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Review Article

The challenges of curtailing the outbreak and spread of Lassa Fever in Nigeria

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Abstract. In Nigeria, the Lassa Fever outbreak of 2015 had been persistent up till the present (end of 2019), with significant mortality and morbidity. The epidemiology of Lassa Fever is gradually changing towards assuming an endemic dimension despite several evidence-based efforts taken by stakeholders towards disease control. Several challenges militate against prevention and control efforts. These are related to environmental and climatic factors, poor knowledge risk perception and preventive practices among community members and health care workers, poor diagnosis and treatments of the disease. It is doubtful that Nigeria could successfully win the war against Lassa Fever without surmounting the challenges identified in this review article. The efforts to curtail Lassa Fever would yield significant reduction in prevalence if these challenges militating against prevention and control are removed. This would require collaborative efforts among all stakeholders that are relevant to this task, and Governments creating an enabling environment for prevention and control efforts to thrive.

Keywords: *Lassa Fever, Nigeria, Disease control, Challenges, Surveillance, Prevention*

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1. Introduction

In 2014, Nigeria experienced the most devastating outbreak of acute viral hemorrhagic fever (AVHF) notably the Ebola virus outbreak. The coordinated response of the health system led to the containment of this Ebola virus disease outbreak. However, the Lassa Fever (LF) outbreak of 2015 had been persistent up till the present, and it is a test of how the country and indeed the West African sub-region could fill disease control gaps and respond to emerging health issues. The Lassa virus is now a problem of high public health importance, especially as it causes significant mortality and morbidity, and exerts pressure and undue impact on the public health system (Mofolorunsho, 2016; NCDC, 2017; Tambo, Ugwu and Ngogang, 2014). Other prevalent examples of the diverse mild to a severe group of animal and human illnesses categorized as AVHF include yellow fever and dengue (dengue haemorrhagic fever).

Lassa Fever is caused by the Lassa Fever virus (LASV) which is a member of the *Arenaviridae* family. It is a zoonotic acute viral haemorrhagic disease of humans, which is endemic in West African countries including Sierra Leone, Guinea, Benin Republic, Côte d'Ivoire, Mali, Liberia and Nigeria, where a significant outbreak is ongoing and persistent for some years now. LF was first isolated in 1969 among two infected missionary nurses who eventually died in the town of Lassa in Nigeria (Adewuyi, Fowotade and Adewuyi, 2009; Mylne et al., 2015). Figure 1 shows the distribution of Lassa Fever in Nigeria between 2015-2019 (NCDC, 2019).

Within an incubation period ranging from six (6) days to twenty-one (21) days, the single stranded RNA type LASV finds convenient reservoir in a transmitting rodent vector (the *Mastomys natalensis)* which has adapted to a peri-domestic life in village houses in West Africa (WHO, 2007). Lassa Fever transmission is essentially through contact with infected rodent's faeces, saliva or urine, inhaling contaminated dust, eating contaminated food or by contact with bodily fluids of an infected person dead or alive (human-to-human transmission) (WHO, 2010; Ilori, Furuse and Ipadeola, 2019; Ogoina , 2015). The ongoing epidemic predominantly affects three states of Ondo, Edo and Ebonyin which include 4.6% of Nigeria's population, yet accounts for 74.6% of the increase in confirmed cases during the 2017 and 2018 peak seasons (NCDC, 2018). In Nigeria, the average case fatality (CF) among patients with confirmed LF declined from 154/355 (43%) in 2001, to 183/867 (21.1%), and the decline was found to be statistically significant ($p < 0.001$). The annual CF declined from 94% in 2001 to 15% in 2018 whereas the caseload increased from 0.3% to 3.4% (Akpede, Asogun and Okogbenin, 2019). The observed case-fatality rate (CFR) among patients hospitalised for severe LF is 15%–50% (WHO, 2019; CDC, 2018). Figure 2 shows the number of cases reported on a yearly basis between 2016 and 2019 (NCDC, 2019).

From 1st January 2019 to 10th November 2019 (NCDC, 2019), a total of 4500 suspected cases have been reported from 23 states in Nigeria. Of these, 764 were confirmed positive, 19 probable and 3717 negative. There have been 160 deaths in confirmed cases. The predominant affected age-group is between 21-40 years (Range: >1 month to 98 years, median age: 34 years), and the male to female ratio for confirmed cases is 1:1. As many as 90% confirmed cases have been linked to circumstances such as new agricultural practices (Kafetzopoulou, 2019), yet the role of data on rodent abundance are not available, and need to be determined. An understanding of the genus is also important to ascertain which species and exact subspecies act as a virus reservoir (Safronetz, 2015). Figure 3 shows the number of confirmed cases of Lassa fever in 2019 as reported by the Nigerian Center for Disease Control (NCDC, 2019).

2. Review Methodology

The focus of this review is on Lassa Fever in the African continent with special focus on Nigeria, and to explore reported challenges facing the control of the outbreak in Nigeria: a scenario that has persisted for quite some time in the country. There was no limitation to the number of Lassa Fever cases in an eligible published review article and no restriction on its contents. Articles were identified by electronic searches of popular databases such as PubMed, CINAHL, Web of Science, MEDLINE, EMBASE, the Cochrane Central, Scopus, and Google Scholar. Additional pertinent citations were identified through bibliographies of retrieved studies. Authors were able to screen articles to narrow them down to those touching on the challenges facing the containment of the outbreak using relevant keywords such as Lassa Fever and Nigeria. A literature search strategy was developed by one of the authors, with the help of a University library staff who had expertise in literature search.

All data bases available on the internet were visited, with a rigorous search for studies that were published up to December 2020. The search strategy used a combination of Medical Subject Headings (MeSH terms) and keywords to capture Lassa Fever. All study designs were considered for inclusion. There were no language restrictions. Authors could not conduct a meta-analysis because the number of studies for each of the selected categories of challenges was not enough to pool together meaningful data, thus this is a review article.

3. Challenges curtailing the control of Lassa fever in Nigeria

The five challenges of curtailing the outbreak and spread of Lassa fever in Nigeria are:

1. The changing epidemiological patterns and risk factors associated with Lassa Fever,
2. Environmental and climatic factors affecting the transmission of Lassa Fever,
3. The clinical presentation and diagnosis of Lassa Fever,
4. Treatment of Lassa Fever,
5. Prevention of Lassa Fever.

Challenges associated with changing epidemiological patterns and risk factors associated with Lassa Fever:

Despite the continued threats posed by LASV, comprehensive data on prevalence and pattern are lacking. The huge population of Nigeria could make

disease surveillance and contact tracing a challenging task. If rodents are present in a highly dense population, the number of cases may increase exponentially. Many reports on Lassa Fever are pockets of specific hospital based data conducted by researchers which may not be generalisable to the general population (Ogbu, Ajuluchukwu and Uneke, 2007; Fichet-Calvet and Rogers, 2009).

Community knowledge about Lassa Fever is poor, though awareness may be high. This pattern could brew a poor risk perception to the disease, poor attitude and poor disease preventive practices (Ogboghodo, 2019; Olowookere, 2017; Sagir and Ahmed, 2019; Gobri, 2019; Adebimpe, 2015a; Olayinka et al., 2015; Reuben and Gyar, 2016). Improving community awareness about Lassa Fever would assist to take precautions on animal to human transmission, hygiene practices and good health seeking behaviour related to Lassa Fever epidemiology (Adebimpe, 2015a).

Good knowledge among health care workers is not significantly high, is associated with poor risk perception and poor practices of universal precaution and infection control. When health care workers are familiar with the epidemiology of Lassa Fever and become proficient in clinical diagnosis, then under recognition and under reporting will greatly reduce and the disease would attract the desired attention (Adebayo et al., 2015; Aigbiremolen et al., 2012; Ijarotimi et al., 2018). It is therefore important that formal training, on-the-job and refresher training be organised for health care workers at all levels of care, to improve their knowledge base and reinforce early detection and reporting of cases.

The health system may use the opportunity created by social media and digital cloud-sourcing to develop timely risk communication and reporting systems that would create awareness among the general population. The advent of consumer/provider-generated mHealth technology can also compliment efforts to reach out to the general community, and this is not difficult in Nigeria where mobile phone technology is readily accessible (Giles and Adams, 2015). The possibility of nosocomial transmission of Lassa Fever virus points to the dire need to increase community and health care knowledge, risk perception and preventive practices against Lassa Fever.

Challenges associated with environmental and climatic factors affecting the transmission of Lassa fever:

The proliferation of rodents, most especially in the early rainy season is central to animal-human Lassa Fever transmission. There are several community practices that encourage Lassa Fever transmission such as crowded living rooms and houses, not having a specific space for a store, open storage of raw foods, sun drying of food under processing and poor attitude to rodent control (Mari Saez et al., 2018; Tobin et al., 2015; Swanepoel et al., 2017; Parsons et al., 2017; Salmón-Mulanovich et al., 2016; Aigbiremolen et al., 2012; Abubakar et al., 2018). In a study by Giles and Adams, (2015), 96.1% of houses had seen rodents in the previous 6 months. Rural urban drift is common in Nigeria as people tend to afford the benefits of urbanisation, and would only worsen the present situation about transmission. Thus it is important that all households strive to keep rodents out of homes and food supplies as well as observing proper personal and environmental hygiene (Adewuyi et al.,2009).

Communities may decide to adopt a cultural approach to refuse management by hosting large dump of refuse within traditional settlements before eventual transfer to a public dumping site. This could be made worse when communities depend on the Government bringing trucks to come and evacuate refuse at community level. Such prolonged stay of refuse near habitable houses could facilitate breeding of rodents and proliferation and spread of Lassa fever. Poor community practices towards rodent control has been documented by several studies (Bonner et al., 2007; Awosanya, 2018). It is therefore important for stakeholders to improve community awareness on rodent control, and a need to develop local culturally effective and acceptable design measures that could lead to the elimination of infectious rodents (Giles and Adams, 2015).

In the absence of preventive medication or vaccine against Lassa Fever, increasing community awareness and health education to avoid contact with reservoir sources mainly rats is important. Environmental related measures that stakeholders in Lassa fever control could take include prevention of food infestation by rodents, most especially at night, food safety practice and appropriate waste management, improved water, sanitation and hygiene (WASH) program implementation, controlled mass

movements and urbanisation, and wildlife management and risk reduction for zoonotic diseases.

Climatic factors are also an important determinant of Lassa Fever transmission. In a study to analyse the surveillance-based incidence data of LF in Nigeria from 2016 to 2018 (Shehu et al., 2018), two different (high- and low-) risk periods of Lassa Fever transmission were observed. The high-risk period spanned from the last month of the year to the second to third month of the new year. The relative risk of acquiring LF infection during the high-risk period was five times greater than during the rest of the year, possibly indicating that the rainfall pattern was highly and negatively correlated with LF incidence.

During dry season (as rain ceases in late November), scarcity of food on the ground, force mature rodents to migrate towards human occupied areas or communities, to breed, thereby supporting a higher probability of acquiring LF infection. This high-exposure frequency persists until the rainy season starts again the following year, at which point the rodents migrate back to the ground and a subsequent decline in human cases of Lassa Fever are observed. This seasonal ecology of the animal host (Marie et al., 2018) could explain the seasonality of LF epidemics. This supports the conclusion that the rainfall pattern was the main single abiotic factor contributing to Lassa Fever (Fichet-Calvet, 2009). A strategic design of preventive measures that could contain seasonal epidemics of LF to raise awareness among local residents and disrupt seasonal movements of rodents is recommended. There is a need for stakeholders to prioritise a "One Health" approach technology to strengthen bilateral health systems of animal and humans towards disease control (WHO, 2007; WHO, 2000).

Challenges associated with clinical presentation and diagnosis of Lassa Fever:

The clinical presentation of Lassa Fever mimics that of several other febrile illnesses endemic in West Africa, thus making it difficult to differentiate and diagnose and could lead to late presentation and appropriate treatment (Mertens et al., 1973). A low index of suspicion among clinicians has been reported as Lassa Fever is often considered only after patients have been presumptively treated for malaria and typhoid fever, without improvement (McCormick, 1987).

The clinical presentation of LF varies from asymptomatic or mild illnesses in the majority (80%) of infections (Richmond and Baglole, 2003). Symptomatic cases usually present with fever, weakness, and general malaise, with headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhea, cough, and abdominal pain after a few days (Bausch, 2014; Abdulraheem, 2012), followed by commonly observed complications such as bleeding, facial oedema, convulsions, pericardial effusions and coma (Ehichioya et al., 2012). Diagnostic proficiency of Lassa Fever among health care workers was generally poor (Shaffer et al., 2014; Mazzola and Kelly-Cirino, 2019) and could be a reason for late presentation. Most cases appear mild or even asymptomatic and could call for a high index of suspicion among health care workers

Frequent confusion of Lassa Fever with other febrile illnesses calls for a dire need for reliable laboratory diagnostic tests for early confirmation, initiation of healthcare barrier precautions, patient isolation, treatment and contact tracing. Though knowledge on Lassa Fever in Nigeria is high among medical practitioners, poor access to affordable and simple tests for timely diagnosis and confirmation of Lassa Fever cases is one of the challenges facing Lassa Fever management in Nigeria (Idemyor, 2010). Despite this, it was reported (Eze et al., 2010) that Nigeria has four documented episodes of Lassa Fever occurrences as nosocomial transmissions. In the absence of a reliable diagnosis, conflicting data reporting may occur most especially among subclinical cases.

The World Health Organization (WHO) has recommended the establishment of Centres of Excellence for prompt and effective diagnosis of Lassa Fever in all affected countries ((WHO, 2019). The West Africa sub region accounts for a high Lassa Fever endemicity and outbreaks (Sogoba et al., 2012; Gibbs et al., 2017), however, there have been only two of such centres with recommended biosafety levels (BSL) ranging from 1 to 4 as classified by the World Health Organization (Olayiwola and Bakarey, 2017). Such centeres include the one at Kenema General Hospital, Sierra Leone (Khan et al., 2008), and the Institute of Lassa Fever Research and Control, ILFR&C at Irrua Specialist Teaching Hospital (ISTH), Nigeria (Asogun et al., 2012). The bases for the laboratories classification include the laboratory design,

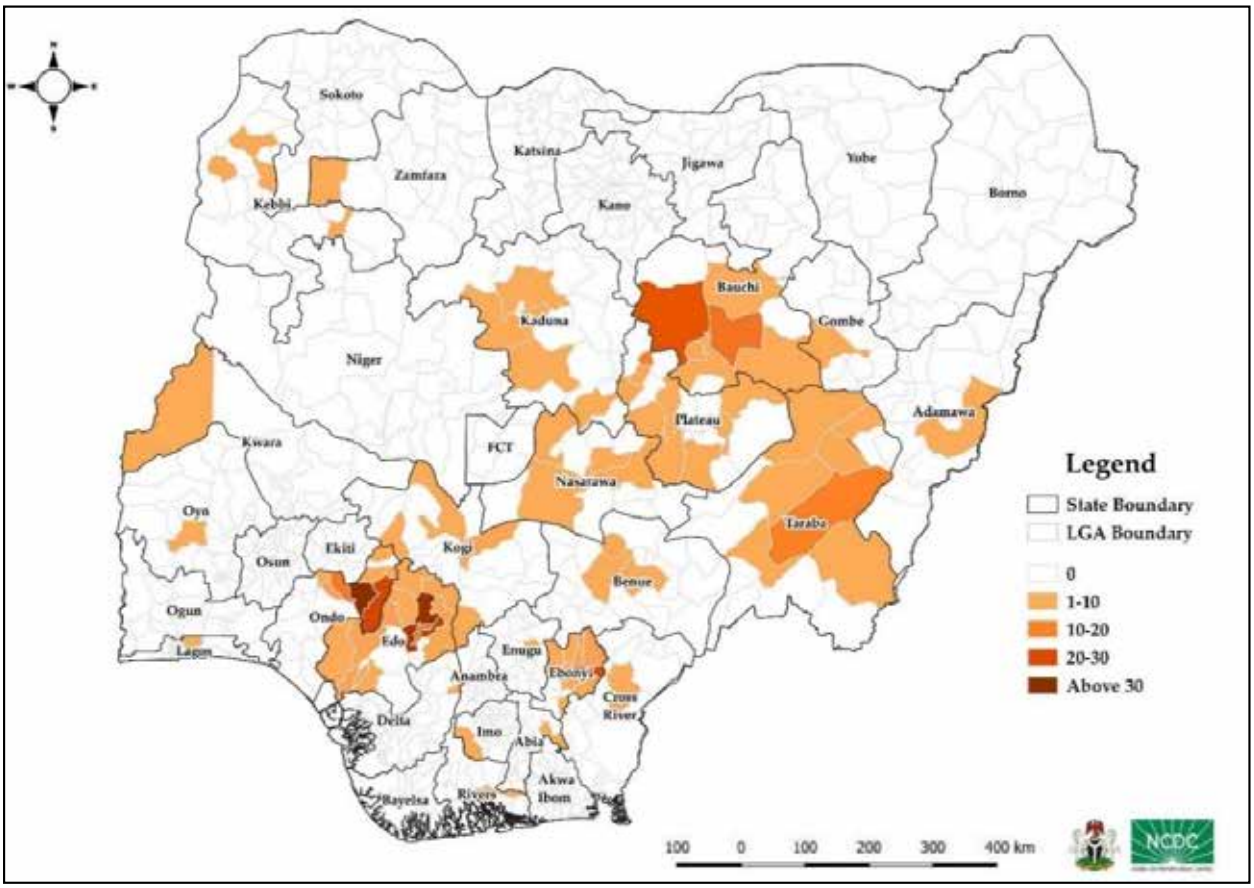

Figure 1: Distribution of Lassa Fever in Nigeria between 2015-2019. (Source: NCDC, 2019)

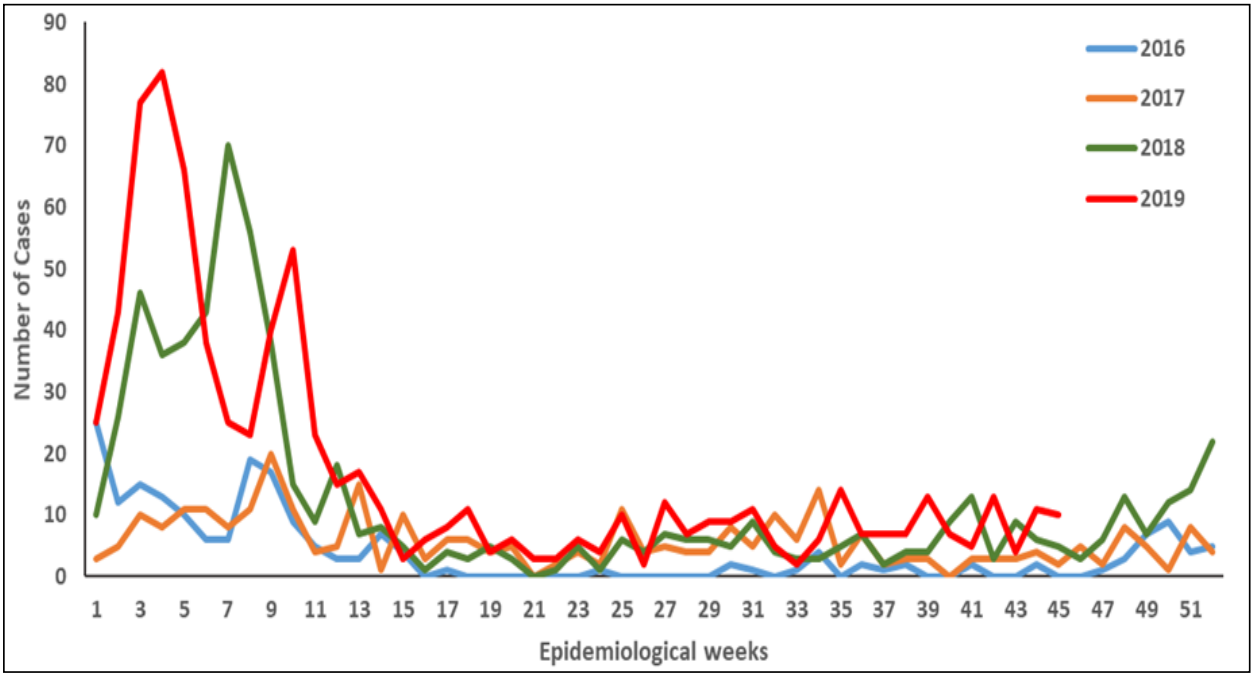

Figure 2: Number of cases of Lassa fever between 2016-2019 (Source: NCDC, 2019)

availability of containment facility, and handling of biological agents (WHO, 2015).

Reliable methods of Lassa fever diagnosis are:

1. Viral antigens detection,
2. Nucleic acids, and IgM/IgG antibodies detection,
3. Reverse transcription polymerase chain reaction (RT-PCR): which is the gold standard, good in early detection, and in rapid and mobile diagnosis (Grove, 2011; Panning, 2010),
4. Enzyme-linked immune-sorbent serologic assays (ELISA): which may be good for secondary confirmation (Panning, 2010),
5. Tissue culture,
6. Postmortem diagnosis through immunohistochemistry from formalin-fixed tissues (Panning, 2010).

Challenges associated with treatment of Lassa Fever:

Like several other VHFS, there is no vaccine for the prevention of Lassa Fever as at present (Lukashevich, 2012). Efforts had been targeted on treatment and supportive care. Ribavirin (1-b-d-ribofuranosyl-1,2,4-triazole-3-carboxamide), is a guanosine analogue, and was found to be active against a broad spectrum of DNA and RNA viruses (Bausch, 2010; NCDC, 2018). This is based on a single clinical trial successfully carried out in Sierra Leone in 1986 by McCormick et al. Its effectiveness is best within six days of administration. While its mode of action is none-specific, it has numerous adverse treatment outcomes (Chew, 2009). Its mode of action in viral replication (Bausch, 2010; Oestereich, 2016) is however unclear.

Rivabirin is currently the recommended medication for Lassa Fever (NCDC, 2019; Bossi et al., 2004). Its therapeutic potentials either as a single drug or in combination therapy is doubtful in some quarters, costly and contraindicated in pregnancy. Common side effects of ribavirin include hemolytic anaemia and infusion-related reactions such as rigors. To confirm efficacy of Ribavirin, a study (Okokhere et al., 2018) at the Irrua Specialist Teaching Hospital was carried out between January 2011 and December 2015, where a total of 291 treated patients were investigated. Overall case-fatality rate (CFR) was 24% (68 out of 284 patients).

Other studies on case fatalities during the 2016 outbreak in Nigeria reported 59.6% among 47 confirmed cases (Buba et al., 2018), 36% among 11 confirmed cases (Shehu et al., 2018) and 60% among 57 confirmed cases reported by ECDC (ECDC, 2016). Probable reasons for high CFR include late presentation in the hospital (McCormick et al., 1986), late diagnosis (Fidelis and Olajolumo, 2018), poor capacity of human and material resources, shortage of ribavirin, low index of suspicion among clinicians, lack of access to ribavirin and poor treatment compliance (Houlihan, 2017).

The susceptibility of healthcare workers at risk of infection from Lassa Fever patients increases when adherence to infection prevention and control is poor (Richmond and Baglole, 2003; Fidelis and Olajolumo, 2018). Unfortunately, there has been no substantial change in the case-fatality rate over the past 3 years. It is thus important to familiarise healthcare workers with the new WHO treatment guidelines, build their capacity to reduce nosocomial transmission and help them to better detect and treat Lassa virus earlier 3.5.

Challenges associated with prevention of Lassa Fever:

To prevent Lassa Fever, a strong health care system that would integrate a good surveillance system, improve stakeholders and community knowledge, reduce exposures to transmission foci, and coordinated by a strong preparedness and response team would be required. Several vaccine trials against Lassa Fever has not been remarkable including a Nigerian trial (Hallam et al., 2018), with the most promising candidates to date being the ML2 (Lukashevich, 2012).

Major efforts should be to prioritise disease prevention. Essentially, Lassa Fever prevention includes the promotion of good community hygiene to discourage rodents from entering homes, sustained good infection prevention and control practices among health care workers, while people or community should practice the use of rodent-proof containers to store food and keeping their homes clean to deter rodents. Prevention of transmission of the virus in hospital settings include: wearing protective equipment around infected individuals such as masks, gloves, gowns, and goggles and other hygienic techniques (Houlihan, 2017).

4. Recommendations

The following six-point agenda for effective prevention of Lassa Fever in Nigeria are recommended:

Sustained awareness creation on Lassa Fever targeted at the general population.

There is a need to improve risk communication and social mobilisation on all matters related to Lassa Fever control to break the chain of the ongoing outbreak (Sumo et al., 2019; Gillespie et al., 2016).

To repress the spread of Lassa Fever and help prevent the zoonotic transmission of the virus (Olayinka et al., 2015), people should practice the use of rodent-proof containers to store food and keep their homes clean to deter rodents.

Building and strengthening interdisciplinary teams to cover preventive and control measures.

This should include setting up an emergency response team and a national body to coordinate Lassa Fever response, institutionalising a standard operating procedure related to diagnosis and treatment and galvanising NGO support for Lassa Fever prevention through awareness creation are steps in the right direction taken by Nigeria.

Gathering strong political support for Lassa Fever management and prevention.

Currently, diagnosis of LASV is achieved through support from international donors. There is a need to remove barriers of transportation logistics for specimens, and address the issue of poor quality of samples submitted to the reference laboratories as well as improve laboratory networks.

Improved funding through budgetary allocation.

For surveillance, prompt case management include laboratory facilities, training of health personnel, isolation of cases, barrier nursing, contact tracing, provision of antiviral drugs and vaccines development. Lassa Fever management in Nigeria is still largely donor dependent.

Strengthening Lassa fever epidemiologic risks surveillance and early laboratory detection.

Improving the diagnostic proficiency of health works both in terms of clinical and laboratory diagnosis is important. Bleeding which is a characteristic symptom may not show in more than 20% of cases, thus a need for high index of suspicion among health care workers. Most patients present at a late stage of the disease, also stressing the importance of effective case management and the use of personal protective equipment to improve diagnostic proficiency (Olowookere et al., 2017).

Enhanced active surveillance activities targeting Lassa Fever: timely and complete reporting of all probable, suspected and confirmed cases of Lassa Fever, contact tracking and outbreak investigations would assist in watching over the course of the disease and taking preventive actions through regular data collection. Surveillance activities carried out by Nigerian Government in the ongoing outbreak include:

1. Increase in number of reference laboratories,
2. Improved sample transport logistics, and patients' samples, transported and tested without charge,
3. Laboratory capacity building,
4. Training of surveillance officers at the different levels of care,
5. Development of Standard Operating Procedures (SOP)
6. Rapid response teams provide capacity building and support to affected states 4 weeks earlier than in 2017,
7. More treatment centers were created,
8. Ribavirin was available to patients without charge, with the media actively advertising this message, encouraging patients to seek medical treatment,
9. Improved media attention.

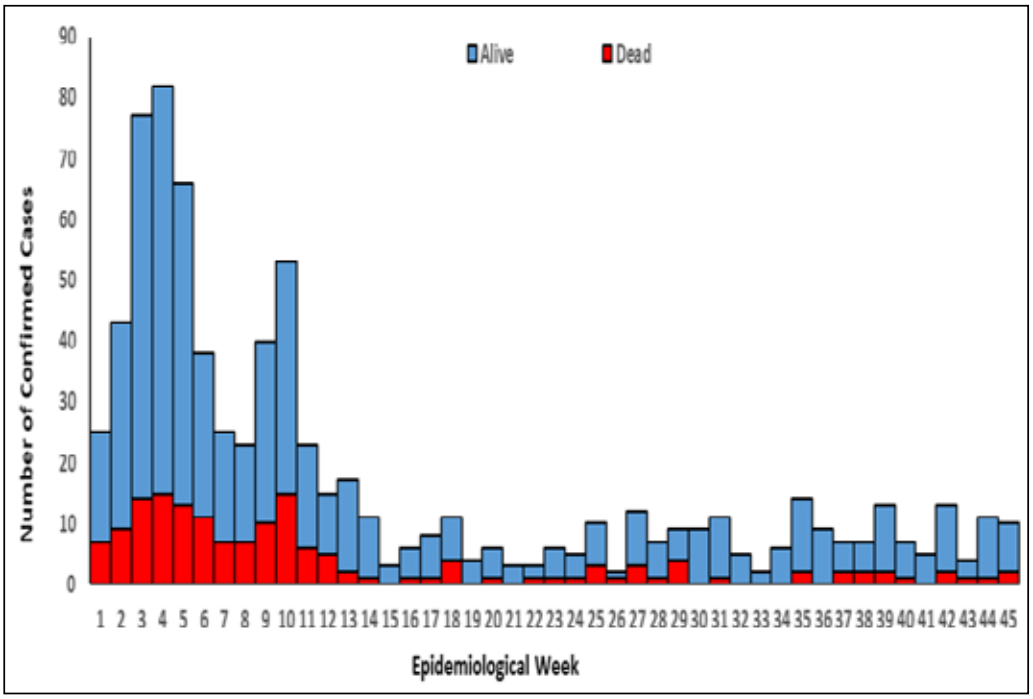

Figure 3: Number of confirmed cases in 2019 (Source: NCDC, 2019)

Building capacity for effective emergency preparedness, outbreak investigation and response

Poor preparedness for an outbreak is an important challenge facing Lassa Fever prevention and control. It is thus important to build early warning indicators and rapid response to adequately prevent or respond to Lassa fever. A list of required medicines and supplies to prepare for an outbreak should be made accessible (WHO/NCDC, 2013; NCDC, 2017).

Accelerating research and development to bridge the gaps in diagnosis, environmental transmission, treatment and diagnosis through data collection.

In order to achieve this, there is a need to identify and fund key research priorities in Lassa Fever prevention, to cover strain variation, cross contamination, vaccine development, biological behaviour of the viral agents and its activity in rodent host, person to person transmission, rodent distribution and control, surveillance, environmental factors and biting behaviour of the vector.

5. Conclusion

Epidemics of emerging and re-emerging infectious diseases are on the increase, with devastating health, social and economic consequences. Lassa fever as a prototype is a preventable and treatable disease that is currently ravaging Nigeria and the West African sub-region, with a single case of Lassa Fever regarded as an outbreak. Despite measures to prevent and control the spread of Lassa virus (LASV), the fight against Lassa Fever is hampered by several challenges relating to diagnosis, poor knowledge risk perception and preventive practices among community members and health care workers, poor treatments and general prevention. The efforts to curtail Lassa Fever would yield significant reduction in prevalence if these challenges militating against prevention and control are removed. This would require collaborative efforts among all stakeholders that are relevant to this task, and Governments creating an enabling environment for prevention and control efforts to thrive.

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Conflict of interest

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