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Review

Lassa Fever: Critical Review and Prospects for Control

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Abstract: Lassa Fever is a deadly viral haemorrhagic disease, causing annually several hundreds of deaths in West Africa. This zoonotic disease is primarily transmitted to humans by rodents of the genus *Mastomys*, even though other rodents reportedly carry the Lassa virus, while secondary interhuman transmission accounts for approximately 20% of cases. Although this disease has been endemic in rural zones of Nigeria, Sierra Leone, Liberfia, and Guinea for hundreds of years, it is also characterised by epidemic outbreaks in the dry season, responsible for heavy death tolls. No licensed vaccine or satisfying treatment is currently available. Disease management is hindered by the incomplete knowledge of the epidemiology and distribution of the disease, resulting from an inadequate health and surveillance system. Additional scientific constraints such as the genetic diversity of the virus and the lack of understanding of the mechanisms of immune protection complexify the development of a vaccine. The intricate socio-economic context in the affected regions, and the lack of monetary incentive for drug development, allow the disease to persist in some of West Africa's poorest communities. The increase in the number of reported cases and in the fatality rate, the expansion of the endemic area, as well as the threat Lassa Fever represents internationally should urge the global community to work on the disease control and prevention. The disease control requires collaborative research for medical countermeasures and tailored public health policies. Lassa Fever, created by the interconnection between animals, humans, and ecosystems, and embedded in an intricate social context, should be addressed with a 'One Health' approach. This article provides an overview of Lassa Fever, focusing on Nigeria, and discusses the perspectives for the control of disease.

Keywords: neglected tropical disease; emerging disease; zoonosis; viral haemorrhagic fever; Lassa Fever; global health

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1. Lassa Fever: An Overview of the Virology, Clinical Course, and Epidemiology

1.1. Understanding Lassa Virus: Genome, Proteins, and Pathogenesis

Lassa Fever (LF) is a zoonotic haemorrhagic fever caused by Lassa virus (LASV), an enveloped single-stranded RNA virus belonging to the *Arenaviridae* family. LASV was first identified in 1969, in the village of Lassa, located in the northeastern Borno State of Nigeria [1].

Arenaviruses have an ambisense segmented genome. It contains two RNA segments, large (L) and small (S) [2]. LASV shows a high genetic variability, that comes mainly from transcription errors, although intrasegmental or intersegmental recombinations may also occur [3,4]. This high genetic diversity, with a nucleotide diversity up to 32% [5] and 7 circulating lineages identified [6], complexifies control measures.

Each segment comprises two genes, oriented in different senses and separated by an intergenic noncoding region. Therefore, each segment encodes one protein in each sense. The large segment encodes the RNA-dependent RNA polymerase and the Z protein, while

the small segment encodes the nucleoprotein and the pre-envelop glycoprotein complex [7]. Proteins serve different roles in the infection. Among other functions, the Z protein interact with retinoic acid-inducible gene 1 (RIG-i)-like receptors (RLRs), significantly reducing type I interferon response and therefore suppressing innate immune response [8]. The nucleoprotein masks RNA and binds to the kinase domain of IKK-ε, inhibiting immune response [9].

Immature dendritic cells and macrophages are the initial target cells of LASV [10]. Replication occurs within those cells without either activating the immune response or stimulating T cells. Cytopathic effects (abnormal coagulation, endothelial barrier disruption, and dysfunctional platelet aggregation) and evasion of the immune response contribute to the processes by which viral infection develops and to the pathogenesis of the virus [11,12]. Recent reviews of mechanisms of immune suppression are provided in [13,14].

1.2. Lassa Fever: Clinical Course and Mortality Rates

About eighty percent of infections are asymptomatic. In clinical infections, initial symptoms are usually unspecific: high fever, weakness, myalgia, chest and abdominal pain. It is often followed by headaches, sore throat, vomiting and diarrhea. This non-specific clinical picture commonly leads to misdiagnoses, which hinders early diagnosis and patient management [15]. In severe cases, the clinical course evolves to haemorrhages, facial swelling, central nervous system symptoms, multi-organ impairment and hypovolemic shock [16–18]. Traditionally, the average case fatality rate (CFR) for symptomatic patients was reported between 15% and 20% [16]. A comparison of confirmed cases to confirmed death by Yaro et al. [19] showed a CFR at 18.5% from 2017 to 2021. Although the CFR depends on the case definition (suspected, probable, or confirmed), the mortality rate has arguably been high over the past years. Considering only the confirmed and probable cases, the CFR in Nigeria was 29.5% from December 2016 to December 2017 [20] and 29.2% in the 2018 epidemics [21], resulting in 191 deaths over the year [22]. An even deadlier epidemic was reported in Liberia over the first half of 2023, with a 30% CFR [23]. Fatality rate can achieve 50% in hospitalised patients [24]. The case fatality per infection is lower, estimated around 1 to 2% [25,26], even if a more thorough assessment of the prevalence of asymptomatic LASV infection is needed.

1.3. Medical Interventions and Preventive Measures

Ribavirin is used to treat patients but must be given early in the clinical course [27]. Its mechanism of action is not fully understood. It is hypothesized that ribavirin is an RNA virus mutagen, forcing the virus into what is called an "error catastrophe" [28,29]. Despite its administration, the CFR remains as high as 15% in hospitalised cases [30]. It is also highly toxic [31]. Supportive care remains the primary intervention [13,32]. No vaccine is available, although several vaccine candidates have given promising results in preclinical trials [33]. Four candidates have been advanced into Phase I clinical trials [34], and the first Phase II clinical trial has started in April 2024.

1.4. Lassa Fever Epidemiology

Rodents of the species *Mastomys natalensis* (family of *Muridae*) also called multimammate rats, form the primary reservoir of the virus. They were identified through field studies after a large outbreak in Sierra Leone in 1972 [35]. Other rodents have been reported to carry LASV [36]. Zoonotic infection, via indirect or direct contact with rats, accounts for eighty to ninety five percent of the cases [37–39]. Hunting of rodents is frequently reported in West Africa, for meat consumption, pest control [40,41], or as a part of community practices and social activities [42,43]. Preparation and consumption of rodent meat is a well-described mode of transmission [44]. Transmission also occurs through exposure to excreta, urine, or other body fluids (saliva, blood): for instance via contaminated food or household items, or by inhalation of rodent excreta [45]. Inadequate sanitation, unhy-

gienic waste disposal [46–48] and poor housing quality [49] amplify the risk of exposure to rodents fluids.

Most of LF cases are traditionally reported in the dry season (increase in spillover events) [50,51], although the seasonality of the disease tends to fade, with epidemic outbreaks lasting increasingly longer [52].

A secondary interhuman transmission is possible, mainly via direct contact with blood and body fluids [53].

The multimammate rat is a peri-domestic, commensal species, highly abundant in rural zones. It is well adapted to anthropised territories as it prospers in cultivated lands and inside habitations [54]. It shows a wide distribution across Sub-Saharan Africa. The characteristics of traditional houses and granaries facilitate allow rodents to easily access them (Figure 1). Close contact with rats is a common aspect of daily life in rural areas of West Africa.

Figure 1. Architectural design and materials of traditional huts and granaries in Northern Nigeria facilitate rodent infestation (original photograph by Marianne Besson).

2. A Devastating Disease in West Africa

LF is both endemic and epidemic in West Africa. Two areas of endemicity have classically been described: the region of the Mano River (Guinea, Sierra Leone, Liberia), and Nigeria. However, it is now acknowledged that the disease exists in other West African countries [39]. LF is estimated to cause between 300,000 and 500,000 cases and 5000 to 6000 deaths annually [55]. However, no precise data can be obtained due to the lack of surveillance, as it mainly affects socio-economically deprived communities in isolated rural zones [56].

The disease burden is especially severe among pregnant women. In a hospital in Sierra Leone, a 30% CFR was observed among 40 women in the third trimester of pregnancy [57]. Abortions are also frequently described: 51 abortions out of 68 women followed by Price et al. [58]. LF can induce unilateral or bilateral sensorineural hearing loss in up to 30% of infected patients [59–61]. Because only limited treatment options, if any, are available for deafness in the affected countries, this represents a major liability for social and professional reintegration—even more in countries where deafness is sometimes considered as a sign of intellectual deficiency [62]. It is also strongly suspected that LF can generate depression and psychosis [63,64]. The economic losses associated with the disease –including direct and indirect costs, as well as opportunity costs—have never been evaluated. Mateer and co-authors [61] suggest that deafness only (all causes included) costs 43 million dollars annually to Nigeria.

3. An Emerging Disease: Historical and Recent Developments in the Spread of Lassa Fever

LF was first described in the medical literature in the 1920s, under the name "savanna typhus", as a disease causing prolonged fever, severe headache, neurological signs, hypotension, shock and multi-organ failure, with a high CFR (50%). In the following decades, both sporadic cases and outbreaks (notably among health care workers) were frequently reported in West Africa [65]. Lassa virus was identified in 1969, when a contaminated nurse was repatriated in the USA [1]. However, phylogenetic studies showed that LASV probably originated in Nigeria more than a thousand years ago. The virus subsequently spread to neighboring countries between 300 and 500 years ago, through human migrations during the colonial period [5,66]. Its recent emergence in Mali and the Ivory Coast has been attributed to forced displacements of populations caused by the Sierra Leone civil war (1991–2002) [67].

Since 2016, outbreaks annually hitting Nigeria in the dry season have intensified. In 2020 for instance, 6732 suspected and 1181 confirmed cases were reported nationwide, with 224 deaths [68]. In 2023, the deadliest outbreak in decades was sadly recorded: 9155 suspected cases were reported, 1270 cases were confirmed, with 227 deaths among those. Twenty-eight Nigerian states out of 36 were affected [69]. As of 30 June 2024, 7817 suspected cases and 168 deaths were reported since the beginning of the year in Guinea, Liberia and Nigeria [70]. This surge over the years also reflects an increase in surveillance and diagnosis.

Meanwhile, an expansion of the endemic zone has been witnessed in the past decade, with the emergence of new lineages in previously unaffected countries (for instance Ghana, Ivory Coast or Togo) [66,71]. Benin, Burkina Faso, Ghana, Ivory Coast, Mali, Togo are now known as endemic countries, not only because of serological evidence of LF in humans [72], but also because of confirmed autochthonous primary infections [39,73,74] (Figure 2). It is alarming to observe that often, knowledge about the endemic zone is gained when Western travelers contract the disease [75,76].

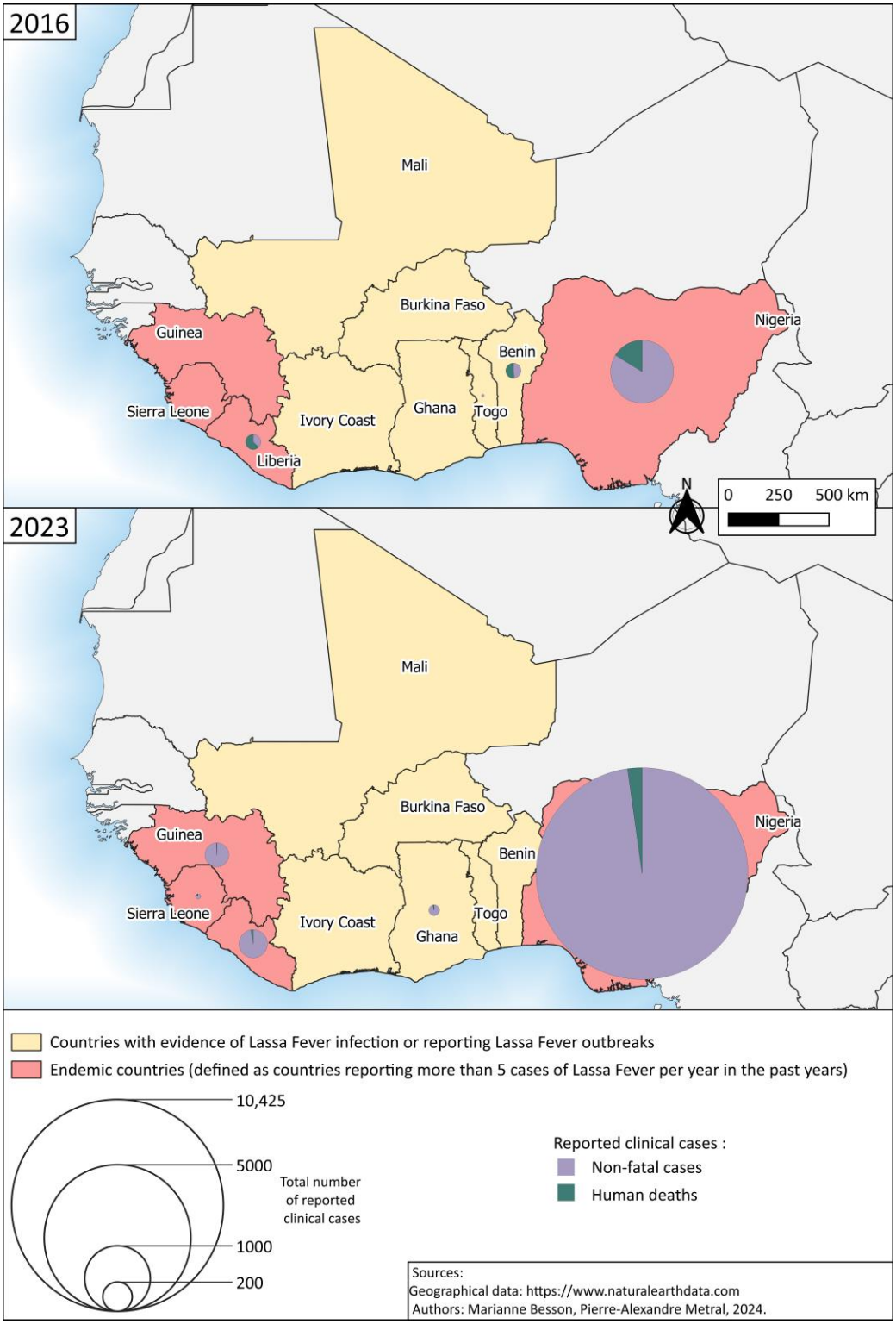

Figure 2. Distribution map showing the numbers of reported clinical cases of LF in 2016 and 2023 in the countries of the endemic zone (estimated numbers only). Based on data from Africa Centres for Disease Control and Prevention [18,77].

4. Mapping the Spatial Distribution of Lassa Fever

For disease management, it is crucial to map the at-risk areas of Lassa zoonotic transmission. The endemicity area of Lassa Fever might extend beyond the regions where human cases have previously been described. First, LASV circulation in rodents has been

evidenced in areas where human cases have not yet been reported [66,78]. The primary reservoir, *Mastomys natalensis*, has the widest distribution of all African rodents, due to its ecological tolerance, adaptability [79,80], and high reproductive capacity. However, the *Mastomys* clade in West Africa is genetically differentiated from the others and could be the only one that carries the virus [81]. LASV has never been isolated east of the border between Nigeria and Cameroon, in a different clade of *M. natalensis* [82]—although LF has been detected in other rodent hosts [83]. Opening ecological corridors (for instance through deforestation) could facilitate the movement of the virus-bearing *Mastomys* populations [84].

Other species have been evidenced to carry the virus, such as *Rattus rattus* and *Mus minutodies* [85,86], as well as species from several other genera of rodents [36,87]. It is still unknown whether the virus can sustain long-term infection in these hosts [88]. As these rodent species occupy different ecological niches, the area of zoonotic infection risk may extend, even more in the context of climate change and increased human mobility [89]. Through modelling of the ecological areas suitable for spillover events, it was estimated than 37.7 million people are at risk of zoonotic infection [78], and this number could drastically increase in the coming years with anthropic changes in West Africa [90]. While non-human primates are susceptible to the infection, LASV and anti-LASV antibodies have also been detected in domestic mammals such as dogs, goats, and pigs, confirming the host plasticity of the virus [91]. These data must urge us to expand research, to fully understand the epidemiological cycle of the virus, the host range, the extent of viral circulation in the reservoir species, and their involvement in the persistence of the virus in wildlife [92]. Active surveillance and surveys of the host species are necessary to prevent and monitor the emergence of the disease.

5. Why Lassa Fever Control Measures Are Failing: Challenges to Disease Management and Prevention

5.1. Viral Diversity

The inherent characteristics of the virus, including its high genetic diversity, pose significant challenges to the implementation of control measures. To date, seven distinct lineages have been identified [6]. Recent genetic analyses have revealed that selective pressure has driven diversification and local adaptation [93]. However, our understanding of the virus is still incomplete, with several lineages only recently discovered [71,94,95]. This combination of extensive genetic diversity and incomplete characterisation complicates the development of effective medical countermeasures.

Differences in pathogenicity between lineages impact the development of medical countermeasure. Strain Josiah (lineage IV) is the prototypic strain and has been used in many pre-clinical studies, but it is not necessarily the most virulent, as evidenced by challenge in guinea pigs [96]. The vaccines developed targeting this strain could exhibit reduced efficacy against other circulating strains [97].

Even if effective medical countermeasures existed, LF cannot be controlled through one-sided measures, such as massive distributions of prophylactics or drugs. The disease is indeed enrooted in an intricate socioeconomic context. To efficiently combat the emergence of LF, it is imperative to comprehend the political, anthropological, and economic processes that facilitate its existence.

5.2. Inadequate Health System

The lack of adequate medical infrastructure and disparities in healthcare accessibility within the affected countries undeniably present significant obstacles to the prevention and control of LF. In Nigeria for instance, above 95% of the population does not have health insurance [98,99]. As an estimated 84 million Nigerians live below the poverty line [100], the financial burden of medical bills is a barrier and only a small proportion of Nigerians benefit from health care [101]. The country presents some of the world worst healthcare indicators [102]. While the urban areas in the South of the country benefit from state-of-the art private hospitals (secondary and tertiary facilities), the vast majority of the rural areas

lacks access to medical structure, and primary health care facilities are often decaying, understaffed, deficient in resources [26,101]. The population vulnerability, and the impact of an inadequate, inequitable health network, must be underscored when apprehending the LF issue.

5.3. Conflicts and Corruption

Civil unrest, terrorism in the Northeast of Nigeria as well as nationwide fraud and corruption prevent an efficient fight against the disease.

These disastrous observations for Nigeria are unfortunately similar in the other endemic countries: Liberia, Sierra Leone and Guinea respectively rank 178, 181 and 182 out of 191 countries in the world human capital index [103] and suffer from systematic corruption in health sectors [104].

5.4. Social Stigma, Mistrust, and Misunderstandings

Richmond and Bagloge [26] also described a fear of social stigma associated with the disease, which consequently dissuades affected individuals from consulting a doctor. Diseases are taboo in many Western African communities, and patients fear rejection from their community. Besides, a defiance towards Western medicine exists [26,105].

Considering that over eighty percent of Lassa Fever cases arise from zoonotic transmission through contact with rodents, sensitization campaigns have been initiated to dissuade communities from hunting and consuming multimammate rats. They do not systematically reach the concerned populations [106], and their messages are often misinterpreted. For instance, through interviews with Sierra Leonean villagers, Bonwitt and co-authors [40] picked up a frequent misidentification of the reservoir (shrews were incriminated instead of the multimammate rats). The general lack of understanding of the attractiveness of rat consumption, and in return a distrust towards public health authorities (reinforced by the bushmeat ban in response to the Ebola crisis) further hindered the campaigns effectiveness [107].

5.5. Delayed Diagnosis and Challenges for Healthcare Workers

Limiting secondary transmission is also challenging. The non-descript symptoms frequently result in a wrong identification of the disease by professional health workers. Woyessa and co-authors [108] emphasise that "clinicians and health facilities, especially primary health facilities, need to consider LF as a differential diagnosis when the patient failed to respond to anti-malaria and broad-spectrum antibiotics". Additionally, endemic zones do not have adequate laboratory capacities, which is a barrier to performing a prompt diagnosis and a confirmation of LASV infection [109].

While rapid diagnostic tests would be an asset, their development is impeded by the high genetic diversity. The pan-Lassa rapid diagnostic test, using a mixture of polyclonal antibodies against LASV recombinant proteins, showed high sensitivity and specificity for patients with a high virus load in a Nigerian specialist hospital setting [110]. It still needs to be tested on more lineages. Distribution to the affected areas remains an issue [111]. Similarly, insufficient supply in ribavirin, which often delays its administration, and limited resources for patient care, hamper cases management [112].

Many non-specialist health facilities also lack personal protective equipment [113]. Instances are also described where, although body protections were available, they were not worn by the health workers, notably when LF diagnosis has not been made yet [15]. The Ebola epidemic in Liberia, Sierra Leone, Guinea led to a heavy death toll among specialist medical forces and weakened capacities for medical response. General practitioners must be sensitised to recognition of communicable diseases so that prophylactic measures can be enforced.

6. An Emerging Threat

Several factors contribute to the emergence of the disease. Genetic diversity of the sequenced isolates shows an increase in spillover phenomena [38], especially in the dry season [51]. The multimammate rat forms the dominant rodent species in human-disturbed habitats, in particular after fires [114,115]. Deforestation (notably through slash-and-burn farming) leads to the proliferation of *Mastomys* rats and increases rodent to human contact rates. Expansion of territories suitable for *M. natalensis* also open corridors between geographically distinct populations of rodents, initiating the transmission of LASV in previously disease-free populations [84]. Deforestation, changes in land use and disturbance of ecosystems have consequently been identified as key factors in LF current emergence. Climate change, through an increase in rainfalls in the Gulf of Guinea, is also expected to increase suitability for *M. natalensis* across the region and its reproductive capacity [116]. Models suggest that the number of spillover events could double in the coming decades [81]. Furthermore, mobility and globalisation increase the number of human-to-human transmissions and of exported cases [89].

LF holds the title for most frequently exported viral haemorrhagic disease, with 37 primary exported cases since 1969 (Figure 3) [117,118]. In 2022, three cases and one death were confirmed in the United Kingdom: the first person contracted the disease while traveling in Mali, and transmitted it to two family members upon return to the United Kingdom [118]. The long incubation period (6 to 21 days) [30,119] and the possibility, even low, of an asymptomatic transmission are additional risk factors for secondary propagation in non-endemic countries [120]. Several West African cities are travel hubs, and this interconnexion facilitates the spread of haemorrhagic viral fevers [121].

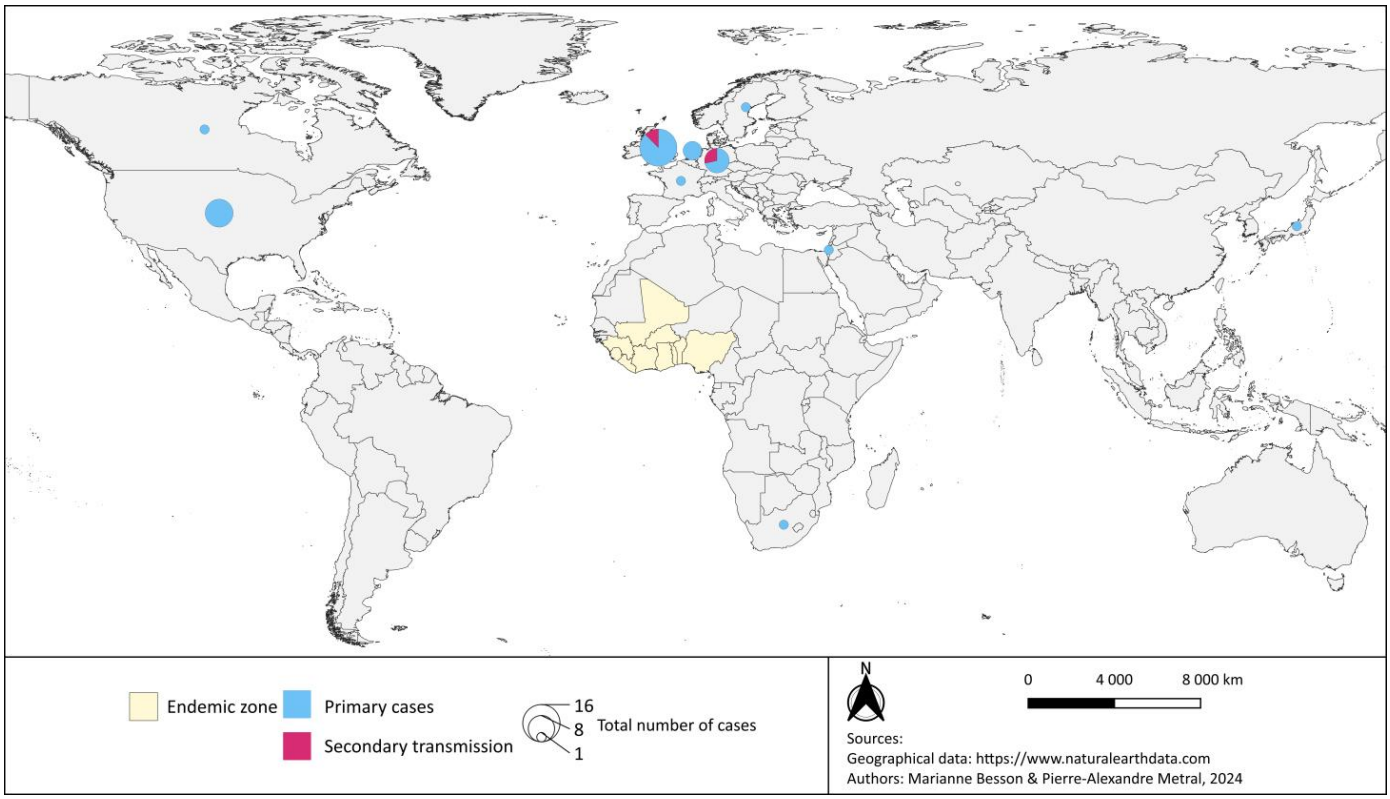

Figure 3. Map of the LF exported cases (primary and secondary transmission) from 1969 to 2024. Based on data from Kofman [122], Choi and Rollin, Wolf et al. [117], World Health Organisation [118].

Even though events presenting a risk of international propagation must be notified to the World Health Organisation (WHO), according to the 2005 International Health Regulations, delays or failures were detected. For instance, in 2016, an outbreak in Benin

Republic was not reported, leading to subsequent cases in Togo and in Germany [122,123]. Similarly, in November 2019, two Dutch healthcare professionals were contaminated while performing surgery on an infected patient in Sierra Leone and were repatriated. While the LASV infection was confirmed by RT-PCR on November 20, the Ministry of Health in Sierra Leone formally notified WHO of the ongoing epidemics only a few days later [76,124]. International Health Regulations' directives for notification of event do not appear in the official Nigerian guidelines for LF case management and infection control [125]. The lack of effective public health surveillance systems in the affected regions and the absence of active surveillance are arguably additional barriers to the disease containment [116].

Nevertheless, because LF is recognised to be a threat for the global community, it received increased international attention over the past decade. It features in the WHO R&D Blueprint list of priority diseases, requiring urgent research and development attention. The international community also aims at improving epidemic preparedness to the disease [126,127]. The Coalition for Epidemic Preparedness Innovations (CEPI) provides increased funding for research efforts [128], and supports programmes for vaccine research or rapid diagnostic tests development [129]. Additionally, CEPI initiated the largest prospective cohort and research capacity building study, the "Enable Lassa Research Programme" following above 23,000 participants in five West African countries (Benin, Guinea, Liberia, Sierra Leone) [130]. This initiative is a key step in strengthening the disease surveillance. It will also help prepare future field trials to assess efficacy and safety of vaccine or therapeutics [131].

7. Prospects for Control of Lassa Fever

First, prospects for control dwell in development of both prophylactic and therapeutic medical countermeasures. Because of the lack of profitability of the market in the endemic countries (limited purchasing power of affected communities), there is little financial incentive for pharmaceutical industries to fund research and development initiatives for LF [132]. Therefore, efforts mostly rely on public health institutions and non-governmental organisations [133]. Therapeutic options are currently limited to supportive care and to off-label use of ribavirin, effective only in the early stage of the disease and potentially harmful. New drugs are being investigated for LF management, as reviewed by Garry [134], Melnik [135], and Aloke and co-authors [13]. Favipiravir, integrated in the genome of the virus during replication, is a broad-spectrum inhibitor of viral RNA polymerase [136]. This RNA suppressor successfully treated LASV infection in mice [137] and in macaques [138]. However, the first report of use in two human patients in Togo described nausea and worsening transaminitis, forcing the discontinuation of therapy [139]. Comparatively, the viral entry inhibitor LHF-535 was well tolerated in healthy human volunteers. It showed efficacy in guinea pigs [140], and had an adequate pharmacokinetics profile, but its performance in diseased patients is yet to be evaluated [141]. Immunotherapy offers promising prospects. Interferon-alfacon-1 [142] and other type I interferons [143] could bolster the host innate immune response. Arevirumab-3, a combination of three monoclonal antibodies, protected macaques against parenteral challenge with both lineage II and III LASV isolates [144] and mucosal challenge with an isolate from lineage II [145]. Challenges remain, such as the need for protection against different circulating lineages with various pathogenicity. Similarly, the safety is to be assessed in patients with comorbidities, immunodeficiencies, undernourished or in poor health condition. The first clinical trial is to be set in West Africa, relying on LF specialized treatment centers in Nigeria (such as the Irrua Specialist Teaching Hospital), to identify and efficiently test new drugs candidates [146]. This initiative, launched by a new international consortium of public institutions, INTEGRATE, demonstrates the international will to pro-actively tackle the disease. The question of conveyance and broad availability of drugs in the affected areas, corroded by conflicts, with inadequate and unsafe transport network, remains unsolved. This is even more crucial as treatment must be initiated early in the disease course to be effective, and therefore should be available in primary health care facilities.

Regarding vaccines, four candidates entered the clinical trials, as described in the review by Sulis, Peebles and Basta [147] and by Moore and co-authors [148]: one recombinant measles-vectored LF (MV-LASV) candidate, two candidates using a recombinant vesicular stomatitis virus platform (rVSV-LASV), and one DNA-based candidate. All initiatives are funded by CEPI. MV-LASV candidate includes the genes encoding the nucleoprotein and the glycoprotein precursor from virus strain Josiah. Immune protection conferred in monkey relied on a robust T-cell and humoral response [149,150]. It showed satisfactory safety and immunogenicity in healthy patients in the Phase I human trial [151]. The DNA-based candidate [152], coding the glycoprotein precursor gene, also induced robust T cell responses [153], but failed to meet CEPI's selection criteria and was discontinued [154]. The rVSV-LASV candidate developed by the International AIDS Vaccine Initiative (IAVI) was also well-tolerated in cohorts from Liberia and from the United States, in the Phase I trial. It elicited robust immune responses, persisting at least one year after vaccination [155]. This candidate has now been advanced into the first-ever Phase II human trial for LF, currently ongoing in Nigeria [156]. Results of Phase I trials for the second rVSV vaccine candidate (developed by Emergent BioSolutions Inc., Gaithersburg, Maryland, USA) [157] and further results for the DNA-based vaccine [152] are to date unpublished.

Because delivery to the affected areas will be complex, several companies are working on reducing the need for cold chain during delivery or storage [158]. However, as highlighted by Leach and Fairfield [159], the challenge is not only to address the "supply-side", but also to prepare the "demand-side". How will the population accept these medical measures? Nigeria's history is marked by instances of vaccine refusal, which can be attributed to several factors, including skepticism towards Western medicine, as well as cultural and religious convictions [160]. In 2003, at the instigation of religious community leaders, five northern states in Nigeria banned the administration of the polio vaccine, claiming that the vaccine was a "Western plot to sterilise women in Nigeria", or contained human immunodeficiency virus [161].

For a vaccine to be accepted, local perspectives and knowledge should be recognised, and trust should be built with affected communities. The Strategic Advisory Group of Experts (SAGE) on Immunization recommends a multi-component strategy to overcome vaccine hesitancy, including mapping of the factors underlying the hesitancy, impactful communication, and education about vaccines in young individuals. Overall, a collaborative approach should be encouraged rather than top-down directives [162].

Similarly, availability of a drug does not mean that diseased persons will seek medical help. To ensure that the affected population will consult, understanding the relationship of affected communities to health, and fighting the caveats of the health system, will be essential [101]. 'Healthcare hesitancy' and the stigma around disease are being more commonly acknowledged, as larger initiatives are now conducted to better characterise the incidence of LF [131]. Understanding local practices will also help limit primary contamination and interhuman transmission.

The 'One Health' paradigm reflects the interconnection between human health, animal health and ecosystem health. Above 60% of emerging infectious diseases are of zoonotic origin [163,164], as epitomised by the COVID-19 pandemic. Besides, the ecosystem changes driving LF emergence (deforestation, urbanization, globalization, climate change) potentiate the risk of emergence of many other zoonotic pathogens [165–167]. Therefore, recognizing this interrelationship is critical to effectively contend with new health threats [168]. In a broader sense, One Health refers to the understanding and integration of the underlying social, economic, and political dimensions of disease [169]. While policy makers cannot hold sway over the general socio-economic and politic context, some practical solutions have been brought forward, to address the anthropogenic factors that allow the disease emergence and persistence. For instance, rodents thrive in poor sanitary conditions [116]. Sanitation policies, implemented while taking into account the cultural and ethnic specificities [170], are a cost-effective way to prevent LF as well as other scourges [171]. Rather than sectoral interventions and divided research or policy efforts,

an integrated approach for surveillance and response, that may address multiple diseases, must be promoted [169].

LF control will be hard to achieve without general economic and sanitary development of the region and reinforcement of health systems. Sufficient resources and supplies in primary care centers, as well as appropriate training of first medical responders, are key to curb the disease progression. Political structures which often underlie zoonotic disease burden must be challenged [172]. Political commitment must be obtained for a sustained effort to achieve LF control. Regional and national leadership is key in the fight against LF, with crucial actors such as the Nigeria Centre for Disease Control, or the Ministries of Health of affected countries. Regional capacity-building for research is also essential [173]. For instance, the Economic Community of West African States (ECOWAS) Regulators and Ethics Committees project aims at empowering regional stakeholders in research initiatives and clinical trials.

At last, Cunningham and co-authors [169] recommend shifting the narrative, from a focus on outbreak control, to addressing LF endemicity. Indeed, despite an increased international awareness in the past decade, LF remains a neglected tropical disease, which receives only limited funding and attention [48].

8. Conclusions

Lassa Fever, a deadly zoonotic viral haemorrhagic fever, exemplifies the intricate web of interactions between the health of animals, humans, and ecosystems. As the number of spillover events drastically increased in the past years, the disease poses a multifaceted challenge. It is both a devastating endemic burden in West Africa, and an emerging threat to the global community. Lassa Fever's emergence and persistence are driven by various ecological and anthropologic factors. The poverty and deep vulnerabilities of the affected population, the inequity in access to healthcare, the lack of sanitation and economic development in the afflicted regions, represent key factors hindering the disease control and prevention. In an endemic region ravaged by conflict and social unrest, a comprehensive, intersectional approach, that considers the complexity of the socio-economic context is essential. International cooperation for research should be reinforced to bridge knowledge gaps (ecology and transmission of the virus, genetic diversity and lineage distribution, accurate mapping of at-risk areas, correlate of immune protections) and to develop effective medical countermeasures. Active and passive surveillance must be strengthened for a better understanding of the epidemiology of the disease. To allow a quick diagnosis, more research institutions are needed in the endemic region, and alternative methods (rapid diagnostic test) should be validated. Because LF is a neglected tropical disease and receives only limited funding, public health interventions ought to be guided by appropriate modelling to target the at-risk populations. Recent advancements, such as the enhancement of the surveillance system and the progress in vaccine development, provide promising prospects for control. A collaborative and sustained effort, led by scientific research, brings hope that the impact of Lassa Fever could be lessened in the West Africa, and its global threat managed. Recognizing the multifaceted nature of Lassa Fever will enable the development of comprehensive strategies that not only tackle the disease but also reduce the risk of other emerging zoonotic diseases.

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