Review Article

The unending threat of Lassa fever in Nigeria, what can be done; what should be done

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Abstract

Background: Lassa fever is known to be endemic in West African region, and Nigeria bears the most burden of the disease and case fatalities. It is worrisome and disheartening for an emerging infectious disease such as Lassa fever, to linger for 49 years but surge in incidence in a country such as Nigeria, endowed with both human and natural resources.

Methods: The sources of the information presented was obtained through detailed review of literatures using Medline, Ovid and PubMed (search terms Lassa fever, Arenaviridae and viral haemorrhagic fever), case analysis, and surveys undertaking from the field, and relevant websites (such as Nigeria Center for Disease Control, Nigerian Federal Ministry of Health, Centers for Disease Control and Prevention).

Results: The possibility of a large outbreak in Nigeria and other sub-Saharan Countries characterised by dearth of laboratory facilities for prompt diagnosis and personal protective equipment (PPE) and its potential use as a biological weapon has also raised the profile of this disease. Health education of the communities, improved funding through budgetary allocation for surveillance, prompt case management including laboratory facilities, training of health personnel, isolation of cases, barrier nursing, contact tracing, provision of antiviral drugs and vaccines that is effective against this disease and supply of PPE is not only necessary but also expedient in the light of the threat due to Lassa fever.

Conclusion: The weak health-care delivery system in Nigeria, would continue to impede effective control of emerging and re-emerging infectious diseases including Lassa fever. There is an urgent need to provide resources to effectively control and prevent Lassa fever.

Keywords: Lassa fever, Nigeria, threat

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INTRODUCTION

Lassa fever is caused by Lassa virus (LASV), a member of the family Arenaviridae.[1] The virus is enzootic in the multimammate rat *Mastomys natalensis*, a peridomestic rodent commonly found in West Africa.[2] The rodents can become chronically infected at birth and excrete infectious virus in urine and other body fluids, with consequent transmission to humans.[3,4] Although Lassa fever is endemic in West Africa, Nigeria bears the most burden and case

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fatalities from this disease.[5-7] This prompted us to review the current Lassa fever situation and National guideline on its treatment, prevention and control, to optimise it to conform to universally accepted Standard Treatment and Preventive guidelines.

METHOD OF REVIEW

The sources of the information presented were obtained through detailed review of literatures using Medline, Google Scholar, Scopus, African Journal Online, Ovid and PubMed. The last search was performed 4th March 2017. Search terms used include Lassa fever, Arenaviridae, viral haemorrhagic fever, Nigeria, and similar terms such as LASV, very high frequency, were crossed. Case management and surveys undertaking from the field was studied and reviewed. Relevant websites (such as Nigeria Center for Disease Control [NCDC], Nigerian Federal Ministry of Health (FMoH) and Centres for Disease Control and Prevention were visited for updates on Lassa fever. References were reviewed to extend the search, and Nigerian content experts were consulted for additional materials. Our searches yielded 320 citations. Fifty-two articles with either extensive review, comprehensive data and/or from meta-analysis were included.

VIROLOGY

LASV is a single-stranded RNA virus, a member of arenaviruses (AV) family. LASV 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 (GP). The envelope encloses the genome which has helical nucleocapsid measuring between 400 and 1300 nm in length.[8,9] AV are endowed with two segments of ambisense RNA and a nucleoprotein, surrounded by a lipid envelope and a GP. When viewed under an electronic microscope, often the interior contains electron dense granules, traced to be host ribosomes, from where it derive its name (Arena = sandy). The AV are classified according to their geographic distribution.

Genetic sequencing and molecular characterisation indicate the existence of four strains of LASV. These include the strain Josiah, originating from Sierra Leone,[9] the strain Nigeria[10] and strain LP,[11,12] both from Nigeria and the strain AV imported into Germany by a traveller who had visited Ghana, Côte D'Ivoire and Burkina Faso.[13] There is a considerable genetic variation among the strains of the virus, however, phylogenetically, strain AV appears to be the most closely related to strain Josiah from Sierra Leone.[13]

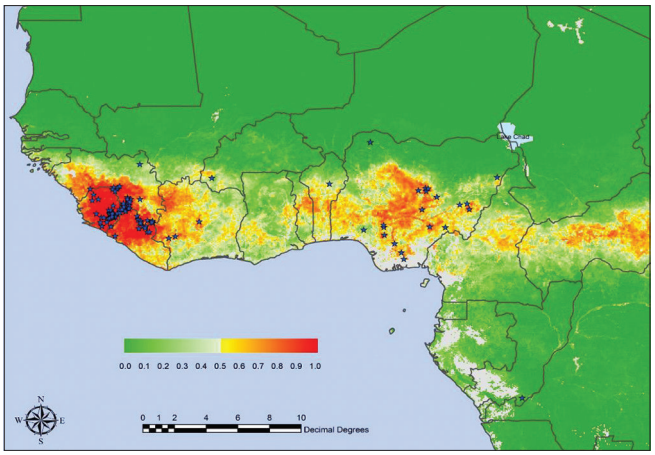

Figure 1: Risk map of Lassa fever in West Africa18. Positive localities indicated by stars. The posterior probability colour scale, from 0.0 (no risk) to 1.0 (highest risk) is shown as an inset

EPIDEMIOLOGY

Lassa fever is endemic in parts of West Africa including Sierra Leone, Liberia, Guinea and Nigeria; however, other neighbouring countries are at risk as the animal vector for LASV, the 'multimammate rat' (*M. natalensis*) is distributed throughout the region [Figure 1]. The global community is not spared due to increased international travel.[13,14] The number of LASV infections per year in West Africa is estimated at 100,000–300,000, with approximately 5,000 deaths.[15-17] Unfortunately, such estimates are crude, because surveillance for disease is not uniformly performed. The lack of laboratory facility for diagnosis, low level of awareness of the disease among both health-care workers and the community, fear of managing the disease among health workers and sociocultural consideration are other factors responsible for under reporting. Lassa fever is responsible for as high as 10%–16% of annual hospital admissions in some parts of Sierra Leone and Liberia, this clearly underscores the negative impact of the disease on the population in West African region.[18]

Lassa fever outbreak in Nigeria is a regular occurrence especially during the dry season every few years. However, it is gradually becoming perennial with high case fatalities [Figure 2]. A serious outbreak in recent memory in Nigeria began in December 2011 and was confirmed in early 2012. Within 6 months of the outbreak i.e., June 2012, 623 suspected cases, including 143 confirmed cases and 93 deaths had been recorded in 23 states out of 36 states of the federation. Based on the 2015 official figures, case fatality rate is significantly high at 37.9% of all cases (53 officially reported deaths). Local media has reported that the Nigerian National Council of Health warned of up to 1,000 potential deaths resulting from the 2015 Lassa fever outbreak [Figure 3]. However, as shown

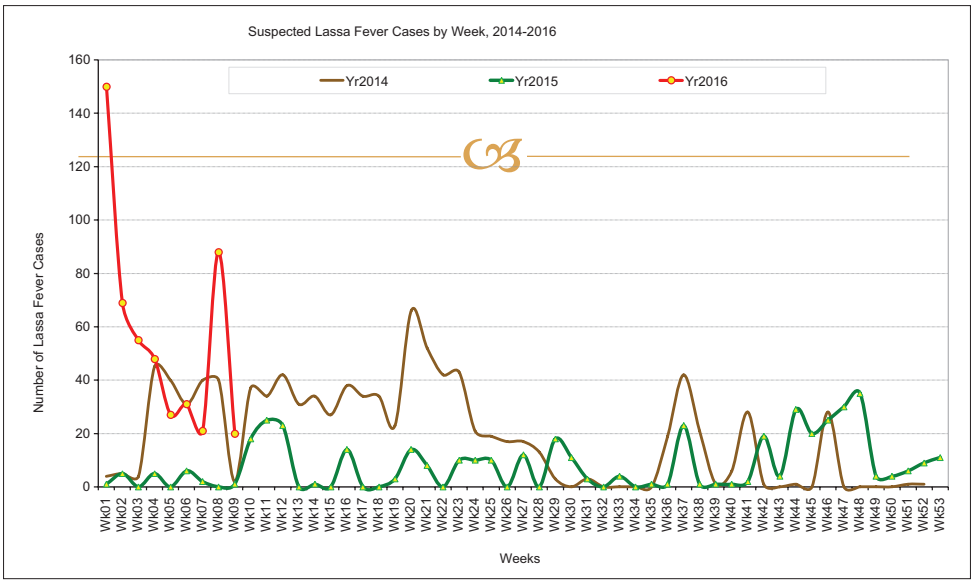

Figure 2: Seasonal variation in the incidence of Lassa fever in Nigeria (2014–2016); Source: Weekly IDSR002 report from State to National, NCDC, Nigeria as presented at ADRM, Ibadan, 23rd March 2016

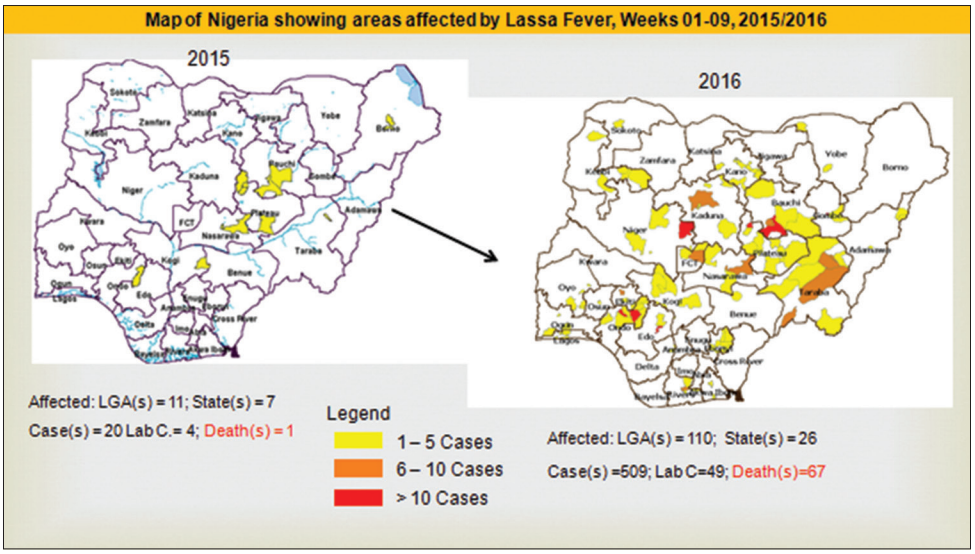

Figure 3: Map of Nigeria showing the incidence of Lassa fever (2015–2016); Source: Weekly IDSR002 report from State to National, NCDC, Nigeria as presented at ADRM, Ibadan, 23rd March 2016

in Figure 4, the official cumulative suspected case count as of January 2016 stood at 159.[7,19]

Despite the lingering threats pose by LASV, there is lack of comprehensive data and often conflicting report of cases of Lassa fever Nigeria. The population density of Nigeria currently stands at 195 people/km^2, disease surveillance and contact tracing may be challenging in densely populated areas; it spread faster among the population, and if rodents are present, the number of cases may increase exponentially. So far most of the densely populated states in Nigeria such as Lagos, the most densely populated with 2607 people/km^2, Imo counts 758 people/km^2 and Kano with estimated 442 people/km^2 have all reported cases of Lassa fever.[20] Other factors militating against effective National Lassa fever response includes weak surveillance reporting, cultural and religious beliefs, especially in the northern Region. Most of the states hosting large numbers of internally displaced persons fleeing Boko Haram insurgents such as Borno, Abuja, Bauchi, Gombe, Kano, Plateau, Taraba and Edo states have recorded an outbreak.[20] Furthermore, at present, health system capacity is weak as most Government owned health facilities in Nigeria lack facility for confirmatory diagnosis of Lassa fever with the exception of two tertiary health facilities currently serving as a national reference laboratory.

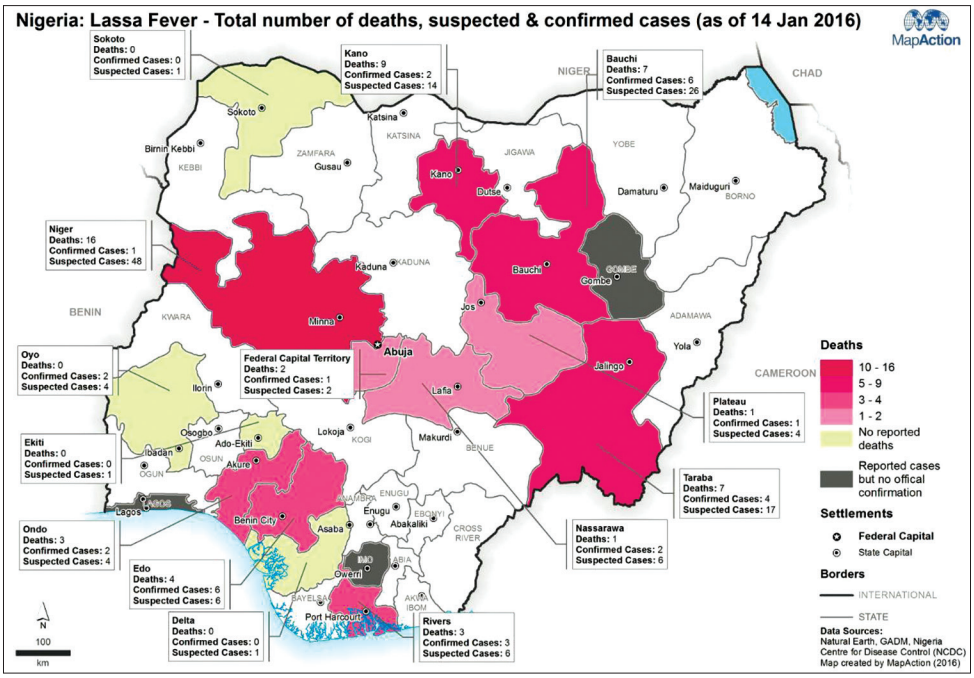

Figure 4: Map of Nigeria showing mortality, suspected and confirmed cases of Lassa fever as of January 2016; Source: ACAPS briefing note: Nigeria – Lassa fever Available at http://reliefweb.int/sites/reliefweb.int/files/resources/start-acaps-nigeria-lassa-epidemic-briefing-note.pdf. Accessed January 2016

PATHOGENESIS

In spite of advances in the understanding of LASV-host receptor interaction, the detailed mechanism of how LASV gain entry into the host cell and further evades and crosses the respiratory and gastrointestinal epithelial cell barrier remains unclear.[21] Respiratory and gastrointestinal entry of AV including LASV has been shown to occur through basolateral receptors.[22] The requirement of the virus for basolateral entry suggests that integrity of the epithelia must be compromised for the virus to get access to the basolateral site. However, as LASV infection is not known to be cytopathic to epithelial[22,23] and endothelial[24] cells and does not appear to alter barrier function,[23,25] external factors affecting epithelia integrity may, therefore, contribute to the infection.

Fortunately, ~80% of LASV-infected individual express subclinical or flu-like manifestations and the overall case-fatality rate is ~1%–2%. However, in hospitalised patients and in some risk groups (pregnant women, children <5 years old, immunocompromised individuals, etc.), the fatality rate can be higher than 50%.[26] After recovery, in 29% of LF patients, acute manifested infection is accompanied by a sensorineural hearing deficit, which accounts for a permanent hearing loss in 18% of survivors.[27,28] Severe LASV infection is characterised by unchecked viraemia, functional liver damage and immunosuppression.[26,29] Host factors such as a cell receptor polymorphism,[30] innate immunity,[31-34] pro-inflammatory cyto/chemokines,[24,34-36] adaptive cell-mediated immunity responses[37,38] as well as differences in pathogenic potential of LASV isolates[39] seem to play a role in the outcome of LASV infection in humans. LASV replicates in target tissues (liver, spleen, lymph nodes and adrenal) without cytopathic effect, and the pathological damage to these tissues is usually not sufficient to implicate organ failure as the cause of death.[40-42] Death from Lassa feer is often due to uncontrolled sepsis-like terminal cardiogenic shock and internal bleeding. In contrast to other causes of viral haemorrhagic fevers such as Ebola and Marburg viruses,[43] a disseminated intravascular coagulation is not involved in Lassa fever pathogenesis, bleeding abnormalities are not common. Indeed, it has been even questioned if Lassa fever is pathologically a haemorrhagic fever.[40,43]

Clinical studies have demonstrated that high viraemia (≥1 × 103 TCID 50/ml) was associated with high fatality rate and elevated viraemia together with a high aspartate aminotransferase (AST) level (AST ≥ 150 IU/L) carried a risk of death in 78% of the cases.[42-44]

CLINICAL MANIFESTATION

The incubation period ranges between 3 and 21 days, most often within 7–10 of exposure. It is estimated that 80 of cases result in mild or asymptomatic infection. Twenty per cent of cases have a severe disease, requiring

hospitalisation.[5,28,45] The case fatalities depend on the stage of the disease at presentation, those that present in stages 3 or 4 carries poor prognosis especially if prompt management is not instituted. The mortality rate among hospitalised patients in Africa is estimated at 15%–20%,[5,46] with reports of up to 50% and even more in some outbreaks among those with severe disease.[47]

The onset of the symptoms and signs of Lassa fever is usually insidious and indistinguishable from those of other febrile illness that are endemic in Africa such as malaria, typhoid fever, Rickettsial infections and infl uenza. Lassa fever is difficult to diagnose clinically but should be suspected in patients with fever (≥38°C) not responding adequately to antimalarial and antibiotic drugs [Table 1]. Early manifestations include fever, headache and generalised malaise; this could be followed by sore throat, nausea, vomiting abdominal pain and diarrhoea. After 4–7 days, those cases that follow mild course will improve. Lassa fever virus clearance is usually complete among those that improve and chronic infection has not been established, and subsequent reinfection is also associated with mild disease. Severe disease seen in about 20% of cases usually manifest with features such as oedema, hypertension, bleeding and shock.[48] Mortality most commonly occurs 10–14 after the onset of the symptoms often due to multi-organ dysfunction. The most useful predictors of Lassa fever are fever, pharyngitis, retrosternal pain and protenuria for diagnosis; and fever, sore throat and vomiting for outcome. Other complications of Lassa fever include mucosal bleeding, pleural effusion, pericardial effusion and acute kidney failure often requiring haemodialysis or haemofiltration. Predictors of poor outcome include high viraemia, high level of AST. Other predictors of poor outcome include a delay between onset of symptoms and admission and delay in commencing ribavirin within the critical first 6 days of the manifestation of the disease.

Neurological abnormalities have also been described including sensorineural hearing loss, tremors and encephalitis.

Table 1: Clinical stages of Lassa fever (adapted from McCarthy 2002)

Stage	Symptoms
1 (days 1-3)	General weakness and malaise. High fever, >39°C, constant with peaks of 40°C-41°C
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side or abdominal pain; conjunctivitis; nausea and vomiting; diarrhoea; productive cough; proteinuria; low blood pressure (systolic <100 mmHg); anaemia
3 (after 7 days)	Facial oedema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

Deafness occurs to some degree in 25%–33% of both mild and severe disease and is often permanent, though hearing may partially returns after 1–3 months in 50% of cases. Spontaneous abortion is a serious complication, with estimated 95% mortality in foetuses of an infected mother especially those in the third trimester of pregnancy.

DIAGNOSIS

Lassa fever is diagnosed by detection of Lassa antigen, antibodies or virus isolation techniques.[8] Specimen for laboratory analysis should be collected as soon as possible from the patient suspected of having the infection. LASV is infectious by aerosol, and the human and rodent specimens should be processed with appropriate precautions in bio safety level IV laboratories.[49,50] LASV can be inactivated in ultraviolet, gamma irradiation, heating from 56°C to 100°C and pH range between 5.5 and 8.5. Chemical agents such as 0.5% sodium hypochlorite, 0.5% phenol and 10% formalin inactivates the virus.[15,51]

Although the real time polymerase chain reaction assays are very sensitive in establishing the diagnosis,[52] their applicability in the West African countries where Lassa fever is endemic is limited by issues of strain variation, cross contamination, lack of qualified personnel, inadequate facilities and expense.[53-55] Another valuable diagnostic tool is the rapid diagnostic immunoblot assay for Lassa fever. Unfortunately, its usefulness is limited by its low capacity to provide prognostic information and also its low sensitivity.[56]

Virus antigen can be detected by enzyme linked immunosorbent assays (ELISA) using LASV-specific antibodies. These tests are easy to handle and rapid and can be performed with inactivated specimens, which is advantageous in the field if sophisticated equipment is not available. The indirect fluorescent-antibody (IFA) test has traditionally been employed in the laboratory diagnosis of acute LASV infection.[57,58] Although the interpretation of IFA results is complicated by the presence of IFA during both acute and convalescent stages of infection and by the subjective nature of the assay, the appearance of IFA antibody early in the course of Lassa infection may be useful in identifying patients with poor prognosis. However, due to lack of specificity in populations in non-endemic areas,[59] the technique has been largely replaced by ELISA for LASV antigen and LASV-specific immunoglobulin M and immunoglobulin G antibodies.[60-63]

TREATMENT

The antiviral drug ribavirin is reported to be an effective treatment if given early in the course of clinical illness

preferably within 6 days of onset of signs and symptoms for maximum benefit. Ribavirin, a broad spectrum guanosine analogue antiviral, possesses good activity against LASV. Intravenous treatment in standard doses leads to plasma concentrations that are significantly higher than the minimal inhibitory concentration, while oral treatment, limited by side effects and a 50% bioavailability, leads to low to borderline concentrations, doubtfully inhibiting LASV *in vivo*.[46] In a study of Lassa fever in Sierra Leone, West Africa.[64] it was observed that patients with a high risk of death who were treated for 10 days with intravenous ribavirin, begun within the first 6 days after the onset of fever, had a case-fatality rate of 5% (1 of 20) ($P = 0.0002$ by Fisher's exact test), while patients whose treatment began seven or more days after the onset of fever had a case fatality rate of 26% (11 of 43) ($P = 0.01$). The study confirmed the efficacy of ribavirin in the treatment of Lassa fever and that it should be used at any point in the illness, as well as for post-exposure prophylaxis. Both oral and intravenous ribavirin were beneficial, with the latter showing a stronger effect in higher risk cases. The recommended intravenous dosing is based on this pivotal study, with a 2.4 g loading dose, followed by 1 g every 6 h for 10 days, for average weight adults. Oral ribavirin may also be indicated for post-exposure prophylaxis in the dose of 500–600 mg every 6 h for 7–10 days. It is noteworthy to note that dosage adjustment is required for patients with creatinine clearance <50 ml/min. Ribavirin's main adverse effect is dose-dependent haemolysis, appearing in ~20% of patients, usually resulting in the modest decrease in haematocrit.[64] Oral treatment is associated with many more adverse effects, including nausea, vomiting, diarrhoea, metal taste, dry mouth, myalgia, fatigue, headache, jaundice, rash, tachycardia, thrombocytosis, increased lipase levels, mood changes and insomnia. However, no mortality was reported after ribavirin treatment.[46] Ribavirin is teratogenic and embryotoxic in rodents and is contraindicated during pregnancy and lactation, although due to the grave prognosis of Lassa fever in pregnant women, the risk should be weighed against its benefit.

Similar to other severe haemorrhagic fevers, supportive treatment is the cornerstone of clinical management of Lassa fever. Early supportive care with rehydration and symptomatic treatment has also been seen to improve survival (WHO 2015).[6] The main goal is volume resuscitation, accounting for third spacing, diarrhoea and vomiting while avoiding volume overload due to the risk of pulmonary oedema. Other goals are electrolyte balance and respiratory support. Convalescent plasma, although beneficial in some animal experiments, has failed clinical studies, probably due to lack of neutralising antibodies.[64,65] There is currently no vaccine to protect against Lassa fever.

CHALLENGES IN LASSA FEVER MANAGEMENT

Clinical

Clinical diagnosis requires a high index of suspicion as signs and symptoms are indistinguishable from malaria, typhoid and other endemic infectious diseases in sub Saharan Africa. Bleeding is a late complication, often seen in about 20% of cases on presentation, high index of suspicion is, therefore, necessary to make a prompt diagnosis. Lassa fever may masquerades as acute surgical abdomen; this may pose serious threats especially in health facilities with dearth of personal protective equipment or suboptimal standard infection prevention and control measures. Most patients present late with stage 3 or 4 diseases; this underscores the need for capacity building (prompt diagnosis and treatment). Need to have dedicated intensive care gadgets (dialysis, theatre, monitors - electrocardiogram, electroencephalogram, USS, i-STAT etc.).

Logistics

Currently, diagnosis of LASV is achieved through support from international donors. Early diagnosis and favourable treatment outcome of Lassa fever management are impeded by unnecessary delay in transportation of specimen and poor quality of samples submitted to the reference laboratory laboratories. Federal Government through the FMoH and NCDC need to step up and strengthen the health care delivery system to contain Lassa fever and other emerging and re-emerging infectious diseases in Nigeria.

Surveillance

The weak surveillance system of reporting epidemic prone diseases such as Lassa fever need to be strengthened. This can be achieved through training and provision of logistic support to disease surveillance and notification officers involved in surveillance activities to facilitate prompt reporting of cases at both wards, local government and state levels.

CONCLUSION

The weak health-care delivery system in Nigeria, unarguably due to misplaced priority by policymakers to appropriate enough resources to strengthen the health institutions would continue to impede effective control of emerging and re-emerging infectious diseases including Lassa fever. There is an urgent need to provide resources to effectively control and prevent Lassa fever. As it is currently in Nigeria, outbreaks of Lassa fever and other epidemic prone diseases

containment is to a large extent is achieved with the support of international health organisations. The country needs to show commitment by providing all the needed resources to combat Lassa fever.

Health-care workers need to be adequately trained on diagnostics, active case management in designated isolation centres, contact tracing and active surveillance, infection prevention and control measures while managing cases and handling infectious wastes, laboratory specimens and safe burial practices of patients that had died from Lassa fever. Other measures include health education on control of the rodent that harbour the LASV.

RECOMMENDATION

Lassa fever seems a perennially important health problem in Nigeria. Under recognition and underreporting will diminish as clinicians become more familiar with the disease and as medical facilities expand in rural areas. This can be achieved through continued clinician/health workers training and reinforcement to ensure early detection and reporting of cases. There is urgent need to strengthen and reinforce active surveillance, contact tracing and continued outbreak investigation. Health education and community education resource development and policy development at state level for coordination, surveillance, case management, communication and social mobilisation is expedient. Strengthening of laboratory network and logistic support for prompt transportation of specimen and prompt release of documented results is essential for effective case management and planning. Furthermore, the geographical distribution of Lassa fever in Africa remains ill-defined; knowledge of it is essential to the establishment of surveillance, to the selection of areas for study of endemic transmission and host relationships, and to the eventual institution of control measures. This can be achieved through collaborative studies and surveys within and outside the African region. The research should include studies on the biological behaviour of the viral agents and its activity in rodent host, person to person transmission, rodent distribution and control, surveillance, environmental factors and evidence-based case management of cases.

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Conflicts of interest
There are no conflicts of interest.

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