A STANDARDISED PHASE III CLINICAL TRIAL FRAMEWORK TO ASSESS THERAPEUTIC INTERVENTIONS FOR LASSA FEVER

NCDC

NIGERIA CENTRE FOR DISEASE CONTROL

A STANDARDISED PHASE III CLINICAL TRIAL FRAMEWORK

TO ASSESS THERAPEUTIC INTERVENTIONS FOR LASSA FEVER

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Lassa fever (LF) is an acute viral haemorrhagic fever endemic to West Africa, causing an estimated 500,000 new infections and 10,000 deaths per year, of which there were 1189 infections and 244 deaths in Nigeria in 2020. (1) At present, no treatment has been developed and explicitly registered to treat LF, and the evidence base for the current treatment recommendation, ribavirin, is weak. Before a new era of LF clinical trials can begin, it is essentialto develop standardised methods and tools to ensure that trials are conducted in a consistent way and can generate reliable, comparable data that could be used to support registration and adoption. The aim of this project was to improve the comparability of LF studies by developing a standardised Phase III clinical trial methodology for LF therapeutics that could be applied in low-resource settings while meeting high-quality standards. Through multi-stakeholder consultations, we established a Phase III clinical trial framework, consisting of four key outputs: a Core Eligibility Criteria (CEC), Core Case Definition (CCD), Core Outcome Set (COS) and Core Data Variables (CDV).

CHAPTER 1: OVERVIEW OF LASSA FEVER IN NIGERIA AND WEST AFRICA

Lassa fever (LF) is an acute viral haemorrhagic fever endemic to Nigeria and other parts of West Africa, caused by the Lassa virus, LASV, an arenavirus. LF was first described in Sierra Leone in the 1950s, but it wasn't until 1969 that the Lassa virus was officially identified. (2) Since then, cases of LF have continued to be reported across the West African region – most prominently in Sierra Leone and Nigeria. Although LF is also known to be endemic in Benin, Ghana, Guinea, Liberia and Mali, it is widely thought that LF exists in other West African countries. (2) An ongoing project, 'Enable', supported by the Coalition for Epidemic Preparedness Innovations (CEPI), is expected to provide more up-to-date evidence of the actual distribution of cases in the region. (3)

While the exact incidence rate of LF is not known, it is estimated to cause approximately 300,000-500,000 new infections and 5,000 deaths per year in West Africa, and with this comes a significant economic, social and public health burden. (4) Nigeria reported 1189 infections and 244 deaths in 2020. (1) The largest outbreak of LF occurred in 2019 in Nigeria – where LF is a notifiable disease to the IDSR platform – 833 laboratory-confirmed cases were reported with a case fatality rate of approximately 21%. (5)

an increasing number of lineages of the LASV are identified, with lineages II and III being prevalent in southern and northern Nigeria. (6)main, genetic diversity is a challenge for diagnosis, , vaccine, and drug development in Nigeria. (7)

Transmission to humans generally occurs via direct or indirect contact with the main animal reservoir – the multimammate rat, *Mastomys natalensis* – or contact with contaminated food or household items. (2) Human-to-human transmission occasionally occurs and is most common in

resource-limited healthcare settings where infection prevention and control measures may be suboptimal. (8)

The incubation period of LF is wide-ranging, with onset of symptoms occurring typically between 6 – 21 days. (2, 9) Symptoms of LF are non-specific and usually include fever alongside one or more gastrointestinal symptoms, weakness, muscle pains or – in more severe cases – bleeding. (9, 10) In pregnant women, LF may also be suspected in the event of spontaneous abortion or vaginal bleeding. (10) Complications of LF include acute kidney injury, shock, encephalopathy, acute respiratory failure and severe bleeding. (10) The overall case fatality rate is estimated to be around 1%, increasing to 12-15% for hospitalised cases – although reliable epidemiological data are missing. (2, 11)

LF poses a significant risk in pregnancy, with pregnant women three times more likely to have a fatal outcome than non-pregnant patients. (12) Children are also a significant risk group for LF for whom the case fatality rate (CFR) has been reported up to four times higher than the WHO's estimated CFR. (13)

1.1 Treatment guidelines for Lassa fever

There is no LF-specific treatment that has received full regulatory approval, and there have been no clinical trials conducted to assess the safety and efficacy of LF therapeutics since the 1980s. (14)

However, antiviral treatment with ribavirin is the recommended treatment option for LF under national and international treatment guidelines. (2, 10, 15) Intravenous ribavirin is given for 10 days in conjunction with supportive care, and dosing is based on weight, age and pregnancy status.

Evidence for this recommendation is based on the results of a single study published in 1986, which has recently drawn some concern about its methods, analysis , and safety when used to treat mild cases of LF (14, 16, 17).

1.2 The Lassa fever clinical research landscape

The requirement for novel therapeutics, a small number of which have been identified as candidates to be tested, and the reassessment of ribavirin is urgent. (18-20)

However, before a new era of LF clinical trials can begin, robust methods must be developed to ensure that trials are conducted in a consistent way and can generate reliable, comparable data. Given that clinical trial registries show no record of plans to conduct Phase III clinical trials for LF therapeutics at the time of this report, there is an opportunity to set the groundwork for well-conducted trials to begin. Plans for future research must prioritise efficient generation of results and the inclusion of pregnant women and children, for whom there are significant risks and an absence of comparable treatment efficacy data. (12, 13)

CHAPTER 2: A CONSULTATION TO DEVELOP A STANDARDISED PHASE III CLINICAL TRIAL FRAMEWORK TO ASSESS THERAPEUTIC INTERVENTIONS FOR LASSA FEVER

This project aims to improve the comparability of LF studies by developing a standardised Phase III clinical trial methodology for LF therapeutics that could be applied in low-resource settings whilst meeting high standards of clinical research.

We established a consultation group to develop a framework consisting of four key outputs for future Phase III clinical trials of LF therapeutics (**Box 1**). The aim of the group was to standardise and delineate Core Eligibility Criteria (CEC), Core Case Definition (CCD), Core Outcome Set (COS) and Core Data Variables (CDV).

Box 1 – Definitions of the consultation outputs

The definitions of the four key outputs of the consultation are as follows:

Core Eligibility Criteria (CEC) – the characteristics of the study population

Core Case Definition (CCD) – how to identify a patient with suspected Lassa fever

Core Outcome Set (COS) – what, how and when to measure outcomes in order to assess treatment efficacy

Core Data Variables (CDV) – list of recommended data variables for collection in all patients to standardise the characterisation of Lassa fever

The intention of a harmonised approach to LF clinical studies is to improve comparability of LF data and accelerate knowledge about LF therapeutics, which is urgently needed. Prioritising an efficient

clinical trial pathway will also optimise the use of the limited resources that are available to conduct studies of this nature.

The breadth of this framework also ensures that key populations are accounted for in future research studies. Specifically, pregnant women and paediatric populations have been deliberately incorporated to ensure these important groups, who are disproportionately affected by LF and face increased risks, are actively included. (12, 13, 21)

Overall, this framework has been developed to promote efficiency in the advancement of LF clinical research through a regionally-centred, collaborative methodology. It forms part of a broader objective to delineate a clear pathway through which LF clinical trials can progress efficiently, ensuring sustainable investments are made in a research capacity at a regional level.

Note: The development of COS is supported by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (22), and the methodology for developing COS is described in the COMET Handbook. (23) The group also recognised the value of developing additional outputs (CEC, CCD and CDV) that would improve the comparability of LF clinical trials.

2.1 Methodology

The project was conducted in two steps: first, a systematic review was performed to describe the clinical characterisation of LF; second, a stakeholder consultation was established to develop the criteria for the CEC, CCD, COS and CDV. (9) A full report of our methodology can be found in the corresponding journal publication of the consultation. (24)

Figure 1 – the development process to define a Phase III clinical trial framework for Lassa fever

Systematic review

A systematic review was conducted ahead of the consultation to identify the clinical characteristics and outcomes of LF patients and describe how LF has historically been defined and assessed in the scientific literature. (9) These results formed the basis of an initial list of potential inclusion and exclusion criteria, case definitions, patient outcomes and data variables.

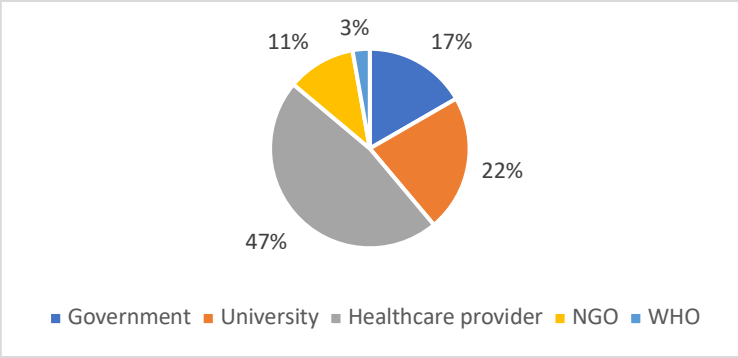
While the results somewhat corroborated the current understanding of the characterisation of LF, a number of other non-specific signs and symptoms were also identified that aren't typically acknowledged as indicators of LF. There was also widespread variations in the consistency of reporting making it challenging to generate generalisable conclusions.

Consultation

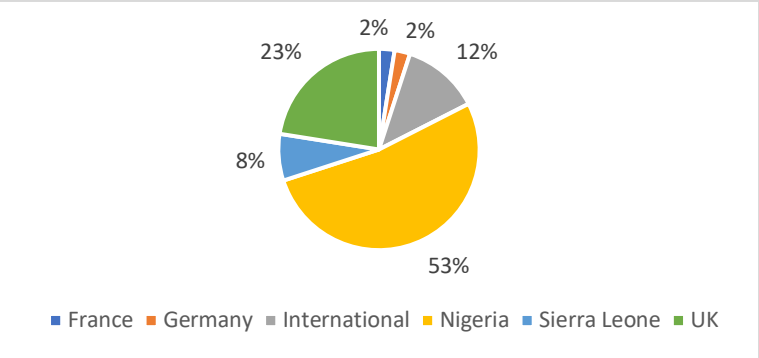
40 stakeholders in LF clinical management, public health and clinical research from regional and international organisations participated in a remote consultation. The stakeholders represented various organisations (government, international governing bodies, healthcare providers, universities and NGOs) (**Figure 2**).

Figure 2 – stakeholder representation by participating industry/ organisation and by participating country

1. **Participating industries and organisations**



2. **Proportion of participating stakeholders by country**



This collaboration of health agencies, humanitarian organisations and academics with significant experience of LF clinical management and research was important to the development of a framework that ensures regional ownership over the direction for future LF clinical research. Establishing these partnerships is crucial to avoid a piecemeal approach to conducting trials for a disease that requires an efficient, coordinated research strategy.

The consultation took place remotely over the course of one initial kick-off meeting, two quasi-Delphi consultations (with two follow-up meetings to discuss results) and one final consensus meeting.

Delphi consultations

A Delphi-type survey was developed based on the evidence gathered during the systematic review. The questionnaire listed items for consideration to be included as CEC, CCD, COS and CDV in the trial framework. Stakeholders indicated their agreement with the inclusion of each item by using a 5-point Likert scale or an equivalent scale appropriate to the needs of the question. Space for comments was also provided for stakeholders to propose additional items for consideration by the group and add explanatory comments. Stakeholders were asked to consider their responses for three patient populations: non-pregnant adults, pregnant women and children.

Consensus was determined when 60% or more of the stakeholders selected the same response. Where 60% or more of the stakeholders stated “Strongly Agree” or “Agree”, items were taken forward to the next Delphi round for further assessment. Where 60% or more of the stakeholders stated “Strongly Disagree” or “Disagree”, items were excluded from the framework. At the end of two Delphi rounds, all remaining items gaining ≥60% agreement for inclusion in the framework were taken forward to a consensus call for discussion and a final voting round.

Following the analysis of each round, a study report was circulated to all stakeholders, which included an anonymised summary of the results and additional comments provided by the group.

Consensus meeting

A final consensus meeting was held in lieu of a third Delphi-type round for stakeholders to discuss and vote on the remaining items that required consensus. Based on feedback from Round 2, workable proposals to navigate the key challenges around these discussion points were developed as a starting point for discussion, following which each proposal was presented in a poll during the meeting on which stakeholders cast an anonymous vote. The proposal with the highest number of votes was included within the framework. If consensus was not achieved, the poll was relaunched following discussion until stakeholders reached an agreement.

2.2 Results

The questionnaire was circulated to 30 stakeholders for completion in Round 1 and 35 stakeholders in Round 2; 43% and 69% of the stakeholders completed the questionnaires, respectively.

The final CEC, CCD, COS, CDV are presented in **Table 1**.

Core Eligibility Criteria Of the 33 items proposed for the Core Eligibility Criteria in Round 2, 10 items achieved a consensus. Across both rounds, it was evident that stakeholders did not favour a restrictive list of exclusion criteria but stated a preference for inclusive eligibility criteria that would not exclude patients on the basis of disease severity or comorbidity. There was also an explicit agreement that inclusion should be based on a combination of clinical diagnosis and laboratory confirmation.

The group also agreed that clinical suspicion of LF should be based on a list of pre-specified signs and symptoms that are as inclusive as possible so as not to limit recruitment to a clinical trial. Following discussion and poll, the stakeholders agreed that clinical suspicion of LF should be based on "History of fever or presence of fever unresponsive to treatment for common illnesses AND at least one of the following: headache; weakness; back pain; joint pain; dizziness; sore throat; bleeding; abdominal pain; vomiting; diarrhoea; seizures; haematuria or proteinuria on dipstick urinalysis. A definition was also developed to account for pregnancy-specific signs and symptoms (**Table 1**).

Core Case Definition All stakeholders agreed that a confirmed case should be defined on the same basis as the inclusion criteria (clinical diagnosis + laboratory confirmation). All stakeholders agreed that laboratory confirmation of LF should be conducted using RT-PCR alone, and sites without access to RT-PCR should not participate in a clinical trial.

Core Outcome Set While there was an initial preference within the group to include survival or mortality as the primary outcome measure, it was recognised that this might not be feasible for a clinical trial due to the large sample size required to detect a treatment effect.

Instead, a composite primary outcome measure – "unfavourable outcome" – was developed and is defined as mortality + progression to severe disease, for which the presence of 4 vital clinical syndromes were included for assessment (Acute Kidney Injury, Acute Respiratory Distress Syndrome, Shock and Encephalopathy). The methods for assessing each of the pathologies were agreed upon, including separate assessment methods for children, and are described in **Tables 2 and 3**.

Core Data Variables Finally, 20 Core Data Variables were identified for inclusion in future Phase III trials.

Table 1 – Core outputs and definitions included in the final framework

Item	Criteria	Additional considerations
Core Eligibility Criteria		
Clinical suspicion of LF (non-pregnant adults and children)	Non-pregnant adults and children should be enrolled in clinical trials based on clinical suspicion of LF, defined as: • History of fever or presence of fever unresponsive to treatment for common illnesses • AND at least one of the following: headache; weakness; back pain; joint pain; dizziness; sore throat; bleeding; abdominal pain; vomiting; diarrhoea; seizures; haematuria or proteinuria on dipstick urinalysis	At the point of enrolment, a sample should be taken for case confirmation by RT-PCR (see section 1.2), with results returned within 48 hours. Upon receipt of a negative test result for Lassa fever, patients should be removed from the study immediately.
Clinical suspicion of LF (pregnant women)	Pregnant women should be enrolled in clinical trials based on clinical suspicion of Lassa fever, defined as: • History of fever or presence of fever unresponsive to treatment for common illnesses • AND at least one of the following: headache; weakness; back pain; joint pain; dizziness; sore throat; bleeding; abdominal pain; vomiting; diarrhoea; breast swelling or engorgement; unexplained pregnancy loss (miscarriage or intrauterine death); seizures; haematuria or proteinuria on dipstick urinalysis	
Inclusion criteria	Confirmed cases of Lassa fever	See **Core Case Definition**
Exclusion criteria	• Patients receiving end-of-life care for other concomitant conditions • Patients involved in another clinical trial	Additional exclusion criteria will be based on study design and treatments involved.

Item	Criteria	Additional considerations
Core Case Definition		
Definition of a confirmed case of LF	Patients who have a positive result on RT-PCR for Lassa fever	Sites that do not have the facilities or capacity to conduct RT-PCR do not qualify for conducting Phase III clinical trials.
Core Outcome Set		
Primary Outcome Measure	Unfavourable Outcome: a composite outcome consisting of mortality or deterioration from baseline assessed at Day 14	See **Table 3; Table 4**
Secondary Outcome Measures	• Presence of severe anaemia (defined according to: WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System (2011) Geneva, World Health Organization (WHO/NMH/NHD/MNM/11.1)) • Hearing loss • Pregnancy outcome • The time between the start of treatment and discharge/recovery • The time between treatment start and delivery/miscarriage (only for trials enrolling pregnant patients) • The time between delivery/miscarriage and hospital discharge/recovery (only for trials enrolling pregnant patients)	
Core Data Variables		
Signs, symptoms and assessments critical to	• Date of symptom onset • Date of contact with a confirmed case (optional)	Data on other signs and symptoms or assessments conducted from the point of inclusion until patient

Item	Criteria	Additional considerations
evaluate treatment safety and/or efficacy	• Frank bleeding • Pregnancy complications (including vaginal bleeding in pregnancy and excessive bleeding in labour) • Level of consciousness (ACVPU or GCS, as specified in **Table 3** and **Table 4**) • Seizure • Temperature • Blood pressure • Creatinine • Urine output (if creatinine testing is not available) • The partial pressure of oxygen (PaO_2) • Fraction of inspired oxygen (FiO_2) • Oxygen saturation (SpO_2) • Blood urea nitrogen • Aspartate aminotransferase • Alanine transaminase • Pulse Rate • Potassium • Haemoglobin • Point of care ultrasound (pregnant patients only)	outcome should be collected where they meet CTCAE definition of Grade 3 or Grade 4.

Table 3 –Definition of Unfavourable Outcome (pregnant and non-pregnant adults).

Body system	**Renal**	**Respiratory**	**Cardiovascular**	**Nervous**
Pathology	AKI (Acute kidney injury)	ARDS (Acute respiratory distress syndrome)	Shock	Encephalopathy
Assessment method	Creatinine, Urine output	Arterial blood gas (ABG) analysis: PaO2 or Pulse oximetry: SpO2	Blood Pressure: Mean Arterial Pressure (MAP)	ACVPU (25)
Acceptable definitions	SOFA (26) 0-4 (creatinine test preferred; where creatinine testing is not available, urine output is acceptable provided it is measured accurately)	SOFA (26) 0-4 1. If ABG available: PaO2/FiO2 2. if ABG not available: SpO2/FiO2	1. SOFA (26) 0-4 2. SOFA (26) 0-4 (if inotropes used, dose recorded; if not available tick box 'not available')	ACVPU (25) + seizure

Table 4 – Definition of Unfavourable Outcome (children)

Body system	**Renal**	**Respiratory**	**Cardiovascular**	**Nervous**
Pathology	AKI (Acute kidney injury)	ARDS (Acute respiratory distress syndrome)	Shock	Encephalopathy
Assessment method	Creatinine, Urine output	Arterial blood gas (ABG) analysis: PaO2 or Pulse oximetry: SpO2	Blood Pressure: Mean Arterial Pressure (MAP)	Paediatric GCS (27)
Acceptable definitions	pSOFA (26) 0-4 (creatinine test preferred; where creatinine testing is not available, urine output is	pSOFA (26) 0-4 3. If ABG available: PaO2/FiO2	3. pSOFA (26) 0-4 4. pSOFA (26) 0-4	Paediatric GCS (27) +/- seizure (single prolonged >15 min, or multiple)

	acceptable provided it is measured accurately)	4. if ABG not available: SpO2/FiO2	(if inotropes used, dose recorded; if not available tick box 'not available')	

CHAPTER 3: FUTURE WORK

Overall, this framework has been developed to promote efficiency in the advancement of LF clinical research through a regionally-centred, collaborative methodology. It forms part of a broader objective to delineate a clear pathway through which LF clinical trials can progress efficiently, ensuring sustainable investments are made in a research capacity at a regional level.

Planned future work will involve working directly with regulatory authorities to identify a clear regulatory pathway for Lassa fever therapeutics, including for the involvement of pregnant women and children in clinical trials.

We are now undertaking a project that aims to build capacity in regional research centres to support the sustainable uptake of future clinical trials by local research groups. Part of this project will also involve the development of a pre-positioned protocol for Phase II/III clinical trials, which along with the above will further define the primary outcome measure.

Contrary to our initial plans for this project, our framework has been developed exclusively by experts in the field of LF. Due to restrictions enforced as a result of the COVID-19 pandemic, it was not possible to involve patients in the development of the framework at this stage, unfortunatley. However, funding has been secured to complete this activity and collect data on patients' expectations of LF clinical trials and therapeutics which is to be completed towards the end of 2021. The results of this activity will be assessed against the current framework by ISARIC and NCDC, the coordinators of this project, and incorporated into reports that are to be published by the NCDC. (11)

ACKNOWLEDGEMENTS

The authors would like to thank all participants involved in the development of this project for their contributions:

Chikwe Ihekweazu, Nigeria Centre for Disease Control, Abuja, Nigeria
Piero Olliaro, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Adebola Tolulope Olayinka, World Health Organisation, Abuja, Nigeria
Josephine Bourner, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Chioma Dan-Nwafor, Nigeria Centre for Disease Control, Abuja, Nigeria
Peter Horby, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Alex Paddy Salam, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Laura Merson, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Joseph Okoeguale, Department of Obstetrics and Gynaecology, Irrua Specialist Teaching Hospital, Irrua, Edo, Nigeria
George O. Akpede, Lassa Fever Research and Control, Irrua Specialist Teaching Hospital, Irrua, Edo, Nigeria; College of Medicine, Ambrose Alli University, Ekpoma, Nigeria
Nzelle Delphine Kayem, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Annelies Gillesen, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Nnennaya A Ajayi, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
Christian Akude, Bingham University Teaching Hospital, Jos, Nigeria
Oluwafemi Ayodeji, Federal Medical Center Owo, Ondo State, Nigeria
Chukwuyem Abejegah, Department of Medicine, Infection Control and Research Center, Federal Medical Center Owo, Ondo State, Nigeria
Tolulope Jegede, Department of Paediatrics, Infection Control and Research Center, Federal Medical Center Owo, Ondo State, Nigeria
Maria-Lauretta Orji, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
Pierre Formenty, World Health Organisation, Geneva, Switzerland
Marie Jaspard, The Alliance for International Medical Action (ALIMA), Dakar, Senegal; Institut Nationale de la Santé et de la Recherche Medicale (Inserm), Infectious Disease in Low Income Contries, unit 1219, Bordeaux
Sylvanus Okogbenin, Irrua Specialist Teaching Hospital, Irrua, Edo, Nigeria
Sampson Omagbemi Owhin, Department of Medicine, Infection Control and Research Center, Federal Medical Center Owo, Ondo State, Nigeria
Ephraim Ogbaini-Emovon, Irrua Specialist Teaching Hospital, Irrua, Edo, Nigeria
Olalekan Ezekial Ojo, Federal Medical Center Owo, Ondo State, Nigeria
Nathan Shehu, Jos University Teaching Hospital, Jos, Plateau State, Nigeria
Cyril Erameh, Irrua Specialist Teaching Hospital, Irrua, Nigeria
Sulaiman Jalloh, Ola During Children's Hospital, Freetown, Sierra Leone
Kwame O'Neill, Ministry of Health and Sanitation Sierra Leone

Justus Ndulue Eze, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
Dan Bausch, UK Public Health Rapid Support Team, Public Health England; London School of Hygiene & Tropical Medicine, London, UK
Denis Malvy, The Alliance for International Medical Action (ALIMA), Dakar, Senegal ; Institut Nationale de la Santé et de la Recherche Medicale (Inserm), Infectious Disease in Low Income Contries, unit 1219, Bordeaux
Hilde de Clerck, Médecins sans Frontières, Brussels, Belgium
Michael Ramharter, Bernhard Nocht Institute for Tropical Medicine & Dept. of Medicine University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Jake Dunning, National Infection Service, Public Health England, London, UK; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Robert J Samuels, Kenema Government Hospital, Kenema, Sierra Leone
Jacob Maikere, Médecins Sans Frontières, Brussels, Belgium

This work was supported by the UK Foreign, Commonwealth and Development Office and Wellcome [215091/Z/18/Z] and the Bill & Melinda Gates Foundation [OPP1209135]. This project is part of the EDCTP2 programme supported by the European Union [RIA2016E-1612 - African coaLition for Epidemic Research, Response and Training (ALERRT)].

MEMBERS OF THE NATIONAL LASSA FEVER TECHNICAL WORKING GROUP

S/N	NAMES	Pillar
1	Elsie Ilori	National coordinator
2	Chioma Dan-Nwafor	Coordination
3	Adejoke Akano	Coordination & Research
4	Banji Ipadeola	Surveillance
5	Michael Amedu Onoja	Surveillance
6	Geoffrey Namara	Surveillance/Data Management
6	Akanimo Iniobong	Surveillance/Data Management
8	Amina J. Mohammed	Surveillance
9	Makava Favour	Surveillance
10	Ifeanyi Ike	Surveillance
11	Monica. O. Okoye	Surveillance
12	Bright Friday Onwe	Surveillance
13	Winifred Ukponu	Case Management
14	Sandra Mba	Case Management
15	Lateefat Amao	Case Management
16	Adebola Olayinka	Research
17	Blessing Ebhogaghe	Research
18	Kamji Jan	Research
19	Sunday Eziechina	Research
20	Akinpelu Afolabi	Laboratory
21	Anthony Ahumibe	Laboratory
22	Okafor Obiora	Infection, Prevention & Control
23	Chimezie Anueyiagu	Risk Communication
24	Sarah Peters	Risk Communication
25	Abara Erim	Risk Communication
26	Gbenga Joseph	Logistics
27	Kachalla Mairo G.	Federal Ministry of Agriculture
28	Okoli Ihekerenma	Federal Ministry of Agriculture

29	Okenyi Collins	Federal Ministry of Environment
30	Chika Okpala	Federal Ministry of Environment
31	Omowunmi Precious Oluwafehinti	Incident Management Support
32	Ebere Chinonye Onuebunwa	Incident Management Support
33	Ibrahim A Hussaini	Incident Management Support
34	Geraldine Anoliefo	Incident Management Support

References

1. Nigeria Centre for Disease Control. Lassa fever Situation Report: Epi Week 53: 28 December 2020 – 03 January 2021. Nigeria Centre for Disease Control; 2020.
2. World Health Organisation. Lassa fever https://www.who.int/en/news-room/fact-sheets/detail/lassa-fever2017 [
3. Largest-ever Lassa fever research programme launches in West Africa [press release]. CEPI2020.
4. Nigeria Centre for Disease Control. Lassa Fever 2019 [Available from: https://ncdc.gov.ng/diseases/info/L.
5. Nigeria Centre for Disease Control. Disease Situation Reports. An update of Lassa fever outbreak in Nigeria for Week 52 – December 2019. Abuja, Nigeria; 2019.
6. Ehichioya DU, Dellicour S, Pahlmann M, Rieger T, Oestereich L, Becker-Ziaja B, et al. Phylogeography of Lassa Virus in Nigeria. J Virol. 2019;93(21).
7. Günther S, Lenz O. Lassa virus. Crit Rev Clin Lab Sci. 2004;41(4):339-90.
8. 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(11):e1011-6.
9. Merson L BJ, et al. Clinical characterization of Lassa fever: a systematic review of clinical reports and research to inform clinical trial design. Manuscript submitted for publication. 2021.
10. Nigeria Centre for Disease Control. National Guideline for Lassa Fever Case Management. 2018.
11. Duvignaud A, Jaspard M, Etafo IC, Gabillard D, Serra B, Abejegah C, et al. Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort study. The Lancet Global Health. 2021;9(4):e469-e78.
12. Kayem ND, Benson C, Aye CYL, Barker S, Tome M, Kennedy S, et al. Lassa fever in pregnancy: a systematic review and meta-analysis. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2020;114(5):385-96.
13. Samuels RJ, Moon TD, Starnes JR, Alhasan F, Gbakie M, Goba A, et al. Lassa fever among children in eastern province, Sierra Leone: a 7-year retrospective analysis (2012-2018). American Journal of Tropical Medicine and Hygiene. 2021;104(2):585-92.
14. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever. Effective therapy with ribavirin. New England Journal of Medicine. 1986;314(1):20-6.
15. Centers for Disease Control and Prevention. Lassa fever: Treatment https://www.cdc.gov/vhf/lassa/treatment/index.html#:~:text=Ribavirin%2C%20an%20antiviral%20drug%2C%20has,the%20course%20of%20the%20illness.2014 [
16. Eberhardt KA, Mischlinger J, Jordan S, Groger M, Günther S, Ramharter M. Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis. Int J Infect Dis. 2019;87:15-20.
17. Salam AP CV, Edwards T, Olliaro P, Sterne J, Horby P. Time to reconsider the role of ribavirin in Lassa fever. PLoS NTD (In print). 2021.
18. NCT03993704 Multiple Ascending Oral Dose 14-Day Trial of LHF-535 in Healthy Participants [Internet]. USS National Library of Medicine. 2000 [cited 18/02/2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT03993704?cond=Lassa+Fever&draw=3&rank=12.
19. NCT04055454 A Trial to Evaluate the Optimal Dose of MV-LASV [Internet]. US National Library of Medicine. 2000 [cited 18/03/2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04055454?cond=Lassa+Fever&draw=2&rank=10.
20. World Health Organisation. An R&D blueprint for action to prevent epidemics. Geneva, Switzerland; 2016.
21. Okogbenin S, Okoeguale J, Akpede G, Colubri A, Barnes KG, Mehta S, et al. Retrospective cohort study of Lassa fever in pregnancy, southern Nigeria. 2019;25(8):1494-500.
22. COMET Initiative. Core Outcome Measures in Effectiveness Trials [Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1788-8.
23. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.

24. Olayinka A, Bourner J, et al. A standardised Phase III clinical trial framework to assess therapeutic interventions for Lassa fever. Manuscript submitted for publication. 2021.
25. Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. London: RCP; 2017.
26. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Medicine. 1996;22(7):707-10.
27. Reilly PL, Simpson DA, Sprod R, Thomas L. Assessing the conscious level in infants and young children: a paediatric version of the Glasgow Coma Scale. Childs Nerv Syst. 1988;4(1):30-3.