to infection prevention and control (IPC) measures challenging. [12,13] Pregnant women are three-times more likely to have a fatal outcome than non-pregnant adults. [14]

No drug has so far received regulatory approval for treating LF. Ribavirin, in conjunction with supportive care, is currently used as the primary treatment for LF and has been incorporated into national and international treatment guidelines. [2,15] Ribavirin is on the World Health Organisation (WHO) list of essential medicines for treating viral haemorrhagic fevers. [16] However, this treatment recommendation has a small evidence base, as only a single clinical trial has been conducted to evaluate its effectiveness. [17,18] Further evidence in the form of clinical trials is required both to confirm the efficacy and safety of ribavirin and to test new therapies.

Multiple reasons conspire to make LF a neglected, difficult-to-study infectious disease of poverty. The narrow geographical spread of LF, which translates into a relatively limited number of patients who can be treated and studied in the few available specialised healthcare facilities, may contribute to low commercial interest for pharmaceutical companies. Consequently, a significant challenge to building the clinical evidence base is the lack of a methodological framework in which LF clinical trials can be reliably conducted in a consistent and comparable manner.

To establish a basis for the development of a standardised clinical trial methodology, we conducted a systematic review to identify the clinical characteristics and outcomes of LF, and to understand how LF has historically been defined and assessed in the scientific literature. The clinical characterisation enabled by this review is examined in combination with the diagnostics and demographics across the literature to expose the full spectrum of the disease that should be considered in optimising clinical trial methods.

This approach has previously been used to establish a foundation for the development of harmonised clinical trial methodologies, and specifically for the development of Core Outcome Sets, for other infectious diseases. For example, two systematic reviews of cutaneous leishmaniasis interventions conducted by Gonzalez and colleagues (2008 & 2009) [19,20] formed the knowledge-base for standardised trial methodology proposed by Olliaro and colleagues (2013)[21], and a review of tuberculosis meningitis research informed the definition of standardised diagnostic criteria, [22] data collection and outcomes for future clinical trials.[23]

Methodology

An initial search of Epistemonikos and Prospero was conducted to understand if any high-quality reviews were available or in progress that covered portions of the planned review.

For the main search, the following databases and clinical trial registries were searched for clinical studies: African Journals Online, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Global Health (Ovid), Global Index Medicus, PubMed/MEDLINE, clinicaltrials.gov, ISRCTN, Pan African Clinical Trials Registry, and WHO International Clinical Trials Registry. Cochrane Database of Systematic Reviews, Cochrane Clinical Answers, and COMET databases were also searched (**S1 Text**). Studies of LF published before 15 April 2021 were included with no language restrictions applied. We registered this review in PROSPERO, the international prospective register of systematic reviews of the University of York and the National Institute for Health Research, under protocol number CRD42020220365. [24]

We included only studies reporting primary results of patients with a laboratory or clinically confirmed diagnosis of LF (including all diagnostic methods and studies that report patients with sequelae from a previous infection) and describing LF clinical features and/or treatments.

All identified studies underwent screening for inclusion/exclusion in two stages: first by review of titles and abstracts, then by review of the full text manuscripts. Screening was conducted in Rayyan, [25] aided by pre-defined inclusion/exclusion key words. At both stages of the review, decisions on the inclusion or exclusion of each study required the agreement of two unique reviewers assessing the reference or manuscript independently. Each reviewer's decisions were blinded to the second reviewer. When a dataset was fully screened by both reviewers, decisions were unblinded and conflicts were resolved by discussion between the two reviewers, or with a third reviewer when required, to agree on inclusion or exclusion.

Data were extracted from the selected manuscripts and entered into a Research Electronic Data Capture (REDCap) database using a predefined variable dictionary available in **S1 Table**. [26] A second reviewer verified all extracted data and resolved any discrepant data by reviewing the manuscript with a third reviewer. During full-text screening, the most frequently reported signs and symptoms of interest were identified by the review team. For each publication, the presence or absence of information on each of these 19 pre-defined signs and symptoms was recorded where available. Several other signs and symptoms of LF were also reported. Data on these characteristics were extracted and assessed for clinical significance by clinicians in the study team. Signs and symptoms considered to be clinically significant are reported alongside those that were pre-identified. All other reported signs and symptoms can be found in **S2 Table**.

For the sections in this systematic review that report data relating to case fatality, signs and symptoms of LF, data are presented only for studies that include populations with 100% laboratory confirmation (N = 122)–all other sections in this review report data for all publications (N = 147) regardless of the proportion of the study population with laboratory confirmation of LF.

The prevalence of signs and symptoms is reported based on the number of patients for whom there was evidence of assessment of each sign or symptom in the publication (number of patients with sign or symptom reported/over number of patients assessed). Results relating to bleeding site are reported as a percentage of publications that include both location of bleeding site and number (or proportion) of individuals exhibiting bleeding at specified sites.

The minimum and maximum time in days were extracted for data relating to time from symptom onset to presentation and is reported alongside the median, interquartile range (IQR) and range. For data relating to time from presentation to death, the median of reported mean times in days, the IQR and the range are reported. Aspartate aminotransferase (AST) is reported categorically as $<$150 IU/L and $\geq$150 IU/L to understand liver enzyme levels in the context of the evidence base that has informed current treatment guidelines. [17]

Risk of bias assessments were conducted using the Joanna Briggs Institute (JBI) critical appraisal tools due to the compatibility of these tools with the variety of study types in this review. [27,28] Tools were applied to each study based on criteria outlined in the JBI Manual for Evidence Synthesis. [29] Diagnostic methods were evaluated for confidence of acute LF diagnosis based on acceptance in the existing literature and the results of recent reviews. [30,31]

Results

Search results

In total, 4,794 publications were identified in the literature search. After removing duplicates, 2,704 titles and abstracts were screened and 195 full-text publications were assessed for eligibility, resulting in the inclusion of 147 publications in the data synthesis (**Fig 1**).

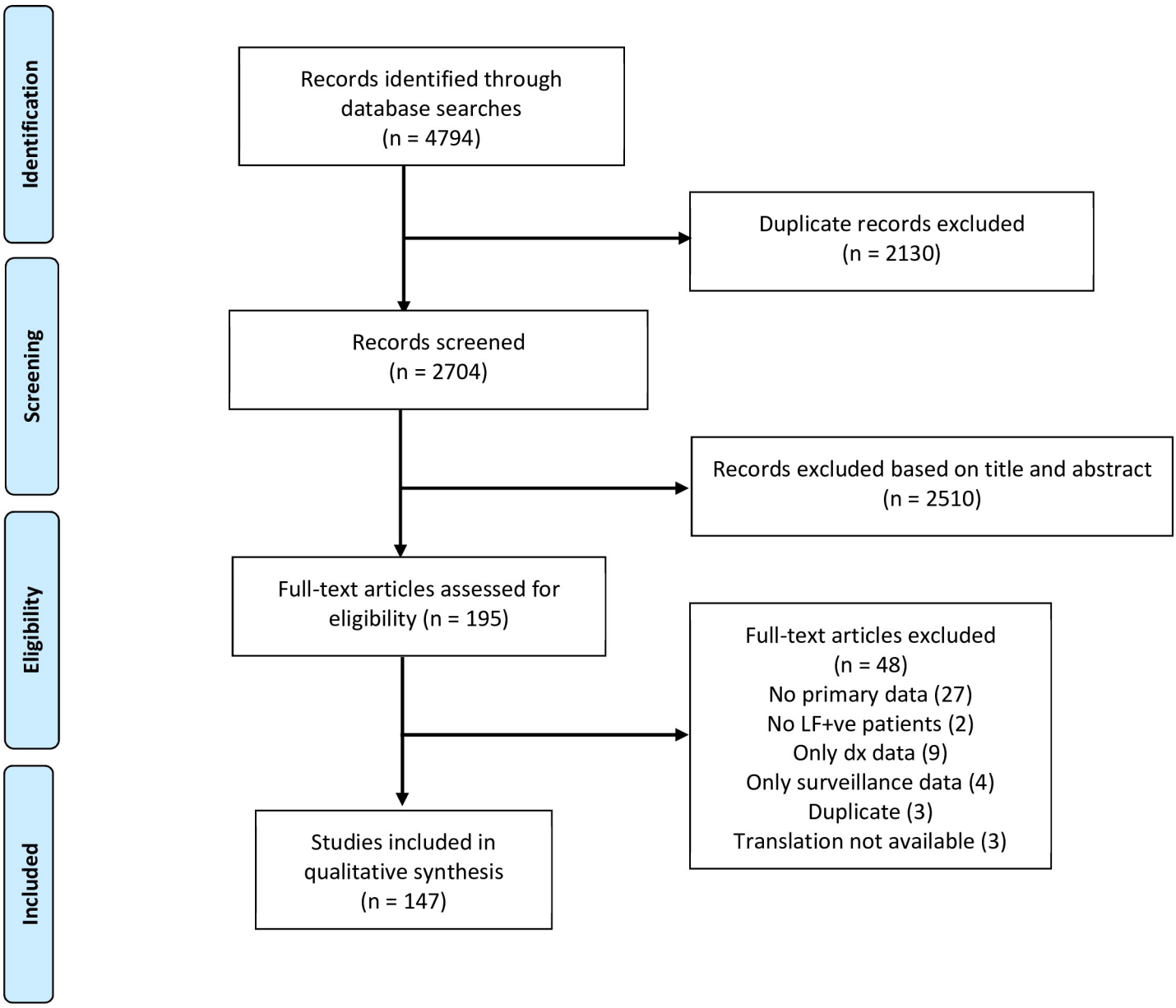

Fig 1. PRISMA 2009 flow diagram.

https://doi.org/10.1371/journal.pntd.0009788.g001

Of the included publications, 53 (36%) were case reports, 41 (28%) were case series, 30 (20%) were cohort studies, 10 (7%) were case-control studies, 11 (7%) were cross sectional studies, and 2 (1%) were quasi-randomised studies (**Table 1 and S2 Text**).

The publication years ranged from 1970 to 2021 with increasingly higher numbers of publications being generated after 2010 (**Fig 2**).

Risk of bias assessments

Overall, there was a moderate risk of bias across all outcomes evaluated in the risk of bias assessment (**Fig 3**). An average of 62% (IQR 44–83%) of study-specific criteria in the JBI Critical Appraisal Checklists were included in the publications. The criteria most relevant to this review

Table 1. Number of studies included by study type.

Total publications (N)	147
Publication type	N (%)
Full text publication	132 (89.7)
Conference abstract	10 (6.8)
Letter/short communication	5 (3.4)
Study type[1]	N (%) [2]
Case report(s)	53 (36) ***[32–85]***
Case series	41 (28) ***[86–125]***
Cohort study	30 (20) ***[6,126–154]***
Case-control study	10 (7) ***[155–164]***
Cross-sectional study	11 (7) ***[165–175]***
Quasi-randomised	2 (1) ***[17,176]***

[1]Definitions have been adapted from the Cochrane Community Glossary, available at community.cochrane.org/glossary (**S2 Text**)

[2] Citations shown in bold italics

https://doi.org/10.1371/journal.pntd.0009788.t001

were often missing or unclearly reported including: Inclusion criteria clearly defined in 51% of 47 publications, Demographic characteristics described in 34% of 88 publications, Exposure measured reliably in 62% of 109 publications, and Adverse events reported in 53% of 60 publications. These gaps in reporting may result in an incomplete characterisation of LF throughout the clinical course of disease. Though an appropriate statistical analysis was reported in 96% of 79 publications, strategies to deal with confounders were reported in only 19% of 79 publications.

Furthermore, 74 (50%) publications are case reports or case series describing fewer than 6 individuals. The basis for the selection of the enrolled participants is often unclear and may not be representative of the patient population who present to the health centre, meaning generalising the findings of these studies to the wider LF patient population is not feasible.

Population characteristics

In total, data on 8550 individuals were reported in the selected publications (**Table 2**). Most individuals (91%) in the reported population were enrolled in studies conducted in either Sierra Leone or Nigeria. The remainder of the study population were enrolled in studies conducted in West Africa, Europe, Asia and North America (**Table 2**).

Note that reporting details do not enable the delineation of overlapping patient populations reported across multiple publications. Therefore, some patients may have been included in more than one publication.

Of the individuals included in the publications where sex was noted, 3477 individuals (48%) were male and 3839 were female (52%). Sex was not reported for 1234 individuals (14%).

Of the publications in which the age range of patients was reported (N = 129), 48 (37%) included a patient under the age of 16 years. 35 publications (24%) reported the inclusion of at least one pregnant participant.

Eligibility criteria

68 publications (46%) documented eligibility criteria (**Table 3**). Of these, all 68 (100%) reported inclusion criteria and 5 (7%) reported exclusion criteria.

Within the inclusion criteria, 20 publications (29%) specified signs and symptoms that must be present for inclusion, 17 (25%) specified fever should be present upon enrolment. 27

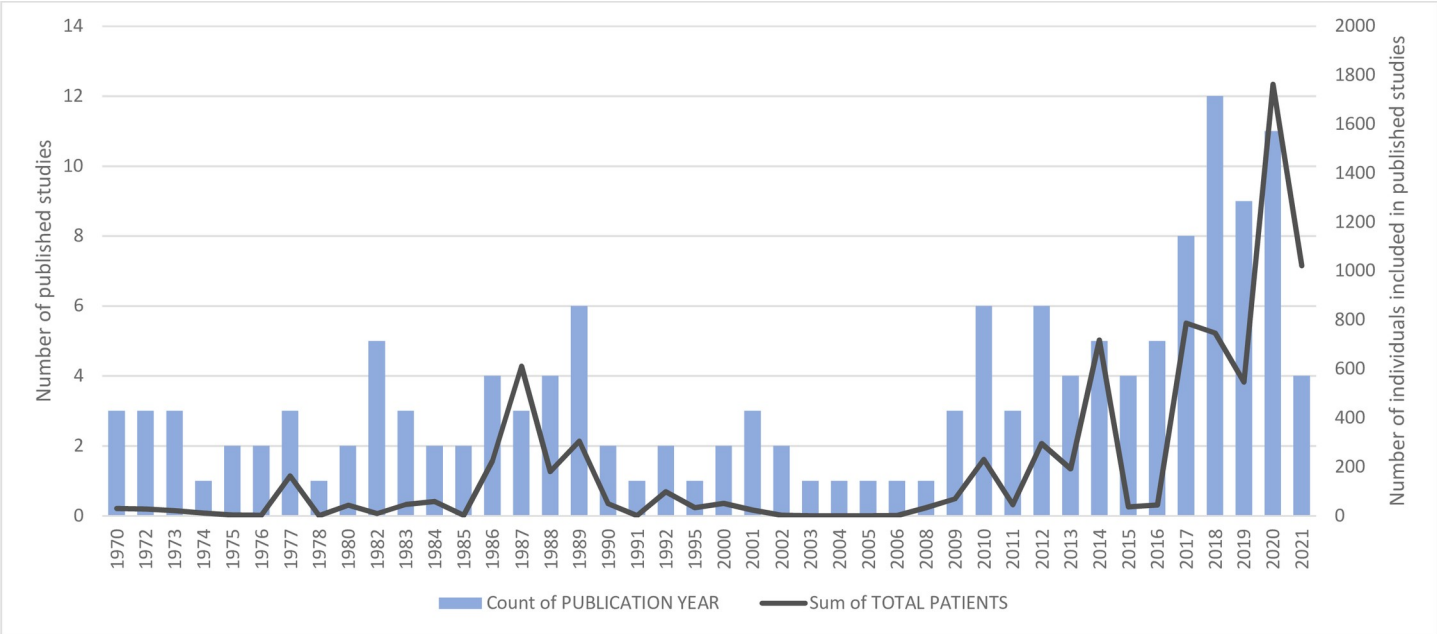

Fig 2. Number of Lassa fever clinical studies published per year.

https://doi.org/10.1371/journal.pntd.0009788.g002

publications (40%) required laboratory confirmation of LF either alone or in conjunction with clinical symptoms. 26 publications (38%) required a confirmation or diagnosis of LF without specifying a method of diagnosis.

Exclusion criteria were based on geographic location in 2 publications (3%). Hearing loss, co-infection with Marburg virus, contacts of an index LF case, patients with an incomplete data set, and LF patients managed on an out-patient basis were each an exclusion criteria in 1 publication (1%).

Outcome measures

Six publications (4%) defined a primary endpoint or outcome measure, 5 (83%) of which were cohort studies and 1 (17%) of which was a quasi-randomised trial. Five (83%) publications included mortality as the primary outcome measure and one (17%) included diagnosis of acute kidney injury (AKI).

Three publications (2%) reported at least one secondary endpoint or outcome measure. Viral load throughout treatment was an outcome measure in 2 publications (66%). Aspartate aminotransferase (AST) throughout treatment, live birth, all-cause in-hospital fatality, frequency of acute kidney dysfunction, prognosis of AKI and AKF in terms of estimated glomerular filtration rate (eGFR) at the end of follow-up and time to hospital discharge were each listed as an outcome measure in 1 publication.

The period of follow-up was specified in 97 publications (66%). The median follow-up time was 21 days (IQR 9–67) with a range of 1–10,950 days.

Method of case confirmation

Laboratory-confirmed diagnosis was the most prevalent method of case confirmation, used either alone or in conjunction clinical diagnosis in 141 publications (96%) and 8422 individuals (99%). Two publications (1%) confirmed LF using clinical diagnosis alone and 4 publications (3%) did not specify a method of case confirmation.

Fig 3. Risk of bias assessment summary by outcome and study type.

https://doi.org/10.1371/journal.pntd.0009788.g003

Table 2. Individuals and publications included in the systematic review per country.

Country	N individuals (%)	N publications (%)[1,2]
Nigeria	4461 (52)	61 (41) [6,32,33,37,45,47,54,55,58,68,70,81,84,86–90,93,94,97,99,100,104,109–113,119,121,123,124,126–128,133–135,138,140,141,145,149–152,155–157,159,164,171–173,175]
Sierra Leone	3563 (42)	45 (31) [17,42,46,50,53,67,76,77,82,85,93,95,96,107,118,120,122,130–132,139,142–144,146,148,153,154,158,160–163, 165,169,174,176,177]
Liberia	373 (4)	10 (7) [35,36,69,80,105,106,108,136,148,170]
Benin	73 (1)	2 (1) [39,125]
Guinea	30 (<1)	3 (2) [83,122,129]
United States	16 (<1)	13 (9) [38,43,44,57,60,62,66,73,91,93,103,116,147]
UK	10 (<1)	8 (5) [41,48,49,59,65,78,101,115]
Ghana	6 (<1)	3 (2) [92,98,102]
Germany	4 (<1)	4 (3) [51,61,116,117]
Netherlands	4 (<1)	4 (3) [72,74,75,117]
Canada	2 (<1)	2 (1) [40,64]
Japan	2 (<1)	2 (1) [56,79]
Togo	2 (<1)	1 (1) [114]
Ireland	1 (<1)	1 (1) [63]
Israel	1 (<1)	1 (1) [178]
Ivory Coast	1 (<1)	1 (1) [34]
Sweden	1 (<1)	1 (1) [52]

[1]N >147 and % >100 as some publications include individuals from >1 country

[2]Citations shown in bold italics

https://doi.org/10.1371/journal.pntd.0009788.t002

The largest proportion of laboratory diagnoses, for 2348 individuals (27%), was conducted using RT-PCR alone (Table 4. Results are shaded according to the level confidence of laboratory methods for the identification of acute LF infection.)

When RT-PCR, viral culture and antigen ELISA were used exclusively or in combination with each other, we determined a high level of confidence of acute LF infection. A moderate level of confidence was determined when serology (IgM ELISA and/or IgG ELISA) was used in combination with RT-PCR, viral culture or antigen ELISA. Any other exclusive or combined use of laboratory methods was determined as a lower confidence of acute LF infection.

Baseline clinical characteristics

At baseline, fever was the most reported symptom, identified in 88% of the individuals in whom it was assessed (1527/1730) (Fig 4), followed by headache (809/1622 individuals, 50%), vomiting (806/1613, 49%), abdominal pain (660/1581, 42%) and cough (556/1581, 35%).

Table 3. Specified inclusion criteria by type (N = number of studies).

Criteria	N (%)
Publications specifying eligibility criteria (inclusion or exclusion)	68/147 (46)
Publications specifying inclusion criteria	68/68 (100)
Laboratory confirmation of LF either alone or in conjunction with assessment of clinical symptoms	27/68 (40)
Confirmation or diagnosis of LF (method of diagnosis unspecified)	26/68 (38)
Patients with pre-specified signs and symptoms consistent with LF	20/68 (29)
Patients with fever alone or in conjunction with other symptoms	17/68 (25)
Publications specifying exclusion criteria	5/68 (7)
Geographic location	2/5 (40)
Hearing loss (sensorineural or conductive hearing loss)	1/5 (20)
Co-infection with Marburg virus	1/5 (20)
Contacts of index LF case	1/5 (20)
Patients managed on an out-patient basis	1/5 (20)
Patients with an incomplete dataset	1/5 (20)

https://doi.org/10.1371/journal.pntd.0009788.t003

A smaller number of patients presented with clinically severe or life-threatening signs and symptoms such as shock (12/187, 6%), breathing difficulty (21/310, 7%), and seizure (13/517, 3%). In pregnant women, labour complications were reported in 2/7 (29%).

Overall, musculoskeletal disorders, nervous system disorders and gastrointestinal illnesses were most reported. (**S3 Table**).

The reported timeframe from symptom onset to presentation ranged from 0–32 days (median reported minimum time: 5 days; median reported maximum time: 8 days). The minimum and maximum times to presentation were similar in Nigeria, Sierra Leone and Liberia, the three endemic countries with >5 studies included.

Post-baseline clinical characteristics

In post-baseline assessment, fever was again the most prevalent symptom, reported for 3067/3300 individuals (93%)–representing a 5% increase in prevalence from baseline.

After fever, headache (2033/3200, 64%), vomiting (1695/3077, 55%) and abdominal pain (1594/3039, 52%) occurred in the highest number of individuals. The prevalence of all signs and symptoms related to the gastrointestinal system increased post-baseline, except nausea.

The number and prevalence of reported severe or life-threatening signs and symptoms also increased post-baseline. Shock had the greatest increase in prevalence from baseline to post-baseline, followed by breathing difficulty and seizure. Respiratory failure and renal failure were reported only at post-baseline timepoints.

1896/6373 (30%) individuals were reported to have died. 109 publications (74%) reported at least one death. 41 publications (31%) reported the time in days from presentation to death and within these publications, the median of the mean times reported per publication from presentation to death was 7.5 days (IQR 3–11) with a range of 0–21 days.

Site of bleeding. Bleeding was reported in 30 (20%) and 53 (36%) publications at baseline and post-baseline, respectively. At baseline, site of bleeding was reported for 168 individuals and at post-baseline site of bleeding was reported for 1088 individuals (**Table 5**).

Haematuria/blood in urine was the most reported bleeding type at both baseline and post-baseline–reported for 23 individuals (14% of reported bleeding sites) at baseline and 131 individuals (12% of reported bleeding sites) at post-baseline. Haematuria is specified as macroscopic haematuria in a third of the reported cases, while no differentiation between macroscopic and microscopic haematuria was made in two thirds of these cases.

Table 4. Laboratory Diagnostics—Single and combined testing methods by number of individuals tested.

	Included N (%)*	Exclusively N (%)	RT-PCR N (%)	Viral Culture N (%)	IFA N (%)	IgM ELISA N (%)	Antigen ELISA N (%)	IgG ELISA N (%)	CF N (%)	IHC N (%)	Other N (%)
RT-PCR	4127 (48)	2348 (27)		1497 (18)	79 (<1)	1549 (18)	268 (3)	156 (2)	0 (0)	1355 (16)	46 (<1)
Viral Culture	3192 (37)	28 (<1)	1497 (18)		1638 (19)	1566 (18)	73 (<1)	213 (2)	118 (1)	1355 (16)	155 (2)
IFA	2232 (26)	99 (1)	79 (<1)	1638 (19)		497 (6)	361 (4)	188 (2)	217 (3)	0 (0)	155 (2)
IgM ELISA	3542 (41)	0 (0)	1549 (18)	1566 (18)	497 (6)		2009 (23)	911 (11)	0 (0)	1354 (16)	642 (8)
Antigen ELISA	2204 (26)	78 (<1)	268 (3)	73 (<1)	361 (4)	2009 (23)		775 (9)	0 (0)	1 (<1)	643 (8)
IgG ELISA	919 (11)	4 (<1)	156 (2)	213 (2)	188 (2)	911 (11)	775 (9)		0 (0)	1 (<1)	643 (8)
CF	307 (4)	30 (<1)	0 (0)	118 (1)	217 (3)	0 (0)	0 (0)	0 (0)		1 (<1)	0 (0)
IHC	1357 (16)	0 (0)	1355 (16)	1355 (16)	0 (0)	1354 (16)	1 (<1)	1 (<1)	1 (<1)		0 (0)
Other**	1187 (14)	389 (5)	46 (<1)	155 (2)	155 (2)	642 (8)	643 (8)	643 (8)	0 (0)	0 (0)	

Green = high confidence of acute LF infection; Yellow = moderate confidence; Orange = low confidence.

Abbreviations: Reverse Transcription Polymerase Chain Reaction (RT-PCR); Immunofluoresence Assay (IFA); Immunoglobulin M (IgM); Immunoglobulin G (IgG); Complement Fixation (CF); Immunohistochemistry (IHC)

*Testing method not reported in 3 (2%) publications, including 5 (4%) individuals

** Other includes: Experimental LASV Antigen Rapid Test cassettes and dipstick LFI = 2 (2%) publications and 45 (1%) individuals; Lateral flow immunoassay (LFI) = 2 (2%) publications and 598 (10%) individuals; LF-specific antibody titre = 1 (1) publication and 154 (3%) individuals.

https://doi.org/10.1371/journal.pntd.0009788.t004

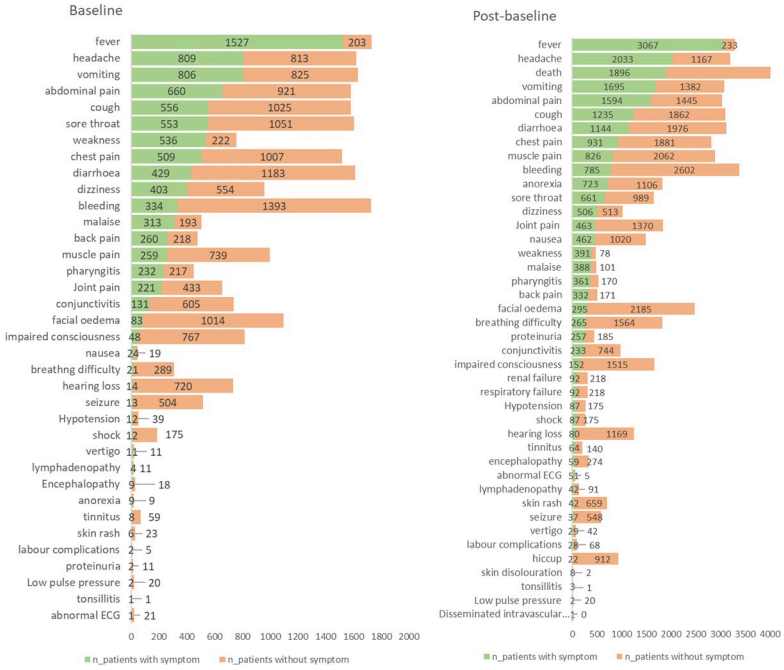

Fig 4. Clinical signs and symptoms reported at baseline and post-baseline by proportion of individuals with and without sign/symptom.

https://doi.org/10.1371/journal.pntd.0009788.g004

Table 5. Number and percentage of bleeding sites reported.

BLEEDING SITES	Baseline n/N (%)	Post-baseline n/N (%)
(Sub) conjunctiva/eyes	10/168 (6)	12/1088 (1)
Ears	0	1/1088 (<1)
Epistaxis (nose)	8/168 (5)	17/1088 (2)
Gingiva/mouth/buccal mucosa	9/168 (5)	20/1088 (2)
Haematemesis/vomit/upper GI	14/168 (8)	38/1088 (3)
Haematuria/urine	23/168 (14)	131/1088 (12)
Haemoptysis/pleural effusion/cough/respiratory/sputum	1/168 (1)	14/1088 (1)
Needle sites/ wounds	2/168 (1)	13/1088 (1)
Stool/rectum/melena/haematochezia/GI/overt	3/168 (2)	78/1088 (7)
Vagina	1/168 (1)	59/1088 (5)

https://doi.org/10.1371/journal.pntd.0009788.t005

Aspartate aminotransferase (AST)

Aspartate aminotransferase (AST) levels were reported at baseline and post-baseline in 29 (20%) and 43 (29%) publications respectively. These publications included 799 (9%) and 1200 (14%) of the populations described in the literature. Detailed, individual patient data were limited. Many publications reported a single AST value from a single patient, others presented a range and mean value for a group of patients. Of the publications that reported AST levels, 10 publications including a total of 19 (2%) individuals reported all patients as having baseline AST levels below 150 IU/L and 15 publications including a total of 459 (57%) of individuals reported AST values ≥150 IU/L for all individuals. AST values reported in other papers showed a wide range of results. (**Table 6**).

Discussion

Despite fifty years of reporting and research, morbidity and mortality caused by LF remain high in patients presenting to health care settings, especially in high-risk populations such as healthcare workers and pregnant women. [11,14] A historic lack of investment in LF clinical research and LF drug development [179] has resulted in the limited anthology of case reports and observational study reports presented in this review, but no well-conducted randomised trials of current or new therapeutics.

Attention and investment in LF have increased in recent years with the launch of the World Health Organisation (WHO) Research & Development Blueprint [180] and the Coalition for Epidemic Preparedness Initiatives (CEPI) 'Enable' project. [181] Since 2018, LF is also included in the US Food and Drug Administration (FDA) list of "infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations", which entitles the developer of an LF drug successfully registered with the US FDA to a priority review voucher (PRV). [182] These developments will hopefully promote new additions to the sparse evidence presented herein.

Challenges and limitations of the current literature

Both the context and the presentation of LF present challenges to timely diagnosis and treatment, which are reflected in the limitations of the literature included in this review. (186–189) Resources, communications, and awareness of LF are reported to be increasing over time in the most affected countries, [183,184] though challenges to the effectiveness of these interventions are frequently met. [185,186] Differences in LF lineages circulating among the reported populations can also not be considered in this review as this information is not included in the

Table 6. AST ranges in papers reporting AST values.

	Total reporting AST values		All AST values <150 IU/L		All AST values ≥150 IU/L	
	Publications N	Individuals n	Publications N (%)	Individuals n (%)	Publications N (%)	Individuals n (%)
AST baseline	29	799	10 (34)	19 (2)	15 (52)	459 (57)
AST anytime	43	1279	9 (21)	18 (1)	14 (33)	284 (22)

https://doi.org/10.1371/journal.pntd.0009788.t006

clinical reports nor is clinical information detailed in publications on strain identification [187–189].

Due to these constraints, the limited quality of the literature, and the risk of bias demonstrated in the analysis, our report is strictly descriptive of LF clinical features and cannot inform the impact of LF treatment.

The purpose of this review is to ensure that future research, including the development of standardised data variables and outcomes for LF clinical trials, reflects the entirety of the available evidence base. Additionally, we aim to improve the uniformity of data collection and reporting in future LF research to support efficiency and comparison across studies.

Case definition

The WHO estimates that 80% of cases are asymptomatic. It further defines common symptoms to include gradual onset of fever, malaise and general weakness; after a few days, extending to headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, and abdominal pain; as well as possible bleeding, neck/facial swelling and shock in severe cases. [190] The Nigeria Centre for Disease Control (NCDC) suspected case definition is similar, but lists a more restricted set of indicative signs and symptoms of LF. [2] The literature reviewed reveals a much broader spectrum of symptoms than that of both the NCDC and WHO. Expanding the case definition may have advantages e.g., increasing the sensitivity of suspect case identification, the likelihood of rapid access to LF diagnostics, and better protecting healthcare works; however, it may also have disadvantages since these symptoms are non-specific and present in many common febrile illnesses across West Africa, [191,192] the reduced specificity of a case definition that includes them would need to be balanced by the availability of appropriate diagnostics to confirm suspect cases. In the context of clinical research, these issues are tempered by requiring laboratory confirmation for inclusion into the study.

Efforts are currently underway to improve the understanding of regional differences in LF presentation. Data from the CEPI-funded "Enable" project–a large multi-country epidemiological study across five countries in West Africa–aims to summarise the regional prevalence of LF and delineate key differences in its characterisation on a country-by-country basis.[181] These results may inform drivers of diversity in case definition.

Diagnostic variation and confidence

11 different diagnostic approaches are used in the publications included in this review. This variety reflects the history of LF diagnostic development, resource limitations and research on new methods. When multiple tests are used to confirm LF diagnosis, the reported results do not specify which of the tests had a positive result. Furthermore, despite evidence that testing methods, kits and quality assurance protocols have a significant impact on diagnostic quality, [193–195] these details are rarely included in clinical reports and could therefore not be evaluated.

The US Centers for Disease Control and Prevention (CDC) guidelines recommend nucleic acid detection by RT-PCR, antigen detection by ELISA, or serology (IgG or IgM ELISA) for LF diagnosis. [196] The World Health Organisation guidelines concur and further add viral culture as acceptable. [197] In this review, results of studies that confirm LF diagnosis using RT-PCR, antigen ELISA and viral culture exclusively or in combination with each other are determined to have a high level of confidence in the diagnosis. Studies that accept IgM and/or IgG ELISA testing equally with these methods have a reduced confidence on the basis of evidence that detection of IgG and IgM can occur across a wide range of time points ranging from early in an infection and after resolution of acute illness. [198] Investment to improve the accuracy and availability of rapid diagnostics appropriate for LF endemic settings is needed.

Need for more clinical trials

To date, a single clinical trial has been conducted to assess the safety and efficacy of ribavirin, the only recommended treatment for LF. [17] No further clinical trials for LF have been conducted in the subsequent 35 years. The analysis of this trial includes only a fraction of the cohort who received ribavirin and reports only those with an AST >150 IU/L. Reassessment of the results of this trial, and a subsequent report released under the Freedom of Information Act 2000, [199] identified harmful effects of using ribavirin to treat LF in patients with AST <150 IU/L. [18] Despite this significant limitation, ribavirin has been incorporated in to LF treatment guidelines without reference to AST-dependent dosing. [2]

This review cannot contribute much to knowledge of AST levels in LF, as they are minimally reported in the literature (15% of patients in this review). Where results are available, they are not sufficiently detailed to understand the distribution of AST values, possibly due to limited laboratory capacity. [200] In the reported data, publications including 459 (57%) patients reported all patients as having baseline AST levels ≥150 IU/L, above the limit of where harm from ribavirin has been identified. However, publications including only 284 (22%) patients reported all patients having AST levels ≥150 IU/L throughout admission. The potential for harm when AST levels are <150 IU/L after the start of ribavirin treatment has not been examined. Systematic assessment of AST and publication of comprehensive data needs to be undertaken to build understanding of the use of ribavirin in LF.

The shortcomings of ribavirin demonstrate an urgent need for its reassessment and highlight the need for other therapeutic options to be explored–particularly those that can be used in LF patients at heightened risk of death, including pregnant women. [14] There are a number of antivirals that are currently in development or under investigation for LF. [201] With data urgently needed on the safety and efficacy of these new treatment prospects, and in the interest of efficiency, it is vital that clinical trials are conducted and reported in a comparable manner. The spectrum of symptoms and sequalae described in this review provides focus to the targets of therapeutic action and safety considerations.

The importance of standardising data collection and reporting

By collating and describing this history of results, we have shown that understanding of the prevalence of many signs and symptoms of LF is significantly limited by a lack of consistency in reporting of clinical features. There is a clear need for robust reporting of clinical studies and consensus in approaches to clinical characterisation that will allow for comparability of the characterisation of LF across regions and strains of the Lassa virus. The synthesises reported herein serves as a baseline for defining a standardised way to capture and report clinical characteristics across future LF research studies.

Ways forward

Despite the growing number of research outputs on LF, the limited number of cases and the challenges of mounting clinical trials in LF-endemic regions highlight the need for efficient approaches to research. The results of this review have been leveraged to inform the development of standardised clinical trial methodologies with efficient and pragmatic design to address the research priorities above. A consultation group has been established to develop–through a consensus approach–clinical trial eligibility criteria, case definition, core data collection variables and outcomes. [202]

These criteria, definitions and measures can be integrated into pre-positioned protocols, available for future outbreaks. Pre-positioned protocols have been proposed and adopted for other emerging infections as a way of tackling the challenges of conducting research on sporadic diseases that require a rapid response. [203] Not only do pre-positioned protocols have the advantage of accelerating the pace at which research can start, but they also enable multiple studies to be conducted in a comparable way.

Our systematic review demonstrates the need to collect data on LF clinical characteristics and clinical management in a structured and harmonised fashion with defined core data requirements. This will lead to improvements in the understanding and clinical diagnosis of LF. It will further inform the design of clinical trials of existing and new treatments, and the potential application of indicators for pharmacological treatments, including the severity of disease requiring treatment. Coordinating high-quality research methods across the LF research community can contribute to building a strong evidence base on new treatments for all LF patients and foster confidence in their integration into clinical care.

Supporting information

S1 Text. Search Strategy.
(DOCX)

S2 Text. Study type definitions.
(DOCX)

S1 Table. Data dictionary and extraction manual.
(DOCX)

S2 Table. Other reported signs and symptoms.
(DOCX)

S3 Table. Prevalent and clinically significant signs and symptoms.
(DOCX)

S1 Data. Full raw data.
(XLSX)

Acknowledgments

The authors would like to thank Eli Harriss who conducted the search, Fernando Gouvea Reis who assisted with screening and data extraction, Maren Jeleff-Entscheff, Jared Palazza and Wahdae-Mai Harmon who assisted with screening, Andrew Dagens and Louise Sigfrid who contributed to data extraction, Kristen Eberhardt who provided results from the literature search for comparison and Jake Dunning for his critical review.

Author Contributions

Conceptualization: Laura Merson, Astrid Erber, Piero L. Olliaro.

Data curation: Laura Merson, Sulaiman Jalloh.

Formal analysis: Laura Merson, Josephine Bourner.

Funding acquisition: Laura Merson.

Methodology: Laura Merson, Astrid Erber, Antoine Flahault, Piero L. Olliaro.

Project administration: Laura Merson, Josephine Bourner.

Supervision: Antoine Flahault, Piero L. Olliaro.

Visualization: Josephine Bourner.

Writing – original draft: Laura Merson, Josephine Bourner.

Writing – review & editing: Laura Merson, Josephine Bourner, Sulaiman Jalloh, Astrid Erber, Alex Paddy Salam, Piero L. Olliaro.

References

1. World Health Organisation. Lassa fever [12 October 2020]. Available from: https://www.who.int/health-topics/lassa-fever/#tab=tab_1.
2. Nigeria Centre for Disease Control. National Guideline for Lassa Fever Case Management. 2018.
3. Centers for Disease Control and Prevention. Lassa fever 2019 [12 October 2020]. Available from: https://www.cdc.gov/vhf/lassa/index.html.
4. Günther S, Lenz O. Lassa virus. Crit Rev Clin Lab Sci. 2004; 41(4):339–90. Epub 2004/10/19. https://doi.org/10.1080/10408360490497456 PMID: 15487592.
5. Kenmoe S, Tchatchouang S, Ebogo-Belobo JT, Ka'e AC, Mahamat G, Simo REG, et al. Systematic review and meta-analysis of the epidemiology of lassa virus in humans, rodents and other mammals in Sub-Saharan Africa. PLoS Neglected Tropical Diseases. 2020; 14(8):1–29. https://doi.org/10.1371/journal.pntd.0008589 PMID: 32845889.
6. Duvignaud A, Jaspard M, Etafo IC, Gabillard D, Serra B, Abejegah C, et al. Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort study. The Lancet Global Health. 2021; 9(4):e469–e78. https://doi.org/10.1016/S2214-109X(20)30518-0 PMID: 33740408.
7. Nigeria Centre for Disease Control. 2016/2017 Lassa fever Outbreak in Nigeria: Epi Week 51: 24 December, 2017. 2017.
8. Nigeria Centre for Disease Control. 2018 Lassa fever Outbreak Situation Report: Epi Week 52: 31st December 2018. 2018.
9. Nigeria Centre for Disease Control. Lassa fever Situation Report: Epi Week 53: 28 December 2020–03 January 2021. 2020.
10. Nigeria Centre for Disease Control. Disease Situation Reports. An update of Lassa fever outbreak in Nigeria for Week 52 –December 2019. Abuja, Nigeria: 2019.
11. Kenmoe S, Tchatchouang S, Ebogo-Belobo JT, Ka'e AC, Mahamat G, Guiamdjo Simo RE, et al. Systematic review and meta-analysis of the epidemiology of Lassa virus in humans, rodents and other mammals in sub-Saharan Africa. PLOS Neglected Tropical Diseases. 2020; 14(8):e0008589. https://doi.org/10.1371/journal.pntd.0008589 PMID: 32845889
12. Mba S, Ukponu W, Saleh M, Dan-Nwafor C, Adekanye U, Olajide L, et al. Lassa fever infection among health care workers in Nigeria, 2019. International Journal of Infectious Diseases. 2020; 101:279. https://doi.org/10.1016/j.ijid.2020.09.731
13. Ajayi NA, Nwigwe CG, Azuogu BN, Onyire BN, Nwonwu EU, Ogbonnaya LU, et al. Containing a Lassa fever epidemic in a resource-limited setting: outbreak description and lessons learned from Abakaliki, Nigeria (January-March 2012). Int J Infect Dis. 2013; 17(11):e1011–6. Epub 2013/07/23. https://doi.org/10.1016/j.ijid.2013.05.015 PMID: 23871405.
14. Kayem ND, Benson C, Aye CYL, Barker S, Tome M, Kennedy S, et al. Lassa fever in pregnancy: a systematic review and meta-analysis. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2020; 114(5):385–96. https://doi.org/10.1093/trstmh/traa011 PMID: 32125412

15. Centers for Disease Control and Prevention. Lassa fever: Treatment https://www.cdc.gov/vhf/lassa/treatment/index.html#:~:text=Ribavirin%2C%20an%20antiviral%20drug%2C%20has,the%20course%20of%20the%20illness.2014 [cited 2021 18/03/2021].
16. WHO Model List of Essential Medicines [Internet]. World Health Organization. 2017. Available from: https://list.essentialmeds.org/.
17. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever. Effective therapy with ribavirin. New England Journal of Medicine. 1986; 314(1):20–6. Epub 1986/01/02. https://doi.org/10.1056/NEJM198601023140104 PMID: 3940312.
18. Eberhardt KA, Mischlinger J, Jordan S, Groger M, Günther S, Ramharter M. Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis. Int J Infect Dis. 2019; 87:15–20. Epub 2019/07/30. https://doi.org/10.1016/j.ijid.2019.07.015 PMID: 31357056.
19. González U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database Syst Rev. 2009;(2):Cd004834. Epub 2009/04/17. https://doi.org/10.1002/14651858.CD004834.pub2 PMID: 19370612.
20. González U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. Cochrane Database Syst Rev. 2008;(4):Cd005067. Epub 2008/10/10. https://doi.org/10.1002/14651858.CD005067.pub3 PMID: 18843677.
21. Olliaro P, Vaillant M, Arana B, Grogl M, Modabber F, Magill A, et al. Methodology of clinical trials aimed at assessing interventions for cutaneous leishmaniasis. PLoS Negl Trop Dis. 2013; 7(3):e2130. Epub 2013/04/05. https://doi.org/10.1371/journal.pntd.0002130 PMID: 23556016; PubMed Central PMCID: PMC3605149.
22. Marais S, Thwaites G, Schoeman JF, Török ME, Misra UK, Prasad K, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. The Lancet Infectious Diseases. 2010; 10(11):803–12. https://doi.org/10.1016/S1473-3099(10)70138-9 PMID: 20822958
23. Marais BJ, Heemskerk AD, Marais SS, van Crevel R, Rohlwink U, Caws M, et al. Standardized Methods for Enhanced Quality and Comparability of Tuberculous Meningitis Studies. Clinical Infectious Diseases. 2016; 64(4):501–9. https://doi.org/10.1093/cid/ciw757 PMID: 28172588
24. Clinical characterization of Lassa fever: a systematic review of clinical reports and research to inform clinical trial design (CRD42020220365) [Internet]. PROSPERO. 2020. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020220365.
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016; 5(1):210. https://doi.org/10.1186/s13643-016-0384-4 PMID: 27919275
26. Harris PA TR, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics J Biomed Inform. 2009; 42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010 PMID: 18929686
27. Joanna Briggs Institute. Critical Appraisal Tools. Available from: https://jbi.global/critical-appraisal-tools.
28. Ma L-L, Wang Y-Y, Yang Z-H, Huang D, Weng H, Zeng X-T. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Military Medical Research. 2020; 7(1):7. https://doi.org/10.1186/s40779-020-00238-8 PMID: 32111253
29. Aromataris E MZ. JBI Manual for Evidence Synthesis. JBI. 2020. https://doi.org/10.46658/JBIMES-20-01.
30. Takah NF, Brangel P, Shrestha P, Peeling R. Sensitivity and specificity of diagnostic tests for Lassa fever: a systematic review. BMC Infect Dis. 2019; 19(1):647. Epub 2019/07/22. https://doi.org/10.1186/s12879-019-4242-6 PMID: 31324229; PubMed Central PMCID: PMC6642489.
31. Mazzola LT, Kelly-Cirino C. Diagnostics for Lassa fever virus: a genetically diverse pathogen found in low-resource settings. BMJ Global Health. 2019; 4(Suppl 2):e001116. https://doi.org/10.1136/bmjgh-2018-001116 PMID: 30899575
32. Agboeze J, Nwali MI, Nwakpakpa E, Ogah OE, Onoh R, Eze J, et al. Lassa fever in pregnancy with a positive maternal and fetal outcome: A case report. 2019; 89:84–6. https://doi.org/10.1016/j.ijid.2019.08.023 PMID: 31465848.
33. Duvignaud A, Doutchi M, Abejegah C, Etafo I, Jaspard M, Serra B, et al. Delayed-onset paraparesis in Lassa fever: A case report. 2019; 19. rayyan-48809698. https://doi.org/10.1016/j.ijid.2019.12.022 PMID: 31866549
34. Mateo M, Picard C, Sylla Y, Kamo E, Odegue D, Journeaux A, et al. Fatal Case of Lassa Fever, Bangolo District, Cote d'Ivoire, 2015. 2019; 25(9):1753–6. https://doi.org/10.3201/eid2509.190239 PMID: 31441759.

35. Sandige H. Learning in the Lassa belt. 2018; 99(5):1110–1. rayyan-48809956. https://doi.org/10.4269/ajtmh.18-0287 PMID: 30404683

36. Woyessa AB, Maximore L, Keller D, Dogba J, Pajibo M, Johnson K, et al. Lesson learned from the investigation and response of Lassa fever outbreak, Margibi County, Liberia, 2018: case report. 2019; 19(1):610. https://doi.org/10.1186/s12879-019-4257-z PMID: 31296177.

37. Ajayi NA, Ifebunandu NA, Ukwaja KU, Nnabu R, Onwe FI, Asogun DA. Lassa fever—full recovery without ribavarin treatment: a case report. African Health Sciences. 2014; 14(4):1074–7. https://doi.org/10.4314/ahs.v14i4.40 20153093090. PMID: 25834520

38. Amorosa V, MacNeil A, McConnell R, Patel A, Dillon KE, Hamilton K, et al. Imported Lassa fever, Pennsylvania, USA, 2010. Emerging Infectious Diseases. 2010; 16(10):1598–600. Epub 2010/09/30. https://doi.org/10.3201/eid1610.100774 PMID: 20875288; PubMed Central PMCID: PMC3294406.

39. Attinsounon CA, Ossibi Ibara BR, Alassani A, Ade S, Sake K, Glele Kakai C, et al. Report of a fatal case of Lassa fever in Parakou in 2018: clinical, therapeutic and diagnostic aspects. BMC infectious diseases. 2018; 18(1):667. Epub 2018/12/19. https://doi.org/10.1186/s12879-018-3587-6 PMID: 30558538; PubMed Central PMCID: PMC6296101.

40. Best EW. The Lassa fever episode, Metro Toronto, August, 1976. Canadian journal of public health = Revue canadienne de sante publique. 1976; 67(5):361–6, 9–74. Epub 1976/09/01. PMID: 991041.

41. Bowell E. Journal of Infection Control Nursing. Nursing the isolated patient: Lassa fever. Nursing Times. 1986; 82(38):72–81. Epub 1986/09/17. PMID: 3640375.

42. Branco LM, Boisen ML, Andersen KG, Grove JN, Moses LM, Muncy IJ, et al. Lassa hemorrhagic fever in a late term pregnancy from northern Sierra Leone with a positive maternal outcome: case report. Virology Journal. 2011; 8:404. Epub 2011/08/17. https://doi.org/10.1186/1743-422X-8-404 PMID: 21843352; PubMed Central PMCID: PMC3177908.

43. and CfDC Prevention. Imported Lassa fever—New Jersey, 2004. MMWR—Morbidity & Mortality Weekly Report. 2004; 53(38):894–7. Epub 2004/10/01. PMID: 15457145.

44. 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 Infectious Diseases. 2018; 5(7):ofy131. Epub 2018/07/24. https://doi.org/10.1093/ofid/ofy131 PMID: 30035149; PubMed Central PMCID: PMC6049013.

45. Chundusu CM, Isa SE, Jonathan B, Datong P. Lassa fever: A case report. Research Journal of Health Sciences. 2015; 3(2):133–8. rayyan-33333338.

46. Cummins D, Bennett D, Machin SJ. Exchange transfusion of a patient with fulminant Lassa fever. Postgraduate Medical Journal. 1991; 67(784):193–4. Epub 1991/02/01. https://doi.org/10.1136/pgmj.67.784.193 PMID: 2041853; PubMed Central PMCID: PMC2398981.

47. Edo AE, Okaka E, Ezeani IU. Hyperglycemic crisis precipitated by Lassa fever in a patient with previously undiagnosed type 2 diabetes mellitus. Nigerian Journal of Clinical Practice. 2014; 17(5):658–61. Epub 2014/09/23. https://doi.org/10.4103/1119-3077.141445 PMID: 25244282.

48. Emond RT, Bannister B, Lloyd G, Southee TJ, Bowen ET. A case of Lassa fever: clinical and virological findings. British Medical Journal Clinical Research Ed. 1982; 285(6347):1001–2. Epub 1982/10/09. https://doi.org/10.1136/bmj.285.6347.1001 PMID: 6812716; PubMed Central PMCID: PMC1500383.

49. Emond RT, Weir WR, Bowen ET, Lloyd G, Southee T. Managing Lassa fever. Lancet. 1984; 2 (8408):926. Epub 1984/10/20. https://doi.org/10.1016/s0140-6736(84)90679-2 PMID: 6148643.

50. 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 (8466):1227–9. Epub 1985/11/30. https://doi.org/10.1016/s0140-6736(85)90752-4 PMID: 2866301.

51. Fleischer K, Kohler B, Kirchner A, Schmid J. [Lassa fever]. Medizinische Klinik (Munich, Germany: 1983). 2000; 95(6):340–5. Epub 2000/08/10. https://doi.org/10.1007/pl00002133 PMID: 10935419.

52. Grahn A, Brave A, Lagging M, Dotevall L, Ekqvist D, Hammarstrom H, et al. Imported Case of Lassa Fever in Sweden With Encephalopathy and Sensorineural Hearing Deficit. Open Forum Infectious Diseases. 2016; 3(4):ofw198. Epub 2016/12/16. https://doi.org/10.1093/ofid/ofw198 PMID: 27975074; PubMed Central PMCID: PMC5152670.

53. Grove JN, Branco LM, Boisen ML, Muncy IJ, Henderson LA, Schieffellin JS, et al. Capacity building permitting comprehensive monitoring of a severe case of Lassa hemorrhagic fever in Sierra Leone with a positive outcome: Case Report. Virology Journal. 2011; 8. https://doi.org/10.1186/1743-422X-8-314 WOS:000293964200001. PMID: 21689444

54. Grundy DJ, Bowen ETW, Lloyd G. Isolated case of Lassa fever in Zaria, Northern Nigeria. Lancet. 1980; 2(8195):649–50. Epub 1994/02/28. https://doi.org/10.1016/s0140-6736(80)90322-0 PMID: 6107442.

55. Gunther 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. Journal of Infectious Diseases. 2001; 184(3):345–9. Epub 2001/07/10. https://doi.org/10.1086/322033 PMID: 11443561.

56. Hirabayashi Y, Oka S, Goto H. An imported case of Lassa fever with late appearance of polyserositis. Journal of Infectious Diseases. 1988; 158(4):872–5. Epub 1988/10/01. 12-03-2019 15:53 UTC. https://doi.org/10.1093/infdis/158.4.872 PMID: 3171229.

57. 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. New England Journal of Medicine. 1990; 323(16):1120–3. Epub 1990/10/18. https://doi.org/10.1056/NEJM199010183231607 PMID: 2215580.

58. Ikerionwu SE, Sato K, Katchy KC, Suseelan AAV. Lassa fever—An autopsy report from the Eastern part of Nigeria. Journal of Tropical Medicine and Hygiene. 1978; 81(7):134–6. Epub 1996/01/01. PMID: 702621.

59. Kitching A, Addiman S, Cathcart S, Bischop L, Krahe D, Nicholas M, et al. A fatal case of Lassa fever in London, January 2009.[Erratum appears in Euro Surveill. 2009;14(11):pii/19155]. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 2009;14(6):12. Epub 2009/02/14. https://doi.org/10.2807/ese.14.06.19117-en. PMID: 19215723.

60. 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. American Journal of Tropical Medicine & Hygiene. 2018; 30(4):30. Epub 2018/08/01. https://doi.org/10.4269/ajtmh.17-0316 PMID: 30062993; PubMed Central PMCID: PMC6159566.

61. Lehmann C, Kochanek M, Abdulla D, Becker S, Boll B, Bunte A, et al. Control measures following a case of imported Lassa fever from Togo, North Rhine Westphalia, Germany, 2016. Eurosurveillance. 2017; 22(39):15–23. https://doi.org/10.2807/1560-7917.es.2017.22.39.17–00088 WOS:000412080700004.

62. 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. American Journal of Tropical Medicine & Hygiene. 1970; 19(4):677–9. Epub 1970/07/01. https://doi.org/10.4269/ajtmh.1970.19.677 PMID: 4987546.

63. Lloyd G, Barber GN, Clegg JC, Kelly P. Identification of Lassa fever virus infection with recombinant nucleocapsid protein antigen. Lancet. 1989; 2(8673):1222. Epub 1989/11/18. https://doi.org/10.1016/s0140-6736(89)91833-3 PMID: 2572935.

64. Mahdy MS, Chiang W, McLaughlin B, Derksen K, Truxton BH, Neg K. Lassa fever: the first confirmed case imported into Canada. Canada Diseases Weekly Report. 1989; 15(39):193–8. Epub 1989/09/30. PMID: 2590947.

65. Marigold JH, Clarke SE, Gaunt JI, Croft DN. Lung uptake of Tc-99m-tin colloid in a patient with Lassa fever. Journal of Nuclear Medicine. 1983; 24(8):750–1. Epub 1983/08/01. PMID: 6875688.

66. McElroy AK, Akondy RS, Harmon JR, Ellebedy AH, Cannon D, Klena JD, et al. A Case of Human Lassa Virus Infection With Robust Acute T-Cell Activation and Long-Term Virus-Specific T-Cell Responses. Journal of Infectious Diseases. 2017; 215(12):1862–72. Epub 2017/09/03. https://doi.org/10.1093/infdis/jix201 PMID: 28863472; PubMed Central PMCID: PMC5853890.

67. Jt Meulen, Lenz O, Koivogui L, Magassouba N, Kaushik SK, Lewis R, et al. Short communication: Lassa fever in Sierra Leone: UN peacekeepers are at risk. Tropical Medicine and International Health. 2001; 6(1):83–4. https://doi.org/10.1046/j.1365-3156.2001.00676.x PMID: 11251899.

68. Okokhere PO, Erameh CO, Alikah F, Akhideno PE, Iruolagbe CO, Osazuwa OO, et al. Acute Lassa Virus Encephalitis with Lassa Virus in the Cerebrospinal Fluid but Absent in the Blood: A Case Report with a Positive Outcome. Case Reports in Neurology. 2018; 10(2):150–8. Epub 2018/07/31. https://doi.org/10.1159/000490374 PMID: 30057542; PubMed Central PMCID: PMC6062684.

69. Sarrat H, Camain R, Baum J, Robin Y. [Histopathological diagnosis of hepatitis due to Lassa virus]. Bulletin de la Societe de Pathologie Exotique et de Ses Filiales. 1972; 65(5):642–50. Epub 1972/09/01. PMID: 4679205.

70. Sato K, Ikerionwu SE, Katchy KC. An autopsy report of Lassa fever in Onitsha/Nigeria/1974. Japanese Journal of Tropical Medicine and Hygiene. 1982; 10(1):23–31. https://doi.org/10.2149/tmh1973.10.23. PMID: 19842010424.

71. Schlaeffer F, Bar-Lavie Y, Sikuler E, Alkan M, Keynan A. Evidence against high contagiousness of Lassa fever. Transactions of the Royal Society of Tropical Medicine & Hygiene. 1988; 82(2):311. Epub 1988/01/01. https://doi.org/10.1016/0035-9203(88)90458-0 PMID: 3188161.

72. Swaan CM, van den Broek PJ, Kampert E, Berbee GA, Schippers EF, Beersma MF, et al. Management of a patient with Lassa fever to prevent transmission. Journal of Hospital Infection. 2003; 55(3):234–5. Epub 2003/10/24. https://doi.org/10.1016/j.jhin.2003.08.002 PMID: 14572492.

73. Ufberg JW, Karras DJ. Update on emerging infections: news from the Centers for Disease Control and Prevention. Imported Lassa fever—New Jersey, 2004. Annals of emergency medicine. 2005; 45 (3):323–6. Epub 2005/02/24. https://doi.org/10.1016/j.annemergmed.2004.12.015 PMID: 15726058.

74. Van Der Heide RM. A patient with Lassa fever from Upper Volta, diagnosed in the Netherlands. [Dutch]. Nederlands Tijdschrift voor Geneeskunde. 1982; 126(13):566–9. rayyan-26247921. PMID: 7200196

75. Veldkamp PJ, Schippers EF. A man with fatal Lassa fever following a stay in Sierra Leone. [Dutch]. Nederlands Tijdschrift voor Geneeskunde. 2002; 146(46):2201–4. PMID: 12467165.

76. Walker DH, McCormick JB, Johnson KM, Webb PA, Komba-Kono G, Elliott LH, et al. Pathologic and virologic study of fatal Lassa fever in man The American journal of pathology. 1982; 107(3):349–56. Epub 1982/06/01. PMID: 7081389; PubMed Central PMCID: PMC1916239.

77. Winn WC Jr, Monath TP, Murphy FA, Whitfield SG. Lassa virus hepatitis. Observations on a fatal case from the 1972 Sierra Leone epidemic. Archives of Pathology & Laboratory Medicine. 1975; 99 (11):599–604. Epub 1975/11/11. PMID: 1227472.

78. Woodruff AW, Monath TP, Mahmoud AA, Pain AK, Morris CA. Lassa fever in Britain: an imported case. British Medical Journal. 1973; 3(5881):616–7. Epub 1973/09/22. https://doi.org/10.1136/bmj.3.5881.616 PMID: 4755184; PubMed Central PMCID: PMC1586880.

79. Yanase O, Motomiya T, Watanabe K, Tokuyasu Y, Sakurada H, Tejima T, et al. Lassa fever associated with effusive constrictive pericarditis and bilateral atrioventricular annular constriction: A case report. Journal of Cardiology. 1989; 19(4):1147–56. rayyan-29371481. PMID: 2486633

80. Keita M, Kizerbo GA, Subissi L, Traore FA, Dore A, Camara MF, et al. Investigation of a cross-border case of Lassa fever in West Africa. 2019; 19(1):606. https://doi.org/10.1186/s12879-019-4240-8 PMID: 31291900.

81. Oloniniyi OK, Unigwe US, Okada S, Kimura M, Koyano S, Miyazaki Y, et al. Genetic characterization of Lassa virus strains isolated from 2012 to 2016 in southeastern Nigeria. 2018; 12(11):e0006971. https://doi.org/10.1371/journal.pntd.0006971 PMID: 30500827.

82. Lotz E, Raffin H. Aeromedical evacuation using an aircraft transit isolator of a patient with Lassa fever. Aviat Space Environ Med. 2012; 83(5):527–30. Epub 2012/05/23. https://doi.org/10.3357/asem.3094.2012 PMID: 22606871.

83. Magassouba N, Koivogui E, Conde S, Kone M, Koropogui M, Soropogui B, et al. A Sporadic and Lethal Lassa Fever Case in Forest Guinea, 2019. Viruses. 2020; 12(10):23. https://doi.org/10.3390/v12101062 PMID: 32977629.

84. Ogunkunle TO, Bello SO, Anderson CI, Musa R, Olaosebikan R, Imam A. Fatal case of newborn Lassa fever virus infection mimicking late onset neonatal sepsis: a case report from northern Nigeria. Infect. 2020; 9(1):110. https://doi.org/10.1186/s40249-020-00731-1 PMID: 32778167.

85. Overbosch F, de Boer M, Veldkamp KE, Ellerbroek P, Bleeker-Rovers CP, Goorhuis B, et al. Public health response to two imported, epidemiologically related cases of Lassa fever in the Netherlands (ex Sierra Leone), November 2019. Eurosurveillance. 2020; 25(15):6–10. https://doi.org/10.2807/1560-7917.ES.2020.25.15.2000265 PMID: 32317052.

86. Dan-Nwafor CC, Ipadeola O, Smout E, Ilori E, Adeyemo A, Umeokonkwo C, et al. A cluster of nosocomial Lassa fever cases in a tertiary health facility in Nigeria: Description and lessons learned, 2018. 2019; 83:88–94. https://doi.org/10.1016/j.ijid.2019.03.030 PMID: 30930184.

87. Akhiwu HO, Yiltok ES, Ebonyi AO, Gomerep S, Shehu NY, Amaechi EP, et al. Lassa fever outbreak in adolescents in North Central Nigeria: report of cases. Journal of virus eradication. 2018; 4 (4):225–7. Epub 2018/12/06. PMID: 30515301; PubMed Central PMCID: PMC6248838.

88. Akpede G, Odike A, Okokhere P, Olomu SC, Asogun D, Happi C, et al. Prevalence and presentation of Lassa fever in Nigerian children. International Journal of Infectious Diseases. 2010; 1:e380. https://doi.org/10.1016/j.ijid.2010.02.465 PMID: 70125912.

89. Akpede GO, Kayode-Adedeji BO, Dawodu SO. Manifestations and outcomes of lassa fever in nigerian children: A case series. Archives of Disease in Childhood. 2012; 1(97):A38–A9. http://dx.doi.org/10.1136/archdischild-2012-301885.96. PMID: 71049875.

90. Bello OO, Akinajo OR, Odubamowo KH, Oluwasola TA. Lassa Fever in Pregnancy: Report of 2 Cases Seen at the University College Hospital, Ibadan. Case Reports in Obstetrics and Gynecology. 2016; 2016:9673683. Epub 2016/04/07. https://doi.org/10.1155/2016/9673683 PMID: 27051545; PubMed Central PMCID: PMC4804058.

91. Bond N, Schieffelin JS, Moses LM, Bennett AJ, Bausch DG. A historical look at the first reported cases of Lassa fever: IgG antibodies 40 years after acute infection. American Journal of Tropical Medicine & Hygiene. 2013; 88(2):241–4. Epub 2013/02/08. https://doi.org/10.4269/ajtmh.2012.12–0466 PMID: 23390223; PubMed Central PMCID: PMC3583312.

92. Bonney JHK, Nyarko EO, Ohene SA, Amankwa J, Ametepi RK, Nimo-Paintsil SC, et al. Molecular confirmation of Lassa fever imported into Ghana. African Journal of Laboratory Medicine. 2016; 5(1). https://doi.org/10.4102/ajlm.v5i1.288 WOS:000384242500001. PMID: 28879105

93. Clayton AJ. Lassa immune serum. Bulletin of the World Health Organization. 1977; 55(4):435–9. Epub 1977/01/01. PMID: 304386; PubMed Central PMCID: PMC2366682.

94. Bowen GS, Tomori O, Wulff H, Casals J, Noonan A, Downs WG. Lassa fever in Onitsha, East Central State, Nigeria in 1974. Bulletin of the World Health Organization. 1975; 52(4–6):599–604. Epub 1975/01/01. PMID: 1085214; PubMed Central PMCID: PMC2366632.

95. Cummins D, Bennett D, Fisher-Hoch SP, Farrar B, McCormick JB. Electrocardiographic abnormalities in patients with Lassa fever. Journal of Tropical Medicine & Hygiene. 1989; 92(5):350–5. Epub 1989/10/01. PMID: 2810453.

96. Cummins D, Bennett D, Fisher-Hoch SP, Farrar B, Machin SJ, McCormick JB. Lassa fever encephalopathy: clinical and laboratory findings. Journal of Tropical Medicine & Hygiene. 1992; 95(3):197–201. Epub 1992/06/01. PMID: 1597876.

97. Dongo AE, Kesieme EB, Iyamu CE, Okokhere PO, Akhuemokhan OC, Akpede GO. Lassa fever presenting as acute abdomen: a case series. Virology Journal. 2013; 10:7. WOS:000318405700001. https://doi.org/10.1186/1743-422X-10-7 PMID: 23282224

98. Dzotsi EK, Ohene SA, Asiedu-Bekoe F, Amankwa J, Sarkodie B, Adjabeng M, et al. The first cases of Lassa fever in Ghana. Ghana Medical Journal. 2012; 46(3):166–70. Epub 2013/05/11. PMID: 23661832; PubMed Central PMCID: PMC3645162.

99. Edington GM, White HA. The pathology of Lassa fever. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1972; 66(3):381–9. Epub 1972/01/01. https://doi.org/10.1016/0035-9203(72)90268-4 PMID: 5046378.

100. 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. American Journal of Tropical Medicine & Hygiene. 1970; 19(4):670–6. Epub 1970/07/01. https://doi.org/10.4269/ajtmh.1970.19.670 PMID: 4246571.

101. Gilles HM, Kent JC. Lassa fever: retrospective diagnosis of two patients seen in Great Britain in 1971. British Medical Journal. 1976; 2(6045):1173. Epub 1976/11/13. https://ezproxy-prd.bodleian.ox.ac.uk:4563/10.1136/bmj.2.6045.1173 PMID: 791445; PubMed Central PMCID: PMC1689623.

102. Kyei NN, Abilba MM, Kwawu FK, Agbenohevi PG, Bonney JH, Agbemaple TK, et al. Imported Lassa fever: a report of 2 cases in Ghana. BMC infectious diseases. 2015; 15:217. Epub 2015/05/30. https://doi.org/10.1186/s12879-015-0956-2 PMID: 26022703; PubMed Central PMCID: PMC4448534.

103. Macher AM, Wolfe MS. Historical Lassa fever reports and 30-year clinical update. Emerging Infectious Diseases. 2006; 12(5):835–7. Epub 2006/05/18. https://doi.org/10.3201/eid1205.050052 PMID: 16704848; PubMed Central PMCID: PMC3374442.

104. Maigari IM, Jibrin YB, Umar MS, Lawal SM, Gandi AY. Descriptive features of Lassa fever in Bauchi, Northeastern Nigeria—a retrospective review. Research Journal of Health Sciences. 2018. http://dx.doi.org/10.4314/rejhs.v6i3.7. rayyan-33333386.

105. Mertens PE, Patton R, Baum JJ, Monath TP. Clinical presentation of Lassa fever cases during the hospital epidemic at Zorzor, Liberia, March-April 1972. American Journal of Tropical Medicine & Hygiene. 1973; 22(6):780–4. Epub 1973/11/01. https://doi.org/10.4269/ajtmh.1973.22.780 PMID: 4745237.

106. Monath TP, Mertens PE, Patton R, Moser CR, Baum JJ, Pinneo L, et al. A hospital epidemic of Lassa fever in Zorzor, Liberia, March-April 1972. American Journal of Tropical Medicine & Hygiene. 1973; 22(6):773–9. Epub 1973/11/01. https://doi.org/10.4269/ajtmh.1973.22.773 PMID: 4745236.

107. Monath TP, Maher M, Casals J, Kissling RE, Cacciapuoti A. Lassa fever in the Eastern Province of Sierra Leone, 1970–1972. II. Clinical observations and virological studies on selected hospital cases. American Journal of Tropical Medicine & Hygiene. 1974; 23(6):1140–9. Epub 1974/11/01. https://doi.org/10.4269/ajtmh.1974.23.1140 PMID: 4429183.

108. Monson MH, Cole AK, Frame JD, Serwint JR, Alexander S, Jahrling PB. Pediatric Lassa fever: a review of 33 Liberian cases. American Journal of Tropical Medicine & Hygiene. 1987; 36(2):408–15. Epub 1987/03/01. https://doi.org/10.4269/ajtmh.1987.36.408 PMID: 3826501.

109. Okogbenin SA, Asogun D, Akpede G, Okokhere P, Gunther S, Happi C. New lessons from a case series review of Lassa fever in Pregnancy. International Journal of Infectious Diseases. 2010; 14:E380–E. https://doi.org/10.1016/j.ijid.2010.02.466 WOS:000276298201426.

110. Okokhere PO, Ibekwe TS, Akpede GO. Sensorineural hearing loss in Lassa fever: two case reports. Journal of Medical Case Reports [Electronic Resource]. 2009; 3:36. Epub 2009/01/31. https://doi.org/10.1186/1752-1947-3-36 PMID: 19178735; PubMed Central PMCID: PMC2642856.

111. Okokhere P, Asogun D, Okogbenin SA. The effect of malaria on the outcome of Lassa Fever. International Journal of Infectious Diseases. 2010; 14:e333. https://doi.org/10.1016/j.ijid.2010.03.002 PMID: 20579914.

112. Okokhere PO, Bankole IA, Akpede GO. Central nervous system manifestations of lassa fever in Nigeria and the effect on mortality. Journal of the Neurological Sciences. 2013; 1:e604. https://doi.org/10.1016/j.jns.2013.07.2107. rayyan-26218237.

113. Okokhere PO, Bankole IA, Iruolagbe CO, Muoebonam BE, Okonofua MO, Dawodu SO, et al. Aseptic Meningitis Caused by Lassa Virus: Case Series Report. Case Reports in Neurological Medicine Print. 2016; 2016:1978461. Epub 2016/12/14. https://doi.org/10.1155/2016/1978461 PMID: 27957363; PubMed Central PMCID: PMC5124455 publication of this paper.

114. Patassi AA, Landoh DE, Mebiny-Essoh Tchalla A, Halatoko WA, Assane H, Saka B, et al. Emergence of Lassa Fever Disease in Northern Togo: Report of Two Cases in Oti District in 2016. Case Reports Infectious Diseases. 2017; 2017:8242313. Epub 2018/02/03. https://doi.org/10.1155/2017/8242313 PMID: 29391958; PubMed Central PMCID: PMC5748105.

115. Public Health Laboratory Service Communicable Disease Centre. Lassa fever 1982. British Medical Journal. 1983; 287(6384):48. PMID: 6407689

116. Raabe VN, Kann G, Ribner BS, Morales A, Varkey JB, Mehta AK, et al. Favipiravir and Ribavirin Treatment of Epidemiologically Linked Cases of Lassa Fever. Clinical Infectious Diseases. 2017; 65 (5):855–9. Epub 2017/10/12. https://doi.org/10.1093/cid/cix406 PMID: 29017278; PubMed Central PMCID: PMC5682919.

117. Schmitz H, Kohler B, Laue T, Drosten C, Veldkamp PJ, Gunther S, et al. Monitoring of clinical and laboratory data in two cases of imported Lassa fever. Microbes and Infection. 2002; 4(1):43–50. Epub 2002/02/05. https://doi.org/10.1016/s1286-4579(01)01508-8 PMID: 11825774.

118. Sharp PC. Lassa fever in children. Journal of Infection. 1982; 4(1):73–7. Epub 1982/01/01. https://doi.org/10.1016/s0163-4453(82)91133-1 PMID: 7185979.

119. Troup JM, White HA, Fom AL, Carey DE. An outbreak of Lassa fever on the Jos plateau, Nigeria, in January-February 1970. A preliminary report. American Journal of Tropical Medicine & Hygiene. 1970; 19(4):695–6. Epub 1970/07/01. https://ezproxy-prd.bodleian.ox.ac.uk:4563/10.4269/ajtmh.1970.19.695. PMID: 4987549.

120. Walls B. Lassa fever and pregnancy. Midwives Chronicle. 1985; 1168(98):136–8. Epub 1985/05/01. PMID: 3846752.

121. White HA. Lassa fever. A study of 23 hospital cases. Transactions of the Royal Society of Tropical Medicine & Hygiene. 1972; 66(3):390–401. Epub 1972/01/01. https://doi.org/10.1016/0035-9203(72)90269-6 PMID: 5046379.

122. Bausch DG, Rollin PE, Demby AH, Coulibaly M, Kanu J, Conteh AS, et al. Diagnosis and clinical virology of Lassa fever as evaluated by enzyme-linked immunosorbent assay, indirect fluorescent-antibody test, and virus isolation. Journal of Clinical Microbiology. 2000; 38(7):2670–7. Epub 2000/07/06. https://doi.org/10.1128/JCM.38.7.2670-2677.2000 PMID: 10878062; PubMed Central PMCID: PMC86994.

123. Ajayi NA, Nwigwe CG, Azuogu BN, Onyire BN, Nwonwu EU, Ogbonnaya LU, et al. Containing a Lassa fever epidemic in a resource-limited setting: outbreak description and lessons learned from Abakaliki, Nigeria (January–March 2012). International Journal of Infectious Diseases. 2013; 17(11): e1011–e6. https://doi.org/10.1016/j.ijid.2013.05.015 PMID: 23871405

124. Siddle KJ, Eromon P, Barnes KG, Mehta S, Oguzie JU, Odia I, et al. Genomic Analysis of Lassa Virus during an Increase in Cases in Nigeria in 2018. 2018; 379(18):1745–53. https://doi.org/10.1056/NEJMoa1804498 PMID: 30332564.

125. Salu OB, James AB, Bankole HS, Agbla JM, Da Silva M, Gbaguidi F, et al. Molecular confirmation and phylogeny of Lassa fever virus in Benin Republic 2014–2016. 2019; 8(1):803. https://doi.org/10.4102/ajlm.v8i1.803 PMID: 31534915.

126. Okogbenin S, Okoeguale J, Akpede G, Colubri A, Barnes KG, Mehta S, et al. Retrospective cohort study of Lassa fever in pregnancy, southern Nigeria. 2019; 25(8):1494–500. PMID: 20193372982.

127. Akpede GO, Adetunji AE, Udefiagbon EO, Eluehike SO, Odike AI, Ewah-Odiase RO, et al. Acute Abdomen in Pediatric Patients With Lassa Fever: Prevalence and Response to Nonoperative Management. Journal of the Pediatric Infectious Diseases Society. 2018. Epub 2018/10/03. https://doi.org/10.1093/jpids/piy093 PMID: 30272215.

128. Asogun DA, Adomeh DI, Ehimuan J, Odia I, Hass M, Gabriel M, et al. Molecular diagnostics for lassa fever at Irrua specialist teaching hospital, Nigeria: lessons learnt from two years of laboratory operation. PLoS Neglected Tropical Diseases [electronic resource]. 2012; 6(9):e1839. Epub 2012/10/03. https://doi.org/10.1371/journal.pntd.0001839 PMID: 23029594; PubMed Central PMCID: PMC3459880.

129. Bausch DG, Demby AH, Coulibaly M, Kanu J, Goba A, Bah A, et al. Lassa fever in Guinea: I. Epidemiology of human disease and clinical observations. Vector Borne & Zoonotic Diseases. 2001; 1(4):269–81. Epub 2003/03/26. https://doi.org/10.1089/15303660160025903 PMID: 12653127.

130. Branco LM, Grove JN, Boisen ML, Shaffer JG, Goba A, Fullah M, et al. Emerging trends in Lassa fever: redefining the role of immunoglobulin M and inflammation in diagnosing acute infection. Virology Journal. 2011; 8:478. Epub 2011/10/26. https://doi.org/10.1186/1743-422X-8-478 PMID: 22023795; PubMed Central PMCID: PMC3223505.

131. Chiosi J, Shaffer J, Schieffelin J. Clinical outcomes of lassa fever in children compared to adults in Sierra Leone. Journal of Investigative Medicine. 2018; 66:580. https://doi.org/10.1136/jim-2017-000697.559 PMID: 621291552.

132. Cummins D, McCormick JB, Bennett D, Samba JA, Farrar B, Machin SJ, et al. Acute sensorineural deafness in Lassa fever. JAMA. 1990; 264(16):2093–6. https://doi.org/10.1001/jama.1990.03450160063030 PMID: 2214077.

133. Ehichioya DU, Asogun DA, Ehimuan J, Okokhere PO, Pahlmann M, Olschlager S, et al. Hospital-based surveillance for Lassa fever in Edo State, Nigeria, 2005–2008. Tropical Medicine & International Health. 2012; 17(8):1001–4. Epub 2012/05/19. https://doi.org/10.1111/j.1365-3156.2012.03010.x PMID: 22594713.

134. Fisher-Hoch SP, Tomori O, Nasidi A, Perez-Oronoz GI, Fakile Y, Hutwagner L, et al. Review of cases of nosocomial Lassa fever in Nigeria: the high price of poor medical practice. BMJ. 1995; 311 (7009):857–9. Epub 1995/09/30. https://doi.org/10.1136/bmj.311.7009.857 PMID: 7580496; PubMed Central PMCID: PMC2550858.

135. Frame JD, Verbrugge GP, Gill RG, Pinneo L. The use of Lassa fever convalescent plasma in Nigeria. Transactions of the Royal Society of Tropical Medicine & Hygiene. 1984; 78(3):319–24. Epub 1984/01/01. https://doi.org/10.1016/0035-9203(84)90107-x PMID: 6464130.

136. Frame JD. Clinical features of Lassa fever in Liberia. Reviews of Infectious Diseases. 1989; 11 Suppl 4:S783–9. Epub 1989/05/01. https://doi.org/10.1093/clinids/11.supplement_4.s783 PMID: 2749109.

137. Inegbenebor U, Okosun J, Inegbenebor J. Prevention of Lassa fever in Nigeria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2010; 104(1):51–4. https://doi.org/10.1016/j.trstmh.2009.07.008 PMID: 19712954

138. Iroezindu MO, Unigwe US, Okwara CC, Ozoh GA, Ndu AC, Ohanu ME, et al. Lessons learnt from the management of a case of Lassa fever and follow-up of nosocomial primary contacts in Nigeria during Ebola virus disease outbreak in West Africa. Tropical Medicine & International Health. 2015; 20 (11):1424–30. Epub 2015/07/15. https://doi.org/10.1111/tmi.12565 PMID: 26171669.

139. Johnson KM, McCormick JB, Webb PA. Clinical virology of Lassa fever in hospitalized patients. Journal of Infectious Diseases. 1987; 155(3):456–64. Epub 2006/10/13. https://doi.org/10.1093/infdis/155.3.456 PMID: 3805773.

140. Okokhere P, Ugheoke J, Erameh C. Pulmonary manifestation of lassa fever and the impact on mortality. European Respiratory Journal Conference: European Respiratory Society Annual Congress. 2012; 40. PMID: 71923785.

141. Okokhere P, Colubri A, Azubike C, Iruolagbe C, Osazuwa O, Tabrizi S, et al. Clinical and laboratory predictors of Lassa fever outcome in a dedicated treatment facility in Nigeria: a retrospective, observational cohort study.[Erratum appears in Lancet Infect Dis. 2018 Mar 16;:; 29555583]. The Lancet Infectious Diseases. 2018; 18(6):684–95. Epub 2018/03/11. https://doi.org/10.1016/S1473-3099(18)30121-X PMID: 29523497; PubMed Central PMCID: PMC5984133.

142. Price ME, Fisher-Hoch SP, Craven RB, McCormick JB. A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy. BMJ. 1988; 297(6648):584–7. Epub 1988/09/03. https://doi.org/10.1136/bmj.297.6648.584 PMID: 3139220; PubMed Central PMCID: PMC1834487.

143. Roth PJ, Grant DS, Ngegbai AS, Schieffelin J, McClelland RS, Jarrett OD. Factors associated with mortality in febrile patients in a government referral hospital in the Kenema district of Sierra Leone. The American journal of tropical medicine and hygiene. 2015; 92(1):172–7. Epub 2014/11/17. https://doi.org/10.4269/ajtmh.14-0418 PMID: 25404077.

144. Schieffelin JS, Shaffer J, Krousel-Wood M, Garry RF, Grant DS. Pregnancy but Not Sex Impacts Lassa Fever Outcome. Journal of Womens Health. 2017; 26(9):1035–. WOS:000411072500052.

145. Shehu NY, Gomerep SS, Isa SE, Iraoyah KO, Mafuka J, Bitrus N, et al. Lassa Fever 2016 Outbreak in Plateau State, Nigeria-The Changing Epidemiology and Clinical Presentation. Frontiers in Public Health. 2018; 6:232. Epub 2018/09/14. https://doi.org/10.3389/fpubh.2018.00232 PMID: 30211144; PubMed Central PMCID: PMC6123362.

146. Webb PA, McCormick JB, King IJ, Bosman I, Johnson KM, Elliott LH, et al. Lassa fever in children in Sierra Leone, West Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1986; 80(4):577–82. Epub 1986/01/01. https://doi.org/10.1016/0035-9203(86)90147-1 PMID: 3810792.

147. Zweighaft RM, Fraser DW, Hattwick MAW, Winkler WG, Jordan WC, Alter M, et al. LASSA FEVER—RESPONSE TO AN IMPORTED CASE. New England Journal of Medicine. 1977; 297(15):803–7. https://doi.org/10.1056/nejm197710132971504 WOS:A1977DX39100004. PMID: 895819

148. Knobloch J, McCormick JB, Webb PA, Dietrich M, Schumacher HH, Dennis E. Clinical observations in 42 patients with Lassa fever. Tropenmedizin und Parasitologie. 1980; 31(4):389–98. Epub 1980/12/01. PMID: 7233535.

149. Adetunji AE, Ayenale M, Akhigbe I, Akerele LO, Isibor E, Idialu J, et al. Acute kidney injury and mortality in pediatric Lassa fever versus question of access to dialysis. International Journal of Infectious Diseases. 2021; 103:124–31. https://doi.org/10.1016/j.ijid.2020.11.006 PMID: 33176203.

150. Chandra NL, Bolt H, Dan-Nwafor C, Ipadeola O, Ilori E, Namara G, et al. Factors associated with delayed presentation to healthcare facilities for Lassa fever cases, Nigeria 2019: a retrospective cohort study. BMC infectious diseases. 2021; 21(1):143. https://doi.org/10.1186/s12879-021-05822-4 PMID: 33541278.

151. Chika-Igwenyi NM, Harrison RE, Psarra C, Gil-Cuesta J, Gulamhusein M, Onwe EO, et al. Early onset of neurological features differentiates two outbreaks of Lassa fever in Ebonyi state, Nigeria during 2017–2018. PLoS Neglected Tropical Diseases [electronic resource]. 2021; 15(3):e0009169. https://doi.org/10.1371/journal.pntd.0009169 PMID: 33684118.

152. Okogbenin EOOT Obagaye MO, Aweh BE Eriyo WO, Author SAOT Okokhere PO. One-year retrospective review of Psychiatric consultations in Lassa fever, Southern Nigeria. Emerging Infectious Diseases. 2020; 26(12):3091–3. https://doi.org/10.3201/eid2612.200084 PMID: 33219806.

153. Samuels RJ, Moon TD, Starnes JR, Alhasan F, Gbakie M, Goba A, et al. Lassa fever among children in eastern province, Sierra Leone: a 7-year retrospective analysis (2012–2018). American Journal of Tropical Medicine and Hygiene. 2021; 104(2):585–92. http://dx.doi.org/10.4269/ajtmh.20-0773. PMID: 20210113327.

154. Wauquier N, Couffignal C, Manchon P, Smith E, Lungay V, Coomber M, et al. High heart rate at admission as a predictive factor of mortality in hospitalized patients with Lassa fever: An observational cohort study in Sierra Leone. Journal of Infection. 2020; 80(6):671–93. https://doi.org/10.1016/j.jinf.2020.01.021 PMID: 32027872.

155. Ilori EA, Furuse Y, Ipadeola OB, Dan-Nwafor CC, Abubakar A, Womi-Eteng OE, et al. Epidemiologic and Clinical Features of Lassa Fever Outbreak in Nigeria, January 1-May 6, 2018. 2019; 25(6):1066–74. https://doi.org/10.3201/eid2506.181035 PMID: 31107222.

156. Akhuemokhan OC, Ehiemua J, Adomeh DI, Odia I, Olomu SC, Becker-Ziaja B, et al. Lassa fever and convulsions associated with fever: A case-control study. Archives of Disease in Childhood. 2017; 102: A122. http://dx.doi.org/10.1136/archdischild-2017-313087.304. PMID: 616986937.

157. Akhuemokhan OC, Ewah-Odiase RO, Akpede N, Ehimuan J, Adomeh DI, Odia I, et al. Prevalence of Lassa Virus Disease (LVD) in Nigerian children with fever or fever and convulsions in an endemic area. PLoS Neglected Tropical Diseases [electronic resource]. 2017; 11(7):e0005711. Epub 2017/07/04. https://doi.org/10.1371/journal.pntd.0005711 PMID: 28671959; PubMed Central PMCID: PMC5510890.

158. Fisher-Hoch S, McCormick JB, Sasso D, Craven RB. Hematologic dysfunction in Lassa fever. Journal of Medical Virology. 1988; 26(2):127–35. Epub 1988/10/01. https://doi.org/10.1002/jmv.1890260204 PMID: 3183637.

159. Ibekwe TS, Okokhere PO, Asogun D, Blackie FF, Nwegbu MM, Wahab KW, et al. Early-onset sensorineural hearing loss in Lassa fever. European Archives of Oto-Rhino-Laryngology. 2011; 268(2):197–201. Epub 2010/09/03. https://doi.org/10.1007/s00405-010-1370-4 PMID: 20809263.

160. McCormick JB, King IJ, Webb PA. A case-control study of the clinical diagnosis and course of Lassa fever. Journal of Infectious Diseases. 1987; 155(3):445–55. Epub 2006/10/13. https://doi.org/10.1093/infdis/155.3.445 PMID: 3805772.

161. Shaffer JG, Grant DS, Schieffelin JS, Boisen ML, Goba A, Hartnett JN, et al. Lassa fever in post-conflict sierra leone. PLoS Neglected Tropical Diseases [electronic resource]. 2014; 8(3):e2748. Epub 2014/03/22. https://doi.org/10.1371/journal.pntd.0002748 PMID: 24651047; PubMed Central PMCID: PMC3961205.

162. Ficenec SC, Percak J, Arguello S, Bays A, Goba A, Gbakie M, et al. Lassa fever induced hearing loss: the neglected disability of hemorrhagic fever. International Journal of Infectious Diseases. 2020; 100:82–7. https://doi.org/10.1016/j.ijid.2020.08.021 PMID: 32795603.

163. Horton LE, Cross RW, Hartnett JN, Engel EJ, Sakabe S, Goba A, et al. Endotheliopathy and platelet dysfunction as hallmarks of fatal lassa fever. Emerging Infectious Diseases. 2020; 26(11):2625–37. https://doi.org/10.3201/eid2611.191694 PMID: 33079033.

164. Ipadeola O, Furuse Y, Ilori EA, Dan-Nwafor CC, Akabike KO, Ahumibe A, et al. Epidemiology and case-control study of Lassa fever outbreak in Nigeria from 2018 to 2019. Journal of Infection. 2020; 80 (5):578–606. https://doi.org/10.1016/j.jinf.2019.12.020 PMID: 31926184.

165. Dahmane A, van Griensven J, Van Herp M, Van den Bergh R, Nzomukunda Y, Prior J, et al. Constraints in the diagnosis and treatment of Lassa Fever and the effect on mortality in hospitalized children and women with obstetric conditions in a rural district hospital in Sierra Leone. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2014; 108(3):126–32. Epub 2014/02/19. https://doi.org/10.1093/trstmh/tru009 PMID: 24535150; PubMed Central PMCID: PMC4023273.

166. Fisher-Hoch SP, Gborie S, Parker L, Huggins J. Unexpected adverse reactions during a clinical trial in rural west Africa. Antiviral research. 1992; 19(2):139–47. Epub 1992/08/01. https://doi.org/10.1016/0166-3542(92)90073-e PMID: 1444324.

167. Keane E, Gilles HM. Lassa fever in Panguma Hospital, Sierra Leone, 1973–6. British Medical Journal. 1977; 1(6073):1399–402. Epub 1977/05/28. https://doi.org/10.1136/bmj.1.6073.1399 PMID: 861652; PubMed Central PMCID: PMC1606930.

168. Li WG, Chen WW, Li L, Ji D, Ji YJ, Li C, et al. The etiology of Ebola virus disease-like illnesses in Ebola virusnegative patients from Sierra Leone. Oncotarget. 2016; 7(19):27910–5. Epub 2016/04/09. https://doi.org/10.18632/oncotarget.8558 PMID: 27058894; PubMed Central PMCID: PMC5053697.

169. McCormick JB, Walker DH, King IJ. Lassa virus hepatitis: A study of fatal Lassa fever in humans. American Journal of Tropical Medicine and Hygiene. 1986; 35(2):401–7. Epub 1986/03/01. https://doi.org/10.4269/ajtmh.1986.35.401 PMID: 3953952.

170. Monson MH, Frame JD, Jahrling PB, Alexander K. Endemic Lassa fever in Liberia. I. Clinical and epidemiological aspects at Curran Lutheran Hospital, Zorzor, Liberia. Transactions of the Royal Society of Tropical Medicine & Hygiene. 1984; 78(4):549–53. Epub 1984/01/01. https://doi.org/10.1016/0035-9203(84)90082-8 PMID: 6485062.

171. Ehichioya D, Asogun D, Hass M, Becker-Ziaja B, Gunther S, Omilabu S. A retrospective laboratory analysis of clinically diagnosed Lassa fever cases in a tertiary hospital in Nigeria. International Journal of Infectious Diseases. 2010; 14:e209–e10. https://doi.org/10.1016/j.ijid.2010.02.1953. PMID: 70125529.

172. Getso KI, Balogun MS, Nasidi A, Gidado S, Nguku P, Oladejo J, et al. Lassa fever outbreak involving healthcare workers in Taraba State, Nigeria, March 2012. International Journal of Infectious Diseases. 2014; 21:216–. https://doi.org/10.1016/j.ijid.2014.03.871 WOS:000209704000455.

173. Buba MI, Dalhat MM, Nguku PM, Waziri N, Mohammad JO, Bomoi IM, et al. Mortality Among Confirmed Lassa Fever Cases During the 2015–2016 Outbreak in Nigeria. American Journal of Public Health. 2018; 108(2):262–4. Epub 2017/12/22. https://doi.org/10.2105/AJPH.2017.304186 PMID: 29267063.

174. Li AL, Grant D, Gbakie M, Kanneh L, Mustafa I, Bond N, et al. Ophthalmic manifestations and vision impairment in Lassa fever survivors. PLoS ONE [Electronic Resource]. 2020; 15(12):e0243766. https://doi.org/10.1371/journal.pone.0243766 PMID: 33301526.

175. Owhin SO, Abejegah C, Fasipe OJ, Oke C, Abidoye A, Osagbaekhoe A, et al. Association of hypoalbuminemia and reversal of albumin-to-globulin ratio with morbidity outcome among hospitalized Lassa fever infected patients at a dedicated treatment center in Ondo state, south-western Nigeria. Future Sci OA. 2020; 6(10):FSO620. https://doi.org/10.2144/fsoa-2020-0075 PMID: 33312698.

176. Cummins D, Fisher-Hoch SP, Walshe KJ, Mackie IJ, McCormick JB, Bennett D, et al. A plasma inhibitor of platelet aggregation in patients with Lassa fever. British journal of haematology. 1989; 72 (4):543–8. Epub 1989/08/01. https://doi.org/10.1111/j.1365-2141.1989.tb04321.x PMID: 2775659.

177. Chiosi J, Shaffer J, Schieffelin J. Applying clinical prediction tools to patients with lassa fever. 2018; 5: S35. PMID: 629389871.

178. Shlaeffer F, Sikuler E, Keynan A. Lassa fever—first case diagnosed in Israel. [Hebrew]. Harefuah. 1988; 114(1):12–4. PMID: 3350404.

179. Policy Cures Research. Landscape of emerging infectious disease research and development: Preventing the next pandemic. 2020.

180. World Health Organisation. An R&D blueprint for action to prevent epidemics. Geneva, Switzerland: 2016.

181. Largest-ever Lassa fever research programme launches in West Africa [Internet]. 2020 [cited 13/07/2021]. Available from: https://cepi.net/news_cepi/largest-ever-lassa-fever-research-programme-launches-in-west-africa/

182. U.S Food & Drug Administration. Tropical Disease Priority Review Voucher Program 2020 [14/08/2021]. Available from: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program.

183. Gouglas D, Christodoulou M, Plotkin SA, Hatchett R. CEPI: Driving Progress Toward Epidemic Preparedness and Response. Epidemiol Rev. 2019; 41(1):28–33. Epub 2019/11/02. https://doi.org/10.1093/epirev/mxz012 PMID: 31673694; PubMed Central PMCID: PMC7108492.

184. Ben-Enukora C, Oyero O, Okorie N, Oyesomi K, Adeyeye B. Effectiveness of Yoruba language radio jingles in promoting knowledge, attitude and practices regarding Lassa fever among women in Ondo state, Nigeria. J Public Health Afr. 2020; 11(2):1323. Epub 2021/03/09. https://doi.org/10.4081/jphia.2020.1323 PMID: 33680412; PubMed Central PMCID: PMC7922361.

185. Usuwa IS, Akpa CO, Umeokonkwo CD, Umoke M, Oguanuo CS, Olorukooba AA, et al. Knowledge and risk perception towards Lassa fever infection among residents of affected communities in Ebonyi State, Nigeria: implications for risk communication. BMC Public Health. 2020; 20(1):217. Epub 2020/02/14. https://doi.org/10.1186/s12889-020-8299-3 PMID: 32050926; PubMed Central PMCID: PMC7017500.

186. Wogu JO, Chukwu CO, Nwafor KA, Anikpe EA, Ugwuoke JC, Ugwulor-Onyinyechi CC, et al. Mass media reportage of Lassa fever in Nigeria: a viewpoint. J Int Med Res. 2020; 48(1):300060518821552. Epub 2019/01/19. https://doi.org/10.1177/0300060518821552 PMID: 30657006; PubMed Central PMCID: PMC7140189.

187. Bowen MD, Rollin PE, Ksiazek TG, Hustad HL, Bausch DG, Demby AH, et al. Genetic Diversity among Lassa Virus Strains. Journal of Virology. 2000; 74(15):6992–7004. https://doi.org/10.1128/jvi.74.15.6992-7004.2000 PMID: 10888638

188. Oloniniyi OK, Unigwe US, Okada S, Kimura M, Koyano S, Miyazaki Y, et al. Genetic characterization of Lassa virus strains isolated from 2012 to 2016 in southeastern Nigeria. PLOS Neglected Tropical Diseases. 2018; 12(11):e0006971. https://doi.org/10.1371/journal.pntd.0006971 PMID: 30500827

189. Ehichioya DU, Dellicour S, Pahlmann M, Rieger T, Oestereich L, Becker-Ziaja B, et al. Phylogeography of Lassa Virus in Nigeria. Journal of Virology. 2019; 93(21):e00929–19. https://doi.org/10.1128/JVI.00929-19 PMID: 31413134

190. World Health Organisation. Technical Guidance [31 March 2021]. Available from: https://www.who.int/health-topics/lassa-fever/technical-guidance.

191. Asogun D, Okokhere P, Tobin E, Okogbenin SA, Akpede G, Happi C, et al. Lassa fever practice challenges in Nigeria. International Journal of Infectious Diseases. 2012; 16:e69. https://doi.org/10.1016/j.ijid.2012.05.170

192. Ibekwe T. Lassa fever: the challenges of curtailing a deadly disease. The Pan African medical journal. 2012; 11:55–. Epub 2012/03/23. PMID: 22593791.

193. Ölschläger S, Lelke M, Emmerich P, Panning M, Drosten C, Hass M, et al. Improved Detection of Lassa Virus by Reverse Transcription-PCR Targeting the 5′ Region of S RNA. Journal of Clinical Microbiology. 2010; 48(6):2009–13. https://doi.org/10.1128/JCM.02351-09 PMID: 20351210

194. Nikisins S, Rieger T, Patel P, Müller R, Günther S, Niedrig M. International External Quality Assessment Study for Molecular Detection of Lassa Virus. PLOS Neglected Tropical Diseases. 2015; 9(5):e0003793. https://doi.org/10.1371/journal.pntd.0003793 PMID: 25996783

195. Boisen ML, Hartnett JN, Shaffer JG, Goba A, Momoh M, Sandi JD, et al. Field validation of recombinant antigen immunoassays for diagnosis of Lassa fever. Scientific Reports. 2018; 8(1):5939. https://doi.org/10.1038/s41598-018-24246-w PMID: 29651117

196. Centers for Disease Control and Prevention. Lassa fever: Diagnosis 2014 [14/08/2021]. Available from: https://www.cdc.gov/vhf/lassa/diagnosis/index.html.

197. World Health Organisation. Lassa fever https://www.who.int/en/news-room/fact-sheets/detail/lassa-fever2017 [cited 2021 18/03/2021].

198. Gabriel M, Adomeh DI, Ehimuan J, Oyakhilome J, Omomoh EO, Ighodalo Y, et al. Development and evaluation of antibody-capture immunoassays for detection of Lassa virus nucleoprotein-specific immunoglobulin M and G. PLOS Neglected Tropical Diseases. 2018; 12(3):e0006361. https://doi.org/10.1371/journal.pntd.0006361 PMID: 29596412

199. Office of The Surgeon General DotA. Final Report Analysis of a Clinical Trial Ribavirin and the Treatment of Lassa Fever. 1992.

200. Sierra Leone Ministry of Health and Sanitation. Sierra Leone National Rapid Assessment of Laboratory Capacity and Systems. 2015.

201. Hansen F, Jarvis MA, Feldmann H, Rosenke K. Lassa Virus Treatment Options. Microorganisms. 2021; 9(4):772. https://doi.org/10.3390/microorganisms9040772 PMID: 33917071

202. Olayinka A, Bourner J. A standardised Phase III clinical trial framework to assess therapeutic interventions for Lassa fever. Manuscript submitted for publication. 2021.

203. Sigfrid L, Maskell K, Bannister PG, Ismail SA, Collinson S, Regmi S, et al. Addressing challenges for clinical research responses to emerging epidemics and pandemics: a scoping review. BMC Medicine. 2020; 18(1):190. https://doi.org/10.1186/s12916-020-01624-8 PMID: 32586391