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A REVIEW OF LASSA FEVER, AN EMERGING OLD WORLD HAEMORRHAGIC VIRAL DISEASE IN SUB-SAHARAN AFRICA

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ABSTRACT

Lassa fever is an acute immunosuppressive illness of increasing public health concern causing severe morbidity and significant mortality (Case fatality rate (CFR) ≥ 50%) especially in epidemic cases. Although Lassa fever has emerged (following its first detection (1969) in Lassa town, Nigeria) as one of the most prevalent and debilitating viral haemorrhagic fevers endemic in West Africa region (Nigeria inclusive), yet, the control/prevention of the regular outbreak of the disease has become an herculean task in the areas affected; there is inadequate healthcare facility (including Laboratory/diagnostic and care centres), poor socio-economic environment, lack of awareness among the populace and presence of favourable ecologic niche for the survival and propagation of the natural host and reservoir mouse (*Mastomys natalensis*) of Lassa virus . Lassa fever is mainly transmitted by contact with excretions and secretions of infected rats via foods and water as well as exposure to other contaminated items. Lassa virus is a member of an Old World Arenariruses, of family *Arenaviridae*. It is an enveloped, single-stranded (SS) bisegmented RNA virus with ability to replicate very rapidly. It consists of 4 lineages; 3 members are identified as ancenstral strains found in Nigeria, while the fourth is domiciled in other West Africa Countries. Lassa virus infects almost every tissue in human body resulting in multisystemic dysfunction. The incubation period is generally between 6 to 21 days resulting in 3 stages of clinical manifestation viz: Acute phase characterized by flu-like, non-specific illness; haemorrhagic phase accompanied with gastrointestinal symptoms and cardiovascular/neurologic complications. Currently, there is no clinically certified Lassa fever vaccine thus complicating deterrent or preventive measures. Hence, there is need for intensification of educational programs for the populace on the useful control measures against Lassa fever. The stakeholders need to prioritize intervention and support program and also speed up the processes leading to the production of effective vaccine to limit the menace of Lassa fever outbreak and associated morbidity, fatality and high socio-economic cost.

Key words: Lassa fever, endemic, epidemic, reservoir rodent, West Africa.

UN EXAMEN DE LA FIEVRE DE LASSA, UNE MALADIE VIRALE HEMORRAGIQUE EMERGENTE D'ANCIEN MONDE EN AFRIQUE SUB – SAHARIENNE.

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RESUME

La fièvre de Lassa est une maladie immunosuppressive aiguë de plus en plus préoccupant de la sante publique causant plusieurs morbidités et de mortalités (taux de fécondité de cas CFR ≥ 50%) en particulier dans les cas d'épidémie. Bien que la fièvre de Lassa a émergé (après sa premièredétection (1969) dans la ville Lassa, Nigeria) comme l'une des fièvres virales hémorragiques les plusrépandues et débilitantes dans la région d'Afrique de l'Ouest (le Nigeria inclus), mais le contrôle et la prévention de l'épidémierégulière de la maladie est devenue une tache herculéenne dans les zones touchées ; il y a des facilités inadéquates de soins de santé (ycompris les laboratoires /centres de diagnostic et de soins),une mauvaise environnement socio – économique, le manque de sensibilisation de la population et la présence de niche écologique favorable pour la survie et la propagation de l'hôte naturel et le réservoir souris (*Mastomysnatalensis*) de virus de Lassa. La fièvre de Lassa se transmet principalement par contact avec les excrétions et secrétions des rats infectés à travers des aliments et de l'eau ainsi que l'exposition à d'autres objets contaminés. Virus de Lassa est membre de famille Arénavirus*Arenaviridae*d'Ancien Monde. C'est un virus à ARN enveloppé, simple brin (SS), àdeux segmenté avec la capacité de se répliquer rapidement. Il se compose de quatre lignées, 3 membres sont identifiéscomme des souches ancestrales trouvé au Nigeria, tandis que le quatrième est domicilié dans d'autres pays africain. Virus de Lassa infecte presque tous les tissus dans le corps humain entrainant a un dysfonctionnement multi systémique. La période d'incubation est généralement entre 6 à 21 jours résultant en 3 étapes de

manifestations cliniques à savoir : la phase aiguëcaractérisée par la grippal, une maladie non – spécifique, la phase hémorragiqueaccompagnée par des symptômes gastro – intestinaux et les complications cardiovasculaires/neurologiques. Actuellement il n'y a pas de vaccine certifié cliniquement contre la fièvre de Lassa compliquant ainsi de dissuasion et des mesures préventives. Par conséquent, il est nécessaire d'intensifier des programmes éducatifs pour la population sur les mesures de contrôle utiles contre la fièvre de Lassa. Les parties prenantes doivent donner la priorité à l'intervention et le programme de soutien et également d'accélérer les processus menant à la production de vaccine efficace pour limiter la menace de l'épidémie de la fièvre de Lassa et de la morbiditéassociée, la fatalité et le coût socio – économiqueélevé.

Mots clés : La fièvre deLassa, endémique, l'épidémie, réservoirde rongeurs, Afrique de l'Ouest.

INTRODUCTION

Lassa fever is an acute immunosuppressive and multisystemic viral disease characterized by severe morbidity and high mortality especially during epidemic outbreak and among hospitalized patients [1-3]. It is one of the most common viral haemorrhagic fevers endemic in sub-Saharan Africa, particularly West Africa sub-region (Nigeria inclusive). [4-6] Increasing outbreak of Lassa fever in the past decade involving expanded region of endemicity with serious public health and socio-economic implications has become worrisome[2,5].

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Lassa virus (a member of *Arenaviridae* family and Old World Arenaviruses) [7] was first discovered in 1969 at a small town of Lassa in Borno State, Northeast Nigeria [8]. It's reservoir and natural host was later identified as the Natal multimammate (with many beasts) African mouse (*Mastomys natalensis*), commonly found in the forest and Savannah grass land of sub-Saharan Africa [9]. These rodents (with inherent capacity to reproduce at high rate) shuttle between surrounding bushes and human houses in villages, towns and cities where they co-habit human populace in their residences and commercial or business centres [6].

Reports of various investigations [2,8,9] have suggested that Lassa virus is probably transmitted by contact with excretions or secretions (including faeces and urine) of infected rats accessing food items and water inside human residences and other centres with human activities. Other possible routes of transmission of Lassa fever such as broken skin or mucus membrane directly exposed to infectious material have also been suggested by other investigators [5,9]. Epidemics arising from human-to-human transmission have equally been established in healthcare institutions in Africa [10].

Lassa fever virus infects about half a million people in countries where the disease is endemic (including Nigeria, Guinea, Sierra Leone, Liberia as well as Central Africa Republic, (CAR) and recently Senegal and Mali[5] resulting in over 5,000 deaths annually. [6] However, between 70-80% of Lassa virus infection remains asymptomatic, mild or self-limiting and in most cases may pass unnoticed. Nonetheless, about 20-30% of cases progress to severe disease condition and fatality rate may be up to 50 percent or more in such situation [2,11,12]. Increased population (with population explosion in some poor-resourced areas of sub-Saharan Africa), large scale deforestation (by either natural or manmade e.g. for industrial, housing and other social facility thus depriving the rodents of their natural habitat) and poor environmental hygiene are believed to contribute to the increased incidence of Lassa fever in the affected areas of West Africa [6,13].

Lassa fever is endemic in Nigeria. However, the increasing frequency of epidemic outbreak of the disease in the last decade has become worrisome in view of its threat to public health and associated severe morbidity, significant mortality and high socio-economic cost [11]. The national government's efforts geared towards curtailing the regular outbreak of Lassa fever in Nigeria via public enlightenment campaigns especially during epidemic outbreak of the disease have not yielded the desired results. Therefore, the present effort is meant to further sensitize the stakeholders in healthcare system and the populace about the health and socio-economic consequences/effects of the menace of Lassa fever, and the crucial need to adopt effective control/preventive strategies to checkmate the increasing menace of the disease, and thus limit associated morbidity, mortality and high socio-economic cost in this environment.

Epidemiological Trend of Lassa Fever

Previous studies [2,6,7,13] have reaffirmed the initial widespread speculation that Lassa virus probably evolved from the Eastern part of sub-Saharan Africa, and then gradually spread to the West African sub-region. A large area of West Africa is now considered as Lassa fever belt due to its recurrent outbreak in that geographical location [14].

As earlier stated, Lassa fever virus was first detected (1969) and reported (1970) by Frame and his colleagues [8] in Lassa town (from where the virus derived its name) located in the North east geopolitical zone of Nigeria. The first victim of Lassa

virus infection is believed to be an American Missionary working in the area who later died of complications arising from the illness. Two other female Nurses who attended to the index case also contracted the disease; one of them later died while her counterpart survived after she was flown to the United States (U.S.) for medical care. Tissues and blood specimens were collected from index case for analysis through which Lassa virus was identified [8].

Since its historical discovery in Nigeria, Lassa virus has been transported across borders of Central and West Africa affecting between 300,000 – 500,000 people (predominantly) in Nigeria, Guinea, Sierra Leone and Liberia (Table 1) resulting in over 5,000 deaths annually [2,6,15]. In endemic situation, the overall case fatality rate (CFR) of Lassa fever is estimated to be in the range of 1-10 percent. However, during epidemic outbreak, the CFR of Lassa virus may be up to 50 percent while higher rate has been recorded in severe cases [3,9,10,14]

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In contrast to the above scenario, there is relatively low incidence of Lassa fever in advanced countries of the West including North America and parts of Europe [16]. Hence, the risk of contracting the disease or its possible large scale transmission or spread among the populace is highly limited. Understandably, aside the near absence of the natural reservoir or host animal (*M. natalensis*) of Lassa virus in the aforementioned areas, availability of highly developed environmental hygiene and sanitation, as well as large scale accessibility to advance and well-managed social and healthcare infrastructure appear to greatly influence the low risk status of those industrialized countries of the West [15,17]. Nonetheless, there have been sporadic cases of Lassa fever outbreak among travellers and tourists returning from endemic regions to Europe and America [16,18,19].

It is estimated that between 15-20% of all hospitalized Lassa fever patients are likely to die from the illness if appropriate medical intervention is not instituted early [3,10] On the other hand, epidemiological and immunological studies have shown that immunity developing in those who survived Lassa virus infection is long lasting [20,21].

In Nigeria, Lassa fever outbreak has been a recurrent event over the last two decades. In recent outbreak of the disease (August, 2015-March, 2016), over 200 people were affected across 18 States (out of 36 States and Federal Capital Territory, Abuja) of Nigeria. [22] Initially, there were 92 confirmed cases which resulted in 43 deaths constituting 46.7% CFR. By the end of March, 2016, the number of deaths had risen to 80, making it one of the worst outbreaks of Lassa fever in Nigeria in recent times [22].

TABLE 1: PREVALENCE OF LASSA FEVER IN THE POPULATIONS OF MOSTLY AFFECTED COUNTRIES IN WEST AFRICA

Prevalence of Lassa fever	
Country	**Range in percentage**
Nigeria	**21 – 45**
Guinea	**4 – 55**
Sierra Leone	**8 – 52**
Liberia	**12 – 48**

Sogoba *et al.*, (201)[6]; WHO, (2016)[2]

Mechanism of Transmission of Lassa fever

Lassa fever is a zoonotic disease (ie infectious disease of animal or originating from animal source) transmitted to humans via contact with an infected rodent (*M. natalensis*), or through inhalation of air contaminated with infected rat's excretions or excretions such as faeces, urine or nasal discharges (aerosols) [9,23]. Lassa virus infection can also be acquired through broken skin or mucous membrane directly exposed to infectious material or item [5,9,18]. Nosocomial acquisition of Lassa virus infection is mainly through contact with infected patient, exposed hospital workers or unscreened infected blood [24]. Such blood and its products pose a serious risk to patients receiving them by transfusion in health care institutions. Similarly, direct contact with infected semen, or vaginal fluids including consumption of infected breast milk have been suggested as possible mode of transmission of Lassa fever[24,25].

It has been shown that immunosupression arising from certain underlying communicable or non-communicable diseases, chemotherapy as well as pregnancy (especially if infection occurs during the third trimester) can enhance the acquisition and establishment of Lassa fever, and may aggravate mortality rate pushing it up to about 80 percent [1, 14,15,26]. Infection during pregnancy can lead to fetal death (because the virus has high affinity for placenta and other highly vascularized tissues), abortion, including loss of newborn (in 90% of cases) or maternal death. [3,26,27] Serious congenital defects or abnormalies are common sequelae in children born with Lassa fever infection [27,28].

Virology of Lassa Fever Virus

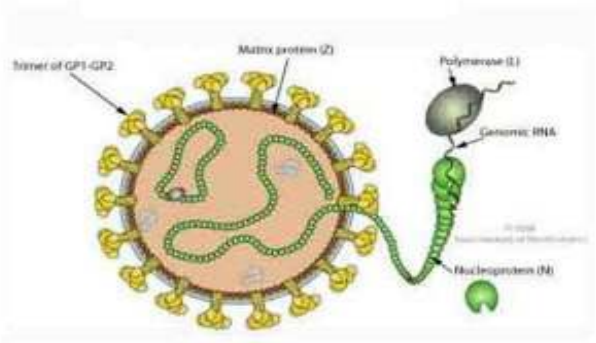
Lassa virus (a member of Arenaviridae family) is categorized under the group known as 'Old World Arenaviruses' on the basis of their antigenic and molecular properties [7,29, 30]. The group consists of Lassa virus and Lymphocytic choriomeningitis virus (LCMV). Lassa virus is characterized by high genetic

variability hence there was initial difficulty regarding the design of primers for Polymerase Chain Reaction (PCR) in molecular studies of the virus. Consequently, some Lassa virus strains were believed to escape, detection by PCR during the early studies [15,21].

Other members of the Old World African Arenaviruses that share similar properties and closely related to Lassa virus include Ippy virus, Mobala and Mopeia (Table 2) [7,13,31,32]. However, these strains of Arenaviruses have not yet been associated with any human disease [7].

Lassa virus is an enveloped, single-stranded (SS) bisegmented RNA virus. It is a rapidly replicating virus but has inherent ability to temporarily control its replication. This attribute preferentially allows the spike proteins component of that virus to be produced last during replication, and therefore, delay the recognition of the virus by the host's immune system. Consequently, the process is believed to aid the virus pathogenicity, pathogenesis and evasion of the host's defense mechanism [33,34].

Studies [35, 36] on Lassa virus genome nucleotide have revealed the existence of lineages of the virus; 3 members of which are found in Nigeria while the fourth was traced to other parts of West Africa including Liberia, Guinea and Sierra Leone [29].



Lassa Fever Virus. Information Nigeria [30]

TABLE 2: PHYLOGENETIC, GEOGRAPHICAL AND PATHOGENIC GROUPING OF ARENAVIRIDAE FAMILY

Group	Arenavirus complex	Geography/virus Species	Family Arenaviridae: Pathogenicity	Associated Disease
1	Old World	Lassa	P	Lassa Fever: Flu-like illness, Gastrointestinal symptoms, Bleeding, Organ failure, Neurological Complications
		Mopeia	NP	NE
		Mobala	NP	NE
		Ippy	NP	NE
		Lymphocytic Choriomeningitis Virus (LCMV)	P	Mild febrile illness, Benign meningitis, Birth defects: Hydrocephalus, Chorioretinitis, Blindness, Deafness, Mental retardation. Lassa fever-like illness in Primates, Calitrichide hepatitis
2	New World	Junin	NA	NE
		Tacaribe	NA	NE
		Pichinde	NA	NE

Bowen *et al.* (1997); [7] Gonzalez *et al.*, (1983); [13] WHO, (2016; [17] Whulff *et al.* (1977); [31] Swanepoel *et al.* (1985) [32].
LCMV- Lymphocytic Choriomeningitis Virus, P- Pathogenic, NP-Non-pathogenic, NE-Not established, NA-Not available.

Pathogenesis of Lassa Fever

The pathogenesis of Lassa fever has not been clearly understood. [20] However, studies [34,37] show that Lassa virus infection leads to immunosuppression while the main targets of Lassa virus once inside the host are the antigen-presenting cells. Lassa virus infects almost every tissue in human body leading to multisystemic dysfunction, and can suppress host's innate interferon (IFN) response by inhibiting the translocation of interferon regulatory factor -3 (IRF-3). In addition, Lassa virus characteristically exhibits exonuclease activity to only double-stranded RNAs (ds RNAs), which often blocks IFN responses. This is achieved through digestion of Pathogen-associated molecular pattern (PAMP), which enables the virus to evade host's immune responses [33,34,37,38].

Clinical Manifestation of Lassa Virus Infection

[3,11,12]. Generally, incubation period ranges from 6 to 21 days [12,15]. The typical case progression can be divided into 3 main stages (Table 3) as shown below.

Stage 1: Prodromal Illness/Acute Stage
At this stage, the onset of the disease mimics malaria or typhoid fever. First, it begins with respiratory flu-like (non-specific illness) symptom characterized by headache, myalgia (general body's weakness) febrile illness (fever ≥ 38^0C, which does not respond to standard treatment for malaria or typhoid; accounts for 10-16% of total cases and about 30% of deaths) cough, pharyngitis (sore throat and back ache). Other signs include tremors chest paid, insommia (restlessness), sometimes rashes coupled with gastrointestinal symptoms including diarrhea and vomiting. [11,24] These early symptoms often appear

Lassa fever is a grave illness of significant fatality (CFR, 40≥ 50%) especially during epidemic outbreak indistinguishable from other bacterial, viral or parasitic infections [24] and can be treated with antiviral drug such as Ribavirin if diagnosed at early stage [39].

Stage 2: Haemorrgagic Stage
This stage involves internal haemorrhage whereby victim bleeds from inside through nostrils, mouth and other orifices resembling that of Ebola. This may lead to organ failure and death [8,21,23].

Stage 3: Neurologic Complications
This constitutes part of the late Stage of the illness manifesting as neurological complications including encephalopathy or encephalitis (Table 3) [28]. The virus can be detected in the urine of infected patient for 3-9 weeks and in semen for up to three months [2].

TABLE 3: STAGES OF CLINICAL MANIFESTATIONS OF LASSA FEVER

Stages/Signs and Symptoms of Lassa Fever:		
Stage 1: Prodromal/Acute Phase	**Stage 2: Haemorrhagic Phase**	**Stage 3: Cardiovascular/Nervous System/ Neurological Complications**
*Flu-like illness characterized by:	* Gastrointestinal Manifestations:	* Hypotension
- Fever (≥38^0C)	- Stomach ache	* Pericarditis
- Headache	- Diarrhoea	* Tachycardia
- Myalgia	- Vomiting	* Hypertension
- Cough	- Dysentery	* Meningitis
- Pharyngitis	- Hepatitis	* Encephalitis
- Chest Pain	- Facial swelling	* Seizures
- Tremors	- Conjunctivitis	
- Back ache	- Muscle fatigue	
- Rashes (in some cases)	* Haemorrhage via:	
- Insomnia	- Mouth, nostrils, skin etc	
	- Bloody vomiting	
	- Bloody diarrhoea	

Frame *et al.,* (1970); [8] Richmond *et al.,* (2003) [11] Emound *et al.,* (1982); [21] WHO, (2015; [23] Bausch *et al.,* (2001); [24] Gunther *et al.,* (2001) [28].

Diagnosis of Lassa Fever
Lassa fever has emerged as one of the most prevalent viral haemorrhagic fevers in West Africa (Nigeria inclusive) [6,40]. However, in most Lassa fever endemic areas of the region, there are serious challenges regarding the laboratory diagnosis and confirmation of the disease due to inadequate facility and low capacity [23, 40]. For instance, in Nigeria (with estimated population of over 170 million), there are only two diagnostic centres (Irua, Edo State in South-South Nigeria, and Lagos, South-West Nigeria) where Lassa virus infection could be confirmed[40].

The currently used Laboratory investigations for the detection of Lassa virus infection include:
*Enzyme-Linked Immunosorbent Assay (ELISA) test for the detection of IgM antibodies in patient's serum. The test gives 88% sensitivity and 90% specificity for the presence of Lassa fever.

- Analysis of cerebrospinal fluid (CSF) to detect the presence of Lassa virus.
*Confirmation of Lassa fever by molecular analysis using Reverse Transcription-Polymerase Chain Reaction (RT-PCR) method [41] (Table 4). Notably, due to non-specific nature of the early symptoms of Lassa fever, molecular diagnostic method is very crucial and plays a decisive role in the early diagnosis of Lassa virus infection [36,42-45]. On the other hand, cell foci infected with Lassa virus can equally be detected with Lassa virus NP-Specific monoclonal antibody such as the use of L_2F_1 test [46, 47].

Regardless of the method adopted, Lassa fever will require a Biosafety Level 4 – equivalent containment during Laboratory diagnosis to prevent the acquisition and spread of the disease in the Laboratory and hospital environment [2].

TABLE 4: LABORATORY INVESTIGATIONS FOR DETECTION OF LASSA VIRUS INFECTION

Laboratory Test	Finding Suggestive/Confirmation of Infection
- ELISA	IgMAntibodies;Sensitivity=88%,Specificity=90%
- Lyphopenia	Decrease/low White Blood Cell Count
- Thrombocytopenia	Low Platelet Count
- Blood Aspartate Aminotransferase levels	Elevated
- Detection of Lassa Virus in Cerebrospinal Fluid (CSF)	
- Lassa Virus NP-Specific Monoclonal Antibody (L_2F_1) Test	Positive
- Molecular Analysis by:	
RT-PCR Assay, eg targeting L RNA segment of Lassa virus	Detection of Lassa Virus Infected Cell Foci. - Confirmation of Lassa fever. - Detection of conserved regions in the polymerase domain of the L gene.

Gunther *et al.,* (2001); [28] Demby *et al.,* (1994); [41] Drosten *et al.,* (2002); [44] Vieth *et al., (2007);* [36] Hufert *et al,.* (1989); [46] ter Meulen *et al.,* (1998) [47].

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 [9,22]. 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 by such 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) [39] 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) [49] is crucial in checkmating the spread of Lassa fever.

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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