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# An Overview of Lassa fever, an Rising Old World Haemorrhagic Viral Disease

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Abstract

Lassa fever is an acute immunosuppressive illness of increasing public health concern causing severe morbidity and significant mortality especially in epidemic cases. Lassa fever is an acute viral zoonotic illness caused by Lassa virus, an arenavirus known to be responsible for a severe haemorrhagic fever characterised by fever, muscle aches, sore throat, nausea, vomiting, chest and abdominal pain. The virus exhibits persistent, asymptomatic infection with profuse urinary virus excretion in the ubiquitous rodent vector, *Mastomys natalensis*. Lassa fever is endemic in West Africa and has been reported from Sierra Leone, Guinea, Liberia, and Nigeria. The virus replicates through a strategy known as the Ambisense, where two RNA strands code for genes in both the sense and antisense direction that is rapid and demonstrate temporal control in replication. Different diagnostic tests for the virus are available, which range from viral culture to serological and molecular diagnostic tests. There is an urgent need to develop drugs and vaccines against the virus because the World Health Organization (WHO) has identified Lassa virus as one of the viruses that is likely to cause a future epidemic, although a research is ongoing to evaluate Lassa virus vaccine immunogenicity in the CBA/J-ML29 mouse model. This review gives an overview on the structure, replication cycle, pathogenesis and diagnosis of the virus.

**Keywords:** Lassa fever, Lassa virus, Arenavirus, Replication, Pathogenesis, Diagnosis

## Introduction

Lassa virus (LASV) is first described in the 1950s[1] but not identified until 1969 in Jos, Nigeria[2, 3]. The virus causes Lassa fever that is hemorrhagic in nature, which is severe and fatal. It affects 2-3 million people annually[4,5] and has been known to be endemic in Benin Republic in 2014, Ghana in 2011, Guinea, Liberia, and Mali in 2009, Sierra Leone, and Nigeria[3,4,6], but probably exists in other West African countries as well[4]. It is a reemerging virus with a select agent, which requires Biosafety Level 4-equivalent containment[7]. It is endemic in West African countries including Sierra Leone, the Republic of Guinea, Nigeria, and Liberia, where cases of the infection is between 300,000 and 500,000 yearly resulting in 5000 deaths annually[4,8,9]. About 80% infected with the virus are asymptomatic and 1 in 5 infection results in severe disease, where the virus affects several organs such as the liver, spleen, and kidneys[10]. The virus is harbored by the multimammate rats of the genus *Mastomys* and transmitted to Mans through primary aerosols of the rat's urine, close contact with urine, feces, saliva, or ingestion of contaminated foods of the rat[11]. LASV is also spread through contaminated hospital equipment but interestingly, it cannot be contracted by humans to humans only via bodily fluids contacts[12]. Findings have reported the presence of the virus in seminal fluids up to 3 months after infection of the virus. Research to show that Lassa virus can be gotten via sexual intercourse has not been reported but there are speculations that LASV might possibly be used for bioterrorism, so it is now being studied at greater lengths[13,14]. Due to the variability of the clinical course of the disease, detection of the disease in affected patients has been challenging. When presence of the virus is confirmed in a locality, quick isolation of infected patients, good infection prevention and control practices, and rigorous contact tracing can help halt epidemicity[15].

## Epidemiology

LASV is a single-stranded RNA virus of the *Arenaviridae* family. First identified in 1969 in Nigeria, Lassa fever is now endemic in West Africa including Nigeria, Sierra Leone, Guinea, Liberia, Benin, Ghana and Mali and has spread to neighboring countries (Figure 1). In some areas, 10%-16% of people admitted to hospitals every year have LASV. Cases have also been identified in Germany, the Netherlands, Sweden, the USA, the UK and Japan, largely imported after travel in West Africa. The long incubation period of LASV (~7–10 days) makes it one of the most commonly exported VHFs to countries outside its endemic range[16].

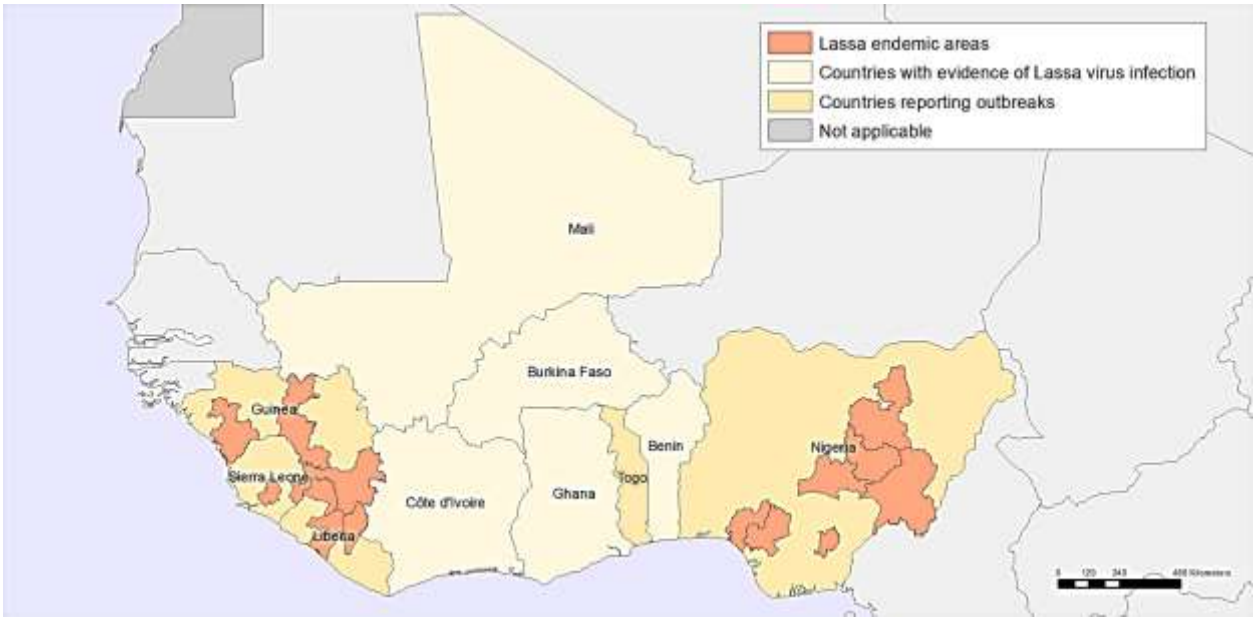


**Figure 1 Geographic distribution of Lassa fever in West Africa, Adapted from Emergencies-Lassa fever, WHO, Geographic distribution of Lassa fever in West African affected countries, 1969-2018**

## Lassa virus structure

Lassa virus is an envelope, single-stranded, bisegmented RNA virus belonging to the Arenaviridae family. Like other arenaviruses, Lassa virus lacks a conventional negative-strand coding arrangement and the isolates of the virus differ in their genetic, serologic and pathogenic characteristics[17-19]. Lassa virus is spherical in shape and measures between 70 and 150 nm in diameter (Figure. 2). It has a smooth surface envelope with T-shaped spikes measuring 7-10 nm and built with glycoprotein. The envelope encloses the genome which has helical nucleocapsid measuring between 400 and 1300 nm in length[20,21]. Often the interior contains electron dense granule identified as the host cell ribosome from where the name "arena" was derived meaning sandy[22]. Lassa virus can be inactivated in ultraviolet, gamma irradiation, heating from 56-100°C and pH range between 5.5 and 8.5. Chemical agents like 0.5% sodium hypocorite, 0.5% phenol and 10% formalin are good inactivants against the virus[23,24]. The single-stranded arenavirus genome consists of a small (s) and a large (l) RNA fragment, sizes 3.4 and 7 kb, respectively and the sRNA encodes the viral glycoprotein precursor protein (GPC) and the nucleoprotein (NP), while the lRNA encodes the viral polymerase and a small, zinc-binding (Z) protein[25]. New methods for full-length sRNA amplification are facilitating research efforts on the identification and molecular analysis of new arenaviruses or arenavirus strains[26]. The sequencing of Lassa virus sRNA has enabled the identification and molecular characterization of four Lassa virus strains. These include: the strain Josiah, originating from Sierra Leone, the strain Nigeria and strain LP[27,28], both from Nigeria and the strain AV imported into Germany by a traveler who had visited Ghana, Côte D'Ivoire, and Burkina Faso. Sequencing of sRNA of Lassa virus indicated a considerable genetic variation among the strains of the virus, however, phylogenetically, strain AV appears to be the most closely related to strain Josiah from Sierra Leone.

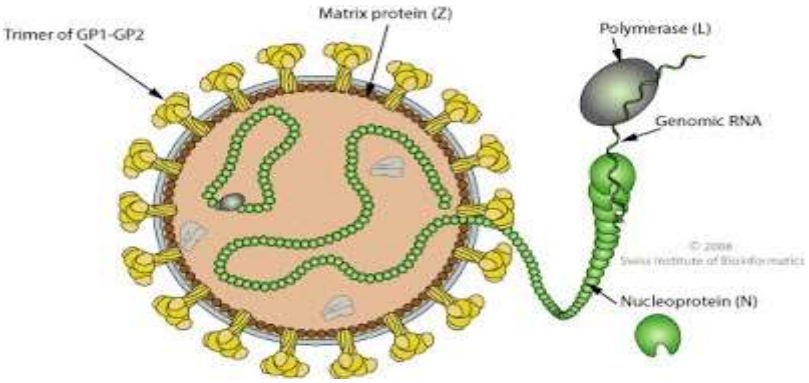


**Figure 2 Structure of Lassa virus**

## Replication of Lassa virus

The first step in viral replication is adsorption on cell surface receptors that are found to be widely distributed and highly conserved molecules[29]. The glycoprotein of the spikes is responsible for the interactions with cell surface receptors[30]. The next step is the penetration of the virus, then deproteinisation, and finally liberation of RNA genome into the infected host cytoplasm where both replication and transcription take place. During the process, the cell nucleus provides capped cellular mRNA for priming transcription, and the nuclear membranes provide structural support. It has been observed that the 5' end of the S derived subgenomic mRNAs extend beyond the end of the genomic RNA template and thelength of such an extension varies between 1 and 7 nucleotides and terminate at 5' cap structure[31]. The initiation

of replication and transcription starts from the terminus of the template. As the RNA polymerase rails on the template to add new nucleotides that will form polynucleotide of the new strand, the first two slip back on the template to create nontemplated nucleus, a process peculiar to arenaviruses. After biosynthesis of macro-molecules, the virions are assembled through a process not yet understood. Matured virions are released through budding from the plasma membrane of acutely infected cells.

## Reservoir

*Mastomys natalensis* multimammate rodents are the most common rodent across the African continent, found predominantly in rural areas and human dwellings. These rodents show persistent LASV infection but are largely unaffected by the disease and shed the virus in their excrement. Seroprevalence has been reported to be as high as 60%-80% in *M. natalensis* populations. More recently, other rodent species including *Hylomyscus pamfi* and *Mastomys erythroleucus* have been shown to host LASV. Transmission to humans occurs primarily through contact with infected rodent urine or faeces; handling and consumption of infected rodents is also a pathway to infection. Airborne transmission may occur from aerosolised rodent excretions (dust) during cleaning activities. *M. natalensis* rodents readily colonise human areas where food is stored, contributing a significant risk for spillover, especially in communities with poor sanitation or crowded living conditions. Human-to-human transmission is less common, but LASV can be spread through direct contact with bodily secretions of persons infected with Lassa fever, presenting a higher risk for healthcare and humanitarian personnel, who increases with progression of disease and increasing viral load. There are suspected sexual transmission risks, as LASV can be detected in semen for 3 months past symptomatic infection[16].

## Pathogenesis

The Lassa virus is well-known to cause Lassa fever[32]. Its symptoms include flu-like illness characterized by fever, general body weakness, cough, tonsillitis, headache and gastrointestinal disorders. Hemorrhagic manifestations are other features of Lassa fever, which include vascular permeability[10]. The virus pathogenesis is still unclear, but it has been shown that the virus chiefly target the antigen-presenting cells (mainly dendritic cells) and endothelial cells[33]. Lassa virus infects most tissues in the human body when gained entry. It starts with the mucosa, intestine, lungs, and urinary system, and then moves to the vascular system. There are findings that the viral agent can prevent a host's innate immune system by NP activity[34]. Usually, when a microbe penetrates a host, the innate defense system detects the pathogen-associated molecular patterns (PAMPs) and aggravates the response of the immune system. One of themechanisms identifies double-stranded RNA that is only produced by negative-sense viral agents[35]. In the cytoplasm, dsRNA receptors, such as melanoma differentiation-associated gene 5 (MDA-5) and retinoic acid-inducible gene I (RIG-I), detects dsRNAs and facilitates ignaling pathways that results in the translocation of interferon regulatory factor 3 (IRF-3) and other transcription factors to the nuclear material[9]. Translocated transcription factors enhance expression of interferons **α** and **β**, and secreted interferons facilitate antiviral responses including adaptive immunity. NP encoded in the viral agent is important in the replication and transcription of the virus, but it also stops host innate IFN response by inhibiting translocation of IRF-3. NP of the virus is reported to have an exonuclease activity to only dsRNAs[12]. Double-stranded RNA exonuclease activity of the NP leads to counteract IFN responses by digesting the PAMP that leads to the evasion of host immune responses. The recent understanding of the pathogenesis of the viral fever does not involve the chain of functions that take place during development of the disease state and leads to mortality of severed ill patients[36]. The high death and truly dramatic course of the disease state, the pathological findings do not give the bench that would explain the mechanism of disease progression and the cause of mortality by the viral agent[5,8]. Development of the cellular immune response failure, which would control dissemination of LASV is indicated by high serum titers of the virus, together with dispersed replication in tissues and lack of neutralizing antibodies that could lead to the fatal Lassa fever development[6,37]. Patientscheck physically after fever onset usually depicts facial oedema, bilateral conjunctival hemorrhages, purulent pharyngitis, and abdominal disorders[5]. Pathological changes physically may include pulmonary oedema, ascites, pleural effusions, and hemorrhagic signs in the gastrointestinal mucosa while examination under the microscope reveals splenic necrosis, hepatocellular necrosis, adrenocortical necrosis and apoptosis, mild mononuclear interstitial myocarditis without myocardial fiber necrosis, alveolar oedema with capillary blockage and mild interstitial pneumonitis, lymph nodal sinus histiocytosis with mitoses, gastrointestinal mucosal petechiae, renal tubular injury, lymph nodal sinus histiocytosis with mitoses, and interstitial nephri. More often, lesions of Lassa fever in man happen in the hepatic cells[5,8]. There are four major characteristic hepatitis of LASV, which is derived:

**i.** Focal cytoplasmic degeneration of hepatocytes related to phagocytosed apoptotic fragments. **ii.** Distribution of multifocal hepatocellular necrosis randomly.

**iii.** Monocytic reaction to necrotic hepatocytes.

**iv.** Hepatocellular mitoses.

The physical impacts do not happen uniformly in all cases, rather in some instances can be observed simultaneously. The virus fever is not associated with coagulation dysfunction, for example, decrease in the coagulation factors and disseminated intravascular coagulation (DIC) have been revealed in infected subjects. More so, moderate thrombocytopenia with importantly damaged functionality of thrombocytes is reported in severe Lassa fever subjects[7,37]. One significant mechanism involved in the pathogenesis of Lassa fever is infection-triggered induction of uncontrolled cytokine expression, which looks like what is seen in sepsis[9]. In this subject that died from hemorrhagic shock and multi-organ failure, the proinflammatory cytokines, tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ) rises to extremely high level just before death. In a related study, no increase of both cytokine levels was reported in the checked fatal cases of the virus fever, and it is suggestive that the levels of IFN-γ and TNF-α are either elevated only in a fraction of patients or during a limited period that would involve frequent sampling for assay[12,35]. Virus-induced immunosuppression may be involved in a severe Lassa fever pathogenesis where the LASV infection fails to trigger macrophages (MP) and monocyte-derived dendritic cells (DC) of human. Human-infected DC with the naturally nonpathogenic mopeia virus induces stronger CD4 and CD8 T-cell responses when compared with those infected with LASV[5,8]. Infected DC fail to secrete proinflammatory cytokines, do not upregulate costimulatory molecules, such as CD40, CD80, and CD86, and poorly induce proliferation of T cells. Downregulation of immune responses due to infection by LASV has been depicted in vitro, and it is also in consonance with findings of clinical reports demonstrating that the virus fever fatal outcome relates with low levels interleukin (IL) 8 and IFN inducible protein 10 (IP-10) in the system[14].

## Diagnosis

The signs and symptoms of Lassa fever may be difficult to distinguish from diseases that are common in the tropics such as severe malaria, typhoid fever, yellow fever and other viral haemorrhagic fevers[38-40], but diagnosis can be assisted with simple laboratory support but definitive diagnosis requires testing that is available only in highly specialized laboratories[42]. As the symptoms of Lassa fever are so varied and nonspecific, clinical diagnosis is often difficult especially early in the course of infection. Hence, to make accurate diagnosis of Lassa fever, clinical manifestation, epidemiological data and result of laboratory findings should be taken into consideration.

*Laboratory investigation:* Lassa fever is diagnosed by detection of Lassa antigen, antibodies, or virus isolation techniques. In the laboratory, the virus can be isolated using laboratory animals such as albino mice, guinea pigs, Vero cell or African green mon keys. Albino mice inoculated intracerebrally die between 3 and 5 days. Lassa fever virus causes conspicuous cytopathic effect on confluent monolayer of Vero cell culture within 96 h. The antigens to be used for viral isolation can be obtained from the patients blood, urine, pleural fluid, throat swab and in case of death, pathological materials from liver, kidney, spleen and heart[41]. The virus can be seen under electron microscope using specimens obtained from infected persons. Although virus isolation remains the most sensitive, it is still uniquely a research tool. The classical method to detect Lassa virus is inoculation of Vero cells with serum, cerebrospinal fluid (CSF), throat washing, pleural fluid or urine of the patient. Specimen for laboratory analysis should be collected as soon as possible from the patient suspected of having the infection. Lassa virus is infectious by aerosol and the human and rodent specimens should be processed with appropriate precautions in biosafety level IV laboratories [42]. The specific diagnosis is readily made by the isolation and identification of the virus. This is usually done by the inoculation of blood from the patient into Vero cell cultures. Virus antigen can be detected by enzymelinked immunosorbent assays (ELISA) using Lassa virus-specific antibodies. These tests are easy to handle and rapid, and can be performed with inactivated specimens, which is advantageous in the field if sophisticated equipment is not available. Results should be mentioned as soon as they are ready to help in monitoring the prognosis of the disease. The indirect fluorescent-antibody (IFA) test has traditionally been employed in the laboratory diagnosis of acute Lassa virus infection[43,44]. Although the interpretation of IFA results is complicated by the presence of IFA during both acute and convalescent stages of infection and by the subjective nature of the assay, the appearance of IFA antibody early in the course of Lassa infection may be useful in identifying patients with poor prognosis. However, due to lack of specificity in populations in non-endemic areas[45] the technique has been largely replaced by ELISA for Lassa virus antigen and Lassa virus-specific immunoglobulin M (IgM) and G (IgG) antibodies[46-48]. A thorough evaluation of the Lassa virus ELISA on field-collected samples to assess its true sensitivity and specificity was performed in Sierra Leone and Guinea in West Africa[49]. In the study, isolation of virus as detected by immunofluorescent stains for viral antigen along with a positive reverse transcription-PCR (RT-PCR) test on the isolate wasemployed as the "gold standard" test of Lassa virus infection. The results showed that the combined ELISA Ag/IgM assay was highly sensitive and specific for the diagnosis of Lassa fever and the antigen detection assay offered a particular advantage in providing early diagnosis as well as prognostic information. From this research, the technique appeared to be a better diagnostic tool for Lassa virus infection compared to other serological techniques. Although the RT-PCR assays are very sensitive, their applicability in the West African countries where Lassa fever is endemic is limited by issues of strain variation, cross contamination, lack of qualified personnel, inadequate facilities and expense[50,51]. Another valuable diagnostic tool is the rapid diagnostic immunoblot assay (RDIA) for Lassa fever. Unfortunately, its usefulness is limited by its low capacity to provide prognostic information and also its low sensitivity.

*Differential diagnosis:* Lassa haemorrhagic fever must be differentiated from other febrile diseases like Ebola (Marburg) haemorrhagic fever, malaria, diphtheria, legionella, yellow fever, Congo-haemorrhagic fever, etc. Lassa fever virus has a peculiar natural reservoir rodent host (*M. natalensis*). It is very imperative that clinical assessment be combined with specific laboratory diagnosis to adequately identify the Lassa fever virus in order to commence early treatment which is paramount to the survival of infected individual[52].

## Useful prevention/control measures

Lassa fever transmission is enhanced by cohabitation of *M. natalensis* species of rodent with humans in their residences in the affected areas having access to water and food items in the household. These rats are also prepared and consumed as delicacies by many inhabitants of West African region[53,54]. Therefore, any control/preventive measures to be adopted must take cognizance of routes and mechanism of transmission of Lassa fever. The following measures are imperative in curtailing the regular epidemic outbreak and spread of Lassa fever in sub-Saharan region of Africa. These include:

- Observance of general hygiene including personal and environmental hygiene by the populace.
- Since Lassa fever transmission is associated with infected mouse (*M. natalensis),* therefore, every household needs to device all means geared towards preventing rats from having any contact with foods, water and utensils utilized by the household. This may be achieved by: -Covering of foods and water meant for human consumption regularly. -Foods should be kept in tightly sealed containers. -Ready-to-eat food item (such as gari) should not be spread in the open or by the roadside where rats can have access to it.
- Public enlightenment campaign about Lassa fever should be conducted regularly in areas where the disease is prevalent.
- Every community should be counseled to avoid foods and other items contaminated with rat's excretions and secretions.
- People should be admonished to kill and destroy rats in and around the house, shops or market places.
- Foods and water should be boiled adequately before consumption.
- Encourage members of the community to always attend healthcare centre nearest to them for medical attention when they are sick or have had contact with contaminated environment.
- All persons suspected of Lassa virus infection should be admitted to isolation facilities and promptly attended to with utmost care. -Hospital workers should take universal precautions and protective measures when attending to such patients. -Every body fluids and excreta produced bysuch patients should be handled with care and properly disposed of.

- Early detection of the disease and aggressive treatment (such as the use of intravenous ribavirin) [55] is important for the survival of infected patient.
- Healthcare workers should be sensitized about the need to adopt universal preventive measures in their routine hospital procedures to limit the transmission and acquisition of Lassa virus infection and indeed all infectious diseases in hospital setting.
- Governments at all levels (National, State and Local) should demonstrate political will in mobilizing logistics and necessary materials and financial support to aid adequate management and effective control of Lassa fever.
- More diagnostic and treatment centres for Lassa fever should be established at various regions of each country endemic for Lassa fever.
- Development of effective vaccine against Lassa fever (which has reached advanced stage with positive results in animal trials) [56] is crucial in checkmating the spread of Lassa fever.

## Treatment

Ribavirin the antiviral drug is effective in the treat ment of Lassa fever, but only if administered early in the course of illness[57]. In a study of Lassa fever in Sierra Leone, West Africa, it was observed that patients with a high risk of death who were treated for 10 days with intravenous ribavirin, begun within the first six days after the onset of fever, had a case-fatality rate of 5% (1 of 20) ($p = 0.0002$ by Fisher's exact test), while patients whose treatment began seven or more days after the onset of fever had a case fatality rate of 26% (11 of 43) ($p = 0.01$). The study confirmed the efficacy of ribavirin in the treatment of Lassa fever and that it should be used at any point in the illness, as well as for post-exposure prophylaxis. Because of its expense, need for intravenous administration, potential toxicity and teratogenicity, empiric therapy with ribavirin is undesirable[58-60]. In a remote area of eastern Sierra Leone, West Africa, brief episodes of rigors were reported in patients receiving ribavirin. However, the occurrence or number of rigors in an individual patient was not associated with sex, age, weight, volume of loading dose, cumulative dose, and administration of other drugs and use of intravenous lines or heparin traps. The report indicated slowing the infusion rate, generated no further episodes and concluded that epidemiologic techniques are important tools in rapid assessment of unexpected events particularly when conducting trials in remote locations. Supportive treatment is often necessary and includes fluid replacement, blood transfusion, administration of paracetamol, phylometadione, ringer lactate, haemocoel quinine and broad spectrum antibiotics[61].

## Conclusion/recommendations

Lassa fever has emerged as one of the most prevalent, immunosuppressive and highly fatal haemorrhagic fevers endemic in sub-Saharan Africa particularly West and Central Africa. Transmission of the disease is influenced by cohabitation of reservoir rodent (*M. natalensis*) with human population and poor environmental hygiene common in most parts of the region resulting in regular outbreak of the disease and fatality. Currently, there are no clinically certified vaccines against Lassa fever which limits the scope of control/preventive measures against Lassa fever.

Hence, there is need to intensify public educational or enlightenment program in all affected areas on the useful control measures against Lassa fever. The stakeholders need to prioritize the intervention, support and deterrent program and speed up the process leading to production of effective vaccine to checkmate the menace of Lassa fever outbreak and associated morbidity and mortality.

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