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A COMPREHENSIVE ANALYSIS OF LASSA FEVER EPIDEMIOLOGY, CLINICAL PRESENTATION, AND MOLECULAR VARIABILITY IN ETHIOPIA: IMPLICATIONS FOR PUBLIC HEALTH PREPAREDNESS

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Abstract

Lassa fever, caused by the Lassa virus, is a significant public health concern in many regions of Africa, including Ethiopia. This comprehensive study delves into the epidemiology, clinical presentation, and molecular variability of Lassa fever in Ethiopia, shedding light on critical aspects of this viral zoonosis.

Lassa fever, with its origins in West Africa, has raised global alarm due to its high morbidity and mortality rates. In Ethiopia, where the disease has been recognized as a growing threat, understanding its epidemiology is paramount for effective public health preparedness.

This study reveals that the virus primarily resides in the Mastomys natalensis rodent population, which cohabits with humans, posing a constant risk of zoonotic transmission. Recent findings suggest that over 30 million individuals in several countries, notably in West Africa, are living in areas vulnerable to Lassa fever transmission due to the presence of these rodent reservoirs.

Clinical diagnosis of Lassa fever is challenging, given its nonspecific symptoms that overlap with other tropical diseases. The disease's incubation period can vary widely, making early identification and containment crucial. Laboratory-based surveillance and molecular assays play pivotal roles in detecting and confirming Lassa fever cases.

Moreover, this study explores the genetic diversity of the Lassa virus within Ethiopia, emphasizing the need for a nuanced understanding of local strains. Despite promising advancements in vaccine development, no approved vaccines currently exist for Lassa fever.

In conclusion, this research underscores the urgency of Lassa fever preparedness and control measures in Ethiopia. It highlights the importance of surveillance, diagnosis, and public health interventions to mitigate the impact of this life-threatening disease. The findings provide essential insights into the multifaceted nature of Lassa fever, offering valuable guidance for policymakers, healthcare professionals, and researchers working to protect public health in Ethiopia and beyond.

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1. Introduction

Zoonotic diseases remain an important cause of morbidity and mortality in many regions of the world including Africa [1]. At least 75% of emerging and re-emerging infectious diseases have an animal origin [2]. The virus was first described in West Africa in the 1950s [3]. However, the Lassa virus was isolated, recognized and named in 1969 from a missionary nurse who worked in a clinic in a small town, Lassa, in Northeastern Nigeria [4]. The Lassa fever is endemic in the West African countries and causes 300,000 to 500,000 cases annually with about 5,000 deaths. Lassa fever (LF) is a zoonotic disease and potentially deadly hemorrhagic illness caused by Lassa Virus (LASV), a single-stranded RNA and a member of the *Arenaviridae* family [5, 6].

The main natural reservoir of Lassa fever is the rodent *Mastomys natalensis* that lives in proximity with humans [7]. A recent study showed that up to 30.7 million individuals in fourteen-countries in geographical region , significantly in West Africa, were living in areas that were liable to Lassa fever zoonotic transmission, because of the presence of rodent reservoirs in these countries [8].

Lassa fever is a viral infectious disease that can be transmitted to humans through contact with virus-infected rodent excreta via eating rodent-contaminated food, exposure to contaminated objects, and inhalation of tiny particles in the air contaminated with virus-infected rodent excretions [9]. Person-to-person transmission may theoretically occur during the acute febrile phase and an infected person may excrete the virus in urine for 3–9 weeks from the onset of illness [10]. Infection may also be acquired through the skin wound [5].

Epidemiological data from zoonotic viruses, such as Lassa fever in humans and animals are crucial in guiding common responses to this health threat. Furthermore, a recent study reported that the detection rate of the Lassa fever in asymptomatic individuals and the identification of populations at high risk were at crucial importance [11]. Most infections with Lassa fever in Africa are asymptomatic, mild or subclinical, the case fatality rate in symptomatic, hospitalized patients range from 15–20%, but could be as high as 90% for pregnant women. Recent studies suggest that outbreaks are largely fueled by independent zoonotic transmission events from infected rodent hosts, whilst approximately 20% of cases result from secondary human-to-human transmission, typically in hospital [11].

The symptoms of Lassa fever are often protean and nonspecific and clinical diagnosis is very difficult as the signs and symptoms are indistinguishable from diseases that are common in the tropics, such as severe malaria, typhoid fever, yellow fever and other viral hemorrhagic fevers [12]. The incubation period of Lassa fever is usually around 10days (6–21 days) after exposure to the virus [13].

Diagnostics play a polar role within the management of a pestilence of Lassa fever by allowing early designation, which may necessitate prompt antiviral medical care and scale back morbidity and mortality; aiding in the tracking of community contacts as well as providing the true picture of the epidemic [14]. Clinically, most Lassa fever patients are asymptomatic, and even when symptoms are present, they can be non-specific [15].

Laboratory based surveillance programs are essential for the prevention, management and control of outbreaks of Lassa virus infections [16]. Molecular assays are widely used in reference laboratories for Lassa fever diagnosis [17]. Although promising results have been reported in the preclinical phase of the vaccine development [18], there are currently no approved vaccines against Lassa virus infection [19].

The main preventive step of Lassa fever is rodent control in and around dwellings, avoiding contact with rats and consumption of them [20]. Lassa fever virus is listed among the WHO priority diseases in would like of imperative analysis and development efforts and it's classified as a class ―A‖ terrorism agent that can serve as biological weapons [21]. The prime objective of this manuscript is to present comprehensive review on the epidemiology, diagnosis and control of Lassa fever , a life threatening viral zoonosis of public health importance.

2. Lassa Fever

2.1. Causative Agent

However, the Lassa fever was isolated, recognized and named in 1969 from a missionary nurse who worked in a clinic in a small town, Lassa, in Northeastern Nigeria [4]. The Lassa virus is a single stranded RNA virus belonging to the *Arenaviridae* family of viruses. The virus is usually named viral hemorrhagic fever virus attributable to the tendency to cause hurt from body orifices. It is round, oval, or pleomorphic, 110 to 130 nm in diameter, and enveloped [22].The virus is inactivated by heating from 56–100˚C, ultraviolet and gamma radiations and pH range between 5.5 and 8.5, as well as by chemical agents like 0.5% sodium hypocrite, 0.5% phenol, 10% formalin and detergents [23].

2.2. Virology of Lassa Fever Virus Lassa virus (a member of *Arenaviridae* family) is categorized under the group known as ‗Old World Arenaviruses' on the basis of their antigenic and molecular properties [24]. The cluster consists of Arenavirus and Lymphocytic choriomeningitis virus (LCMV). Lassa virus is a single-stranded, enveloped, bisegmented RNA virus. It is a rapidly replicating virus but has inherent ability to temporarily control its replication. Consequently, the process is believed to aid the virus pathogenicity, and evasion of the host's defense mechanism [25].

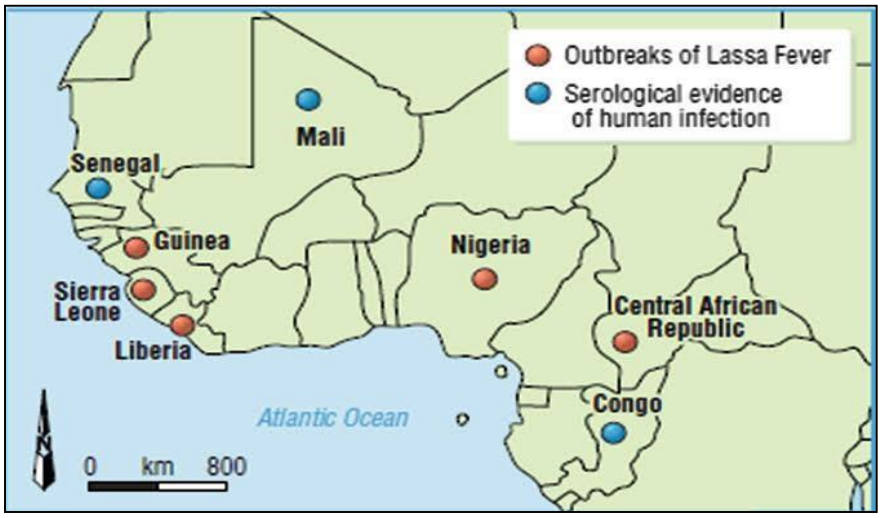
2.3. Epidemiology

The Lassa virus is sustained in nature in chronically infected rodents. The natural host of Lassa virus is Mastomyces natalensis, the most common rat in rural West Africa, commonly found in the households. The virus is shed within the rat's pee, feces, and metabolic process secretions, and is found in blood. Humans get infected by direct contact with the rat's excretions, by inhaling dust contaminated with it, or by eating the rat [26]. Person to person transmission occurs by direct contact, and there is very little epidemiological support for significant airborne transmission [20].

Contagiousness begins with symptom onset and will increase with unwellness severity, in step with the looks of tubular cavity shedding, vomiting, diarrhoea and hemorrhage, and increasing levels of infectious agent load in body fluids [27]. The virus is shed in the urine for 3–6 weeks, and up to 3 months in semen, with risk for sexual transmission, prompting condom use in survivors [28].

The disease is endemic in Nigeria, Liberia and Sierra Leone, with seroprevalence rates of 7 % to more than 20 % [15]. The distribution of Lassa fever in Africa is shown in Figure 1. Proven cases or seropositivity were also reported in Cote d'Ivoire, Guinea, Central African Republic, Mali, Senegal and Congo. These regions are also endemic to other hemorrhagic fever viruses, including Ebola, and indeed an outbreak of Lassa fever occurred in Liberia during 2014, as the activity of Ebola viral disease was high, complicating the differential diagnosis of suspected cases [29].

Figure-1. Map of Lassa fever distribution in Africa [29].



2.3.1. Reservoir

Forty-seven years after Lassa fever was first described as a disease, the isolation of Lassa virus has now been reported from rodent hosts other than *Mastomys natalensis*. These new Lassa fever reservoirs are the Guinea multimammate mouse *Mastomys erythroleucus* in both Nigeria and Guinea, the African wood mouse *Hylomyscus pamfi* in Nigeria and the Pygmy mouse *Musbaoulei* in Ghana and Benin [30]. The multimammate rat (*Mastomys natalensis*) discovered in 1974 as a natural host and reservoir of Lassa virus is a commensal rodent ubiquitous in Africa [31]. However, other reservoirs, such as *Hylomyscus pamfi* and *Mastomys erythroleucus* had also been discovered to harbor Lassa [32].

The Lassa virus is sustained in nature in chronically infected rodents. The multimammate mouse, *Mastomys natalensis*, is the primary host species for Lassa virus and widely distributed throughout West, Central, and East African countries [33].The multimammate rats (*M.natalensis*) were well known as the primary host species for Lassa virus [34].

They have some unique features which include characteristics foul odour, long hairless tail, soft body fur, pointed rostrum and ventral surface lined by multiple mammary glands [22]. Once infected, the rats don't become sick however shed the virus in their body fluids for the remainder of their lives. The virus is shed within the rat‘s pee, feces, and metabolism secretions and is found in blood. Humans get infected by direct contact with the rat‘s excretions, by inhaling dust contaminated with it, or by eating the rat [26]. Due to the poor understanding of the taxonomy of the genus, it is uncertain, which species and exact subspecies act as a virus reservoir [35].

Ecological factors such as height, variability and seasonal timing of rainfall are other possible explanatory variables for the discordance in the Lassa fever and *Mastomys natalensis* distribution in Africa. Since most outbreaks of hemorrhagic fever are ascertained to occur in regions with annual precipitation higher than 1500mm, it has been steered that Lassa virus could survive higher in humid conditions during the rainy season [36].

2.3.2. Transmission

Lassa fever is transmitted to humans when they ingest food contaminated by the feces and urine of *Mastomys species*. Once human‘s area unit infected, transmission additionally happens from human to human through contact with fluid and aerosol secretions within the variety of physiological reaction, sputum, body fluid, stool, urine and blood [37]. Rodent-to-human transmission of Lassa fever occurs via contact with rodent‘s body fluids, excreta, urine, tissues, or blood, as well as inhalation of infectious aerosols [38]. Additionally, direct or indirect contact with the blood, urine, faeces, or other bodily secretions of infected person appears to be the route often involved in the transmission of Lassa Fever from person to person. All age groups are susceptible and possibly affected by Lassa virus [39].

Although Lassa fever can be transmitted between humans, the majority of cases are thought to be transmitted by contact with urine or feaces of the wide spreads commensals rodent of *Mastomys natalensis*.*Mastomys erythroleuca* and *Hylomyscus pamfi* might also play a role in disease transmission [40].

2.3.3. Risk Factors

Rainfall seems to be an important ecological factor because a recent longitudinal study in rodents demonstrated that Lassa virus infection was two to three times higher in the rainy season than in the dry season. There are no studies to date indicating that the virus can survive better in humid than in dry soil [33].

Men are more commonly affected than women. However the case fatality rate is nearly two times higher in women. Although the high case-fatality of viral hemorrhagic fever is thanks to delayed cellular immunity, development of partial immunity as a result of frequent exposure to contaminated food is also to blame for the milder kinds of the malady and lower case-fatality rate in men. There‘s no age, gender or racial predilection. Outbreaks in endemic regions are promoted by factors that lead to increased rodent-man contact such as civil unrest, crowding, poor sanitation, deforestation, rodent hunting, bush burning, and agricultural developments such as rice cultivation that provide food supplies for rodents [20].

The rural dwellers in West Africa geographic region are in danger of Lassa fever attributable to proximity to animal reservoir, open construction of African villages, the applying of drying grains by roadsides or outside homes, and unprotected grain storage within homes. Certain cultural and personal habits have been implicated as factors promoting high incidence of Lassa fever. These factors included use of rat meat as a source of protein by people in some communities, contamination of exposed food by rat feces and urine, and traditional autopsy, where the operator may be injured with scalpel, and the injury contaminated with the blood of the deceased [41].

2.3.4. Morbidity and Mortality

Presentation of Lassa fever cases are at their peak during the dry season while some cases take place during the wet season. Latest reports revealed that hospital cases of Lassa fever on admissions peaked during the change period from the dry to the wet season. This occurrence might be partly due to population movements overcrowding. As the wet season advances there is progressive difficulty in travelling and may be responsible for the reduction in number of cases soon after in the season [42].

The infection can affect people of all age categories. Despite the mildness of the disease, up to about 80% of infected people are asymptomatic, while 20% are with severe multisystem disease. The Lassa virus is excreted in urine between 3 to 9 weeks of infection while it takes 3 months in semen and the scope of sexual transmission of Lassa virus is not known. Lassa fever tends to be more severe during pregnancy, mainly in its late stages, with fatality rates of up to 50 % and fetal loss in 75–100 % of cases [43].

The incubation period is usually 7–10 days, with a reported range of 3–21 days [43]. Twenty percent of cases have a severe disease, requiring hospitalization, while 80 % have a mild or asymptomatic infection. The general case morbidity is calculable at 1–2 %. The mortality rate of hospitalized cases in Africa is 15–20 % with reports of up to 50 % in some outbreaks [44].

2.4. Pathogenesis

The pathogenesis of Lassa fever is underlined by unchecked viremia, microcirculatory instability and impaired haemostasis mediated by immunological mechanisms [45]. The virus enters the physical structure through the blood, body fluid vessels, tract, and/or GI tract. It then multiplies within the native tissues or within the cells of the system. Lassa virus infects virtually each tissue in physical structure resulting in multisystemic dysfunction, and may suppress host‘s innate antiviral(IFN). This is achieved through digestion of Pathogen-associated molecular pattern (PAMP), which enables the virus to evade host‘s immune responses [25].

After infection, the virus proliferates primarily in macrophages, nerve fiber and epithelium cells. The infection does not result in lytic injury, and pathologic process is expounded to immune suppression, unrepressed infectious agent proliferation and host responses. Lassa virus inhibits host immune response in various ways. The foremost vital pathological modification is a rise in capillary porosity, with development of lump and shock. Other changes include hepatitis with hepatic necrosis, and necrosis of the spleen and adrenals [46].

The immune response to Lassa virus is not completely understood. Cellular immunity is most important, with strong T cell responses in survivors [47].Antibody responses are in all probability more modest, and though specific antibodies are created early within the sickness, neutralizing antibodies seem solely once weeks or months with low titers and enthusiasm [26].

2.5. Diagnosis

Diagnostics play a crucial role within the management of an endemic of viral hemorrhagic fever by: allowing early diagnosing which might necessitate prompt antiviral medical care and cut back morbidity and mortality; helping in the tracking of community contacts as well as providing the true picture of the epidemic [48]. The diagnosis of Lassa fever is done by both clinical and laboratory methods but that of laboratory is more reliable due to similarity in clinical presentations with other disease conditions. The need for prime containment safety needs and therefore the inadequacy of high containment laboratories in several components of the globe could have crystal rectifier to restricted viral haemorrhagic fever assay development and validation studies [49].

2.5.1. Clinical Presentation

The symptoms of Lassa fever are often protean and nonspecific and clinical diagnosis is very difficult as the signs and symptoms are indistinguishable from diseases that are common in the tropics, such as severe malaria, typhoid fever, yellow fever and other viral hemorrhagic fevers [12]. An individual may fall sick between 6 and 21 days after the Lassa virus gains entry into the body. The commonest ideal clinical predictors of Lassa fever include fever, pharyngitis, retrosternal pain and proteinuria; and fever, sore throat, and nausea for outcome [50]. The typical case progression can be divided into 3 main stages which include:-

Stage 1: Prodromal Illness/Acute Stage

At this stage, the onset of the sickness mimics protozoan infection or infectious disease. First, it begins with metabolism flulike (non-specificillness) symptom characterized by headache, pain (general body‘s weakness) feverish unhealthiness (fever≥ 38^0C, that does not reply to customary treatment for malaria or typhoid; accounts for 10-16% of total cases and about 30% of deaths) cough, pharyngitis (sore throat and back ache). Other signs include tremors chest paid, insomnia (restlessness), sometimes rashes coupled with gastrointestinal symptoms including diarrhea and vomiting [28].

Stage 2: Haemorrgagic Stage

This stage involves internal haemorrhage whereby victim bleeds from inside through nostrils, mouth and other orifices resembling that of Ebola. This may lead to organ failure and death [51].

Stage 3: Neurologic Complications

At this phase, hypotension, pericarditis, tachycardia, hypertension, Meningitis, Encephalitis and Seizures can be observed .The virus can be detected in the urine of infected patient for 3-9 weeks and in semen for up to three months [52].

Severe abdominal pain with peritoneal signs was reported, with many cases operated for suspected surgical and gynecological emergencies and some of these cases led to the infection of the staff working in surgical unit [53].

2.5.2. Laboratory Diagnosis

Lassa fever has emerged in concert of the foremost prevailing infective agent trauma fevers in West Africa. However, in most Lassa fever endemic areas of the region, there are serious challenges regarding the laboratory diagnosis and confirmation of the disease due to inadequate facility and low capacity [54].

A/ Virus Culture and Electron Microscopy

Culture of live agents was considered the gold standard but is rapidly being challenged by polymerase chain reaction (PCR) and next generation sequencing [52]. Electron microscopy (EM) may be used to identify virus based on structural characteristics from clinical materials or culture [55].

B/ Nucleic Acid Detection

RT-PCR has become the cornerstone for molecular diagnosis, and RT-PCR assays have been developed for the majority of VHF associated viruses [56]. The most helpful approach for diagnosis is polymerase enzyme chain reaction from blood. In fact, RT-PCR is a gold standard diagnosis for Lassa virus [49]. Clinically, most Lassa fever patients are asymptomatic, and even when symptoms are present, they can be non-specific. The need for prime containment safety needs and the insufficiency of high containment laboratories in several elements of the planet could have crystal rectifier to restricted haemorrhagic fever assay development and validation studies [49].

2.5.3. Differential Diagnosis

Since Lassa fever presents with signs and symptoms related to numerous other febrile endemic diseases such as malaria, dengue, influenza and yellow fever, differentiating between the agents of these illnesses remains a major challenge [49].

3. Prevention and Control Measures

Prevention and control Measures of Lassa fever transmission is enhanced by cohabitation of *Mastomys natalensis* species of rodent with humans in their residences in the affected areas having access to water and food items in the household. These rats are also prepared and consumed as delicacies by many inhabitants of West African region [57].Therefore, any preventive and control measures to be adopted should take cognizance of routes and mechanism of transmission of viral haemorragic fever. The subsequent measures area unit imperative in curtailing the regular epidemic natural event and unfold of VHF in Africa. These include that very unit has to device all means that engaged towards preventing rats from having any contact with foods, water and utensils utilized by the unit. This may be achieved by:

- ❖ Covering of foods and water meant for human consumption regularly.
- ❖ Foods should be kept in tightly sealed containers. Ready-to-eat food item should not be spread in the open or by the roadside where rats can have access to it.
- ❖ People should be admonished to kill and destroy rats in and around the house, shops or market places.
- ❖ Foods and water should be boiled adequately before consumption.
- ❖ All persons suspected of Lassa virus infection should be admitted to isolation facilities and promptly attended to with utmost care. Hospital workers should take universal precautions and protective measures when attending to such patients.
- ❖ Development of effective vaccine against Lassa fever (which has reached advanced stage with positive results in animal trials) is crucial in checkmating the spread of Lassa fever [58].

3.1. Treatment

Similar to other severe hemorrhagic fevers, supportive treatment is the cornerstone of clinical management of Lassa fever. Foods ought to be unbroken in tightly sealed containers. Ribavirin, a broad spectrum nucleoside analogue antiviral, possesses smart activity against LASV. Intravenous treatment in standard doses leads to plasma concentrations that are significantly higher than the minimal inhibitory concentration (MIC), while oral treatment,

limited by side effects and a 50 % bioavailability, leads to low to borderline concentrations, doubtfully inhibiting Lassa virus in vivo. Animal studies with parenteral ribavirin treatment proved it to be protective, with survival benefit in nonhuman primates, even when treatment was begun 5 days after infection [27].

Ribavirin efficiently suppresses the replication of Lassa fever in vitro but showed only moderate efficacy in reducing viremia in vivo [59]. Instead, ribavrin was found to protect infected cells from cell death, thereby significantly reducing the circulation of cell damage rather than suppressing viral transmission, viral production or enhancing the host immune response in animal model [59].

3.2. Vaccination

Unlike many other infectious diseases where preventive vaccines are available, there is yet no licensed vaccine for use in humans, although many candidate vaccines show promise in studies conducted in animals [60]. Presently, there is no licensed vaccine or immunotherapy available for prevention or treatment of this disease. International transportation to and from Africa had increased dramatically in the last decade, further increasing the risk for infectious disease exportation from endemic areas [61].

4. Conclusion and Recommendations

Lassa fever is an infectious viral zoonotic disease and potentially deadly hemorrhagic illness and the multimammate mouse, *Mastomys natalensis*, is the primary host species for it. Lassa fever is a highly virulent and contagious viral infection and rodent-to-human transmission occurs via contact with rodent‘s body fluids, excreta, urine, tissues, or blood, as well as inhalation of infectious aerosols. Lassa fever remains an important cause of morbidity and mortality in Africa, especially in West Africa. Except supportive treatment, there is no effective preventive vaccine against Lassa fever.

According to the above conclusions, the next recommendations are forwarded:-

- Public awareness and resilience strategies and mitigation measures in attaining national should be taken.
- More diagnostic and treatment centers for viral haemorrhagic fever ought to be established at numerous regions of every country endemic for viral haemorrhagic fever. Furthermore, fast-tracking research and development for more sensitive diagnostic tools, safer and effective drugs and vaccine development is imperative in improving contextual community-based immunization decision making policy to effectively outwit Lassa fever outbreak
- Further research should be done on Lassa virus and it natural reservoir (*Mastomys natalensis*) in northern, eastern, southern and central African countries.

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Contribution of Authors

All the authors contributed equally. They read the final version, and approved it for the publication.

Conflict of Interest

The authors declare that they do not have conflict of interest.

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