Title:
Lassa Fever - Epidemiology, Clinical Features, Diagnosis, Management and Prevention.

Running title: Lassa Fever

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KEYPOINTS

- Lassa fever (LF) is an acute zoonotic disease of humans endemic to West Africa, caused by the Lassa virus (LASV), an enveloped, single-stranded RNA arenavirus.
- First discovered in 1969 in Nigeria, Lassa fever outbreaks continue in West Africa with up to 500,000 cases of LF annually with 10,000 deaths. Case fatality rates in hospitalised patients is up to 50%.
- Primary infection of humans occurs from contact with LASV-infected rodents. Secondary person to person transmission occurs and can be prevented by instituting strict infection control measures.
- The incubation period ranges from 2-21 days. Initial presentation of LF is difficult to distinguish from other febrile illnesses.
- LF presents with a wide spectrum of clinical manifestations from the asymptomatic, mild, moderate to severe fulminant haemorrhagic disease.
- Treatment involves supportive care with appropriate fluid and electrolyte balance, oxygenation, organ support and specific antiviral treatment with Ribavirin or Favipiravir. Vaccines are under development.

Author declarations:

Conflicts of Interest: All authors have an interest in global public health and emerging and re-emerging infections. All authors have no other conflict of interest to declare.

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**SUMMARY**

Fifty years after its first discovery in 1969 in Nigeria, Lassa fever outbreaks continue in West Africa. Annually, an estimated 300,000 to 500,000 cases of LF occur in west Africa with up to 5 to 10,000 deaths. Travel associated LF cases outside West Africa have been recorded in the USA, Canada, United Kingdom, Netherlands, Israel, Sweden and Germany. Primary infection of humans occurs from contact with Lassa virus (LASV)-infected rodents and exposure to their excreta (urine or faeces) or blood or meat. Secondary person-to-person transmission in humans has been recorded in people living in the rural communities, and within hospitals where proper infection prevention and control practices are inadequate. Sexual transmission occurring months after recovery from acute disease can occur. The incubation period of LF ranges from 2–21 days. Symptoms of Lassa fever are difficult to distinguish from malaria, typhoid, dengue, yellow fever and other viral haemorrhagic fevers. LF presents with a wide spectrum of clinical manifestations from the asymptomatic, mild to severe fulminant disease. Upto 80% of LF cases have non-specific symptoms and may remain undiagnosed. In severe cases multi-organ failure, with disseminated intravascular coagulation, and bleeding from mucosa of all organs occurs. Neurological involvement leads to fits, tremors, gait disturbance, disorientation and loss of consciousness and sensorineural deafness, and abortion. Treatment with Ribavirin can improve treatment. Whilst the overall mortality is between 1% to 15%, the mortality in hospitalised patients is much higher up to 70%. Lassa Fever should be considered in the differential diagnosis of anyone returning from travel to West Africa. There is an urgent need for rapid field-friendly diagnostics and preventive vaccine.
INTRODUCTION

Lassa fever (LF), is an acute zoonotic disease of humans that is mainly endemic to West African countries of Guinea, Liberia, Nigeria, and Sierra Leone.\(^1\)\(^-\)\(^3\) Other countries such as Mali, Benin, Togo, Cote d’Ivoire, Burkina Faso, and Ghana have reported sporadic LF cases.\(^1\),\(^5\) LF is caused by the Lassa fever virus (LSAV), one of several viral causes of ‘haemorrhagic fever’ which can result in severe life-threatening systemic illness, characterized by disseminated intravascular coagulation, widespread mucosal bleeding, multi-organ failure and shock requiring advanced life support.\(^6\) Fifty years after its first discovery in 1969 in Nigeria, LF outbreaks have continued in West Africa and LF is now on the WHO Blueprint list of priority pathogens under its Research and Development blueprint for action.\(^7\),\(^8\) Travel associated LF cases been recorded in several countries outside West Africa including the USA, Canada, United Kingdom, Netherlands, Israel, Sweden and Germany, creating much media hype.

HISTORICAL

Lassa fever first attracted global attention when missionary nurses in Nigeria developed a mysterious febrile illness in 1969.\(^9\)\(^-\)\(^12\) They are thought to have acquired LASV infection while working in the mission station in the town of Lassa in the State of Borno, north-eastern Nigeria. The nurses were evacuated to ECWA Hospital in Jos for further treatment. Two of three missionary nurses at ECWA Hospital died, and a doctor who performed an autopsy on one of the nurses\(^11\)\(^-\)\(^13\) also fell ill and subsequently died. The third missionary nurse was flown to the United States where she was diagnosed with Lassa fever and survived. The Lassa fever virus itself was first isolated from the nurse at the Yale Arbovirus Unit, Yale School of Medicine in 1970.\(^11\),\(^12\) The chain of Lassa virus transmission was traced back to the missionary nurses.

EPIDEMIOLOGY

**Causative agent - Lassa virus (LASV):**

Lassa virus (LASV) is an enveloped, single-stranded, bi-partite Ribonucleic acid (RNA) virus which belongs to the family Arenaviridae.\(^11\),\(^14\) The virus is spherical with an average diameter of 110-130 nanometers, and in cross-section, they show ‘grainy particles’ (ribosomes acquired from host cells) and thus the Latin name “arena”, which means “sandy”. The RNA genome encodes 4 proteins: the nucleoprotein (NP) and glycoprotein precursor (GPC) on the Small (S) segment, and the RNA-dependent RNA-polymerase (L) and matrix RING Zinc-finger protein (Z) on the Large (L) segment.\(^14\),\(^15\) The LASV has a high
level of nucleotide diversity between strains which is correlated to clustering of strains around geographic locations. This has led to recognition of 6 major LASV clades or lineages: I–III in Nigeria; clade IV covering the countries of Sierra Leone, Guinea, and Liberia; and clade V in southern Mali, and a more recent clade VI, originating from Togo. An important feature is the ability of these strains to evolve over time. A new lineage has recently been discovered in the recent Nigerian LF outbreak and if confirmed will make a total of 7 lineages. The high genetic variability of Lassa virus is relevant for the design of diagnostic molecular assays as well as for the development of a universal LF vaccine that can be used in different geographical settings irrespective of circulating strain. It may also have a bearing on the clinical presentation and severity of infection.

Geographical distribution:
Lassa fever is endemic to West Africa (Fig.1) with cases being reported from Nigeria, Benin, Liberia, Sierra Leone, Guinea, Mali, Senegal and Ghana. However, the true geographical prevalence, incidence and distribution of LF has been difficult to ascertain due to a large proportion of cases being asymptomatic; the protean and non-specific wide spectrum of clinical presentations; paucity of effective surveillance systems; lack of specific point of care diagnostic tests for LF, human migration, civil unrest, deforestation, among other. Exportation of travel associated Lassa fever cases outside West Africa to the USA, Canada, United Kingdom, Netherlands, Israel, and Germany by aid workers, missionaries, foreign military personnel is well documented.

Animal reservoir:
The animal reservoir for LASV is considered to be the “multimammate rat” Mastomys natalensis (Fig.2a, 2b). This is a rodent of the genus Mastomys which is ubiquitous in West Africa and breeds prolifically. The rats are infected in utero and remain infected for the rest of their life. Rats infected with LSAV do not become ill, but they shed the virus in their urine and faeces. Whilst M. natalensis was considered to be the natural reservoir of LASV, but other rodent reservoirs (M. erythroleucus and Hylomyscus pamfi) discovered recently could also affect distribution of LASV and LF cases over time.

Mode of transmission of LASV to humans:
Primary infection of humans occurs from direct or indirect contact with LSAV-infected rodents. Persons at greatest risk of acquiring LASV infection are those living in rural areas where the Mastomys rodents are usually found, especially in communities with poor sanitation or crowded living conditions. The Mastomys rodents invade homes of humans during the dry season in search of food. The source of LSAV infection for humans is exposure to urine, faeces, blood or meat from LSAV-infected Mastomys rodents. Direct
contact with these materials, through touching soiled objects, eating contaminated food, or exposure to open cuts or sores, can lead to infection.\textsuperscript{39-47} Infection is thought to occur from direct inoculation of mucous membranes or from inhalation of aerosols produced when rodents urinate or defecate. The relative frequency of these modes of transmission remains unknown.

Secondary person- to- person spread in among humans has been recorded in people living in the community in overcrowded dwellings, families in the context of providing care to a sick person and in communities in the context of burial practices. Healthcare workers are at increased risk of LASV infection. Nosocomial transmission of LASV occurs within hospitals among and between patients and healthcare workers because of poor adherence to infection prevention and control practices.\textsuperscript{46-54} LSAV can transmit through direct contact with the blood, urine, faeces, or other bodily secretions or via accidental inoculation with sharp needles and contact with contaminated equipment.\textsuperscript{50,51} Large healthcare facility LF outbreaks are fuelled by transmission where barrier nursing and infection control practices are inadequate.\textsuperscript{52} Staff and other patients on maternity wards are at increased risk since Lassa fever is an important cause of spontaneous abortion and the virus is present in the blood and placenta of aborted foetuses.\textsuperscript{56}

There have been reports of sexual transmission occurring months after recovery from acute disease.\textsuperscript{51} Aerosol transmission between humans in natural settings has not been proven but artificial production of infectious aerosols has.\textsuperscript{36} The 1970 LF outbreak in Nigeria\textsuperscript{10,12} was attributed to airborne transmission from a female patient with severe pulmonary disease although definitive evidence of airborne transmission from subsequent outbreaks has not been forthcoming. Disease outbreaks appear to occur commonly through multiple independent reservoir-to-human transmissions.\textsuperscript{17,22} The period of infectivity of patients with LF is dependent on the clinical state, with the highest infectivity periods being in late in the course of severe disease in the haemorrhagic phase.\textsuperscript{48,52,59,60}

\textit{Age, gender and susceptibility:}

Lassa fever can affect all age groups and both genders.\textsuperscript{4,49,47} Paediatric Lassa fever is known to occur more commonly in male children for yet unknown reasons. Presenting as an acute febrile illness, the case fatality rate may approach 30\% in children with generalised oedema, abdominal distension and bleeding. Genetic and immunological studies are ongoing in to provide better understanding of the pathogenesis and underlying protective mechanisms operating in LF.\textsuperscript{57-60}

\textit{Environmental and seasonal factors and risk of transmission:}
Mastomys rats live in savannah and forests of west Africa, and breed frequently, producing large numbers of offspring. They rapidly colonize human homes, huts, sheds and food storage areas. Since they live in and around humans and scavenge on leftover human food items or poorly stored food, direct contact transmission is common, resulting in the relatively efficient spread from LASV infected rats to humans. The seroprevalence of LASV antibodies among people living in houses correlates with households with large numbers of rats, due to close contact with contaminated surfaces, utensils and foodstuffs. Human LASV infection may also occur when rodents are trapped and prepared for cooking and consumption, a common practice in some parts of West Africa.

Factors which may affect the increase in LASV transmission and spill-over into human populations include seasonal changes, urbanization, environmental sanitation, deforestation and occurrence of disasters with involuntary migration. This reinforces the need for a One-Human-Environmental-Animal Health (ONE HEALTH) approach for surveillance, control, early detection of spill-over into human populations, and rapid emergency public response during outbreaks.

**LASSA FEVER OUTBREAKS (2016-2019)**

Since 2016, there has been an increase in the number of reported LF cases from West Africa, especially in Nigeria, Benin and Togo. Whilst this increase seems unlikely to be due to the emergence of a new LASV variant other factors may be playing a significant role: increased human-roden interactions, improved case recognition, increasing awareness and availability of diagnostics and therapy, increase in surveillance, changing demographics, other environmental changes or a combination of these factors. Nigeria has experienced several outbreaks with large numbers of LF cases in 2018 and 2019. There have been LF cases reported from Benin (54 cases and 28 deaths), Togo (2 cases), Liberia (7 cases, 3 deaths) and Sierra Leone (2 cases). Cases have also been reported outside West Africa, exported by travellers to Sweden and Germany. The case in Germany resulted in limited secondary transmission when twelve days after having been exposed to the corpse of a Lassa fever case imported from Togo, a symptomatic undertaker tested positive for LASV RNA.

Out of the countries in West Africa that have reported LF outbreaks, Nigeria by far has had the largest LF disease burden with 23 states reporting LF cases (Fig.3). In Edo State, a recent spatial mapping and analysis of outbreaks supports earlier reports that some communities in the often-crowded university town of Ekpoma have geographical hotspots of LF cases. Hotspot identification is important in planning of an effective control
programs because it can reveal common environmental factor(s) causing the dense clustering of the disease in particular geographical areas.23,71,72

**Ongoing outbreak of LF in Nigeria:**
The Nigeria Centre for Disease Control (NCDC) reported an unusually large increase in Lassa fever cases in 2018, with a total of 3498 suspected cases from 1 Jan to 31 Dec 2018.22,28,54 Of these, 633 cases were confirmed positive by laboratory testing. Public health officials were concerned that the Lassa fever outbreak in Nigeria in 2018 might be driven by previously unknown factors, or a new or more virulent Lassa virus strain. From 1st January - 24th March 2019, a total of 1,924 suspected cases were reported from 73 local government areas involving 21 States (Fig.3), with each state having recorded at least one confirmed LF case. Out of these, 495 were confirmed positive, with 117 deaths giving a Case Fatality Rate of 22.9% for confirmed LF cases.68 An important challenge is to define the diversity across LSAV lineages and strains and the ability of these strains to evolve over time. Global public health authorities are concerned that the 2018-2019 LF outbreak in Nigeria might be driven by previously unknown factors, or a new or more virulent LSAV strain. Real-time analysis of 36 LASV genomes from the 2018 Nigeria LF outbreak17 revealed that LSAV genomes appear to be drawn from a diverse range of viruses previously observed in Nigeria rather than from a single dominant strain. The extensive diversity and phylogenetic due to intermingling with previous LSAV strains suggest independent zoonotic transmission events with humans becoming infected through contact with rodent faeces or urine rather than human to human transmission.

**CLINICAL FEATURES**

**Incubation period, Symptoms and Signs:**
The incubation period of LF ranges from 2-21 days.1,2,4 Signs and symptoms of Lassa fever manifest upto 3 weeks after primary LSAV infection. The infection to disease ratio is not known. A wide spectrum of clinical manifestations occur in patients with LF, ranging from the asymptomatic, through mild, moderate to the severe and fulminant disease (Table 1).4,6,9,52 Upto to 80% of LASF human infections cause mild illness and thus LF may remain undetected and undiagnosed in the community. The onset of the disease is usually gradual, starting with non-specific symptoms of fever, general weakness, malaise and headache. After a few days, symptoms worsen and sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, arthralgia, and pain in the abdomen and back may follow. In up to one fifth of infected individuals, the disease may progress to more serious symptoms. In severe cases there may be facial swelling, petechiae and bruising,
respiratory distress, hepatitis, renal failure, bleeding from the mucosa of the mouth, nose, vagina or gastrointestinal tract, fits, tremors, gait disturbance, disorientation and loss of consciousness.\textsuperscript{4,6,9,52} Bleeding is a feature of about 30\% of LF patients (Fig. 4).\textsuperscript{9,67,52} LF can present as an acute abdomen and should be considered as a differential diagnosis of ‘febrile surgical acute abdomen’ and acute appendicitis in in children in West Africa.\textsuperscript{73,74}

**Clinical Complications:**

Severe cases of LF manifest bleeding from mucosal surfaces (conjunctiva, mouth and gut), disseminated intravascular coagulation, pleural or pericardial effusion, spontaneous abortion. renal failure, multi-organ failure, hypovolaemic sepsis-like shock, encephalitis, encephalopathy and bilateral or unilateral eighth-nerve deafness.\textsuperscript{4,9,75-77} The specific pathogenesis and molecular pathways that underlie these features remain poorly understood.\textsuperscript{24,59}

A common long-term sequelae of Lassa fever is deafness from sensorineural hearing loss.\textsuperscript{77-80} Auditory nerve spiral ganglion degeneration and damage to cochlear hair cells and immune-mediated systemic vasculitis have been suggested as underlying causes.\textsuperscript{80} Various degrees of deafness occur in approximately one-third of infections, and in many cases hearing loss is permanent. Severity of the disease does not appear to affect this complication and deafness has been reported in mild as well as in severe cases. Other long-term neurological complications include seizures, gait disturbances, tremors and encephalitis.

Lass Fever occurring in pregnancy can cause severe disease, high maternal death rates in the third trimester, and spontaneous abortion with an estimated 95\% mortality in foetuses.\textsuperscript{56,81,82}

**Mortality, risk and clinical predictors of management outcomes:**

Whilst the overall mortality of LF in the community is low with only 1\% of all LASV infections result in death, approximately 15\% to 50\% of hospitalized patients die within 14 days of onset of disease.\textsuperscript{82,83} Pregnant women, children under 5 years, and individuals with HIV or other immunosuppressive conditions have an increased risk of death. Complications associated with poor management outcomes in hospitalised patients include acute kidney injury, liver failure, encephalopathy, seizures, reduced consciousness, disseminated intravascular coagulation with mucosal bleeding, septic shock progressing to multi-organ failure.\textsuperscript{79,82,83} Studies of LF outbreaks in Nigeria show that patients with ≥1 feature of severe illness such as acute kidney injury, encephalopathy, shock, DIC and bleeding are associated with increased case fatality rates (Table 1).\textsuperscript{20,23,75,84}
LABORATORY DIAGNOSIS

Early identification of patients with LF is crucial for maximizing the benefit of available antiviral therapy, and for instituting infection control measures. Identifying the causative microbial cause of an acute febrile illness in sub-Saharan Africa can be challenging diagnostically. Since the symptoms of LF are non-specific, LF is difficult to distinguish from other common endemic microbial causes of fever such as malaria, shigellosis, typhoid fever and other viral haemorrhagic fevers such as Ebola virus disease and yellow fever, both of which are also endemic to West Africa.

Specimen collection:
Making an accurate and specific definitive diagnosis of LSAV requires tests that are available for use only in high containment laboratories. Since LSAV can spread from person-to-person virus spread via bodily fluids, laboratory staff should be aware of the risk of LSAV infection when processing potentially infectious patient specimens. Poor sample handling poses a safety hazard. The WHO has issued step-by-step guidance on how to safely collect blood and other clinical samples from patients suspected to be infected with LSAV and how to transport the patient samples to diagnostic reference laboratories. Laboratory specimens may be hazardous and must be handled with extreme care. Ideally, every laboratory specimen for diagnosis of Lassa fever should be tested in a BSL-3 or 4 laboratory and should be treated as a highly infectious specimen. Lassa fever and other VHFs are category 4 pathogens. In outbreak situations, rapid deployment of mobile biosafety level-3 laboratories have been successfully used in the field.

Lassa virus diagnostic tests:
A range of LASSV diagnostic tests are available from cell culture, immunofluorescence assay, complement fixation tests, Enzyme-Linked Immunosorbant Assays (ELISA) for LASSV antigens and IgM antibodies, Polymerase chain reaction (PCR) with several assayd and targets, lateral flow assays and other in house rapid tests developed by research groups. Definitive testing for LASSV can only be done at reference laboratories, through virus isolation by cell culture. The virus itself may be cultured in 7 to 10 days, but this procedure should only be done in a high containment laboratory (BSL-4). Active infections can also be diagnosed by LASSV-specific PCR, and LASSV-specific IgG or IgM antibody response or LASSV antigens shed during replication. LASV RNA is detected using a nucleic acid amplification test, which can include techniques such as PCR, loop-mediated isothermal amplification (LAMP) and strand displacement assays. However, Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) is the gold
standard for making a definitive diagnosis of LASV infection in the early stages of the LF disease. 89,90, 93, 94

Detection of LASV antibodies and antigens can be used to complement diagnosis. These can be detected by indirect immunofluorescence assay test (IFA or IIFT), western blot (WB), rapid diagnostic test (RDT) formats or by Enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies. Many laboratories use in-house LASV assays.91 For making post-mortem diagnosis, immunohistochemistry is performed on formalin-fixed tissue specimens.

**Diagnostic tests under evaluation:**

A rapid immunoassay for the LASV subtypes found in Sierra Leone and a similar test that is designed to detect all strains is being assessed in Nigeria.93,94 Emerging technologies, such as CRISPR-based specific high-sensitivity enzymatic reporter unlocking, may soon provide multiplexed and portable nucleic acid detection platform for testing for new LASV strains.95 There remains an urgent need for field friendly, cheap, accurate and rapid diagnostic tests for outbreak investigation and patient management.96

**Specimen type and LASV detection:**

LASV can be present in several body fluid or tissues such as blood, urine, pleural fluid, semen, cerebrospinal fluid, throat swabs and sputum. Acute LASV infections detected in the CSF can be negative in blood76 and LASV can persist in the central nervous system, urine and semen long after viral clearance in the blood.97

**MANAGEMENT OF PATIENTS**

**Supportive care:**

Supportive care is important and appropriate fluid and electrolyte balance, oxygenation, and blood pressure control must be maintained.1,2,4,98 To maintain renal function dialyses is necessary (Fig. 5). Secondary bacterial infections should be treated with antibiotics. The treatment of patients with suspected or confirmed LSAV infections during outbreaks in dedicated LF treatment wards with facilities for enhanced supportive care including dialysis and respiratory support could reduce nosocomial case fatality and transmission rates.

**Specific anti-viral therapy:**

Specific antiviral therapy with the antiviral agent Ribavirin can improve treatment outcome if given early in the course of illness.98,99 However, whilst Ribavirin has been extensively used for treatment and as post-exposure prophylaxis, treatment of LF with
ribavirin has been evaluated in only a single non-randomized clinical\textsuperscript{100} and in retrospective analyses of field studies.\textsuperscript{83} Animal and/or human studies of the efficacy of ribavirin against the multiple LASV lineages and at various stages of LF disease progression are needed, as well as assessment of different administration routes and dosing regimens.\textsuperscript{7}

**Newer therapies:**

Favipiravir is another broad-spectrum RNA inhibitor that has broad-spectrum activity against RNA viruses and has been shown to decrease LASV viremia in animal models.\textsuperscript{101} Monoclonal antibodies specific for LASV neutralization cloned from West African LF survivors\textsuperscript{102} appear to bind to individual or combined Lassa GP protein subunits, which can potently neutralise all four LASV lineages—an early start to immunotherapeutic development. Human monoclonal antibody therapy appears to protect non-human primates against advanced Lassa fever.\textsuperscript{103}

**PREVENTION**

*Avoiding or reducing contact with rats:*

Avoiding contact with *Mastomys* rodents can reduce the risk of primary transmission of LASV to humans.\textsuperscript{104} Placing food away in rodent-proof containers and keeping the home and surroundings clean, as well as trapping in and around homes can help reduce rodent populations and contact with their droppings or urine. Further, educating people in high-risk areas about ways to decrease rodent populations in their homes will reduce risk of LASV infection.

*Preventing nosocomial spread:*

Strict adherence to standard infection prevention and control precautions is mandatory for prevention of human LASV infection spread in health-care settings especially when caring for patients with fever of undetermined origin and suspected viral haemorrhagic fevers. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe burial practices. Health-care workers caring for patients with suspected or confirmed Lassa fever should take measures to prevent contact with the patient’s blood and body fluids and contaminated surfaces or materials such as clothing and bedding. Laboratory workers should be trained to handle and process biological samples and process these in suitably equipped laboratories under maximum biological containment conditions.

When caring for patients with confirmed or suspected LF, transmission of LASV in healthcare facilities through person-to-person contact or nosocomial routes can be avoided by following strict infection control procedures and use of VHF isolation...
precautions and barrier nursing methods). All healthcare facilities caring for suspected or confirmed LF cases should use generic precautions include wearing protective clothing, such as masks, gloves, gowns, and goggles; using infection control measures, such as complete equipment sterilization; and isolating infected patients from contact with unprotected persons until the disease has run its course.

**Vaccines:**
The recurrent and increasing epidemic of Lassa fever has had major socio-economic consequences on West Africa countries making the development of effective medical counter-measures urgent. One of these measures is development of effective vaccines against LF. Currently there are no effective LF vaccines. In 2017, the WHO released a Target Product Profile for LASV vaccine development, and in 2018, the US Food and Drug Administration added LF to its priority list of infections for development of preventive measures. Several vaccines are under development, including LASSARAB and an inactivated recombinant LASV. The recombinant VSV-LASV-GPC vaccine is among one of the leading candidates developed thus far and is targeted for accelerated development by The Coalition for Epidemic Preparedness Innovations (CEPI) who are supporting the development of Lassa vaccine candidates.

**CONCLUSIONS**

Whilst malaria, typhoid fever, and many other tropical infections are much more common, the diagnosis of Lassa fever should be considered in febrile patients returning from West Africa, especially if they have had exposures in rural areas or hospitals in countries where Lassa fever is known to be endemic. Health-care workers should have a high index of clinical suspicion of the possibility of Lassa in returning travelers to Europe or USA with fever. When a patient suspected to have Lassa fever is seen, the health worker or attending physician should immediately contact local and national public health authorities for advice and to arrange for laboratory testing. There is a great need for point-of-care diagnostics for detecting LF cases to enable timely isolation and treatment and for defining outbreaks more accurately.

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**Figure 2:**

2a: The multimammate rat *Mastomys natalensis* (courtesy of Prof Danny Asogun)

2b: Ventral surface of *Mastomys natalensis* showing two rows of mammary glands (Courtesy of Prof George Akpede)

**Figure 3:** Geographical distribution of Lassa Fever cases in Nigeria (2018-2019)

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<td>COMPLICATIONS</td>
<td>POOR PROGNOSTIC INDICATORS</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Renal failure</td>
<td>High viral load and viraemia</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Grossly abnormal Liver function tests (High AST levels)</td>
</tr>
<tr>
<td>Multi-organ Failure</td>
<td>Renal failure (high urea and creatinine)</td>
</tr>
<tr>
<td>Widespread bleeding</td>
<td>Severe bleeding</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Shock - hypovolaemic and sepsis</td>
<td>Third trimester pregnancy</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Generalised oedema</td>
</tr>
<tr>
<td>Foetal loss (spontaneous abortion)</td>
<td></td>
</tr>
<tr>
<td>Deafness due to 8th nerve sensorineural loss</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
## Table 2

Case studies of Lassa Fever at Irrua Specialist Teaching Hospital, Irrua, Nigeria

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Adults</th>
<th>Children</th>
<th>Pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okokhere et al</td>
<td>2011 - 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asogun et al</td>
<td>2009 - 2010</td>
<td>2009 - 2015</td>
<td></td>
</tr>
<tr>
<td>Akpede et al</td>
<td>2009 - 2017</td>
<td></td>
<td>2009 - 2018</td>
</tr>
<tr>
<td>Okogbenin et al</td>
<td>2009 - 2018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. of patients *: 198, 284, 57, 30

Deaths - No. (%): 61 (30.8), 68 (24.0), 16 (28.1), 11 (36.7)

### Factors associated with death (**Odds ratio [95% CI])**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>Pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.2 [2.11, 18.2]</td>
<td>1.9 [1.1, 3.4]</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17.68 [4.38,71.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>(not applicable*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Shock</strong></td>
<td>ND</td>
<td>No</td>
<td>Yes (30.8 [3.39, 285.4])</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Yes** (ND)</td>
<td>Yes (15 [8, 28])</td>
<td>Yes (31.5 [2.98, 333.2])</td>
</tr>
<tr>
<td>Yes</td>
<td>29.57 [3.17, 275.7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31.5 [2.98, 333.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>No (2.86 [0.78, 10.58])</td>
<td>Yes (15 [7, 34])</td>
<td>Yes (31.5 [2.98, 333.2])</td>
</tr>
<tr>
<td>Yes</td>
<td>15.6 [4.21, 72.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(not applicable*)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND = no data

*The same factors were associated with both maternal death and fetal loss;

*9/11 patients with versus 0/19 without extra-vaginal bleeding died.

**Data not available on the numbers with acute kidney injury but both the mean blood urea nitrogen (p<0.001) and mean serum creatinine (p <0.001) were significantly higher among those who died compared with those that survived.

*Defined by the presence of coma and/or seizures.