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Vaccine 43 (2025) 126479

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Burden of Lassa fever disease in pregnant women and children and options for prevention

Manu Chaudhary [a], Clare L. Cutland [b], Mercedes Bonet [c], Angela Gentile [d], Christine E. Jones [e], Helen S. Marshall [f], Andy Stergachis [g], Gerald Voss [h], Delese Mimi Darko [i], Esperanca Sevene [j], Terri Hyde [k], Lee Fairlie [b], Beate Kampmann [l,1], Darcie Everett [i], Flor M. Munoz [m,*]

[a] Department of Infectious Diseases, Rainbow Children's Hospital, Bangalore, India
[b] African Leadership in Vaccinology Expertise (Wits-Alive), Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[c] UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland
[d] Epidemiology Department, Ricardo Gutierrez Children Hospital, University of Buenos Aires, Argentina
[e] Faculty of Medicine and Institute for Life Sciences, University of Southampton and NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[f] Kaurna Country, Women's and Children's Health Network and Adelaide Medical School, The University of Adelaide, Adelaide, 5006, SA, Australia
[g] School of Pharmacy, University of Washington, Seattle, WA and School of Public Health, University of Washington, Seattle, WA, USA
[h] Coalition for Epidemic Preparedness and Innovation, London, UK
[i] Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA
[j] Department of Physiological Science, Clinical Pharmacology, Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique
[k] Centers for Disease Control and Prevention, Atlanta, GA, USA
[l] Centre for Global Health, Charite Universitätsmedizin, Berlin, Germany
[m] Departments of Pediatrics and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA

ARTICLE INFO

Keywords:
Lassa fever
Lassa vaccine
Maternal immunization
Pediatrics
Pregnancy
Infants

ABSTRACT

Lassa fever is a serious epidemic viral disease in West Africa affecting an estimated 2 million people annually with about 5000–10,000 deaths, although supporting data is sparse. Lassa fever significantly affects neonates, children, and pregnant women, however, comprehensive data on its impact in these populations are lacking. We reviewed the available literature on Lassa fever to assess its prevalence and impact in these populations and implications for vaccine development. Clinical features in children were similar to those observed in adults, with complications such as bleeding. Altered mental status, anasarca (swollen baby syndrome), bleeding, and poor urine output were risk factors for death. The case fatality rate (CFR) in 16 paediatric studies ranged from 6 % to 63 % and was 66.7 % and 75.0 % in two neonatal studies. In a systematic review of studies on pregnant women the CFR was 33.73 %. The adverse foetal outcomes included miscarriage, stillbirth, and intrauterine death associated with maternal death. Since Lassa fever significantly affects neonates, children, and pregnant women, developing a safe and effective, single-dose vaccine for these high-risk populations is vital. Currently, there are four clinical trials assessing Lassa virus vaccines. Only one of these trials is enrolling children aged ≥18 months, and exclude pregnant and breast-feeding women. It is essential that pregnant and breast-feeding women and young children are included in clinical trials that incorporate robust safety surveillance and risk mitigation measures. In our review, potential approaches to address the specific gaps in the areas of diagnosis, management, and prevention of Lassa fever in these specific populations, such as disease surveillance systems and vaccine development, were identified. A comprehensive strategy with investment focused on addressing specific knowledge gaps will be essential in protecting the health of these specific populations in Lassa virus endemic regions.

* Corresponding author at: 1102 Bates St. Suite 1150, Houston, TX 77030, USA.
E-mail address: florm@bcm.edu (F.M. Munoz).
[1] (ORCID: 0000-0002-6546-4709).

https://doi.org/10.1016/j.vaccine.2024.126479
Received 12 July 2024; Received in revised form 21 October 2024; Accepted 22 October 2024
Available online 1 November 2024
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1. Introduction

Lassa fever is an acute viral disease that is endemic in West Africa, particularly in Nigeria, where the disease was first identified in 1969 (Fig. 1) [1,2]. It is known to be endemic in Benin, Ghana, Guinea, Liberia, Mali, Nigeria, Sierra Leone, and Togo. Although there are distinct peaks at the beginning and the end of the dry season (January to March), cases can occur all year round [3]. Lassa virus is transmitted to humans through contact with the urine or faeces from infected rodents, particularly the *Mastomys natalensis* rat species [4]. Human-to-human transmission can occur via contact with infected secretions. Lassa fever can cause severe illness, including haemorrhagic fever, and can be fatal in some cases [5]. Annually, it has been estimated to affect 2 million people, with between 5000 and 10,000 deaths in West Africa, although supporting data is sparse [6]. The crude case fatality rate (CFR), up to week 11in 2023, was 18.1 % during the Lassa fever outbreak that year in Nigeria [7]. A spillover risk model predicted that 897,700 humans are infected by the Lassa virus each year across West Africa, with Nigeria accounting for more than half of these human infections [8].

While Lassa fever can affect people of all ages, children and pregnant women are particularly at high risk of adverse outcomes and mortality [9–12]. Neonates are at risk of infection with Lassa virus through both vertical and horizontal transmission of Lassa virus [11]. Early symptoms, which are nonspecific, include fever, headache, vomiting, fatigue, and abdominal pain [13]. These non-specific symptoms can lead to delays in diagnosis, management, and implementation of appropriate infection control measures. In addition, co-infection with malaria is common in Africa, which increases the complexity of diagnosis and treatment.

Ribavirin, a guanosine nucleoside analogue with broad antiviral activity, has been widely used off label for the management of Lassa fever. However, due to the limited evidence available from randomised controlled clinical trials, its efficacy remains uncertain, particularly in the treatment of mild Lassa fever [14,15]. Treatment with ribavirin has been reported to reduce viral titers and mortality in patients when initiated within six days after onset of symptoms [15–21]. The potential risk for teratogenicity limits the use of ribavirin in pregnancy. Other antivirals, including favipiravir, an RNA-dependent RNA polymerase inhibitor, and the viral entry inhibitor compound LHF-535, have shown activity against Lassa fever in animal models and are under evaluation in phase I clinical trials [15,22–29]. Several candidate vaccines are currently under evaluation for the prevention of Lassa fever in at risk populations [30–32].

The goal of this review was to performa critical evaluation of the available, albeit limited, data on Lassa fever in children and pregnant women, to gain a deeper understanding of the burden of disease and epidemiologic impact in these populations, to identify knowledge gaps, and to inform the approach to prioritising control strategies, such as vaccine research and development.

2. Methods

The review was performed by the Safety Platform for Emergency vACcines (SPEAC) Maternal Immunization Working Group (see appendix for full list of members). We searched PubMed and Google Scholar for English language publications using the search terms ‘Lassa fever’, ‘children’, ‘infants’, ‘paediatric’, ‘newborn’, ‘pregnant women’, ‘pregnancy’, and ‘vaccine’. The search was performed from inception dates through 30 April 2024. All study designs were considered for inclusion, including case reports, case series, retrospective and prospective observational studies and meta-analyses. The references from relevant reviews and included studies were also searched for additional publications. In addition, we searched clinical trial registries, including Clinical Trials.gov and the Pan-African Clinical Trial Registry, relevant reports, and online press releases for information about Lassa virus vaccines.

Data were extracted on the year of publication, location, design, demographics, clinical features, diagnosis, treatment, and Lassa fever outcomes in children and pregnant women (including gestational age when available). The data collected on vaccine candidates included the year of publication, location, vaccine type, manufacturer, phase, design, population, sample size, primary outcome, and results.

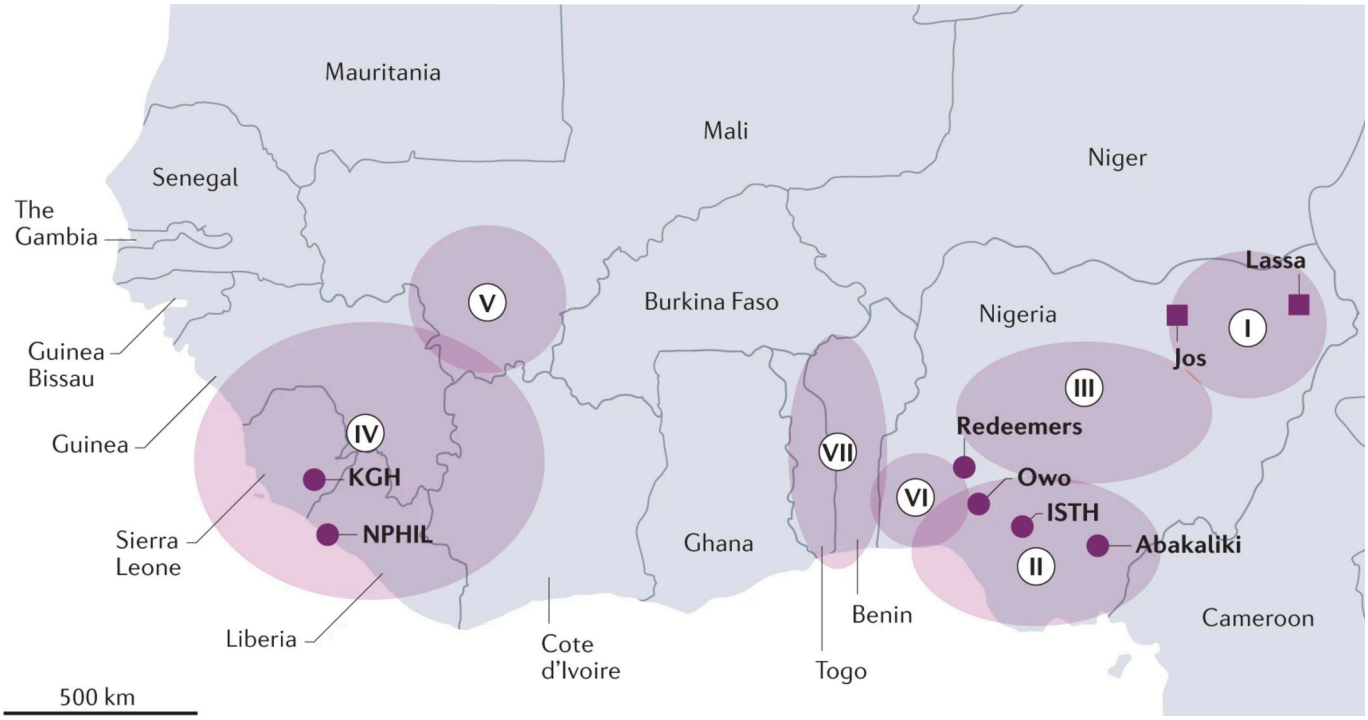

Fig. 1. Geographic distribution of Lassa fever virus and its seven known lineages in West Africa.

3. Results

3.1. Lassa fever in paediatric populations

We identified 16 studies, conducted between 1982 and 2022 in Nigeria ($n = 9$), Sierra Leone ($n = 4$) and Liberia ($n = 3$), that provided data for paediatric populations (Table 1) [10,12,13,16,33–44]. Six of the studies were prospective, and 10 were retrospective. Six studies included both paediatric and adult participants, and provided limited paediatric data. The studies included 591 children aged from <1 to 19 years old (2 to 111 children in each study). Gender was available in 6 studies, including 195 (50.4 %) females and 192 (49.6 %) males. Lassa fever diagnosis was made using Lassa virus real-time reverse transcription-polymerase chain reaction (RT-PCR) in 11 of the 16 studies. Ribavirin was used for treatment in 11 studies.

Data on the prevalence of Lassa fever in children, which was only available in the six studies including adult and children, ranged from 0 % to 40.5 % [13,33,38–41]. Common symptoms included fever, vomiting, abdominal pain, cough and headache (Table 2). Hepatomegaly and splenomegaly were also frequently observed. Bleeding, including conjunctival haemorrhage, haematuria, hematemesis, melena and bleeding from orifices and puncture sites, was reported in between 10 % to 52 % of the children.

The overall CFR ranged from 6 % to 49.3 % in 14 of the studies and in the remaining 2 studies, all children survived ($n = 5$ and $n = 9$). In two studies, the CFR was reported to be higher in girls, ranging from 36.8 % to 80 %, compared with 20 % to 63.1 % in boys [13,38]. One study reported 'swollen baby syndrome', a condition characterised by widespread oedema, abdominal distension, and bleeding [10]. In this study the CFR was 75 %, with children aged 4 days, 6 weeks, 7 months, and 9 years who died.

Altered mental status, such as coma and convulsions, bleeding, and poor urine output were reported to be risk factors for death [12,16,42]. Malaria was reported to be a common co-infection in four studies, with rates ranging from 19 % to 56 % [34–37]. In one study tuberculosis was reported as a co-infection in two out of five children [43].

3.2. Lassa fever in neonatal populations

Two case studies and two retrospective cohort studies reported data for Lassa fever disease in neonatal populations (<28 days old) (Table 3) [10,11,45,46]. The clinical features of Lassa fever disease in neonates were fever, poor feeding, abnormal bleeding, and convulsions. One study reported a case of congenital Lassa fever disease [10]. The source of infection in the neonates was thought to be transplacental, breast milk or through direct contact with an infected individual, such as an infected mother [11]. Two cohort studies that included 6 and 14 neonates, reported a CFR of 66.7 % and 75 %, respectively [11,45]. The neonates described in the two case reports died [10,46].

3.3. Lassa fever in pregnancy

Lassa fever virus has a high affinity for placental and foetal tissue, which may contribute to increased disease severity and poorer prognosis in infected pregnant women [47]. Lassa fever virus has been isolated from foetal organs after spontaneous abortion and the highest viral titres have been obtained from human placenta [48–52]. Most of the symptoms experienced by pregnant women with Lassa fever are non-specific and similar to those seen in other adults, however some pregnant women experience breast pain without expression of colostrum or milk which is considered pathognomonic to Lassa fever [51,52].

One systematic review and meta-analysis was identified that included individual patient data from 13 studies on Lassa fever for 276 pregnant women from Nigeria, Sierra Leone & Liberia between 1972 and 2019 (Table 4) [9]. The pooled maternal CFR was 33.73 % (95 % CI: 22.05–46.42; $I^2 = 72.40$ %; $p = 0.0014$). The pooled OR for death in pregnant women, compared with non-pregnant women, was 2.86 (95 % CI: 1.77, 4.63, $p = 0.239$).

The foetal outcomes from pregnancies in women who had Lassa fever disease were poor, with a CFR of 61.5 % (95 % CI: 28.32–89.86; $p < 0.0001$) [9]. A prospective cohort study conducted in Nigeria between April 2018 and March 2020 included 24 women who were pregnant at the time of symptom onset [38]. Seven of these women experienced pregnancy loss prior to hospital admission. Pregnancy outcomes were known for 14 of the remaining 17 women who were pregnant at the time of hospital admission: 6 had live births with Lassa fever negative infants and 8 suffered foetal loss: 6 miscarriages, 1 stillbirth and 1 intrauterine death due to maternal death [38].

3.4. Lassa fever vaccines

Currently, four Lassa virus vaccine candidates are undergoing evaluation in clinical trials. (Table 5) [30,31,53–58]. A vaccine based on a recombinant vesicular stomatitis virus platform (rVSVΔG-LASV-GPC) developed by the International AIDS Vaccine Initiative (IAVI) was evaluated in Liberia and the US in adults aged 18 to 50 years in a phase 1 study [31,53]. A phase 2b trial is currently enrolling in West Africa adults and children aged between 18 months to 70 years, including adults living with HIV AIDS [55,58]. The other vaccine candidates being evaluated in phase 1 studies are the EBS_LASV, a dual attenuated rVSV vectored vaccine created by Emergent BioSolutions Inc., the INO-4500, a DNA vaccine developed by Inovio Pharmaceuticals, and the MV LASV, a recombinant live attenuated viral vectored vaccine that has a backbone of measles Schwarz virus strain developed by Themis Bioscience GmbH [30,54,56]. These clinical trials are being supported by the Coalition for Epidemic Preparedness Innovations (CEPI).

3.5. Gaps in understanding Lassa fever in children and pregnant women

We identified specific knowledge gaps in the diagnosis, management, and prevention of Lassa fever in children and pregnant and breastfeeding women that we consider should be prioritised and have proposed potential approaches to address them in Table 6.

4. Discussion

This review summarised published data on the prevalence and clinical manifestation of Lassa fever disease in neonates, children, and pregnant women, as well as the latest information on ongoing phase 1 and 2 vaccine clinical trials. Lassa fever has a significant impact in these specific populations, with the highest CFRs observed in neonates (66.7 % and 75 % in two studies), followed by children (6 % to 49.3 %) and pregnant women (33.7 %). These rates are higher than the CFR of 16 % reported in the recent LASCOPE trial in adults [38]. The broad range of CFRs in the individual studies reflects heterogeneous study designs and data sources, including small observational studies and cases series as well as genuine age-related differences in fatality rates. This emphasises the need for more robust data to understand the burden of disease.

Among the six studies including adult and children in our review, the prevalence of Lassa fever in children ranged from 0 % to 40.5 % [13,33,38,40,41,44]. During the 2015 Ebola epidemic, which is another haemorrhagic viral infections, the prevalence of Ebola infection in children under the age of 15 years was reported to be 20 % [59]. A one-year prospective study of children with undifferentiated fever admitted to the hospital found that 5.4 % of paediatric cases had Lassa fever disease [42]. These findings highlight the burden of haemorrhagic disease in West African children. The infection probably spreads through the placenta, contact with secretions at the time of delivery, and breast milk [10,11,52]. National surveillance data from Nigeria reported that slightly more males were infected with Lassa virus between 2018 and 2021 [60]. In contrast, our review showed an equal distribution of cases between sexes, with a CFR in females of between 36.8 % and 80 %

Table 1
Description of studies reporting characteristics of Lassa fever infections in paediatric populations.

Study [ref]	Location	Study design	Total, N (Females, N)	Age range	Clinical features (%)	Diagnosis	Treatment	Outcomes
Duvignaud 2021 [38]	Nigeria	Prospective 5 Apr 2018–15 Mar 2020	84 (41)	0–18 y <1 y $n = 4$ 1–4 y $n = 14$ 5–17 y $n = 66$	Fever (76), headache (37), abdominal pain (31), myalgia (20), chest pain (12), sore throat (12), dizziness (25), seizure and delirium (2), meningeal syndrome, focal deficiency (1), aphasia(<1), impaired hearing and vision (<1) ($n = 2$), vomiting (38), watery diarrhoea (24), facial swelling and lower limb oedema (2), cough (19), bleeding of any type (19)	RT PCR	Ribavirin	CFR = 6 % Ages = 2 weeks, 4 months, 1 y, 12 y, 15 y F:M = 4:1
Orji 2020 [42]	Nigeria	Prospective observational Jan 2019–Jan 2020	24 (15)	0–17 y <6 y n = 7 6–12 y $n = 10$ >12 y $n = 7$	Fever (100), history of contact (50), abdominal pain and vomiting (41.7), cough and dyspnoea, convulsion, coma, bleeding, poor urine output (25), sore throat (16.7), headache, diarrhoea, facial puffiness (12.5), yellow eye (8.3), deafness (4.2)	RT -PCR 13 % prevalence of Lessa fever in suspected cases	Ribavirin 87.5 % patients	CFR = 29.2 %
Samuels 2020 [12]	Sierra Leone	Retrospective 1 Jan 2012–31 Dec 2018	57 (NA)	<18 y 0–9 y = 60 %	Cough (86), vomiting (75), headache (74), sore throat and pain (58), head/neck oedema (56), diarrhoea (56), unexplained bleeding (48), fever (37), confusion (35)	Rapid diagnostic test, ELISA IgM and IgG RT-PCR disease positivity rate = 19.5 %	67 % received ribavirin, of whom 23 died (64 %)	CFR = 21 % Higher in antigen positive children (63 % vs. 11 %)
Ilori 2019 [13]	Nigeria	Prospective Jan 1–May 6, 2018	111 (43)	NA	Fever (96.4), headache (59), vomiting (49), fatigue (43), abdominal pain (40), anorexia (33), cough (30), diarrhoea (27), sore throat (22), chest pain (21), myalgia (18.5), haemorrhaging (17), arthralgia (16.5), dyspnoea (14.8) other <5 %: unconsciousness, conjunctivitis, disorientation, skin rash, photophobia, hiccup, and jaundice	RT PCR	Ribavirin	CFR = 17.7 % 19 deaths F:M = 7:12
Akhiwu 2018 [34]	Nigeria	Retrospective Jun–Aug 2017	10 (8)	12–17 y Median 14.4 y	Fever (100), prostration (90), abdominal tenderness (90), headache (70), renal angle tenderness (70), urine leucocytosis (60), vomiting (50), dysuria (50), diarrhoea (40), conjunctivitis (40), tachycardia (40), tachypnoea (30) bleeding (10)	RT PCR	Ribavirin	CFR = 10 %
Akpede 2019 [36]	Nigeria	Retrospective 2009–2017	58 (24)	1–15 y <5 y $n = 45$ >5 y $n = 13$	Acute abdomen complaint (AAbd) $n = 12$, acute appendicitis (AApp) n = 3, 6/58 (10.3 %) children with LF had AAbd, including AApp in 3 (5.2 %) Group I: n = 6 (10.3 %) had AAbd (tenderness with peritonism). Group II: $n = 27$ (46.6 %) tenderness without peritonism; IIA: $n = 19$ with upper abdominal tenderness; IIB: $n = 8$ with mid or lower abdominal tenderness Group III: n = 25 (43.1 %) had no tenderness GI and GII ($n = 33$) vs. GIII ($n = 25$): fewer with fever that had lasted for ≤5 days on admission (8 of 22 vs. 13 of 16, respectively; $P = 0.016$) bleeding manifestations (31 %), haematuria (38 %)	RT PCR	Ribavirin Group 1: 6/6 with AAbd with peritonism had surgery	CFR = 28.5 %
Okokhere 2018 [41]	Nigeria	Retrospective, observational Jan 2011–Nov2015	9	≤15 y	NA	RT PCR	Ribavirin	All survived

(*continued on next page*)

Table 1 (*continued*)

Study [ref]	Location	Study design	Total, N (Females, N)	Age range	Clinical features (%)	Diagnosis	Treatment	Outcomes
Akhuemokhan 2017 [35]	Nigeria	Prospective 1 Dec 2009–Nov 2010	13	6 months–7 y	Pallor (38.5), dyspnoea and bleeding manifestations (31), hepatomegaly (30.8), convulsion (23) [generalized tonic-clonic seizure (15.3), focal seizure (7.7)], cough and diarrhoea (23), splenomegaly (15.4), vomiting, abdominal pain, malaise, poor oral intake (7.7), undifferentiated fever (4.5), fever with convulsion (4)	RT PCR	Ribavirin	CFR = 23 %
Dahmane 2014 [37]	Sierra Leone	Retrospective April 2011–Feb 2012	73 (28)	<2 y *n* = 34 2–5 y *n* = 28 >5–15 y n = 10	Abnormal bleeding (52), swollen face and/or neck (32), conjunctivitis or sub-conjunctival haemorrhage (10)	Antigen (72 % positive) IgM WHO clinical criteria		CFR = 49.3 % Deaths: <2 y = 20 2–5 y = 11 5–15 y = 5
Ajayi 2013 [33]	Nigeria	Retrospective Jan–Mar 2012	2 (Adult *n* = 18)	10–19 y	Fever (100), abdominal pain (85), sore throat (70), vomiting (50), headache (35), body pain and weakness (25), bloody vomiting and stool (15)	RT-PCR and epidemio-logical definition	Ribavirin	Overall CFR = 30 %
Akpede 2010 [16]	Nigeria	Retrospective Sept 2008–Oct 2009	22	<2 y n = 8 2–5 y n = 5 >5 y n = 9 11 M:3F versus 2 M:6F in younger children; *p* = 0.024	Hepatomegaly (82), toxic appearance (54.5), jaundice (50), pallor (45), vomiting (45), respiratory distress (41), convulsions and/or loss of consciousness (36), splenomegaly (32), pain (22.7), bleeding (22.7), coma (22.7), passage of coke coloured urine (18), cough (18)	RT PCR	NA	CFR = 29 %
Monson 1987 [10]	Liberia	Retrospective Jan 1980–Mar 1984	15	<5 days n = 1 <2 y n = 7 2–12 y n = 7	Fever, cough, enema, bleeding, abdominal pain, vomiting and diarrhoea (66.7), convulsions (26.7), sore throat, conjunctivitis, and obtundation, palpebral and/or bulbar conjunctivitis, Lassa pneumonia (26.7), swollen baby syndrome (SBS) (death 3/4 cases), 1 with SBS recovered with deafness and mental regression	IFA ≥ 1:64 Virus isolation Maternal history	NA	CFR = 27 %
Frame 1989 [39]	Liberia	Retrospective 1 July 1980–30 Apr 1986	15	<12 y	Abnormal bleeding (11)	IFA, Virus isolation, Sero-conversion 4 times		CFR = 27 %
Jetoh 2022 [40]	Liberia	Retrospective Jan 2019-Dec 2020	42	0–19 y 0–4 y n = 6 5–9 y *n* = 20 10–19 y *n* = 22	Fever (97.0), fatigue (92.9), loss of appetite (60.4), sore throat (60.6), haemorrhage (34.3)	RT PCR	Ribavirin	CFR = 40.5 %
Webb 1986 [44]	Sierra Leone	Prospective Aug 1977–1981	51	<1 y n = 3 1–4 y n = 13 5–9 y *n* = 21 10–14 y n = 12 Unknown n = 2	Fever (100), cough (65), vomiting (62) abdominal pain (38), splenomegaly (38), diarrhoea (35), hepatomegaly (26), pharyngitis (27), lethargy and chest signs (26), abdominal tenderness (19), adenopathy, facial oedema, bleeding, seizure, dehydration (15), anorexia and sore throat (12)	Virus isolation Sero-conversion 4 times IgG = 256 in a single serum specimen	NA	CFR = 11.8 %
Sharp 1982 [27]	Sierra Leone	Prospective	5	2 mo–6 y	Fever (100), vomiting (80), hepatomegaly (80), abdominal pain, cough, malaise, seizure (60), hepatosplenomegaly (60), splenomegaly (60), sore mouth, joint pain, dysuria, diarrhoea (40), backache, dizziness (20), enlarged axillary, cervical lymph node (20), cervical axillary (20)	4 times rise in antibody titres or titre ≥1:256	NA	Reported follow up in 4 with full recovery

Abbreviations: CFR, case fatality rate; ELISA, enzyme-linked immunosorbent assay; F, female; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; M, male; mo, months; N, number; NA, not available; RT PCR, reverse transcriptase polymerase chain reaction; Y, year; WHO, World Health Organization.

Table 2
Frequency of clinical symptoms and signs reported in children with Lassa fever.

Clinical symptoms and signs	Number of studies reporting variable	Range (%)
Bleeding	12	10–52
Fever	9	37–100
Vomiting	9	38–80
Abdominal pain	8	7.7–90
Diarrhoea	8	12.5–56
Sore throat	8	12–70
Cough	7	18–86
Headache	6	12.5–74
Fatigue	5	7.7–92.9
Dyspnea	4	14.8–41
Hepatomegaly	4	26–82
Seizure	4	2–25
Splenomegaly	4	15.5–60
Jaundice	3	2.2–50

compared with between 20 % and 63.1 % in males.

The clinical features of Lassa fever disease in children were similar to those in adults, with fever, fatigue, vomiting, and abdominal pain being common presenting symptoms. These symptoms are similar to those seen with malaria and other viral haemorrhagic fever diseases, such as Ebola, which occur in the same geographic areas [59]. Bleeding was more common than in other viral haemorrhagic fevers, with some publications reporting rates as high as 48 % to 52 % [12,37]. The odds ratios for death for unexplained bleeding and altered sensorium were 3.58 and 5.00, respectively [12]. Hepatomegaly and splenomegaly were also frequent observed in children with Lassa fever disease. Anasarca, also called the swollen baby syndrome, was more severe and generally a poor prognostic factor [10]. However, underlying risk factors for severity of disease and mortality, other than age and some clinical features of the disease, have not been sufficiently described.

Coinfection with malaria was common in paediatric populations, which potentially delayed the diagnosis of Lassa fever and therefore may have had an impact on the overall prognosis, especially in severe cases. Similarly, clinical pneumonia was present in about 33 % to 40 % of children with Lassa fever, which can also cause delays in diagnosis, as pneumonia is commonly associated with bacterial infections [10,37]. Testing for Lassa fever, as well as for co-infections such as malaria, typhoid, shigellosis, yellow fever, HIV, and tuberculosis, will be an important approach for differential fever and sepsis diagnosis in children in endemic regions of Africa.

In the systematic review, hearing loss was reported as a sequela in 3 out of 509 evaluable children but 25 % of adults who survive the illness were reported to suffer from hearing loss [5,9]. The low rate of hearing loss reported in children could be due to limited screening for hearing loss in surviving children. Thus, data about this and other long-term consequences of Lassa fever in young children is limited.

Ribavirin has been considered as the treatment of choice for Lassa fever disease, although there is no direct evidence of efficacy or safety in children or pregnant women since these populations have not been included in clinical trials. Evaluation of treatments in these populations is needed to ensure appropriate doses are used to provide efficacy and safety.

The urgent need for effective vaccines against Lassa fever is driven by the significant morbidity and mortality associated with the disease, as well as the challenges around controlling reservoirs and the risk of outbreaks and potential pandemics. Lassa virus vaccine trials should not only assess the vaccine's ability to prevent infection, but also its ability to prevent disease manifestation and reduce disease severity. Further considerations include post-exposure prophylaxis with vaccines and their ability to prevent post-infection sequelae, such as sensorineural hearing loss.

Protective immunity has been correlated with cellular immune responses with severe cases being associated with delayed T cell and neutralising antibody responses [17,18,20,21]. T cell responses to natural Lassa virus infections have been reported to persist for 1 to 2 years post-infection, while cross-protective antibody responses have been reported to persist for at least 4 years emphasising the need for vaccines,

Table 3
Description of studies reporting characteristics of Lassa fever infections in neonatal populations.

Study [ref]	Location	Study design	Neonates, N (Female, N)	Gestation	Age at diagnosis	Clinical features (%)	Diagnosis	Ribavirin	Outcomes
Obu 2020 [45]	Nigeria	Retrospective	6 (5)	34.8 (26–39) weeks	30 min–12 days	Apgar 1 min: 7 (5–9) Apgar 5 min; 8.8 (8–10) Weight: 2.4 kg (0.85–3.4) Fever (67); bleeding from an orifice, tachypnoea, respiratory distress, lethargy (50); pallor, seizure (33)	RT PCR History of maternal Lassa fever	3 received ribavirin	CFR = 66.7 %
Ogunkunle 2020 [46]	Nigeria	Case report	1 (0)	Term	26 days	Fever, poor feeding, pre-auricular lymphadenopathy, abnormal bleeding and multiple convulsions	RT PCR	NA	Died in 30 h
Monson 1987 [10]	Liberia	Retrospective Jan 1980–Mar 1984	1 (0)	NA	2 days	Swollen baby syndrome, congenital Lassa fever fever, vomiting, convulsions, pneumonia, oedema, abdominal pain and distention, bleeding, anorexia, cough, diarrhoea, stomatitis, irritability, lethargy, and obtundation, palpebral or bulbar conjunctivitis.	IFA $\geq$ 1:64 Virus isolation Maternal history		Died on day 4
Price 1988 [11]	Sierra Leone	Prospective	14 (NA)	NA	NA	NA	Seroconversion 4 times IgG = 256 in a single serum specimen with IgM Virus isolation	NA	CFR = 75 %

Abbreviations: CFR, case fatality rate; ELISA, enzyme-linked immunosorbent assay; F, female; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; M, male; mo, months; N, number; NA, not available; RT PCR, reverse transcriptase polymerase chain reaction; Y, year.

Table 4
Description of studies reporting characteristics of Lassa fever infections in pregnancy.

Study [ref]	Location	Study design	Mothers / neonates, N/N	Age range	Clinical features	Diagnosis	Ribavirin	Outcomes
Abejegah 2020 [51]	Nigeria	Retrospective cohort	18	19–44	Fever 88.9 %, generalized body weakness 83.3 %, abdominal pain 72.2 %, anorexia 55.6 %, vaginal bleeding 50 %, Bilateral breast engorgement and headache 33.3 % each, bleeding from puncture sites, dyspnea and dizziness 27.8 % each, vomiting and myalgia 16.7 % each	RT-PCR		Maternal CFR: 22.2 % Miscarriage or intra uterine fetal death: 83.3 %
Adewole 2022 [69]	Nigeria	Case report	2	20–30 years	Case 1: 30 years old, 32 weeks, 5 days gestation; presented with fever, bleeding from puncture sites, cough/ sore throat, breast pain, intrauterine foetal death.	RT-PCR	Case 1: Supportive IV Ribavirin	Case 1: maternal death with intrauterine dead foetus.
					Case 2: 20YO primiparous woman, admitted with PPH following delivery of macerated foetus at home. Had fever, vaginal and puncture site bleeding and hematemesis, cough/sore throat, confusion, hypotension	RT-PCR	Case 2: placental evacuation, supportive	Case 2: maternal death after delivery of macerated stillborn infant, PPH
Duvignaud 2021 [38]	Nigeria	Prospective cohort study, 510 participants of whom 252 were female	24	NA	7 had aborted between onset of Lassa fever symptoms and hospitalisation. 17 were pregnant on admission with confirmed Lassa fever	RT-PCR	IV Ribavirin	Pregnancy outcomes known for 14/17 women: livebirth: 6(42.9 %), foetal loss: 8 (57 %): [miscarriage: 6 (42.9 %), stillbirth: 1 (7.1 %), materno-foetal demise: 1 (7.1 %)]
Okogbenin 2019 [52]*	Nigeria	Retrospective Jan 2009–Mar 2018	30/31	16–39	16 women had fever and complications (coma, convulsions, irrational behavior, extravaginal bleeding, or oliguria) 14 women had midler, non-specific symptoms (fever, malaise, cough, sore throat)	RT-PCR	IV Ribavirin	With complications: maternal CFR 59 %; foetal CFR 100 % Without complications: maternal CFR 7 % foetal CFR 6 %
Monson 1987 [10]*	Liberia	Retrospective Jan 1980- Mar 1984	18	NA	Abortions: 16 (3–9 months of gestation)	Virus isolation, serology, presumptive		Maternal CFR 17 %
Kayem 2020 [9]	Nigeria, Sierra Leone, Liberia	Systematic review and meta-analysis	276	NA	Non-specific	Various	Various	Maternal CFR = 33.7 %

Abbreviations: CFR, case fatality rate; ELISA, enzyme-linked immunosorbent assay; F, female; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; M, male; mo, months; N, number; NA, not available; RT PCR, reverse transcriptase polymerase chain reaction; Y, year.

* Studies also included in the meta-analysis by Kayem 2020 [9] but used to extract details of pregnancy outcomes of interest relevant to our review that were not provided in meta-analysis.

possibly with booster doses, particularly for high-risk groups including pregnant and breast-feeding women and children [61]. Physiological modifications during pregnancy, including immune responses and altered drug metabolism, can increase risk of infection, and therefore, require careful consideration of the timing and dose of vaccination and the need for booster [62]. Age-related immune immaturity, genetic factors, and comorbidities necessitate tailored vaccine doses and formulations in children, particular younger infants [63]. Hence, it is important to assess what age children should be vaccinated so that evidence-based decisions can be taken to include Lassa virus vaccination in routine childhood vaccination programmes for younger children, or in school-based programmes for older children. In addition to the important implications for organisational and vaccine uptake issues, the age at which children are vaccinated could have implications for their immunological response.

A sociodemographic study from Nigeria reported that the majority of Lassa fever cases and related fatalities were among individuals aged 25–44 years (41.8 %) [64]. Women might encounter rodent-contaminated environments more often than others due to their traditional roles involving food preparation and cleaning. Additionally, healthcare workers, regardless of age or gender, are at a heightened risk if they do not adhere to appropriate protective measures. As such, these groups could be prioritised for vaccination to protect the individuals themselves and reduce community transmission of the disease.

The ongoing clinical trials assessing Lassa vaccines specifically exclude pregnant and breast-feeding women and only one includes children aged ≥18 months, although they are one of the most vulnerable populations with high maternal and foetal CFRs [30,31,54–57].

Table 5
Description of clinical trials assessing Lassa virus vaccines.

Trial registration number – Clinical study phase [ref]	Year first posted	Location(s)	Vaccine description (manufacturer)	Study design	Study population	Sample size	Primary outcome (s)
NCT05868733 / PACTR202210840719552 – Phase 2b [55,58]	2023 / 2022	Ghana, Liberia, Nigeria, Sierra Leone	rVSVΔG-LASV-GPC recombinant vesicular stomatitis virus, native glycoprotein replaced with the Lassa glycoprotein (Josiah strain) (IAVI)	Randomised, double-blind, placebo-controlled	18 months to 70 years including PLWH (VL < 50 copies/ml)	612	Tolerability and Immunogenicity
PACTR202108781239363 – Phase 1 [56]	2021	Ghana	EBS-LASV a dual- attenuated rVSV-vectored vaccine (Emergent BioSolutions Inc)	Randomised, blinded, placebo-controlled	18 to 50 years	108	Safety and immunogenicity
NCT04794218 / PACTR202106625781067 – Phase 1 [31,53]	2021	Liberia, U.S.	rVSVΔG-LASV-GPC (IAVI)	Randomised, placebo-controlled	18 to 50 years	110	Safety and tolerability
NCT04093076 – Phase 1 [54]	2021	Ghana	INO-4500, DNA vaccine (Inovio Pharmaceuticals)	Randomised, blinded, placebo-controlled	18 to 50 years	220	Safety, tolerability, and immunological profile
NCT04055454 – Phase 1 [30]*	2019	Belgium	MV-LASV, recombinant live attenuated viral vectored vaccine backbone of the measles Schwarz virus strain (Themis Bioscience GmbH)	Randomised, placebo-controlled	18 to 55 years	60	Safety, tolerability, and immunogenicity
NCT03805984 – Phase 1 [57]	2019	U.S.	INO-4500, DNA vaccine (Inovio Pharmaceuticals	Randomised, double-blind, placebo-controlled	18 to 50 years	60	Tolerability and immunological profile

Abbreviations: GPC, glycoprotein complex; LASV, Lassa virus; IAVI, International AIDS Vaccine Initiative; N, number; PACTR, Pan-African Clinical Trial Registry; PLWH, person living with HIV-AIDS; rVSV, recombinant vesicular stomatitis Virus; VL, Viral load; US, United States; US CTR, United States Clinical Trial Registry.
* Only clinical trial terminated – key results: acceptable safety and tolerability profile and immunogenicity seemed to be unaffected by pre-existing immunity against the vector.

Although investigators in Lassa virus endemic areas in sub-Saharan African countries have limited experience with maternal vaccination clinical trials, they said they would agree with pregnant women participating in well-designed vaccine clinical trials provided adequate measures to ensure safety were in place [65]. A report from a CEPI meeting in 2020 emphasised the need to progress towards the initial inclusion of pregnant women in Phase 2 and 3 vaccine trials to ensure that vaccines are effective and safe for all populations, including those who are most vulnerable to the disease [66]. In addition, effective safety surveillance would have to be implemented once a vaccine becomes available.

Estimates from the Enable Lassa research programme for the incidences of Lassa fever infections and disease in West Africa should provide data about the feasibility of clinical trials for Lassa fever vaccine candidates [67]. Direct evidence of Lassa fever vaccine safety and efficacy in pregnant and breast-feeding women and children could be obtained if vaccine clinical trials included sufficient numbers of individuals from these populations. The use of a licensed vaccine could reduce the incidence and severity of Lassa fever disease, including hospitalisation and mortality.

In conclusion, Lassa fever significantly affects neonates, children, and pregnant women. We have identified important knowledge gaps about Lassa fever in children and pregnant and breast-feeding women, including diagnosis, management, and prevention, that the Maternal Immunization Working Group consider deserve prioritisation and have proposed potential approaches to address them in Table 6. Despite limited available data, the potential severity of disease in these populations highlights the need for enhanced disease surveillance and research focusing on prevention strategies. Developing an effective vaccine for these high-risk populations, with a focus on including them early in clinical trials and implementing robust safety surveillance, is vital. A comprehensive approach with investment focused on addressing specific knowledge gaps will be essential in protecting the health of these vulnerable groups in affected regions.

Maternal Immunization Working Group

- Flor M, **Muñoz**, Baylor College of Medicine, Houston, TX US (Chair)
- Manu **Chaudhary**, Rainbow Children's Hospital, Bangalore, Karnataka, India
- Magdalena **Babinska**, WHO, Geneva, Switzerland
- Mercedes **Bonet**, WHO, Geneva, Switzerland
- Clare L **Cutland**, University of the Witwatersrand, Johannesburg, South Africa
- Delese Mimi **Darko**, Ghana Food and Drugs Authority, Ghana
- Sascha **Ellington**, US CDC, Atlanta, Georgia, USA
- Darcie **Everett**, US FDA, Silver Spring, Maryland, USA
- Lee **Fairlie**, Wits RHI, Johannesburg, South Africa
- Angela **Gentile**, Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina
- Terri **Hyde**, US CDC, Atlanta, Georgia, USA
- Chrissie **Jones**, University of Southampton, Southampton, UK
- Tara **Jatlaoui**, US CDC, Atlanta, Georgia, USA
- Beate **Kampmann**, Charite Center for Global Health, Berlin, Germany and Vaccine Centre, LSHTM, London, UK
- Ruth **Karron**, Johns Hopkins Center for Immunization Research, Baltimore, MD, USA
- Asma **Khalil**, University of London, London, UK
- Helen **Marshall**, Public Health, University of Adelaide, Adelaide, Australia
- Dana M **Meaney Delman**, US CDC, Atlanta, Georgia, USA
- Samantha **Olson**, US CDC, Atlanta, Georgia, USA
- Sara **Oliver**, US CDC, Atlanta, Georgia, USA
- Proma **Paul**, LSHTM, London, UK
- Anna **Seale**, BMGF, Seattle, Washington, USA
- Esperança **Sevene**, Eduardo Mondlane University, Maputo, Mozambique
- Geeta **Swamy**, Duke University School of Medicine, Durham, NC, USA
- Andy **Stergachis**, University of Washington, Washington, US
- Gerald **Voss**, CEPI, Oslo, Norway

Table 6
Lassa fever knowledge gaps and proposed approaches to address them.

Knowledge gap	Approach to address the gap
• Knowledge gaps specific to neonates, children and pregnant women	
Limited understanding of burden of Lassa fever disease in neonates, children and pregnant women	Establish disease surveillance systems with systematic reporting of Lassa fever cases in pregnancy and children during seasonal epidemics and assessment of variability of incidence of disease over time in these populations Establish systems for collecting robust data concerning Lassa fever case fatality rates in different populations
Limited understanding of pathophysiology and immunology of Lassa fever disease in neonates, children and pregnant women (including transmission risk to the foetus)	Establish observational and epidemiological studies, laboratory pathology and post-mortem examinations, animal models, and laboratory evaluations and investigations of the pathophysiology and immunological mechanisms of Lassa fever in pregnancy and early childhood
Poor understanding of the immediate and long-term outcomes of Lassa fever in neonates, children and pregnant women	Establish disease surveillance systems and longitudinal observational and natural history studies with standardised data collection on clinical manifestations and outcomes of the disease in these populations: • obstetric outcomes in pregnant women, • immediate and long-term consequences of infection and disease other than hospitalisation and mortality (e.g., sensorineural hearing loss, other neurologic effects, acute kidney injury)
Optimal time for Lassa virus vaccination in children	Design studies to provide data to inform evidence-based decisions about inclusion of Lassa virus vaccination in childhood or school-based vaccination programmes: • understand implications for organisational and vaccine uptake issues • assess implications for duration of protection
Lack of safety and efficacy data for treatment options available (e.g., ribavirin) and future treatments and vaccines	Involve pregnant and breast-feeding women and children in drug and vaccine efficacy and safety trials
Vaccine hesitancy in pregnant and breast-feeding women and children	Develop and implement effective strategies to communicate the results from clinical trials and observational studies and information about the burden of Lassa fever disease to key stakeholders, including pregnant and breast-feeding women and also the parents and guardians of children and infants
Poor understanding of the specific risks for pregnant and breast-feeding women and children by healthcare workers and the general public	Develop and implement effective communication strategies to increase the understanding of healthcare workers and the general public about the high risk from Lassa fever disease in pregnant and breast-feeding women and children
• General knowledge gaps	
Lack of adequate diagnostic tests and timely diagnosis	Invest in technology to develop rapid testing (e.g., Nucleic Acid Amplification Technique (NAT)-based test) for Lassa fever in the region
Poor understanding of transmissibility and risk factors for infection within households, as well as of risk factors contributing to severe disease and mortality in these populations	Support and implement household transmission studies to determine risk and potentially consider strategy of post-exposure prevention through vaccination or passive immunity
Lack of safe and effective Lassa virus vaccines	Investment in vaccine development in endemic areas and identification of highest risk populations for vaccination, including, pregnant and breast-feeding women and children Involve these highest risk populations in early phase clinical trials to ensure adequate assessment of vaccine safety and efficacy
Lack of vaccine safety surveillance systems at sites where vaccine implementation will be necessary	Investment in establishing active safety surveillance systems at sentinel sites in endemic regions. Support inclusion of vaccine safety surveillance in national and global healthcare and safety surveillance systems

Funding

This work was supported by funding from the Coalition for Epidemic Preparedness Innovations (CEPI) to the Safety Platform for Emergency vACcines (SPEAC) Project.

Author contributions

FM and MC conceptualized the manuscript; FM, MC, CC wrote the first draft and managed subsequent drafts; All authors reviewed the drafts and validated the final manuscript for submission.

CRediT authorship contribution statement

Manu Chaudhary: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Clare L. Cutland:** Writing – review & editing, Writing – original draft, Data curation. **Mercedes Bonet:** Writing – review & editing, Writing – original draft. **Angela Gentile:** Writing – review & editing, Writing – original draft. **Christine E. Jones:** Writing – review & editing, Writing – original draft. **Helen S. Marshall:** Writing – review & editing, Writing – original draft. **Andy Stergachis:** Writing – review & editing, Writing – original draft. **Gerald Voss:** Writing – review & editing, Writing – original draft. **Delese Mimi Darko:** Writing – review & editing, Writing – original draft. **Esperanca Sevene:** Writing – review & editing, Writing – original draft. **Terri Hyde:** Writing – review & editing, Writing – original draft. **Lee Fairlie:** Writing – review & editing, Writing – original draft. **Beate Kampmann:** Writing – review & editing, Writing – original draft. **Darcie Everett:** Writing – review & editing, Writing – original draft. **Flor M. Munoz:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Flor M Munoz reports financial support, administrative support, article publishing charges, and writing assistance were provided by Coalition for Epidemic Preparedness Innovations. Clare L Cutland reports a relationship with Pfizer that includes: funding grants. Clare L Cutland reports a relationship with BMGF that includes: funding grants. Clare L Cutland reports a relationship with GIZ that includes: funding grants. Flor M. Munoz is an associate editor for Vaccine. Helen Marshall declared being an investigator on vaccine clinical trials with institutional funding by pharmaceutic industry with no personal payments If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data used in this review were published

Acknowledgements

The authors would like to acknowledge support from the Coalition for Epidemic Preparedness Innovations (CEPI) to the Safety Platform for Emergency vACcines (SPEAC) Project, as well as medical writing and editorial services provided by Margaret Haugh, PhD, MediCom Consult (France) funded by CEPI/SPEAC, and the project management support provided by Maria de la Paz Aguirre, MSc, WeDo Project Intelligence Made Easy (Spain), also funded by CEPI/SPEAC.

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