

**Epidemiological Trends of Lassa Fever Outbreaks and Insights for Future Control in
Nigeria**

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Abstract

The pattern of Lassa fever outbreaks in Nigeria over the years is worrisome and increasingly becoming more challenging with frequent and widening geographical spread. Lassa fever is endemic and fast becoming hyper-endemic in Nigeria. It affects the largest number of people, creating a geographical network of endemic foci encompassing a population of perhaps 180 million from Guinea to Nigeria. Lassa fever presents signs and symptoms indistinguishable from those of febrile illnesses such as malaria and other viral haemorrhagic fevers such as Ebola. 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. 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, cell culture and molecular techniques is reliable although very expensive. For now there is supportive treatment but no licensed vaccine yet; 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 in Nigeria and its environs. This review summarizes the trends and pattern of outbreaks of Lassa fever in Nigeria and other aspects of diagnosis and prevention including reasons for the lack of a vaccine and proposes plans to prevent future outbreaks

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

Literature Search

The literature search was based on PubMed, Embase, and Web of Science. The initial search term used was: Lassa/Lassa outbreaks/Lassa Epidemiology in Nigeria/Arenaviruses in West Africa/Lassa trends in Nigeria AND (Lassa infection/Lassa virus). Titles and abstracts were screened to exclude irrelevant publications.

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 reservoir of Lassa virus is a multimammate rat, a peridomestic rodent widely distributed across sub-Saharan Africa (3).

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 (4). 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 (5). 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. *Mastomys natalensis* species complex are widely distributed in sub-Sahara Africa but the ones harboring Lassa virus are autochthonous of West Africa and that's why Lassa still spreads only in West Africa and any case out of this niche (like the German cases) are regarded as secondary human-human transmission or prior exposure in the propagation foci (5).

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 (6). The co-speciation of arenaviruses and rodents has recently been confirmed by molecular analyses. Using a sequence near the 3kb end of the

nucleoprotein gene, analysis confirms the historical division of arenaviruses (originally based on geographical distribution and antigenic typing) into Old World (Lymphocytic Choriomeningitis Virus (LCMV), Lassa Fever Virus (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 (7). The LCMV, LASV complex viruses are monophyletic with three distinct lineages, one of which contains Lassa, Mopeia and Mobalaviruses (7).

Furthermore, Mopeia comes from Southern Africa and Mobala from Central Africa, and both are carried by related *Mastomys* species (8). 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 (9). 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 (10). 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 does not have a conventional coded arrangement which is negative when compared with other arenaviruses making the virus isolates unique or different in characteristics such as serology, genetics and in pathology (11). The shape of Lassa virus is spherical with a diameter between 70 and 150 nm. Its surface envelope is smooth and has 7-10 nm T-shaped spikes and inbuilt glycoprotein. Inside the envelope is the genome containing nucleocapsid with a length between 400 and 1300 nm (12). The electron dense granule is usually located internally referred to as host cell ribosome from which its name 'arena' which is interpreted as sand (4). The inactivation of Lassa virus can be done in ultraviolet, gamma irradiation, heating from 56–100°C with a pH ranging from 5.5 and 8.5 (13).

The virus can be inactivated chemical substances such as 10% formalin, 0.5% sodium hypochlorite and 0.5% phenol (12). The genome of arenavirus which is single stranded has a small and large (1) 3.4 and 7 kb respectively while the precursor of the viral glycoprotein (GPC)

is encoded by sRNA in addition to the viral polymerase and a small, zinc-binding (Z) protein encoded by the RNA (14). The research efforts are being facilitated by the newly introduced methods for full-length amplification for identification and molecular diagnosis of latest arenavirus(es).

Replication of the Virus

Arenaviruses begin their life cycle with attachment and entry of the virus into the cells (figure 1). A few strains such as Old World (OW) and New World (NW) clade C arenaviruses adopt α -dystroglycan (α DG) strains as their receptor primarily (15,16) (Figure 2). A universally expressed glycoprotein called Dystroglycan connects cells to the extracellular matrix (ECM). The Dystroglycan is made up of two non-covalently associated subunits, α DG and β DG which takes part in cellular function and virus attachment. The α -dystroglycan is an extracellular subunit whose role is associated with ECM proteins e.g. neurxins, agrin, perlecan and laminin. As virus infection takes place, the viral glycoprotein 1 subunit (GP1) ensures viral attachment to the α DG which helps internalize viral particles and convey it to the late endosomes. The β -dystroglycan a transmembrane protein β DG is a transmembrane protein joins with the cytoskeletal adaptor proteins and signaling molecules, but not needed for arenaviral infection and binding (17). Studies (16,17) have revealed that post-translational modification of α DG (a highly glycosylated protein) is required for viral binding. There is involvement of a lot of cellular enzymes in modification processes as well as cellular like-acetylglucosaminyltransferase (LARGE), LARGE2, putative glycosyl transferases protein O-mannosyltransferase 1/2 (POMT 1/2), protein O-mannose β 1,2-N-GlcNAc transferase 1(POMGnT1), fukutin, and fukutin-related protein (FKRP) (18). According to an *in vivo* study, the glycosylation is not vital for LCMV infection but may be as a result of mechanism of *in vivo* compensation or when an alternate receptor is used. There is joining of LCMV and LASV bind to the N-terminal and C-terminal domains of α DG in regions which overlap the laminin binding site (20), suggesting the competition with laminin for α DG binding (21). There is designing of small peptides which is based on the binding site residues of laminin and have been capable of causing the neutralization of these viruses (22). Fascinatingly, as the OW arenaviruses infects, there is downregulation of α DG from the cell membrane without affecting the precursor DG expression

This process is anchored by the viral GP targeting the interaction between DG and LARGE in the Golgi with ultimate disruption of α DG proper glycosylation. Nevertheless, the process may be highly significant in the viral release but the entry step may not be inevitable (18,23). Moreover, according to a previous report, both animal studies and human clinical data have proven high viral titers in the liver in spite of the fact that express α DG by hepatocytes has not been demonstrated (24).

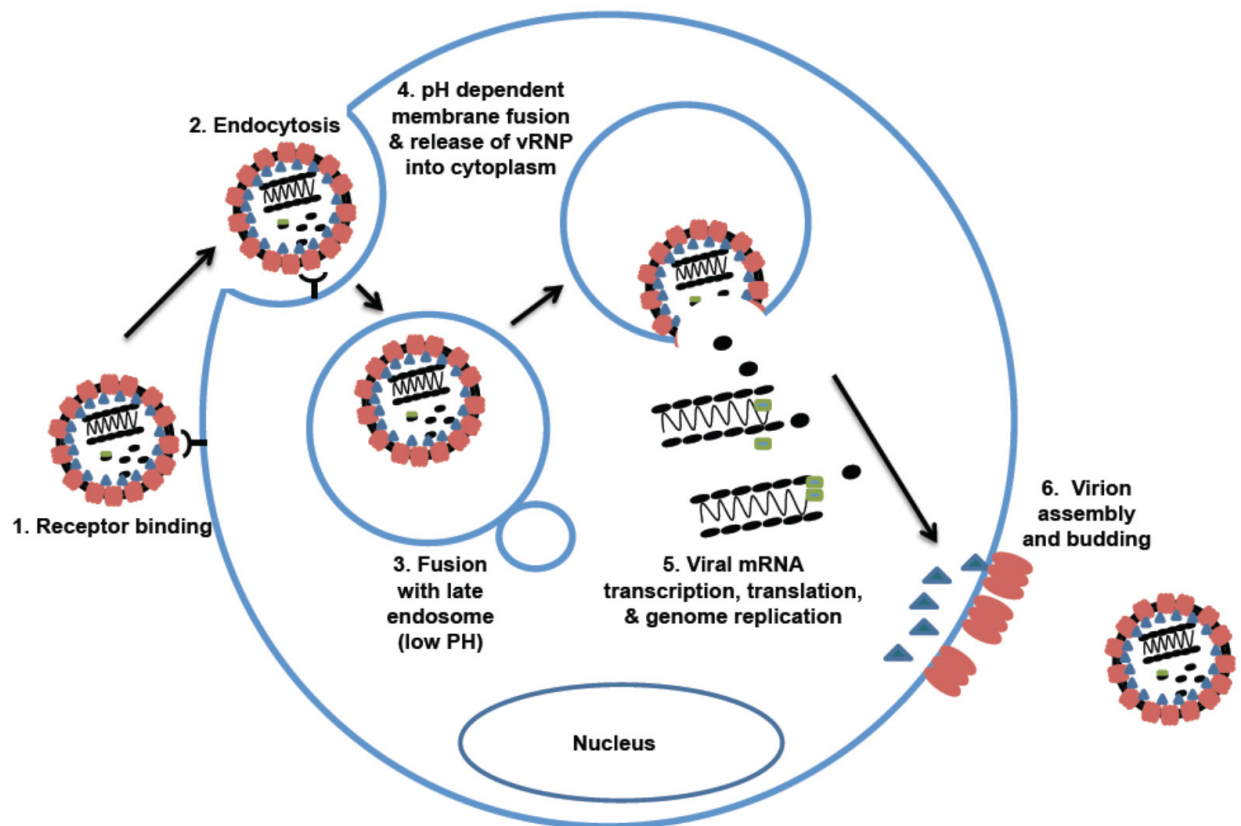


Figure 1: Arenavirus Life Cycle.

- i. There is mediation of cellular entry by various cellular receptors (α DG for OW and NW clade C arenaviruses; TfR1 for NW Clade B) (Fig 2). The entry of some viruses such as LASV may require a pH-dependent switch into intracellular receptor (LAMP1) found in the lysosomes.
- ii. The entry of the virus requires virus uptake into cells via receptor mediated endocytosis (OW arenaviruses: clathrin-independent, NW: clathrin-dependent).

- iii. The fusion of the virus takes place with the late endosome and viral ribonucleoprotein (RNP) which is released into the cytoplasm via a pH-dependent membrane fusion mechanism.
- iv. The replication of viral genome, transcription, and expression of protein firmly takes place inside the infected cells cytoplasm.
- v. The assembly and budding of the virion takes place in the plasma membrane of the infected cells.

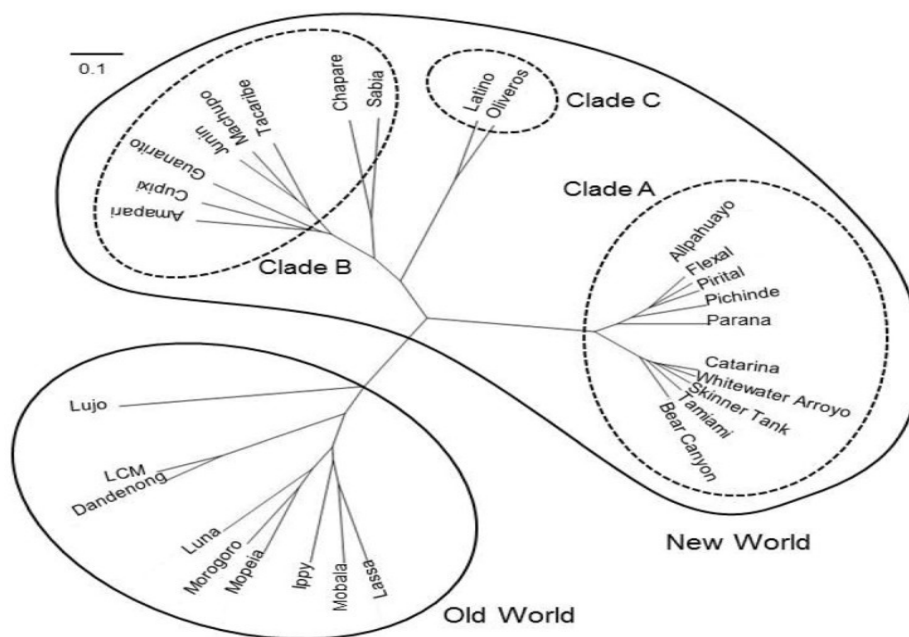


Figure 2: Phylogenetic tree of arenavirus Z protein. Amino acid sequences of Z protein were used for analysis.

Genetic Diversity of Lassa Fever Virus

Genetic diversity among LASV strains is the highest among the *Arenaviridae*, and causes a great challenge for vaccine development. Based on the partial NP sequences of 54 strains of LASV, Bowen et al. (25) showed that LASV isolates comprise four lineages, three of which are found in Nigeria, with the fourth found in Guinea, Liberia, and Sierra Leone. This diversity even raised concern about the status of LASV as a single species (26,27). The prototype LP strain isolated by Buckley & Casals in 1969 from Eastern Nigeria occupied the most basal lineage I. Strains

isolated from Southern Central and Northern Central Nigeria were placed in lineage II and III, respectively, and the largest group of strains from Guinea, Liberia, and Sierra Leone occupied lineage IV are sufficiently related to suggest that Nigerian strains from lineages I and II diverged prior to strains from northern part of central Nigeria and Guinea, Liberia, and Sierra Leone. A fifth lineage, which falls between III and IV, has been proposed for the AV strain isolated from a patient that was infected (presumably) in Ghana or Ivory Coast (28).

Reservoir Species

The multimammate rats (*Mastomys natalensis*) are the virus natural hosts which frequently reproduce and widely spread throughout East, West and central Africa. The multimammate rats (*Mastomys natalensis*) were well known as the primary host species for LASV (29). As a result of inadequate knowledge of the taxonomy of the genus, it is unclear. However, due to the poor understanding of the taxonomy of the genus, it is uncertain which species and exact subspecies act as a virus reservoir (30). Previous studies stressing on the significance of *M. natalensis* for the circulation of LASV in nature affirmed that newborn animals inoculated intraperitoneally developed continual asymptomatic infection (31).

Considerable infectious virus titers were found in several organs, tissues, and fluids as well as lymph node, liver, spleen, lung, blood, and brain after inoculation for up to 74 days. Besides, LASV was secluded from the urine and throat swabs of infected animals. There were no considerable histopathological alterations found in these animals. Fascinatingly, adult *M. natalensis* that were infected with LASV also produced a disseminated infection that stayed up to 30 days. A number of animals completely removed the virus from some organs, but in other organs for about 103 days the virus persisted after the study was over. The only constant histopathological result found in adult animals was a moderate chronic meningoencephalitis (31). These results have proven that *M. natalensis* possesses the best possible pattern of infection and virus shedding which naturally maintains LASV.

Historical Epidemiological Trends of Lassa Virus Infection in Nigeria

The epidemic of Lassa fever in Nigeria is hastily becoming hyper-endemic with associated cases of nosocomial infection at higher rate (figure 1). The virus antibodies rate among Nigerians is about 21% (32). In addition, Lassa fever is endemic in Liberia, Sierra-Leone and Guinea.(33). The sero-positivity of Lassa fever has also been reported in other countries such as Central African Republic, Democratic Republic of the Congo, Mali, and Senegal (34) and hence the virus is estimated to have infected about 300,000 – 500,000 people every year with annual approximation of 5,000 deaths.(5) Notably and so far the greater percentage of the reported deaths in Nigeria are among the youths, particularly the health workers and pregnant women (33,35). Information gathered from Epidemiology Division of the Federal Ministry of Health in Nigeria, stated that Lassa fever has been reported in more than 23 of the 36 States in which Ebonyi, Edo, Nassarawa and Plateau States are the worst hit repeatedly of all States in which Lassa fever cases have been reorted (33,34). Currently, repeated Lassa fever outbreaks have also been reported in Adamawa and Taraba States.

There were 430 suspected cases with 25 laboratory confirmed cases and 40 deaths (CFR, 9.30%) from 37 LGAs in 14 States and FCT in 2015. However, throughout 52 weeks in 2016, there were 921 suspected Lassa fever cases with 109 laboratory confirmed cases and 119 deaths (CFR, 12.92%) from 144 LGAs in 28 States and FCT were reported. Interestingly, between week 1 and 10 in 2017, there were 166 suspected Lassa fever cases with 40 laboratory confirmed cases and 24 deaths (CFR, 14.46%) from 33 LGAs in 11 States were reported compared with 517 suspected cases with 50 laboratory confirmed cases and 68 deaths (CFR, 13.15%) from 110 LGAs in 26 States during the same period in 2016 (36) (Table 1). A total of 937 cases of Lassa fever was reported of which 148 (15.7%) were confirmed in the laboratory. Two laboratories which were situated at the Lassa Research Institute, Irrua, Edo State and Lagos University Teaching Hospital, Idi-Araba Lagos confirmed the tests.

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, Ondo, Nasarawa & Ebonyi	2007/2008
	Edo, Nasarawa, Gombe, Kaduna, Plateau, Ondo, Lagos States and FCT	2009
	Kaduna, Kebbi, Plateau, Taraba, Edo, Kogi & Ondo	2010
	Edo, Taraba, Ebonyi, Rivers, Plateau and Yobe	Feb. 2011-June 2012
	Ten states including FCT	Dec 2015-Jan 2017

Data is from the Nigerian Federal Ministry of Health, Epidemiology Division and NCDC 2017

Epidemiology of Lassa Fever in West Africa

Lassa fever virus was first identified and taken separately in 1969 from a missionary nurse working in a clinic Lassa (a small town), in northeastern Nigeria (37). This nurse may have been presumed infected from an obstetrical patient living in Lassa. She died about a week after the commencement of symptoms. Afterward, two other nurses who managed the first patient were also infected with the disease which was subsequently named as Lassa fever resulted into the death of one of them. The contagious virus was detected from all the three nurses (1).

Consequently, many West African countries were found to be endemic for Lassa fever (29,38). Moreover, a serological investigation carried out among patients under admission for fever, and missionaries with febrile illness experienced revealed that Lassa fever was also currently ravaging Ivory Coast, Mali, and Central African Republic (2). The impression about the endemicity of LASV in larger areas of West Africa was in concordance with the results of research carried out on a Lassa fever case in Germany brought into the country in the year 2000 Figure 3. While the incubation period was on, the index patient in question visited many countries such as Burkina Faso, Ghana and Ivory Coast, Togo, Ivory Coast, Ghana, Senegal, Gambia and Mali (30). Furthermore, in Benin Republic (2016-2017), an overall 54 suspected cases, as well as 28 deaths, were reported from eight regions as follows: (31 cases, 16 deaths) in Borgou, (7 cases, 5 deaths) in Donga, (6 cases, 3 deaths) in Collines, Alibori had (3 cases, 1 death), Plateau with (3 cases, 2 deaths), (2 cases, 1 death) in Ouémé while Atlantique reported (1 case) and Littoral (1 case). Out of this number of suspected cases, 16 were confirmed from laboratory in three regions as thus: Borgou with (13 cases), (2 cases) in Donga and (1 case) in Ouémé. Five of the total suspected cases are hospital staff from the Borgou region. Three out of the 5 health workers were confirmed in the laboratory the remaining two died. While this outbreak was on, the technical support for the confirmation of Lassa fever cases by polymerase chain reaction (PCR) were given by five laboratories. Lassa fever was also reported recently in Togo and Burkina Faso in March this year (36).

The incidence of the disease, although variability high based on the geographical location (i.e ranging from 1.8% in developed to 55% in developing countries) shows that majority of infections are mild or probably without symptom and hospitalization. This is also in concordance with a report showing elevation of LASV-specific seroconversion incidence, ranging from 5% to 20% of the nonimmune population yearly (5). Hospital acquired outbreaks are linked with higher death rates from 36% to 65% (31). Moreover, findings from hospital-based serosurveillance associated with suspected cases of Lassa fever revealed that the hospital staff that adopted basic hygiene measures routinely were not at higher risk of infection compared with the local inhabitants. LASV Infection most likely takes place via contact with body fluids or excreta, or inhalation of aerosols which are released from infected animals. The disease is prevalent in West

Africa, with several thousand people probably killed yearly. With the rising spread of the pathogen there it is necessary to advance our perception of this disease.

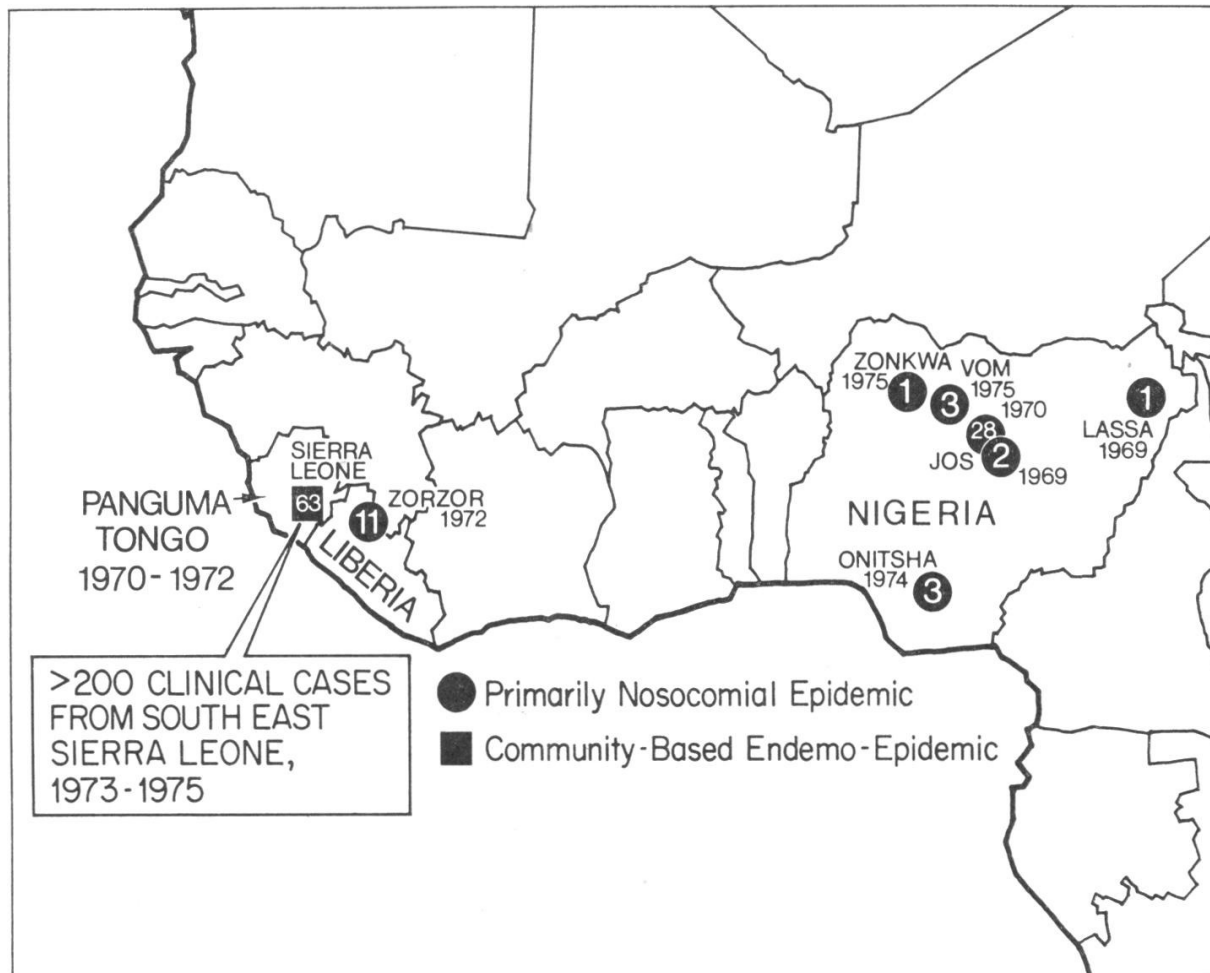


Figure 3: Pattern of the disease transmission common in Nigeria and some neighboring West African countries (Adapted from 39).

Morbidity and mortality

Presentation of Lassa fever cases are at their peak during the dry season (January to March) while some cases take place during the wet season (May to November). Nevertheless, latest reports from Kenema (1999-2002) revealed that hospital cases of Lassa fever on admissions peaked during the change period from the dry to the wet season. This occurrence might be partly

264 due to population movements overcrowding. As the wet season advances there is progressive
265 difficulty in travelling and may be responsible for the reduction in number of cases soon after in
266 the season. Confirmation by laboratory analysis before 1998 was available in retrospect (40).
267 More often than not many of the cases are wrongly diagnosed unless laboratory confirmation is
268 adopted.

269
270 Therefore, these current evident changes in the patterns of infection should be must be deduced
271 cautiously. The infection can affect people of all age categories. Despite the mildness of the
272 disease, up to about 80% of infected people are asymptomatic, while 20% are with severe
273 multisystem disease. The LASV has an incubation period of 6-21 days. It is excreted in urine
274 between 3 to 9 weeks of infection while it takes 3 months in semen (34). The scope of sexual
275 transmission of LASV is not known. One of the features of the disease is sensorineural hearing
276 deficit and this was detected in 29% of confirmed cases as against the non febrile controls in
277 inpatients under hospital admission (41). About 81% of patients with sudden deafness in the
278 general population had detectable antibodies to Lassa virus against 19% of corresponding
279 controls. There is no noticeable relation between the viral illness severity, early hearing loss, or
280 recovery later on (41). The disease was accountable for 10-16% of the whole adult medical
281 admissions in 1987 and for up to 30% of adult casualties in two Sierra Leonean hospitals
282 investigated (5). There was variation of 12% to 23% in case fatality rate in Kenema for the
283 period 1997-2002. A recent case series revealed low preponderance of admission including high
284 case fatality rates for people who are not 18 years age.

285
286 There have been reported high rates of maternal death (29%) and fetal and neonatal loss (87%)
287 during pregnancy (evacuation of uterine improves outcome considerably), and 25% of all
288 maternal deaths in Sierra Leone being were as a result of Lassa fever (42). There is an estimate
289 of 1-2% the case fatality rate in the general population which is a lot lower than in hospitalized
290 cases, possibly as a result of disparity in disease severity and the epidemiology. It was also
291 estimated that the seronegative population “at risk” in Sierra Leone, Guinea, and Nigeria could
292 be as high as 59 million, with a yearly incidence of illness of three million, casualties of about 67
293 000 and re-infections of up to three million (33). All these data are rough estimates for Lassa

fever until a comprehensive picture is known. There is unavailable comparable information for the other countries in which seropositivity has been reported.

Clinical Pattern of Lassa Fever

Up to 80% of LASV victims experience mild disease but asymptomatic while the rest 20% show stern multisystem disease. Moreover, there are casualty rates of between 15-20% of patients under hospital admission for Lassa fever and this causing panic with serious socio-economic outcomes. The casualty rates are indeed on the rise for pregnant women and their expectant babies. Approximately one-third of the survivors may experience mild to severe degrees of deafness, and in major cases the hearing loss is everlasting. At the onset of epidemics, the case-fatality rate of Lassa fever may be up to about 50%.

Clinical Syndromes of Lassa fever

An individual may fall sick between 6 and 21 days after the Lassa fever virus gains entry into the body. The onset of Lassa fever is accompanied with a gradual fever with illness feelings and body pain. The typical febrile condition is not cured with anti-malaria and antibiotic treatment. The patient may experience clinical signs such as sore throat, cough, chest and abdominal pain, headache, vomiting, diarrhoea, dizziness, red eyes and swollen face and neck after some days. Subsequently during the illness (i.e. after 14 days) the victim may commence bleeding in the gums, stool, in urine, in the eyes or below the skin spontaneously. The victim may also not survive consequently. Although Lassa fever appears like Malaria at the onset the fact remains that the victim does not respond to any anti-malarial drug while the typical symptoms of sore throat and swollen face, will notify us of Lassa fever.

Lassa fever feverish condition is accompanied with symptoms and signs impossible to differentiate from those of febrile sicknesses including malaria and other viral haemorrhagic fevers e.g. Ebola. Clinically it is not easy to diagnose but suspect patients with fever ($\geq 38^{\circ}\text{C}$) who do not adequate response to antimalarial and antibiotic drugs. The commonest ideal clinical predictors of Lassa fever include the diagnosis fever, pharyngitis, retrosternal pain and proteinuria; and fever, sore throat, and nausea for outcome (5). Complications include mucosal bleeding, sensorineural hearing deficit, pleural effusion, and pericardial effusion. The outcome of

Lassa fever infection is highly related to the degree of viraemia, not the antibody response, and is worse with high levels of aspartate aminotransferase (34).

The frequent period between the commencement of symptoms and discharge was seventeen days (i.e. about half of the patients had been hospitalized for 10 days) while between onset and death was 5 days (i.e. about half died within 2 days of their admission). However, any delay between onset of symptoms and admission prevented nearly all patients not being given ribavirin during the grave period of the first 6 days. All these information contribute to the indecision adjoining diagnosis and death.

Surveillance and Disease Control

Surveillance must find out all the patients close contacts for 3 weeks after commencement of illness, and look out for unreported or undiagnosed cases (34). The following are 3 concerned areas for suspicion during the disease outbreak or episode::

- i. Management of undiagnosed cases in health care facilities with poor hygiene and overcrowding can extend the disease to other patients, visitors or health workers;
- ii. Sharing food items and other materials where in some parts of Nigeria which cultural practices encourage.
- iii. Possible risk of disease spread to a lot people as a result of traditional burial ceremonies to respect infected corpses.
- iv. Lassa suspected cases must be taken to isolation facilities for admission and properly managed because many of the outbreaks are hospital-based. Hospital transmission takes place via insufficient infection control measures.
- v. Stringent isolation of cases and procedures requiring body fluids and excreta must be maintained (41).
- vi. Community awareness is vital in ascertain the knowledge, attitude and practice of adequate control of Lassa fever among the community and health workers.

Diagnostic methods of Lassa Fever virus

The diagnosis of Lassa fever is done by both clinical and laboratory methods but that of laboratory is more reliable due to similarity in clinical presentations with other disease conditions.

Laboratory Diagnosis

Laboratory diagnosis of VHF has traditionally taken place in highly specialized reference laboratories. These laboratories have been classified with biosafety levels (BSL) ranging from 1 to 4 by the World Health Organization. The laboratories are categorized according to the laboratory design, containment facility, and handling of biological agents classified into 4 specific risk groups (RG 1–4) (43). According to the Centers for Disease Control and Prevention, the VHF viruses e.g. Lassa virus are members of RG-2 through RG-4 (44). There are a limited number of BSL-4 laboratories throughout Europe, the United States, and Africa, and the distance of BSL-4 laboratories from endemic areas often lengthens time to diagnosis when most needed. Some countries, but not all with endemic VHF, often make diagnoses in their laboratories, but they are not BSL-4 certified. Personal protective equipment can be modified to be effective in these resource-limited environments.

Virus Culture and Electron Microscopy

Culture of live agents was considered the gold standard but is rapidly being challenged by polymerase chain reaction (PCR) and next generation sequencing (45). Culture of live agents remains helpful for characterization of new or divergent viruses, but next generation sequencing can also aid in identifying these viruses. Electron microscopy (EM) may be used to identify virus based on structural characteristics from clinical materials or culture (46). Agent-specific antibodies in conjunction with EM may be used to further identify or classify an agent e.g. Lassa virus and to increase the sensitivity of this method, depending on the protocol used. Due to challenges of EM and culture of live viruses, these methods are no longer used as a first line of diagnosis in many instances.

Nucleic Acid Detection

Nucleic acid detection has become a common diagnostic tool for identifying viral diseases, including VHF. Such detection surpasses the limit of detection for many culture methods and eliminates the need for the virus to be viable at the time of testing. Reverse transcription PCR

(RT-PCR) has become the cornerstone for molecular diagnosis, and RT-PCR assays have been developed for the majority of VHF-associated viruses (47–50). Multiplex assays have now been developed for a range of VHFs with sensitivity and specificity comparable to other RT-PCR assays. Microarrays are a specialized type of multiplex PCR that uses a solid matrix spotted with oligonucleotides that represent specific genes of different organisms. An unknown fluorescently labeled DNA anneals and releases a positive signal that is compared with the intensity of known positive signals. Microarrays have a high specificity and sensitivity to detect virus families that encompass VHF (51).

Vaccine

Vaccination has been regarded as one of the most valuable weapons against infectious diseases and has led to a significant decline in mortality and morbidity. However, for most viral hemorrhagic fevers caused by arenaviruses such as Lassa virus, no prophylactic vaccine is available. This is particularly problematic as these diseases are notoriously difficult to diagnose and treat and this poses a serious challenge for a potent vaccine. Lassa fever is globally the most important of the fevers caused by arenaviruses, potentially affecting millions of people living in endemic areas, particularly in Nigeria. Annually, an estimated 300,000 humans are infected and several thousands succumb to the disease (13). The successful development of the vaccine Candid#1 against Junin virus, the causative agent of Argentine hemorrhagic fever has provided a clue that an effective arenavirus vaccine can be developed for Lassa fever. Although several promising studies toward the development of a Lassa fever vaccine have been published, no vaccine candidate has been tested in human volunteers or patients in this part of the world (12).

Presently there is no licensed vaccine against LF or approved treatment but recently, several promising vaccine candidates have been developed which can potentially target different groups at risk. When lassa fever vaccine is finally available for use, the vaccination strategies may differ for the various recipient populations. It is proposed that a multi-dose immunization regimen might be practical for medical providers and for military personnel while a single-dose vaccine would be ideal in endemic areas, where most of the target population is poor and live far from health care facilities (52). Nevertheless, it is however suggested that a cell-mediated immunity

(CMI) plays the major role in the recovery and prevention and a single dose of live attenuated candidate vaccine conferring life-long immunity is much preferred (52).

Production of a pooled/joint vaccine in single dose used against yellow fever and Lassa fever has been anticipated/suggested (53). Certain challenges such as cost and logistics of supplying it would be enormous, especially since less than 20% of districts in the countries studied attained childhood vaccination of about 80% (42) For financial viability it is advisable to make use of visitors from the United Nations, non-governmental organizations, and business, though this may be most costly of all 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 administered before the incubation period of six days, deaths rate may decrease by 90%. Clinical conditions such as dehydration, oedema, hypotension, and poor renal function are frequent with infection, hence blood transfusion or fluid replacement 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 makes 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

Lassa fever outbreak in Nigeria is a yearly occurrence during the dry season but, the recent outbreaks are more widespread. In the most recent outbreak of Lassa Fever in Nigeria from 2015 to date which affected 10 states, there was apparent increased fatality rate observed affecting 140

suspected and 30 confirmed cases. The case fatality rate (CFR) is significantly high at 53 or 37.9% of all cases (36). In order to prevent future outbreaks in Nigeria, it has been further revealed that, a total of sixty Disease Surveillance and Notification Officers (DSNOs), thirty seven secondary health facilities medical directors, fifty five community health workers, forty medical laboratory scientists and forty four nomadic representatives have already been trained on case management and surveillance of the disease.

A sudden surge of Lassa fever outbreak in Nigeria if not curtailed may have a spillover effect across West African countries due to so many factors. 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. The apparent underrecognition of LASV infection in West African region is likely multifactorial. However the wide range of clinical features and nondescript symptoms that appear early in LASV infection impedes a diagnosis based strictly on clinical manifestations, even for experienced physicians (33)

West Africa as a region is seeing a flare-up of the disease, but Nigeria -- where Lassa fever was first discovered in 1969 -- is experiencing much higher mortality rates than usual. On average, Lassa fever is deadly in 1% of all individuals infected, with higher rates of 15% morbidity among people hospitalized for the illness, but the current outbreak in Nigeria has seen more than 50% of those affected dying from their infection. According to a recent reports, the total number of Lassa fever cases in Nigeria is 254 (129 of which confirmed by lab tests) and the total number of deaths (suspected, probable and confirmed) is 137, with a Case Fatality Rate (CFR) of 53.9% (36). Furthermore, a 2012 outbreak of Lassa fever in Nigeria caused more than 1,700 people to become infected, but 112 deaths, according to the (36). Despite lower case numbers, the death toll such outbreak was already considered higher than expected. Nevertheless in previous outbreaks, infections often went unreported as the disease mainly affects rural areas where populations can be highly infected, but don't notify the authorities.

Many challenges have been observed which promotes the continual outbreaks of Lassa fever in Nigeria and its spread to other neighboring West African countries. Firstly, Lassa fever is a neglected tropical disease and the affected countries are Nigeria, Ivory Coast, Mali, Guinea, Sierra Leone, Republic of Benin, Togo, Burkina Faso, Guinea and Liberia. The rodent hosts play

a pivotal role in maintaining the virus in our environment also survives due to poor hygienic practices in Nigeria and its environs. Another challenge is the specific socioeconomic problem related to Lassa fever vaccination and probably remains the biggest hurdles to be crossed (53). People who are at the highest risk of infection are also the poorest in the above-mentioned endemic countries. Poor hygiene and sanitation in these countries increases the probability of Lassa fever virus exposure. Furthermore, many people living in these countries are unable to pay for vaccination. 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.

Conflicts of interest

The authors declare to conflict of interest whatsoever

Author's contributions

All authors contribute to this manuscript maximally

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