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Lassa Fever in Nigeria

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Authors' contributions

This work was carried out in collaboration between both authors. Author OJA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OJA and AMI managed the analyses of the study. Author AMI managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

World Health Organization defines Lassa fever as a viral haemorrhagic fever that is transmitted to people through contact with food or household items contaminated with rat pee or defecation. Secondary transmission occurs in human to human through direct contact with the blood, discharges, organs and other body liquids of infected person's which greater percentage are of nosocomial infections. This acute viral hemorrhagic fever brought about by the Lassa infection which was first described in 1969 and named after the town of Lassa (Yedseram River valley), in Borno State, Nigeria. The Lassa fever is a member of are naviridiae virus family like Ebola; clinical cases of the disease had been known for longer than three decades but had not been associated with a viral pathogen. The virus targets antigen-presenting cells, (mainly dendritic cells) and endothelial cells majorly. ELISA test for antigen and IgM antibodies gives 88% sensitivity and 90% specificity of the virus in cells. High clustering of incidence near high intensity sampling is the reason for inadequate view at the impact of Lassa in Nigeria. All persons suspected to have contracted Lassa fever infection should be quarantined in isolation facilities, body fluids and feaces of persons infected with Lassa virus should be properly disposed. Ribavirin has been approved for the treatment of Lassa fever, but prevention is still the best. Rodents should be kept out of homes and food supplies. Effective personal hygiene is will go a long way in eradicating this disease, also grains and other foodstuffs should be stored in rodent-proof containers.

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1. INTRODUCTION

1.1 Lassa Fever or Lassa Hemorrhagic Fever (Lhf)

This acute viral hemorrhagic fever brought about by the Lassa infection which was first described in 1969 and named after the town of Lassa (Yedseram River valley), in Borno State, Nigeria [1]. Lassa fever belongs to the family arenaviridae. Lassa fever is endemic in West African nations, and causes over 500,000 cases every year, with around more than 5,000 deaths [2]. The essential animal host of the Lassa infection is the Natal Multimammate Mouse (Mastomys natalensis), a animal indigenous to the greater part of Sub-Saharan Africa [2]. The infection is most likely transmitted by contact of stored grains or food with the faeces or pee of animals in households. Given its high rate of occurrence, Lassa fever has become a significant issue in the West African region [3].

1.1.1 Lassa virus

Lassa infection (LASV) is an Old-World arenavirus that causes Lassa hemorrhagic fever, [4] a sort of viral hemorrhagic fever (VHF) in human and non-human primates. Lassa infection is an emerging infection and a selective agent, it requires Bio-safety Level 4- containment. It is endemic disease in West African nations [5]. There are no certified vaccines against Lassa fever for humans use [4].

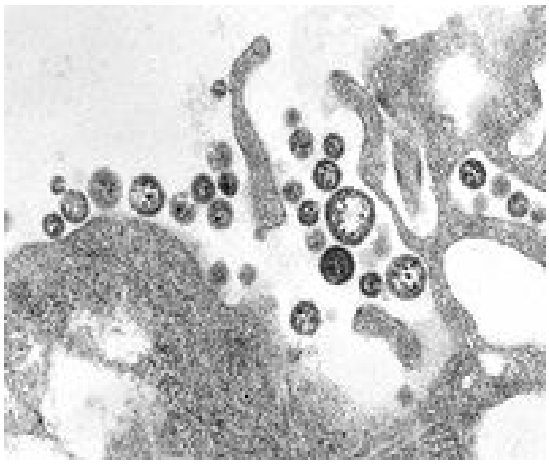

Plate 1. Lassa virus as seen under scanning electron microscope
Source: [6]

1.1.2 Lassa virus classification

Group: Group V (−) ssRNA)
Order: Unassigned
Family: Arenaviridae
Genus: Arenavirus
Species: Lassa virus

1.1.3 Virology

Lassa viruses are enveloped, single-stranded, bi-segmented, ambisense RNA viruses [7]. Their genome is enveloped in two RNA segments that code for two proteins each, one in each sense, for a total of four viral proteins [4]. The large segment encodes a small zinc-binding protein (Z) that controls transcription and replication, (8) and the RNA polymerase (L). The small segment encodes the nucleoprotein (NP) and the surface glycoprotein precursor (GP, also known as 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 [9]. Lassa fever causes hemorrhagic fever frequently shown by immune suppression. Lassa virus replicates very rapidly, and demonstrates temporal control in replication [9]. The first replication step is transcription of mRNA copies of the negative- or minus-sense genome. This ensures required supply of viral proteins for subsequent steps of replication, as the NP and L proteins are translated from the mRNA [7]. The positive- or plus-sense genome then makes viral complementary RNA (vcRNA) copies of itself. The RNA copies are 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 [7]. This temporal control allows the spike proteins to be produced last, and therefore, delays recognition by the host immune system. Nucleotide studies of the genome have shown that Lassa virus has four lineages in which three are found in Nigeria and the fourth in Guinea, Liberia, and Sierra Leone [7]. The Nigerian strains seem likely to have been ancestral to the others but additional work is required to confirm this claim [7]. The Lassa virus gain access to host cell by means of the cell-surface receptor i.e the alpha-dystroglycan (alpha-DG), [10] a versatile receptor for proteins of the extracellular matrix. It shares this receptor with the prototypic Old-World arenavirus lymphocytic choriomeningitis virus. Receptor recognition

depends on a specific sugar modification of alpha-DG by a group of glycosyltransferases known as the LARGE proteins.

1.2 Pathogenesis

Lassa fever is usually caused by the Lassa virus. The symptoms include flu-like illness characterized by fever, general weakness, cough, sore throat, headache, and gastrointestinal manifestations. Hemorrhagic manifestations include vascular permeability [4]. Upon entry, Lassa virus infects almost all tissue in the human body. It starts with the mucosa, intestine, lungs and urinary system, and then progresses to the vascular system [6]. In Lassa fever infection, gastrointestinal symptoms, including vomiting and abdominal pain have been found to be fairly common [11,12]. Less commonly there may be bleeding from the mouth or gastrointestinal tract [13]. Individuals who are at a higher risk of contracting the infection are those who live in rural areas where Mastomys are discovered, and where sanitation is not prevalent. Infection typically occurs by direct or indirect exposure to animal excrement through the respiratory or gastrointestinal tracts [13].

The major targets of the virus are antigen-presenting cells, mainly dendritic cells and endothelial cells. Generally, when a pathogen gain access into a host, innate defense system recognizes the Pathogen-associated molecular patterns (PAMP) and activates an immune response [6]. One of the mechanisms detects double stranded RNA (dsRNA), which is only synthesized by negative-sense viruses. 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 [6]. Translocated transcription factors activate expression of interferons α and β, and this initiate adaptive immunity. NP encoded in Lassa virus is essential in viral replication and transcription, but it also suppresses host innate IFN response by inhibiting translocation of IRF-3. NP of Lassa virus is reported to have an exonuclease activity to only dsRNA [14]. The NP dsRNA exonuclease activity counteracts IFN responses by digesting the PAMPs, thus allowing the virus to evade host immune responses [14]. Lassa virus is zoonotic, in that it spreads to man from rodents, specifically multi-mammate rats (*M. natalensis*). This is the most common rodent in equatorial Africa, ubiquitous in human households and taken as food in some areas. The rat infection is in a persistent asymptomatic state. The virus is shed in their excreta (urine and feces), which can be aerosolized. In fatal cases, Lassa fever is characterized by impaired or delayed cellular immunity leading to fulminant viremia [9].

Plate 2. Mastomys *natalensis*, the natural reservoir of the lassa fever virus
Source: [9]

Infection in humans typically occurs via exposure to animal excrement through the respiratory or gastrointestinal tracts [15]. Inhalation of tiny particles of infective material (aerosol) is believed to be the most significant means of exposure. The infection can also be acquired through broken skin or mucous membranes that are directly exposed to infective material. Transmission from person to person has also been established, presenting a disease risk for healthcare workers. Frequency of transmission via sexual contact has not been established [15].

1.3 Vector

The rat specie *Mastomys natalensis* as been a major reservoir host for the Lassa virus because of congenital neonatal infection, which results in rats with long-lasting and or lifelong infection [16]. The mechanism of infection play a major role with no break in the natural chain from virus to host species. The rats might be asymptomatic to the disease, but they shed the virus freely in urine, faeces and their saliva. Transmission occurs via direct contact with rat urine, faeces, and saliva; via contact with excretion or secretion-infected materials; or via ingestion of excretion-contaminated food. Victims can also be infected via skin breakage and via mucous membranes from aerosol transmission from dust-borne particles. In some areas, the rodents are consumed as food, thereby providing additional exposure to the infected rat blood, as well as allowing ingestion of potentially contaminated meat. Laboratory workers become infected usually from contact with rodent saliva [16].

2. PREVALENCE

The prevalence of the infection can be assessed by prevalence of antibodies to the virus in populations of Sierra Leone 8–52%, Guinea 4–55% and Nigeria approx. 29% [17]. Studies show more than a million cases of Lassa fever per year in West Africa, with about 5,000 fatalities recorded [18]. Positive results test of Lassa virus was detected in 25 of 60 (42%) patients in Northern and Central Edo. [19]. The Lassa virus affects adults and children similarly with no respect for age. Every age grouo can be at risk of contracting the virus. [18]. Just like hemorrhagic fevers, Lassa fever can be transmitted through aerosol, contact and droplet transmission. Transmission through breast milk has also been observed [20].

2.1 Symptoms of Lassa Fever

The incubation period of Lassa fever ranges from 6–21 days. When the disease is symptomatic, It is usually gradual, starting with fever, general weakness, and malaise. After a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, and abdominal pain may follow. In severe cases facial swelling, fluid in the lung cavity, bleeding from the mouth, nose, vagina or gastrointestinal tract and low blood pressure may develop. Protein may be noted in the urine, shock, seizures, tremor, disorientation, and coma may be seen in the later stages [21]. Deafness occurs in 25% of patients who survive the disease. Hearing returns partially after 1–3 months in half of these cases, transient hair loss and gait disturbance may occur during recovery. Death usually occurs within 14 days of onset in fatal cases. The disease is especially severe in late pregnancy period, with maternal death and or fetal loss occurring in more than 80% of cases during the third trimester [16].

2.2 Transmisson

Lassa virus is known to spreads to humans through zoonotic transmission, specifically the natal multimammate rat or African rat *M. natalensis* [22]. The multimammate rat which can rapidly replicate in large number tends to colonize human settlements increasing the risk of transmission [23]. The virus is probably transmitted by contact with the faeces or urine of animals accessing grain stores in homes [22]. The people who lives in rural settings are at higher risk of contracting the infection due to poor sanitation [3]. Infection typically occurs by direct or indirect exposure to animal excrement through the respiratory or gastrointestinal tracts [3]. Aerosol transmission is believed to be the most significant means of exposure. Health workers caring for Lassa fever patients without proper medical hygienic standard of case management, increase the means of transmission. The virus is present in urine for three to nine weeks after infection, and it can be transmitted in semen for up to three months after becoming infected [3].

2.3 Diagnosis

There are numerous laboratory investigations that may be performed to diagnose the disease and assess its causes and complications. ELISA

test for antigen and IgM antibodies gives 88% sensitivity and 90% specificity for the presence of the infection. Other laboratory findings in Lassa fever include lymphopenia (low white blood cell count), thrombocytopenia (low platelets), and elevated aspartate aminotransferase (AST) levels in the blood [1]. Lassa fever can also be found in cerebrospinal fluid [24]. In West Africa, where Lassa is most prevalent, it is difficult for scientist to diagnose due to the absence of proper equipment for diagnosis. [25]. In cases with abdominal pain, diagnoses in endemic countries are often made for other illnesses, such as appendicitis and intussusceptions, delaying treatment with Ribavirin [1].

2.4 Prognosis

Over 15% of hospitalized Lassa fever patients will die from the illness. The overall mortality rate is estimated to be 1%. The mortality rate may rise as high as 50% during epidemics. The mortality rate is greater than 80% when it occurs in pregnant women during their third trimester; fetal death also occurs in nearly all those cases. Abortion decreases the risk of death to the mother [9]. Some survivors experience lasting effects of the disease, and can include partial or complete deafness [16]. The treatment of Lassa fever with the use of antiviral drug ribavirin has proven to reduce the fatality rate recorded [17].

2.5 Epidemiology

The study of the epidemiology of Lassa fever is complicated due to lengthy incubation period, which may be up to three weeks [26]. Lassa fever may affect spatial clustering of the disease by limiting the understanding of the incidence and distribution of the disease. The spatial clustering for this disease is still in development as a lack of easy-available diagnosis, limited public health surveillance infrastructure, and high clustering of incidence near high intensity sampling make for an incomplete look at the impact of Lassa in Nigeria [26]. It was recorded that over three million were infected in a year, with up to 5,000 fatalities per year in West Africa alone [27]. The first occurrence was in 32-year-old pregnant lady with bleeding disorder who died after a stillbirth. Post-mortem examination confirmed she died of Lassa fever. In January 2016, an 18-year-old student nurse, who was admitted with history of fever, headache and sore throat was suspected and confirmed to have lassa fever. Throughout the outbreak Ekiti state recorded 10 cases [28]. The 10 cases were detected from four LGAs across the state – Ado LGA [4], Ido-Osi LGA [3], Emure LGA [2] and Ikere LGA [1,28]. Ekiti state is one of the 3 states in Nigeria that carries the burden of Lassa Fever [17]. In January, 2013, 21 cases were reported in Ose L.G.A. of Ondo state. There were 19 confirmed cases, one person was recorded dead in Ose L.G.A. of Ondo State in January 2018. In 2012 at Egbeda Local government, there were 2 cases of Lassa fever virus. One confirmed and one suspected case, both were male age 32 and 28. Only one fatality was recorded, there is no linkage between the confirmed and suspected case [29]. In 2016, an eight-month-old named Aishat was infected. It was confirmed at UCH Ibadan [29].

3. TREATMENT

All persons suspected of Lassa fever infection should be admitted to isolation facilities and their body fluids and excreta properly disposed. Early and aggressive treatment using Ribavirin was pioneered by Joe McCormick in 1979 after extensive testing, it was determined that early administration is critical to success. Additionally, Ribavirin is almost twice as effective when administered intravenously as when taken orally [30]. Ribavirin is a prodrug which appears to interfere with viral replication by inhibiting RNA-dependent nucleic acid synthesis, although the precise mechanism of action is unclear [31]. The drug is relatively expensive in West African states. Fluid replacement, blood transfusion and fighting hypotension are usually required. Intravenous interferon therapy has also been used [31]. When Lassa fever infects pregnant women late in their third trimester, it is necessary to induce delivery for the mother to have a good chance of survival [32]. This is because the virus has an affinity for the placenta and other highly vascular tissues [30]. The fetus has one in ten chance of survival; hence focus is always on saving the life of the mother [33]. After delivery, the patient should receive the same treatment as other Lassa fever patients. Research is ongoing for possible vaccine for Lassa fever with multiple approaches showing positive results in animal trials [16].

4. PREVENTION

Control of the *Mastomys* rodent population is not feasible. Rodents should be kept out of homes and food supplies, effective personal hygiene should be encouraged, grain and other foodstuffs should be stored in rodent-proof containers, and

garbage are better disposed of far from the home to help sustain clean households. The use of personal protective equipment such as Gloves, masks, laboratory coats, and goggles are advised while in contact with an infected person, to avoid contact with blood and body fluids [19]. These issues in many countries are monitored by a department of public health. In less developed countries, these types of organizations may not have the adequate means to effectively control outbreaks [19]. Researchers at the United States Army Medical Research Institute of Infectious Diseases facility, where military biologists study infectious diseases are working on a prospective vaccine for lassa fever [19]. They have developed a replication-competent vaccine against Lassa virus based on recombinant vesicular stomatitis virus vectors expressing the Lassa virus glycoprotein. After a single intramuscular injection, test primates have survived lethal challenge, while showing no clinical symptoms [34].

The use of standard precautions is recommended with all patients in a healthcare environment [35]. This includes a minimum level of standard precautions for use with all people regardless of their infection status, routine handwashing practices, safe handling and disposal of used needles and syringes, and intensifying standard precautions. It also includes VHF isolation precautions when needed [35]. Limited supplies and resources may prevent a health facility from using all the standard precautions all the time. However, health facilities should establish and maintain a basic, practical level of standard precautions that can be used routinely with patients in their health facility [35]. This requires a source of clean water, routine hand washing before and after any contact with a person who has fever, and safe handling and disposal of sharp instruments and equipment [35]. Washing hands with soap and water eliminates microorganisms from the skin and hands. This provides some protection against transmission of Lassa fever and other diseases [35]. This requires at least soap cut into small pieces, soap dishes with openings that allow water to drain away, running water or a bucket kept full with clean water, a bucket for collecting rinse water and a ladle for dipping, if running water is not available, and one-use towels [35]. The hand washing technique that is recommended is to place a piece of soap in the palm of one hand, wash the opposite hand and forearm, rub the surfaces vigorously for at least 10 seconds, move soap to the opposite hand and repeat, use clean water to rinse both hands and then the forearms, dry the hands and forearms with a clean one-use towel, or let rinsed hands and forearms air-dry [35]. Reusable needles and syringes are not recommended. If reusable needles and syringes are used, clean, disinfect and sterilize them before reuse. Needles and syringes used with VHF patients require special care. Cleaning staff should wear two pairs of gloves when handling needles and syringes used with any patient with a known or suspected Lassa fever [35].

5. CONCLUSION

The Lassa fever outbreak has provided a crucial opportunity to reveal challenges and improve preparedness for managing subsequent outbreaks. Nevertheless, close monitoring, active case search, contact tracing, laboratory support and disease awareness (both in community in general and specific training for health care workers) should continue. Infectious diseases control department should ensure and implements guidelines for control of Lassa fever during epidemic. These guidelines include implementation of social distancing in social gathering, self-isolation of individuals exposed to positive cases and quarantine of individual tested positive to the virus causing the fever.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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