

Lassa fever clinical course and setting a standard of care for future randomized trials: A protocol for a cohort study of Lassa-infected patients in Nigeria (LASCOPE)

Alexandre Duvignaud^{a,b,c,1,*}, Marie Jaspard^{a,c,d,1}, Ijeoma Chukwudumebi Etafo^{e,1}, Béatrice Serra^{a,c,d}, Chukwuyem Abejegah^e, Delphine Gabillard^{a,c}, Mahamadou Doutchi^{d,f}, Josephine Funmilola Alabi^e, Moses Adeniyi Adedokun^e, Adewale Oladayo Akinpelu^e, Oyebimpe Ope Oyegunle^e, Johnson Etafo^g, Ayoleyi Omowunmi Dede^g, Macdonald Nonso Onyechi^g, Moronke Uzuajemeh Ireneh^g, Olufunke Gbenga-Ayeni^g, Kehinde Gbemisola Fadiminiyi^g, Patience Iziegbe Ehigbor^g, Eric Ouattara^{a,c}, Claire Levy-Marchal^d, Sophie Karcher^{a,c}, Larissa N'guessan-Koffi^{a,c}, Irmine Ahyi^{a,c}, Elvis Amani^{a,c}, Mamoudou Diabaté^{a,c}, Bertine Siloué^{a,c}, Justine Schaeffer^d, Augustin Augier^d, Ephraim Ogbaini-Emovon^h, Alex Paddy Salamⁱ, Peter Horbyⁱ, Liasu Adeagbo Ahmed^j, Stephan Günther^k, Akinola Nelson Adedosu^g, Xavier Anglaret^{a,c,2}, Oladele Oluwafemi Ayodeji^{e,2}, Denis Malvy^{a,b,c,2}

^a Inserm U1219, University of Bordeaux, 146 Rue Léo Saignat, 33076, Bordeaux, France

^b Department of Infectious Diseases and Tropical Medicine, Division of Tropical Medicine and Clinical International Health, CHU de Bordeaux, Hôpital Pellegrin, Place Amélie Raba Léon, 33076, Bordeaux, France

^c Programme PAC-CI/ANRS Research Site, CHU de Treichville, 18 BP 1954 Abidjan 18, Abidjan, Côte d'Ivoire

^d The Alliance for International Medical Action, Route de l'Aéroport, Rue NG 96 BP: 15530, Dakar, Senegal

^e Lassa Fever Response Team, Infection Control and Research Centre, Federal Medical Centre Owo, Michael Adekun Ajasin Road, PMB 1053, Owo, Ondo State, Nigeria

^f Department of Infectious Diseases, Centre Hospitalier National de Zinder, Zinder, Niger

^g Viral Hemorrhagic Fever Laboratory, Infection Control and Research Centre, Federal Medical Centre Owo, Michael Adekun Ajasin Road, PMB 1053, Owo, Ondo State, Nigeria

^h Institute of Lassa Fever Research and Control, Irrua Specialist Teaching Hospital, KM 87 Benin Auch Rd, Irrua, Edo State, Nigeria

ⁱ Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Old Road Campus, Roosevelt Drive, Headington, Oxford, OX3 7FZ, United Kingdom

^j Department of Family Medicine, Owo Federal Medical Centre, Michael Adekun Ajasin Road, PMB, 1053, Owo, Ondo State, Nigeria

^k Department of Virology, Bernhard Nocht Institute for Tropical Medicine, Bernhard-Nocht-Straße 74, 20359, Hamburg, Germany

* Corresponding author. Department of Infectious Diseases and Tropical Medicine, Division of Tropical Medicine and Clinical International Health, Hôpital Pellegrin, CHU de Bordeaux, Place Amélie Raba Léon, F-33076, Bordeaux, France.

E-mail addresses: alexandre.duvignaud@chu-bordeaux.fr (A. Duvignaud), marie.jaspard@coral.alima.ngo (M. Jaspard), eziunorijeoma2014@yahoo.com (I.C. Etafo), beatrice.serra33@gmail.com (B. Serra), cabejegah2007@gmail.com (C. Abejegah), delphine.gabillard@u-bordeaux.fr (D. Gabillard), m.doutchi@yahoo.fr (M. Doutchi), adefunmikola72@gmail.com (J.F. Alabi), maadedokunmoses@yahoo.com (M.A. Adedokun), couragewith@yahoo.com (A.O. Akinpelu), bimpad2003@yahoo.com (O.O. Oyegunle), johnsonetafo@gmail.com (J. Etafo), joyousd2019@gmail.com (A.O. Dede), macdonaldonyechi@gmail.com (M.N. Onyechi), emeraldmay337@gmail.com (M.U. Ireneh), ibitoks@yahoo.com (O. Gbenga-Ayeni), kehinde.fadiminiyi@gmail.com (K.G. Fadiminiyi), pretty_patizzy@yahoo.com (P.I. Ehigbor), eric.ouattara@chu-bordeaux.fr (E. Ouattara), claire.levy-marchal@coral.alima.ngo (C. Levy-Marchal), sophie.karcher@u-bordeaux.fr (S. Karcher), larissa.nguessan@pacci.ci (L. N'guessan-Koffi), irmine.ahyi@pacci.ci (I. Ahyi), elvis.amani@pacci.ci (E. Amani), mamoudou.diabate@pacci.ci (M. Diabaté), siloue.bertine@pacci.ci (B. Siloué), schaeffer.justine.91@gmail.com (J. Schaeffer), aug@alima.ngo (A. Augier), epogbaini@yahoo.com (E. Ogbaini-Emovon), alex.salam@ndm.ox.ac.uk (A.P. Salam), peter.horby@ndm.ox.ac.uk (P. Horby), akahmed2@yahoo.co.uk (L.A. Ahmed), guenther@bni.uni-hamburg.de (S. Günther), nelsonadedosu@gmail.com (A.N. Adedosu), Xavier.Anglaret@u-bordeaux.fr (X. Anglaret), femiayodeji@yahoo.com (O.O. Ayodeji), denis.malvy@chu-bordeaux.fr (D. Malvy).

¹ these three authors contributed equally to this work.

² these three authors contributed equally to this work.

<https://doi.org/10.1016/j.tmaid.2020.101557>

Received 6 August 2019; Received in revised form 28 December 2019; Accepted 16 January 2020

1477-8939/ © 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ARTICLE INFO

Keywords:

Lassa fever
Lassa virus
Viral hemorrhagic fever
Nigeria
Pregnancy
Acute kidney injury

ABSTRACT

Background: Lassa Fever (LF), is a severe viral disease prevalent in Western Africa. It is classified as a priority disease by the World Health Organization (WHO). Ribavirin is the recommended therapy despite weak evidence of its efficacy. Promising therapeutic agents are becoming available for evaluation in human. Before launching therapeutic trials, we need data on the evolution of the disease under the best possible conditions of care.

Methods: We have initiated a prospective study in Nigeria to better understand the clinical course and prognostic factors of LF while implementing high quality standardized care. Inclusion criteria are: suspected or confirmed LF and informed consent. Participants are followed 60 days from admission and receive free of charge standardized supportive care and biological monitoring, as well as intravenous ribavirin for those with confirmed LF. Data are collected using standardized case report forms (CRF). Primary and secondary outcomes are fatality and severe morbidity, with special focus on acute kidney dysfunction and pregnancy complications. Factors associated with outcomes will be investigated.

Results: The cohort is planned for 3 years. Inclusions started in April 2018 at the Federal Medical Center Owo in Ondo State. A second site will open in Nigeria in 2020 and discussions are underway to open a site in Benin. 150 to 200 new participants are expected per year.

Conclusions: This cohort will: provide evidence to standardize LF case management; provide key inputs to design future clinical trials of novel therapeutics; and establish clinical research teams capable of conducting such trials in LF-endemic areas.

Study registration: The LASCOPE study was registered on [ClinicalTrial.gov](https://clinicaltrials.gov/ct2/show/study/NCT03655561) (NCT03655561).

1. Introduction

The first human cases of Lassa fever (LF) were described in 1970 in the North-East of Nigeria [1]. Lassa virus was first isolated in 1974 [2] from its zoonotic reservoir, the multimammate rat *Mastomys natalensis*. It can be transmitted to humans through direct or indirect exposure to rodent excreta, including droplets, dust and contaminated food [3]. Human to human transmission is also possible, although less frequent [4–6], and is most common in a nosocomial context [7]. Clinical presentation of Lassa fever is nonspecific, especially at the early stages, rendering clinical diagnosis difficult. In more severe cases, the clinical course can be complicated by hemorrhage, neurologic symptoms, multi-organ failure, and death [3]. More than five decades after its discovery, despite an estimated burden of 300,000 cases and 5000 to 10,000 deaths annually [8,9] throughout more than 14 West African countries [10] and more than thirty cases exported to non-endemic countries [11], including very recently in two Dutch healthworkers returning from Sierra Leone [12], there are still many knowledge gaps regarding the pathophysiology and appropriate clinical management of this disease [13]. Most data on LF natural history are retrospective [8,14,15]. Ribavirin has been recommended as the specific therapeutic option for forty years despite weak evidence of its efficacy [14,16,17] and concerns about its possible detrimental effect when administered to mild LF cases [18]. In addition, its use poses many problems: its cost is high for endemic countries, the optimal dose is not known [19], its handling by health workers wearing personal protective equipment is cumbersome and takes a long time.

For all these reasons, LF has been included in the WHO R&D Blueprint list of high priority diseases [20].

Several new antivirals [21,22] and immunotherapeutics [23] have been identified as potential therapeutic candidates in future drug trials for LF. However, prior to starting any drug trial it is essential to standardize severity classification systems, drug dosing and duration, study outcome measures and concomitant supportive care strategies. This process would ensure standardization of care in the best possible way across clinical sites that will take part in future drug trials.

In 2018, the annual outbreak of LF in Nigeria was characterized by an unprecedented caseload, with secondary cases and deaths among health workers and caregivers [24]. This prompted our consortium to initiate a prospective study entitled “Lassa fever clinical course and prognostic factors in an epidemic context” (LASCOPE).

2. Material and methods

2.1. Design

LASCOPE is a prospective cohort study.

2.2. Objectives

The primary objective is to describe the frequency of fatality and the factors associated with a fatal outcome in hospitalized patients with laboratory-confirmed LF.

The secondary objectives are to describe:

- The clinical and biological course of LF with a particular focus on the frequency, prognosis, clinical and biological patterns of acute kidney dysfunction;
- Pregnancy outcomes;
- Length of hospital stay;
- Semi-quantitative viral load evolution;
- Time to negative Lassa RT-PCR in blood;
- Time to normalization of key clinical/biological parameters;

Operational objectives are to:

- Help harmonizing case management guidelines;
- Set-up a platform for clinical research on LF and to build the capacity to conduct future randomized controlled trials (RCT);
- To inform the design of future RCTs by producing core preliminary clinical data.

2.3. Calendar

The study inclusion period is at least three years (April 2018–April 2021). Patients will be followed 60 days from admission.

2.4. Setting

The study is conducted in tertiary reference hospitals with diagnostic and treatment capacities for patients with LF. It started at the Federal Medical Centre Owo (FMCO), Ondo State, South-Western Nigeria (Fig. 1). A second clinical site will be selected in 2019 by the

Abbreviations

AKF	acute kidney failure
AKI	acute kidney injury
ALERRT	African coalItion for Epidemic Research, Response and Training
ALIMA	Alliance for International Medical Action
BSL	Biosafety Level
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
Ct	cycle threshold
DFiD	Department for International Development
EDCTP	European and Developing Countries Clinical Trials Partnership
eGFR	estimated Glomerular Filtration Rate
FMCO	Federal Medical Centre Owo
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for

Human Use

INSERM	Institut National de la Santé et de le Recherche Médicale
IRD	Institut de Recherche pour le Développement
ISTH	Irrua Specialist Teaching Hospital
KDIGO	Kidney Disease – Improving Global Outcome
LASCOPE	Lassa fever clinical course and prognostic factors in an epidemic context in Nigeria
LASV	Lassa virus
LF	Lassa fever
NCDC	Nigeria Center for Disease Control
NGO	Non-Governmental Organization
NHREC	Nigeria National Health Research Ethics Committee
R&D	Research and Development
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Test
REACTing	REsearch and ACTion targeting emerging infectious diseases
RT-PCR	reverse transcriptase and polymerase chain reaction
WHO	World Health Organization

Nigeria Center for Disease Control (NCDC), with an expected opening in early 2020, and discussions are underway to open a site in Benin.

2.5. Population

All patients admitted for suspected or already RT-PCR confirmed LF in one of the participating care centers are eligible.

There is no age restriction. Pregnant women and newborns are eligible.

Patients are included in the cohort if they meet the following criteria: (i) Suspected or confirmed LF; (ii) Signed informed consent.

Suspected and confirmed LF definitions are in line with the November 2018 NCDC's guidelines [25]:

Suspected LF: History of fever (body temperature measured above 38 °C more than 24 hours without the use of anti-pyretics) beginning

3–21 days prior to presentation, with one or more of the following conditions: abdominal pain, vomiting, diarrhea, sore throat, myalgia, generalized body weakness, abnormal bleeding (mucosal bleeding, punctures sites bleeding, uncontrolled intra operational and/or immediate post operational bleeding).

OR.

Neonates (with or without signs and symptoms) from women infected by Lassa virus.

Any of the following scenarios should lead to a high index of suspicion:

- Absence of response to standard anti-malaria treatment and treatment for other common infectious causes of fever within 48–72 h.
- History of recent contact with a probable or confirmed case of LF within 21 days of onset of fever.

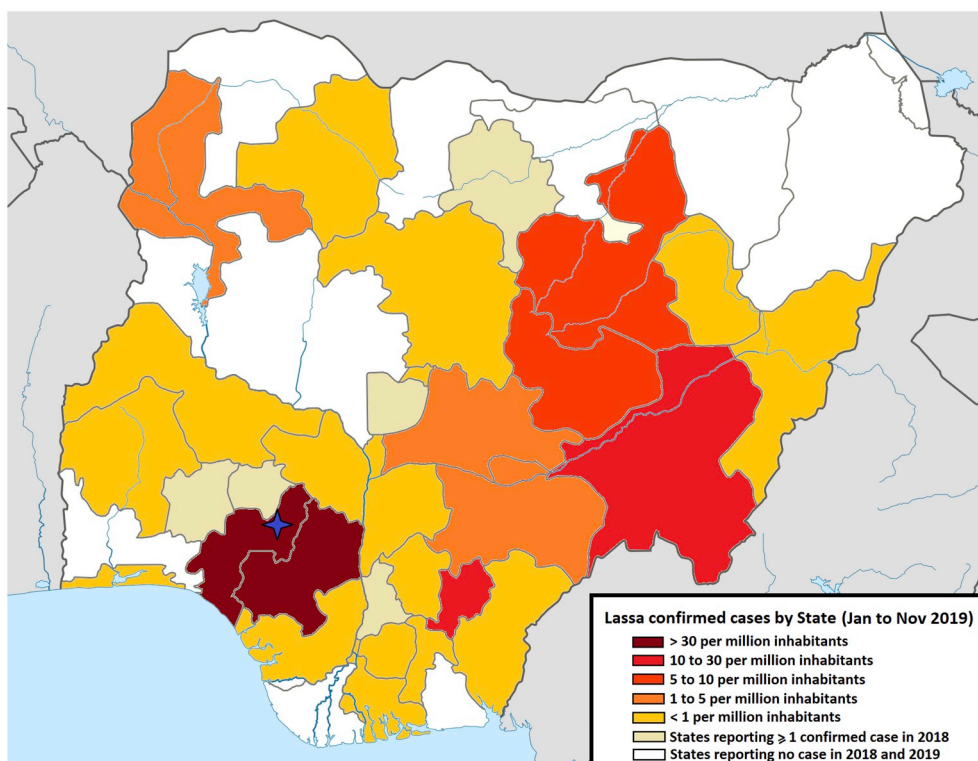


Fig. 1. Lassa fever confirmed cases reported in Nigeria per million of inhabitants for each State between January and November 2019 (colored scale) as well as the location of the Federal Medical Centre Owo, Ondo State (blue star). Map background: adapted from Uwe Dederich at German Wikipedia under Creative Commons Attribution Unported 3.0 license (https://commons.wikimedia.org/wiki/File:Nigeria_location_map.svg). Epidemiological data source: Nigeria Centre for Disease Control situation reports, an update of Lassa fever outbreak in Nigeria (<https://www.ncdc.gov/diseases/sitreps/?cat=5&name=An%20update%20of%20Lassa%20fever%20outbreak%20in%20Nigeria>). Demographic data source: National Bureau of Statistics, Demographic Statistics Bulletin 2017 (<https://nigerianstat.gov.ng/download/490>). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

- c. History of recent travel to high risk/burden area of LF within 21 days of onset of fever.
- d. Contact with body fluids or tissues of a dead patient with a febrile illness, symptoms and signs highly suggestive of LF leading to death within 21 days of onset of fever.

Confirmed LF: any criteria for suspected LF AND **positive** Lassa RT-PCR from any body fluid.

Participants enrolled as suspected cases and subsequently found to have a negative Lassa RT-PCR (referred as “non-LF” cases) remain followed in the study as a control group up to day 60 from admission.

2.6. Number of participants

We expect to enroll between 150 and 200 new participants per year, depending on the magnitude of annual outbreaks. The total number of participant will therefore reach 450 to 600 at the end of the study.

2.7. Routine case management

In accordance with NCDC's guidelines for LF case management (2017 and 2018 updates), all patients with confirmed LF receive intravenous ribavirin therapy. Different regimen can be used, depending on age, pregnancy status, and physicians' preference among the two NCDC recommended protocols for non-pregnant adults. Suspected LF patients are not started on ribavirin before RT-PCR confirmation, unless they have had a documented contact with a confirmed LF case or they are deemed highly suspect for LF according to above-mentioned criteria [25,26]. Supportive care includes oral or intravenous fluid administration, antimalarials, antibacterials, analgesics, oxygen and renal replacement therapy according to patients' clinical status. Mechanical ventilation, invasive hemodynamic monitoring and vasopressor drugs are not available.

The minimum biological monitoring includes: Malaria Rapid Diagnostic Test (RDT) (admission [Day-0]); Lassa RT-PCR, full blood count, renal function, electrolytes (in blood and, if relevant, in urine) and liver function (Day-0, Day-5 and Day-10). Additional tests are performed if deemed useful by the treating physician (e.g. in patients undergoing renal replacement therapy or admitted to the Intensive Care Unit of the Lassa ward). Women of childbearing age undergo a urine pregnancy test at Day-0. During the first months of the study, Lassa RT-PCR testing was performed at Irrua Specialist Teaching Hospital (ISTH), Edo state, 110 km from Owo. Laboratory equipment for Lassa RT-PCR was then installed on site in Owo, where the laboratory staff received appropriate training and where LF diagnosis is now performed as of March 2019.

All other biological tests are performed on site. At each blood collection, a sample of serum is stored locally at -20°C . Further upgrading of biobanking capacities to allow long term storage of serum and cells at -80°C is planned (Fig. 2).

2.8. Follow-up

Participants are followed for a total of 60 days. After hospital discharge, patients with specific issues (e.g. pregnant women and patients with renal impairment) are asked to show up at the study center for additional visits if deemed necessary by their treating physician. All the participants have at least one scheduled visit at day 60 from admission specifically for study purpose. In case a participant is not able to come back to the study centre, he or she is visited at home or reached by phone at Day-60 by study staff. Discharged pregnant women receive appropriate antenatal care and are followed 60 days after delivery. Newborns are followed a minimum of 60 days after birth. Longer follow-up is possible if the doctors think that problems specifically related to the disease are still in progress.

All hospital stay (including neonatal care), outpatient care



Fig. 2. (A) Patient care by a health worker wearing personal protective equipments at the Infection Control and Research Centre and (B) laboratory scientists processing samples from Lassa-infected patients in the Viral Hemorrhagic Fever laboratory, Federal Medical Centre Owo, Ondo State, Nigeria. ©Yvonne Etinosa – ALIMA.

(including antenatal care and transportation), treatments (including ribavirin and renal replacement therapy), and biological tests are provided free of charge for patients hospitalized in the LF wards of the study sites, whether they participate in the study or not.

2.9. Data collection

De-identified study data are collected on standardized CRFs by the investigators or their designated representatives, all of whom have been trained in clinical research and are dedicated to clinical research tasks. The CRFs contains all variables of the WHO standardized CRF for LF, plus additional variables that were deemed necessary to document specific issues (see Appendix). Data recorded on CRFs are entered into a centralized database. The system ensures data encryption, restricted access to the database, daily back-up and tracking of edits. A data management plan describes the quality control process to ensure completeness, validity, consistency, timeliness and accuracy. Specific training is provided to all members of the study team involved in the data collection, entry, check and monitoring. A dedicated clinical research unit hosted by the PAC-CI program (Abidjan, Côte d'Ivoire) conducts data review and handle queries on a monthly basis.

An anonymized database will be made available to the scientific community in a publicly accessible data repository after publication of final results at the end of the study.

2.10. Outcomes

The primary outcome is all-cause fatality at day 60.

Secondary outcomes of interest are: all-cause in-hospital fatality, the frequency of acute kidney dysfunction, defined as either “acute kidney

injury" (AKI) or "acute kidney failure" (AKF) according to "Kidney Disease – Improving Global Outcome" (KDIGO) criteria [27,28]; the prognosis of AKI and AKF in terms of estimated glomerular filtration rate (eGFR) at the end of follow-up; time to hospital discharge; viral load kinetics; time to negative Lassa RT-PCR in blood; time to normalization of key clinical/biological parameters; and pregnancy outcomes in terms of maternal morbidity/mortality, pregnancy issues (miscarriage, preterm delivery, type of delivery, delivery complications) and neonatal mortality.

2.11. Analysis

We will first describe baseline characteristics (age, sex, geographical location, syndromic categorization, severity score, viral load expressed as RT-PCR cycle threshold (Ct) value, other biological characteristics), follow-up characteristics (evolution of severity parameters and scores, tests conducted, ribavirin therapy, renal replacement therapy, oxygen therapy, intensive care unit admission, other therapies and organ support), as well as the occurrence of primary and secondary outcomes over time.

Second, we will use univariate and multivariate analysis to study the association of outcomes with baseline and follow-up characteristics, with special attention being paid to ribavirin exposure and baseline viral load. Finally, we will investigate whether some of these variables should become randomization stratification variables in future trials based on their prognostic value (association with fatality rate and with delay to death).

The putative sources of LASV infection (interhuman vs. rodent to human) will be looked for through a case-control approach looking at different types of exposure to rodents or to potentially Lassa infected human beings among RT-PCR LF confirmed cases and among their non-LF counterparts (controls).

2.12. Ethical considerations

The protocol was approved by the FMCO Research Ethics Committee and by the Nigeria National Research Ethics Committee (approval numbers: NHREC/01/01/2007-24/05/2018 and NHREC/01/01/2007-06/06/2019B). The research is carried out in compliance with current national and international regulations, including the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects; the Declaration of Helsinki; the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice E6 (ICH-E6); and the Nagoya protocol. All data from the participants recorded in study documents and in the database are made confidential through de-identification using a unique participant identification number.

Prior to inclusion, participants are asked for a written informed consent. For underage children, the consent form is signed by a legal representative. For children over twelve (referred as "mature minors"), the child's assent is requested in addition to the consent of the legal representative. For unconscious or incapacitated adults, provisional consent is given by the patient's representative. The consent of the participants is solicited as soon as they are able to understand.

Participants are free to withdraw their consent anytime, without justification and with no consequence. Unless they are opposed to, data and samples collected before withdrawal are used for the purpose of the study.

The datasets generated and/or analyzed during the current study will be made available upon publication of the final results in a public data repository after further anonymization. Sample stored in the bio-bank will be made available for national scientists on request to the co-principal investigators.

3. Discussion

Despite its discovery in 1969 and being identified by WHO as a priority for research and preparedness, there is still a limited body of literature on LF. Interestingly, the scientific production on the topic has dramatically declined from the 1980s to recent years and only a small proportion is coming from endemic countries [29]. This represents a major challenge for the scientific community. The protocol proposed here is part of a North-South collaboration effort addressing the gap of LF clinical research in a high endemic area.

3.1. Challenges of research on a high consequence infectious disease

Clinical research on Lassa fever needs to integrate the priority of care and the imperative of research. This implies several challenges.

The first challenge is biosafety [30], as the Lassa virus belongs to the group 4 of dangerous pathogens [31] and therefore needs to be handled in at least Biosafety level 3 (BSL-3) laboratories. The second is the need to combine short-term responsiveness with long-term efforts. LF is an endemic-epidemic disease with seasonal recrudescence [32], in which research actions must be considered and conducted both in the discontinuity of outbreaks and in the continuity of the endemic. It is a kind of cross-country race in which one has to know how to accelerate suddenly. The third challenge is the context, mixing limited resources with a limited experience in clinical research by local health care workers. This complicates logistical support and scientific engineering, and leads to the need to balance scientific ambition and operational feasibility. The context may also sometimes lead researchers to participate with their own resources to everyday care, in order to ensure access for all patients to the best possible standard of care. This can represent a challenge for the sustainability of the research project funding.

There are two conditions for any research to live up to these challenges:

First, the research must integrate smoothly into the everyday practice and participate in a virtuous way in the dynamics of improvement of the standard of care. In particular, this means research should: interfere in the most marginal way possible on the daily course of care activities; integrate rapidly new evidence from research into care; take into account that the vulnerability of the patients and affected communities may lead to suspicion towards the researchers and health care workers [33].

Second, the multiple actors concerned by research (national public health authorities, international public health institutions, hospital teams, non-governmental organizations, academic networks, secular or religious community leaders, patients and their relatives) must work together under the coordination of legitimate national institutions, favoring the establishment of a relationship of trust and ownership and the emergence of a true long-term collaborative research program.

3.2. Major issues to be solved before future phase 3 Lassa fever therapeutic trials

Fatality in hospitalized LF confirmed cases is high, including among patients receiving ribavirin. The most recent national estimate of LF case fatality rate in Nigeria is 23%, with a range of local estimates varying from 15% to more than 65% [32]. There are good reasons to believe that fatality varies according to the quality of supportive care, as previously reported for Ebola disease [34–37].

Fatality would be the best endpoint for future phase 3 trials. To estimate the sample sizes needed, we have to accurately estimate mortality in the centers that will participate in these trials. We also need to identify the predictors of fatality, and examine whether stratifying the randomization for some factors would be appropriate. Since fatality and some of its predictors are closely linked to the quality of care, the question of how to harmonize the standard of care and provide the best

possible care at each level, from remote hospitals or clinics to tertiary centers, is key to the success of future trials [33,34]. Improving care also reinforces the attractiveness of treatment facilities, thereby favoring an earlier presentation and isolation of patients [15,38] and improving disease prognosis [14]. Attractiveness is also a necessary condition to the successful recruitment of future phase 3 clinical trials.

Once future trials centers are trained in the application of the best care, it is possible that the estimated fatality in these centers improves and becomes such that it cannot serve as a trial primary endpoint of its own as it would imply to recruit an unreachable number of participant to obtain a sufficient power. As a consequence, a composite primary endpoint combining mortality with other clinically significant outcome(s) should be considered. Strong evidence for the choice of these outcomes is needed. For those reasons, we need: to prospectively confirm predictors of fatality that have been previously been identified retrospectively [14,15]; to identify new predictors, if any; and to provide an as precise as possible estimation of their frequency in hospitalized LF patients.

Finally, future phase 3 trials will compare new treatment(s) to the best standard of care, which currently includes ribavirin. However, the recommendation to use ribavirin is based on evidence from of a single trial, which included historical controls as comparator group and which suffer from multiple other design flaws and biases [14], raising concerns about the effectiveness and even the safety of ribavirin in LF [16–18]. As a result, ribavirin might need to be investigated alongside other drugs in future phase 3 trials and compared against the best available standard of supportive care (with or without placebo) [39]. Meanwhile, observational studies of the pharmacokinetics and safety of ribavirin could inform dosages regimes to be tested in trials. The LASCOPE cohort will help tackle all these challenges, and provide new evidence to help design future trials.

3.3. A focus on renal dysfunction

Acute renal dysfunction was reported to be the main harbinger of fatality in patients with Lassa fever in Nigeria [15,38], in contrast to older reports from Sierra Leone [14,40]. One of our objectives is to better understand the mechanisms leading to acute renal dysfunction in LF, as well as its prognosis, in order to better prevent or treat it. The hypothesis of primary intrinsic renal damage (either directly induced by Lassa virus or immune-mediated) has been advanced in previous studies [15] on the basis of a high serum urea/creatinine ratio and other indirect elements, in the absence of evidence of significant fluid loss in some patients (lack of vomiting, diarrhea or bleeding) [15]. Nevertheless, it remains difficult to assess the relative proportion of pre-renal and intrinsic mechanisms in the genesis of acute kidney dysfunction during LF because of limited research capabilities in treatment centers. The use of conventional biochemical urine tests is quite easily feasible in this setting and allows the calculation of simple parameters such as the excreted fraction of urea, which can help discriminate pre-renal and intrinsic kidney dysfunction more accurately than the simple serum urea/creatinine ratio [41–44]. This could be of added value to guide clinical management. Indeed, in a context favoring hypovolemia (diarrhea, vomiting, fever) and thereby prerenal azotemia, the first challenge is to provide appropriate rehydration and correction of electrolyte disorders. Meanwhile, it is also important to optimize the use of renal replacement therapy, an expensive technique which can expose patients to adverse events [45] and health care workers to the risk of nosocomial transmission of LASV [7]. To do this, patients progressing to intrinsic acute renal failure should be identified accurately and in a timely manner [41–45].

3.4. Pregnancy

Another important challenge is the management of LF during pregnancy. Pregnant women are thought to have a higher mortality in

LF but discrepancies and knowledge gaps remain regarding both the prognosis of LF and its management in this population [46–49]. Importantly, pregnant women were excluded from the ribavirin arm in the Sierra Leone trial and assigned *ex officio* to a control group [14]. Current recommendations include the administration of ribavirin in this population, even though it has never therefore been evaluated [25]. Lastly, the management of obstetrical events, including deliveries, under isolation conditions imposed by Lassa fever, represents a challenge for health workers.

3.5. Capacity building

LASCOPE addresses the need to strengthen the clinical research infrastructure in Nigeria's major LF treatment centers, mainly situated in rural or peri-urban areas. Of these, only the ISTH (Edo State) has a long structured research activity [15]. We opened the study at another care center, the FMCO (Ondo State), a regional hospital situated in an epidemic focus, but with no experience in clinical research.

Beyond the support given to patients' care, including free access to clinical care, the standardized framework of a research study promotes systematic clinical monitoring. It provides caregivers with tools originally designed for research but which can be integrated into the daily care process. In the same spirit, the opening of a BSL-3 laboratory on the Owo site made it possible to improve the biosafety conditions in which the analyzes dedicated to Lassa patients were carried out, while developing a team of biologists and technicians trained in good laboratory practices.

4. Conclusions

The LASCOPE study will provide health authorities and the scientific community with key data on LF course, prognostic factors, and management that will be useful both to refine clinical management guidelines and to design future efficacy trials evaluating innovative treatment strategies for LF. It will allow participating treatment centers to build multidisciplinary teams experienced in clinical research according to international standards. Lastly, it will favor the ownership of the Lassa fever research topic by national and local actors, in order to put them in real acting principal investigators positions in future clinical trials.

CRedit authorship contribution statement

Alexandre Duvignaud: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Marie Jaspard:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Ijeoma Chukwudumebi Etafo:** Conceptualization, Data curation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Béatrice Serra:** Conceptualization, Data curation, Methodology, Project administration, Writing - review & editing. **Chukwuyem Abejegah:** Conceptualization, Data curation, Writing - review & editing. **Delphine Gabillard:** Conceptualization, Methodology, Writing - review & editing. **Mahamadou Doutchi:** Conceptualization, Data curation, Project administration, Writing - review & editing. **Josephine Funmilola Alabi:** Conceptualization, Data curation, Writing - review & editing. **Moses Adeniyi Adedokun:** Conceptualization, Data curation, Writing - review & editing. **Adewale Oladayo Akinpelu:** Conceptualization, Data curation, Writing - review & editing. **Oyebimpe Ope Oyegunle:** Conceptualization, Data curation, Writing - review & editing. **Johnson Etafo:** Data curation, Writing - review & editing. **Ayoleyi Omowunmi Dede:** Data curation, Writing - review & editing. **Macdonald Nonso Onyechi:** Data curation, Writing - review & editing. **Moronke Uzuajemeh Ireneh:** Data curation, Writing - review & editing. **Olufunke Gbenga-Ayeni:** Data curation, Writing -

review & editing. **Kehinde Gbemisola Fadiminiyi**: Data curation, Writing - review & editing. **Patience Iziegbe Ehigbor**: Data curation, Writing - review & editing. **Eric Ouattara**: Conceptualization, Writing - review & editing. **Claire Levy-Marchal**: Conceptualization, Methodology, Writing - review & editing. **Sophie Karcher**: Conceptualization, Data curation, Writing - review & editing. **Larissa N'guessan-Koffi**: Conceptualization, Data curation, Writing - review & editing. **Irmine Ahyi**: Conceptualization, Data curation, Writing - review & editing. **Elvis Amani**: Conceptualization, Data curation, Writing - review & editing. **Mamoudou Diabaté**: Conceptualization, Data curation, Writing - review & editing. **Bertine Siloué**: Data curation, Writing - review & editing. **Justine Schaeffer**: Data curation, Writing - review & editing. **Augustin Augier**: Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Ephraim Ogbaini-Emovon**: Conceptualization, Data curation, Writing - review & editing. **Alex Paddy Salam**: Conceptualization, Writing - review & editing. **Peter Horby**: Conceptualization, Funding acquisition, Writing - review & editing. **Liasu Adeagbo Ahmed**: Conceptualization, Data curation, Writing - review & editing. **Stephan Günther**: Conceptualization, Data curation, Funding acquisition, Writing - review & editing. **Akinola Nelson Adedosu**: Conceptualization, Data curation, Methodology, Writing - review & editing. **Xavier Anglaret**: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Oladele Oluwafemi Ayodeji**: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Denis Malvy**: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

All authors declared that they have no competing interests.

Acknowledgments

Funding support: this work was supported by the Institut National de la Santé Et de la Recherche Médicale (INSERM)/REsearch and ACTION targeting emerging infectious diseases (REACTing), the African coalition for Epidemic Research, Response and Training (ALERT) consortium (European and Developing Countries Clinical Trials Partnership (EDCTP) grant agreement RIA2016E-1612), the University of Oxford (Department For international Development (DFID)/Wellcome Trust discretionary award) and the Institut de Recherche pour le Développement (IRD). The funding sources had no role in the study design; the collection, analysis and interpretation of data; and in the writing of the report and making the decision to submit the article for publication.

The authors thank all the participants in the cohort, as well as the following persons: Dr. Chikwe Ihekweazu (Nigerian Centre for Disease Control) and Prof. Adebola Olayinka (Nigerian Centre for Disease Control and WHO Nigeria Country Office) for their technical assistance to the LASCOPE project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tmaid.2020.101557>.

References

- [1] Frame JD, Baldwin JM, Gocke DJ, Troup JM. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *Am J Trop Med Hyg* 1970;19:670–6.
- [2] Monath TP, Newhouse VF, Kemp GE, Setzer HW, Cacciapuoti A. Lassa virus

- isolation from *Mastomys natalensis* rodents during an epidemic in Sierra Leone. *Science* 1974;185:263–5.
- [3] What-you-need-to-know-about-Lassa-factsheet.pdf n.d <https://www.cdc.gov/vhf/lassa/pdf/What-you-need-to-know-about-Lassa-factsheet.pdf>, Accessed date: 28 December 2019.
- [4] Lo Iacono G, Cunningham AA, Fichet-Calvet E, Garry RF, Grant DS, Khan SH, et al. Using modelling to disentangle the relative contributions of zoonotic and anthroponotic transmission: the case of lassa fever. *PLoS Neglected Trop Dis* 2015;9:e3398. <https://doi.org/10.1371/journal.pntd.0003398>.
- [5] Siddle KJ, Eromon P, Barnes KG, Mehta S, Ju Oguzie, Odiya I, et al. Genomic analysis of lassa virus during an increase in cases in Nigeria in 2018. *N Engl J Med* 2018;379:1745–53. <https://doi.org/10.1056/NEJMoa1804498>.
- [6] Kafetzopoulou LE, Pullan ST, Lemey P, Suchard MA, Ehichioya DU, Pahlmann M, et al. Metagenomic sequencing at the epicenter of the Nigeria 2018 Lassa fever outbreak. *Science* 2019;363:74–7. <https://doi.org/10.1126/science.aau9343>.
- [7] Ajayi NA, Nwigwe CG, Azuogu BN, Onyire BN, Nwonwu EU, Ogbonnaya LU, et al. Containing a Lassa fever epidemic in a resource-limited setting: outbreak description and lessons learned from Abakaliki, Nigeria (January–March 2012). *Int J Infect Dis* 2013;17:e1011–6. <https://doi.org/10.1016/j.ijid.2013.05.015>.
- [8] McCormick JB, Webb PA, Krebs JW, Johnson KM, Smith ES. A prospective study of the epidemiology and ecology of Lassa fever. *J Infect Dis* 1987;155:437–44.
- [9] Günther S, Lenz O. Lassa virus. *Crit Rev Clin Lab Sci* 2004;41:339–90. <https://doi.org/10.1080/10408360490497456>.
- [10] Mylne AQN, Pigott DM, Longbottom J, Shearer F, Duda KA, Messina JP, et al. Mapping the zoonotic niche of Lassa fever in Africa. *Trans R Soc Trop Med Hyg* 2015;109:483–92. <https://doi.org/10.1093/trstmh/trv047>.
- [11] Kofman A, Choi MJ, Rollin PE. Lassa fever in travelers from West Africa, 1969–2016. *Emerg Infect Dis* 2019;25:245–8. <https://doi.org/10.3201/eid2502.180836>.
- [12] Lassa fever in The Netherlands ex Sierra Leone 2019:9.
- [13] Kerber R, Reindl S, Romanowski V, Gómez RM, Ogbaini-Emovon E, Günther S, et al. Research efforts to control highly pathogenic arenaviruses: a summary of the progress and gaps. *J Clin Virol* 2015;64:120–7. <https://doi.org/10.1016/j.jcv.2014.12.004>.
- [14] McCormick JB, King LJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever. Effective therapy with ribavirin. *N Engl J Med* 1986;314:20–6. <https://doi.org/10.1056/NEJM198601023140104>.
- [15] Okokhere P, Colubri A, Azubike C, Iruolagbe C, Osazuwa O, Tabrizi S, et al. Clinical and laboratory predictors of Lassa fever outcome in a dedicated treatment facility in Nigeria: a retrospective, observational cohort study. *Lancet Infect Dis* 2018;18:684–95. [https://doi.org/10.1016/S1473-3099\(18\)30121-X](https://doi.org/10.1016/S1473-3099(18)30121-X).
- [16] Final report analysis of a clinical trial ribavirin and the treatment of lassa fever report, 7 February 1992, SUBJECT: IND 16666 - Ribavirin (Virazole) (Serial No. 011) n.d.. <https://isatic.tghn.org/ribavirin-and-treatment-lassa-fever/final-report-analysis-clinical-trial-ribavirin-and-treatment-lassa-fever-7-february-1992/>, Accessed date: 28 December 2019.
- [17] Ludwig George V. To Dr. Peter William Horby, “on behalf of major general Holcomb”, memorandum 4 March 2019 n.d. <https://isatic.tghn.org/ribavirin-and-treatment-lassa-fever/george-v-ludwig-phd-dr-peter-william-horby/>, Accessed date: 28 December 2019.
- [18] Eberhardt KA, Mischlinger J, Jordan S, Groger M, Günther S, Ramharther M. Ribavirin for the treatment of Lassa fever: a systematic review and meta-analysis. *Int J Infect Dis* 2019;87:15–20. <https://doi.org/10.1016/j.ijid.2019.07.015>.
- [19] Bausch DG, Hadi CM, Khan SH, Lertora JJJ. Review of the literature and proposed guidelines for the use of oral ribavirin as postexposure prophylaxis for Lassa fever. *Clin Infect Dis* 2010;51:1435–41. <https://doi.org/10.1086/657315>.
- [20] WHO | A Research and Development Blueprint for Action to Prevent Epidemics. WHO n.d. <http://www.who.int/csr/research-and-development/en/> (accessed December 28, 2019).
- [21] Oestereich L, Rieger T, Lüdtke A, Ruibal P, Wurr S, Pallasch E, et al. Efficacy of favipiravir alone and in combination with ribavirin in a lethal, immunocompetent mouse model of lassa fever. *J Infect Dis* 2016;213:934–8. <https://doi.org/10.1093/infdis/jiv522>.
- [22] Safronetz D, Rosenke K, Westover JB, Martellaro C, Okumura A, Furuta Y, et al. The broad-spectrum antiviral favipiravir protects Guinea pigs from lethal Lassa virus infection post-disease onset. *Sci Rep* 2015;5:14775. <https://doi.org/10.1038/srep14775>.
- [23] Mire CE, Cross RW, Geisbert JB, Borisevich V, Agans KN, Deer DJ, et al. Human monoclonal-antibody therapy protects nonhuman primates against advanced Lassa fever. *Nat Med* 2017;23:1146–9. <https://doi.org/10.1038/nm.4396>.
- [24] Ilori EA, Furuse Y, Ipadeola OB, Dan-Nwafor CC, Abubakar A, Womi-Eteng OE, et al. Epidemiologic and clinical features of lassa fever outbreak in Nigeria. *Emerg Infect Dis* 2019;25:1066–74. <https://doi.org/10.3201/eid2506.181035>. January 1–May 6, 2018.
- [25] Nigeria Centre for Disease Control. National guidelines for Lassa fever case management. Niger cent Dis control. 2018 https://ncdc.gov.ng/themes/common/docs/protocols/92_1547068532.pdf, Accessed date: 28 December 2019.
- [26] Nigeria Centre for Disease Control. Standard operating procedures for Lassa fever case management. 2017 https://www.ncdc.gov.ng/themes/common/docs/protocols/30_1502277315.pdf, Accessed date: 2 November 2018.
- [27] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179–84. <https://doi.org/10.1159/000339789>.
- [28] Kellum JA, Lameire N, Kdigo Aki Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17:204. <https://doi.org/10.1186/cc11454>.
- [29] Almeida-Guerrero A, Olaya-Gómez JC, Sánchez-Ramírez N, Murillo-García DR, Cardona-Ospina JA, Lagos-Grisales GJ, et al. Mitigation of the global impact of

- Lassa fever: have we investigated enough about this Arenavirus? - a bibliometric analysis of Lassa Fever research. *Trav Med Infect Dis* 2018;24:13–4. <https://doi.org/10.1016/j.tmaid.2018.06.012>.
- [30] Health, Executive Safety, Advisory Committee on Dangerous Pathogens. Management of Hazard Group 4 viral haemorrhagic fevers and similar human infectious diseases of high consequence. 2015 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/534002/Management_of_VHF_A.pdf, Accessed date: 28 December 2019.
- [31] Health, Executive Safety, Advisory Committee on Dangerous Pathogens. The Approved List of biological agents. third ed. 2013 <http://www.hse.gov.uk/pUbns/misc208.pdf>, Accessed date: 28 December 2019.
- [32] Nigeria Centre for Disease Control. An update of Lassa Fever Outbreak in Nigeria n. d. <https://ncdc.gov.ng/diseases/sitreps/?cat=5&name=An%20update%20of%20Lassa%20fever%20outbreak%20in%20Nigeria> (accessed December 28, 2019).
- [33] Malvy D, McElroy AK, de Clerck H, Günther S, van Griensven J. Ebola virus disease. *Lancet* 2019;393:936–48. [https://doi.org/10.1016/S0140-6736\(18\)33132-5](https://doi.org/10.1016/S0140-6736(18)33132-5).
- [34] Lamontagne F, Clément C, Kojan R, Godin M, Kabuni P, Fowler RA. The evolution of supportive care for Ebola virus disease. *Lancet* 2019. [https://doi.org/10.1016/S0140-6736\(19\)30242-9](https://doi.org/10.1016/S0140-6736(19)30242-9).
- [35] Uyeki TM, Mehta AK, Davey RT, Liddell AM, Wolf T, Vetter P, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med* 2016;374:636–46. <https://doi.org/10.1056/NEJMoa1504874>.
- [36] WHO Ebola Response Team, Aylward B, Barboza P, Bawo L, Bertherat E, Bilivogui P, et al. Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections. *N Engl J Med* 2014;371:1481–95. <https://doi.org/10.1056/NEJMoa1411100>.
- [37] Lamontagne F, Clément C, Fletcher T, Jacob ST, Fischer WA, Fowler RA. Doing today's work superbly well—treating Ebola with current tools. *N Engl J Med* 2014;371:1565–6. <https://doi.org/10.1056/NEJMp1411310>.
- [38] Asogun DA, Adomeh DI, Ehimuan J, Odia I, Hass M, Gabriel M, et al. Molecular diagnostics for lassa fever at Irrua specialist teaching hospital, Nigeria: lessons learnt from two years of laboratory operation. *PLoS Neglected Trop Dis* 2012;6:e1839. <https://doi.org/10.1371/journal.pntd.0001839>.
- [39] World Health Organization, R&D Blueprint. Efficacy trials of Lassa fever therapeutics: endpoints, trial design, site selection 2018 WHO workshop Meeting report 1.0, Paris, France https://www.who.int/blueprint/what/norms-standards/LassaTxeval_FinalmeetingReport.pdf?ua=1, Accessed date: 28 December 2019.
- [40] McCormick JB, King LJ, Webb PA, Johnson KM, O'Sullivan R, Smith ES, et al. A case-control study of the clinical diagnosis and course of Lassa fever. *J Infect Dis* 1987;155:445–55.
- [41] Lima C, Macedo E. Urinary biochemistry in the diagnosis of acute kidney injury. *Dis Markers* 2018;2018:4907024. <https://doi.org/10.1155/2018/4907024>.
- [42] Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int* 2002;62:2223–9. <https://doi.org/10.1046/j.1523-1755.2002.00683.x>.
- [43] Dewitte A, Biais M, Petit L, Cochard J-F, Hilbert G, Combe C, et al. Fractional excretion of urea as a diagnostic index in acute kidney injury in intensive care patients. *J Crit Care* 2012;27:505–10. <https://doi.org/10.1016/j.jcrc.2012.02.018>.
- [44] Hall IE, Coca SG, Perazella MA, Eko UU, Luciano RL, Peter PR, et al. Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. *Clin J Am Soc Nephrol* 2011;6:2740–9. <https://doi.org/10.2215/CJN.04960511>.
- [45] Gaudry S, Quenot J-P, Hertig A, Barbar SD, Hajage D, Ricard J-D, et al. Timing of renal replacement therapy for severe acute kidney injury in critically ill patients. *Am J Respir Crit Care Med* 2019;199:1066–75. <https://doi.org/10.1164/rccm.201810-1906CP>.
- [46] Price ME, Fisher-Hoch SP, Craven RB, McCormick JB. A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy. *BMJ* 1988;297:584–7.
- [47] Monson MH, Cole AK, Frame JD, Serwint JR, Alexander S, Jahrling PB. Pediatric Lassa fever: a review of 33 Liberian cases. *Am J Trop Med Hyg* 1987;36:408–15.
- [48] Keane E, Gilles HM. Lassa fever in panguma hospital, Sierra Leone, 1973–6. *Br Med J* 1977;1:1399–402.
- [49] Okogbenin SA, Asogun D, Akpede G, Okokhere P, Gunther S, Happi C. New lessons from a case series review of Lassa fever in pregnancy. *Int J Infect Dis* 2010;14:e380. <https://doi.org/10.1016/j.ijid.2010.02.466>.