International Journal of Current Medical Research *http://www.wrpjournals.com/IJMSC*
Vol. 4, No. 6, pp. 372-378, June 2015

Full Length Research Article

UNDERSTANDING LASSA FEVER VIRUS AND DIVERSIFICATION OF THE RODENT VECTOR IN THE TROPICS

***Dr. Yunusa, Thairu and Dr. Nonye Egenti**

Department of Medical Hicrobiology, University of Abuja Teaching Hospital, P.M.B. 228, Gwagwalada, Abuja, Nigeria

Received 24th May 2015; Published 29th June 2015

Introduction: Lassa fever is an acute viral zoonotic illness caused by Lassa virus, an arenavirus known to be responsible for a severe haemorrhagic fever characterized by fever, muscle aches, sore throat, nausea, vomiting, and chest and abdominal pain. The virus exhibits persistent, asymptomatic infection, with profuse urinary virus excretion in Mastomysnatalensis, the ubiquitous and highly commensal rodent host. Lassa fever is endemic in West Africa and has been reported from Sierra Leone, Guinea, Liberia, and Nigeria where it was first discovered. LASV (Lassa virus) is responsible for 100,000-300,000 infections, and approximately 5,000 deaths annually. The aim was to examine the burden of lassa fever and identify the epidemiological diversity of the rodent vector of lassa fever in humans.
Findings: It shows that although the general public may know or might have heard about the virus and the disease, but they still do not understand the mode of transmission and role of the vector which is a key component in the control and eradication programme for lassa virus disease.
Conclusion: Advancing knowledge significantly improves our understanding of lassa virus biology, as well as the mechanisms that allow the virus to evade the host's immune system. However, further investigations are required in
order to design improved diagnostic tools, an effective vaccine, and therapeutic agents.

Key words: Lassa fever, burden, epidemiological diversity of vector, Nigeria

INTRODUCTION

Lassa fever is a viral haemorrhagic fever caused by an arenavirus, first described in West Africa in the 1950s, although the virus was not isolated until1969 (Buckley and Casals, 1970). Arenaviruses produce mostly silent, 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 (Bishop, 1993). 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 successful African rat, Mastomysnatalensis, has adapted to a peridomestic life in village houses in West Africa (McCormick *et al*., 1987). Accidental human exposure to the virus is therefore frequent. With the human population explosion in the endemic area over the past 50 years or so, the opportunities for infection with this virus, and thus disease, have increased exponentially. Among the haemorrhagic fevers, Lassa fever affects by far the largest number of people, creating a geographical patchwork of endemic foci encompassing a population of perhaps 180 million from Guinea to Eastern Nigeria (Imported Lassa fever, 2004). The co-speciation of arenaviruses and rodents has recently been confirmed by molecular analyses.

Corresponding author: Dr. Yunusa, Thairu,
Department of Medical Hicrobiology, University of Abuja Teaching Hospital, P.M.B. 228, Gwagwalada, Abuja, Nigeria.

Using a sequence near the 3k end of the nucleoprotein gene, analysis confirms the historical division of arenaviruses (originally based on geographical distribution and antigenic typing) into Old World (LCMV, LASV), which includes Lassa virus, Mopeia, Lymphocytic Choriomeningitis Virus (LCMV) and New World (Tacaribe complex) viruses, which include at least four viruses highly pathogenic for humans (Bowen *et al*., 1997). The LCMV, LASV complex viruses are monophyletic with three distinct lineages, one of which contains Lassa, Mopeia and Mobalaviruses (Bowen *et al*., 2000). Mopeia comes from Southern Africa and Mobala from Central Africa, and both are carried by related Mastomys species (Wulff *et al*., 1977). Both can infect humans, but are apparently unable to cause significant clinical disease. Experimental infection of non-human primates with Mopeia virus is also silent. As will be discussed later, Mopeia virus has been proposed as a potential live attenuated Lassa vaccine, and it is certainly effective as such in nonhuman primates. 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 (Bowen *et al*., 1997). These conclusions are based on S-segment sequence analysis, but virulence may not in fact be associated with the S segment. Indeed, there are data suggesting that virulence determinants in LCMV are located on the L gene (Riviere, 1987). Whatever the case, the ecological evidence is clear; virulence for primates is a chance event, unrelated to the natural history of the virus.

The distribution of Mastomys in West Africa is highly variable and in some areas, 50% of domestic rodents may be Mastomys.[3] Since the rodents do not move far from their nest, and because Lassa virus is transmitted vertically in rodents, infection in local populations of rodents tends to cluster. Thus, human infections tend also to be focal with periodic familial or village clusters with secondary cases due to person-to-person spread. These outbreaks are seen against the background of primary infections from rodents that make up the bulk of endemic disease. Infections peak between January and May – during the dry season – but cases are seen year round. Over 300,000 Lassa virus infections are estimated to occur annually, with several thousand deaths (Tomori *et al*., 1988). Lassa fever occurs in all age groups and sexes, and not surprisingly given the ubiquity of the rodent host, antibody prevalence increases with age. This is compatible with virustransmission to humans in and around the homes where the Mastomys live. Estimates of antibody prevalence range from 4%–6% in Guinea to 15%–20% in Nigeria, though in some villages in Sierra Leone as many as 60% of the population have evidence of past infection. Among hospitalized patients, the mortality is 17% if untreated. In endemic areas, Lassa fever may account for about 30% of adult deaths. Lassa fever also affects children, with considerable mortality in infants (Monson *et al*., 1984).

Person-to-person spread of Lassa virus occurs within homes as well as in hospitals. This is where the major outbreaks have been and continues to be. The outbreaks are associated with inadequate disinfection and direct contact with infected blood and contaminated needles. Increasing and indiscriminate use of needles for intravenous therapy, or intramuscular injections in West African hospitals along with inadequate needle and syringe sterilization has led to large scale epidemics. These epidemics can be devastating, resulting in the deaths, not only of patients but also medical staff, surgeons, nurses and other trained laboratory personnel (Fisher-Hoch *et al*., 1995). Since 1990, severe social disruption from conflicts and terror campaigns in Sierra Leone and Liberia have displaced up to 2 million people – 25% of the population of the area – with a substantial increase in the already large number of Lassafever cases and deaths (Allan *et al*., 1998).

Lassa fever is the exotic haemorrhagic fever most likely to occur in developed countries due to infection in returning travellers. In the year 2000, at least four cases were imported into Europe (CDC, 2012), all died mainly due to delay in diagnosis, and therefore delay in instituting antiviral therapy. Increased cases in non-West Africans in 2000 have been seen as a result of United Nations (UN) peacekeeping efforts in Sierra Leone, where the rebels' stronghold is the centre of the Lassa fever endemic area. One of the fatal cases in expatriates was an Englishman who had been working to disarm the rebelsoldiers in the diamond mining area of eastern Sierra Leone (CDC, 2012).

THE VIRUS

Lassa virus is an enveloped, single-stranded, bisegmented RNA virus belonging to the arenaviridae family. Like other arenaviruses, Lassa virus lacks a conventional negative strand coding arrangement and the isolates of the virus differ in their genetic, serologic, and pathogenic characteristics (Ruo *et al*., 1991). Lassa virus is spherical in shape and measures between 70 and 150 nm in diameter.

It has a smooth surface envelope with T-shaped spikes measuring 7–10 nm and built with glycoprotein. The envelope encloses the genome which has helical nucleocapsid measuring between 400 and 1300 nm in length (Auperin *et al*., 1986). Often, the interior contains electron dense granule identified as the host cell ribosome from where the name "arena" was derived meaning sand (McCormick, 1987). Lassa virus can be inactivated in ultraviolet, gamma irradiation, heating from 56–100^{o}C and pH range between 5.5 and 8.5. Chemical agents like 0.5% sodium hypochlorite, 0.5% phenol and 10% formalin will inactivate the virus (McCormick, 1987). The single-stranded arenavirus genome consists of a small (s) and a large (l) RNA fragment, sizes 3.4 and 7 kb respectively and the sRNA encodes the viral glycoprotein precursor protein (GPC) and the nucleoprotein (NP), while the lRNA encodes the viral polymerase and a small, zinc-binding (Z) protein (Gunther, 2000). New methods for full-length sRNA amplification are facilitating research efforts on the identification and molecular analysis of new arenaviruses or arenavirus strains (Gunther, 2000).

EPIDEMIOLOGY OF LASSA FEVER

LASV was first isolated in 1969 from a missionary nurse who worked in a clinic in a small town, Lassa, in northeastern Nigeria (Frame *et al*., 1970). The nurse presumably acquired infection from an obstetrical patient residing in Lassa. She died approximately one week after the onset of symptoms. Subsequently, two more nurses that attended the first patient contracted the disease, which was later named Lassa fever and caused the death of one of them. Infectious virus was isolated from all three cases (Buckley, 1970). Initially, several countries of West Africa were identified to be endemic for LASV, namely Sierra Leone (Monath *et al*., 1974; Lukashevich *et al*., 1993; Monson *et al*., 1984; Tomori *et al*., 1988). However, a serological survey among patients admitted with a history of fever, and missionaries that had experienced a febrile illness showed that LASV was also present in Ivory Coast, Mali, and Central African Republic (Frame, 1975).

The notion that LASV was endemic in larger areas of West Africa was further supported by the results of investigation of an imported case of Lassa fever in Germany in 2000. During the incubation period, the index patient travelled through several countries, namely Ghana, Ivory Coast, and Burkina Faso, which were not considered to be endemic at that time. Later, cases of Lassa fever have been reported from Burkina Faso, Ivory Coast, Ghana, Senegal, Gambia and Mali (Safronetz *et al*., 2010). The incidence of the disease, although highly variable depending on the geographical location (from 1.8% in developed to 55% in developing countries) indicates that most infections are mild or possibly even asymptomatic and do not result in hospitalization. This is also supported by findings indicating a high incidence of LASV-specific seroconversion, from 5% to 20% of the nonimmune population per year (McCormick *et al*., 1987). Nosocomial outbreaks are associated with higher mortality rates ranging from 36% to 65% (Fisher-Hoch *et al*., 1995). However, serosurveillance studies in hospitals dealing with suspected Lassa fever cases showed that the hospital staff that routinely practiced basic hygiene measures had no higher risk of infection than the local population. Infection with LASV presumably occurs through contact with body fluids or excreta, or inhalation of aerosols produced by infected animals.

LASV is stable in aerosol, (Helmick *et al*., 1986) and animal-to-animal transmission via the airborne route had been demonstrated in the laboratory setting (Peters *et al*., 1987). Hunting of peridomestic rodents and consumption of their meat is another important route of LASV transmission to humans residing in endemic areas of West Africa (Meulen *et al*., 1996).

MODE OF TRANSMISSION

The multimammate mouse, Mastomysnatalensis, was originally identified as the primary host species for LASV (Meulen *et al*., 1996). However, due to the poor understanding of the taxonomy of the genus, it is uncertain which species and particular subspecies serve as a reservoir for the virus (Salazar-Bravo *et al*., 2002). The studies addressing the importance of M. natalensis for the circulation of LASV in nature demonstrated that newborn animals inoculated intraperitoneally develop persistent asymptomatic infection (Walker *et al*., 1975). Significant infectious virus titers were detected in many organs, tissues, and fluids including lymph node, liver, spleen, lung, blood, and brain up to 74 days after inoculation. Moreover, LASV was isolated from the urine and throat swabs of infected animals. No significant histopathological alterations were observed in these animals. Interestingly, adult M. natalensis infected with LASV also developed a disseminated infection that lasted up to 30 days. Some animals cleared the virus from some organs, but there was persistence in other organs up to 103 days when the study was terminated. The only consistent histopathological finding observed in adult animals was a moderate chronic meningoencephalitis (Walker *et al*., 1975). These data demonstrate that M. natalensis has an optimal pattern of infection and virus shedding for the maintenance of LASV in nature.

Recent Lassa Outbreak in Nigeria

At the beginning of 2012, the World Health Organization (WHO) was notified by the Federal Ministry of Health in Nigeria of an outbreak of Lassa fever (WHO, 2012). Twenty - three states in the country were affected, out of which 87 deaths were recorded. Laboratory analysis confirmed the presence of Lassa virus infection in 108 patients (WHO, 2012). Three doctors and four nurses were reported to be among the fatalities. Over 100,000 lives were lost to Lassa fever between 1969 and 2013, even as he explained that many unrecorded deaths occurred in rural areas. A patient was admitted on 4thJanuary 2014 with symptoms of severe fever with bleeding, which compelled the medical personnel to send his blood specimen to the Lassa fever diagnostic Centre at Irrua, Edo state, where it was confirmed positive and that was the first case in 2014.

Risk Factors for Transmission

- Use of rat meat as a source of protein by people in some communities; contamination of exposed food by rat feces and urine;
- Traditional autopsy, where the operator may injure himself with scalpel and contaminate the injury with the blood of the deceased, who may have died of Lassa fever
- Forceful ingestion of water used in bathing a dead husband by a widow suspected to be involved in his death. In many communities, family members may be forced to drink water used in bathing dead relatives in order to prove their innocence.
- Corrupt practices by staple food producers, which involve drying cassava flour (garri) in the open air in the daytime and sometimes at night. This enables all types of rat including Mastomysnatalensis to contaminate the flour with their excreta. This constitutes a public health hazard when the infected cassava flour (garri) is sold to consumers in the market. The common habit of eating garri soaked in water may favor Lassa fever infection. Many other types of staple foods are also processed in the open sun; these include rice, plantain chips, yam chips and cassava chips, which are processed into rice flour, plantain flour, yam flour, and raw cassava flour. Though these are also processed into staple foods such as tuwoshinkafa, plantain based amala, yam based amala and lafun respectively, the amount of heat involved in processing them into edible pastes, may be enough to denature the lassa fever virus, which is heat labile (Tomori *et al*., 1988).
- Bush burning of savannahs may be carried out by meat-hungry youths during the dry season, in order to be able to have access to rodents and other animals.

IMMUNOLOGY OF LASSA FEVER

Design of an effective vaccine requires some understanding of the immunology of the disease against which the vaccine must protect. Clearly, this rodent virus is handled quite differently by the immune systems of rodents and primates. The immunological response in primates to arenavirus infection is complex. In general, the evidence we have indicates that Lassa and LCM viruses depend primarily on cytotoxic T-cell responses for virus clearance, while neutralizing antibodies are associated with clearance of viraemia due to the South American arenaviruses (Mertens *et al*., 1973). The reappears to be a brisk B-cell response to Lassavirus with a classic primary IgG and IgM antibody response early in the illness. Development of antibody does not however coincide with virus clearance, and high viraemia and high IgG and IgMtitres often coexist in both humans and primates. Indeed, virus may persist in the serum and urine of humans for several weeks after infection, and possibly in occult sites, such as renal tissue, for longer periods. Lassa virus specific cytotoxic T cell responses can be measured in patients recovered from Lassa fever (Jahrling *et al*., 1985).

Neutralizing antibodies to Lassa virus cannot be measured in the serum of patients at the beginning of convalescence; in most people, and in experimentally infected monkeys, they are never detectable in a classical plaque-reduction neutralization assay. In a minority of patients some low-titre serum neutralizing activity may be observed several months after resolution of the disease, but only using a fixed-serum, varying virus dilution assay (log neutralization assay). (Johnson *et al*., 1987). Passive protection from Lassa virus has been demonstrated in animals given selected antiserum but only at the time of or soon after inoculation with virus. While there have been anecdotal reports of the clinical effectiveness of lassa immune plasma, controlled clinical trials with human convalescent plasma containing high titre antibodies have shown no protective effect.

Thus the clearance of lassa virus appears to be independent of antibody formation, and presumably depends on the CMI response.

In lassa fever infections, the presence of antibody to neither glycoprotein nor nucleoprotein at the time of hospital admission is associated with survival, or even attenuation of disease. Indeed there is some correlation between death and early detection of IgM antibody (TerMeulen, 2000). These consistent observations contrast sharply with those made in Argentinian haemorrhagic fever (AHF), caused by the South American arenavirus and Junin virus. Here neutralizing antibodies can be detected easily, and immune therapy has been shown to be very effective in this disease, and to correlate with the level of neutralizing antibody. Nevertheless there is evidence from vaccine studies in Argentina that patients who do not produce measurable neutralizing antibodies following vaccination do mount a Junin-virus specific lymphocytic proliferative response (McCormick, 1987). The precise nature of protective immune responses in arenaviruses remains to be elucidated using the more sophisticated assays now available, which for reasons of biosafety and inaccessibility of patients and specimens have not yet been applied to arenaviruses.

DIAGNOSIS

The signs and symptoms of lassa fever may be difficult to distinguish from diseases that are common in the tropics such as severe malaria, typhoid fever, yellow fever and other viral haemorrhagic fevers, but diagnosis can be assisted with simple laboratory support but definitive diagnosis requires testing that is available only in highly specialized laboratories (Lassa fever, 2014). As the symptoms of lassa fever are so varied and nonspecific, clinical diagnosis is often difficult especially early in the course of infection. Hence, to make accurate diagnosis of lassa fever, clinical manifestation, epidemiological data, and result of laboratory findings should be taken into consideration.

LABORATORY INVESTIGATIONS

Lassa fever is diagnosed by detection of lassa antigen, antibodies, or virus isolation techniques. In the laboratory, the virus can be isolated using laboratory animals such as albino mice, guinea pigs, Vero cell or African green monkeys. Albino mice inoculated intracerebrally die between 3 and 5 days. Lassa fever virus causes conspicuous cytopathic effect on confluent monolayer of Vero cell culture within 96 hours. The antigens to be used for viral isolation can be obtained from the patients' blood, urine, pleural fluid, throat swab and in case of death, pathological materials from liver, kidney, spleen and heart (Cummins, 1990). The virus can be seen under electron microscope using specimens obtained from infected persons. Although virus isolation remains the most sensitive, it is still uniquely a research tool. The classical method to detect Lassa virus is inoculation of Vero cells with serum, cerebrospinal fluid (CSF), throat washing, pleural fluid or urine of the patient. Specimen for laboratory analysis should be collected as soon as possible from the patient suspected of having the infection. Lassa virus is infectious by aerosol and the human and rodent specimens should be processed with appropriate precautions in biosafety level IV laboratories (Lassa fever, 2005). The specific diagnosis is readily made by the isolation and identification of the virus. This is usually done by the inoculation of blood from the patient into Vero cell cultures. Virus antigen can be detected by enzyme linked immunosorbent assays (ELISA) using lassa virus-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. Results should be mentioned as soon as they are ready to help in monitoring the prognosis of the disease. The indirect fluorescent-antibody (IFA) test has traditionally been employed in the laboratory diagnosis of acute lassa virus infection (Wulff and Lange, 1975). 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, the technique has been largely replaced by ELISA for lassa virus antigen and lassa virus-specific immunoglobulin M (IgM) and G (IgG) antibodies (Niklasson *et al*., 1984). A thorough evaluation of the lassa virus ELISA on field-collected samples to assess its true sensitivity and specificity was performed in Sierra Leone and Guinea in West Africa. In the study, isolation of virus as detected by immunofluorescent staining for viral antigen along with a positive reverse transcription-PCR (RT-PCR) test on the isolate was employed as the "gold standard" test of lassa virus infection. The results showed that the combined ELISA Ag/IgM assay was highly sensitive and specific for the diagnosis of lassa fever and the antigen detection assay offered a particular advantage in providing early diagnosis as well as prognostic information.

From this research, the technique appeared to bea better diagnostic tool for lassa virus infection compared to other serological techniques. Although the RT-PCR assays are very sensitive, 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 expenses (Trappier *et al*., 1993). Another valuable diagnostic tool is the rapid diagnostic immune blotassay (RDIA) for lassa fever. Unfortunately, its usefulness is limited by its low capacity to provide prognostic information and also its low sensitivity. Differential diagnosis: Lassa haemorrhagic fever must be differentiated from other febrile diseases like Ebola (Marburg) haemorrhagic fever, malaria, diphtheria, legionella, yellow fever, Congo-haemorrhagic fever. Lassa fever virus has a peculiar natural reservoir rodent host (M. natalensis). It is very imperative that clinical assessment be combined with specific laboratory diagnosis to adequately identify the lassa fever virus in order to commence early treatment which is paramount to the survival of infected individuals (Fleischer *et al*., 2000).

FINDINGS

Most patients recover completely if diagnosed early and when treatment with ribavirin is commenced within 6 days of illness. In studies carried out in special referral centres in Nigeria and Sierra Leone, lassa fever was responsible for 13% and 30% of adult deaths respectively. The death rates were in adult medical wards where only 7% and 10-16 % respectively of the total number of admissions were for lassa fever. In an unpublished report conducted over a six month period in Gwagwalada area council, to determine the knowledge of lassa fever and the rodent vector, where two hundred adults comprised of 110 (55.0%) males and 90 (45.0%) females (M:F, 1:1) revealed that 167 (83.5%) knew lassa fever virus as a dangerous viral infection, 30 (15.0%) did not know the virus while three (1.5%) subjects were indifferent.

Fifty-six (28.0%) subjects knew the rodent vector as a rat, 124 (62.0%) subjects did not know the rodent nor mode of transmission while 20 (10.0%) subjects were indifferent. One hundred and two (51.0%) subjects knew that the disease was similar to Ebola viral disease, 80 (40.0%) respondents did not agree with the similarity while 18 (9.0%) respondents were indifferent.

PROGNOSIS

Prognosis depends on how early a patient presents at the clinic and better in males who may acquire partial immunity due to the habit of patronizing food vendors. In a study done in Nigeria, the case fatality rate in males was 23% compared to women with 44%, though males were four times more commonly affected than females.

PREVENTION AND CONTROL

The individual

The affected person should be admitted to a special centre for the treatment of lassa fever. Where this is not possible, the patient should be barrier-nursed. Health care providers and close associates of the patient should wear protective clothing, masks and gloves. Excreta from affected persons should be properly disposed.

The community

Legislation is needed to prevent widowhood rites, traditional autopsies, bush burning and unhygienic preparation of cassava flour and other staple foods. Animal husbandry and fisheries should be encouraged in order to provide alternative sources of first-class proteins for rat eaters. Regular and sustainable environmental sanitation is needed to prevent rat breeding (WHO, 2012). The public should be made aware of the mode of contact of lassa fever and its high casefatalityrate using print and electronic media. Community involvement and participation is necessary to provide sustainable lassa fever control. Food vendors should be educated on the need to prevent food contamination with lassa fever virus. Grains, flours and left-over foods should be adequately covered to prevent contamination by rats. Rodenticides should be used for the destruction of rats in homes, and development of lassa fever vaccine should be facilitated. Regular seminars should be held for health-care providers on early diagnosis and treatment of lassa fever, while diagnostic kits should be made available in districthospitals. Affected people should be referred early to the special center in order to prevent or limit disability, while those with disabilities should be rehabilitated functionally, socially and psychologically so that they can be gainfully employed (CDC, 2004).

Vaccine

Although the prevention of human contact with the Mastomys rodents is an essential factor in the control of lassa fever, widespread prevention of such contact is presently impractical in the endemic regions of West Africa, so provision of a vaccine for community and hospital use is an imperative public health need because vaccination is the most viable control measure.

CHALLENGES OF LASSA ERADICATION

Poor education of people in high-risk areas about ways to decrease rodent populations in their homes and other challenges include developing more rapid diagnostic which has led to very poor disease control in Nigeria. Presently we have only one lassa fever diagnostic centre in the country at the Institute of Lassa Fever Research and Control of the Irrua Specialist Teaching Hospital (ISTH), Irrua, Edo State. This is partly because of the unavailability of laboratory containment facilities (BSL-3 or 4), laboratory reagents and equipment. More so, another thing worthy of note is the poor re-training of laboratory personnel on the technical-know-how of laboratory procedures.

THERAPEUTIC OPTIONS FOR LASSA FEVER

Ribavirin the antiviral drug is effective in the treatment of lassa fever, but only if administered early in the course of illness.[29] In a study of lassa fever in Sierra Leone, West Africa, it was observed that patients with a high risk of death who were treated for 10 days with intravenous ribavirin, begun within the first six days after the onset of fever, had a case-fatalityrate of 5% (1 of 20) ($p = 0.002$), while patients whose treatment beganseven or more days after the onset of fever had a casefatalityrate 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. Supportive treatment is often necessary and includes fluid replacement, blood transfusion, administration of paracetamol, phylometadione, ringer lactate, haemocoel, quinine and broad spectrum antibiotics (Holmes *et al*., 1990).

DISCUSSION

Lassa virus, an Old World arenavirus (family Arenaviridae), is the etiological agent of lassa fever, a severe human disease that is reported in more than 100,000 patients annually in the endemic regions of West Africa with mortality rates for hospitalized patients varying between 5-10%. Currently, there are no approved vaccines against lassa fever for use in humans. Here, we review the published literature on lassa virus with the specific focus on lassa fever pathogenesis in humans and relevant animal rodent involved. Advancing knowledge significantly improves our understanding of lassa virus biology, as well as of the mechanisms that allow the virus to evade the host's immune system. However, further investigations are required in order to design improved diagnostic 'tools, an effective vaccine, and therapeutic agents. Furthermore, it goes to show that although the general public may know or might have heard about the virus and the disease but still did not understand the mode of transmission and role of the vector which is a key component in the control and eradication programme against lassa virus disease. Lack of knowledge concerning the vector, Mastomys natalensis is a source of concern in this era, considering the recent burden of Ebola virus in West Africa.

Conclusion and Recommendations

It is unequivocally established that lassa fever is a very important vector borne disease that has assumed epidemiological proportion in West Africa where it records high endemicity. The public health implication of this cannot be overstated. Apart from possible periodic outbreaks of lassa

fever epidemic within the region, the unprecedented increase in inter-border traffic and international travels elevates the chances of introducing the virus to other regions within and outside the African continent. The scarcity of resources available for healthcare delivery and the political instability that characterize the West African countries would continue to impede efforts for the control of both emerging and currently ravaging infectious diseases in the region. However, adequate education of healthcare providers and other public health personnel as well as the establishment of well-equipped infectious disease laboratories and research centers would aid in the prompt diagnosis and treatment of highly infectious diseases like lassa fever and would help in averting possible outbreaks. Furthermore, ribavirin should be made available in hospitals and health centres in the endemic areas particularly in rural communities. This would help to control the disease.

DECLARATION OF CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

REFERENCES

Allan, R., Ladbury, R., Skinner, K. and Mardel, S. 1998. Emergence of epidemic Lassa fever during civil conflict in Sierra Leone. *International Conference on Emerging Infectious Diseases*, 21.16;134.

Auperin, D.D., Sasso, D.R. and McCormick, J.B. 1986. Nucleotide sequence of the glycoprotein gene and intergenic region of the Lassa virus S genome RNA. Virology, 154: 155–67.

Bishop, F.Y. 1993. Lassa fever, a new virus disease of man from West Africa. 3. Isolation and characterization of the virus. *Am. J. Trop. Med. Hyg., 19*, 680-691.

Bowen, M.D., Peters, C.J. and Nichol, S.T. 1997. Phylogenetic analysis of the Arenaviridae: patterns of virus evolution and evidence for cospeciation between arenaviruses and their rodent hosts. MolPhylogenetEvol, 8: 301–16.

Bowen, M.D., Rollin, P.E. and Ksiazek, T.G. 2000. Genetic diversity among Lassa virus strains. *J. Virol*, 74: 6992–7004.

Buckley, S.M. and Casals J. 1970. Lassa fever, a new virus disease of man from West Africa. Isolation and characterization of the virus. *Am. J. Trop Med. Hyg.*, 19: 680–691.

Centers for Disease Control and Prevention (CDC). 2012. Lassa virus strain. *Emerg Infect Dis.*, 6(5): 466–76.

Cummins, D., McCormick, J.B., Bennett, D., Samba, J.A., Farrar, B., Machin, S.J. and Fisher-Hoch, S.P. 1990. Acute sensorineural deafness in Lassa fever. *J. Am. Med. Assoc*., *264*(16): 2093–6.

Fisher-Hoch, S.P., Tomori, O., Nasidi, A., Perez-Oronoz, G.I. Fakile, Y., Hutwagner, L. and McCormick. J.B. 1995. Review of cases of nosocomial Lassa fever in Nigeria: the high price of poor medical practice. BMJ, 311, 857-859.

Fleischer, K., Kohler, B., Kirchner, A. and Schmid, J. 2000. Lassa fever (Article in German). *Med Klin (Munich)*; 95(6): 340–5.

Frame, J.D. 1975. Surveillance of Lassa fever in missionaries stationed in West Africa. *Bull. World Health Organ.*, *52*, 593-598.

Frame, J.D., Baldwin, J.M., Gocke, D.J. and Troup, J.M. 1970. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *Am. J. Trop. Med. Hyg.,* 19: 670–6.

Gunther, S., Emmerich, P., Laue, T., Kuhle, O., Asper, M., Jung, A., Grewing, T., terMeulen, J. and Schmitz, H. 2000. Imported Lassa fever in Germany: molecular characterization of a new Lassa virus. *Crit. Rev. Clin. Lab. Sci*., 41(4): 339–90.

Helmick, G.P., McCormick, J.B., Trock, S.C., Chase, R.A., Lewis, S.M. and Mason, C.A. 1986. Lassa fever in the United States. Investigation of a case and new guidelines for management. *New Engl J Med., 323:* 1120–6.

Holmes, G.P., McCormick, J.B., Trock, S.C., Chase, R.A., Lewis, S.M. and Mason, C.A. Lassa fever in the United States. Investigation of a case and new guidelines for management. *New Engl J Med* ; 1990, *323:* 1120–3.

Imported Lassa fever. New Jersey: Centers for Disease Control and Prevention (CDC) 2004. MMWR Morb Mortal Wkly Rep 2004; 53(38): 894–7.

Jahrling, P.B., Frame, J.D., Smith, S.B. and Monson, M.H. 1985. Endemic Lassa fever in Liberia. III. Characterization of Lassa virus isolates. *Trans R Soc Trop. Med Hyg*., 79: 374–9.

Johnson, K.M., McCormick, J.B., Webb, P.A., Smith, E.S., Elliott, L.H. and King, I.J. Clinical virology of Lassa fever in hospitalized patients. *J Infect Dis.,* 1987, 155: 456–464.

Lassa fever. October 2014. WHO Newsletter, Geneva 2005. Updated June 2009.Accessed .

Lukashevich, I.S., Clegg, J.C.S. and Sidibe, K. 1993. Lassa virus activity in Guinea: Distribution of human antiviral antibody defined using enzyme-linked immunosorbent assay with recombinant antigen. *J. Med. Virol*, *40*, 210-217.

McCormick, J.B., Webb, P.A., Krebs, J.W., Johnson, K.M. and Smith, E.S. 1987. A prospective study of the epidemiology and ecology of Lassa fever. *J. Infect. Dis.,* 155: 437–444.

Mertens, P.E., Patton, R., Baum, J.J., Monath, T.P. 1973. Clinical presentation of Lassa fever cases during the hospital epidemic at Zorzor, Liberia, March–April 1972. *Am. J. Trop. Med. Hyg.*, *22:* 780-4.

Meulen, J.T., Lukashevich, I., Sidibe, K., Inapogui, A., Marx, M., Dorlemann, A., Yansane, M.L., Koulemou, K., Chang-Claude, J. and Schmitz, H. 1996. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of Lassa virus in the Republic of Guinea. *Am. J. Trop. Med. Hyg*., *55*, 661-666.

Monath, T.P., Newhouse, V.F., Kemp, G.E., Setzer, H.W. and Cacciapuoti, A. 1974. Lassa virus isolation from Mastomysnatalensis rodents during an epidemic in Sierra Leone. *Science*, 185, 263-265.

Monson, M.H., Cole, A.K., Frame, J.D., Serwint, J.R., Alexander, S., Jahrling, P.B. 1984. Pediatric Lassa fever: a review of 33 Liberian cases. *Am. J. Trop. Med. Hyg.,* 36: 408–415.

Niklasson, B.S., Jahrling, P.B. and Peters, C.J. 1984. Detection of Lassa virus antigens and Lassa virus-specific immunoglobulins G and M by enzyme-linked immunosorbent assay. *J ClinMicrobiol*, 20: 239–44.

Peters, C.J., Jahrling, P.B., Liu, C.T., Kenyon, R.H., McKee, K.T. 1987. Jr; Barrera Oro JG. Experimental studies of arenaviral hemorrhagic fevers. *Curr. Top. Microbiol. Immunol*, 134, 5-68.

Riviere, Y. 1987. Mapping arenavirus genes causing virulence. *Curr Top Microbiol Immunol*, 133: 59–65.

Ruo, S.L., Mitchell, S.W., Kiley, M.P., Roumillat, L.F., Fisher-Hoch, S.P. and McCormick, J.B. 1991. Antigenic

relatedness between arenaviruses defined at the epitope level by monoclonal antibodies. *J. Genet, Virol,* 72: 549–55.

Safronetz, D., Lopez, J.E., Sogoba, N., Traore, S.F., Raffel, S.J., Fischer, E.R., Ebihara, H., Branco, L., Garry, R.F., Schwan, T.G. and Feldmann, H. Detection of Lassa virus, Mali. *Emerg. Infect. Dis;* 2010, *16*, 1123-1126.

Salazar-Bravo, J., Ruedas, L.A. and Yates, T.L. 2002. Mammalian reservoirs of arenaviruses. *Curr. Top. Microbiol. Immunol*, *262*, 25-63.

TerMeulen, J., Badusche, M., Kuhnt, K. 2000. Characterization of human CD4(+) T-cell clones recognizing conserved and variable epitopes of the lassa virus nucleoprotein. *J Virol*, 74: 2186–2192.

Tomori, O., Fabiyi, A., Sorungbe, A., Smith, A. and McCormick, J.B. 1988. Viral hemorrhagic fever antibodies in Nigerian populations. *Am. J. Trop. Med. Hyg.,* 38, 407-410.

Trappier, S.G., Conaty, A.L., Farrar, B.B., Auperin, D.D., McCormick, J.B. and Fisher-Hoch, S.P. 1993. Evaluation of the polymerase chain reaction for diagnosis of Lassa virus infection. *Am J Trop Med Hyg, 49:* 214–21.

Walker, D.H., Wulff, H., Lange, J.V. and Murphy, F.A. 1975. Comparative pathology of Lassa virus infection in monkeys, guinea pigs, and Mastomysnatalensis. *Bull. World Health Organ.,* 52, 523-535.

WHO. 2012. Lassa fever. A study of 23 hospital cases. *Trans. R. Soc. Trop. Med. Hyg*., 66, 390-401.

Wulff, H. and Lange, J.V. 1975. Indirect immunofluorescence for the diagnosis of Lassa fever infection. Bull WHO, 52: 429–36.

Wulff, H., McIntosh, B.M., Hamner, D.B. and Johnson, K.M. 1977. Isolation of an arenavirus closely related to Lassa virus from Mastomys natalensis in south-east Africa. *Bull World Health Organ*, 55: 441–444.

Yunusa, T. May 2014. Altitude and knowledge of Lassa fever and the rodent: The burden of viral haemorrhagic disease in West Africa. Reported in. Unpublished data.

****