Review Article

Dynamic and Epidemiology of Lassa Fever Infection in West Africa's Population from 1969 to 2019

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Abstract | Lassa virus (LASV) is a highly prevalent arenavirus that affects two to three million people in West Africa. A retrospective was conducted review through literatures search using the AGORA, PubMed, Science Direct, Scopus, Researchgate and Google Scholar Databases on Lassa fever (LF) from West Africa. A total of 34 articles were studied from 11 countries. Studies were categorized by host and country, and analysis conducted to determine pooled prevalence estimates for each category Analysis was done using the metaprop command in STATA version 15 and MetaXL software. A total of 18.111 individual samples from 11 countries, described in 34 articles were studied. Analysis of twenty-six studies indicated that the pooled prevalence was 19.0% [95% CI (15.0-23.0 %), I2 = 97.93%]. There was a high level of heterogeneity between studies; however, the high prevalence of LASVwas noted in several countries as Nigeria (12-42%), followed by Sierra Leone (8-43%), and Guinea (9-40%). Pooled prevalence of LASV in human populations in studies conducted over the entire review period was 22.0% [95% CI (17.0-28.0 %), I2 = 98.0%]; eighteen studies), while she was 9.0% [95% CI (4.0-15.0 %), I2 = 97.0%]; eight studies) for *Mastomysspp.* The knowledge of the geographical distribution and epidemiology may help disease control efforts and limit the risk of transmission, both locally and internationally. This study is also important in order to guide interventions, public health authorities and inform on the evolution of the disease.

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Introduction

Lassa fever (LF) is acute and viral hemorrhagic fever, which can lead neurological disorders. This pathogenic agent of Arenaviridae family wasfirst discovered in 1969 in Nigeria, in one missionary nurse infected in Lassa town(Frame *et al.*, 1970). Since then, this virus, which causes LF, has been reported in many West African countries (Mylne *et al.*, 2015). LF in this zone is endemic and has already affected 2 million people. Studies indicated that 300,000 to 500,000 cases are diagnosed and 5000 deaths are

noted yearly (Sogoba *et al.*, 2012). The animal reservoir of infection is the multimammate rat (*Mastomys* spp.). The majority of human infectious diseases are zoonotic, that is they have a wild or domestic animal origin or reservoir (Han *et al.*, 2015). LF is transmitted to humans when they ingest food contaminated by feces and urine of *Mastomys* spp. Once humans are infected, transmission also occurs from human to human through contact with contaminated fluid-sputum, seminal fluid, stool, urine and blood, and is spread through aerosol secretions during sneezing (Bonwitt *et al.*, 2017). The World Health Organization listed LF among priority diseases requiring urgent research and development attention (Mehand *et al.*, 2018). Due to travel of people from endemic areas to non-endemic regions, prevalence of LASVbeing in addition its air of distribution (ECDC, 2016). However, seroprevalence's studies have noted high rate in Guinea, Nigeria and Sierra Leonea, but also in non-endemic areas (Brosh-Nissimov, 2016). Cases of Lasa fever have observed in new area and official incidence reports have seen a substantial increase in the number and geographical extent, which suggests that the true incidence and spatial distribution of the disease may be underestimated (ECDC, 2016). Most infections with LF in Africa are asymptomatic, mild or subclinical, the case fatality rate in symptomatic, hospitalized patients ranges 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 humantohuman transmission, typically through super-spreader events in hospital settings (Shehu *et al.*, 2018). In severe cases, death usually occurs within two weeks following onset of symptoms. Epidemiology's study of LF in endemic zones is important about the transmission human to human or *Mastomys* spp. to human and can facilitate decision on control strategies. Although there are extensive studies, a systematic review of different publications on LF is important. As a whole, this set of studies improves our understanding of the geographical distribution of viral hemorrhagic fever. The study was conducted to investigate the prevalence and dynamism of LF in West African's population.

Materials and Methods

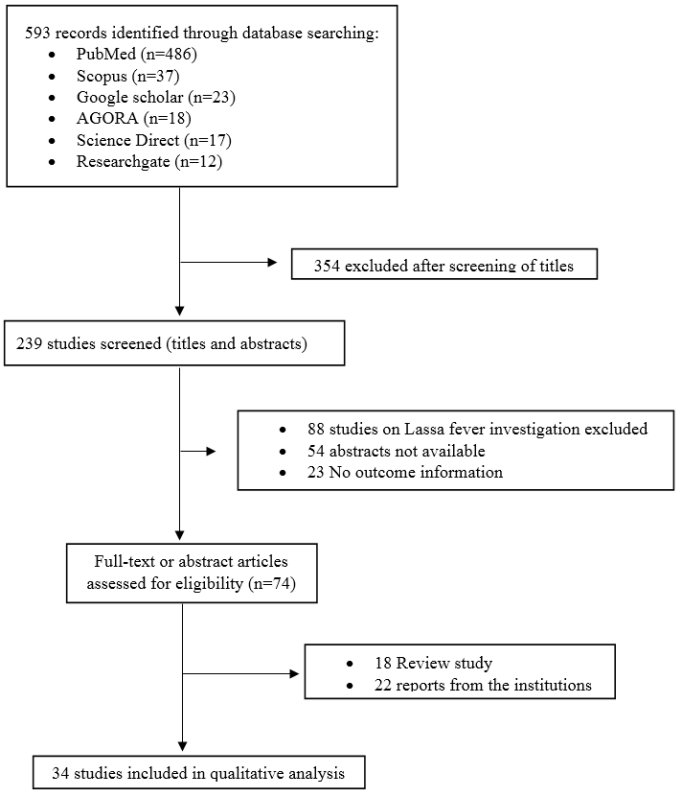
We've searched in AGORA, PubMed, Science Direct, Scopus, Researchgate and Google Scholar database. The last search was run on March 31, 2019. To search relevant articles for this study, we've used following keywords "Lassa fever", "prevalence"and "West Africa country (Benin, Burkina Faso, Cape Verde, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Togo)". The key terms were used separately and/ or in combination using Boolean operators like "OR" or "AND". Studies eligible are the ones which reported or allowed to calculate of the prevalence of LF by both Enzyme-Linked Immunosorbent Assay (ELISA) and Reverse Transcription Polymerase Chain Reaction (RT-PCR) or ELISA/RT-PCR on the Human or *Mastomys* spp. population. The authors agreed that the articles included from the search should meet the following criteria:
(1) the study participants consisted of a population sample of individuals in an endemic area who were chosen on the basis of LF symptoms and confirmed by laboratory test, (2) the study population came from a defined geographical area, and (3) studies published between 1959, and 2019, in any language were included in the analysis if they explicitly reported the presence of LF.

Data extraction

From each study, the following information was extracted by 2 independent researchers into records for analysis: countries, location, citation details, study sample, laboratory methods and prevalence of LASV as determined by ELISA or PCR. When possible, relevant information was extracted from abstracts or publications. The computerized search identified 593 papers, of which 354 excluded after screening of titles. 165articles did not meet inclusion criteria and were rejected. 74 articlesdescribing ELISA/RT-PCR wereused to distinguish prevalence, only the data from confirmed result were used. Hence complete information wereextracted from a total of 34 eligible studies.

Quality assessment

Two researchers independently assessed the articles included using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the methodological quality of eligible studies (Whiting *et al.*, 2011). The study QUADAS-2 quality criteria are given by Review Manager 5.2, which consists of four domains (patient selection, index test, reference standard, and flow and timing).



Statistical analysis

Data for analysis were collected into spreadsheets Excel according to the following categories: Study's country, biological material, methods used to be identify LASV, number of sick cases and sero-epidemiology. Following data extraction and checking, all members of the Literature Review Group were provided with all original data sources and the extraction tables for review. I2 values higher than 25%, 50%, and 75% are considered evidence of low, moderate, and high heterogeneity among studies, respectively. Software MetaXL was used to calculate the forest plot of LASV infection prevalence in *Mastomys* spp. and Humans (random-effects model). Sub-group analysis of the studies, which assessed the relationship between LASV prevalence and countries was performed using the Statistical Software Package (STATA) Version 15.0 (Stata Corp, College Station, TX, USA). We used the newly developed metaprop command (Nyaga *et al*., 2014).

Results and Discussion

In total, 34 studies were selected from 11 West African countries,(Nigeria (n=8), Guinea (n=6), Mali (n=3), Ghana (n=3), Ivory Coast (n=3) Sierra Leone (n=3) Benin (n=2), Burkina-Faso(n=1), Liberia (n=2), Togo (n=2) and Senegal (n=1). Data for prevalence of LASVhavebeen extracted from 26 studieswith prevalence highest noted respectively 6/25 (24%) forMali and 36/84 (43%) forSierra Leone. In alphabetic orderstudies have revealed the prevalence of LASVin Benin (9.9%), Guinea (9.15-40.3%), Ivory Coast (0.7-26%), Liberia (5.3-14%), Mali (6.8-33.2%), Nigeria (12-42%), Senegal (1.2%) and Sierra Leone (29-43%) (Table 1). Cases studies ofLASVhave been noted in 8 articles mainly in Benin, Burkina-Fasa, Ghana, Nigeria and Togo (Table 2).

Prevalence of Lassa virus in Mastomys spp.

Data from 8 studies in4 countries were obtained about*Mastomys* spp. A total number of individual samples was 4442. Prevalence of LASV in *Mastomys* spp. varied from 0.7% to 24.00%. Therandom effect model used in theanalysis (Figure 1) gave an overall estimated prevalence of 9.0% (95% confidence interval [CI] 4.0-15.0%). The result of heterogeneity was also 97.0% (95% CI 96.10-98.13%) for the degree of inconsistency.

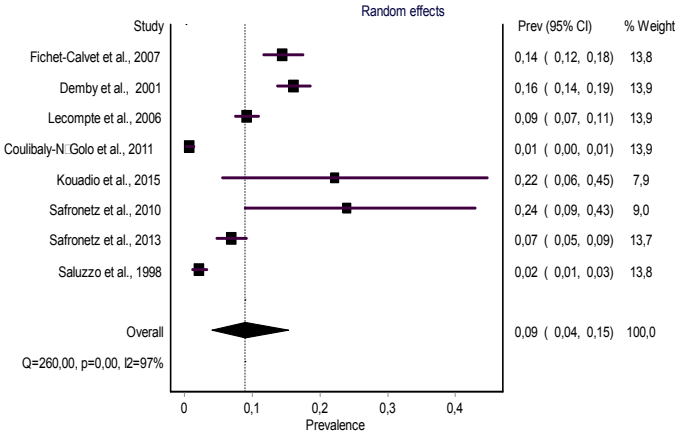


Figure 1: *Forest plot of Lassa virus infection prevalence in Mastomys spp. (random-effects model).*

Prevalence of Lassa virus in human

Data from 18 studies from 8 countries were obtained among Human. A total number of individual samples was 13653. Prevalence of LASV in Human varied from 5.3% to 40.3%. The random effect model used in the analysis (Figure 2) gave an overall estimated prevalence of 22.0% (95% confidence interval [CI] 17.0-28.0%). The result of heterogeneity was also 98.0% (95% CI 97.77-98.53%) for the degree of inconsistency.

Subgroup analyses

Summary statistics of the prevalence of Lassa virus among human and *Mastomys* spp. in West Africa: This analysis was conducted to identify the pooled prevalence of LASV in countries (West Africa) using

the available published studies. Figure 3 shows the results of subgroup analyses stratified by the country. Due to the high heterogeneity among studies within most subgroups, pooled prevalence for each subgroup were calculated using the random-effects model. On stratification by country, the prevalenceinGuinea and Nigeria wereestimated respectively 19% (95% CI 12.0-25.0%, p<0.001) and 20% (95% CI 15.0-24.0%, p<0.001). High heterogeneity was noted also forGuinea (I2 = 97.93%) and Nigeria (I2 = 92.86%). This analysis included 26 studies where the overall pooled prevalence of LASV was estimated 19% (95% CI 15-23%, p<0.001) with the heterogeneity of 98.99% (Figure 3).

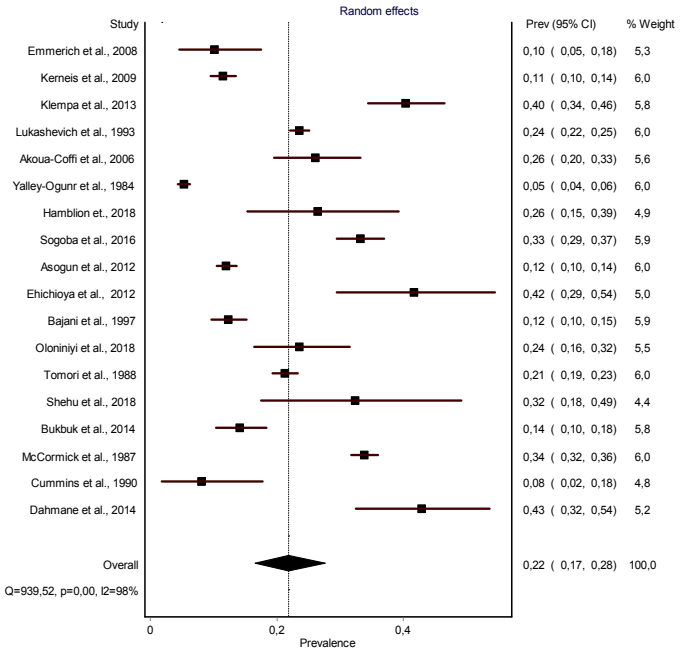


Figure 2: *Forest plot of Lassa virus infection prevalence in Human (random-effects model).*

Dynamics of Lassa virus in West Africa, 1969-2019

These results give an overview of the dynamics of LASV in 11 West African countries from 1969-2019. A total of 1811 samples were examined and 3166 were found to be positive (LASV) in the 34 articles that were subject of this study. Among the studies conducted from 1969-1979, we noted 3 cases of LF in Nigeria. From 1979-1989 a prevalence of 20.57% (1140/5547) was noted with 684 positive sample in Sierra Leone, 357 in Nigeria, 98 in Liberia and one in Burkina Faso. The work showed a prevalence of 18.88% (820/4343) from 1989-1999 with 738 cases in Guinea, 68 in Nigeria and 14 in Senegal. The same finding was also made from 1999-2009 with a prevalence of 12.95% (655/5059) distributed in 4 countries namely Benin (9), Guinea (532), Ivory Coast, (47) and Nigeria (67). During the period 2009-2019 we had a prevalence of 17.53% (548/3159) in 8 countries including Benin (1), Ghana (6), Ivory Coast (4), Liberia (14), Mali (240), Sierra Leone (40), Nigeria (238) and Togo (5) (Figure 4).

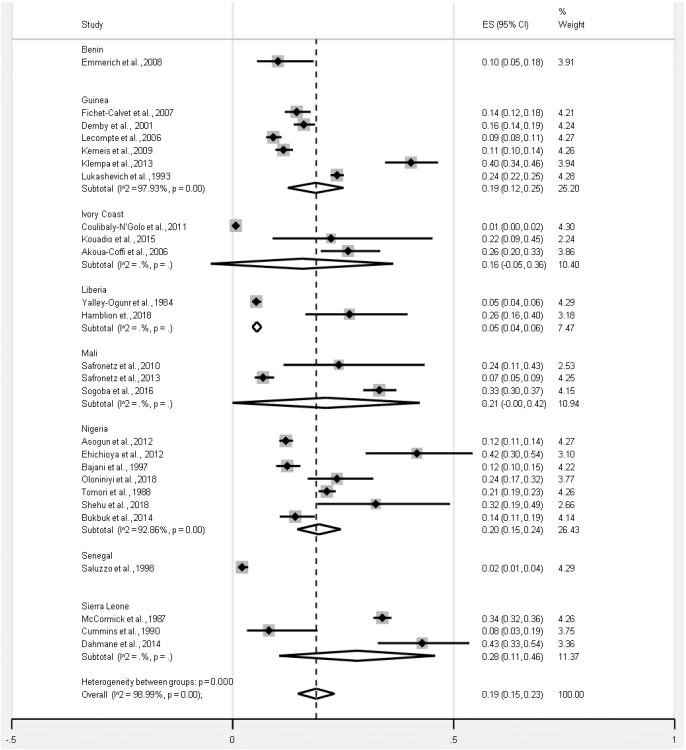


Figure 3: *Forest plot showing stratified of Lassa virus infection prevalence by country estimated by the random effects model (Benin, Guinea, Ivory Coast, Liberia, Mali, Nigeria, Senegal and Sierra Leone).*

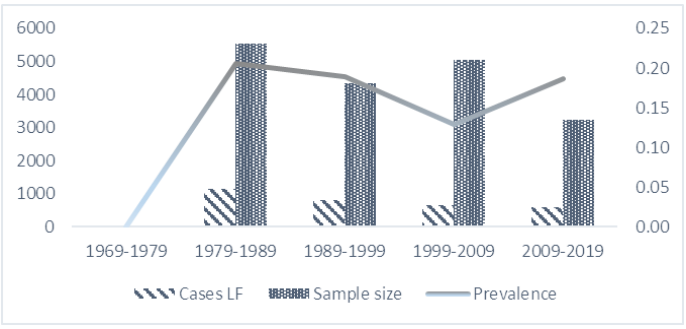


Figure 4: *Prevalence of West African LF infection of 1969-2019.*

This article presents prevalence of LASV for the endemicareas and provides an important baseline for guiding LF surveillance. LASV was discovered in Nigeria 1969, but this virus was confirmed later in other countries like Guinea (9-40%), Liberia (5-14%) and Sierra Leone (8-43%) where highest infection was beingnoted. In bordering countries cases of the LF were declared out Nigeria, human populations, particularly in Benin, Mali, Cote d'Ivoire, Ghana, Burkina Faso and Togo. The findings of analysis showed that the overall prevalence of LASV was 19%

Table 1: *Characteristics of included studies for analysis of Lassa virus infection.*

Country	Authors	Year of study	Hosts	Method	Sample size	Prevalence (%)
Benin	Emmerich *et al.*, 2008	2008	Human	ELISA	88	9(9.9)
Guinea	Fichet-Calvet *et al.*, 2007	2003-2004	*Mastomys* spp.	RT-PCR	553	80(14.5)
Guinea	Demby *et al.*, 2001	2001	*Mastomys* spp.	ELISA	884	142(16)
Guinea	Lecompte *et al.*, 2006	2002-2005	*Mastomys* spp.	RT-PCR	1049	96(9.15)
Guinea	Kerneis *et al.*, 2009	2000	Human	ELISA	977	112(11.46)
Guinea	Klempa *et al.*, 2013	2004	Human	ELISA	253	102(40.3)
Guinea	Lukashevich *et al.*, 1993	1990-1992	Human	ELISA	3126	738(23.6)
Ivory Coast	Coulibaly-N'Golo *et al.*, 2011	2003-2005	*Mastomys* spp.	RT-PCR	737	5(0.7)
Ivory Coast	Kouadio *et al.*, 2015	2013	Mastomysspp	RT-PCR	18	4(22.2)
Ivory Coast	Akoua-Coffi *et al.*, 2006	2000	Human	ELISA	161	42(26)
Liberia	Yalley-Ogunr *et al.*, 1984	1980-1982	Human	ELISA	1848	98(5.3)
Liberia	Hamblion *et al.*, 2018	2016	Human	RT-PCR/ELISA	53	14(14)
Mali	Safronetz *et al.*, 2010	2009	*Mastomys* spp.	RT-PCR	25	6(24)
Mali	Safronetz *et al.*, 2013	2007-2012	*Mastomys* spp.	RT-PCR/ELISA	511	35(6.8)
Mali	Sogoba *et al.*, 2016	2015	Human	ELISA	600	199(33.2)
Nigeria	Asogun *et al.*, 2012	2009-2010	Human	RT-PCR	1650	198(12)
Nigeria	Ehichioya *et al.*, 2012	2005-2008	Human	RT-PCR/ELISA	60	25(42)
Nigeria	Bajani *et al.*, 1997	1992-1993	Human	ELISA	552	68(12.3)
Nigeria	Oloniniyi *et al.*, 2018	2012-2016	Human	RT-PCR	123	29(23.5)
Nigeria	Tomori *et al.*, 1988	1985	Human	ELISA	1677	357(21.3)
Nigeria	Shehu *et al.*, 2018	2016	Human	RT-PCR	34	11(32.3)
Nigeria	Bukbuk *et al.*, 2014	2003-2004	Human	RT-PCR	297	42(14.1)
Senegal	Saluzzo *et al.*, 1988	1998	*Mastomys* spp.	ELISA	665	14(1.2)
Sierra Leone	McCormick *et al.*, 1987	1983	Human	ELISA	2021	684(33.84)
Sierra Leone	Cummins *et al.*, 1990	2018	Human	RT-PCR	49	4(8.16)
Sierra Leone	Dahmane *et al.*, 2014	2011-2012	Human	ELISA	84	36(43)

Table 2: *Cases reports of Lassa virus infection.*

Country	Authors	Year of study	Hosts	Method	Cases of LF
Benin	Attinsounon *et al.*, 2018	2018	Human	RT-PCR	1
Burkina-Fasa	Van Der Heide *et al.*, 1982	1982	Human	ELISA	1
Ghana	Kyei *et al.*, 2015	2015	Human	RT-PCR	2
Ghana	Bonney *et al.*, 2016	2013	Human	RT-PCR	2
Ghana	Dzotsi *et al.*, 2012	2011	Human	RT-PCR	2
Nigeria	Frame *et al.*, 1970	1969	Human	ELISA	3
Togo	Raabe *et al.*, 2017	2016	Human	RT-PCR	2
Togo	Whitmer *et al.*, 2018	2016	Human	RT-PCR	3

(95% CI 15-23%, p<0.001). This indicates, despite substantial heterogeneity, that West Africa remains an endemic area where 300 000 to 500 000 cases of LFwere estimated annually (Ogbu *et al.*, 2007). The predominant prevalence of LF in West Africa was noted in Sierra Leone, Liberia, Guinea et Nigeria because may be due to relative the culinary attitude of the population (Brosh-Nissimov, 2016). This prevalence might be related partly to population movements during the civil unrest in some West African's countries in the 1960 especially in Sierra Leone. Despite the presence of the reservoir host of this virus in other parts of the world, it is only in West Africa that it is rife, which was due to favorable

climatic factors that favor the maintenance and development of the virus in West Africa (Fichet-Calvet and Rogers, 2009). According Manning *et al.* (2015), the prevalence of LF is highest in forested regions of West Africa.This is likely due to the fact that forested parts of endemic regions harbor large populations of the reservoir rodents (*Mastomys* spp.) capable of transmitting the virus to human population. This is the case of Sierra Leone and Guinea where high prevalence is observed in the forest regions. Thatcould explain the presence of LF cases in other West African's countries. ECDC (2016) reports have shown that 80% of LF cases are asymptomatic. Symptoms of LF varied and are non-specific, making clinical diagnosis often difficult, especially early in the course of the disease. Most LASV human infections are asymptomatic and Clinical recognition can be challenging due to the similar symptoms suchas general weakness,muscle aches, fever, nausea, vomiting, sore throat, pharyngitis, dry cough, chest and abdominal pain, which are known to the clinical sign of malaria by the population (McCormick *et al.*, 1987). It is necessary to take concrete and consistent action to implement recommendations and findings of many researcheson LF. The analysis of LASV in the rodent'spopulation *Mastomys* spp. showed a high prevalence of LASV, with the overall pooled prevalence of 9.0% (95% confidence interval [CI] 4.0-15.0%). Studies of the evolutionary history of LF showed that *Mastomysnatalensis* infected is the main source of human infection (Lalis *et al.*, 2012). Rodent-to-human transmission was possible contact with the excreta,urine of infected rodents.Mastomysinfected by LASVensure virus'dissemination in the environment and contamination of foodstuff. The result of our study is similar to that reported by Fichet-Calvet *et al.* (2016) who showed that infected *Mastomys* spp. are responsible for spatial distribution of LF in endemic areas. It has been also observed that other rodent species may also be hosts for LASV as the African wood mouse, *Hylomyscuspamfi* (Olayemi *et al.*, 2016). Prevalence of LASV in the *Mastomysnatalensis*, found in the southern Mali near the border of Ivory Coast was 0 to 52% (Safronetz *et al.*, 2013). The presence of LASV was noted in *Rattusrattus*, *Mastomysmusculus* and *Mastomysnatalensis*. But *Mastomysnatalensis* recorded the highest LASV among rodents trapped in Edo (87%), Delta (50%) and Bayelsa (11%) States respectively (Agbonlahor *et al.*, 2017). Human infectious diseases are a significant threat to global human health and with the majority of infectious diseases being zoonotic. Recent investigations have found that LF is more widely distributed throughout the Wooded Savannain West Africa (Sogoba *et al.*, 2016). This is in contrast to the study carried out by Richmond and Baglole (2003), which showed that LF was abundant in urban areas due to poor sanitation and overcrowding.Theanalysis of LASV infection prevalence in human found a higher prevalence of LASV, with the overall pooled prevalence of 22.0% (95% confidence interval [CI] 17.0-28.0%), evidence for theendemicity of LF disease in West Africa. The LF proportion is partly due to underdevelopment, this disease occurs in the poorest areas where, population with poor sanitation and/or crowded living conditions. But disrespect of the most rules regarding on the prevention against LF, can justifies the high prevalence obtained in rural areas, poor and illiterate (Hallam *et al.*, 2018). These findings corroborate the works realized by Richmond and Baglole (2003), which estimated LF prevalence in Sierra Leone (50.2%), Guinea (55%) and Nigeria (21%). A typical example of transmission of LASV is the practice of funeral rites and ancestral burials that have been established. Funeral practices and burials in West Africa were associated with an unusual high risk of the disease. For example, in Liberia and Sierra Leone, some mourners bathe or anoint others with water from the washing of deceased bodies. Some people sleep near the highly infectious deceased bodies for several nights, believing that this allowed a transfer of powers. All of these reasons explain this high prevalence of LASV in the human population. LF outbreaks mostly occur in rural areas and during the dry season (Shehu *et al.*, 2018). Hospitals in endemic areas are also sources of infection and propagation of LASV, according to Dahmane *et al.* (2014), the prevalence of LF in children and women with obstetric conditions in a rural district hospital in Sierra Leone was 43%. The role of human-to-human transmission in the distribution of the disease is very importantand showed how healthcare workers were exposed to LF infection (Ehichioya *et al.*, 2012). Most the hospitals in the endemic areas of LF in West Africa don't have a capacity to perform LASV diagnostics. Case identification and management solely relies on non-specific clinical criteria (Saluzzo *et al.*, 1988), which would be the cause of this prevalence of LF noted among health workers. Many serologic assays (ELISA) based on the identification of antigens and antibodies (Immunoglobulin M "IgM"/ Immunoglobulin G "IgG") and reverse transcription

polymerase chain reaction (RT-PCR), were used for LASV confirmation. RT-PCR is a rapid molecular tool for detection of LASV, this test is effective but present these limits today because of the genetic diversity of the strain of LASV. According to the reports done by ECDC (Mehand *et al.*, 2018) on diagnosis of LF. The serologic testing for IgM and IgG antibodies demonstrated easy use in the field without the need for expensive equipment (Akoua-Koffi *et al.*, 2006). The results of our research have shown a resurgence of the LF in the period 2009-2019 in West Africa and this may continue for the coming years. Causes of Resurgence of LF have been attributed the lacks of early warning system and rapid response, once one case is suspected (Tambo *et al.*, 2018). Health centers in endemic areas lack even the minimum of analysis equipment to identify LF, the total absence of reliable LASV point of care and field diagnostic tools for early detection and rapid molecular case confirmation. For prevent facing of LF, it is necessary to strengthen local, regional epidemiologic surveillance but also regularly strengthen of health staff to the base and especially in the areas at risk on the information relating to the LF. However, our results should be interpreted with caution given the limited number of studies included foreach country.

Conclusions and Recommendations

The present systematic review and analysis has showed that the prevalence for LASV is high in West Africa. The prevalence of LASV varies across different regions of the country and from one country to another. This is a callto the Ministry of Health and all the actors in the community "One Health" and insurveillance system for detection and response to these LASV outbreaks to avoid the epidemic. Informations obtained from this systematic review and analysis may improve knowledge on the dynamic and epidemiology of LASV in West Africa and will certainly guide the measures to be taken in the fight against LF for the years to come.

Abbreviations

CI, Confidence interval; ECDC, European Centre for Disease Prevention and Control; ELISA, Enzyme-Linked Immunosorbent Assay; ES, Error Standard; IgG, Immunoglobulin G; IgM, Immunoglobulin M; LASV, Lassa virus; LF, Lassa fever; Prev, Prevalence; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; RT-PCR, Reverse Transcription Polymerase Chain Reaction.

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Author's Contributions

REY was the principal investigator who contributed to origin, the idea and design of the study, and acted as corresponding author. ID and EYS conducted the literature search and systematic review. REY, NN and ARKW performed analysis. REY, ARKW, JA, RO, AD and SF contributed to drafting the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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Ethics approval and consent to participate

Not applicable.

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