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Insight on the Outbreak of Lassa Fever Amidst Coronavirus Disease (COVID-19) Pandemic

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Abstract

Lassa fever virus (LASV) is seen mainly in some regions of West Africa, however, this disease has been reported in some other countries from travelers coming from endemic regions. Lassa virus is transmitted to human by infected multi-mammate rats, the *Mastomys natalensis*; humans often contact the Lassa virus through direct contact with household items or eating food contaminated with urine or faeces of infected *Mastomys* rats. Nosocomial, hospital-acquired transmission from person to person have also been reported, and occur when appropriate Personal Protective Equipment (PPE) is not worn by health care providers managing Lassa fever cases, just like in COVID-19 management. Lassa fever is highly contagious, however, the mode of transmission of LASV differs from COVID-19 which is a respiratory disease. Lassa fever has potential of wreaking havoc in any Country because it is highly contagious, causing more fatality in pregnant women. Coronavirus disease on the other hand (COVID-19) has been recently declared a pandemic and has caused deaths in thousands of people around the world and has also caused morbidity in millions of people globally. Unfortunately, during the COVID-19 period, West Africa, Nigeria particularly which is the origin of LASV also suffers from the outbreak of Lassa fever. Managing both viral outbreaks could be very strenuous and precarious at the same time. Consequently, this work reviews the recent outbreaks of Lassa fever in this COVID-19 pandemic. Recent update on COVID-19 would be explored; furthermore, Lassa fever disease would be explored with insight on the management of LASV.

Keywords: Coronaviruses; Lassa fever; *Mastomys Natalensis*; Ribavirin; Vaccines

Abbreviations: LASV: Lassa fever Virus; PPE: Personal Protective Equipment; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; TMPPRS: Trans Membrane Serine Protease; ACE-2: Angiotensin-Converting Enzyme-2; VHF: Viral Haemorrhagic Fever; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; ELISA: Enzyme-Linked Immunosorbent Assay; IPC: Infection Prevention and Control; APC: Antigen-Presenting Cells; DC: Dendritic Cell.

Introduction

Coronavirus disease COVID-19 already declared a pandemic started in the City of Wuhan, China in December, 2019. Since then, COVID 19 has caused deaths in about 5,004,855 and infected about 246,951,274 globally as at 2nd November, 2021 [1]. Also a total of 6,893,866,617 vaccine doses have been administered globally [1]. In Africa, the first case of COVID-19 was reported on February, 2020 in Egypt, second

case in Algeria [2]. However, as at November 2nd 2021, Africa has recorded total coronavirus cases of 8,505,505, about 218 737 deaths and, a total of 7 908 837 recoveries. Nigeria the most populous country in Africa recorded the first case of coronavirus in February, and as at November 2nd, 2021 has confirmed COVID-19 of about 212 150 confirmed cases with 5600 being active cases, 203 651 discharged cases and 2 899 deaths [4].

Coronavirus disease also referred to as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) is caused by a beta virus belonging to Coronaviruses which cause diseases in humans and animals [5-10]. Coronaviruses (family Coronaviridiae, order Nidovirales, genus β-coronavirus, subgenus Sarbecovirus) possess crown-like spikes on their surface [11-15]. They are group of single stranded enveloped viruses consisting of positive-strand RNA with a helical nucleocapsid and cause infection in both humans and animals. However, about seven coronaviruses infect humans, but major human infections are caused by three among the seven viz severe acute respiratory syndrome discovered in China, in the year 2002 (SARS), Middle East respiratory syndrome, Saudi Arabia, 2012 (MERS), and SARS-CoV-2 [16-22]. COVID-19 causes lower respiratory system diseases such as severe pneumonia, and also initiates disorders in the digestive system, nervous system, kidneys, heart, liver, which may lead to multiple organ failure. These disorders are seen mainly in geriatrics and patients with comorbidities [15,23-30]. Until date, COVID-19 is believed to be of zoonotic origin just like Lassa fever virus, SARS and MERS. COVID-19 originated through a precursor virus from insectivorous bats (*Rhinolophus affinis*) or pangolins (*Manis javanica*). COVID-19 causes mainly severe acute respiratory syndrome (SARS) by their interaction through its binding for their high affinity to angiotensin-converting enzyme-2 (ACE-2) receptors and trans membrane serine protease (TMPPRS) co-receptors for S protein priming [15]. There is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection as reinfections have recently been reported [31]. Patients who recover from coronavirus infections may lose their immunity to reinfection within months [32].

During this COVID-19 outbreak in West Africa, Nigeria, particularly, there has been outbreaks of Lassa fever. In 2020, Nigeria recorded about 1095 cases of Lassa fever and about 227 deaths [33,34], making the country to be fighting Lassa fever outbreaks amidst COVID-19. Also, in 2021, about 382 cases have been recorded so far as at November 2021 and about 77 deaths [33,34]. This work aims at reviewing Lassa fever outbreaks in west Africa especially during COVID -19 pandemic. Also, details of Lassa fever disease, symptoms, prevention, management and state of Lassa fever vaccine would be explored.

Lassa fever Disease

Lassa fever is a zoonotic disease, from a rodent of the genus *Mastomys*, commonly known as the "multimammate rat." Humans become infected from contact with infected animals [35-38]. Lassa fever is an acute viral haemorrhagic fever (VHF) or illness caused by single-stranded RNA virus in the family Arenaviridae, the Lassa virus [38-40]. Though discovered in the 1950s, the virus was not identified until 1969. Lassa fever was reported first in in Borno State, Nigeria, in a community called Lassa, hence, the origin of the name, where it caused the death of two missionary nurses who died due to unusual febrile illness (1969) [41-45]. It is predominantly found in west Africa [41], and has potential to cause tens of thousands of deaths. The virus remains also in body fluids, including semen even after recovery [35,38]. There have been series of outbreaks in Nigeria and unfortunately, the disease has become endemic in many other parts of West Africa, Viz Ghana, Mali, Benin, Togo, Burkina Faso, Côte d'Ivoire and the Mano River region (Liberia, Sierra Leone and Guinea) as shown in Figure 2. Estimates have shown that about 300,000-500,000 Lassa fever cases and about 5,000 deaths occur annually in West Africa [33]. Lassa fever has also been seen in non-endemic countries viz USA, Germany, United Kingdom amongst others, where it was reported to be imported into the country by humans [33,45]. Lassa fever was first diagnosed in Benin in November 2014, Guinea, Liberia, Mali (diagnosed for the first time in February 2009) and Ghana (diagnosed for the first time in October 2011) [46-48].

Nigeria, a country recently ranked third highest death due to COVID 19 in Africa [32], reported over 600 confirmed cases and over 170 deaths, due to Lassa fever cases in 2018. In 2019, Nigeria reported about 833 were confirmed cases and about 174, case fatality ratio in confirmed cases is 20.9%. Also from January to July 2020, Nigeria has recorded about 1051 cases of Lassa fever and about 219 deaths, making the country to be fighting Lassa fever outbreaks amidst COVID-19 [33]. Cases of Lassa fever can occur anytime during the year, however, it is worthy of note that most Lassa fever outbreaks occur during the dry season (November to April). Recently, cases have been seen during the rainy season [34]. The detection of the disease in affected patients may be difficult because of the variability in the clinical courses of the disease. However, once the diagnosed in community, rigorous contact tracing, good infection prevention and control practices, and prompt isolation of affected patients help to stop further outbreaks [33]. The structure of Lassa fever is shown in Figure 2.

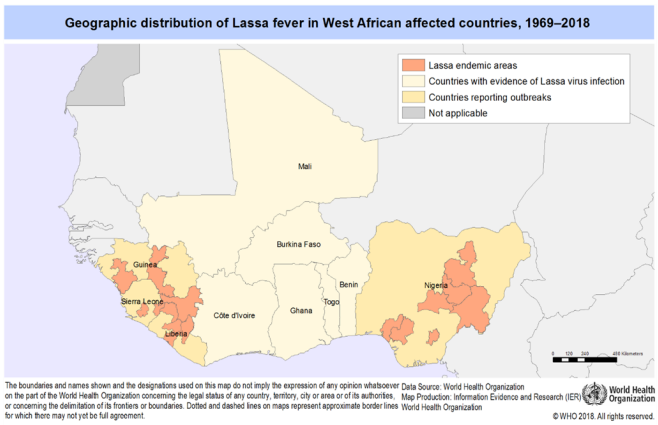

Figure 1: Infographics of the distribution of Lassa fever across West Africa [35].

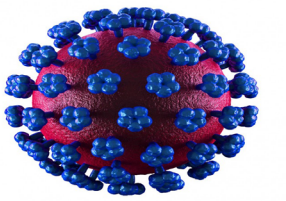

Figure 2: Structure of Lassa fever virus [47].

Transmission

Lassa virus is transmitted to human by infected multi-mammate rats, the *Mastomys natalensis*; humans often contact the Lassa virus through direct contact with household items or eating food contaminated with urine or faeces of infected Mastomys rats [49-52]. The disease is endemic in the rodent population in parts of West Africa [53-57]. Also transmission from person to person (i.e. secondary transmission) can occur following exposure to the virus in the tissue, blood, faeces, urine, or other bodily secretions of infected person(s). Nosocomial, hospital-acquired transmission from person to person have also been reported, and occur when appropriate Personal Protective Equipment (PPE) is not worn by health care providers managing Lassa fever cases [34]. Virus may also spread through contaminated medical equipment, such as re-used needles. Sexual transmission has also been reported [33]. Lassa fever occurs in both sexes and among all age groups, however, people living in rural areas where *Mastomys* are usually found are at greater risk [33].

Clinical sign/symptom	Day of illness		Duration (days)
	Start day	End day	
Fever	1	11	10
Weakness	3	14	11
Cough	3	14	11
Chest pain	4	13	9
Back pain	4	12	8
Joint pain	4	12	8
Sore throat	4	11	7
Dysuria	4	10	6
Headache	4	11	7
Abdominal pain	5	8	3
Vomiting	5	9	4
Diarrhea	5	9	4
Pharyngitis	7	12	5
Conjunctivitis	7	12	5
Bleeding	7	11	4
Rales	9	14	5
Facial oedema	9	16	7

Table 1: Symptoms of Lassa fever with days they may likely present [57].

Symptoms of Lassa fever

Diagnosis of Lassa fever using presenting symptoms may be difficult and often misleading because other severe febrile illnesses abound in West Africa [57]. Also, about 80 % of Lassa virus infected persons are asymptomatic [33-35]. About one in five infected persons suffer severe disease, with the virus affecting vital organs viz spleen, liver and kidneys [33]. The incubation period of Lassa fever ranges from 6 to 21 days [38,58-59]. The disease onset is gradual in symptomatic persons, however it begins as a flu-like illness, presenting as fever [58], severe headache, malaise, cough and sore throat. Also general gastrointestinal disturbance may present viz nausea, vomiting, and diarrhea [38,58]. These symptoms however, subside in a mild case of LASV infection, and recovery typically commences 8–10 days after disease onset [59,60]. The case fatality rate due to LASV infection is 1–2% [3]. Approximately 15–20% of infections result in moderate-to-severe disease [3]. Generally, a high seroprevalence of LASV-specific antibodies have been seen in people living in endemic regions, and this confirmed that most patients were asymptomatic, with mild infections which did not require hospitalization [60,61].

However, several events that happen during Lassa fever disease episodes that leads to death of severely ill patients may be due to failure the infected persons body to develop the cellular immune response which controls the dissemination of LASV causing high serum virus titers, disseminated tissue replication and inadequate neutralizing antibodies [62-66]. Also, in severe cases, patients' condition deteriorates after 6–10 days, causing respiratory distress, facial oedema, haemorrhage and pleural effusion [60]. More detailed clinical signs and symptoms of Lassa fever are shown in Table 1 [57].

Furthermore, Lassa fever may also lead to facial swelling, bleeding from the mouth, nose, vagina or gastrointestinal tract, fluid in the lung cavity, and low blood pressure may be seen in severe cases [57]. Also there may be protein in the urine, can also lead to disorientation, seizures, shock, tremor, and coma in the later stages. The viremia level helps to predict the outcome of this disease and the peak is between 4–9 days from illness onset. Survivors however, have the virus cleared from their blood about three weeks after the onset of illness [57,67-70]. Neurological complications, like encephalopathy and sensorineural hearing loss are commonly seen in patients infected with Lassa fever [35,36]. The deafness can in both mild or severe illness in about 25–30% of cases. Also, in approximately half of the affected persons, hearing loss may be permanent, while the other half may experience partial restoration of hearing between 1-3 months after recovery [71,72]. In fatal cases, death may occur within 14 days of disease onset. Lassa fever is especially severe in late pregnancies (third trimester), causing fetal loss and or maternal death in more than 80% of cases [35]. Among hospitalized persons, the case fatality rate is approximately 20% and increases to greater than 50% in high risk groups viz pregnant women and infants. In pregnant women, severe Lassa fever results in nearly 100% mortality in foetuses [73].

Most lesions caused by Lassa fever in humans occur mostly in the liver [74-76]. There are four The major characteristics of LASV hepatitis which may occur in some persons include focal cytoplasmic degeneration of hepatocytes suggestive of phagocytosed apoptotic fragments, multifocal hepatocellular necrosis which may be randomly distributed, monocytic reaction to necrotic hepatocytes and hepatocellular mitoses [57,60].

Diagnosis

The diagnosis and early detection of Lassa fever may be difficult especially in the outbreak of Corona virus disease COVID-19, because the symptoms of Lassa fever are so non-specific and varies. It is difficult to distinguish Lassa fever from other viral haemorrhagic fevers like COVID-19, Ebola virus disease and other diseases that cause fever viz malaria, typhoid fever, yellow fever and shigellosis [35]. Definitive diagnosis requires testing that is available only in reference laboratories [33-35], using the following tests: reverse transcriptase polymerase chain reaction (RT-PCR) assay, virus isolation by cell culture, antibody enzyme-linked immunosorbent assay (ELISA) and antigen detection tests [35].

In endemic regions or patients returning from endemic regions in West Africa however, a high index of suspicion helps in the diagnosis. Diagnosis is based on clinical features and laboratory confirmation [33-34].

Genetic Diversity of Lassa fever Virus

There is genetic diversity in LASV strains and which have been seen to be clustered based on geographic region; the precise number of circulating strains is however, unknown [77,78]. Hence, induction of heterosubtypic immunity against phylogenetically distant strains is important for Lassa fever vaccine development. It has been observed that there is high variation of LASV nucleotide polymorphism, with strains reaching about 32% for L genomic segments and 25% for the S genomic segments, with variation between respectively [78,79]. Furthermore, about six distinctive lineages or clades have been confirmed. In Nigeria, lineages I-III have been observed to be circulating [57]. Lineage IV is observed in Sierra Leone Guinea, Liberia, and Côte d'Ivoire [78,79]. The lineage IV (Josiah strain) from Sierra Leone and is believed to be the most researched and employed mostly in the design of immunogens for possible vaccine [79-81]. Lineage V is seen

in Côte d'Ivoire and Mali [25], recently, lineage VI (Kako) have been seen [57,77,80,81]. The sequencing data from LASV cluster imported infections from Togo, may reveal a new lineage [82] and strong evidence indicated the occurrence of viral reassortment during multi-strain infection within a single host [57,77-82].

Treatment and Prophylaxis

Treatment of Lassa fever should be conducted only in designated isolation centers by trained medical personnel [33,34]. Also all the standard infection prevention and control (IPC) measures for Lassa fever must be ensured. An antiviral agent ribavirin seems to be affective against Lassa fever virus and often administered orally or parenterally [83]. Early treatment is necessary; treatment with ribavirin usually within six days of onset of symptoms is often advised [84]. Based on clinical assessment of patients, supportive treatment should also be instituted in order to improves treatment outcomes [35].

Immune Responses to LASV Infection

Once a person is infected with LASV, there is a general tissue tropism that affects the adrenal glands, spleen, liver and other organs. The LASV targets majorly the myeloid lineage cells and the antigen-presenting cells (APC) like the macrophages and dendritic cells (DCs) [85-88] which greatly encourage high viral replication. The maturation and activation of APC are greatly affected by LASV resulting in impaired antigen processing resulting in reduced viral clearance due to dysregulation of the adaptive immune response [87-89]. LASV Infection causes failure of activation of monocyte-derived dendritic cells (DC) and macrophages (MP) in humans [90-95]. The infected DC fail to secrete proinflammatory cytokines and there is no upregulation of costimulatory molecules viz CD40, CD80, and CD86, and poorly induce proliferation of T cells [96-100]. Once a person becomes infected with LASV, the antibody responses remain low during clinical disease and increases long after recovery, hence, resolution of LASV infection is mediated majorly by cellular immunity [57], this is supported by the observation of strong transient activation and proliferation of T cells from 5–15 days after infection in animals [47]. However, in humans, there is early activation of LASV-specific CD4+ and CD8+ T cells during infection which are continually detected after recovery [57]. Memory CD4+ T-cell responses against LASV GPC and NP persist for several years after initial infection [57].

Persons infected with LASV generate IgG and IgM antibodies however, these antibodies also seen in patients with viremia are produced at early infections in relatively low levels which are not neutralized [57,60]. It has been observed that neutralizing antibodies are generally low and appear months after infection with LASV [99,101,102]. The antibodies titers however, continue to rise for several months after establishing convalescence which is indicative of constant B cells stimulation caused by persistence of levels of LASV. In seroconverted patients, antibodies are specific to NP, GPC, and, Z protein [99,101-105]. Four sites have been elucidated on B-cell antigenic epitopes including two sites on GP1, NP, and six sites on GP2 [60,106]. Also, some of the antibodies are majorly LASV strain-specific, while other react with a broad range of arena viruses including African and South American members of Arena viruses [60].

State of Lassa fever Vaccine

Several efforts have been put in place for the development of vaccines that can protect against LASV [107-114]. However, until date, there are no licensed vaccines against LASV infection. Many candidate vaccines undergoing development have proven to be effective in animal models, however, only one candidate vaccine has already moved to clinical trials stage [60,57]. Development of vaccines against LASV have been suffering from the limitation of the absence of established correlates of protection, high cost of biocontainment requirements, and uncertainty on how the efficacy seen in animal models can positively been translated in humans [60].

Conclusion

West Africa have suffered various epidemic ranging from Lassa fever, Ebola and recently COVID-19. Managing COVID-19 and Lassa fever is very challenging and may overwhelm a country's health care system. Individuals should take responsibility and protect themselves against these viruses. Furthermore, research into the field of vaccines to protect against Lassa fever should also be sponsored heavily just like COVID-19 vaccines development, so that the menace caused by Lassa fever would be averted.

Future Perspective

Developing natural antiviral drugs to combat most zoonotic virus is important in order to be ever ready for any virus that may pose treat to the world. Vaccine production for Lassa fever that would consider the diversity of Lassa virus is focal so that the problem of Lassa fever virus would be defeated. More vigorous research on possible cure of natural origin for COVID-19 is eminent, so that the threat posed by this pandemic may be subdued.

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Conflict of Interest

The authors state no conflict of interest.

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