Factors Associated with Lassa fever Mortalities in Ondo State, Nigeria

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Factors Associated with Lassa fever Mortalities in Ondo State, Nigeria

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A Master's Thesis

Submitted to the Department of Global Health Policy and Financing, Division of Global Health Policy Financing and the Graduate School of Public Health Yonsei University

In partial fulfillment of the requirements for the degree of

Master of Public Health

Anwar Abubakar Mohammed

November 2022

This certifies that the Master's thesis

of Anwar Abubakar Mohammed is approved.

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DECLARATION

I, Anwar Abubakar Mohammed, hereby declare that the research "Factors Associated with Lassa fever mortalities in Ondo State, Nigeria." is submitted as a thesis for the completion of my Master's Degree in Global Health Policy and Financing at Yonsei University, Seoul. This paper reports the full results of my investigation; all ideas, references, and content have been acknowledged. Additionally, I certify that the results of this study have not been submitted in any degree and neither currently submitted as a candidate of any degree.

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Anwar Abubakar Mohammed 1st November 2022

Acknowledgment

I would like to express my deepest appreciation to my committee chair, Prof Tae Hyun Kim, for his invaluable advice that provided me with the needed direction right from the early stages of my research. I would also like to thank my committee members, Prof. Su Min Kim and Prof. Ji Young Lee, for their brilliant comments and suggestions that greatly enriched this study.

Additionally, I would like to express my appreciation to Prof Suk Yong Jang for introducing analysis with Jamovi software to us in our research methodology course and Prof Han for initial guidance on the science and art of scientific writing.

As Isaac Newton famously remarked, 'if I have seen further, it is by standing on the shoulders of giants' I would like to acknowledge the scholarly works of the global consortium of Lassa fever researchers whose works I have cited and given due credit to in several sections of these study. Thank you for providing me with the giant shoulders that enabled me to peep further to make this modest contribution to the body of knowledge about Lassa fever.

Studying at the prestigious Yonsei University graduate school is a rare privilege that I will be forever grateful for. I appreciate the Nigerian government for nominating me and the KOICA for sponsoring my education here. My sincere appreciation to the KOICA program coordinator, Mr. Ryung Robert Hoh, and the ever-active teaching assistants, Miss Hayun Kim and Steve Minuk.

I salute the perseverance and commitment of my lovely wife Maryam to the success of my study; she provided strong moral support and eliminated all distractions that could hamper my academic sojourn in faraway lands.

My family, friends, and colleagues are well appreciated for their support, prayers, and guidance, I thank you all.

Finally, I thank Almighty Allah for sparing my life and for creating ways and means for me to achieve whatever I have accomplished thus far. To Him belongs all glory. Wa Billahi Taufiq. Alhamdulillah.

Dedication

This work is dedicated to the loving memory of my younger brother Mohammed Bashir Abubakar who passed away on Sunday 21st March 2022. May Allah forgive his shortcomings and grant him the highest level of paradise. Amin.

Table of Contents

List of Tables

List of Figures

ABSTRACT

Background: Lassa fever is a viral hemorrhagic disease that is endemic in at least nine countries in West Africa. The virus causes significant morbidity and mortality, especially in the endemic region. Several studies have been conducted on epidemiological drivers and clinical management of Lassa fever cases; however, extremely few studies focused on factors responsible for Lassa fever mortalities. This study describes epidemiological and clinical factors that are associated with Lassa fever deaths in Ondo State, Nigeria. Ondo State is one of the hotspot states which has been recording extremely high mortality rates in recent years, hence it is crucial to identify factors associated with increased mortality to provide valuable insights for public health emergency managers to tailor effective outbreak response interventions that could improve case outcomes and reduce Lassa fever mortality.

Objectives: The general objective of the study is to evaluate factors associated with Lassa fever deaths in Ondo State, Nigeria, and to determine case fatality rates and epidemiological and clinical characteristics of Lassa fever deaths recorded in Ondo State over four years between 2018 and 2021.

Methods: Secondary data on Lassa fever cases and deaths recorded in Ondo State between 2018 to 2021 were obtained from Nigeria's national Surveillance system. The data were retrospectively analyzed, and case fatality rates were determined. The Association between clinical and epidemiological factors and the outcome of confirmed Lassa fever cases were evaluated.

Result: During the study period, a total of 1028 cases were laboratory confirmed out of which 233 died CFR 22.7%. The highest CFR at 28.2% was recorded in 2021 while the lowest CFR at 19.3% was recorded in 2018. Of the total cases, 538 (50.7%) confirmed cases are males while 490 (49.3%) are female. About 53.4% of all cases are adults between 26–59 years while children aged five and below totaled 49 representing 4.8%. Urban dwellers accounted for 83% of all cases while only 16.8% of cases were reported from rural areas. However, a higher CFR of 28.3% (49/173) was recorded among rural dwellers than

among those residing in urban centers. The most common clinical features of symptomatic cases among patients with laboratory-confirmed Lassa fever were fever 863(83.9), fatigue 584 (56.8%), headache 515 (50.1%), abdominal pain 388 (37.3) and cough 331 (32.2%). Mortalities among confirmed cases that also had cough is highest at CFR 26.3 (87/331) followed by those with abdominal pain at CFR 23.2 (90/388). Confirmed cases that had a fever as a symptom had a 21.8% CFR (188/863) those with headaches had a CFR of 19.8% (102/515), and those with fatigue has a CFR of 18.5%. The odds of fatal outcomes for patients that are positive for Lassa fever and present with symptoms of fatigue remain significant even after adjusting for age, sex, education, and occupation. Moreover, the odds of death from Lassa fever remain significant for adults aged 60 and above after controlling for symptoms, sex, education, and occupation.

Conclusion: This study observed a steady increase in case fatality rates among confirmed Lassa fever cases in Ondo State. Health authorities in the State need to critically review health system factors to ensure rapid case detection and access to quality case management for all confirmed Lassa fever cases in the State. Lassa fever is more fatal among adults aged 60 and above and more deaths were recorded among less educated individuals in the study population. Targeted risk communication messages and radio/TV jingles in local languages should be tailored to address this segment of society with preventive messaging and good health-seeking behavior. Symptomatic cases should quickly be brought under the care and close attention should be paid to patients that are 60 years and above and those who presented with fatigue as they are more likely to die from Lassa fever infection.

CHAPTER ONE
INTRODUCTION

1.1 Background of the Study

Lassa fever is associated with significant morbidity and mortality. The annual incidence of Lassa Fever in the endemic region of West Africa is estimated at 100,000 to 300,000 cases with about 5000–10,000 deaths and 58 million people at risk (Yaro et al., 2021). Seasonal Lassa fever outbreaks occur yearly during the dry season, especially in Nigeria, Liberia, and Sierra Leone. Case are also reported in Cote d'Ivoire, Guinea, the Central African Republic, Mali, Ghana, Senegal, and Congo. (Grace et al., 2021). Several studies have been conducted on epidemiological drivers and clinical management of Lassa fever cases; however, extremely few studies focused on factors responsible for mortalities due to Lassa fever.

Lassa fever virus was first identified as a disease in humans in a small village in Northern Nigeria called Lassa Village from where it got its name and spread quickly to other regions and countries. Today, Lassa fever is endemic in at least nine countries in West Africa (Samuels et al., 2021). Lassa fever is a viral hemorrhagic fever caused by infection with a Lassa virus- a single-stranded Ribonucleic Acid (RNA) virus of the *Arenaviridae* family.

Lassa fever is transmitted to humans primarily via exposure to the excreta of *Mastomys natalensis* (multimammate rat) deposited on floors, tables, beds, foodstuff, and other household utensils while secondary human-to-human transmission occurs when a person comes into close contact with someone with bodily fluid or aerosol containing the virus (Ejikeme et al., 2021).

Healthcare workers are a high-risk group especially if the standard precautions for infection prevention and control are not applied as they come into close contact with suspected Lassa fever cases before diagnosis. Studies have documented nosocomial

infections and outbreaks in healthcare settings, especially in endemic areas. This occurrence constitutes a considerable burden on the healthcare system (Ilori et al., 2019).

With a long incubation period usually between 3 to 21 days, an infected individual from a Lassa fever endemic area can travel to non-endemic regions and spread the virus locally and internationally within the incubation period resulting in epidemics. Grace et al. (2021) reported that previous Lassa fever outbreaks in Nigeria resulted in the exportation of cases to other countries, especially via international travel. Other studies have also demonstrated a changing trend in the spread of the virus within Nigeria. Abdulkarim et al. (2020) observed that non-endemic states like Bauchi State, which had never reported a case before 2012, have quickly become some of the high-risk states for Lassa fever in Nigeria.

Several studies have shown a progressive increase in the Lassa fever virus infection in Nigeria since the outbreak was first reported. The infection exhibited seasonal variability with the dry season having a significantly higher infection rate than the wet season (Ilori et al., 2019).

Factors that are responsible for the increase and spread of Lassa fever infections across Nigeria as established by some researchers include the exponential growth of the human population and the attendant urbanization, bush-burning practice, local food processing practices, and poor personal and environmental hygiene. Improvement in surveillance and diagnosis capabilities for Lassa fever in recent times is also believed to have contributed to detecting several cases across multiple states.

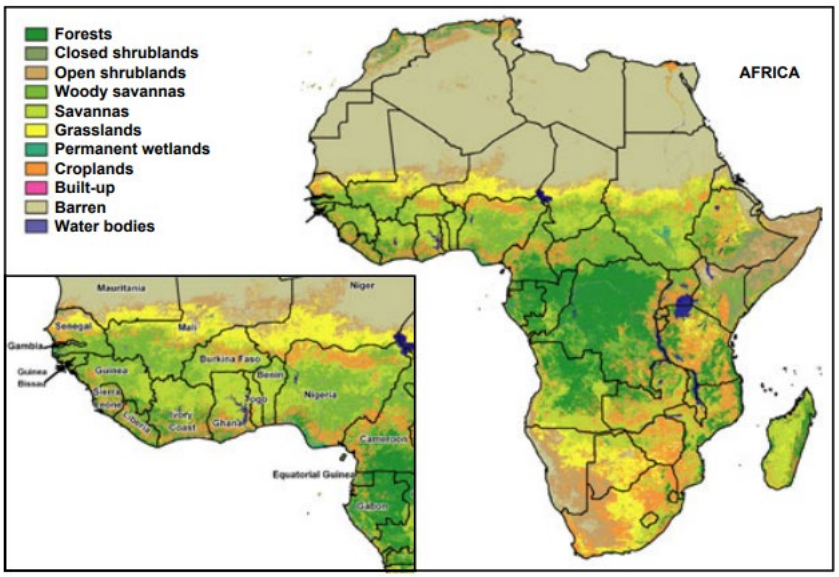


Figure 1. Map of the major ecozones present in Africa

showing similar ecological characteristics seen in Mali, Burkina Faso, Ghana, and Togo as seen in the Lassa virus endemic regions of Sierra Leone, Liberia, Guinea, and Nigeria (Sogoba et al., 2012).

Most Lassa fever infections are asymptomatic, especially within one (1) week of exposure. Delay in diagnosis often occurs because of non-specific symptoms such as fever and the assumption that the febrile illness is caused by other factors, especially malaria which is endemic in sub-Saharan Africa (Grace et al., 2021). Hospitalized patients may present with nonspecific clinical features, such as high fever, general body weakness and malaise, sore throat, abdominal pain, headache, nausea and vomiting, diarrhea, productive cough, proteinuria, and anemia (Samuels et al., 2021).

Clinical presentations typical of severe Lassa fever cases, such as mucosal bleeding, facial edema, convulsions, confusion or disorientation, pleural effusion, hypotension, elevated transaminases, renal impairment, and coagulation abnormalities, either appear late (after 1 week) or may not appear at all. Death also occurs in severe cases (Samuels et al., 2021).

The fatality rates for hospitalized severe Lassa fever cases is between 15%–50%; however, higher CFR is usually recorded during epidemics (Ilori et al., 2019). A study by Abdulkarim et al. (2020) demonstrated that Lassa fever has become a highly fatal disease in Nigeria with attending negative socioeconomic impact caused resulting from the fatalities, particularly among the productive age group being the most affected by the virus.

During the third trimester of pregnancy, Lassa fever poses a high risk of death to the fetus and the mother. This is because the virus has a high affinity for the placenta and vascular tissues and harbors a significantly higher viral load than in the non-pregnant population (Agboeze et al., 2019). Thus, Mothers with Lassa fever improved rapidly after the evacuation of the uterus by spontaneous abortion or normal delivery.

Despite the cross boarder spread with significantly high mortality and morbidity from Lassa fever infections and over 50 years since the first case was identified, there is no vaccine for Lassa fever, and treatment options are still extremely limited. However, several efforts have been put in place to change the status quo. The World Health Organization (WHO) listed the virus as a high-priority organism requiring prophylaxis and treatment.

Since then, different vaccine candidates involving human monoclonal antibodies have undergone preclinical trials, with some showing efficacy in animal models (Grace et al., 2021). Thus far, only one vaccine candidate progressed to the clinical trial stage.

Individuals infected with Lassa fever are treated with Ribavirin- a drug of choice for the management of Lassa fever patients in Nigeria. Ribavirin is also used as a post-exposure prophylaxis and is administered both orally and intravenously. Initiating early treatment is vital to improving the rate of survival (Grace et al., 2021). Abdulkarim et al demonstrated that a more than 24-hour delay in seeking care after the onset of bleeding was a strong predictor of death among cases while treatment with ribavirin improve survival chances of symptomatic patients

Previous research has focused extensively on epidemiological drivers and clinical management of Lassa fever infections in Nigeria and there are few studies on the clinical and epidemiological factors associated with Lassa fever mortalities, especially in Ondo state which has maintained the highest CFR for Lassa fever over the years. This study is aimed at highlighting and evaluating factors associated with Lassa fever death in Ondo state Nigeria to enable health administrators and public health managers to formulate effective interventions.

1.2 Problem Statement

An estimated half of all deaths in Africa are caused by emerging and re-emerging infectious diseases (Nyaruaba et al., 2022). Infectious diseases such as Lassa fever with yearly recurrent outbreaks in the endemic region of West Africa cause a significant death burden including deaths of Health care workers who are trying to manage the already fragile and understaffed healthcare system in this region. In addition to the healthcare burden caused by such regular outbreaks, the economic burden is equally enormous. The WHO estimated that it costs countries as much as US$15 million to provide an adequate response to one viral hemorrhagic fever outbreak (WHO 2011).

In Africa, the prevalence of antibodies to the Lassa fever virus ranges from 7% in Guinea to 8–52% in Sierra Leone to 21% in Nigeria (Bello et al., 2016). The age group that is most affected by the Lassa fever virus happens to be the most productive, a study of the largest documented outbreak of Lassa fever outbreak in Nigeria reported that the median age was found to be 32 years (interquartile range 20–44 years) and CFR was highest among adults less than 61 years (Ilori et al., 2019). Thus, a single death in a family unit can throw the whole family into poverty as the breadwinner of the family is taken away by Lassa fever. Farming which is a mainstay of the rural economy is also affected as several man-hours are lost due to sickness caused by the Lassa fever virus.

In Nigeria, Lassa fever is endemic in 32 out of the 37 states of the federation. Nigeria recorded its largest Lassa fever outbreak in 2018 (Ejikeme et al., 2021). The 2018 Lassa fever outbreak was not only large in the number of cases detected but also large in the geographical spread as cases and deaths were reported from states that had never reported a case before.

Since the 2018 outbreak, Nigeria continues to report large numbers of Lassa fever cases and deaths annually. About 15% of hospital admissions in specific regions of Nigeria each year are due to Lassa fever infection (Monath, 2019). Lassa fever also accounts for about 22% of maternal mortalities in endemic regions (Hasan et al., 2021).

Ondo state is one of the three hotspot states for Lassa fever in Nigeria- others are Edo and Ebonyi states. These three states constitute over half of the total Lassa fever cases reported in Nigeria yearly. Incidentally, Ondo state has had the highest number of mortalities due to Lassa fever in the last couple of years. A 2021 study of infection patterns, case fatality rates, and spread of Lassa fever in Nigeria established that Ondo state recorded a total of 131 deaths among confirmed Lassa fever patients within the four year study period (Yaro et al., 2021). There are limited studies that specifically consider factors associated with Lassa fever mortalities in Ondo state.

The aim of this study, therefore, is to carry out a retrospective analysis of the Lassa fever outbreak in Ondo State with a focus on mortalities due to Lassa fever infection between 2018 and 2021.

1.3 Main Objective: Evaluate factors associated with Lassa fever deaths in Ondo State Nigeria. The aim within the context of this thesis is to determine epidemiological and clinical factors associated with Lassa fever deaths in Ondo State between 2018 to 2021. Findings will provide better insights into the association between these factors and death, and this may contribute to public health knowledge and help in developing interventions.

1.4 Specific Objectives:

1. To determine case fatality rates among Lassa fever cases in Ondo state.
2. To describe epidemiological factors associated with Lassa fever deaths.
3. To identify clinical factors associated with Lassa fever deaths.

1.5 Research Questions

1. What is the rate of mortality among Lassa fever cases in Ondo state?
2. What are the epidemiological factors associated with Lassa fever deaths?
3. Which clinical features are predictors of deaths among Lassa fever cases?

1.6 Hypothesis

1. Age is associated with an increased chance of death from Lassa fever infection.
2. Being symptomatic is associated with death.
3. Gender does not affect the outcome of a Lassa fever case.

1.7 Justification of the study

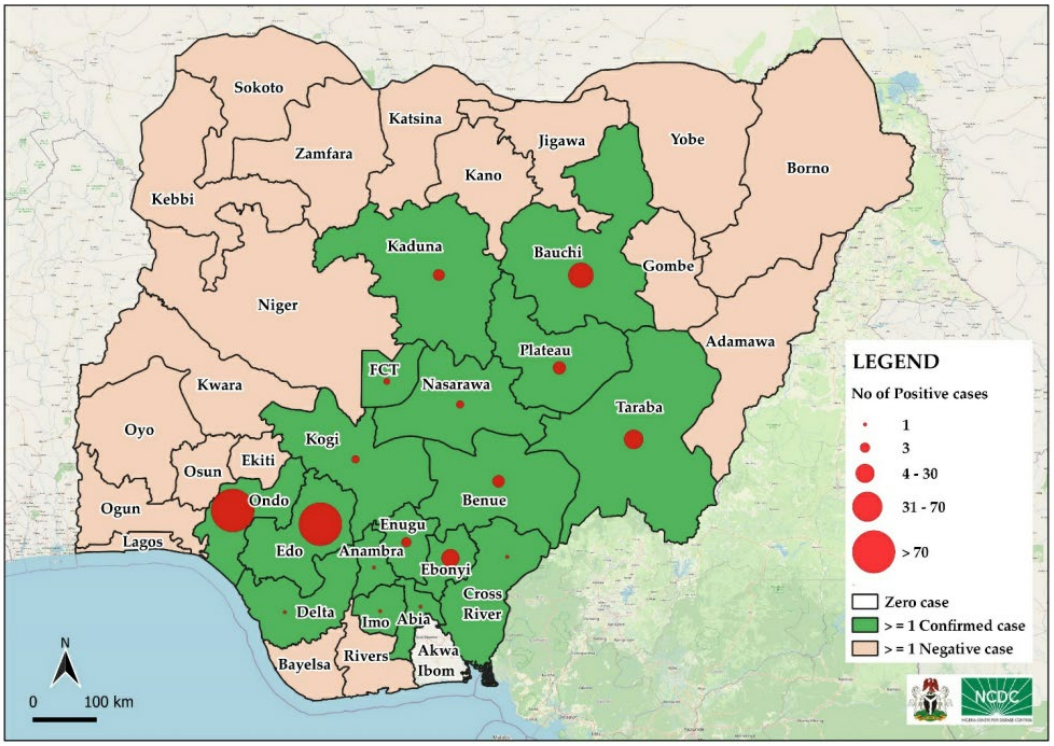
Ondo State is one of the three hotspot states for Lassa fever in Nigeria, in addition to recording a high number of cases yearly, the State has the highest recorded number of deaths due to Lassa fever in the last couple of years. There is a need to identify factors associated with such mortalities. This study will bridge the existing knowledge gap and dearth of evidence on factors responsible for Lassa fever deaths in Ondo state. An analysis of the four-year outbreak data, specifically epidemiological and clinical factors associated with Lassa fever deaths, will provide invaluable insights for public health emergency managers to be able to tailor effective outbreak response interventions to better improve treatment outcomes and reduce Lassa fever mortality.

1.8 Significance of the study

This study will highlight the critical factors responsible for high Lassa fever mortalities recorded in Ondo State annually and provide evidence for policy planning, medical treatment, and disease outbreak interventions.

Identifying the factors associated with Lassa fever mortalities in Ondo state will provide information for policy implementation and interventions such as training clinicians and surveillance officers. Findings from this study will also enable health educators and administrators to design targeted risk communication messages aimed at educating the general public on the implications of these factors to the overall outcome of Lassa fever infection in the study area.

Figure 2. Confirmed Lassa fever cases by States in Nigeria, week 52, 2021 (NCDC 2021)



1.9 Conceptual framework

The theoretical framework established by Gomes and Higginson (2006) is appropriate for this study. The model conceptualized three constructs on factors associated with an outcome, where each factor applies individually or interacts to cause changes in the outcome variable.

- ❖ Individual factor
- ❖ Clinical factor
- ❖ System factor

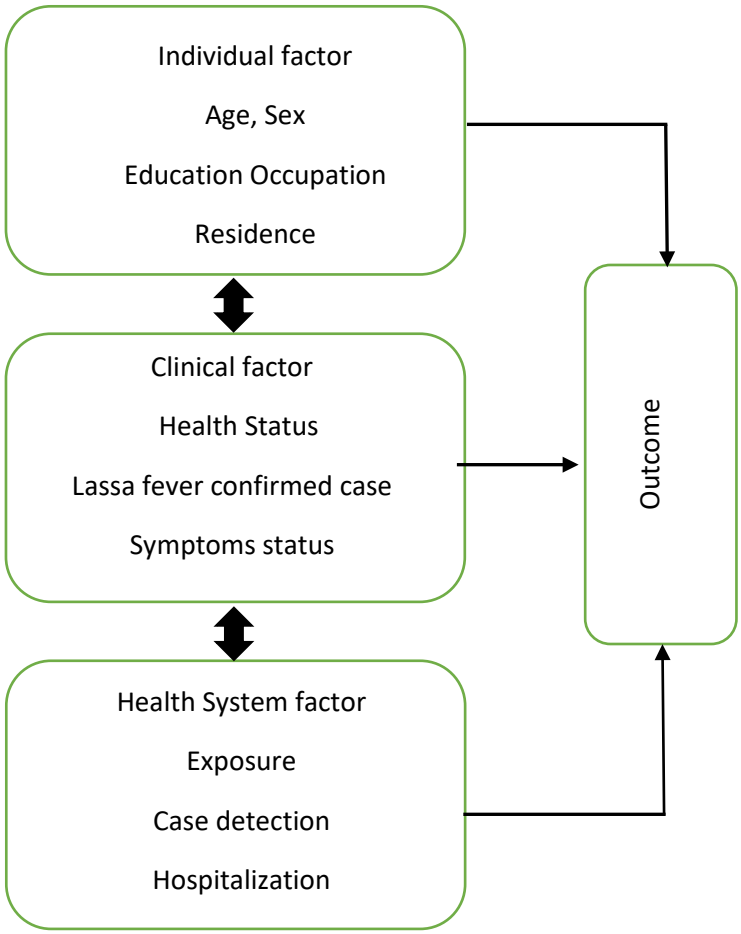


Figure 3. Conceptual framework for factors associated with LF mortalities

CHAPTER TWO
Literature Review

2.1 Lassa fever Overview

Lassa fever was first identified in 1969 when a small outbreak of a strange disease claimed the lives of two missionary nurses serving in the town of Lassa, Nigeria (Sogoba et al., 2012). Lassa fever is a viral hemorrhagic fever caused by infection with the Lassa virus; a single-stranded Ribonucleic Acid (RNA) virus of the Arenaviridae family. The animal reservoir or host of the Lassa virus (LASV) is a rodent of the genus Mastomys, commonly known as the "multimammate rat (Ejikeme et al., 2021). Reportedly, this specific rat breeds regularly and is commonly found in West African rural communities (Ilesanmi et al., 2015).

2.2 Lassa fever Epidemiology

Lassa fever is endemic in at least nine countries in West Africa (Samuels et al., 2021). The prevalence of Lassa fever antibodies varies from region to region with Nigeria, Sierra Leone, Guinea, and Liberia having significantly higher prevalence (Bello et al., 2016). Reportedly, seasonable outbreaks occur annually during the dry season, especially in this hyperendemic region. There are also reported cases in Cote d'Ivoire, Guinea, Central African Republic, Mali, Ghana, Senegal, and Congo (Grace et al., 2021; Ilori et al., 2019). To date, about 29 cases of Lassa fever infections have been exported worldwide including to areas as far away as Asia and Europe and majority of the cases resulted in mortalities (Sogoba et al., 2012).

There are two known endemic zones of Lassa fever virus in Africa: the Mano river region comprising Sierra Leone, Guinea, and Liberia and the Nigerian region. However, recent studies suggest that the endemicity zone has expanded beyond these two zones, thus, signaling that the Lassa fever virus is more widely distributed throughout the Tropical Wooded Savanna ecozone in West Africa (Sogoba et al., 2012).

2.2.1 Transmission

The main transmission route for the Lassa fever virus is zoonotic in nature, that is, the virus is transmitted from animals to humans via exposure to excreta of the animal reservoir host of the virus- *Mastomys natalensis.* The rat is known to shed the virus through its urine and feces which is usually deposited on surfaces or even on food items (Ejikeme et al., 2021; Ilesanmi et al., 2015). While secondary transmission of the virus is documented to occur via human-to-human transmission through contact with body fluids, especially if the body fluid contains blood. This occurs during the care of sick relatives or among healthcare personnel in healthcare settings (Ilori et al., 2019).

Researchers agreed that the overall pattern of transmission is primarily driven by environmental exposure to Lassa fever rather than sustained human-to-human transmission chains as obtained in Ebola Virus Disease or COVID-19. Some studies relayed that human-to-human transmission accounts for about 19% of all reported Lassa fever cases (Akhmetzhanov et al., 2019).

2.2.2 Symptoms and Diagnosis

About 80% of Lassa fever cases are asymptomatic or present initially with non-specific symptoms (Samuels et al., 2021). Usually, the signs and symptoms presented are extremely common with other viral and bacterial infections and indistinguishable from those of febrile illnesses such as typhoid, malaria and other viral hemorrhagic diseases like Ebola and Yellow fever (Ilesanmi et al., 2015). Only about 20% of cases progress to severe stages with serious symptoms including hemorrhaging (in gums, eyes, or nose), respiratory distress, repeated vomiting, facial swelling, pain in the chest, back, and abdomen, shock, hearing loss, tremors, encephalitis, and multiple organ failure (Ejikeme et al., 2021).

Lassa fever is most often diagnosed by using enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies as well as Lassa antigen. Reverse transcription-polymerase chain reaction (RT-PCR) can be used in the early stage of the disease (CDC, 2014). In Nigeria, two protocols for molecular diagnosis of Lassa

fever are used to cover the heterogeneous Lassa virus present in the region (Ilori et al., 2019).

2.2.3 Treatment and Control

Treatment of Lassa fever with Ribavirin has shown some success. Ilori et al. (2019) has reported that Ribavirin has been shown to reduce the Case Fatality Rate (CFR) for Lassa fever and the Nigerian national guidelines for the management of Lassa fever cases recommend that parenteral ribavirin be administered over 10 days for patients with confirmed Lassa fever. Ribavirin is also used as a post-exposure prophylaxis through both oral and intravenous administration. Initiating early treatment is vital to improving the rate of survival (Grace et al., 2021). Currently, there is no vaccine for Lassa fever; however, there is an ongoing effort to develop a vaccine and expand the limited treatment options (Grace et al., 2021).

The use of Personal Protective Equipment and compliance with standard Infection Prevention Control measures has been shown to reduce nosocomial infections (Ilori et al., 2019). The CDC recommends that individuals can protect themselves from the virus by avoiding contact with rodents carrying the virus and by maintaining good personal and environmental hygiene. Public health institutions usually activate a multisectoral “One Health” approach in managing outbreaks of Lassa fever using the incident management system (Ejikeme et al., 2021).

The Nigerian CDC has developed standardized treatment regimens for various categories of Lassa fever patients. The guideline also corroborates that the drug of choice for the treatment of Lassa fever is intravenous Ribavirin. Intravenous Ribavirin is administered over a period of 10 days as seen in the table below. The outcome is more avorable if treatment is commenced within six days of the onset of symptoms.

Table 1: National Treatment Algorithm for Lassa fever case management in Nigeria

1A Adults including non-pregnant adults (McCormick regimen)

Period	Dose	Frequency
Loading Dose	33mg/kg (maximum dose of 2.64 g)	Stat
Day 1-4	16mg/kg (maximum dose of 1.28 g)	6 hourly
Day 5-10	8mg/kg (maximum dose of 0.64g)	8 hourly

1B Adults including non-pregnant adults (Irrua regimen)

Period	Dose	Frequency
Loading Dose	100mg/kg (maximum of 7g)	In 2 divided doses: 2/3 given stat & 1/ given 8 hours later
Day 2-7	25mg/kg	Daily (single dose)
Day 8-10	12.5 mg/kg	Daily (single dose)

ISTH Regimen for Pregnant women (Modified McCormick regimen)

Period	Dose	Frequency
Loading Dose (Day 1)	100mg/kg	In 2 divided doses. 2/3rd of loading dose given sta and after 8 hours, remaining 1/3rd is given
Day 2-5	16mg/kg	6 hourly
Day 6-10	8mg/kg	8 hourly

For a pregnant woman who weighs 70kg, total calculated dose will be 7000mg. 2/3rd of the total calculated dose (4700mg) will be given stat and balance of 2300mg given 8 hours later). From day 2-5, total calculated daily dose will be 1120mg given 6 hourly and from Day 6-10, total calculated daily dose will be 560mg given 8hourly

2.3 Trends of Lassa fever Outbreaks 2017–2021

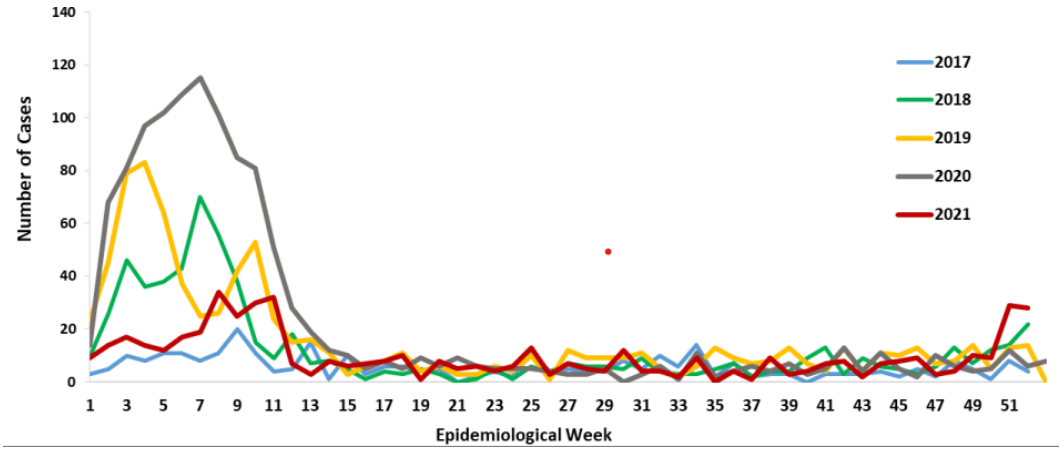
There has been an increase in the number of reported Lassa fever cases from West Africa, especially in Nigeria, Benin, and Togo. The increasing trend has become worrisome for public health stakeholders, especially with the growing number and frequency of

outbreaks and the expanding regions of the virus' endemicity (Grace et al., 2021; Sogoba et al., 2012).

Whilst this increase seems unlikely to be due to the emergence of a new Lassa virus variant, other factors may be playing a significant role: increased human-rodent 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 (Asogun et al., 2019).

In Nigeria, before 2018, the yearly confirmed cases ranged from 25 to 143 the country experienced large outbreaks of Lassa fever cases in 2018 and 2019 (Ejikeme et al., 2021; Grace et al., 2021). There have been Lassa fever cases reported from Benin (54 cases and 28 deaths), Togo (2 cases), Liberia (7 cases, 3 deaths), and Sierra Leone (2 cases). A WHO report has indicated that cases have also been reported outside West Africa, exported by travelers to Sweden and Germany within these periods (WHO 2019). Previous studies have shown that high mortalities are recorded among exported cases.

Figure 4 Weekly epidemiological trend of Lassa fever confirmed cases in Nigeria from 2017 to 2021 (retrieved from NCDC Lassa Fever Situation Report, 2021) (NCDC 2021).



2.4 Lassa fever Case Fatality Rates

CFRs are the proportion of people who die from a specified disease among all individuals diagnosed with the disease over a certain period. It is commonly used to measure the severity of a disease and can be used to make a prognosis.

It is estimated that annually, about 5000–10,000 lives are lost due to Lassa fever infection in the endemic region of West Africa (Duvignaud et al., 2021; Ilori et al., 2019). Studies have shown that Lassa fever case fatality rates vary across regions, seasons, and the affected demography. For instance, Samuels et al found a case fatality rate of CFR 63% among the pediatric Lassa fever positive cohort in Sierra Leone which is much higher than the 29.2% CFR reported in a similar pediatric cohort from Ebonyi State, Nigeria (Samuels et al., 2021). Furthermore, since only about 20% of cases progressed to the severe stage, higher case fatality rates are usually recorded among hospitalized patients.

Generally, published accounts of Lassa fever case fatality rates tilted towards a CFR range of 10–15%, although CFR increases of up to 50% are observed during epidemics in Lassa fever endemic regions (Ilori et al., 2019). However, there is a significant difference in CFR ranges across previously healthy populations without underlying co-morbidities as a CFR of 2–5% is usually documented, whereas that of severely sick and hospitalized positive cases ranges from 20–60% (Akhmetzhanov et al., 2019). This is almost similar to what was observed in another study by Ilori et al. that reported 15–50% CFR for hospitalized cases.

Higher CFR is documented among pregnant women than non-pregnant women particularly during the later stages of the gestation period, with high rates of fetal or perinatal loss associated with the Lassa fever infection (Krubiner & Schwartz, 2019). In a retrospective study of 30 pregnant women infected with Lassa fever on treatment at a teaching hospital in Southern Nigeria, 11 (36.7%) of 30 women died, and 20/31 (64.5%) pregnancies ended in fetal or perinatal loss (Okogbenin et al., 2019). Thus, a higher chance of death is indicated among pregnant women infected with the Lassa fever virus.

Abdulkarim et al. reported that more fatalities were recorded among adults less than 60 years. This is consistent with similar studies in Plateau State Nigeria. Duvignaud et al. (2021) found that age 45 and older is a baseline factor that is independently associated with Lassa fever mortality.

Early diagnosis and access to treatment are shown to impact CFRs. According to Ilori et al., the CFRs for patients who did not receive treatment with ribavirin was 71.4% compared with 20.7% for patients who received ribavirin. Similarly, higher chances of survival and favorable prognosis are documented for patients that commence treatment immediately after symptoms begin than those that started treatment more than seven days after symptom onset (Abdulkarim et al., 2020; Grace et al., 2021; Ilori et al., 2019).

In Nigeria, where a yearly outbreak of Lassa fever is recorded a national CFR average of above 20% is documented between 2017–2021 (NCDC 2022)

2.5 Epidemiological factors associated with Lassa fever deaths

Epidemiology is often described as a cornerstone of public health in that it helps bring out the relationship between risk factors and the occurrence of disease and mortality in a population within a specific point in time with the view of preventing further spread and designing a public health intervention (Bouter et al., 2018). For the Lassa fever virus, several epidemiological risk factors have been identified by researchers.

Grace et al. (2021) established that the significantly high mortality rates associated with Lassa fever are a result of poor sanitary conditions and daily environmental lifestyles that is common among people residing in high-risk endemic areas. Given the importance of human-animal interface on the environment, it is anticipated that environmental factors may be key drivers of the frequent Lassa fever outbreaks (Akhmetzhanov et al., 2019).

Reportedly, about 58 million people are at risk of contracting Lassa fever by being residents in regions endemic to the virus. Traveling to those regions too can increase chances of infection as the exportation of travel associated with 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 (Asogun et al., 2019; Sogoba et al., 2012).

Previous studies linked the increase and spread of Lassa fever infections across Nigeria with a variety of factors such as the increasing proximity of the human population to the natural habitat of rodents responsible for transmitting the virus. 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 foodstuff (Asogun et al., 2019). In two separate studies, it was found that about 17% and 19% of confirmed cases have a history of contact with rodents a few days before falling sick (Akhmetzhanov et al., 2019; Ilori et al., 2019). However, since this information is obtained by patient interview, recall bias might have influenced the accuracy and reliability of the exposure history.

Secondary attack rates were found to be higher among adults, especially those that had contact with confirmed cases than those among the general population. This type of exposure is mostly documented among healthcare workers and caregivers at home (Ejikeme et al., 2021; Monath, 1975). Cultural practices such as unsafe traditional embalming and burial rites of deceased relatives and forceful ingestion of water used in bathing dead persons, especially by widows to prove their innocence in the event of accusations of causing the death of their husbands have been identified as another reason for a human to human spread of Lassa fever and other communicable diseases in rural communities (Ilesanmi et al., 2015).

Studies have shown that Lassa fever can affect all age groups and both genders. However, certain age groups are at a higher risk of infection and death than others. For instance, pediatric Lassa fever is known to occur more commonly among male children for yet unknown reasons. Presenting as an acute febrile illness, the case fatality rate may approach 30% in children with generalized edema, abdominal distension, and bleeding

(Samuels et al., 2021). There is a sharp contrast between the findings here and what was reported by Abdulkarim et al. In their studies, they found that more fatalities were recorded among adults below 60 years, this agrees with similar studies in Plateau State Nigeria. Duvignaud et al. (2021) found that being adult and 45 years and older qualified as a baseline factor that is independently associated with Lassa fever mortality

During pregnancy and in the third trimester, Lassa fever poses a high risk of death to the fetus and the mother, this is because the virus has a high affinity for the placenta and vascular tissues and harbors a significantly higher viral load than in the non-pregnant population (Agboeze et al., 2019). Thus, mothers with Lassa fever improved rapidly after the evacuation of the uterus by spontaneous abortion or normal delivery. Staff and other patients in 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 fetuses (Okogbenin et al., 2019)

2.6 Clinical factors associated with Lassa fever deaths

Studies have established that of the about 20% of Lassa fever cases that progressed into severity and got admitted into treatment centers, key predisposing factors for mortality are found to include: acute kidney injury, liver failure, encephalopathy, seizures, reduced consciousness, disseminated intravascular coagulation with mucosal bleeding, septic shock progressing to multi-organ failure. Moreover, pregnant women, children under 5 years, and individuals with HIV or other immunosuppressive conditions have an increased risk of death (Asogun et al., 2019; Okogbenin et al., 2019).

Earlier studies that consider the clinical management of Lassa fever in Nigeria have discovered 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 (Akpede et al., 2019; Ilori et al., 2019).

In the study of caseloads and case fatality among hospitalized Lassa fever cases in Nigeria, Akepede et al argued that while several factors could account for high case

fatalities, including late presentation and other delays in diagnosis, the dearth of human and material resources for diagnosis and treatment may be important but somewhat overlooked factors. Other researchers such as Abdulkarim et al and Ilori et al agree with this position adding that late presentation, low index of suspicion among clinicians, and lack of timely access to ribavirin are other factors.

Four other observational studies from the Center of Excellence in Management of Lassa fever in Nigeria indicated that the presence of shock, bleeding, encephalopathy (as evidenced by seizures and/or coma), and acute kidney injury (AKI) were the major determinants of outcomes. Presentation with abnormal bleeding and ≥1 feature of AKI was associated with increased case fatality in all four studies while encephalopathy was associated with increased case fatality in three of the four studies. Presentation with ≥2 of these complications or danger signs would be a strong criterion for diagnosis of severe Lassa fever infections. These studies are pointers that clinical factors are predictors of deaths in Lassa fever cases (Akpede et al., 2019; Ilori et al., 2019).

The reviewed literature on this crucial part of the intended study has several limitations, particularly in identifying compounding factors, and a heavy focus on clinical management. This study seeks to elucidate all factors and their level of involvement in Lassa fever deaths in Ondo state.

CHAPTER THREE
METHODS

3.1 Study Area

Ondo State is located in the South-West region of Nigeria and consists of 18 Local Government Areas otherwise known as districts. It shares a common boundary with Delta, Edo, Ekiti, Kogi, Ogun, and Osun States which are known to be endemic for Lassa fever. The population was 4,671,700 in 2016 based on the 2006 population census ("Ondo State, Nigeria). It covers an area of 15,500 km² with longitudes 40 151 E and 60 001 E, latitudes 50 451 N and 70 451 N, which are to the north of the equator, and has a high daily temperature of about 30 0C. Many of the residents of Ondo state are civil servants, traders, and farmers.

Figure 5. An Administrative Map of Ondo State –(Source Ondo Connect 2020)

3.2 Study Population

The Study population is the Lassa fever cases and deaths recorded in Ondo State from January 2018 to December 2021.

3.3 Inclusion Criteria

Only Laboratory-confirmed cases are included in the study analysis.

3.4 Exclusion Criteria

Suspected cases and laboratory negative cases were excluded from the analysis.

3.5 Study Design

The retrospective descriptive analytical design was used to analyze secondary data on Lassa fever cases and deaths recorded in Ondo State between 2018 and 2022. This study method is used because there is existing high-quality secondary data that is adequate for analysis that could answer the research questions. This method also saves time which is extremely limited for this study. A key limitation of this study method is that significant biases may affect the selection of variables and one must rely on others for accurate recordkeeping.

3.6 Study Variables

3.6.1 Outcome Variable

The dependent variable in this study is death from Lassa fever infection. This is determined by the case outcome among all confirmed Lassa fever cases recorded in the study area within the study period. Case outcome is a binary variable and is recorded as “Alive” or “Dead”.

3.6.2 Independent Variables

The demographic and epidemiological characteristics such as age, sex, residential address, education, occupation, exposure history, and clinical information, such as first symptoms presented, symptom at death, and status of hospitalization are evaluated and the association between these variables and case outcome is determined.

3.7 Data Sources

During the study period, all suspected Lassa fever cases were reported to the Disease Surveillance and Notification Officers for each Local Government Area and the Ondo State Epidemiologist through the national surveillance system by using a surveillance reporting form developed for integrated disease surveillance and response in Nigeria. Samples were collected and tested for all suspected cases as long as the case patient was alive. If the test was positive, detailed demographic (age, sex, and residential address), clinical (symptoms, outcome), and epidemiologic (occupation, onset date, and exposure history) information were collected using a standardized case investigation form (CIF). All suspected, probable, and confirmed cases were line listed. The CIF data is harmonized with Laboratory data and data collected electronically through the Surveillance Outbreak Response Management and Analysis System (SORMAS).

3.8 Case Definition

Following the Nigeria Centre for Disease Control Standard Operating procedures for Lassa fever case management (NCDC 2018), a suspected case of Lassa fever is defined as an illness meeting one of the following criteria: 1) >1 signs/symptoms (e.g., malaise, fever, headache, sore throat, cough, nausea, vomiting, diarrhea, myalgia, central chest pain or retrosternal pain, and hearing loss) and a history of contact with excreta or urine of rodents; 2) >1 signs/symptoms and a history of contact with a person with probable or confirmed Lassa fever within 21 days of symptom onset; or 3) inexplicable bleeding or hemorrhaging. A probable Lassa fever case is defined as any suspected case of a patient who died without the collection of a specimen for laboratory testing. Confirmed Lassa fever cases are defined as any suspected case with a laboratory confirmation (positive for IgM antibody, reverse transcription PCR [RT-PCR], or virus isolation).

Samples collected from suspected cases within the study period are sent to the designated accredited molecular laboratories for Ondo state where laboratory confirmation was performed by using RT-PCR using the RealStar Lassa Virus RT-

PCR Kit (Altona Diagnostics, https://www.altona-diagnostics.com), the Lassa fever diagnosis protocol developed by Nikisins et al. as adopted by the NCDC (Nikisins et al., 2015) or both. More than 95% of samples were tested by using both protocols to ensure greater sensitivity for the heterogeneous Lassa virus in Nigeria. A positive result in either or both of the protocols was regarded as positive (NCDC 2018).

3.9 Statistical Analysis

Frequencies and percentages are used to describe the socio-demographic characteristics of the study population. A Chi-square analysis is then used to test the association between the independent variables and the dependent variable. A Binomial logistic regression analysis has been conducted to determine the adjusted odds ratio (aOR) for sex, age, education, and occupation alongside the most common symptoms among survived and deceased patients with laboratory-confirmed Lassa fever. Likewise, an odd ratio s is used to compare the presence of each symptom and the outcome among these cases. Statistical tests are performed using Jamovi software version 2.2.5. A 95% CIs and p-values are computed to test statistical significance and then adjusted p-values by the Bonferroni correction for multiple comparisons. A p-value of <0.05 is considered statistically significant.

3.10 Ethical Approval

Approval was obtained from the Nigeria Center for Disease Control and Prevention's Ethics boards and other relevant regulatory bodies in Nigeria.

3.11 Data Accessibility

Anonymized clinical and epidemiologic data of case patients will be made available on request, conditional on the recipient agreeing to appropriate guidelines for their usage.

CHAPTER FOUR
RESULTS

The results of the data analysis conducted in this study are represented in tables to visualize the findings.

Table 1 shows a general description of the study population vis-à-vis demographic, epidemiological, and clinical characteristics of all confirmed Lassa fever cases within the study period (Jan 2018-Dec 2021).

During the study period, 1028 cases were laboratory-confirmed in Ondo state. In 2018, 109 cases were confirmed (CFR 19.3%), in 2019, 294 were confirmed (CFR 20.1%), in 2020, there were 451 confirmed cases (CFR 23.1%), and in 2021, 174 cases were confirmed with (CFR 28.2%). The highest CFR of 28.2% was recorded in 2021 while the lowest CFR of 19.3% was recorded in 2018 with an average CFR of 22.7% within the four years.

Of the total laboratory-confirmed cases, 549 representing 53.4% of all cases were adults between 26 and 59 years while children aged 5 and below totaled 49, representing 4.8% of total cases. Deaths among adults aged 60 and above were highest at 42.3% (156/66), followed by deaths among children between 0–4 years at 30.6% (15/49). Significantly high mortalities are also recorded among adults between 26 and 59 years while the lowest deaths were recorded among children between ages 5 and 12 at 8.5% (4/59).

A total of 538 (50.7%) laboratory-confirmed cases were males while 490 (49.3%) were female. The case fatality rate among males is 25.1% while that among females is 20.0%. Case fatality rates were higher among males; however, they were not statistically significant.

Urban dwellers accounted for 83% of all cases while only 16.8% of cases were reported from rural areas. However, a higher CFR 28.3% (49/173) was recorded among

rural dwellers than among those residing in urban centers; however, no significant P-value was observed for residential locations.

About 74% of all cases had secondary or tertiary education (Secondary 31.4% and Tertiary 44.7%). Mortalities among those with no form of education was 43.4% while those with tertiary education had the lowest CFR of 16.5%. The education status variable was statistically significant with a P-value of 0.001.

In the occupation category, most reported cases were on the student and self-employed groups: Student n-285(27.7%), and self-employed n-260 (25.3%) respectively. The highest mortality was observed among the farmers' group at 36.7% (55/150). This was followed by the unemployed group with a CFR of 27.9% (104/29).

Healthcare workers and students recorded the lowest CFR at 10.7 (3/28) for healthcare workers and 14.4% (41/285) for students.

A total of 116(11%) of all cases were exposed to the virus out of which 23 died representing 19.8%, while 908 (88.5%) of all cases were symptomatic and 192 of them died, representing 21% (n-192). A total of 898 cases (87.4%) were hospitalized out of which 205 died, representing 22.8% of all hospitalized cases.

Statistically significant P- values were observed on age (P-value 0.001), education (P-value 0.001), occupation (P-value 0.001), and those who were symptomatic (P-value 0.002).

Table 2: Demographic, Epidemiological, and clinical characteristics of confirmed Lassa fever cases 2018–2021

				Outcome of condition				
Characteristics	**Stratum**	**Total**	**%**	**Alive**	**%**	**Dead**	**%**	**P-value**
		N-1028		**N-795**		**N-233**		
Mortality (Years/CFR)								
	2018	109	14	88	80.7	21	19.3	
	2019	294	37	235	79.9	59	20.1	
	2020	451	57	347	76.9	104	23.1	
	2021	174	22	125	71.8	49	28.2	
Age(Years)								0.001
	0-4	49	4.8	34	69.4	15	30.6	
	5-12	59	5.7	54	91.5	4	8.5	
	13-17	58	5.6	47	81.0	11	19.0	
	18-25	157	15.3	141	89.8	16	10.2	
	26-59	549	53.4	429	78.1	120	21.9	
	60+	156	15.2	90	57.7	66	42.3	
Sex								0.051
	Female	490	49.3	392	80.0	98	20.0	
	Male	538	50.7	403	74.9	135	25.1	
Residence								0.051
	Rural	173	16.8	124	71.7	49	28.3	
	Urban	855	83.2	671	78.5	184	21.5	
Education Status								0.001
	Tertiary	460	44.7	384	83.5	76	16.5	
	Secondary	323	31.4	246	76.2	77	23.8	
	Primary	99	9.6	83	83.8	16	16.2	
	Nursery	6	0.6	5	83.3	1	16.7	
	Others	11	1.1	4	36.4	7	63.6	
	No Education	129	12.5	73	56.6	56	43.4	
Occupation Category								0.001
	Civil/Public Servant	201	19.6	159	79.1	42	20.9	

	Health worker	28	2.7	25	89.3	3	10.7	
	Self employed	260	25.3	197	75.8	63	24.2	
	Farmer	150	14.6	95	63.3	55	36.7	
	Unemployed	104	10.1	75	72.1	29	27.9	
	Child/Student	285	27.7	244	85.6	41	14.4	
Exposure								0.438
	Yes	116	11.3	93	80.2	23	19.8	
	No	912	88.7	702	77.0	210	23.0	
Symptomatic								0.002
	Yes	908	88.5	716	78.9	192	21.1	
	No	118	11.5	78	63.1	40	33.9	
Hospitalization								0.743
	Yes	898	87.4	693	77.2	205	22.8	
	No	130	12.6	102	78.5	28	21.5	

Table 3 represents the top five symptoms commonly found distributed among confirmed Lassa fever cases recorded in Ondo state between 2018 and 2021.

The most common signs and symptoms among patients with laboratory-confirmed Lassa fever were: fever 863(83.9), fatigue 584 (56.8%), headache 515 (50.1%), abdominal pain 388 (37.3), and cough 331 (32.2%). Mortalities among confirmed cases that also had cough was highest at CFR 26.3 (87/331) followed by those with abdominal pain at CFR 23.2 (90/388). Confirmed case that had fever as a symptom had a 21.8% CFR (188/863), those with headache had a CFR of 19.8% (102/515), and those with fatigue had a CFR of 18.5% (108/584). A statistically significant P-value was observed on those that presented with fatigue.

Table 3: Most common symptoms and outcomes among patients with laboratory-confirmed Lassa fever cases in Ondo State 2018–2021

			Outcome of condition				
	Total	**%**	**Alive**	**%**	**Dead**	**%**	**P-value**
Symptom	**N-1028**		**N-795**		**N-233**		
Fever							0.123
Yes	863	83.9	675	78.2	188	21.8	
No	165	16.1	120	72.7	45	27.3	
Fatigue							0.001
Yes	584	56.8	476	81.5	108	18.5	
No	444	43.2	319	71.8	125	28.2	
Headache							0.028
Yes	515	50.1	413	80.2	102	19.8	
No	513	49.9	382	74.5	131	25.5	
Abdominal Pain							0.752
Yes	388	37.7	298	76.8	90	23.2	
No	640	62.3	497	77.7	143	22.3	
Cough							0.056
Yes	331	32.2	244	73.7	87	26.3	
No	697	67.8	551	79.1	146	20.9	
Others							0.908
Yes	50	4.9	39	78.0	11	22.0	
No	978	95.1	756	77.3	222	22.7	

In table 4, the five most common clinical symptoms among confirmed Lassa fever cases are analyzed while controlling for age, sex, education, and occupation. Lassa fever patients that presented with fatigue had an adjusted odd ratio of 1.7 at 95%. They had a Confidence Interval range of (1.2–2.5) and no statistical significance was observed with the remaining four most common symptoms.

Similarly, the odds of a fatal outcome among adults 60 years and above was 2.2 at a 95% Confidence Interval range of (1.2–2.5). No significant association was observed between education and occupation with fatal outcomes.

Table 4: Multivariate analysis of clinical factors and demographic factors

			95% Confidence Interval	
Characteristics	**Stratum**	**Odd ratio**	**Lower**	**Upper**
Symptoms				
	Fever	1.082	0.6818	1.718
	Fatigue	1.791	1.2663	2.533
	Headache	1.282	0.9081	1.811
	Abdominal pain	0.702	0.4959	0.994
	Cough	0.689	0.4853	0.979
	Other symptoms	0.977	0.4724	2.021
Age (Years)				
	26-59	Ref		
	0-4	0.633	0.1926	2.079
	5-12	1.947	0.4909	7.72
	13-17	0.689	0.2277	2.083
	18-25	2.947	0.4909	3.207
	60+	2.189	1.675	5.699
Sex				
	Male	Ref		
	Female	0.69	0.4961	0.959
Education				
	Tertiary	Ref		
	Secondary	0.532	0.2893	0.979
	Primary	1.449	0.1436	14.621
	Nursery	0.337	0.0902	1.258
	Others	1.006	0.4889	2.071

	No Education	1.584	0.9968	2.516
Occupation				
	Civil/Public Servant	Ref		
	Health worker	2.068	0.852	5.02
	Self employed	1.093	0.5824	2.052
	Farmer	1.789	0.5052	6.333
	Unemployed	1.038	0.6157	1.751
	Child/Student	0.894	0.481	1.661

CHAPTER FIVE
DISCUSSION

This study set out to provide a description of epidemiological and clinical characteristics of confirmed Lassa fever cases in Ondo state and to investigate potential factors associated with mortality within the study period. Between 2018 and 2021, 1028 Lassa fever cases in Ondo state were laboratory confirmed. This further confirmed the ranking of Ondo state as a hyperendemic area for LF.

The study found that 233 persons died from Lassa fever between 2018 and 2021 (CFR 22.7). The highest CFR of 28.2% was recorded in 2021 while the lowest CFR of 19.3% was recorded in 2018 with a CFR average of 22.9%. The average CFR observed in this study CFR of 22.9% is slightly lower than a CFR of 27% found in a similar study in Ondo state by Ejikeme et al. (2021) and significantly higher than the overall CFR of 15% commonly reported by the WHO for hospitalized patients with Lassa fever. However, it agrees with the national CFR average of 22.9 as documented by the Nigeria CDC. The CFR trend for Lassa fever showed a major increase from 19.3% in 2018 to 28.2% in 2021. Evidently, there is a continued rise in yearly fatality rates recorded of confirmed Lassa fever cases in Ondo state within the study period.

Findings from these studies show that Lassa fever can affect all age groups; however, the highest CFR was found among adults aged 60 and older as death among this

age group is at 42.3% which is statistically significant than that of children between ages 5 and 12 at 8.5%. Adults 26–59 years of age also had statistically higher CFRs (21.9%) compared with children <12 years. The observed higher CFR among older adults corroborates similar findings by Abdulkarim et al.(2020) and Ilori et al. (2019) where they found a CFR of 38.2% and 32.5% respectively among adults aged 60 and older.

This study also found an extremely high CFR among children, especially those between the ages of 0–4 years CFR of 30.6% (15/49). Although the CFR recorded here is much lower than the fatality rate of CFR 63% was found among the pediatric Lassa fever-positive cohort in Sierra Leon reported by Samuels et al. (2021). However, this is not very different from the 29.2% CFR reported among children by Orji et al. (2020) in their study of the prevalence of Lassa fever among the pediatric population in Ebonyi State, Nigeria.

Males accounted for a slightly higher proportion of laboratory-confirmed Lassa fever cases than females (Males 50.3% vs. Females 49.7%). Previous studies of Lassa fever incidence among males and females in Nigeria (Ejikeme et al., 2021; Ilori et al., 2019) and Liberia (Yalley-Ogunro et al., 1984) have shown no or little difference in Lassa fever incidence between male and female Lassa fever cases. It is unclear whether the slight difference in this study is because men were at higher risk for infection or more susceptible to the disease than women.

Although more Lassa fever confirmed cases were found among the urban population than the rural population in this study, more mortalities were recorded among rural settlers as they accounted for 28.3% of all deaths. Access to prompt treatment and knowledge of what actions to take when one is infected with Lassa fever might have played a role in this outcome as the only treatment center for Lassa fever in Ondo state is the Federal Medical Centre located at Owo, which is also an urban center. Ilesanmi et al. (2015) found that awareness regarding Lassa fever is extremely poor among rural communities in Southwestern Nigeria where our study area is located.

Students constituted the majority of Lassa fever cases found in Ondo state within the study period. A total of 285 (27.7%) students were laboratory confirmed with Lassa fever. This might be a result of poor risk perception on prevention practices for Lassa fever among the student population. Ighedosa et al. (2016), in their study of the knowledge attitude and practice of Lassa fever prevention among students in Edo state, found that the knowledge and understanding of Lassa fever disease, transmission, prevalence, and predisposing factors were poor among students surveyed at the University of Benin, Edo state; however, a higher proportion of mortalities was recorded among those with no form of education (CFR 43.4%) compared to students (CFR 14.4%).

The education status variable in this study is found to be statistically significant with a P-value of 0.001. Although about 74% of all cases found in this study had secondary or tertiary education (Secondary 31.4% and Tertiary 44.7%), mortalities among those with no form of education were higher at CFR 43.4% compared to those with tertiary education CFR 16.5%. In a study by Uduak (2018), respondents who had tertiary education were 0.2 times more likely to have good knowledge of Lassa fever risk factors than those with less education. Additionally, positive attitudes towards the Lassa fever virus improved with an increase in the level of education, as respondents with no formal education were two times more likely to have negative attitudes. Thus, one may adduce that those who had secondary education are more likely to have a higher risk perception and positive disposition towards getting appropriate care in case of infection with the Lassa fever virus than those with less education. Similar responses were obtained by Asogun et al. (2010).

In the occupation category, the highest CFR was recorded among the famers' group at a CFR of 36.7% (55/150). This is followed by the unemployed group with a CFR of 27.9% (104/29). While the lowest incidence and CFR were recorded among healthcare workers (10.3). The Chi-square analysis conducted in this study shows a statistical association between outcome and occupation. However, Asogun et al. (2010) found no association between occupation and risk of infection with Lassa fever among the rural

population who were mostly farmers. Furthermore, Helmick et al. (1986) found no evidence of an increased risk of Lassa fever infection among hospital staff, nonetheless more recent findings by Gobir et al. (2019) show increased chances of contact with Mastomys rats or their droppings is a recognized risk factor. Additionally, healthcare workers in contact with patients infected at a community level are also at an increased risk of contracting this disease, especially if they do not adhere to basic infection control measures during patient care (Ilori et al., 2019).

Moreover, the incidence of healthcare workers' infection found in the study suggests that there is a possibility of nosocomial infections, although infection from other sources such as exposure to rodents cannot be ruled out. Nevertheless, good infection prevention and control practices and readily available personal protective equipment are important tools needed to protect healthcare workers from infection with the virus and potential death.

Lassa fever virus is primarily transmitted to humans from exposure to rodents' excreta. The virus is also occasionally transmitted through the body fluids of infected persons. In this study, only 11% (116) of the study population had any form of exposure to rodents or bodily fluids from infected persons. Because this information was obtained by patient interview, recall bias might have influenced the accuracy of exposure history.

A high number of mortalities was observed among hospitalized confirmed Lassa fever cases but there was no statistical association between hospitalization and fatal outcomes. Although this study was not able to explore the date of symptom onset and time to hospitalization, investigation of the 2018/2019 national Lassa fever outbreak in Nigeria has revealed higher CFR among people presenting late to healthcare facilities, suggesting that time to presentation and treatment may indeed be an extremely crucial intervention point to reduce mortality.

The most common signs and symptoms among patients with laboratory confirmed Lassa fever were: fever 863 (83.9), fatigue 584 (56.8%), headache 515 (50.1%), abdominal

pain 388 (37.3), and cough 331 (32.2%). Mortalities among confirmed cases that also had cough is highest at CFR 26.3 (87/331) followed by those with abdominal pain at a CFR of 23.2 (90/388). Confirmed cases that had a fever as a symptom had a 21.8% CFR (188/863), those with headache had a CFR of 19.8% (102/515), and those with fatigue had a CFR of 18.5% (108/584). A statistically significant P-value was observed in those that presented with fatigue.

At least three out of the five most prevalent symptoms observed in this study consistently appeared in different studies. Ilori et al. (2019) found in the study of the 2018 national outbreak in Nigeria that fever, abdominal pain, and cough were among the most prevalent symptoms and (Monath et al., 1974) in clinical observation of Lassa fever cases in the eastern region of Sierra Leon found fever, hemorrhage. Headache and fatigue, and Wolf et al. (2020) found chest pain, fever, and abdominal pain, in a systematic review of imported cases of Lassa fever over 50 years.

At the multivariate level of analysis of the most common clinical symptoms and epidemiological factors and their association with death, the odds of a fatal outcome for patients that are positive for Lassa fever and presented with symptoms of fatigue remains significant even after adjusting for age and sex, education, and occupation. Furthermore, the odds of death from Lassa fever remain significant for adults aged 60 and above after controlling for symptoms, sex, education, and occupation.

Limitations of the Study

This study has some limitations. One of the limitations of this study is that significant biases may affect the selection of variables and one must rely on others for accurate recordkeeping. Data quality issues also affected our ability to analyze factors such as duration of hospital stay, treatment with ribavirin, and date of symptom onset.

Nevertheless, this study analyzed the four-year data of Lassa fever cases and deaths recorded in Ondo state and described epidemiological and clinical features of the mortalities due to Lassa fever in the state, and provided recommendations for prevent infection with the virus and measures that could ultimately reduce mortality.

CHAPTER SIX
Conclusion and Recommendation

This study observed that mortalities resulting from Lassa fever virus infections in Ondo state were on a steady increase from 2018–2021. The average case fatality rate for Lassa fever in Ondo state within the study period was 22.7% which is slightly higher than the national CFR average of 20.0%. Case management teams and health authorities in Ondo State should critically review health system factors to ensure rapid case detection and access to quality case management for all confirmed Lassa fever cases in the State. Setting up an additional Lassa fever treatment center in Ondo state will help in addressing access to treatment, especially for those in rural areas as this study found that more deaths were recorded in the rural communities.

Lassa fever is more fatal among male adults aged 60 and above as compared to their female counterparts in the study population. A higher proportion of deaths was found among the study population with basic or no form of education compared to those with higher education. Targeted risk communication messages and radio/TV jingles in local languages should be tailored to address this segment of society with preventive messaging and good health-seeking behavior.

Most confirmed cases were found to be primary cases as only 11% of all cases and less than 20% of all mortalities had a history of exposure to the virus. There is a need to focus more on reducing rodent-to-human transmission of Lassa fever and carry out further environmental studies. It is also recommended that there should be continuous health education on infection prevention control in communities, contact tracing, and enforcement of environmental sanitation measures across the state to mitigate future outbreaks.

Currently, there is no approved vaccine for Lassa fever infection and the treatment option is limited. While concerted efforts are been made to fast-track the development of a vaccine and expand treatment options, health authorities should invest in creating

awareness of risk factors for contracting the virus, especially among people living in rat-infested environments, such as Ondo State, which increases their chances of coming in contact with rats and people who consume potentially contaminated foodstuff, particularly those left open over-night or dried outside in the open.

The whole-of-society approach is recommended to control the spread of Lassa fever spread in the communities. Community members should take responsibility for their health and practice good personal hygiene by frequently washing hands with soap under running water/or use of hand sanitizers when appropriate. They should always keep their environment clean and block all holes in homes to prevent rats from entering. They should also cover their dustbins and dispose of refuse properly. Communities should establish dump sites extremely far from their homes to reduce the chances of having rodents within their homes. Rats should not be allowed to be circulating in households as such communities in Ondo state should establish traps and other de-ratting methods to eliminate rats from their households.

Oyo state residents and other communities battling yearly outbreaks of Lassa fever should employ hygienic food processing and storage methods. They should avoid drying foodstuff outside on the floor or by the roadside where it will be exposed to contamination by rodents. Staple foods should be stored in well-covered containers with tight-fitting lids.

Healthcare workers should be alert and maintain a high level of suspicion and strictly adhere to infection prevention and control measures by wearing appropriate personal protective equipment before coming into contact with any suspected case or any patient with febrile illness. Since Lassa fever is seasonal and usually peaks during the dry season, health authorities in the state should replenish essential commodities needed for Lassa fever outbreak response including adequate personal protective equipment, and organize refresher training on infection prevention and control for all healthcare workers in the state ahead of each outbreak season.

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