

Review paper

Epidemiological Trend of Lassa Fever and Insight for the Control of Future Outbreaks in Nigeria

This review provides an overview of pattern of the spread of Lassa fever infection and the need to guide against the nosocomial transmission whenever patients with symptoms of fever are admitted to the hospital in Nigeria.

Abstract

Lassa fever is endemic and fast becoming hyper-endemic in Nigeria. Lassa fever affects the largest number of people, creating a geographical network of endemic foci encompassing a population of perhaps 180 million from Guinea to Nigeria. The causative agent is an enveloped, single-stranded, bi-segmented RNA virus belonging to the arenaviridae family. Lassa fever presents signs and symptoms indistinguishable from those of febrile illnesses such as malaria and other viral haemorrhagic fevers such as Ebola. Clinical diagnosis of Lassa fever is difficult however it should be suspected in patients showing fever with temperature ($\geq 38^{\circ}\text{C}$) not responding adequately to antimalarial and antibiotic treatments. Laboratory diagnosis by serological and molecular techniques is reliable although very expensive. Frequent human exposure to the virus is therefore possible due to the human population explosion in the endemic area and therefore given opportunities for infection with this virus, and subsequently the disease. Significantly, 15-20% of patients infected with Lassa fever will die hence this necessitates the need to prevent the epidemic. There is higher risk of death for infected pregnant women and neonates. It is important to know that about one-third of those who survive may have mild to severe degrees of deafness, and in many cases the hearing loss is permanent. The pattern of Lassa fever outbreaks in Nigeria over the years is worrisome and increasingly becoming more worrisome with frequent and widening geographical spread. For now, there is no vaccine; therefore, public awareness and advocacy are vital in educating and sensitizing the citizenry on the risk associated with overcrowding and unhygienic practices both in our communities and health institutions.

Keywords: *Lassa virus, haemorrhagic fever, laboratory diagnosis, endemic, Nigeria*

Introduction

Lassa fever is an acute viral haemorrhagic illness caused by the arenavirus commonly referred to as Lassa virus, which is endemic in West Africa. This disease condition can be severe and death occurs in around 15–20% of severe hospitalized cases. It was first described in West Africa in the 1950s until the virus was later isolated 1969 (1). The pathogen was identified in 1969 when three American nurses became infected in Lassa, a village in Niger State, Nigeria (2). The virus responsible for the disease is an enveloped bi-segmented negative sense RNA virus from the Arenaviridae family. The reservoir of Lassa virus is a multimammate rat, a peridomestic rodent widely distributed across sub-Saharan Africa.

Arenaviruses cause silent and persistent infection in rodents, and their origin is thought to date back to the evolution of different rodent species, perhaps as much as 9 million years ago (3). Accidental human infection, therefore, must have been happening for as long as virus infected rodents and humans shared habitats. The principal risk to humans from Lassa virus is that the natural host, a very small multimammate African rat, *Mastomys natalensis*, has adapted to a peridomestic life in village houses in West Africa (4). Accidental human exposure to the virus is therefore frequent. With the human population explosion in the endemic area over the past 50 years or so, the opportunities for infection with this virus, and thus disease, have increased exponentially.

Among the haemorrhagic fever infections, Lassa fever affects the largest number of people, creating a geographical patchwork of endemic foci encompassing a population of perhaps 180 million from Guinea to Eastern Nigeria (5). The co-speciation of arenaviruses and rodents has recently been confirmed by molecular analyses. Using a sequence near the 3k end of the nucleoprotein gene, analysis confirms the historical division of arenaviruses (originally based on geographical distribution and antigenic typing) into Old World (LCMV, LASV), which includes Lassa virus, Mopeia, Lymphocytic Choriomeningitis Virus (LCMV) and New World (Tacaribe complex) viruses, which include at least four viruses highly pathogenic for humans (6). The LCMV, LASV complex viruses are monophyletic with three distinct lineages, one of which contains Lassa, Mopeia and Mobalaviruses (6).

Furthermore, Mopeia comes from Southern Africa and Mobala from Central Africa, and both are carried by related *Mastomys* species (7). Both can infect humans, but are apparently unable to cause significant clinical disease. Among the South American arenaviruses, pathogenicity for

humans does not appear to be monophyletic; suggesting that virulence in arenaviruses is the result of independent evolutionary events (8). The segment sequence analysis showed that virulence may not in fact be associated with the S segment. However, there are data suggesting that virulence determinants in LCMV are located on the L gene (9). Whatever the case, the ecological evidence is clear; virulence for primates is a chance event, unrelated to the natural history of the virus.

The Biology of the Virus

Lassa virus is an enveloped, single-stranded, bi-segmented RNA virus belonging to the arenaviridae family. Like other arenaviruses, Lassa virus lacks a conventional negative strand coding arrangement and the isolates of the virus differ in their genetic, serologic, and pathogenic characteristics (10). Lassa virus is spherical in shape and measures between 70 and 150 nm in diameter. It has a smooth surface envelope with T-shaped spikes measuring 7–10 nm and built with glycoprotein. The envelope encloses the genome which has helical nucleocapsid measuring between 400 and 1300 nm in length (11). Often, the interior contains electron dense granule identified as the host cell ribosome from where the name “arena” was derived meaning sand (4). Lassa virus can be inactivated in ultraviolet, gamma irradiation, heating from 56–100°C and pH range between 5.5 and 8.5 (12).

Chemical agents like 0.5% sodium hypochlorite, 0.5% phenol and 10% formalin will inactivate the virus (12). The single-stranded arenavirus genome consists of a small and a large (l) RNA fragment, sizes 3.4 and 7 kb respectively and the sRNA encodes the viral glycoprotein precursor protein (GPC) and the nucleoprotein (NP), while the RNA encodes the viral polymerase and a small, zinc-binding (Z) protein (13). New methods for full-length sRNA amplification are facilitating research efforts on the identification and molecular analysis of new arenaviruses or arenavirus strains (13).

The Vector

The natural hosts for the virus are multimammate rats (*Mastomys natalensis*), which breed frequently and are distributed widely throughout West, Central, and East Africa. The multimammate mouse, *Mastomys natalensis*, was originally identified as the primary host species for LASV (14). However, due to the poor understanding of the taxonomy of the genus, it is uncertain which species and particular subspecies serve as a reservoir for the virus (15). The

past studies addressing the importance of *M. natalensis* for the circulation of LASV in nature demonstrated that newborn animals inoculated intraperitoneally developed persistent asymptomatic infection (16).

Significant infectious virus titers were detected in many organs, tissues, and fluids including lymph node, liver, spleen, lung, blood, and brain up to 74 days after inoculation. Moreover, LASV was isolated from the urine and throat swabs of infected animals. No significant histopathological alterations were observed in these animals. Interestingly, adult *M. natalensis* infected with LASV also developed a disseminated infection that lasted up to 30 days. Some animals cleared the virus from some organs, but there was persistence in other organs up to 103 days when the study was terminated. The only consistent histopathological finding observed in adult animals was a moderate chronic meningoencephalitis (16). These data demonstrate that *M. natalensis* has an optimal pattern of infection and virus shedding for the maintenance of LASV in nature.

Historical Epidemiological Trend of Lassa Fever in Nigeria

Lassa fever is endemic and fast becoming hyper-endemic in Nigeria with higher rate of nosocomial associated cases (fig. 1). The prevalence of antibodies to the virus has been approximately 21% in the Nigerian population (17). Also, it is endemic in Liberia, Sierra-Leone and Guinea.(18) In Africa, Lassa fever sero-positivity has also been found in the countries like Central African Republic, Democratic Republic of the Congo, Mali, and Senegal(19) and therefore it is estimated that, the Lassa virus infects about 300,000 – 500,000 people per year with approximately 5,000 deaths annually.(4) Importantly, majority of the deaths reported in Nigeria so far have been among the youths, most especially health workers and pregnant women(18,20). Data from the Nigerian Federal Ministry of Health, Epidemiology Division revealed that Lassa fever has been occurring in more than 23 of the 36 States of Nigeria in which Ebonyi, Edo, Nassarawa and Plateau States are the most frequently affected of all States with reported cases of Lassa fever (18,19). In recent times, frequent outbreaks have also been observed in Adamawa and Taraba States.

The pattern of Lassa fever outbreaks in Nigeria over the years shows a worrying trend where outbreaks are increasingly becoming more frequent with widening geographical spread. Historically, it started at Lassa Village near Maiduguri, Borno State (1969), that same outbreak had a nosocomial spread to Jos, Plateau State (1969-1970). Thereafter, Lassa fever outbreaks occurred in Zonkwa, Kaduna State and Onitsha, Anambra State (1974), Pankshin, Plateau State (1976), Ekpoma, Aboh Mbaise, and Aba (1989), Ekpoma (endemic for Lassa) (1989 till date), Lafia (December 1993 to February 1994) Northern part of Edo State, including Ekpoma, Igarra, and Ibilo (2001 and 2004), Ebonyi and Ogun States (2005) Edo, Plateau, Kogi, Benue, Ondo, Nasarawa, Ebonyi (2007/2008), Edo, Nasarawa, Gombe, Kaduna, Plateau, Ondo, Lagos States and FCT(2009), Kaduna, Kebbi, Plateau, Taraba, Edo, Kogi, Ondo (2010) as shown in table 1.

Nigeria experienced its worst outbreak of the Lassa fever December 2011 to June 2012 which peaked during the month of February 2012. The outbreak involved the entire country affecting 41 LGAs in 23 States, with Edo, Taraba, Ebonyi, Rivers, Plateau and Yobe States being the most affected (Table 1). On the whole 937 cases and 95 deaths were recorded, with a Case Fatality Rate (CFR) of 10.14%. Out of the 937 cases 148 (15.7%) were laboratory confirmed. The confirmation was carried out by two laboratories located at the Lassa Research Institute, Irrua, Edo State and Lagos University Teaching Hospital, Idi-Araba Lagos.

Table 1: Epidemiological Pattern of Lassa Fever in Nigeria.

Town	State	Period Case Occurrence
Lassa	Borno	1969
Jos	Plateau	1969
Zonkwa	Plateau	1969 – 1970, 1974, 1975, 1976
Onitsha	Anambra	1974
Vom	Plateau	1975
Pankshin	Plateau	1976
Ekpoma, Aboh Mbaise	Aba	1989
Ekpoma	Edo	1989
Aboh-Mbaise and Owerri	Aba	1980

Ekpoma		1990 & 1992
Lafia	Edo	1993 – 1994
Ekpoma, Igarra and Ibilo		2001 & 2004
	Ebonyi & Ogun	2005
	Edo, Plateau, Kogi, Benue,	2007/2008
	Ondo, Nasarawa & Ebonyi	
	Edo, Nasarawa, Gombe,	2009
	Kaduna, Plateau, Ondo,	
	Lagos States and FCT	
	Kaduna, Kebbi, Plateau,	2010
	Taraba, Edo, Kogi & Ondo	
	Edo, Taraba, Ebonyi, Rivers,	Feb. 2011-June 2012
	Plateau and Yobe	

Data is from the Nigerian Federal Ministry of Health, Epidemiology Division

Epidemiology of Lassa Fever in West Africa

LASV was first isolated in 1969 from a missionary nurse who worked in a clinic in a small town, Lassa, in northeastern Nigeria (21). The nurse presumably acquired infection from an obstetrical patient residing in Lassa. She died approximately one week after the onset of symptoms. Subsequently, two more nurses that attended to the first patient contracted the disease, which was later named Lassa fever and caused the death of one of them. Infectious virus was isolated from all three cases (1). Incidentally, several countries of West Africa were identified to be endemic for LASV (22; 23). However, a serological survey among patients admitted with a history of fever, and missionaries that had experienced a febrile illness showed that LASV was also present in Ivory Coast, Mali, and Central African Republic (2). The notion that LASV was endemic in larger areas of West Africa was further supported by the results of investigation of an imported case of Lassa fever in Germany in 2000. During the incubation period, the index patient travelled through several countries, namely Ghana, Ivory Coast, and Burkina Faso, which were not considered to be endemic at that time. Later, cases of Lassa fever have been reported from Burkina Faso, Ivory Coast, Ghana, Senegal, Gambia and Mali (24).

The incidence of the disease, although highly variable depending on the geographical location (from 1.8% in developed to 55% in developing countries) indicates that most infections are mild or possibly even asymptomatic and do not result in hospitalization. This is also supported by findings indicating a high incidence of LASV-specific seroconversion, from 5% to 20% of the nonimmune population per year (4). Nosocomial outbreaks are associated with higher mortality rates ranging from 36% to 65% (25). However, serosurveillance studies in hospitals dealing with suspected Lassa fever cases showed that the hospital staff that routinely practiced basic hygiene measures had no higher risk of infection than the local population. Infection with LASV presumably occurs through contact with body fluids or excreta, or inhalation of aerosols produced by infected animals. Lassa fever is endemic in West Africa, where it probably kills several thousand people each year. With increasing spread of the virus there is the need to improve our understanding of this disease.

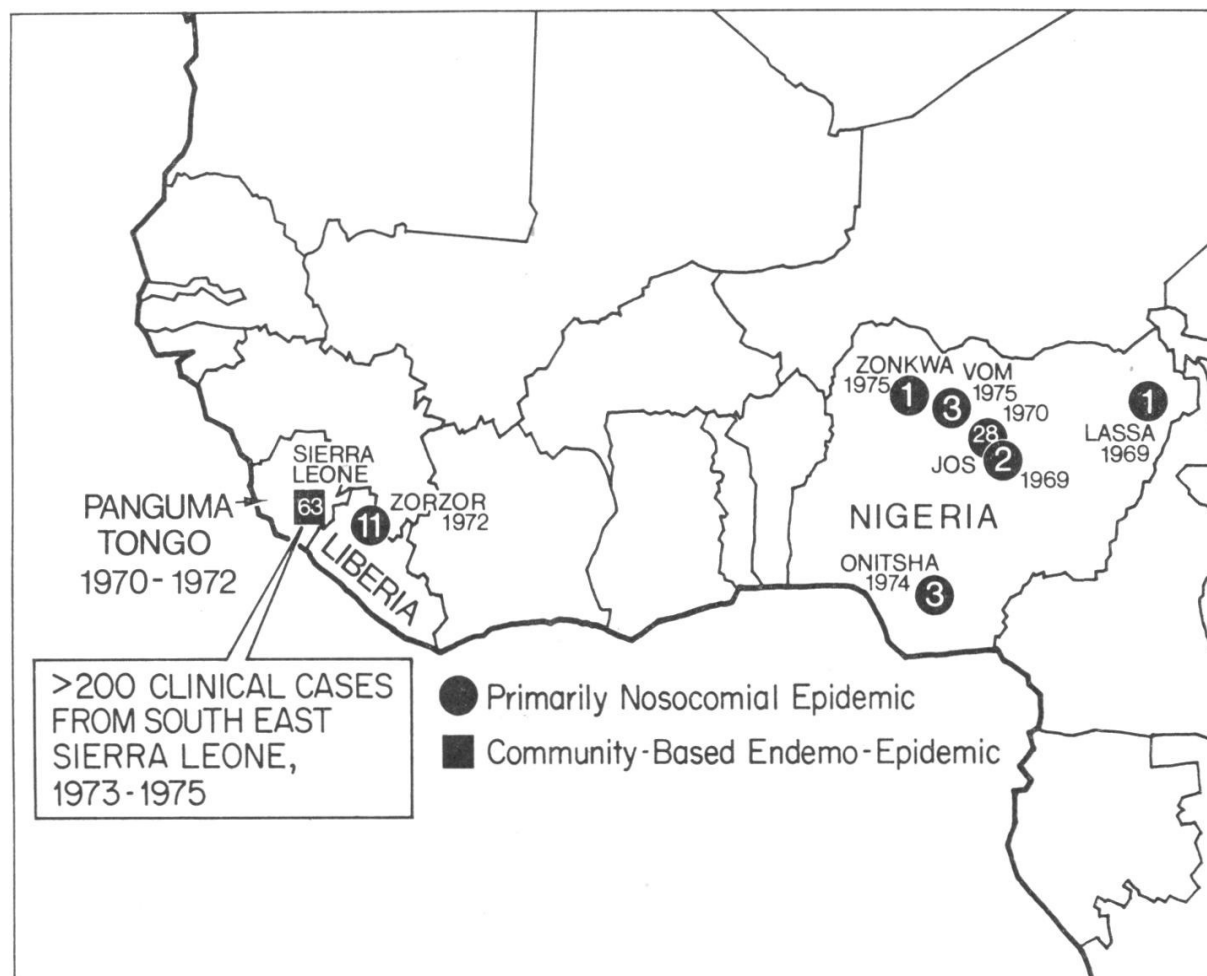


Fig. 1: Pattern of the disease transmission common in Nigeria (Adapted from 26).

Morbidity and mortality

Presentation of Lassa fever cases used to be highest during the dry season (January to March) while very few cases occur during the wet season (May to November). However, recent data from Kenema (1999-2002) showed that hospital admissions on Lassa fever cases were highest during the transition period from the dry to the wet season. This occurrence might be partly due to population movements overcrowding. Travel becomes increasingly difficult as the wet season progresses and may help to account for the decrease in number of cases later in the season. Until 1998 laboratory confirmation of diagnosis was available retrospectively (27). Most of the cases are usually wrongly diagnosed except when laboratory confirmation is employed.

Thus, these recent apparent changes in infection patterns must be interpreted with caution. People of all ages are susceptible. The disease is mild or has no observable symptoms in about 80% of people infected, but 20% have a severe multisystem disease. The incubation period is 6-21 days. The virus is excreted in urine for three to nine weeks from infection and in semen for three months (19). The extent of sexual transmission is unknown. Sensorineural hearing deficit is a feature of the disease: it was found in 29% of confirmed cases compared with none of febrile controls in hospital inpatients (28). In the general population, 81% of those who experienced sudden deafness had antibodies to Lassa virus versus 19% of matched controls. There is no apparent relation between the severity of viral illness, initial hearing loss, or subsequent recovery (28) Lassa fever was responsible for 10-16% of all adult medical admissions in 1987 in two hospitals studied in Sierra Leone and for about 30% of adult deaths (4) The case fatality rate in Kenema varied from 12% to 23% for the period 1997-2002. A recent case series showed low admission rates and high case fatality rates for people aged less than 18 years.

During pregnancy, high rates of maternal death (29%) and fetal and neonatal loss (87%) have been recorded (uterine evacuation improves outcome significantly), with 25% of all maternal deaths in Sierra Leone being due to Lassa fever (29) An estimate of the case fatality rate in the general population is 1-2%, much lower than in hospitalized cases, possibly as a consequence of differences in severity and the epidemiology of the disease, we estimate that the “at risk” seronegative population (in Sierra Leone, Guinea, and Nigeria) may be as high as 59 million, with an annual incidence of illness of three million, fatalities up to 67 000, and up to three million re-infections. Until a complete picture of Lassa fever is known, these are rough estimates. Comparable data are unavailable for the other countries where seropositivity has been recorded.

Clinical Course of Lassa Fever

While Lassa fever is mild or has no observable symptoms in about 80% of people infected with the virus, the remaining 20% have a severe multisystem disease. Approximately 15-20% of patients hospitalized for Lassa fever will die and this could cause panic with serious socio-economic consequences. The death rates are particularly high for pregnant women and their unborn babies. About one-third of those who survive may have mild to severe degrees of

214 deafness, and in many cases the hearing loss is permanent. During epidemics, Lassa fever case-
215 fatality rate may reach 50%.

216 **Symptoms of Lassa fever**

217 It takes between 6 and 21 days for an individual to fall sick after the Lassa fever virus enters
218 their body. Lassa fever starts with a gradual fever, a feeling of being ill and with body pain. The
219 fever typically does not respond to anti-malaria and antibiotic treatment. After a few days, the
220 patient may have sore throat, cough, chest and abdominal pain, headache, vomiting, diarrhoea,
221 dizziness, red eyes and swollen face and neck. Later in the illness (after 14 days) the person may
222 start to bleed spontaneously from the gums, in the stool, in urine, in the eyes or under the skin.
223 The person may also have fits and die. Although Lassa fever may start like Malaria, the fact that
224 it does not respond to any anti-malarial drug and the typical signs of sore throat and swollen face,
225 will warn of Lassa fever.

226 Lassa fever presents with symptoms and signs indistinguishable from those of febrile illnesses
227 such as malaria and other viral haemorrhagic fevers such as Ebola. It is difficult to diagnose
228 clinically but should be suspected in patients with fever ($\geq 38^{\circ}\text{C}$) not responding adequately to
229 antimalarial and antibiotic drugs. The most useful clinical predictors of Lassa fever are fever,
230 pharyngitis, retrosternal pain, and proteinuria for diagnosis; and fever, sore throat, and vomiting
231 for outcome (4) Complications include mucosal bleeding, sensorineural hearing deficit, pleural
232 effusion, and pericardial effusion(4). The outcome of Lassa fever infection is highly related to
233 the degree of viraemia, not the antibody response, and is worse with high levels of aspartate
234 aminotransferase.

235 The commonest interval between onset of symptoms and discharge was 17 days (half of the
236 patients were in hospital for 10 days) and between onset and death was five days (half died
237 within two days of admission). Delays between onset and admission resulted in most patients not
238 receiving ribavirin within the critical period of the first six days. These data add to the
239 uncertainty surrounding diagnosis and lethality.

240

241 **Surveillance and Disease Control**

Surveillance should identify all close contacts of the patients for three weeks after the start of illness, and a search initiated for unreported or undiagnosed cases (19). Three suspected areas of concern during the disease outbreak or occurrence are:

- i. The treatment of undiagnosed cases in hospitals where overcrowding and poor hygiene can spread the disease to other patients, staff, or visitors;
- ii. Cultural practices in some part of Nigeria that encourage sharing edible things and other materials.
- iii. Traditional burial ceremonies for infected corpses, with the possible risk of spread to many people.
- iv. It should be noted that all suspected cases should be admitted to isolation facilities and handled with adequate care because a lot of the outbreaks are hospital associated. Hospital transmission occurs through inadequate infection control measures.
- v. Strict isolation of cases and procedures for handling body fluids and excreta must be maintained (30).
- vi. Community awareness is vital in ascertain the knowledge, attitude and practice of adequate control of Lassa fever among the community and health workers.

Vaccine

Production of a combined, single dose vaccine against yellow fever and Lassa fever has been proposed (31). The cost and logistical problems of delivering it would be huge, particularly since fewer than 20% of districts in the countries studied achieve 80% uptake of childhood vaccination (30) Use for visitors from the United Nations, non-governmental organizations, and business communities might make it financially viable, even though it is the most expensive of the possible control strategies.

Treatment and Community Perspectives

Ribavirin and general support are required for the management of Lassa fever infection. It has been suggested that Ribavirin is more effective when administered intravenously than oral administration of the anti-viral drug. Early diagnosis will enable the commencement of the drug administration. It is known that if the drug is given within six days of incubation period, this may reduce deaths by 90%. Dehydration, oedema, hypotension, and poor renal function are common with infection therefore fluid replacement or the use of blood transfusion will be required though

has to be monitored carefully. Civil trade practice and migration disrupt agricultural cycles hence reduces farming activities and spread of rats. Migration enables overcrowding thereby stimulates the spread of communicable diseases. Adverse effect of the socioeconomic conditions in the developing countries affects the chances of getting healthcare immediately infection set up in an individual in the community. Cases may not be reported during the early stage of the infection which make the treatment difficult and subsequently exposes the healthcare workers to work hazards. This condition may be responsible for high death rate in hospital, nosocomial transmission to health-workers. Hence, the need for community constant awareness on the epidemic of Lassa fever becomes imperative.

Conclusion

The vectors of the virus live in close contact with humans and capable of shedding the virus in urine which result in contamination of unprotected food. Consumption of contaminated food is one of the likely mode of transmission. Rodents also serve as a food source in many regions and hunting of animals that are always in close contact with the rodents that serve as vector of the Lassa virus is an additional risk factor for Lassa virus transmission (32). Infected rodents remain carriers throughout their lives and can shed the virus through urine, saliva, and respiratory secretions. The virus can be isolated in the blood, feces, urine, and saliva of infected individuals. The speculation is that about 2 to 3 million cases of Lassa fever may occur across West African countries, causing a mortality of between 5000 and 10 000 each year. Therefore, the need for continuous surveillance becomes imperative in endemic region like Africa with Nigeria at the central focus. This will help in no small measures in controlling the scourge.

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