SPEAC

Safety Platform for Emergency vACcines

Updated Landscape Analysis for Priority List of Adverse events of special interest Part 1: Lassa Fever

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DEFINITIONS & ACRONYMS

AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BC	Brighton Collaboration
BUN	Blood urea nitrogen
CD	Case definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CFR	Case fatality rate
CIOMS	Council for International Organizations of Medical Sciences
DIC	Disseminated intravascular coagulation
EBV	Epstein Barr Virus
FiO2	Inspired fraction of Oxygen (expressed as a decimal – e.g., 21% O_2 = 0.21)
LDH	Lactate dehydrogenase
LFT	Liver function test
KDIGO	Kidney Disease – Improving Global Outcome
MVA	Modified vaccinia
NEWS	National Early Warning Score
PAI-1	Plasminogen activator inhibitor 1
PaO2	Partial pressure of arterial oxygen (measured in mm Hg)
RT-PCR	Reverse transcriptase polymerase chain reaction
SPEAC	Safety Platform for Emergency Vaccines
SpO2	Hemoglobin oxygen saturation (expressed as a percentage - %)
sTM	Soluble thrombomodulin
TBD	To Be Decided
TNF	Tumor necrosis factor
VAED	Vaccine-associated enhanced disease
VHF	Viral hemorrhagic fever
VSV	Vesiculostomatitis Virus

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

1. Background

CEPI–contracted the Brighton Collaboration, through the Task Force for Global Health, to harmonize safety assessment across CEPI funded vaccine development. Since inception, a key activity of SPEAC (Safety Platform for Emergency vACcines) has been to establish lists of adverse events of special interest (AESI) that have potential to occur during CEPI funded clinical trials.

1.1 Adverse events of special interest

An adverse event following immunization (AEFI) is defined as 'any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.[1]

The source definition of 'Adverse Event of Special Interest' (AESI) as described in CIOMS VII[2] is:

"An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted."

AESI can be specified in the Program Safety Analysis plan early in product development for safety planning, data collection, analysis, and reporting on AESI data, and eventually form the base of AESI analysis in the Reporting and Analysis Plan.

Vaccine safety needs to be conducted across the entire life cycle of vaccine development, approval, and use. It is essential that the approach be harmonized and standardized so that data are comparable across different trials and populations. Thus, while several if not most of the AESI identified as relevant to CEPI vaccine programs are likely to be rare events and may never occur in the context of a given trial, preparations must be made to maximize the utility of vaccine safety data so appropriate benefit-risk decisions can be made.

SPEAC has chosen to identify AESIs using 4 main approaches as outlined below. The AESI that were included on the 2020 Lassa Fever list are shown for each:

1. AESI that have been previously identified with immunization in general:
    a. Anaphylaxis, thrombocytopenia, generalized convulsion
2. AESI associated with specific vaccine platforms:
    a. **Live vaccine:** aseptic meningitis, encephalitis, myelitis
    b. **Vesiculostomatitis virus vaccine platform**: acute aseptic arthritis
    c. **Modified vaccinia virus platform**: myocarditis
    d. **Pandemic and some seasonal influenza vaccines**: Guillain Barré Syndrome
3. AESI that may occur during the clinical course or as a complication of the chosen target diseases due to viral replication or a host response immunopathogenic mechanism:
    a. Neurologic: Aseptic meningitis, Encephalitis / Myelitis, Sensorineural hearing loss
    b. Hemorrhagic disease (internal/external bleeding)
    c. Vascular leakage (face/neck edema, polyserositis)
    d. Pericarditis
    e. Alopecia

f. Pregnancy outcomes: Spontaneous abortion, Stillbirth, Maternal / Neonatal death

4. Theoretical AESI based on animal models or in vitro experimental data (e.g., Vaccine-associated Enhanced Disease seen in mouse model of SARS1 and MERS).

The initial landscape analysis for Lassa Fever AESI was completed in Feb 2020 and was based on a non-systematic literature review of key review articles. Lassa Fever phase 3 clinical trials are due to commence within the year in West African sites and thus an update to the Lassa Fever AESI list is a high priority for CEPI.

2. Objective of this deliverable

The primary objective is to update the 2020 landscape analysis and AESI list for potential safety issues relevant to development of Lassa Fever vaccines based on a systematic literature review.

3. Methods

A systematic literature search of PubMED was done December 12, 2022 using the following search strategy: *("Lassa virus"[Mesh] OR "Lassa Fever"[Mesh] OR "Lassa virus"[tiab] OR "Lassa fever"[tiab]) AND ("Epidemiology"[Mesh] OR "epidemiology"[tiab] OR "clinical"[tiab] OR "complication"[tiab] OR "complications"[tiab]) AND ("2019/01/01"[PDAT] : "3000/12/31"[PDAT]) NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp]) NOT ("animals"[Mesh] NOT "humans"[Mesh]) AND English[lang]*.

All retrieved articles were screened by the author of this deliverable. After screening out duplicates, article Title or Abstract were reviewed to eliminate those that did not have an epidemiologic or clinical focus on Lassa Fever or were on a topic unrelated to Lassa Fever. Non-English articles were excluded as were any that had a sole focus on treatment. Remaining articles were retrieved for full text review in order to identify those that were:

- Descriptive or analytic studies of patient clinical course and complications
- Reviews focused on evidence for Lassa clinical course and complications
- Articles focused on what is understood about pathogenesis of Lassa Fever

Additional relevant articles were retrieved based on a hand search of the citation lists of included articles.

Each included article was reviewed in detail and descriptive notes made on the key findings. A standard data extraction form was not used.

The above search was focused on Lassa Fever clinical disease as a source for potential AESIs. A separate search was not done for vaccine platforms but information from relevant vaccine safety templates was searched for any possible additional AESI as well as results from Lassa Fever vaccine candidate trials that have been completed.

In addition to what was found in the literature, presentations from Lassa Fever experts presented at the Oct 25-26, 2022, Abuja meeting on 'Accelerating the licensure of Lassa vaccines: Generating robust evidence on vaccine efficacy and safety' were reviewed for anything relevant to updating the Lassa AESI list. (available at this link, visited on July 27, 2023: https://www.who.int/news-room/events/detail/2022/10/25/default-calendar/save-the-date---accelerating-the-licensure-of-lassa-vaccines--generating-robust-evidence-on-vaccine-efficacy-and-safety)

4. Results

4.1 Literature Search

A total of 127 articles published since Jan 1, 2019, were found. There were no duplicates. A total of 72 were screened out based on title/abstract for the following reasons: 37 had a focus on animal models or were primarily opinion pieces or discussed lessons learned re COVID-19; 35 were eliminated because of a focus on therapy, diagnostics, or prevention; 1 was eliminated because it was unrelated, focusing on Viral Hemorrhagic Fevers other than Lassa Fever or Ebola. An additional 29 articles were screened out after full text review: 28 were judged to be noncontributory to the clinical course or complications of Lassa Fever and 1 was focused on therapy without any additional information on clinical features. While these 101 articles were deemed non-contributory to the Landscape analysis for identifying new AESI relative to Lassa Fever vaccine development, a full listing of the citations is provided in Appendix 2, in case they could be of interest to CEPI or vaccine developers. All were published from 2019 to 2022 and most originate from West Africa.

A total of 26 articles were screened in as relevant to the landscape update[3-12, 14-16, 20, 23, 25, 26, 28-32, 36-38, 44] along with an additional 16 that were identified by hand search of the screened in article citation lists[13, 17-19, 21, 22, 24, 27, 33-35, 39-43]. In order to link this updated review to the previous landscape analysis done in 2020, Appendix 1 presents all citations contributing to the 2020 and the updated AESI list, organized as a bibliography by subject matter.

Among the included articles four were reviews[3-6], eight were clinical descriptive studies of Lassa Fever patients from West African centers [7-14] and one was a protocol that described an ongoing Lassa Fever hospitalized patient cohort study in three tertiary reference hospitals with diagnosis and therapy capacity for Lassa Fever.[15] The first location, the Federal Medical Centre Owo (FMCO) in Ondo State in South-Western Nigeria has already published data, representing the largest clinical study to date, and is described below.[7] A second participating site was expected to get started in 2020 (to be selected by Nigeria Center for Disease Control) and a third, under discussion, to be located in Benin. Three studies focused on acute kidney injury (AKI)[16-18], one on liver disease[19], three on bleeding disorders [20-22], two on swelling and capillary leak [23, 24], two on eye involvement [25, 26], three on neurologic manifestations [27-29], two on pediatric populations [30,31], four on pregnancy outcomes [32-35], six on pathogenesis[36-41], one on differential diagnosis of acute viral febrile illnesses, including Lassa Fever[42], one on needing to suspect Lassa Fever in patients presenting with acute abdomen[43] and one recommending a standardized framework for Phase III clinical trials to assess therapeutic interventions for Lassa Fever.[44] Key findings from the screened in articles are presented below.

4.2 Lassa Fever Reviews

The most comprehensive study by Merson et al[4], was a systematic literature review with no language restrictions that extended to Apr 15, 2021. The search yielded 4794 publications of which 147 were included involving 8550 individuals of whom 91% were from Nigeria or Sierra Leone. It wasn't possible to be sure that no individual was double counted. Further, the population with clinical details available was often much smaller than 8550. The papers included: 53 case reports; 41 case series; 30 cohort studies; 10 case-control studies; 11 cross-sectional studies and 2 quasi-randomized studies. Most of the key clinical features were either non-specific presentation

with fever, headache, vomiting and abdominal pain or events already identified on the Lassa Fever AESI list: bleeding, facial edema and encephalopathy. One feature not on the 2020 AESI list was kidney dysfunction. At presentation, proteinuria was documented in 15% of 13 patients and none had renal failure. Over the course of the clinical illness 58% of 442 patients had documented proteinuria and 30% of 310 had acute renal failure. Shock was another feature that was observed, involving only 6% of 187 at presentation but 33% of 262 over the course of the clinical illness. DIC was not a feature – with only 1 documented case observed. Cough was present in 35% of 1581 at admission and 40% of 2097 over the clinical course. Difficulty breathing was seen in 7% of 310 at presentation but increased to 14% of 1829 over the clinical course.

Another systematic review[6] was conducted as research needs appraisal which included articles published from 1969 through 2017. This article didn't provide any new features but was of interest because of the presentation of a 'rapid research needs appraisal methodology' conducted by teams in the UK, Canada, and the Philippines. This could be of interest should a new disease or AESI 'X' emerge, but it did not add anything to the Lassa Fever landscape update.

The other two reviews[5, 6] were non-systematic and did not add anything new, but had similar findings to Merson et al with respect to including acute kidney injury as a key clinical feature in Lassa Fever.

The review studies also provided some additional references, not found in the literature search, that are included in the discussion below.

A key problem with each of the reviews was the lack of comparability for the included studies, many of which were based only on single case reports or series with 6 or fewer cases.

4.3 Descriptive Clinical Studies

In 2020 Duvignaud et al published a protocol[16 for] a prospective cohort study of Lassa Fever cases in Nigeria to be conducted in three different centres. To date only one centre (Federal Medical Center, Owo, Ondo State, Nigeria) following the protocol has published results, but it is the largest prospective cohort study published to date and according to the authors, the first prospective study to enroll patients with acute symptomatic Lassa fever confirmed by RT-PCR.[7] From April 5, 2018 to March 15, 2020, 534 cases were admitted to the Lassa Fever Ward which provides organized, standardized care. The cohort spanned all ages, including newborns and pregnant. All were treated immediately with ribavirin (10-day course) and had supportive care as needed with oral or intravenous fluids, analgesics, oxygen, antimalarials, antibiotics, blood transfusion or intermittent hemodialysis. All were confirmed by RT-PCR to have Lassa Fever and of these 510 consented to be in the study. Lab tests (Lassa RT-PCR, full blood count, serum albumin, creatinine, BUN, electrolytes, aspartate aminotransferase, alanine aminotransferase and bilirubin) were measured on hospital days 0, 5 and 10. The KDIGO (Kidney Disease – Improving Global Outcome) criteria were used to classify kidney function (available at this link, visited July 27, 2023: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf.) National Early Warning Score (NEWS2: available at this link, visited July 27, 2023: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2) were assessed at admission and on follow-up. There was no capacity for mechanical ventilation, invasive hemodynamic monitoring, vasopressor or inotropic drug therapy. All discharged patients were asked to return for an outpatient visit 30 days after admission.
The 30-day case fatality rate was 12%: 13% (95%CI 10.4-16.9%) among adults and 6% (2.2-12.7%) among children. Overall, 82% of the 62 deaths occurred within 7 days of admission. Factors associated with a fatal outcome

included: age ≥45 years (adjusted odds ratio of 16.30; 95% Confidence Interval of 5.31-50.3; p<0.0001); NEWS2 score ≥7 (OR 4.79; 95%CI 1.75-13.1; p=.0023); KDIGO Stage ≥2 (OR 7.52 (95% CI 2.66-21.2; p<0.0001); plasma alanine aminotransferase ≥3 times lab upper limit of normal (OR 4.96; 95%CI 1.69-14.6; p=.0036).

Overall, 13% had some degree of AKI at baseline and a total of 18% over the entire follow-up: 4% (95%CI: 2.2-5.6%) KDIGO stage 1(risk of injury), 2 % (95%CI: 1.0-3.6%) stage 2(Acute kidney injury) and 12% (95%CI: 0.9-14.6%) stage 3 (Acute renal failure).
Bleeding of any type was noted in 19% (16.0-22.8%) of the entire cohort already at admission and 34% (30.0-38.3%) during entire follow up (including baseline). The single most frequent bleeding site was macroscopic hematuria, noted in 5% (95%CI 3.6%-7.5%) of the entire study population at admission and 25% (21.8%-29.4%) during follow-up (including baseline). Other single sites of bleeding (melena, vaginal, hematemesis, gingival, venous puncture point, hematochezia, conjunctival, epistaxis, purpura, hemoptysis) occurred in 1-≤9% of cases at any time during the acute illness. Renal replacement therapy was required by 8% (6.1%-10.9%), 405 cases had serum albumin measured at baseline and at follow-up. Hypoalbuminemia (<28g/L) was documented in 35% (30.5%-39.8%) at baseline and 42% (37.5%-47.1%) over entire follow-up. The cause was not clearly identified but the authors speculated that it could be due to renal or digestive loss, vascular leak, or inflammation. Oxygen saturation was measured in 504 patients and found to be <92% on admission in 7% (95%CI:4.8-9.2%) and during follow up in 15% (including baseline). Of note, among 315 patients tested for malaria, 179 (57%, 95%CI 51.3-62.2%)) were positive at baseline and treated with antimalarials. A noted limitation of the study was inability to measure biologic variables such as clotting parameters, inflammatory markers, platelet function or markers of hemolysis or myolysis which hampered understanding of the pathogenesis of some disease features. Among 17 patients who were pregnant at the time of admission, outcome was known for 14 including 6 spontaneous miscarriages, one intrauterine death, one maternofetal demise and six livebirths all of whom tested negative for Lassa fever.

Ilori et al[8] identified 423 confirmed Lassa Fever cases from multiple locations in Nigeria during the 2018 outbreak. They were able to get detailed information on 414 confirmed cases. The case fatality rate was 25.1% (95%CI: 21.1-29.4%) The highest case fatality rate (38%, 95%CI: 23.2-55.2%)) was noted in adults ≥61 years of age and the lowest (11%, 95%CI 4.2-22.9%)) in children aged ≤10 years. Fatal cases were more likely to have cough, bleeding and altered consciousness. They did not assess acute kidney injury.

Strampe et al[9] investigated the hypothesis that pathogenic host immune responses during Lassa Fever are hyperinflammatory. Out of 5657 suspect Nigerian Lassa cases, 554 were confirmed by RT-PCR. Leftover blood samples taken at admission to hospital were used to examine multiple biomarkers, comparing Lassa Fever patients who died to those who survived, as well as to healthy controls and febrile patients shown to be negative for Lassa Fever. Four factors were found to be correlated with fatal Lassa Fever outcome: in order of highest to lowest association – plasminogen activator-inhibitor 1 (PAI-1), soluble thrombomodulin (sTM), soluble TNF receptor 1, and viral load. High PAI-1 levels were noted to be associated with inactivation of the fibrinolytic system and impaired fibrin breakdown that could cause clot formation in the microvasculature. They cited similar abnormalities seen in fatal outcomes of Ebola and Dengue viral infections. The results were interpreted as suggesting that dysregulated coagulation and fibrinolysis along with endothelial damage play a key role in Lassa Fever pathogenesis and could provide a mechanistic explanation for the clinical findings of edema and bleeding in severe cases. They also concluded that classic DIC is not part of severe Lassa Fever given the fact that no decrease in fibrinogen was seen in the Lassa Fever patients (both fatal outcome and survivors) along with observations by other investigators that platelet counts are not severely decreased in severe Lassa Fever.

Owhin et al [12]conducted univariate analyses in a descriptive retrospective study to investigate the association between hypoalbuminemia with morbidity in Lassa Fever among a cohort of 83 confirmed cases admitted to a Nigerian dedicated treatment facility in Ondo. Hypoalbuminemia was documented in 66 (79.5%, 9%CI: 69.8-87.1%)) patients and was defined as marked if <25g/l, mild if ranging from 25-34.99 g/l, and normal if in the range of 35-45 g/l. was significantly associated with an WBC count of >11,000/mm^3 ($p < 0.0001$), acute kidney injury ($p=.009$), bleeding($p<0.0001$) and pregnancy miscarriage. ($p<0.0001$).

4.4 Acute Kidney Injury

Okokhere et al [17] conducted an observational cohort study involving 291 patients admitted to a specialist teaching hospital in Irrua, Nigeria. Acute kidney injury was documented in 81 (28%, 95%CI: 22.9-33.2) of cases and AKI was strongly associated with fatal outcome (CFR of 60%, 95%CI 49.6-70.7%)). Relative to patients without AKI, those with it were more likely to also have proteinuria, hematuria and a lower BUN to creatinine ratio suggesting intrinsic renal damage as opposed to pre-renal factors. They proposed several mechanisms including direct viral kidney damage, systemic immune response to viral infection or viral induced vascular pathology.

4.5 Liver Disease

Lassa Fever virus has been found in the liver in animal models [18, 31] and at postmortem in human cases[36]. Elevated liver function tests have been observed in Lassa Fever to a variable degree[4, 5] and elevated AST has been shown to correlate with fatal outcome. [7,] In a histopathology study of 21 fatal Lassa cases[21] a variable degree of hepatic necrosis was found (1-40% of hepatocytes) but there was no correlation found between the degree of necrosis and elevated liver transaminases or LDH. Garnett, in a review[22] of what has been learned about Lassa Fever over the last 50 years suggested that the presence of random foci of liver necrosis accompanied sometimes by inflammatory cells could suggest direct viral damage.

4.6 Bleeding and Fluid Shifts in Lassa Fever

Mucosal bleeding is cited in most reviews and descriptive studies of Lassa Fever patients[4,5,7,9,10,20-23, 31, 40,41] with frequency among hospitalized cases varying from 20-33%. The most frequent single site in larger studies was renal with microscopic or macroscopic hematuria.[4,7] Despite the prevalence of bleeding and observation that it is one of several factors associated with higher case fatality [5,8,10,20,30,31,34], the amount of bleeding is insufficient to produce shock.[21] Several authors note that disseminated intravascular coagulation (DIC) is not a feature of Lassa Fever[4,7,9,22,41] citing only moderate decreases in platelet counts[22], lack of decreased fibrinogen[9] , often normal bleeding times when measured[41] and lack of intravascular fibrin thrombi in pathologic studies.[41] Mechanisms proposed for the observed bleeding include endothelial damage along with dysregulated coagulation and fibrinolysis. [9,21, 23, 40, 41]

Facial and neck swelling along with polyserositis are reported in 2-12% of hospitalized Lassa Fever patients[4,7,13] and may be more frequent in children, with Samuels reporting a prevalence of 56% among 57 Lassa confirmed cases.[31] A particularly severe and generalized swelling, known as 'swollen baby syndrome' has been described in young infants and is associated with extremely high case fatality rates.[3] As with bleeding, the pathogenesis is not completely clear. Shieh et al [36] focused on tissue and cellular tropism of Lassa fever virus in 12 fatal human cases. They found virus in endothelial cells of all tissues examined including: nasal, oral and conjunctival mucosa; serous membranes and mesothelial cells; reproductive and endocrine tissues including the placenta. They suggested that

polyserositis, manifest as pleural, pericardial, or abdominal effusion, could be due to viral infection leading to reactive mesothelial cells.

4.7 Eye Complications

Kuthyar et al reviewed ophthalmic abnormalities associated with WHO high priority pathogens.[25] For Lassa Fever they noted that little was known but that conjunctivitis was most seen in acute disease and that cataract, chorioretinal scarring, retinal fibrosis and vitreous opacity had been observed in convalescence. The source of the data on convalescent patients was Li et al[26] who did a retrospective study of 31 Lassa Fever survivors who underwent ophthalmic examination at Kenema Hospital in Sierra Leone in January 2018. The median time from acute Lassa Fever to eye assessment was 10 yrs (interquartile range 6-12 years). Only 5 cases reported symptoms during acute disease consisting of pain, blurry vision, and red eyes (16.1%, 95%CI: 6.1-32.2%). Among the 31 Lassa fever survivors, at the examination in 2018, 42% (n=13) had blurry vision, 13% (n=4) itchy eyes, 6% (n=2) pain, redness or tearing and 3% (n=1) loss of near vision or floaters. Specific ophthalmic findings were: 18% cataract, 6% glaucoma, 5% chorioretinal scarring, 3% retinal fibrosis, 3% drusen (small yellow lipid accumulations under the retina), 2% pterygium, 2% preretinal hemorrhage, 2% lattice degeneration and 2% vitreous opacity. None had active or inactive anterior uveitis. Visual acuity was normal or mildly impaired in 85% of examined eyes and moderately impaired in 10%. Blindness was found in 5% due to a dense mature cataract in 1 and end-stage glaucoma in 2 patients. The long lag time from acute illness to ophthalmic exam made it impossible to conclude that the abnormal findings were due to Lassa Fever. They cited evidence on the overall frequency of visual problems in West African populations. The Tema Eye Survey done in Ghana involved 5603 participants where 17.1% had visual impairment and 1.2% were blind (Budenz DL et al. 2012; https://doi.org/10.1016/j.ophtha.2012.04.017; PMID 22677425). Refractive error was found in 60% of cases. Other causes of impairment included cataract in 53%, glaucoma in 14%, corneal opacification in 7.5% and retinal disease in 7%. They also cited a Sierra Leone retrospective study of a hospital population conducted from 1989-1992 (Ronday MJH et al, 1994; https://doi.org/10.1136/bjo.78.9.690; PMID 7947548). Senile cataract and uveitis were the main causes of blindness in that setting at that time.

4.8 Neurologic Complications

The review yielded nothing new in terms of neurologic complications. One article screened out after full text review (Ficenec et al, 2019 – see appendix 1) focused on sensorineural hearing loss which was already on the Lassa AESI list. The screened in articles included a series of 4 cases of aseptic meningitis in young adults aged 17-25 years.[27] There was a single case report of transverse myelitis that occurred 6 weeks after onset of Lassa Fever. [28] Ezeomah et al[29] discussed cerebellar ataxia as a sequela of Lassa Fever. The 2020 Lassa AESI list included myelitis and encephalitis, with cerebellar ataxia being one of the manifestations of the latter, so neither provided anything new.

4.9 Pediatric Complications

Two articles focused on pediatric cases of Lassa Fever. Adetunji et al[30] studied 58 children, aged 6 months to <15 years old, with proven Lassa Fever. The focus of their study was on acute kidney injury and mortality. They used the KDIGO criteria to classify AKI in 40 patients of whom 40% (95%CI: 25.8-55.6%) had some degree of injury: 5 minimal at stage 1, 4 stage 2 and 7 stage 3. As has been seen in adults, case fatality rates were higher in patients

with KDIGO stages 2 (75% (95%CI: 24-98%) mortality) and stage 3 (87.5%, 95%CI 47-99%) mortality), than those with stage 1 (0% (95%CI: 0-45%) mortality) or without AKI (4% mortality, 95%CI: 0-19%).
Samuels et al [31] did a 7-year retrospective study of children admitted to Kenema Hospital in Sierra Leone from 2012 – 2018. Of 292 suspect cases 57 were confirmed to have Lassa Fever. At the time of admission 37% were febrile, 86% had cough, 75% vomiting, 74% headache, 58% sore throat, 56% head or neck edema, 56% diarrhea, 48% unexplained bleeding, 35% confusion. On admission blood and urine samples were collected on all cases for routine laboratory testing including creatinine and liver function tests. Risk factors for fatal outcome were similar to what has been reported in adult populations: elevated creatinine or ALT, unexplained bleeding, confusion and hypoxia.

4.10 Pregnancy Outcomes

The literature search only identified a single article – a case report of a pregnancy with good maternal and fetal outcome after Lassa fever.[32] Hand search of citations in this and other included articles identified 3 additional articles: one a systematic review and meta-analysis of Lassa fever in pregnancy[33]; a Nigerian retrospective cohort study of Lassa Fever in pregnancy[34]; and another case report of positive maternal outcome but fetal death following Lassa Fever acquired in the 3rd trimester.[35] The 2020 Lassa AESI list included spontaneous abortion, stillbirth, maternal death and neonatal death. Nothing new was identified in the systematic review or retrospective study.

4.11 Pathogenesis

The pathogenesis of Lassa Fever is incompletely understood. Most infections, up to 80%, are asymptomatic but severe and fatal disease does occur. In 2010, Flatz et al[40] noted that "It is generally agreed upon that the level of tissue damage observed at autopsy cannot by itself account for the severe nature of Lassa Fever". They suggested that the host immune response in Viral Hemorrhagic Fevers may have a dual nature – both protective but also potentially contributing to disease. They developed a humanized mouse model of Lassa Fever to study this further. Their data supported a dual role for T-cells during infection: essential for rapid viral clearance, but if that failed, contributing to more severe disease. Unlike Dengue where more severe disease follows a prior infection suggesting a pathogenic role for memory T-cells, the mouse model work suggested disease-enhancement as part of primary infection.

In 2019, this concept was underscored by Perdomo-Celis *et al*. who reviewed T-cell immune responses in Viral Hemorrhagic Fever illnesses.[38] Adequate T-cell priming, and efficient T-cell activation resulted in efficient neutralizing antibody production and immunologic memory and correlated with disease recovery. Two markedly different patterns both correlate with severe disease and death: i) low levels of T-cell priming plus poor T-cell activation are associated with low production of neutralizing antibody and poor immunologic memory resulting in unchecked viral replication; ii) massive T-cell priming plus hyperactivation of T-cells results in multiple organ damage, chronic inflammation and post-acute disease complications.

In a longitudinal immunologic study of a single case of Lassa Fever, McElroy *et al.* characterized the kinetics of innate and cellular immune responses. Robust t-cell responses were noted, and viremia was cleared by 20 days after symptom onset. However, the activated CD8 T-cell population had a biphasic pattern with an early peak matching the clearance of viremia and a second peak, more than a month after symptom onset, that coincided with new onset of chills, lymphadenopathy and epididymitis. Samples of semen were positive for Lassa virus on

day 20 and for Lassa RT-PCR on days 15, 20 and 48 suggesting possible viral persistence in the male genital tract. These findings, while in a single case, raise concern for immune-mediated chronic complications following Lassa Fever. This had also been raised as a possible mechanism for sensorineural hearing loss in Lassa Fever survivors.

In 2020, Port et al characterized T-cell response patterns among 214 PCR confirmed Lassa Fever patients comparing mild, severe and fatal cases.[37] They found that fatal Lassa Fever was marked by poor Lassa-specific effector T-cell responses indicating an inability to control viral replication. This is consistent with observations that poor outcome of infection is associated with high levels of viremia.[5,9] On the other hand fatal cases had evidence of activation of nonspecific T cells (such as those reacting to EBV) with homing capacity to inflamed tissues, especially the respiratory mucosa. Cases with severe, but nonfatal infection, had a high presence of CD8 T-cell clones with homing capability to inflamed tissues in gut mucosa and skin. Mild cases were observed to have low levels of viremia throughout the acute disease and had lower levels of tissue specific homing factors in CD8 effector T-cells relative to those with severe disease.

4.12 Severe Lassa Fever Disease

This review shows there was no harmonized case definition of severe Lassa Fever disease. However, several studies cited above did multivariate analysis of hospitalized patients with confirmed Lassa Fever in order to identify independent risk factors for fatal infection in adults[7, 9, 10, 17, 20] and children [30, 31]. Table 1 summarizes the findings.

TABLE 1. Risk Factors for fatal outcome of Lassa Fever

Risk Factor Category	Odds Ratio (95% Confidence Interval) for fatal Lassa Fever if Risk Factor present versus absent
Age	• Age ≥40 years: 6.2 (1.19-32.53)[10] • Age ≥45 years: 16.30 (5.31-50.30)[7] • Age ≥50 years; incremental increase in mortality with each 10 years of age: 1.4 (1.2-1.6)[17]
Delay in seeking healthcare	• >7 days after symptom onset: 6.2 (1.40-27.60)[20] • ≥24 hours after onset of bleeding: 6.4 (1.40-29.44)[20]
Acute kidney injury	• KDIGO stage 2 or 3: 7.52 (2.66-21.20)[7] • KDIGO stage 1, 2 or 3: 29.3 (3.2-275.7) on admission; pediatric study[30] • Elevated creatinine: 1.34 (1.07-1.74)[17] • Elevated creatininie: 31.6 (6.47-20,143.55); pediatric study[31]
Bleeding	• 2.46 (1.69-3.97)[17] • 10.2 (3.11-33.81) [10] • Pediatric study: 3.58 (1.08-11.86)[31]
Liver dysfunction	• AST more than 3 times upper limit of normal: 4.96 (1.69-14.60) [7] • Elevated ALT: 361 (6.47 – 20,143.55); pediatric study[31]
Neurologic dysfunction	• Severe neurologic manifestations: 2.75 (1.37-5.74)[17] • Confusion: 5.37 (1.34-21.48); pediatric study[31]
Electrolyte abnormalities	• Elevated serum sodium; 14.90 (1.54-127.23); pediatric study[31] • Elevated serum potassium: 3.64 (2.22-6.45)[17] • Elevated serum potassium; 21.0 (1.50-293.25); pediatric study[31]

Composite severity score	• NEWS2 score ≥7: 4.79 (1.75-13.10)[7] (score based on respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, temperature
High viral load	• Lassa Fever RT-PCT-Ct <30: 4.65 (1.50-14.50)[7] • Viral load; presented as area under the curve (0.837)[9]
Elevated Plasminogen Activator-1 (PAI-1)	• Presented as area under the curve (0.878)[9]
Elevated soluble thrombomodulin	• Presented as area under the curve (0.875)[9]
No ribavirin therapy	• 4.4 (1.12-17.57)[10]

4.13 Differential Diagnostic Considerations

Three articles did not contribute to considerations regarding the AESI list but did provide recommendations germane to West African clinical vaccine trials, where occurrence of Lassa Fever would be a study outcome as well as possible AESI post vaccination.

Schoepp et al[42] studied febrile patients admitted to Kenema Hospital in Sierra Leone from Oct 2006 to Oct 2008 and suspected to have Lassa Fever. The case definition for suspect Lassa Fever included Major criteria (known exposure to suspected Lassa fever, abnormal bleeding, edema of the neck or face, conjunctivitis or subconjunctival hemorrhage, spontaneous abortion, petechial or hemorrhagic rash, onset of tinnitus or altered hearing, persistent hypotension or elevated liver transaminases) and Minor criteria (general myalgia or arthralgia, headache, sore throat, vomiting, abdominal pain/tenderness, retrosternal pain, cough, diarrhea, profuse weakness, proteinuria or <4000 leukocytes/uL). The required number of Major or Minor criteria was not specified. Testing for suspected Lassa Fever was done if there was fever >38^{o} C and nonresponse to appropriate antimalarial and antimicrobial drug therapy within 72 hours. In addition to testing for Lassa Fever they routinely tested for the viruses that cause: dengue, West Nile Fever, yellow fever, Rift Valley fever, chikungunya, Ebola, Marburg and Crimean-Congo hemorrhagic fever. Given limited sample size they couldn't test all samples against all pathogens. Overall, among 253 patients tested, 25% of Lassa negative patients had IgM to dengue, West Nile, yellow fever, Rift Valley fever, chikungunya, Ebola or Marburg viruses. Specifically, they found Ebola in 8.6%, Dengue in 4.3%, chikungunya in 4%, Marburg in 3.6%, West Nile virus in 2.8%, yellow fever in 2.5%, Rift Valley fever in 2%. These results suggest that febrile illnesses among Lassa vaccine trial subjects need to be investigated further if found negative for Lassa Fever.

Dongo et al[43] reported a series of 7 cases, aged 17 months to 40 years, seen between 2009 and 2012 in Nigeria who presented as acute abdomen and underwent emergency surgery. Preoperative diagnoses were four appendicitis and one each of: perforated typhoid ileitis, ruptured ectopic pregnancy and intussusception. None of these were confirmed at surgery and all were found to have Lassa Fever postoperatively. Bleeding was noted during surgery or post-operatively in most cases. In two suspect cases of appendicitis, the appendix was noted to be slightly inflamed at surgery and in one case post-op histopathology of the appendix showed tissue edema with polymorphonuclear infiltration of the muscularis propria.

Finally Olayinka et al[44] convened a delphi 'consensus' group of clinicians and researchers to develop a standardized Phase III clinical trial framework for assessing therapeutic interventions for Lassa Fever. While the focus was on therapeutic as opposed to preventive trials, the framework is relevant where Lassa Fever is a clinical trial outcome

in particular severe disease, defined in terms of presence of AKI, ARDS, shock or encephalopathy. They proposed collection of core data variables including date of symptom onset, date of contact with confirmed case, presence of frank bleeding, pregnancy complications, seizure, temperature, pulse, blood pressure, creatinine, urine output, PaO2, FiO2, SpO2, BUN, AST, ALT, potassium, hemoglobin and point of care ultrasound for pregnant patients.

4.14 Review of Slide sets from Oct 25-26, 2022, Abuja meeting on "Accelerating the licensure of Lassa vaccines: Generating robust evidence on vaccine efficacy and safety"

Similar to evidence presented above, acute kidney injury especially with KDIGO stage 2 or higher was recognized as an important complication of Lassa Fever. Dr. Okogbenin, Medical Director of the Nigerian Irrua Specialist Teaching Hospital, also mentioned Acute Respiratory Distress Syndrome (ARDS) as a complication. Several of the clinical studies cited above noted cough, respiratory distress and low oxygen saturation among the clinical features of Lassa Fever but no studies were found that specifically mentioned ARDS. Nevertheless, this could also be a manifestation of severe Lassa Fever disease. Other indicators of severe Lassa Fever disease were noted to be severe bleeding, shock, encephalopathy and elevated liver aminotransferases. In Dr. Krause's presentation on regulatory considerations the incomplete understanding of Lassa Fever pathogenesis was noted along with the caution that since some aspects of disease may be immune-mediated, there is a theoretical possibility that they could be caused by vaccine.

5. Discussion & Recommendations

Based on the evidence presented above Acute Kidney Injury should be added to the Lassa Fever AESI list. There was some circumstantial evidence that it could result from direct viral mediated damage. However, it is clearly a marker of severe infection and strongly associated with fatal outcome seen solely in the context of cases admitted to hospital.

Bleeding, facial swelling and polyserositis were included on the 2020 Lassa Fever AESI list, however the pathogenesis of these was unclear making it difficult to determine what a case definition would focus on. Based on this review disseminated intravascular coagulation is not an explanation for the bleeding. In a 2013 review of pathogenesis of Viral Hemorrhagic Fevers (VHF), Paessler and Walker[41] listed several possible mechanisms of hemorrhage and plasma leakage, including: 1. endothelial injury; 2. activation of mononuclear phagocytes: 3. secretion of pathologic concentrations of cytokines and other mediators; 4. platelet aggregation and consumption; 5. activation of the coagulation cascade; 6. insufficiency of coagulation factors due to severe hepatic damage. It was also pointed out that the specific mechanisms could vary from virus to virus as well as be determined by differential viral cell and organ tropism and pathogenic versus protective host responses. Referring specifically to Lassa Fever, they noted that hemorrhage is less prominent than with other VHFs and that tissue damage and immune cell infiltrates were minimal in fatal cases. The studies of T-cell responses and biomarkers cited above seem to be consistent with the first three mechanisms for hemorrhage and plasma leakage – i.e., endothelial injury, activation of mononuclear phagocytic system and cytokine secretion. Further they raise the potential for immune-mediated enhanced Lassa disease, possibly by a bystander mechanism, involving non-Lassa specific T-cells. The Brighton case definition for Vaccine Associated Enhanced Disease includes several features of severe Lassa Fever Disease: ARDS, multiorgan failure (as possibly indicated by AKI, shock, bleeding, liver dysfunction and failure and encephalopathy). NEWS2, which is also correlated with severe Lassa Disease, was one of the recommended disease severity scoring systems. While any Lassa Fever infection, regardless of severity, will likely

be a primary endpoint for vaccine trials, severe infection has been proposed as a secondary endpoint. It seems reasonable, given the evidence above to include severe infection post-vaccine as an AESI and for this reason it has been added to the list.

This landscape analysis has focused on Lassa Fever clinical course and complications as a source for potential AESI. Specific issues related to candidate vaccine platforms is beyond the scope, however, recent SPEAC recommendations regarding the VSV vectored vaccine candidates have been incorporated. Specifically, single organ cutaneous vasculitis has been added as a potential complication along with aseptic arthritis. Additionally since ChAdOx1 vectored vaccine is one of the Lassa Fever vaccine candidates, vaccine induced thrombosis and thrombocytopenia (VITT) has been added.

Table 2 incorporates the newly identified AESI (highlighted in yellow) with those that were included on the original, 2020 AESI list. AKI has been added as a unique entity. No Brighton case definition exists for this, but as with COVID-19 which also included AKI, the recommended definition is the consensus Kidney Disease Improving Global Outcomes (KDIGO) guidelines which have been applied in West African Lassa Fever studies cited above. A review by Thomas et al[45] compares KDIGO with prior guidelines and also describes the modified pRIFLE criteria for children. The KDIGO criteria are shown below (note: specific information regarding how Stage 1-3 are defined can be found at www.kdigo.org):

- Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; OR
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days OR
- Urine volume ≤0.5 ml/ kg/ hour for 6 hours

The other addition is severe Lassa Fever disease, which as noted above, may arise as a result of disease-enhancing T-cell immune responses. As summarized in Table 1 above, markers of severe Lassa Fever include: acute kidney injury, in particular a KDIGO stage 2 or 3; bleeding; elevated liver transaminases (>3 times the usual upper normal limit); s neurologic dysfunction; a NEWS2 score of ≥7 or high viral load. Aside from AKI, it is difficult to envision any of these markers of severe Lassa infection occurring in any context other than vaccine failure to prevent infection. As such monitoring for severe infection after immunization should be done as a supplement to primary outcome measures of any Lassa Fever infection. Should infection be severe enough to warrant hospitalization, the listed clinical and laboratory markers of severe infection should be investigated and documented (with the possible exception of viral load) upon admission and then followed every few days until discharge of note, existing clinical severity of illness scores may be utilized to identify and classify cases of severe or enhanced disease occurring after vaccination. (Several scores, including NEWS2 were included in the supplementary data for the Brighton case definition of Vaccine Associated Enhanced Disease at this link https://www.sciencedirect.com/science/article/pii/S0264410X21000943?via%3Dihub#s0115

SPEAC recommends that the listed AESI be adopted by CEPI and the Lassa Fever vaccine developers. SPEAC recommends that the developers be prepared to take a uniform

approach to the identification, assessment, investigation, analysis and reporting of any AESI should it occur during a clinical trial.

As a final note, the updated AESI list no longer includes any AESI related to pregnancy, fetal or neonatal outcomes specifically. These are addressed as a separate deliverable from SPEAC Work Package 5 which focuses on special populations.

TABLE 2. Lassa Fever Updated AESI List based on all possible mechanisms related to vaccine, vaccine platform or Lassa Fever disease immunopathogenesis. Abbreviations: MVA - modified vaccinia; VSV – vesiculostomatitis virus; LA – live attenuated; TBD – to be determined; ARDS – acute respiratory disease syndrome; AKI – acute kidney injury; KDIGO – Kidney Disease – Improving Global Outcome; National Early Warning Score 2 - ; LFT – liver function test

Body system	AESI	Rationale for Listing Potential AESI			Brighton CD	Brighton CD Companion Guide
		All Vaccines	Vaccine Platform	Lassa Fever Disease / Immunity		
Cardiovascular / Endovascular	Myocarditis		MVA		☑	☑
	Pericarditis			☑	☑	☑
	Polyserositis / Face & Neck Swelling			☑	TBD	TBD
Hematologic	Hemorrhagic disease (bleeding from mucosa / skin)			☑	TBD	TBD
	Vaccine-associated Immune Thrombotic Thrombocytopenia (VITT)		Ad26 and ChAdOx1 vectors		Oct 2023	Oct 2023
	Thrombocytopenia	☑			☑	☑
Immunologic	Anaphylaxis	☑			☑	☑
	Single Organ Cutaneous Vasculitis		r-VSV		☑	Dec 2023
	Severe Lassa Fever infection (ARDS; AKI with KDIGO ≥2; NEWS2≥7; LFTs≥3X upper limit of normal; shock; multiorgan failure; death)		\	☑	☑ [2]	☑ [2]
Musculoskeletal	Aseptic arthritis		r-VSV		☑	Nov 2023
Neurologic	Aseptic meningitis		LA vaccine	☑	☑	☑
	Encephalitis		LA vaccine	☑	☑	☑
	Myelitis		LA vaccine	☑	☑	☑
	Generalized convulsion	☑		☑	☑	☑
	Guillain-Barré Syndrome		Some[1]		☑	☑
	Sensorineural hearing loss			☑	☑	TBD
Renal	Acute Kidney Injury			☑		
Respiratory	ARDS			☑	☑	☑
Skin	Alopecia			☑	TBD	TBD
~~Pregnancy / Perinatal Outcomes~~	~~Spontaneous abortion~~			~~☑—~~	~~☑—~~	~~☑—~~
	~~Stillbirth~~			~~☑—~~	~~☑—~~	~~Fall 2023~~
	~~Maternal death~~			~~☑—~~	~~☑—~~	~~TBD~~
	~~Neonatal death~~			~~☑—~~	~~☑—~~	~~TBD~~

[1]Influenza H1N1 Pandemic vaccine; some seasonal influenza vaccines; ChAdOx-1 S and Ad26 COVID-19 vaccines

[2] The checkmark refers to the Case definition and Companion Guide for Vaccine-Associated Enhance Disease. In this case the AESI is severe Lassa Fever disease, but as pointed out in the recommendations, the supplemental

data to the case definition and the Companion Guide provide the disease severity scores as recommended by the Working Group, and these could be used to characterize severe Lassa Fever.

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ANNEXES

Annex 1

Lassa Fever Bibliography by Topic

Lassa Fever Citations from Original and Updated Landscape Review Organized by Subject Matter.
References are listed from most recent to oldest publications.
Regular font are new references acquired as part of the updated literature search and landscape analysis.
Gray font are references from the 2020 Landscape review.

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Annex 3

Comprehensive document history

NAME	DATE	VERSION	DESCRIPTION
Barbara Law, Wan-Ting Huang, Matthew Dudley	17/07/19	0.10 LF	Landscape analysis for Lassa Fever completed and presented to EB with proposed AESI list.
Barbara Law, Matthew Dudley	14/08/19	0.11LF	Enhanced Disease (ED) following immunization literature review with PowerPoint slide summary presented to EB and ED added to AESI list.
Robert Chen, Marc Gurwith	10/09/19	0.10 LF	First presentation draft LF AESI Table at WHO LF Meeting, Dakar, Senegal. Based on EB/CEPI discussions leading up to meeting, ED removed from the list for lack of strong evidence.
Steve Black, Inovio, Themis	15/11/19	0.12 LF	LF AESI list shared with CEPI and developers. Based on feedback added an * to neuropsychiatric complications to indicate to be AESI must be: new onset and severe enough to interfere with daily activity.
Daniel Bausch	25/11/19	1.0 LF	Teleconference with clinical LF expert who suggested two changes: 1) remove neuropsychiatric complications as not clear if due to LF or social circumstances for survivors; 2) add alopecia.
Barbara Law, Steve Black	09/11/19	1.1LF	AESI lists modified to incorporate a justification for the inclusion of each AESI in the table as suggested by Steve Black during EB discussion
Miriam Sturkenboom, Barbara Law	13/01/2020	1.0 D2.2	Creation & review of detailed description of Landscape Analysis for methods and results for Lassa Fever.
Miriam Sturkenboom, Barbara Law	06/02/2020	2.0 D2.2	Amended version submitted to EB for review and discussion.
Miriam Sturkenboom, Barbara Law, EB	17/02/2020	3.1 D2.2	Final version of the deliverable discussed, revised and approved for forwarding to TFGH and CEPI. Decision to add this appendix as a document history for this and future landscape outputs.
Barbara Law Emily Martens	22/12/2022	SPEAC 2.0 D2.5.1_LF	Landscape analysis update: literature search strategy created (BL) and run (EM); results screened for inclusion/exclusion (BL)
Barbara Law	31/07/2023	D2.5.1_LF V0.1	Draft Lassa Fever updated landscape analysis and AESI list