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PULMONARY INVOLVEMENT IN LASSA FEVER: A SCOPING REVIEW

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ABSTRACT

INTRODUCTION: Lassa fever (LF) affects all body systems, however, inadequate knowledge exists on the involvement of the pulmonary system in LF infections. This scoping review, therefore, aimed to describe the pulmonary involvement of LF.

MATERIAL AND METHODS: We conducted an extensive search of the literature on two databases, namely PubMed and Google Scholar. Overall, 5,217 articles were retrieved from a database search, out of which 107 duplicates were removed. Overall, 12 articles were included: four review articles, three case reports, three experimental inoculation studies, one retrospective study, and a prospective case-control study.

RESULTS: Symptoms experienced included fever, pharyngitis, retrosternal pain, respiratory distress, and proteinuria. Complications included unique pulmonary arteritis, pulmonary embolization, mucosal bleeding, pleural or pericardial effusion, pulmonary edema, and interstitial pneumonitis. Consequences of the effect of Lassa virus infection were impairment of the immune system alongside continual replication of Lassa virus infection in affected tissues and death of affected individuals. LF has varied but serious effects on the pulmonary system.

CONCLUSIONS: These symptoms, particularly in areas where LF is known to be endemic, should prompt clinicians to request LF polymerase chain reaction for confirmatory diagnosis. These features should promote the provision of respiratory support for patients in need of such.

KEY WORDS: Lassa hemorrhagic fever; lungs; *Mastomys natalensis*; pulmonary involvement in Lassa fever; Lassa virus

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INTRODUCTION

Lassa fever (LF) is an acute hemorrhagic illness caused by Lassa virus (LASV), a member of the *Arenaviridae* family [1]. Outbreaks of the LF have been reported in Nigeria, Liberia, Sierra Leone, Guinea, and the Central African Republic, but it is believed that human infections also exist in the Democratic Republic of Congo, Mali, and Senegal [1]. Imported cases of LF have also been reported from around the globe because of exposure to the vector transmitting LF [2].

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Lassa fever is associated with occasional epidemics, during which the case-fatality rate can reach 50% among hospitalized patients [3]. Eighty percent of LASV-infected persons do not develop the disease, and 1% of infections overall result in death thus corroborating the fact that disease also depends on variations in host susceptibility due to concurrent infections or genetic differences [4, 5]. Among 20% of LASV-infected individuals however, LF may progress to more serious symptoms including hemorrhaging (in gums, eyes, or nose), respiratory distress, repeated vomiting, facial swelling, pain in the chest, back, and abdomen, and shock.

Death can occur within two weeks after the onset of symptoms due to multiple organ failure [3, 6]. Compared to HIV/AIDS, LF is more infectious to close associates and of a high fatality. In all instances, fatality occurs among 15 to 20 percent of all LF hospitalizations, however, only 1% of all LASV infections result in death. A single case of LF is termed an outbreak of LF. Its predominance among the elderly and reproductive age group constitutes a lot of public health concern and economic hazard, however, LF has been grossly underestimated [1]. So far, ribavirin is the only available therapy for LF [7].

The primary transmission route of LASV from its host to humans is by direct exposure to the virus, which may occur via the respiratory tract, through inhalation of infected particulates [8]. During the infection process, LASV makes contact with the epithelial layers of the body and, after breaking through the epithelial tissue barrier, exploits dendritic cells for further dissemination [8]. It has been shown for LASV, as well as for other arenaviruses, that during infection, infectious virus particles are released from epithelia into body fluids and urine [9–12].

All systems in the body could be affected by LF. Neurological effects of LF include hearing loss, tremors, and encephalitis [13, 14]. The pulmonary (respiratory) system is also not spared and has been shown both clinically and pathologically to be involved in LF [12–14]. When affected by LF, the compromised pulmonary system could cause a crash in the entire makeup of an individual [12]. However, there exists limited synthesis of the available evidence, and insufficient knowledge on the involvement of the pulmonary system in LF infections as it relates to mortality and the disease outcome. Scoping reviews are aimed at an unbiased summary synthesis of available evidence on the subject matter under investigation. The pulmonary manifestation of LASV has not gained much reporting over the years, hence the need for the scoping review method in this study. A review of this nature is also important to initiate syndromic case management of LF while confirmatory diagnosis is expected. The review is also important in raising the index of suspicion of physicians working in endemic areas to facilitate the diagnosis and management of individuals affected by LF. This scoping review therefore aimed to assess the pulmonary involvement of LF among confirmed LF cases.

MATERIAL AND METHODS

We searched for articles on the pulmonary involvement of LF on PubMed and Google Scholar databases. A purposive selection of the two databases was done because they are indexed in many journals. OSI and AAA served as independent reviewers in the data extraction from the databases. In instances where both OSI and AAA could not agree on the inclusion of an article, CU assisted in decision-making. This, therefore, helped to eliminate bias in the data collection. Data collection was conducted in two periods; April–May 2022, and December 2022.

Keywords used in the search strategy included: "Lassa fever" OR "Lassa hemorrhagic fever" OR "Hemorrhagic fever" OR "Lassa" AND "Pulmonary system" OR "Respiratory system" OR "Respiration" OR "Lungs" OR "Breathing" OR "Inhalation" OR "Exhalation".

Studies that focused on the involvement of the pulmonary system in LF infection were included in this review. All articles which have been published in the English Language were included in the study for ease of understanding by the authors. All articles that described the pulmonary involvement of LF in human and/or animal models for included to yield robust data. No date restriction was applied because only a few studies had been published on the pulmonary manifestation of LF. Articles that were not specifically tailored to the pulmonary involvement of LF were screened as ineligible literature. Overall, 5,217 articles were retrieved from a database search, out of which 107 duplicates were removed. Of the remaining 5,110 articles, 2,242 articles were excluded for describing the epidemiology and transmission of LF only, 1,209 articles were excluded for describing only the general pathogenesis of LF, 1,213 articles were excluded for comparing general systemic effects of LF with other viral hemorrhagic fevers, and 434 articles were excluded for describing

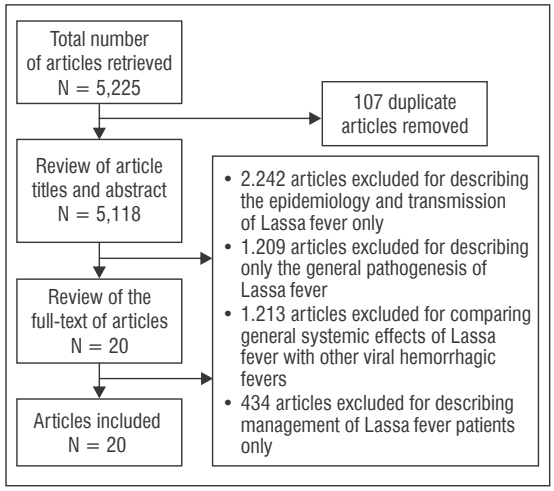

FIGURE 1. PRISMA flowchart showing the article search strategy

the management of LF patients only. Twenty articles were thereafter included in the review: six reviews, six case reports, five experimental studies, one retrospective study, and prospective case-control study, and one qualitative research (Fig. 1).

A three-step method proposed was adopted in the search strategy as follows:

Step One: A search of PubMed and Google Scholar databases was used for index terms and text words contained in the title and abstract.

Step Two: Identified keywords and index terms were used to prompt search on included databases.

Step Three: The reference lists obtained from the articles were searched for additional literature.

Registration

This review was not registered on any public repository. The protocol for the study was prepared and can be accessed upon reasonable request from the corresponding author. No amendment was made to the protocol.

RESULTS

Table 1 summarizes the literature retrieved from a database search. There are limited studies that have outlined the prevalence or mortality associated with the pulmonary manifestations of LF.

A retrospective cohort study conducted among 65 LF patients at Irrua Specialist Hospital, Edo State, Nigeria documented the pulmonary involvement of LF in 10 cases, with pneumonia reported among five of them, pneumonia with pleural effusion among three cases, and acute respiratory distress present among two cases [12]. Among the ten patients with pulmonary involvement, seven died yielding a CFR of 70% [12]. Among LF cases without pulmonary involvement, 21 died out of 55, generating a CFR of 38.2%. Overall, the CFR was 44.6% (29/65). Death (Fatal outcome) was associated with non-administration of ribavirin; the presence of cough, hemorrhage, and being elderly [12]. Pulmonary manifestations of LF can be classified as mild, moderate to severe presentation [12]. Mild to moderate presentation includes retrosternal chest pain and cough. Retrosternal chest pain could occur as a result of the inflammation of serous surfaces (serositis) which could account for the severe retrosternal or epigastric pain seen in many patients [12]. Severe presentation of LF on the pulmonary system includes breathlessness or acute respiratory distress. Focal interstitial pneumonitis has also been reported in LF. It could result from direct respiratory infection or from viremia (Fig. 2).

A case report of a 56-year-old Nigerian seen at the Emdee Medical Center in Jos, Nigeria, because of a 2-week history of fever (38.2°C) and diarrhea. Treatment with antibiotics was initiated. On 23 March, he was admitted to the Life Camp Clinic, Abuja, Nigeria. His temperature was 39.6°C; he was drowsy and intermittently disoriented. The patient later developed signs of pulmonary embolism, which ultimately resulted in his death [14].

A prospective case-control study of LF was conducted in Sierra Leone to measure the case-fatality rate of LF among febrile hospital admissions and to better delineate the clinical diagnosis and course of this disease [15]. Lassa fever (LF) was responsible for 10–16% of all adult medical admissions and for 30% of adult deaths in the two hospitals studied. The CFR for 441 hospitalized patients was 16.5%. Symptoms experienced included fever, pharyngitis, retrosternal pain, and proteinuria. Among the documented complications, pleural effusion was seen in 3% [15]. Others included mucosal bleeding (17%), bilateral or unilateral eighth-nerve deafness (4%), and pericardial (2%) effusion [15].

In an experimental study of nine Rhesus monkeys with LASV and a closely related *Arenavirus*, Mozambique virus, symptoms such as fever, conjunctivitis, and a reduction in the intake of food and water were reported. Interstitial pneumonia and unique pulmonary arteritis were the reported

Table 1. Summary of literature on the pulmonary involvement of Lassa fever

S/N	Title	Study design/ /type	Sample size	Inclusion criteria	Signs/symptoms	Case Fatality Rate	Parts affected	Complications	Outcome
i.	Pulmonary manifestation of Lassa hemorrhagic fever and the impact on mortality (Nigeria) [12]	Retrospective Study	65 persons; 34 males 31 females		Cough and/or breathlessness	70%	Lung parenchyma	Hemorrhage	Death
ii.	Lassa fever encephalopathy: Lassa virus in cerebrospinal fluid but not in serum (Emdee Medical Centre, Jos, Nigeria) [14]	Case report	A 56-year-old Nigerian male		Two-week history of fever and diarrhea, drowsiness, intermittent disorientation		Pulmonary vasculature	Pulmonary edema Pulmonary embolism	Death of the patient
iii.	A case-control study of the clinical diagnosis and course of Lassa fever (Sierra Leone) [15]	Prospective case-control study	441 hospitalized Lassa fever patients of 1,087 febrile adult medical admissions	i. Age: > 10 years ii. Presentation with a febrile illness iii. Admission to the medical ward of either of the two hospitals used in this study	i. Elevated respiratory rate ii. A combination of fever, pharyngitis, retrosternal pain, and proteinuria (pooled predictive value together: 0.81)	16.5%	Sternum, pericardium, and throat	i. Mucosal bleeding: 17% ii. Bilateral or unilateral eighth-nerve deafness: 4% iii. Pleural effusion: 3% iv. Pericardial effusion: 2% v. Severe pharyngeal pain vi. Interstitial pneumonitis	Recovery from milder disease generally began within eight to 10 days of onset, with lysis of fever and resolution of headache, sore throat, and chest pain
iv.	Experimental infection of Rhesus monkeys with Lassa virus and a closely related *Arenavirus*, Mozambique virus [16]	Experimental inoculation	Nine rhesus monkeys		i. Fever ii. Conjunctivitis iii. Reduction in the intake of food and water		Lungs	i. Interstitial pneumonia ii. Unique pulmonary arteritis	Death
v.	Acute abdominal pain in patients with Lassa fever: Radiological assessment and diagnostic challenges [17]	Review	–	i. Presence of abnormal bleeding from mouth, gum, nose, vagina, urinary tract (ii) Haemoptysis, bleeding from the ear; (iii) Swollen neck and face; (iv) Red eyes or conjunctivitis (often bilateral); (v) Spontaneous abortion; (vi) Deafness during illness; (vi) Shock or systolic blood pressure < 100 mmHg vii. Pleural effusion	Swollen lymph nodes	–	Eyes, lungs, abdomen, and internal tissues	i. Pulmonary edema ii. Pulmonary hemorrhage iii. Acute respiratory distress syndrome iv. Aspiration pneumonia v. Pleural effusion or ascites	i. Pericardial effusion with or without pericarditis' ii. Death

Table 1 (cont.). Summary of literature on the pulmonary involvement of Lassa fever

S/N	Title	Study design/ /type	Sample size	Inclusion criteria	Signs/symptoms	Case Fatality Rate	Parts affected	Complications	Outcome
vi.	Lung uptake of Tc-99m-Tin colloid in a patient with Lassa fever (Nigeria) [18]	Case report	An 18-year-old Nigerian girl		Fever (38°C) Hemorrhage			Increased reticuloendothelial system activity, intravascular clumping and embolization	
vii.	A case of Lassa fever imported into Wiesbaden, Germany [19]	Case report	A 57-yar old Nigerian man (Germany)	i. Disorientation ii. Marked stiffness of the neck	Fever, diarrhea, and general malaise	–	–	Seizure Pulmonary embolism	i. Cardiac and respiratory failure ii. Death
viii.	Clinical laboratory, virologic, and pathologic changes in hamsters experimentally infected with pirital virus (*Arenaviridae*): a rodent model of Lassa fever [20]	Experiment	Five hamsters		i. Viremia ii. In the lung sections, scattered neutrophils were seen in the interstitium	100%		Focal pulmonary hemorrhage	Death
ix.	Clinical presentations of Lassa fever in non-endemic parts of the world: a systematic review [21]	Review	22 primary cases of imported Lassa fever		i. Fever ii. Residence in or travel to Lassa fever endemic area	22.7%	Lungs and chest	Cough, pleuritic chest pain and shortness of breath. Pleural effusion was also reported, and pulmonary embolism	i. Acute respiratory distress ii. Death
x.	Infection of type I interferon receptor-deficient mice with various old world arenaviruses: a model for studying virulence and host species barriers [22]	Review (Experimental inoculation)	Type I Interferon receptor-deficient IFNAR$^{-/-}$) mice	Type I Interferon receptor deficiency	–	–	Lungs	Congestion and edema of the viscera, interstitial pneumonitis, presence of mononuclear cells in the focal interstitial compartments, especially in the capillaries	
xi.	The pathology of human Lassa fever [23]	Review	Seven Lassa fever cases		Fever		Lungs (Paren-chyma and pleural space)	Pharyngitis, pleural effusion, pulmonary edema, and interstitial pneumonitis	Impairment of the immune system alongside continual replication of Lassa virus in affected tissues of the body

Table 1 (cont.). Summary of literature on the pulmonary involvement of Lassa fever

S/N	Title	Study design/ /type	Sample size	Inclusion criteria	Signs/symptoms	Case Fatality Rate	Parts affected	Complications	Outcome
xii.	Endotheliopathy and platelet dysfunction as hallmarks of fatal Lassa fever [24]	Case studies	98 confirmed Lassa fever cases	–	Facial and pulmonary edema, pleural effusions, ascites, petechiae mucosal membrane bleeding, and cough	33–80%			
xiii.	Pathology and pathogenesis of Lassa fever: novel immunohistochemical findings in fatal cases and clinico-pathologic correlation [25]	Case reports of postmortem tissue samples	12 confirmed Lassa fever cases	–		100%	Lung alveoli	Intra-alveolar edema in lung	Death
xiv.	Pathogenesis of Lassa fever in cynomolgus macaques [26]	Experimentation	Comparison of tissues from three animals at an early- to mid-stage of Lassa infection with tissues from three animals collected at terminal stages of Lassa infection	–	–	–	Lung interstitial	Mild interstitial pneumonia	Death, among animals at the terminal stage of Lassa infection
xv.	Pathogenesis of recent Lassa virus isolates from lineages II and VII in cynomolgus monkeys [27]	Experimental study of unvaccinated cynomolgus monkeys	–	–			Lung	i. Viremia in the lungs ii. Thickening of the alveolar septum and advanced interstitial pneumonia iii. Widespread neutrophilic infiltration, and acute respiratory distress in fatal cases	Death
xvi.	Late diagnosis of Lassa fever outbreak in endemic areas lead to high mortality, Kenema District, Sierra Leone, February–March 2019 [28]	Case reports	Two people; an eight-year-old male, and a 15-year-old female	–	Fever, headache, and sore throat	100%	Lungs and orifices	Bleeding	Death

Table 1 (cont.). Summary of literature on the pulmonary involvement of Lassa fever

S/N	Title	Study design/ /type	Sample size	Inclusion criteria	Signs/symptoms	Case Fatality Rate	Parts affected	Complications	Outcome
xvii.	Beyond Lassa Fever: Systemic and structural barriers to disease detection and response in Sierra Leone [29]	Qualitative analysis of local policy and guidance documents, key informant interviews with policy and practice actors, and focus group discussions and in-depth interviews withhealth care workers and community health workers	Eight focus group discussions, and eight in-depth interviews	Previous history of handling ill individuals with one or more of the following: malaise, fever, headache, sore throat, cough, nausea, vomiting, diarrhea, myalgia, chest pain, hearing loss and a history of contact with excreta of rodents or with a case of Lassa fever	Abdominal pain, diarrhea, vomiting and fever	–	Lungs and orifices	Seizure and bleeding	Intra-uterine fetal demise; death of the pregnant woman
xviii.	Differential pathogenesis of closely related 2018 Nigerian outbreak clade III Lassa virus isolates [30]	Case reports	i. Five serum samples; samples were obtained during symptomatic illness ii. Ten female cynomolgus macaques	–	–	–	Lung interstitial	i. Weight loss, and increased respiration ii. Mild to marked interstitial pneumonia with edema	Death
xix.	Diagnostics for Lassa fever virus: a genetically diverse pathogen found in low-resource settings [31]	Narrative review	–	–	–	15–20% mortality rate among severe cases	Lungs	Presence of fluid in the lung cavity	Acute respiratory distress, shock, seizures, tremor, disorientation and coma, and death
xx.	Exotic viral hepatitis: A review on epidemiology, pathogenesis, and treatment [32]	Narrative review	–	–	Headache	–	Pleural surfaces	Shock and respiratory distress due to pleural effusion	Death

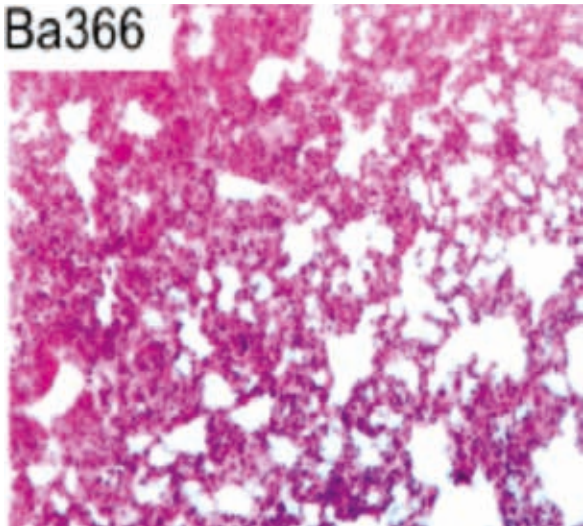

FIGURE 2. Lung tissue showing variable degrees of interstitial pneumonia in Lassa virus infected mice

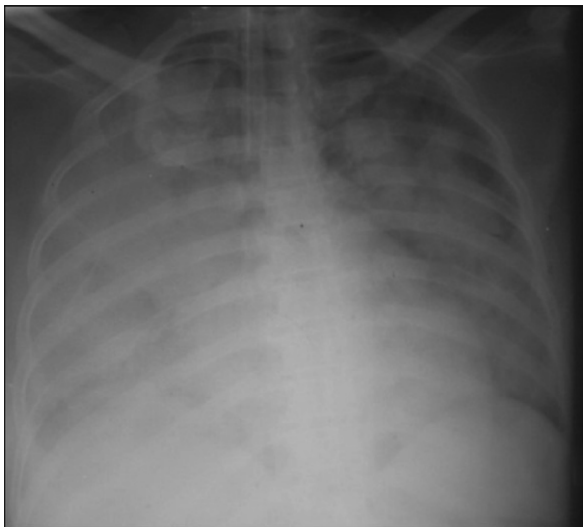

FIGURE 3. Plain chest radiograph of a patient with Lassa fever showing massive bilateral consolidations due to acute respiratory distress syndrome

complications, and death was the only fatal outcome reported [16].

In a review article that reported acute abdominal pain in patients with LF, the inclusion criteria were abnormal bleeding from the orifices, conjunctivitis, deafness, spontaneous abortion (for pregnant females), and shock [17]. The resulting complication of LF on the pulmonary system included pulmonary edema, pulmonary hemorrhage, acute respiratory distress, pleural effusion, and aspiration pneumonia [17].

Findings from a case report of a febrile 18-year-old LF female patient reported complications such as pulmonary embolization, intravascular clumping, and increased reticuloendothelial system activity [18].

Another case report of a 57-year-old Nigerian LF case imported into Wiesbaden, Germany documented symptoms such as fever, diarrhea, and general malaise. Complications reported included seizure and pulmonary embolism, while cardiac and respiratory distress and death were the outcomes [19].

In an experimental study of clinical, laboratory, virologic, and pathologic changes in hamsters experimentally infected with the pirital virus (*Arenaviridae*) using five hamsters; viremia, and scattered neutrophils in the lung interstitium were observed. Focal hemorrhage was the only pulmonary manifestation of LF reported, and this culminated in the death of all the hamsters [20].

In a study that aimed to determine the clinical presentations of LF in non-endemic parts of the world, a CFR of 22.7% was reported among 22 primary cases of imported LF. Cough, pleuritic chest pain, shortness of breath, and pleural effusion were the reported complications, while acute respiratory distress and death were the documented outcomes [21].

In their review article, Rieger et al. [22] reported that the pathological manifestations of LF on the pulmonary system among seven LF cases included congestion and edema of the viscera. Interstitial pneumonitis was also present with mononuclear cells and megakaryocytes in two LF cases. In addition, mononuclear cells were also reported in the focal interstitial compartments, especially in the capillaries (Fig 3).

Also, reports from a review conducted by Winn et al. [23] concerning seven cases of LF documented pulmonary features such as pharyngitis, pleural effusion, pulmonary edema, and interstitial pneumonitis. LASV targets lung parenchyma and the pleural space. A consequence of the effect of LASV was thus impairment of the immune system alongside continual replication of LASV in affected tissues of the body. Pneumonia with or without pleural effusion, and acute respiratory distress syndrome are indicators of a severe case of LF. Acute respiratory distress is a major pulmonary complication of LF and is the frequent cause of death in LF.

A review of seven confirmed LF cases documented symptoms such as fever, pharyngitis, and

breathing difficulties. LF infection affected the lung parenchyma and pleural space, thereby resulting in pleural effusion, pulmonary edema, and interstitial pneumonitis [24].

The summary of other studies is as shown in Table 1 [12, 14–32].

DISCUSSION

Lassa fever (LF) is a multi-systemic disease. However pulmonary presentations are not the initial or primary manifestation. From this review, we found that the involvement of the pulmonary system is an indication of the severity of LF. About 20% of patients may later develop pleural or pericardial "rubs" (grating noises heard as the heart beats) and could ultimately progress to a pleural effusion [12, 13]. Other studies have similarly reported that the common presentation of pneumonia in LF includes cough and dyspnea with frequencies of 23.1 and 30.8% respectively [33, 34]. However, no diagnosis can be made as a result of a cough because the cough is a minor criterion for LF [35]. An LF diagnosis could be possibly made with persistent fever, although this is not a definitive diagnosis [36]. Definite diagnosis for LF is made through polymerase chain reaction (PCR) using throat washing and pleural fluid of the patient [37]. Patients may present with breathlessness and will need to require respiratory support which could be in the form of high-flow oxygen or mechanical ventilation, which is largely unavailable in most hospitals in West Africa [38, 39].

Bowen and colleagues reported inflammation and edema of the local cords which progresses to laryngospasm and eventually reduced air entry in the patients [38]. Patients could present with choky sensations and cyanosis. They also reported a case of pharyngitis, exudative tonsillitis, cervical adenopathy, and facial and neck swelling [38]. The patient was reported to have bled profusely from the site of the tracheostomy, because of prolonged clotting time.

This review revealed that LASV replicates in the lung parenchyma and pleural space, causing pathological changes which result in an impairment of the immune system. When the immune system becomes compromised, the body's defense mechanism becomes weakened, and affected patients become vulnerable to other infections and systemic dysfunction as well [37–39]. The sequence of these events, therefore, explains the observed increase in case fatality rate among LF patients whose pulmonary systems are involved. This occurrence, therefore, posits that primary prevention of LF is key to avoiding complications that are associated with the infection. Also, suspected cases of LF should promptly consult health personnel to avert complications associated with the delay in LF reporting and treatment.

Registration

This review was not registered on any public repository. The protocol for the study was prepared and can be accessed upon reasonable request from the corresponding author. No amendment was made to the protocol.

Limitations

The Scopus and Web of Science databases were not screened as relevant sources of studies and could have introduced some biases in this review. Quality assessment of included studies was not done. In addition, the differences in technologies used, and the lack of universally acceptable strategies for managing the pulmonary manifestations of LF make it impossible to compare and draw conclusions about the effectiveness of one strategy over others. It is therefore pertinent to identify the requirements for managing the pulmonary manifestations of LF for adoption by physicians to improve health outcomes among LF patients.

CONCLUSIONS

The pulmonary manifestations of LF range from pneumonia to pleural effusion, acute respiratory distress, visceral congestion and edema, and pneumonitis. Complications following the involvement of the pulmonary system could result in death. Therefore, clinicians should apply these pulmonary features of LF as a form of high index of suspicion in areas known with LF endemicity in making a presumptive diagnosis for LF. In addition, clinicians should use these features as a prompt to request for LF polymerase chain reaction to makea confirmatory diagnosis. Health workers at the community level in LF-endemic areas in West Africa should be educated on the pulmonary features of LF to improve early presentation in health facilities and prompt case management. It is also required that community members are educated on the pulmonary effects of LF to facilitate timely presentation and management, especially in LF-endemic communities.

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Conflict of interest
The authors declare no conflict of interests.

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SUPPLEMENTARY DOCUMENT			
Section and Topic	Item	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a review	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for the Abstracts checklist	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge	Pages 3 and 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	Page 5
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	Page 5
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect	Page 5–6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	Page 5–6
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis [e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)]	Page 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling missing summary statistics, or data conversions	Not applicable
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression)	Not applicable
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	Not applicable

SUPPLEMENTARY DOCUMENT (cont.).			
Section and Topic	Item	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	Page 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	Pages 5 and 6
Study characteristics	17	Cite each included study and present its characteristics	Page 7–9
Risk of bias in studies	18	Present assessments of risk of bias for each included study	Not applicable
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	Pages 7–9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	10
	23b	Discuss any limitations of the evidence included in the review	10
	23c	Discuss any limitations of the review processes used	
	23d	Discuss the implications of the results for practice, policy, and future research	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including the register name and registration number, or state that the review was not registered	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	6
	24c	Describe and explain any amendments to the information provided at registration or in the protocol	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	12
Competing interests	26	Declare any competing interests of review authors	12
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71; For more information, visit: http://www.prisma-statement.org/