Review article

The Endemicity of Lassa Fever in West Africa; Appropriate Mitigative Measures

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Abstract

Lassa fever is an ancient disease and is endemic in most West African countries. Importantly, Lassa fever is a dangerous and virulent disease because it exerts deleterious effects on many vital organs in the body. Due to its endemic nature and the yearly occurrence of the disease in terms of infection and mortality cases in some West African countries, specifically Nigeria, there is need to reexamine and reemphasize viable prevention alternatives. On this backdrop, this review provides a broad overview of Lassa fever, with the main emphasis on preventive measures. Infection with the Lassa fever virus has severe consequences on health; in this respect, multifaceted preventive measures that ensure and guarantee no contact with multimammate rodents should be adopted. Furthermore, contact with the feces and urine of multimammate rats should be avoided, personal hygiene should always be practiced, environmental sanitation should be ensured and carried out often, the consumption and eating of rats should be discouraged, abolished and ultimately stopped, and food containers should always be kept tight and closed.

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Introduction

Lassa fever develops through the infection by the Lassa virus (LASV) (1, 2). Although the disease was first discovered in the early 1950s, the causative agent was not recognized or known until the late 1960s. The virus that causes the disease belongs to the family of Arenaviridae viruses (3). The history of Lassa fever dates back to the 1950s, when the first case was recorded in Nigeria, Borno State, in the town of Lassa, after which the disease was named Lassa fever in 1969 (3). Presently, the disease is endemic in West African countries because of the yearly cases of infection and death (1, 4-6). Numerical estimates indicate that confirmed cases of Lassa fever range between 350000 and 550000, and over 5000 deaths per year are recorded globally (3).

Hosts of the Lassa virus are infected multimammate rats and rodents, and humans usually become infected with the virus due to contact with urine or feces of infected animals (3). The issue of Lassa fever is a yearly phenomenon in Nigeria, and the surge of infections in humans is usually seen in the dry season between December and April, due to the reproduction cycle of new multimammate rats and rodents in the rainy season (7). The Lassa virus is easily transmitted and highly contagious, and the disease it causes is deleterious because it has severe health consequences for the whole system (3). Once a person is infected with the Lassa virus, the virus weakens organs in the body, consequently resulting in organ malfunctions and depletion of the whole system.

In regard to its public health importance, Lassa fever is a yearly phenomenon in endemic countries because of the rapid multiplication of the virus in the newly infected multimammate rats and rodents, which, once infected, continue to shed the virus in their feces and urine throughout their life (7). Although Lassa fever may not be completely eradicated due to peculiar reasons and lack of existing vaccines against the causative virus, transmission of the Lassa virus could however be diminished and absolutely prevented. Hence, this synopsis presents detailed preventive measures against Lassa fever.

Sources of Information

The review focuses on workable prevention alternatives against Lassa fever. The literature review was purposely selected with keywords on the topic of discourse from PubMed, Google Scholar and SpringerLink databases. All eligible studies included are clinical trials, meta-analyses, randomized controlled trials, systematic and review articles on the topic of discourse. Furthermore, major international and national health agencies' databases were searched to find valuable information for the review.

Biological Description of the Lassa Virus

Lassa viruses are typically enclosed, single-stranded, bisegmented and ambisense RNA in nature (8). Their genome is contained in two RNA segments that code for two proteins each, one in each sense, for a total of four viral proteins. The large segment encodes a small zinc finger protein (Z), which regulates transcription and replication, and the RNA polymerase (L) (9). The small segment encodes the nucleoprotein (NP) and the surface glycoprotein precursor (GP) or the viral spike, which is proteolytically cleaved into the envelope glycoproteins GP1 and GP2 that bind to the alpha-dystroglycan receptor and mediate host cell entry (10).

Lassa fever causes hemorrhagic fever frequently shown by immunosuppression. The Lassa virus replicates very rapidly and demonstrates temporal control in replication. The first replication step is transcription of mRNA copies of the negative- or minus-sense genome. This ensures an adequate supply of viral proteins for subsequent steps of replication, as the NP and L proteins are translated from the mRNA (9, 10). The positive- or plus-sense genome then makes viral complementary RNA (vcRNA) copies of itself. In addition, the RNA copies are a template for producing negative-sense progeny, but mRNA is also synthesized

from it. The mRNA synthesized from vcRNA is translated to make the GP and Z proteins (9, 10). This temporal control allows the spike proteins to be produced last, and therefore delay recognition by the host immune system. Nucleotide studies of the genome have shown that Lassa fever has four lineages: three found in Nigeria and the fourth in Guinea, Liberia, and Sierra Leone (11). The Nigerian strains seem likely to have been ancestral to the others, but further research is needed to substantiate this (11).

The Lassa virus enters the host cell through the cell-surface receptor, the alpha-dystroglycan (alpha-DG), which is a versatile receptor for proteins of the extracellular matrix (10). It shares this receptor with the prototypical Old World arenavirus, the lymphocytic choriomeningitis virus. Receptor recognition depends on specific sugar modification of alpha-dystroglycan by a group of glycosyltransferases known as the LARGE proteins (10). Specific variants of the genes encoding these proteins appear to be under positive selection in West Africa, where Lassa fever is prominent (12). Alpha-dystroglycan is also used as a receptor by viruses of the New World clade Carenaviruses (Oliveros and Latino viruses). In contrast, the New World arenaviruses of clades A and B, which include the important viruses Machupo, Guanarito, Junin, and Sabia, in addition to the non-pathogenic Amapari virus, use the transferrin receptor 1 (12). A small aliphatic amino acid at the GP1 glycoprotein amino acid position 260 is required for high-affinity binding to alpha-DG. Likewise, GP1 amino acid position 259 also appears to be important, since all arenaviruses showing high-affinity alpha-DG binding possess a bulky aromatic amino acid (tyrosine or phenylalanine) at this position (10, 12). Unlike most enveloped viruses, which use clathrin-coated pits for cellular entry and bind to their receptors in a pH dependent fashion, Lassa and lymphocytic choriomeningitis virus instead use an endocytotic pathway independent of clathrin, caveolin, dynamin and actin (12). Once they enter the cell, the viruses are rapidly delivered to endosomes via vesicular trafficking, albeit one that is largely independent of the small GTPases Rab5 and Rab7. On contact with the endosome pH-dependent membrane, fusion occurs and is mediated by the envelope glycoprotein, which at the lower pH of the endosome binds the lysosome protein LAMP1, which results in membrane fusion and escape from the endosome (12).

The lifecycle of the Lassa virus is similar to the Old World arenaviruses. The Lassa virus enters the cell by receptor-mediated endocytosis. The specific endocytotic pathway used is still unknown, but cellular entry is sensitive to cholesterol depletion (13). The receptor used for cell entry is alpha-dystroglycan, a highly conserved and ubiquitously expressed cell surface receptor for extracellular matrix proteins. Dystroglycan, which is later cleaved into alpha-dystroglycan and beta-dystroglycan, is originally expressed in most cells to mature tissues, and it provides a molecular link between the ECM and the actin-based cytoskeleton (13). After the virus enters the cell by alpha-dystroglycan-mediated endocytosis, the low-pH environment triggers pH-dependent membrane fusion and releases the RNP (viral ribonucleoprotein) complex into the cytoplasm. Viral RNA is unpacked, and replication and transcription commence in the cytoplasm (13). As replication starts, both S and L RNA genomes synthesize the antigenomic S and L RNAs, and from the antigenomic RNAs, genomic S and L RNA are synthesized. Both genomic and antigenomic RNAs are needed for transcription and translation. The S RNA encodes GP and NP (viral nucleocapsid protein) proteins, while L RNA encodes Z and L proteins. The L protein usually represents the viral RNA-dependent RNA polymerase (14). When the cell is infected by the virus, L polymerase is associated with the viral RNP and initiates the transcription of the genomic RNA. The 5' and 3' terminal 19 nt viral promoter regions of both RNA segments are necessary for recognition and binding of the viral polymerase. Primary transcription first transcribes mRNAs from the genomic S and L RNAs, which code NP and L proteins, respectively (14). Transcription terminates at the stem-loop (SL) structure within the intergenomic region. Arenaviruses use a cap-snatching

strategy to gain the cap structures from the cellular mRNAs, which is mediated by the endonuclease activity of the L polymerase and the cap-binding activity of NP. Antigenomic RNA transcribes viral genes GPC and Z, encoded in genomic orientation, from S and L segments, respectively. Antigenomic RNA also serves as the template for replication (15). After translation of GPC, it is post-translationally modified in the endoplasmic reticulum. GPC is cleaved into GP1 and GP2 at the later stage of the secretory pathway. Cellular protease SKI-1/S1P is responsible for this cleavage (14). The cleaved glycoproteins are incorporated into the virion envelope with the virus buds and release from the cell membrane (14).

Brief Pathogenesis of Lassa Fever

Lassa fever is mostly caught by humans through exposure to urine or feces of the host rodents, commonly through the contamination of uncovered food items at home (3). Additionally, the spread of the Lassa fever could occur through direct contact between infected humans. People who live in overcrowded areas or environments where the host rodents are abundant, as well as places with a lack of standard hygienic measures, are at a higher risk of infection with the Lassa virus. Furthermore, human-to-human route of Lassa fever transmission has been confirmed, which correlates with infection cases in healthcare workers treating Lassa fever patients. Likewise, family members caring for infected relatives can be infected with Lassa fever through the human-to-human route of transmission (3, 16). Presently, there is no empirical data about viral shielding in human breast milk due to increased and elevated viremia (17).

Symptoms of the disease include a flu-like illness characterized by fever, general weakness, cough, sore throat, headache, and gastrointestinal manifestations. Hemorrhagic manifestations include vascular permeability (15). Upon entry into the body, the Lassa virus infects almost every tissue in the human body. It starts with the mucosa, intestines, lungs and the urinary system, and then progresses to the vascular system (18). The main targets of the virus are antigen-presenting cells, mainly dendritic and endothelial cells (19). Generally, when a pathogen enters a host, the innate defense system recognizes the pathogen-associated molecular patterns (PAMP) and activates an immune response (19). One of the mechanisms detects double-stranded RNA (dsRNA), which is only synthesized by negative-sense viruses (19). In the cytoplasm, dsRNA receptors, such as RIG-I (retinoic acid-inducible gene I) and MDA-5 (melanoma differentiation-associated gene 5), detect dsRNAs and initiate signaling pathways that translocate IRF-3 (interferon regulatory factor 3) and other transcription factors to the nucleus (20). Translocated transcription factors activate the expression of interferons, and these initiate adaptive immunity. NP encoded in the Lassa virus is essential in viral replication and transcription, but it also suppresses the host innate IFN response by inhibiting the translocation of IRF-3 (20). NP of the Lassa virus is reported to have an exonuclease activity to only dsRNAs (20). The NP dsRNA exonuclease activity counteracts IFN responses by digesting the PAMPs, thus allowing the virus to evade host immune responses (21).

Diagnosis of Lassa Fever

Accurate and rapid diagnosis of Lassa fever is especially challenging because of unclear signs and symptoms, different variants of the Lassa virus present in West Africa, and laboratory safety concerns regarding highly virulent pathogens (22). Viral culture remains the “best standard” for Lassa fever diagnosis across the diverse Lassa strains, but requires a clinically nonactionable amount of time and safety level-4 precautions to perform (22). Likewise, nucleic acid-based assays have become the clinical diagnostic standard and may be performed rapidly on inactivated specimens under safety level-2 conditions, but may have false-negative results due to the high variance among viruses (22). Viral antigen assays may provide a rapid diagnosis early on during the illness, but may miss the diagnosis at later stages, once the antigenemia phase has resolved (22). The detection of a new IgM antibody response can

diagnose Lassa fever, but may miss the diagnosis during the early stage of illness, may be falsely negative in severe infections where patients are unable to mount a serological response, and may remain positive for a prolonged period, potentially leading to false-positive results (22). A rise in baseline antibody titers between acute- and convalescent-phase serum or a positive IgM accompanied by the development of a new positive IgG response may be more indicative of acute Lassa fever in regions where it is endemic than a single positive IgM titer (22).

To sum up, an orthogonal diagnostic system employing molecular (PCR-based) and immunological (antibody-based) assays provides the greatest confidence in a diagnostic result for Lassa fever (23). Also, rapid diagnostic tests (RDTs) such as lateral flow immunoassays (LFIs) can be an important addition to the orthogonal system and can significantly reduce infections in ongoing outbreaks and in endemic areas (23). Furthermore, multiplex, magnetic bead-based assays are a significant improvement over traditional enzyme-linked immunosorbent assays (ELISAs) (23).

Clinical Manifestations of Lassa Fever

The period between contact with the Lassa virus and the appearance of signs and symptoms is usually 6 to 20 days (3). There are numerous signs and symptoms of Lassa fever, however, general weakness, migraine and headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhea, cough, and abdominal pain are most commonly reported and seen in patients (3, 24). In addition, protein may be seen in the urine of Lassa fever patients, and patients may also experience shock and seizures, while coma could occur in advanced stages of the disease due to the absence of treatment (3, 24). Although other infectious diseases may present with the aforementioned signs and symptoms, it is imperative to visit a hospital or a healthcare clinic for proper diagnosis and early treatment of any diagnosed infection. About 25% of Lassa fever survivors have hearing problems, which are typically reversible (25, 26). Incidences of hair loss during recuperation from Lassa fever have been reported, and death often occurs within a few days in severe cases of the disease without treatment. Clinical presentation of Lassa fever is serious in pregnancy, especially in the last stage of pregnancy, because the disease usually causes miscarriages and stillbirths due to the strong affinity of the Lassa virus for fetal tissue (3). In addition, once a person is infected with the Lassa virus, the virus weakens the organs in the body and causes organ malfunctions and depletion of the entire system (17, 24).

The Epidemiological Trend of Lassa Fever

The Lassa virus was first identified in the late 1960s by a healthcare worker in a healthcare center in Lassa, a town in Nigeria (4). After diagnosis, the contagious Lassa virus was confirmed (27). Over the years, Lassa fever has spread from the shores of Nigeria, and numerous West African countries, such as Burkina Faso, Ghana, Togo, Ivory Coast, Benin, Liberia, Guinea and Mali, are either Lassa fever-endemic or have had cases of infection (28-31, Table 1). The infection rate of Lassa fever is high based on geographic location (i.e. 1.9% in developed countries compared to 56% in developing countries); likewise, Lassa fever caught in hospitals results in more deaths (32, 33). Furthermore, findings from hospital-based serosurveillance related with suspected cases of Lassa virus infection revealed that basic hygiene measures among medical workers resulted in fewer infection cases compared to local inhabitants in villages, where basic hygiene practices are less common (33). The transmission rate of Lassa fever depends on the geographic location, with higher frequencies in developing countries compared to developed countries (34).

Table 1. Summary of West African Nations with Lassa Fever Cases, 1962-2018. Adapted from: (3)

S/N	West African countries with at least one case of Lassa virus infection	Endemic West African countries with Lassa fever	West African countries reporting Lassa fever outbreaks
1	Mali	Nigeria	Nigeria
2	Burkina Faso	Guinea	Guinea
3	Ghana	Liberia	Liberia
4	Togo	Sierra Leone	Sierra Leone
5	Benin		
6	Ivory Coast		

Lassa Fever in Nigeria

As the world battles the current COVID-19 pandemic, Nigeria faces a double battle with two highly contagious viral infections. Many years after it was discovered, Lassa fever is still a major public health problem in Nigeria (35). The aforementioned statement is evidenced by the massive outbreak of the disease in 2018 in the country, where 18 out of the 36 states of the federation were affected by Lassa fever; this was the biggest and the worst case of the disease in history (36, 37). In this respect, the Nigerian health authority declared the disease an emergency (38). From the beginning of 2020 until 26th December, 6732 associated cases of Lassa fever were accounted for in Nigeria, and 1181 samples returned positive from laboratory reports (39)d. Furthermore, from the beginning of 2020 until the end of 2020, 244 deaths occurred in 27 states, and 131 local government areas were affected by Lassa fever across the federation, while the general case fatality rate (CFR) for 2020 was 20.7% (39). Numerical estimates also revealed that Edo, Ondo and Ebonyi states had altogether 75% of the positive cases of Lassa fever in Nigeria for 2020 (39).

Cases of Lassa fever were evident in virtually all age groups; however, the predominant age range of people with confirmed infection for 2020 was 21-30, while the gender ratio for male and female was 1:0.9 (39). Due to the overburdening effects of the coronavirus disease pandemic (COVID-19) on the healthcare system, Lassa fever also exerted additional effects on health practitioners, because many health workers were infected with both diseases mistakenly, with more than two deaths recorded due to Lassa fever in 2020 (7). Lassa fever patients were treated and managed in various hospitals and healthcare centers across the country, secondary contacts were also identified, and follow-ups were done to ensure proper tracking and monitoring of the disease (39). Lassa fever is predominant in Nigeria and the onset of the disease is usually between December and June every year. Imperatively, the seasonal surge in new Lassa fever infection cases and deaths in the whole of Nigeria is a cause for concern and ought to be observed intently by both national and international health authorities (38). In addition, bordering countries, for example Togo and Benin, have had imported cases of Lassa fever from Nigeria in the past; hence, bordering countries should be closely monitored as well (38).

Main Emphasis on the Prevention of Lassa Fever

There are no protective vaccines against Lassa fever as of 2020 (40). Because of the endemic nature of Lassa fever, the disease was listed among future causes of disease outbreaks by the World Health Organization (41, 42). Lassa fever is prevalent in most West African countries and results in the deaths of thousands of people ever year (3). Due to the exponential rise in

mortality and infection cases of Lassa fever in the West Africa subregion, especially Nigeria, it is imperative to advance and reemphasize knowledge about prevention of the disease.

Prevention at Home

The transmission route of the Lassa virus to the secondary host (humans) should be forestalled, hindered and disrupted by limiting and reducing any exposure or contact with the feces and urine of the primary host (rodents) in Lassa fever hotspot areas and geographic locations, because worthwhile and beneficial efforts regarding the prevention of the disease depend on sustainable, adequate and proper personal and community hygiene efforts (43, Figure 1). Furthermore, successful and effective preventive measures against Lassa fever in the home include keeping edible items in closed, tight and clean containers, discarding, disposing of or burning waste and refuse far away from residential areas, basic personal hygiene practices such as washing hands with clean running water and soap before handling any edible items, immediate cleaning and washing of used plates and pots with detergent and clean water, tidy arrangement of kitchen utensils and other materials in clean and well-ventilated cabinets, always keeping kitchen floors clean and tidy, and proper disposal of leftover foods. In addition, prompt caution and preventive measures should be adopted by relatives when caring for persons with Lassa fever (3)..

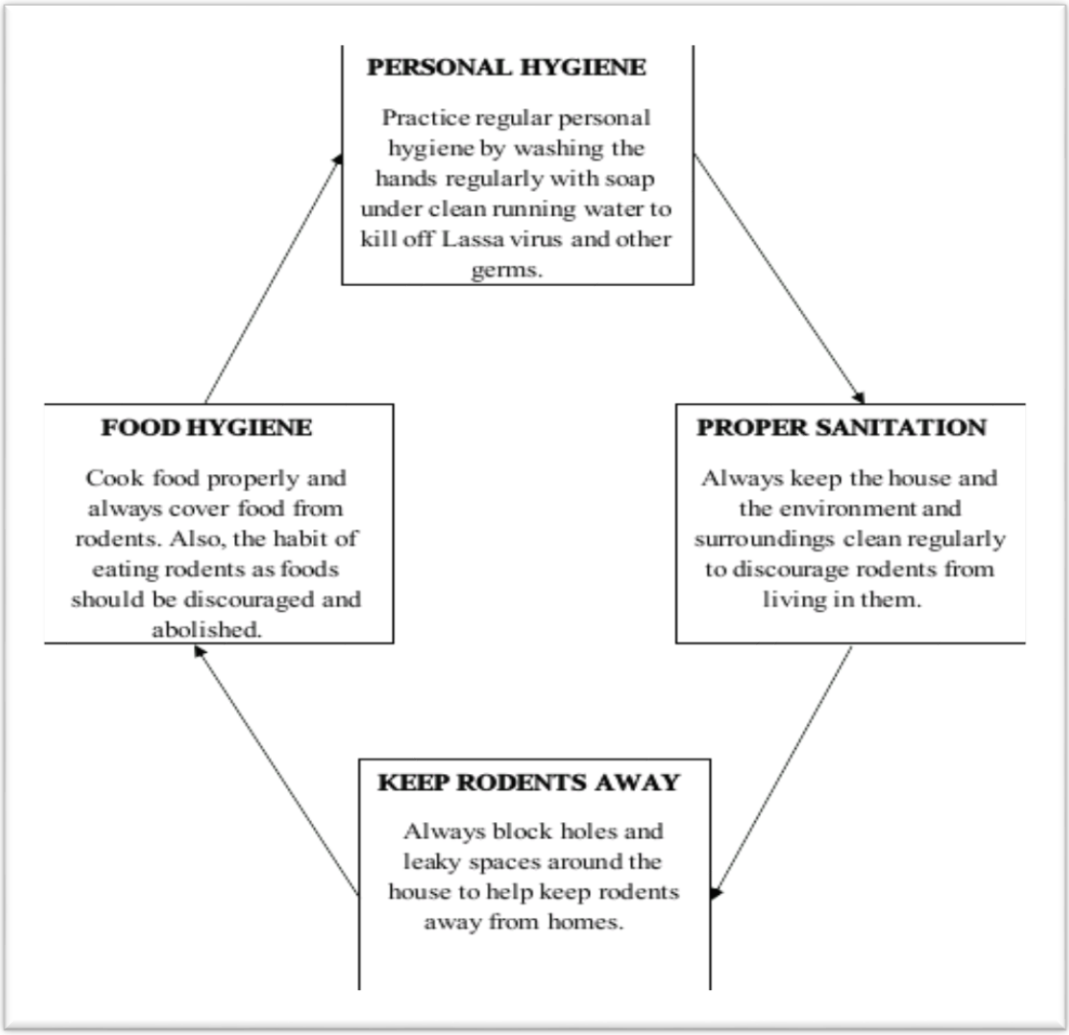

Figure 1. Prevention of Lassa fever at home (self-developed)

Prevention at Hospitals

High safety measures must always be adopted by all healthcare workers in different hospitals, clinics and healthcare centers, even when the diagnosis and cause of infection are unknown. Preventive and control safety measures include essential hand washing with soap, detergent or antiseptic and clean running water, respiratory hygiene and the appropriate use of personal protective equipment (PPE) (3). Furthermore, all rules and guidelines set by the World Health Organization for dealing with cases of highly infectious diseases should be strictly followed by healthcare workers treating Lassa fever patients. In addition, proper checking of personal protective equipment (PPE) should be ensured and the equipment should always be made available to healthcare workers in Lassa fever-prominent areas, such as Nigeria and other neighboring countries. Likewise, laboratory workers are at a higher risk of Lassa virus infection; hence, all Lassa virus samples in the laboratory should be handled with extreme care and caution.

In addition, the infection prevention and control authorities (IPC) should ensure that healthcare centers and laboratories meet the requirements for operation, especially in Lassa fever hotspot areas (44). It is imperative to ascertain that all healthcare centers attending to Lassa fever cases operate with the standard achievable around the world, and routine IPC training should also be made mandatory for all healthcare workers handling cases of Lassa fever (44).

Prevention among Travelers

Migrants moving from countries where Lassa fever is prominent often transfer and import the disease to other locations or regions; this is evident in Togo and Benin, since some of the reported cases in the two countries were imported from Nigeria (38). Strict and continuous border checking and inspection of medical reports of travelers is paramount. Imperatively, all border rules and regulations pertaining to infectious disease checking during border crossing should be strictly enforced by border patrols and healthcare workers stationed at border crossings. Likewise, persons visiting Lassa fever-endemic nations for vacation should visit the respective embassies and consulates in the countries they visit in order to get information on Lassa fever-prone areas in such countries, as well as to get general health information on other infectious diseases prevalent in such countries. Furthermore, febrile migrants who recently returned from Lassa fever-predominant areas should urgently visit a healthcare clinic or hospital in their current location in order to get a proper diagnosis and early treatment (45).

Treatment Options for Lassa Fever

Treatment options for Lassa fever are few and treatments are mainly symptomatic (8). Management of bleeding and hydration is important, particularly in hemorrhagic cases. Likewise, pain management through the use of opiates is prescribed (8). Due to the permeability of blood vessels, pulmonary edema is a concern, and fluid infusion must therefore be carefully monitored (8). An antiviral drug (Ribavirin) offers beneficial effects for Lassa fever patients with poor prognoses, and is usually reserved for patients with higher Herliver enzyme levels (AST value > 150) (8). Even though it is a drug with significant side effects, ribavirin is the drug of choice in many cases of Lassa fever (8, 46).

Recommendations

Based on this study, the following recommendations are made:

a) Contact with multimammate rats, especially their feces and urine, should be avoided.
b) Personal hygiene, such as hand washing with clean running water and antiseptic soap, should be practiced at all times.

c) Environmental sanitation, such as clearing and cleaning of the environment, should be done frequently in order to destroy the habitats of multimammate rats.
d) The barbaric act of eating rats should be discouraged, abolished and ultimately stopped.
e) Containers for food items should be kept tight and closed at all times to prevent rats from accessing them, and any food items with traces of rat feces or urine should be discarded immediately.
f) Healthcare workers, especially nurses, doctors and laboratory scientists, should follow the basic aseptic practices when treating patients infected with Lassa fever.
g) Health education on Lassa fever should be intensified for everyone.
h) The rearing and breading of cats at home should be encouraged. This would help reduce the population of rats in the environment, especially in rural areas.

Conclusions

Lassa virus is highly infectious and could infect any individual, since no one is immune to the disease. Lassa fever is endemic in most West African countries, with yearly cases in terms of infection and mortality in Nigeria. People at severe risk of infection with Lassa fever are individuals living in unhygienic and dirty environments with overcrowded living conditions, because these are the scenarios and situations in numerous Lassa fever-endemic areas. Health consequences caused by the infectious Lassa fever are enormous. In this respect, multifaceted preventive measures that ensure, encourage and guarantee no contact with multimammate rodents and rats should be adopted. Furthermore, there should be a strong synergy and cooperation between governments and border patrol officers of Lassa fever-endemic areas to work out effective ways to minimize the rate of cross-border transmissions of the disease. Likewise, major international health organizations should help and assist with public health experts and personnel, logistic and vital information in curtailing the spread of Lassa fever in developing countries.

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