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Lassa fever and the Nigerian experience: a review

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ABSTRACT: The occurrence, transmission and intervention strategies on the Lassa fever disease in Nigeria are presented. The Lassa virus is an enveloped, single stranded, bi-segmented RNA virus that belong to the Arenaviridae family was first reported in 1969 from Lassa village, Borno State, Nigeria. The primary animal reservoir for the virus is the multi-mammate rat (*Mastomys natalensis*). It is transmitted to humans through the excreta of infected carrier, often via contaminated food and human-to-human transmission. The most common treatment intervention is ribavirin which carries out its function by inhibiting virus replication. Extensive investigation is being carried out to arrive at an effective vaccine. Keeping rodents out of homes and food supplies, as well as maintaining effective personal hygiene are the most viable preventive measures against the disease.

Keywords: Lassa fever; *Mastomys natalensis;* Arenaviridae; Ribavirin; Nigeria.

1. INTRODUCTION

Lassa fever (a rare viral hemorrhagic fever) is a disease of immense public health significance. It was discovered in 1969 in Lassa village in Borno State Nigeria following the death of two American missionary nurses [1]. The etiological agent is the Lassa fever virus that is found in West African countries like Nigeria, Sierra Leone, Liberia and Guinea and spread by its reservoir [2]. The multi-mammate rat *Mastomys natalensis* is the host [3].

It is an acute viral zoonotic disease that may cause multi-organ failure and immune suppression [4]. Transmission is by direct contact with excretions or secretions (including feces and urine) of infected rats on food items and water inside human residences and other centres with human activities. Other possible routes are bruised skin or other body parts directly exposed to infectious material. Epidemics arising from human-to-human transmission have equally been established in healthcare institutions in West Africa. It is endemic in West Africa, with 300,000-500,000 cases and 5,000 deaths occurring yearly across Nigeria, Sierra Leone, Guinea, and Liberia. A significant percentage of the infections remain asymptomatic, mild or self-limiting and may pass unnoticed [5]. The most current outbreak occurred in late 2017 and early 2018, before which there

had been over 13 major outbreaks between 1969 and 2015 [6]. The infection occurs majorly in the dry season even though it can be observed throughout the year. It is not age- or gender-dependent. However, given the ubiquity of the rodent host [7], antibody prevalence tends to increase with age. This may explain the virus transmission to humans in and around the homes where the *Mastomys* live [2].

The virus has been associated with nosocomial outbreaks resulting in high mortality in affected areas [8]. Poverty and lack of education are twin candidate predisposing factors. Compared to Human immunodeficiency virus infection, the spread of the Lassa virus infection is more rapid among close associates and it rapidly kills. Although certain progress was made in understanding the replication pattern, Nigeria and other West African countries have continued to experience frequent community and nosocomial outbreaks, sometimes with significant fatalities and serious economic burden. Therefore control measures targeted at reducing rodent-to-human contact and human-to-human transmission; and early identification of infected individuals and prompt treatment are focal points in curtailing the annual epidemics [9].

Lassa fever has been associated with economic challenge [10]. According to NCDC (2017), Nigeria experiences an outbreak in most of the states, with fatality profile sometimes strange and unclear. The recent Lassa outbreak might have exposed some inherent gaps and improving health system challenges in determining how Nigerian communities and other prone countries can proactively mitigate, prepare and respond to this and other emerging and re-emerging infectious diseases of poverty [11].

Infected rodent's feces or urine, contaminated dust, contaminated food or the fluids of an infected person dead or alive remain the routes of transmission of Lassa fever [12]. Fever, weakness, nausea, vomiting and diarrhea leading to severe cases of bleeding, coma and possible death are the symptoms of Lassa fever [11]. An epidemic of Lassa fever between 2015 and 2016 showed how overwhelming the challenge was on the healthcare system in Nigeria as at that time [13].

2. HISTORICAL PERSPECTIVE

Cases of deaths occurred from undiagnosed clinical entities between 1920 and 1950, in Nigeria, Sierra Leone, and other West African countries. Although the virus was first detected in 1969, it was reported in 1970 in Lassa town (from where the virus derived its name) located in Nigeria [5]. The first victim of Lassa virus infection is an American missionary working in the area, who later died of complications arising from the illness. That same outbreak spread to Jos, Plateau State, North Central Nigeria in subsequent years [14]. Apart from Nigeria, epidemics have been reported in other West African countries, thus establishing the possible cross border route and scare.

3. MORPHOLOGY

Lassa virus (LV), the causative agent of the fever; is an enveloped, single stranded, bi-segmented RNA virus the Arenaviridae family [2]. It is spherical in shape and has a smooth surface envelope with T-shaped spikes measuring 7-10 nm and built with glycoprotein [15]. Envelope encapsulates the genome which has nucleocapsid with a helix shape (Fig. 1) measuring between 400 and 1300 nm in length. Usually, the name

"arena" meaning sand was derived from the internal structure that contains electron dense granule, identified as the host cell ribosome.

Lassa virus is categorized on the basis of their antigenic and molecular properties [16]. It is characterized by high genetic variability sometimes making detection by the host immune system difficult [9].

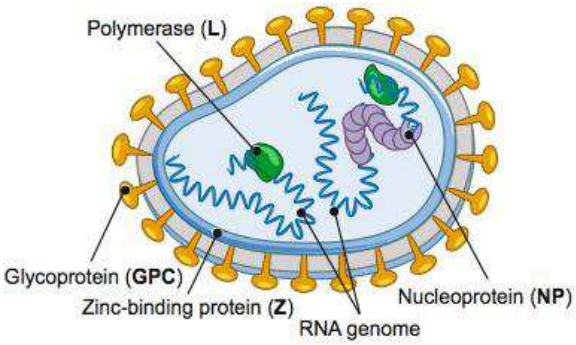

Figure 1. Lassa virion. Source: with permission of Omeh et al. [9].

4. PATHOGENESIS

Infection is started after acquisition of the virus through contact with infected carrier's urine, saliva, respiratory secretion, or blood. The main targets of virus are the antigen presenting cells inside the host (Fig. 2). However, it also infects almost every tissue in human body leading to multi-systemic dysfunction. It does this by suppressing host's innate interferon (IFN) response through the inhibition of the translocation of interferon regulatory factor-3 (IRF-3). In addition, it exhibits exonuclease activity to only double-stranded RNAs (ds RNAs), which often blocks IFN responses. This is achieved by the breakdown of pathogen associated molecular pattern (PAMP), which enables the virus to evade host's immune responses [14].

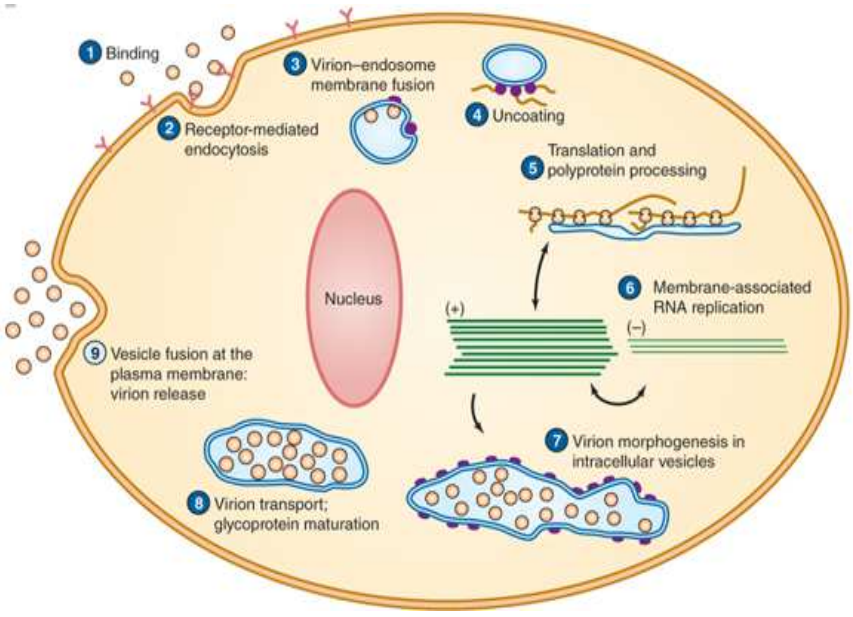

Figure 2. Pathogenesis of Lassa fever. Source: with permission of Omeh et al. [9].

Patients with subclinical infections may pass unnoticed. Therefore, this group, are at risk of developing hearing loss of different degrees later in life. The impairment can affect all dimensions of hearing and according to WHO about 25% of patients exposed to Lassa virus are affected [5]. Other complications may include, gait disturbances, tremors and encephalitis [17].

5. GEOGRAPHICAL DISTRIBUTION

The disease is endemic in several West African countries including Nigeria, Sierra Leone, Guinea, and Liberia [18]. Every year, 300,000-500,000 people in this region are affected, resulting in over 5,000 deaths annually [14]. In endemic situation, like in Nigeria, the overall case fatality rate (CFR) is in the range of 1-10 percent. However, during epidemic outbreak, this may be up to 50 percent and this could be higher in severe cases [9]. The high degree of sero-prevalence of the virus - specific antibodies in the general population residing in the endemic regions, although highly variable depending on the geographical location [19], indicates that most infections are mild or possibly even asymptomatic and do not result in hospitalization [20]. The Lassa fever epidemic has also been found in Mali, Senegal and Central African Republic. Sporadic imported cases have been reported in the United States of America, Europe, and Asia, and laboratory infection has occurred among health workers in the USA during handling of infected specimens [21].

6. THE NIGERIAN EXPERIENCE

This disease has been occurring in Nigeria as endemic and epidemic outbreaks from the year it was identified in 1969. Outbreaks of Lassa fever have been reported in various parts of Nigeria including Edo, Ebonyi, Anambra, Imo, Jos, Taraba, Nasarawa, Yobe, Rivers and Ondo states [8]. Although the disease carries an epidemic nature that attracts sudden response from government, not much sustained intervention programme is in place. Unfortunately, with this nature of infection response, it is very difficult to gain experience from previous outbreaks to improve the management of future re-emergence [2]. Most available reports focused mainly on nosocomial outbreaks or more recently on laboratory diagnosis of blood specimens of suspected cases sent to reference laboratory. These outbreaks became heightened in the last decade. In early 2012, confirmed cases stood at 108, with fatalities among some medical personnel [5]. In 2018, it is reported that Nigeria experienced a huge outbreak, occurring in twenty-three states and having 3,498 suspects with 45 healthcare workers among the 633 confirmed cases [22].

The relevant government regulatory and intervention body reported some cases in the early part of 2015 [23]. Out of the 21 cases, Bauchi state had the most outbreak with 3 confirmed and 1 death [5]. In 2019, the WHO reported 327 cases of Lassa fever (324 confirmed cases and three probable cases) with 72 deaths (case fatality ratio = 22%) reported across 20 states and the Federal Capital Territory (Fig. 3). Edo (108) and Ondo (103) accounted for most of the cases. Sadly, 12 cases were reported among healthcare workers in seven states - Edo (4), Ondo (3), Ebonyi (1), Enugu (1), Rivers (1), Bauchi (1) and Benue (1) including one death in Enugu [24]. Case management centres operate in Anambra, Ebonyi, Edo, and Ondo States [25]. A sero-prevalence of 58.2% where 96.1% of houses had contact with rodents in the previous 6 months was reported

in an investigation in an endemic local government in Southern Nigeria, including 24 cases in Ondo state in January 2018 [15].

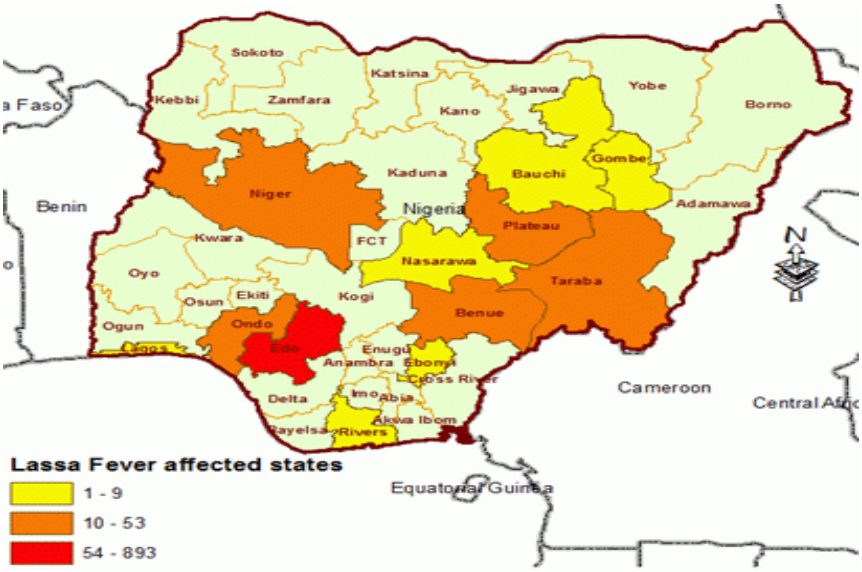

Figure 3. Distribution of Lassa fever in Nigeria. Source: NCDC [25].

7. TRANSMISSION

Outbreaks in endemic areas are incited by conducts that promote increased contact between man and the carrier (*Mastomys natalensis*). These include poor sanitation, overcrowding, deforestation, rodent hunting, and bush burning [26]. Predisposing factors generally include nearness to animal reservoir, the practice of air-drying grains along the roads or outside homes and unprotected grain storage within homes. These could aid an enhanced direct rodent-man contact and contamination of food sources by the secretions of infected rodents [9]. Diseased patient can also be a source of secondary transmission to another person [27]. The exposed persons thereafter carry the virus into the community where the cycle of transmission continues with direct unprotected person to person contact [13].

Immuno-compromise and pregnancy can enhance the acquisition and establishment of the disease, and may increase mortality rate [27]. 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 new-born (in 90% of cases) or maternal death. Serious congenital defects or anomalies are common expressions in children born with the infection [9]. Some trans-border cases have been reported involving adjoining countries with some fatalities.

8. SYMPTOMS

In about 80% of infections, in endemic areas, the symptoms are mild and are undiagnosed. Mild symptoms include slight fever, general malaise and weakness, and headache [9]. In few cases, however, disease may progress to more serious symptoms including hemorrhaging (in gums, eyes, or nose, as examples), respiratory distress, repeated vomiting, facial swelling, pain in the chest, back, and abdomen, and

shock [26]. Generally, incubation period ranges from 6 to 21 days. Three stages are recognized; these are - acute, that marks the onset; hemorrhagic, involving some bleeding and neurologic, which expresses deafness, among other symptoms [5]. The virus can be detected in the urine and semen of infected patient for up to three months [5].

The patient may die within two weeks after symptom onset due to multi-organ failure. On the average, about 20% of patients hospitalized die from the illness. Ideally, only about 1% of all infections result in death [28].

9. DIAGNOSIS

In most Lassa fever endemic areas, there are serious challenges regarding the laboratory diagnosis and confirmation of the disease [9]. Since the symptoms are varied and nonspecific, clinical diagnosis is often difficult. The spatial and epidemiological mapping of vulnerability coupled with laboratory biomarkers (immunoglobulin M (IgM) antibody) or related molecular assays are useful tools in early detection, virus isolation and confirmation of positive case [29].

Diagnosis can be by using enzyme-linked immune-sorbent assays (ELISA), which detect IgM and IgG antibodies as well as the antigen [14]. The reverse transcription-polymerase chain reaction (RT-PCR) procedure is used in the early stage of disease [30, 31]. Generally, this disease requires a biosafety level 4 - equivalent containment during laboratory diagnosis to prevent the acquisition and spread of the disease in the laboratory and hospital environment [14].

10. INTERVENTION STRATEGIES

10.1. Treatment

Like other severe hemorrhagic fevers, clinical management of Lassa fever entails purely supportive treatment. The intention is strictly volume resuscitation from diarrhea and vomiting. It is also targeted at electrolyte balance and respiratory support [26]. The only tested agent with a proven therapeutic effect in patients is the broad-spectrum nucleoside (guanosine) analogue, ribavirin and it is considered the current drug of choice. The exact mechanism of action of ribavirin has not been fully understood, but its incorporation into the RNA strand, leads to lethal mutagenesis of progeny genomes [32]. LV can be inactivated by chemical agents such as 0.5% sodium hypochlorite, 0.5% phenol and 10% formalin [33].

While investigation goes on to develop an acceptable vaccine, increasing community awareness and health education and effective waste management programme are recommended. These can be combined with improved water, sanitation and hygiene (WASH) program [14]. There is also an urgent need to link disease ecology with enhanced surveillance data across Sub-Saharan Africa [28]. Sometimes, however, this approach may have the drawback on inconclusive and paucity of data. A reliable map across national and regional divides with respect to sero-prevalence, reservoirs and case mortality profile, is desirable [5].

Active incorporation of robust and sustainable integrated disease surveillance and response (IDSR) scheme into routine laboratory diagnostic and epidemiologic surveillance services, is critical [14]. Also a community- based social mobilization initiative has been recommended by the WHO [34]. The decentralized

Africa Centres for Diseases Control and Prevention and regional public laboratory network is a welcome step in emergency surveillance, as it contributes to global health security. Moreover, investing in early detection and use of rapid diagnostic tools are core in remote rural settings where vulnerable communities dwell with the rodents as living partners. A well-co-ordinated surveillance capacity building programs will ensure effective and concurrent trans-disciplinary outbreak response actions and clinical case management regime. There is the need to strengthen community health centres, data sharing access and operational logistics in guiding official state policies [35].

At present, Nigeria has embarked on an integrated infectious diseases prevention and control strategy. It is believed that it would be made an important component of the nation's primary healthcare program. Every confirmed epidemic must attract an immediate response [34]. Personal protection equipment and other standard dress codes and ward isolation should be strictly adhered to as a preventive measure [35].

Awareness programmes on the swift recognition of early warning signs, and quick response aimed at prevention, capacity building among health care personnel as well as prompt availability of solutions like vaccines will guarantee an enhanced intervention during epidemics. According to NCDC [32], the following are generally supplied to areas at risk in Nigeria: medications and disinfectants (ribavirin injection, ribavirin tablet, medicine for supportive care, ringers lactate, metronidazole (flagyl), oral dehydration salts, personal protective and biosafety materials (boots, gloves), outer gown, plastic apron, mask, head cover, protective eyewear and bed nets sprayers, plastic sheets meant for mattress and barriers, kerosene lamp, body bags, buckets and containers, electric generator and laboratory supplies. The list also includes needles (different sizes), syringes, tubes (vacutainers) for blood collection, antiseptics [14].

It is important to note that a decisive approach is recommended for effective intervention. Rapid test kits that focus on precise qualitative laboratory analysis to confirm suspected cases must be accessible. The detection and confirmation of this and other emerging viral diseases require Biosafety level 4 (BSL-4) facilities across the world, but very few exist in Africa [30]. Some African countries may not even have any. Nigeria has five Lassa fever diagnosis laboratories with the Irrua Specialist Hospital considered to be fully functional as most suspected cases are sent there for laboratory confirmation. Although knowledge on Lassa fever in Nigeria is high among medical practitioners, low access to affordable and simple tests for timely confirming the disease in the region is observed [27]. These situations may further prolong the time between suspecting a case and confirming it, with its attendant consequences on the disease outbreak and control efforts [14].

10.2. Prevention

This includes measures like the institution of policies, task force, committees for surveillance, prevention and control at national and state levels. There is the need to improve the current state of medical practice if any meaningful and long lasting result will be achieved [3]. Health sensitization of the general public and particularly health workers is necessary [9]. Control of rodents by avoiding bush burning, setting traps in and around homes to reduce rat population, blockage of all rat hideouts, and avoidance of contact with rats such as rat hunting for consumption are also attractive measures. Individual and community preventive

strategies include keeping good and healthy personal hygiene, cleaning of homes and surrounding environment, and effective waste disposal. Road side air drying, should be avoided. All food items should be stored in containers safe from rats. Hospital based prevention should focus on adherence to control measures, isolation of infected patients, barrier nursing of infected patients, and the application of personal protective equipment (PPE) when working with secretions of infected patients [30]. New candidate vaccines like VSV-EBOV-GPC has been reported to have promise, even when it is on record that in 1987, the first successful Lassa virus vaccine that used a recombinant vaccinia virus, was described [36]. It is recalled that viral hemorrhagic antibodies have earlier been reported in Nigeria [37]. The WHO advises healthcare personnel to observe basic rules of reasonable and healthy engagement as they carry out their duties [24]. Tobin et al. [38] stressed the need to embrace measures which are affordable in dealing with the infectious rodents.

12. CONCLUSION AND RECOMMENDATIONS

Lassa fever is a very important zoonotic disease of poverty and compromised environmental hygiene with high endemicity. It remains a public health burden on vulnerable populations in Nigeria. Proactive measures to control this menace should target adequate education of health care professionals, public health enlightenment campaigns, and advocacy. It is also necessary to focus on increasing the number of infectious disease control centres with diagnostic and research laboratory services, as well as treatment facilities across Nigeria.

Efficient and sustainable leadership commitment in the health sector and involvement of vulnerable population is crucial in strengthening an integrated outbreak surveillance and intervention. Collaborative multi-sectorial initiatives are needed to design a reservoir(s) map which is tailored towards designing a proactive solution against this zoonotic disease threats in Nigeria. Furthermore, fast-tracking Research and Development for more sensitive diagnostic tools and effective therapeutic development is a recommended global measure. Community engagement and respect for personal hygiene remain an attractive prevention strategy. This will guarantee avoidance of rats at all times. With renewed awareness and capacity building, Nigeria will be Lassa virus-free, soon.

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Authors Contributions: SEA initiated the topic and made a seminar presentation. SOF encouraged him to present the review in a manuscript form. Both authors contributed to and read final manuscript.

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