CEPI | New vaccines for a safer world

Coalition for Epidemic Preparedness Innovations

Preparing for Lassa vaccine clinical trials with targeted epidemiology studies

8th and 9th November 2018

Noguchi Memorial Institute for Medical Research, Accra, Ghana

Workshop Report

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List of abbreviations

ACEGID	The African Centre of Excellence for Genomics of Infectious Diseases
BNITM	Bernhard Nocht Institute for Tropical Medicine
CCHF	Crimean-Congo hemorrhagic fever
CEPI	The Coalition for Epidemic Preparedness Innovations
CDC	Center for Disease Control
CFR	Case fatality rate
CT	Clinical trial
EBS	Event-based surveillance
ELISA	Enzyme-linked immunosorbent serologic assay
FIND	The Foundation for Innovative New Diagnostics
GPS	Global positioning system
HCW	Health care worker
IDSR	Integrated Disease Surveillance and Response
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ISTH	Irrua specialist teaching hospital (Edo State, Nigeria)
IVI	International Vaccine Institute
KGH	Kenema Government Hospital
LASV	Lassa Fever Virus
LASCOPE	Lassa fever clinical Course and Prognostic factors in an Epidemic
LF	Lassa Fever
MERS-CoV	Middle East respiratory syndrome coronavirus
MoH	Ministry of Health
NCDC	Nigeria Centre for Disease Control
NGO	Non-governmental organizations
NHP	Non-human primates
PQ	Prequalification
Q&A	Questions and answers
ReLASV	Lateral flow assay for Lassa virus nucleoprotein
RKI	Robert Koch Institute
RT-PCR	Real-time polymerase chain reaction
R&D	Research and development
SAC	Scientific advisory committee
S&I	Safety and immunogenicity
SOP	Standard operating procedures
TPP	Target product profile
VHF	Viral hemorrhagic fevers
WHO	World Health Organization

Introduction

Given the current development of multiple vaccine candidates against Lassa Fever Virus (LASV), some of which will begin testing in phase I clinical trials at the beginning of 2019, the Coalition for Epidemic Preparedness Innovations (CEPI) organized a workshop on the "Preparing for Lassa vaccine clinical trials with targeted epidemiology studies",
with the objectives to:

1. Identify data needs, objectives, case definition, study designs, laboratory confirmation and key harmonized elements of CEPI funded studies to facilitate vaccine development for Lassa
2. Discuss options for enhanced collaboration and set up of governance of the targeted epidemiology studies to be funded by CEPI

and to answer key questions:

1. What epidemiological research programs are needed in advance of potential phase I, II and III clinical trials in the next Lassa seasons?
2. What data is essential, and what should be standardized between studies?
3. What work is already underway, and what research gaps currently exist?
4. How can Lassa Fever (LF) research groups most effectively collaborate to address the unmet research needs on epidemiology data to facilitate future field evaluation of Lassa vaccines?

The essential question of the workshop was to discuss the ways to define areas where the incidence of symptomatic cases will be high enough to conduct a vaccine efficacy trial. The experts invited to the workshop were those shortlisted (7 of 10 received submissions) from the Lassa epidemiology Expression of Interest, LF subject matter experts and representatives from Ministries of Health (MoH) in affected countries (Nigeria, Guinea, Sierra Leone, Liberia and Benin), World Health Organization (WHO), Africa Center for Disease Control (CDC), non-governmental organizations (NGOs), academic institutions and groups working in collecting Lassa data, and individuals selected with specific expertise. All attendees provided insights to harmonize protocol elements for targeted epidemiology studies. The agenda of the meeting can be found in Annex 1. This report provides a brief overview of the presentations made at the workshop as well as the outcome of the breakout sessions and the ensuing plenary discussions.

Ghana Health Service: Focus on Lassa

Presenter: Dr Franklin Asiedu-Bekoe, *Ghana Health Service*

At the beginning of the session and following a welcome by Professor Ben Gyan, vice-president (CONFIRM) of the Noguchi Memorial Institute for Medical Research, Dr Franklin Asiedu-Bekoe presented the situation of LF in Ghana. Ghana has a population of about 39 million, has 10 regions and 216 districts. LF is recognized as a public health threat in Ghana and is managed as a viral hemorrhagic fever (VHF). In 2011, there were 2 sporadic cases in Amansie West and 1 in West Akim. In 2013, there were 2 imported cases. The rodents *Mastomys* exist in Ghana. The NTCC (inter-ministerial) coordinates a response and control in outbreaks. Ghana has a community-based surveillance with 54 approved points of entry, looking for fever at people at the entry (non-contact thermometers or walk through thermometers) and using alert or simple case definitions through port health and other staff. There are however a number of unapproved points. The VHF surveillance during 2014-2018 captured 14 – 139 cases/year (with a peak in 2016 related to the Ebola outbreak). Laboratory for LF confirmation is at the Noguchi Memorial Institute of Medical Research, Accra. Any of the following constitutes a confirmed case of Lass fever: isolation of the virus, positive IgM serology, demonstration of Lassa antigen by immunohistochemistry or enzyme-linked immunosorbent serologic assay (ELISA), or a positive real-time polymerase chain reaction (RT-PCR). Detection of cases can be early and confirmed but reported high numbers may face challenges due to limited case management facilities.

Integrated Disease Surveillance and Response for detection and response of Lassa Fever: what lessons can we learn from the enhanced surveillance for meningitis?

Presenter: Dr Zabulon Yoti, *WHO AFRO*

By December 2017, 44 African countries have adapted the 2010 Integrated Disease Surveillance and Response (IDSR) Technical Guidelines and 40 countries started the training at district level. Over 90% of Member States are implementing IDSR including event-based surveillance (EBS) systems with at least 90% coverage by 2020. The examples of mapping Lassa risk areas and monitoring the impact of preventive vaccination against meningitis by using IDSR data was presented highlighting that IDSR data (despite some limitations) provide essential data to build on for monitoring trends, outbreak detection and response and risk mapping to inform preparedness. Focus and investment should be given in conducting research during outbreaks since response to outbreaks is incomplete without research data.

Research gaps for Lassa vaccine development, WHO Roadmap for Lassa Fever

Presenter: Dr Vasee Moorthy, *WHO*

Dr Vasee Moorthy described three main focus areas of WHO Research and Development (R&D) Blueprint framework: coordination & fostering an enabling environment, accelerating R&D processes, norms & standards tailored to the epidemic context. The strategic goal for Lassa is to develop, evaluate, license, and prequalify affordable LASV vaccines and identify broad immunization strategies that optimize the potential public health impact of LASV vaccine. The roadmaps for Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola/Marburg, Lassa fever, Nipah virus and Crimean-Congo hemorrhagic fever (CCHF) had been developed as well. The target product profile (TPP) of a LF vaccine defines two scenarios, including preventive (in non-emergency setting) and reactive use (in emergency setting/outbreak use). WHO gives high priority for the development of vaccines for preventive use. For this purpose, a vaccine with more than one dose would be acceptable. However, efficacy after a first dose for use in a reactive setting would be an added value. Detailed information about LF incidence and LASV seroprevalence by geographic area is required to define communities with and without ongoing transmission within the endemic countries in West Africa. In addition, ecologic research and modelling are needed to assess the impacts of climate, environmental, demographic, and socioeconomic changes occurring in West Africa on the rodent reservoir to improve forecasting for LF. Accelerated vaccine development is crucial, and for that, it is very important among others to understand requirements of regulators, prequalification (PQ), policy and financing groups; ensure good dialogue between manufacturers and regulatory, PQ and policy groups; support generation of needed data and share with WHO.

The opening session was concluded with a short questions and answers (Q&A) session. A participant representing Profectus asked regarding the right time when to contact the WHO in the vaccine development process. Dr Vasee replied that there is no defined time for consultation and developers can contact WHO at any time for discussion. Another participant from the US CDC asked about whether the WHO has a research agenda on social science/community engagement as part of Lassa R&D activities. Dr Vasee replied that this was an important point which is not well defined in the R&D agendas for Lassa and should be addressed. Questions were raised also whether a LF vaccine would be targeted against a single clade. Reference was made to the upcoming presentation of Dr Tornieporth. In reply to a question on the usefulness of ISDR, the use of mobile phone technology was raised as an important tool to collect surveillance data. Finally, caution was raised by Dr Danny Asogun on the expected increase in LF cases for the start of 2019, given the continuous increases over the last years in Nigeria.

Lassa Surveillance and Research

At the beginning of session 2, Dr Tornieporth from CEPI presented the vaccine portfolio and clinical development plan. Afterwards, representatives from the research groups in Nigeria, Sierra Leone, Guinea, Liberia and Benin presented the Lassa surveillance system within the countries and the ongoing research projects. Details per presentation are provided below.

CEPI Lassa vaccine portfolio and clinical development plan

Presenter: Dr Nadia Tornieporth, *CEPI*

CEPI's Scientific Advisory Committee (SAC) chose three diseases (MERS-CoV, Lassa, Nipah) for priority vaccine development, derived from WHO R&D Blueprint. More than 30 proposals were received in the first round and 7 partnership agreements were signed. There is a 5-year funding to advance the most promising vaccine candidates for the three priority pathogens. CEPI funds late preclinical through phase II safety and immunogenicity (S&I) trials and investigational stockpile generation. The currently unknown epidemiological data on LF should be available through cohort studies by year 2022 to inform a potential vaccine efficacy trial. Until end of 2018, it should be ensured that site capacity is available and mapped for S&I studies and by 2022 that sites will be available for efficacy trials. Lassa diagnostics should be validated by Q3 2019, build capacity through epi studies, reference sera and antigen available to developers by early 2019, animal model developed by Q4 2019, and strains available by Q4 2019. Currently, 44 clinical sites in Lassa-affected countries have been mapped (ranked by level of preparedness into categories A-D). According to WHO LF vaccine TPP, vaccine would be used as preventive and reactive, would be safe for all age groups and populations, would have cross-protection against all clades with vaccine effectiveness >70%, and a single dose would be used (booster for LT protection). The WHO workshop in April 2018 assessed the following gaps relevant to clinical trials (CT), such as that true disease burden is highly uncertain (by lineage, role of human-to-human transmission, contribution of asymptomatic and mild Lassa infections to LF burden); there is no immunological surrogate or correlate of protection; and diagnostic assays are not yet licensed. The workshop defined what is needed for CTs, such as well-designed seroprevalence studies and enhanced surveillance, including ecological studies in West-Africa; a thorough analysis of the 2018 Nigeria LF outbreak data to better estimate epidemiological drivers and estimates; integrated data management systems at the national level and standardization of surveillance tools, data collection and standardized validated assays across West-African countries. A randomized placebo-controlled design is preferred if feasible with laboratory confirmed LF and/or severe LFs as co-primary endpoints and laboratory-confirmed LASV infection, LF-caused mortality, and potential immunological surrogates of protection as secondary/exploratory endpoints.

A question was raised if reproductive toxicity studies had been conducted for LF vaccines. In reply, Dr Tornieporth stated that such studies are usually not conducted until late phase development. However, in the case of LF vaccine development, such studies may indeed be needed at an earlier stage.

Nigeria

Presenter: Dr Elsie Ilori, *NCDC* and Dr Adebola Olayinka, *WHO*

Surveillance: Infectious disease surveillance activities are ongoing since 1988 and were revised in 2000 with the monitoring of 41 priority diseases, events and conditions introduced in IDSR strategy. Nigeria has the one health approach regarding Lassa surveillance including animal surveillance. It is about 50 years since LASV was first discovered in Nigeria.
Data collection/flow: Structure of IDSR data flow is in place for coordinated flow of data.

The LF thresholds for use at the national are well-defined (1 LF case= outbreak) and cases are captured from all possible sources (health facilities, laboratories, treatment centers, community, traditional healers), which are recorded in case investigation form or by an active case search form, if cases were searched actively. Cases are reported to the national level via electronic means, where information is collated and disseminated nationwide on a weekly basis as a situation report (weekly sitreps) on Nigeria Centre for Disease Control (NCDC) website (www.ncdc.gov.ng) or on daily basis during outbreak periods.
Management: The LF National Technical Working Group is in charge for management of LF and several national LF guidelines (e.g. Lassa Fever Case Management) have been developed and disseminated to States and treatment centers. Since the last two years there is better structure, coordination, higher community awareness, improved communication (using the SORMAS system) and daily reporting.
Laboratory: There are four LASV testing laboratories with a national sample transportation system in place and a quick turn-around time of 24 hours.
Epidemiology: 22 of 36 states are affected; in 2018 (week 1-44) there were 2950 suspected, 553 confirmed, 17 probable and 143 deaths (CFR=25.9%). There were 8587 contacts, of which 36 symptoms positive. The peak of LF reports was seen from January to March.
Challenges: some traditional and cultural practices propagate spread of the disease; myths about the disease discourages disclosure as well as stigmatization of affected persons/families; poor health seeking behavior; poor human resources; poor documentation and archiving; real time reporting not fully developed; poor index of suspicion among health-care workers (HCWs); poor coordination at sub national level; limited knowledge about the disease.
Recommendations: Strengthen risk communication activities and involving anthropologists; increased sensitization on LF for all communities; capacity building for Health workers on LF management; implement real time reporting across all local government areas and states; establishment of emergency operations centers in all states; research to provide answers to unanswered questions and increase knowledge about the disease
Next steps/ongoing: 1) LF is included in "National Strategic Plan for Lassa fever Control 2019-2023" and is aiming for better LF prevention, detection, treatment and reducing CFR to one-digit percentage. Dr Adebola Olayinka presented Nigeria's R&D plan for the LF: Based on the WHO R&D Blueprint[1] Nigeria has developed a National LF Research plan to improve prevention, detection, response and preparedness and other mechanisms to improve research related to LF, provide answers to unanswered questions (e.g. transmission mechanisms, circulating strains etc.) & increase knowledge about the disease, and expand existing research capacity. Some of the ongoing activities were presented, including the observational cohort study of LF clinical course and prognostic factors in an epidemic (LASCOPE) at federal medical center Owo (2018).

Sierra Leone

Presenter: Dr Donald Grant, *MoH Sierre Leone*

Surveillance: The Kenema Government Hospital (KGH) is an important site for LF research and surveillance since 1970-80s. After 1993 the LF program was hindered by the blood diamonds civil conflict. A new VHF ward with 50 beds was established within the KGH, Khan Center of Excellence. The center collaborates with the VHF Ecology team (collects data on environmental factors and test rodents) and VHF Outreach team (conducts active case finding, community sensitization and informs the community for LF related activities that are planned or ongoing). The KGH is in charge for passive and active LF surveillance, included in e-IDSR. A bilateral hearing loss in LF survivors is also recorded.
Management: The KGH supports referral of both suspected, confirmed cases and or samples to the isolation unit for diagnosis and further management, community education in confirmed case communities, sensitization meetings with HCWs, and supports affected districts in the investigation of all lab confirmed cases and trapping of rodents at case and control houses.
Laboratory: In 2005, an international team established a LF laboratory in KGH, and introduced ELISA diagnostics in 2008 and lateral flow assay for Lassa virus nucleoprotein (ReLASV) in 2010. A rapid test finger prick is also used (results in 5 minutes, 95% sensitivity).

Epidemiology: Kenema (300km east of Freetown) is an area known to have the greatest burden of LF in Sierra Leone and in the world (around 1,500 suspected cases). Statistics are available on morbidity/mortality and seasonality.
Next steps/ongoing: 1) There is an ongoing large (>11,000 subjects) seroprevalence/incidence study on house and village level assessment in 28 endemic communities of Kenema, 25 emerging communities in Tonkolili and 25 non-endemic communities in Port Loco with available information on demographics, history, positioning by using global positioning system (GPS) and collected dried blood spots samples. 2) Development of diagnostics in country (RDTs). 3) MoH is setting up a rapid response team with a data base of those being trained at national and district level. 4) Construction of a new VHF ward in Kenema that will serve as part of a clinical trial site in the future 5) Linking researches to academic institutions 6) MoH is currently working on a LF Road map.
Recommendations for CEPI studies: standardize methods for sample collection (dried blood spots vs. phlebotomy) and common diagnostic tests, collect village and household demographic data and use GPS, and base collections on LF seasonality.

Guinea

Presenter: Dr N'Faly Magassouba, *University Gamal Abdel Nassar de Conakry*

Surveillance: The Haemorrhagic Fever Project in Guinea, the Bernhard Nocht Institute for Tropical Medicine (BNITM) in Hamburg and Robert Koch Institute (RKI) in Berlin, conduct joint research on LF diagnostics, ecology and epidemiology for more than two decades. Guinea is in the process to establish surveillance system in health facilities where the LAROCS project (see below) is active by setting up sentinel sites for screening of patients seeking care in health centers.
Laboratory: There are two operational laboratories for LASV testing: one in Conakry (since 1999), another in Gueckédou (last two years) equipped with Master mix, two class 2 biosafety cabinets, Biobank and cold chain and liquid nitrogen tank and real-time polymerase chain reaction (RT-PCR). There is no possibility to do tests in Faranah Regional Hospital. Testing is performed using RT-PCR of serum (plasma) and indirect immunofluorescence for detection of immunoglobulin M (IgM) and immunoglobulin G (IgG).
Research studies already performed: seroprevalence studies, research on cellular immunity to produce a new recombinant immunoblot, studies on the viral evolution, research on reservoir ecology and anthropological studies were already undertaken.
Epidemiology: Preliminary data indicate high seroprevalence in Faranah (total 84%, range 70,5%-91,9% by villages), despite low incidence of acute LF in hospitals.
Next steps/ongoing: 1) There is an ongoing project (LAROCS) investigating LASV prevalence in rodents and seroprevalence in humans, the impact of rodent control measures on both parameters in villages around Faranah, as well as on perception of the disease and the intervention in rural communities. 2) ongoing hospital-based studies in Gueckedou are focused on patients presenting with symptoms of VHF.
Recommendations for CEPI studies:
1) to continue with rodent control implementation and epidemiological surveillance; 2) to involve primary health centers in the surveillance program to better understand the specific epidemiological pattern and the range of disease manifestation of Lassa fever in Guinea; 3) capacity building, including training in virology and molecular biology in Conakry, training for community and HCWs on LF cases management in Faranah district; to involve young Guinean students in training related to project implementation 4) to include LF in the national surveillance system.

Liberia

Presenter: Dr Jefferson Sibley, *Phebe Hospital & David Wohl* & Dr William Fischer, *UNC* (on PREPARE)

Surveillance: Prior to 2004, Liberia had a vertical surveillance program (including LF) and from 2004 has adopted the IDSR with added diseases/conditions: maternal death, neonatal death, unknown cluster of deaths and human event, and human rabies. Surveillance system was hugely disrupted and collapsed due to Ebola virus outbreak 2014-2015 (silent years).
Data collection/flow: Paper based recording (2004-2014) with reporting from/and to community-health facility-district-county-national level.
Epidemiology: Incidence is closely related to seasonal patterns and is endemic in 4 counties: Nimba, Bong, Grand Bassa, Lofa. Other counties with reported LFs include: Margibi, Grd Kru & and Montserrado. LF cases: in 2016= 67 suspected, 15 confirmed; in 2017=53 suspected, 20 confirmed; in 2018 (week 1-43) =175 suspected, 20 confirmed (12 females, 8 males), with case fatality rate (CFR) of 65% (13/20).
Next steps/ongoing: There is an ongoing 4-years PREPARE (prevalence, pathogenesis and persistence) study in Phebe hospital (by The University of North Carolina at Chapel Hill). PREPARE was launched in 2018 to determine the incidence, pathogenesis, natural history and sequelae of LF in Liberia. Two groups of patients are included in the study: febrile patients admitted to Phebe hospital (intended to enroll 1000 patients per year for 4 years) and patients with confirmed or suspected LF. Febrile patients admitted to Phebe hospital provide one-time blood sample for real time LASV PCR and storage for serological studies to determine background prior to LASV seroprevalence. Febrile patients that have positive LASV RNA PCR (study or clinical test) and/or any persons with clinical presentation compatible LF are eligible for participation in a longitudinal study and are followed throughout the course of acute illness and every 12 weeks for 48 weeks. Blood is obtained at 6 time points during hospitalization for LASV RNA PCR and Real-Time antibody testing and serum storage. Blood and genital fluid are obtained every 3 months for LASV RNA PCR and real time antibody testing (blood) and storage.

Benin

Presenter: Dr Anges Yadouleton, *MoH Benin*

Surveillance: The surveillance of LF is under the IDSR strategy. Strengths of the existing surveillance are: a) good involvement of community HCWs and participation of local authorities and leaders on peripheral level; and b) quick alert during outbreaks and rapid mobilization of funding at the central level. There is also a hospital-based (monthly collection) surveillance using case definition of persistent fever > 38°C and no response to malaria drugs and antibiotics. There are 9 health centers (4 in the north and 5 in the south) that participate in the surveillance of VHF where samples are collected from but need to be transferred to the south of Benin for testing. Delays obtaining the lab results can take up to 3-4 months.
Data collection/flow: Reporting from/and to sub-district-district-regional- departmental-national level. In non-outbreak period reporting is done on monthly basis, in outbreak period on daily basis. Reporting is via telephone (Whatsapp), paper or/and internet (only at departmental level to MoH).
Laboratory: Laboratory of VHF was implemented in Benin in collaboration with BNITM. Conventional RT-PCR is used in laboratory of VHF in Benin (Cotonou, Lazare site), and same laboratory testing protocol is used in BNITM collaboration for comparison of results.
Epidemiology: Benin has on average 10 suspected and 2 confirmed cases per outbreak. LF cases: in 2014= 15 suspected, 9 deaths; in 2016=84 suspected, 83 samples were sent to laboratories, including external laboratories (Lagos, IRRUA, BNITM in Hamburg, Germany and Institute Pasteur in Lyon, France), 16 samples were confirmed, 28 deaths; in 2017=8 suspected, 2 deaths; in 2018=7 suspected, 8 deaths.
Challenges: There are weaknesses in the current surveillance, such as delay of report transmission (> 3-4 month of delay); delay of sample transfer to the central laboratory-Cotonou; high fee of communication (SMS, internet); lack of health staff and CHWs training (< 1 training/year); lack of

sensitization out of outbreak periods; no compensation of community HCWs. There is a high probability of future outbreaks also due to the high migration flow between Benin and Nigeria, low reactivity of health system, lack of preventive strategy.
Next steps/ongoing: 1) Main question which needs to be answered and where no data are currently available is whether LFV reservoirs are autochthonous (if so, where?) or imported. There is an ongoing research on ecology, distribution and habitation of rodents (*Mastomys*), including testing for LFV using P3 laboratory in the field. Some rodents were found to be positive for LFV and sequencing revealed a distinct viral strain (different to Nigeria), prompting further investigation in rodents across the country and investigation whether Benin has its own viral reservoir. 2) Currently a small arranged space for hospitalization of suspected and confirmed cases is under construction and a team of 2 MDs, 2 nurses, 2 midwives, 3 hygienists, 2 biotechnologists and 2 drivers has been formed.

Epidemiology and research needs

Diagnostics for Lassa fever case confirmation and experience from a hospital setting

Presenter: Dr Danny Asogun, *ISTH*

The Institute of Lassa Fever Research and Control (ILFRC), Irrua specialist teaching hospital (ISTH) in Edo State, Nigeria, sampled more than 13000 LASV samples (2008-2018), of which 1650 were LASV positive. In 2018, 2466 samples were tested, of which 497 were LASV positive. The ISTH is using conventional RT-PCR (in house S segment) and since 2017 also real time RT-PCR (Altona v1.0 RealStar & Nikisins). The sensitivity and specificity of the Altona 1.0 and Nikisins were estimated, resulting in sensitivity 88-96%, specificity of > 99%. Use of combined essays showed best sensitivity (>98%) and specificity (>99%). Since 15 Oct 2018, Nigeria and Europe started validation of LASV Altona 2.0 kit (280 samples tested so far). Seroprevalence, incidence and risk factors of LF are being assessed in Edo state in Nigeria in an ongoing pilot study using ELISA (July-October 2018) with 700 participants included. Samples and data will be analyzed in Nov/Dec 2018. There is work in progress by The Foundation for Innovative New Diagnostics (FIND) to define lab testing needed at various levels.

Genomic Analysis of Lassa Virus during an Increase in Cases in Nigeria in 2018

Presenter: Dr Christian Happi, *Redeemer's University*

The African Centre of Excellence for Genomics of Infectious Diseases (ACEGID) is located at Redeemer's University and is a consortium of West African academic and medical institutions that are collaborating with academic and research Centers of excellence in the USA and partners in the Industry. Institutions in this consortium have a long-standing partnership in research and training. In early 2018, Nigeria had a big LF outbreak (with 78 deaths), declared grade II public health emergency by the WHO and NCDC. The ACEGID sequenced in real time over 90% of all positive cases from 2018. No new strains were found during this outbreak, majority found were clade IIA (east), IIB (west), and III (north)[2]. 20% of negatives become positive on meta-genomic analysis.

Data needs to prepare for Lassa vaccines – clinical trials, modelling and vaccine strategies

Presenter: Dr Ira Longini, *University of Florida*

During a recent workshop in Paris organized by WHO, study designs for evaluating the efficacy of a vaccine against LF were discussed. According to the discussions, a prospective, randomized, double-blind, placebo-controlled, efficacy trial would be the best Lassa vaccine efficacy trial design. The trial would be randomized in geographic clusters in areas mapped to have transmission, and HCWs would

be included. It is important to consider the baseline screening for seropositivity of the trial participants to decide whether to vaccinate them or not (answer currently unknown). Screening at baseline could contribute to design an immune correlate of protection, with this design, if the vaccine works. Primary endpoint would be a lab confirmed LF (any illness), while secondary could include infection (could move to primary endpoint); stratified analyses on prior immune measures; stratified analyses on different lineages and/or clades (sieve analysis); death and immunological correlates of risk and surrogates of protection, i.e., surrogates for vaccine efficacy. Multiple vaccines could be tested. Mathematical models for Lassa transmission in Nigeria and other countries at risk of Lassa are under development. Data needed for CT are illness incidence data for confirmed cases, Infection prevalence and incidence data when possible, immune data and rodent data.

Harmonizing protocol elements for targeted epidemiology studies

1. Data needs and objectives for CEPI studies

Participants were divided into 5 groups to discuss and prioritize the data needs and objectives for Lassa research in preparation of Lassa vaccine CTs. Some data elements may be more relevant for the preparation of clinical trials (priority CT) and others to justify the need for the vaccine or in preparation for vaccine implementation, strategy and market (priority impact). The groups prioritized data needs accordingly by using the following priority levels: 1. Critical, must have; 2. Important but not critical; 3. Nice to have.

Outcomes of the session and post-workshop review:

1) Data needs: Table 1 shows the median and average priority levels scores on the data needs as assessed by the groups. Accurate and recent estimates of incidence of LF and pre-existing immunity by age, gender and geography were assumed to be of most critical value for both CTs and impact.

Table 1. Epidemiological data assumed to be of critical/important/good value for vaccine development

	Priority CT		**Priority impact**	
	median	average	median	Average
General LF epidemiology:				
· Accurate and recent estimates of incidence of LF based on a geographically comprehensive area, by age and gender	1.0	1	1	1
· Precise estimates on (acute) LF disease severity (incl. pathogenicity), by age and gender, and among pregnant women	2.0	1.25	1	1.25
· Precise estimates on LF long term disease outcomes, complications	2.0	1.5	1.5	1.5
· Precise estimates of the time intervals in natural disease history/progression of LF	2.5	1.75	2	1.75
· Pre-existing immunity, by age, gender and geography	1.0	1	1	1
LASV Clade specific epidemiology				
· Geographic and temporal spread	1.0	1.5	1.5	1.5
· Incidence by LASV clade	1.0	1.5	1.5	1.5
· Estimating any potential association between disease severity (incl. complications and sequelae) and LASV clade	1.0	1.25	1	1.25
· Estimates of clade-specific seroprevalence by geography	2.0	2	2	2
· Other:				
Transmission and spatial epidemiology				
· Transmission/attack rate and secondary attack rate (5-7%?)	1.5	1.75	2	1.75
· Transmission: a) exposure to rodents/area endemic for Lassa; b) contact with Lassa cases	2.0	1.75	2	1.75
· Serial interval (12 days?)	2.0	2.5	3	2.5
· Role of geographical clusters	2.0	2.25	2	2.25
Referral practices and health systems seeking behavior	1.0	1.25	1	1.25

Priority levels for data needs: 1. Critical, must have; 2. Important but not critical; 3. Nice to have.

2) Objectives for the studies

The group decided on the main **aims** as follows: a) to conduct an epidemiological study that will enable a Phase III placebo-controlled individual-randomized LF vaccine trial to be designed; and b) to conduct an epidemiological study to facilitate decisions regarding introduction of vaccination should a safe and effective vaccine be developed.

The group decided on the main **objectives:**
Primary objectives:
- Age- and sex-specific incidence of LF in a number of well-defined geographical areas;
- Age- and sex-specific seroprevalence in the same well-defined geographical areas.

Secondary objectives:
- Identification of risk groups;
- Formal definition of a case of LF including range of severity;
- Identification of risk factors, and social and ecological drivers of incidence;
- Documenting knowledge, behavior and attitudes towards LF and LF vaccine in communities and health care workers.

The group also discussed that studies should have standardized methodologies with regards primary objectives and that a range of other studies are needed, including studies on severity, clades, phylogeography, etc. These do not have to be conducted in every site, however. It should be ensured that data can be used for other studies, such as to help improve diagnostics.

2. Case definition

A sub-group of 17 workshop participants including representatives from WHO, regulators, clinicians, epidemiologists, clinical trialists from Nigeria, Ghana, Liberia, Guinea, USA, Benin and South Korea, debated questions related to the case definition. This group of experts debated on case definitions to capture most cases (epidemiological case finding with high sensitivity) and on key variables to collect for clinical trial case definition. The group used table 3 to prioritize data elements which should be considered for suspected case definition (for epidemiological studies and for a clinical case definition for clinical trials), for suspected case definition for the epidemiological studies and for differentiation between mild, moderate or severe LF (severity). The group prioritized data needs accordingly by using the following priority levels: 1. Critical, must have; 2. Important but not critical; 3. Nice to have.

Outcomes of the session and plenary discussion:

1) Proposed Case definitions:
   - Suspected Lassa fever case: History of fever or fever for > 48hours, but <21 days AND any of the following additional symptoms (described in detail below)
   - Probable case: Death or loss to follow up of suspected case with no laboratory confirmation.
   - Confirmed case: Febrile illness with temperature ≥ 38°C for 48 hours and up to 21 days OR a history of fever OR Illness clinically suspected to be Lassa Fever by the Investigator with a positive RT-PCR.

The draft WHO case definition for clinical case management (fever and any of the following additional symptoms) was used as a starting point and was updated (changes highlighted blue) by the working group as follows:

Fever
- Any history of fever
- Any temperature ≥ 38°C (Brighton Collaboration)
- Measured by Axillary or non-contact thermometer (during outbreaks)

  Measurement by both methods with comparison of recordings could be done outside outbreak season.

- Duration: 48 hours or more but less than 21 days.

AND any of the following additional symptoms:

- Any symptom: sore throat, malaise, headache, cough, myalgia, nausea, vomiting diarrhea, retrosternal pain, hearing loss, early signs of bleeding e.g. conjunctival bleeding, woman with abnormal vaginal bleeding; OR
- Any complications, such as encephalopathy (seizure, coma, irritability, confusion), shock, bleeding, acute kidney injury; OR
- Pregnant woman with spontaneous abortion, post-partum hemorrhage, intrauterine fetal demise, sepsis; OR
- Travel to endemic area within past 21 days plus contact with rodents; OR
- Contact with LF patient or probable case within past 21 days.

2) For defining severity of the case, draft WHO case definition for clinical case management was used as a starting point and was updated (changes highlighted) by the working group as follows:

Severe case:

- Any complications, such as encephalopathy (seizure, coma, irritability, confusion), shock, bleeding, acute kidney injury; AND/OR
- Abnormal LFT, RFT, Coagulation profile.
- Grading of additional symptoms by functional impairment.
- Pregnant woman with spontaneous abortion, post-partum hemorrhage, intrauterine fetal demise, sepsis.

Moderate and Mild cases:

- TBD based on retrospective analysis of clinical and laboratory data obtained during epidemiological study.
- Ditto other parameters indicative of severity.

3) During the plenary session, the whole group discussed the use of fever or history of fever and the use of AND (after fever) in the suspected case definition. Following the input received during the plenary, the working group agreed to open up the case definition to maximize case finding. The revised case definition would then simply be:
   • Febrile illness with temperature ≥ 38°C for 48 hours and up to 21 days OR a history of fever with a positive RT-PCR.
   These definitions will likely require the field use of rapid diagnostic tests for initial screening, as well as significant laboratory capacity building. Confirmed case definition was revised and agreed as stated above by the whole group.
   During the plenary session, the whole group also discussed and decided on the following considerations for dealing with the additional symptoms:
   - Clinical evaluation will be performed for additional signs and symptoms as per draft WHO case definition;
   - These data will be collected in a standardized manner to allow refinement and performance assessment of case definitions for future epidemiological and clinical trials;
   - Laboratory testing will be done for confirmation of LF as well as clinical labs (minimum liver and renal function tests, coagulation profile, such as haematocrit, platelet count);
   - Local standards of care may require additional tests, based on clinical presentation and at medical discretion;

4) Feedback received on priority rankings (completed table 3) was collated and analyzed from 11 experts of the group. Detailed feedback is shown in Table of Annex 2 with the median and average priority levels scores on which elements should be considered for suspected case definition for clinical trials and epidemiological studies and with the percentage (%) of participants answering that specific data element is important for assessment of severity and probable case definition. As other important variables, the following were mentioned: one

participant mentioned microscopic hematuria (important for epi studies, CT and probable case definition, but not severity), and one participant mentioned the following variables important for assessment of severity: viral load/CT values; LFT; urea/creatinine; age/pregnancy; comorbidity.

3. Study design and methodologies

Participants divided into group to discuss the design of the epidemiological study (studies) that will enable a Phase III trial to be undertaken, and to inform vaccine decision-making should a safe and effective vaccine become available. In all studies the core elements should be standardized across all sites, including having common questions with a common standardized questionnaire to cover basic demographics, household and environmental characteristics and also common clinical variables and coding to ensure that identical definitions of cases will be used in each site. Also, collection and storing of data should be standardized, including common electronic data capture methods (such as tablets) and a common database.

Outcomes of the session and plenary discussion:

1) The group decided that before embarking on main epidemiological study (studies), a comprehensive review of what we know about LF at the moment and data already available should be systematically collated, analyzed and published. It should also be identified if there are existing serum banks or other resources that could be used to perform a seroprevalence survey.

2) To estimate the age-specific incidence of infection and disease (including the full range of severity) in well-defined populations, a prospective cohort study with active follow-up will be conducted, including following elements:
   a) A number of well-defined high-risk populations based on existing data on case loads that are relatively stable and served by well-defined health facilities would be selected;
   b) Households (GPS) from these communities would be recruited and baseline data, demographics, risk status and knowledge and attitudes towards LF obtained. Public health information on how to reduce their risk of LF will be also offered to these communities, as well as rodent control could/should be offered;
   c) Baseline serological status of participants would be obtained;
   d) Follow-up would be for at least 1 year (possibly more, depends on the resource availability);
   e) During the follow-up, there would be an active case-find for which case definition should be wide. Home visits would be every 1-4 weeks (TBD) and those with Lassa-like symptoms would enter a diagnosis algorithm. Testing using RDT would be performed, if available;
   f) At end of study (or perhaps at the end of each year), members of cohort would be tested again to determine sero-incidence;
   g) Cases would be asked about health-seeking behavior.

Also, health authorities would be notified that the case was found.

3) To determine age-specific seroprevalence of LASV across region, the group decided on three possible options, which in terms of answering the question follow as option 1 (best) to 3 (worst), and opposite in terms of cost as option 1 (most expensive) to 3 (least expensive). These options could be used subsequently or as combination of:
   a) Option1: community-based seroprevalence studies in other areas would be conducted and districts based on case-data would be selected as high-medium-low incidence districts.
   b) Option 2: existing serum banks would be used, which could possibly include blood donors or antenatal screening samples (though this would be restricted by age and perhaps sex).
   c) Option 3: sentinel hospitals across the region would be identified, and Lassa testing as part of diagnostic work up for febrile cases would be introduced.

4) To determine risk factors and social and ecological drivers of incidence, the group proposed to conduct two studies:
   a) Study 1: Case-control study as possibly a case-negative design to assess individual, household and community characteristics associated with being a confirmed case. Study would be conducted over different settings using (as far as possible) comparable methods.
   b) Study 2: Analysis of existing data and using a regression (including spatial regression) analyses to identify risk factors and how they may vary over time. This would require analysis of a common standardized database (across all countries), and therefore common questionnaires (as far as possible) variables, etc.
   c) As an option data could be collected also on prevalence of LASV in rodents, and rodent population during main cohort study (particularly if rodent control offered).

5) To document the knowledge, behavior and attitudes towards LF and LF vaccine in communities and HCWs, the group proposed to conduct three studies, which would assess:
   a) Study 1: health systems research could be conducted to understand the extent to which referral patterns and local specimen transport systems/diagnostic processes can support whichever diagnostic/case definition threshold is chosen once the vaccine is developed.
   b) Study 2: health seeking behavior research could be designed to understand how, when and why individuals seek /do not seek care and would include mixture of quantitative and qualitative methods.
   c) Study 3: anthropological studies could be conducted to explore local perceptions of LASV/vaccines to support community engagement strategies required for vaccine trials and subsequent roll out).

6) The group did not have time to discuss how the risk groups could be identified and is for further discussions.

4. Laboratory confirmation

Participants divided into a group of laboratory experts to agree on diagnostic approach (including preferred method and minimal standards for molecular test to confirm LASV, serological test and LASV sequencing), agree on commonly used protocol on laboratory methods and to gain knowledge on main challenges in lab diagnostic of different sites and any other useful information to be collected.

Outcomes of the session and plenary discussion:

1) Molecular tests
Currently, 2 Conventional PCR and 2 RT-PCR molecular tests are used in different research sites. Conventional PCR and/or RT-PCR using blood (plasma) could be used for all study sites to ensure comparability. Four countries currently using the same RT-PCR assays (Altona, Nikkisins), which could be fit for the use of case of case confirmation for a vaccine efficacy trial by all sites, however, these RT-PCR should be validated using a defined panel of Lassa strains. FIND and WHO are validating Nikkisins assays, there is existing validation for the Altona 1.0 and validation needs to be done for all other molecular assays currently in use.

2) Serological tests
To ensure comparability between the sites, the same serological test should be used in all sites. The group recommended 5 possible serological tests which should be used: Ag capture IgM and IgG, Recombinant Lassa Virus ELISA, Mag PIX, Immunofluorescence based on NP and GP. If not, the same serological test would be used, a comparison between the sites could be enabled by well characterized sample panels, standardized, equipment, reagents and antigens.

3) Genome sequencing
The LASV genome sequencing is currently implemented in Nigeria, Sierra Leone, Liberia and not done in Guinea, Benin (support by BNI). Major LASV genome sequencing data gaps identified are lack

of data and lack of in country capacity. To ensure that such data are gathered to inform vaccine design, each country should plan for generating spaciotemporal data on sequencing and set the minimum criteria for number of samples and frequency.

3) Other information
The main barriers to implement RT-PCR in the different research sites identified in the group were funding for consumables and reagent and issues of supply chain, biosafety, cold chain and specimen repository. As part of implementing the WHO R&D Blueprint recommendation on data and sample sharing, a sample sharing mechanism and agreement among the consortium members would be possible (MOU, MTA). As other considerations, the group also mentioned the need for establishment of basic lab SOPS, need for building specific technical capacity, train biomedical engineers and the need for maintained resources.

Further research

Prioritizing exploratory research objectives to facilitate vaccine development

Presenter: Dr Connie Schmaljohn, *USAMRIID*

As research priorities for the LASV vaccine, the virus diversity should be defined (including using gene sequencing/reverse genetics and developing standardized assays to detect all strains) and animal models should be developed/characterized. In defining virus diversity, questions should be answered, such as whether there are differing pathogenicities associated with various strains of LASV and whether there are rodents infected with LASV in regions that have not reported LF. The most common small animal model for LASV is Strain 13 (inbred) guinea pigs. Hartley (outbred) guinea pigs can also be used but require more adaptation of the virus. The Cynomolgus macaques is the most commonly used non-human primates (NHPs) model. In NHP survivors of LF, a hearing loss was observed, autoimmune vasculitis, persistent LASV antigen in the arteries with perivascular lesions in the brain, heart, kidney and liver.

CEPI's approach to standards, essays and animal models

Presenter: Dr Johan Holst, *CEPI*

The International Biological Standards enable calibration and harmonization of assay data. CEPI's special Working Group is working to define the need, specifications and approach for developing biological standards, assays and animal models for CEPI's vaccine development programs. A working Task Force for Lassa Standards & Assays was established, and anyone is invited to join and contribute to discussions. In the next steps it is planned to finalize Lassa biostandards procurement; define key assays & develop the standard operating procedures (SOPs).

Partnership and good governance

Principles of partnership and its governance

Presenter: Dr Nathalie Imbault, *CEPI*

Dr Imbault reviewed the current consortia and proposed four options for governance structures, such as having one large consortium; two consortia based on geographic location and existing networks; country specific projects (five countries each), and seven individual consortia. The group discussed options, such as keeping the existing consortium as one or having different working groups (e.g. lab, data etc.). There was a general consensus that a single large consortium would be the

preferred way forward. CEPI will modify the Program Governance Structure diagram and come back to the countries.

Strengthening the consortium through partnership and capacity building

Presenter: Dr Nicole Lurie, CEPI

CEPI aims to strengthen capacity while conducting epidemiologic studies by building or strengthening relationships, improving the monitoring and quality management of relationships and developing new skills. Current consortia already collaborate with others and networks often overlap. CEPI would like to measure how the research network is developing, i.e. to see which organizations are connected to one another; to strategize how to strengthen ties, fill gaps, increase efficiency; to support capacity building/strengthening; to see how the principles of partnership are being fulfilled, e.g. trust, mutual respect, reliability, equity; and to measure the quality of connections. CEPI plans to conduct some network statistics. CEPI also proposed to consortia to use the Partner Tool to track progress over time within and across consortia so that each consortium has an option to measure its own partnerships and can control its own data. The project steering committee could use overall consortia data to made recommendations and CEPI would need the feedback from consortia about what to measure.

Key meeting outcomes, areas for further discussion

Presenter: Peter Smith, LSHTM and Gunnstein Norheim, CEPI

Dr Peter Smith summarized and concluded the meeting by mentioning that many key groups are already doing studies on Lassa and the way forward is to bring these groups together to work on the common protocol to answer the essential question: “is it possible to define areas where the incidence of symptomatic LF cases is high enough to conduct clinical trials?”.

Dr Gunnstein Norheim added some key outcomes of the workshop:

- Consensus on harmonized protocol synopsis with preferred positions mapped on the data needs and study objectives, case definition, study designs and methodology, laboratory diagnosis and other elements needing harmonization;
- A strong willingness to collaborate was expressed and an insight in preferred options of governance was obtained.

<u>Recommendations:</u>

- Collate available data and ongoing studies relevant for primary & secondary objectives
- Map existing sample collections that would be amenable and inform seroepi studies

Next steps

Presenter: Gunnstein Norheim, *CEPI*

1. Call for proposals: CEPI will launch an initiative to review existing data and will engage consortia in synopsis draft development on prospective cohort study with follow-up and age-specific seroprevalence of LASV across region. CEPI will also internally develop the call mechanism, including the priorities for funding based on objectives, scope and conditions, and shaping the submission requirements (templates will be provided), including project description; integrated epidemiology study work plan with study outlines and work packages; budget, milestones and governance.

2. Selection of proposals: Proposals will be reviewed, including technical review of submission and proposed study designs; budget, financial due diligence and resource review; and governance discussions. In selection the SAC and Board Investment sub-committee will be involved followed by negotiations and contract signing, project initiation by partners and Project Steering Committee.

References

1. WHO. R&D Blueprint: Lassa fever. Draft, May 2018. Available at: http://www.who.int/blueprint/priority-diseases/key-action/lassa-fever/en

2. Siddle, K.J.; Eromon, P.; Barnes, K.G.; Mehta, S.; Oguzie, J.U.; Odia, I.; Schaffner, S.F.; Winnicki, S.M.; Shah, R.R.; Qu, J.; et al. Genomic Analysis of Lassa Virus During an Increase In Cases In Nigeria In 2018. N. Engl. J. Med. 2018.

Annex 1.

Workshop agenda

Thursday 8 November 2018
Chair for Day 1: Vasee Moorthy & Dicky Akanmori

START	DURATION	TOPIC	PRESENTER
08:00	30 mins	Registration	
Session 1: Introduction			
08:30	10 mins	Meeting objectives	Gunnstein Norheim, *CEPI*
08:40	10 mins	Welcome	Ben Gyan, *Noguchi Memorial Inst. for Medical Research*
08:50	10 mins	Ghana Health Service: Focus on Lassa	Franklin Asiedu-Bekoe, *Ghana Health Service*
09:00	20 mins	Research gaps for Lassa vaccine development, WHO Roadmap for Lassa Fever	Vasee Moorthy, *WHO*
Session 2: Lassa Surveillance and Research			
09:20	20 mins	CEPI Lassa vaccine portfolio and clinical development plan	Nadia Tornieporth, *CEPI*
09:40	25 mins	Nigeria: Surveillance, ongoing research Nigeria's R&D plan for Lassa	Elsie Ilori, *NCDC* Adebola Olayinka, *WHO*
10:05	20 mins	Sierra Leone: Surveillance, ongoing research	Donald Grant, *MoH Sierra Leone*
10:25	***25 mins***	***Break***	
10:50	20 mins	Guinea: Surveillance, ongoing research	N'Faly Magassouba, *University Gamal Abdel Nassar de Conakry*
11:10	20 mins	Liberia: Surveillance, ongoing research Overview of the PREPARE study	Jefferson Sibley, *Phebe Hospital* David Wohl & William Fischer, *UNC*
11:30	20 mins	Benin: Surveillance, ongoing research	Yadouleton Anges, *MoH Benin*
11:50	20 mins	Integrated Disease Surveillance and Response for detection and response of Lassa Fever: what lessons can we learn from the enhanced surveillance for meningitis?	Zabulon Yoti, *WHO AFRO*
12:10	***1 hr***	***Lunch***	
Session 3: Epidemiology and research needs			
13:10	30 mins	Diagnostics for Lassa fever case confirmation and experience from a hospital setting Genomic Analysis of Lassa Virus during an Increase in Cases in Nigeria in 2018	Danny Asogun, *ISTH* Christian Happi, *Redeemer's University*
13:40	60 min	Data needs to prepare for Lassa vaccines – clinical trials, modelling and vaccine strategies	Ira Longini, *University of Florida* John Edmunds, *LSHTM*
14:40	***20 min***	***Break***	
Session 4: Data needs and objectives for CEPI studies			
15:00		Introduction Group work (breakout into small groups) Presentation from each group Discussion and conclusion	
Closure 17.00			

Friday 9 November 2018
Chair for Day 2: Peter Smith & Mimi Darko

START	DURATION	TOPIC	PRESENTER
08:30	30 mins	Summary of conclusions: Data needs and objectives Objectives for day 2	Ira Longini, *University of Florida* John Edmunds, *LSHTM*
Session 5: Breakout sessions - Harmonizing protocol elements for targeted epidemiology studies			
09:00	2hr	Breakout sessions • _Case definition • _Study design and methodologies • _Lassa laboratory testing	
11:00	***20 mins***		***Break***
Session 6: Further research			
11:20	20mins	Prioritizing exploratory research objectives to facilitate vaccine development	Connie Schmaljohn, *USAMRIID*
11:40	15 mins	CEPI's approach to standards, assays and animal models	Johan Holst, *CEPI*
11:55	***1h 35mins***		***Lunch***
Session 7: Summary of core protocol elements			
13:30	30 mins	Summary: Case definition	Erin Boateng, *FDA Ghana* Anh Wartel, *IVI*
14:00	30 mins	Summary: Study designs and methodologies	Franklin Asiedu-Bekoe, *Ghana Health Service* Fred Binka, *University of Ghana*
14:30	30 mins	Summary: Laboratory confirmation	William Ampofo, *Noguchi Memorial Institute for Medical Research*
15:00	***20 mins***		***Break***
Session 8: Partnerships and good governance			
15:20	40 mins	Principles of partnership and its governance	Nathalie Imbault, *CEPI*
16:00	15 mins	Strengthening the consortium through partership and capacity building	Nicole Lurie, *CEPI*
Next Steps and Close of Meeting			
16:15	15mins	Key meeting outcomes and areas for further discussion	Peter Smith, *LSHTM* Mimi Darko, *FDA Ghana*
16:30	15 mins	Next steps and close of meeting	Gunnstein Norheim, *CEPI*
Closure 16.45			

Group work sessions:

	Chaired by ***Ira Longini*** ***John Edmunds*** *Facilitated by* ***Kwasi Amfo*** ***Fred Binka*** ***Thomas Verstraeten*** ***Franklin Asiedu-Bekoe***	**Data needs & objectives**	**Outcomes**: Harmonized data needs and objectives
B	*Chaired by* ***Eric Boateng*** ***Anh Wartel*** *Facilitated by* ***Kwasi Amfo***	**Case definition**	**Outcome**: Harmonized case definition
C	*Chaired by* ***Franklin Asiedu-Bekoe*** ***Fred Binka*** *Facilitated by* ***John Edmunds***	**Study designs & methodologies**	**Outcomes**: Type of data collected, at baseline and follow-up, case record form elements, timing of survey and blood samples
D	*Chaired by* ***William Ampofo*** *Facilitated by* ***Christian Happi*** ***Danny Asogun*** ***Connie Schmaljohn***	**Laboratory confirmation**	**Outcomes**: Minimum standards for diagnostics to support regulatory approval of vaccines

Annex 2

Completed table scoring of data needs for case definition and severity

Priority levels for data needs: 1. Critical, must have; 2. Important but not critical; 3. Nice to have. Yellow= most important for probable and suspected case definition for epidemiological studies & CT. Green=more important for definition for CT than for epidemiological studies. Pink=most important for severity.

Category	Sub-category	Variable	Suspected case definition				Severity		Probable case definition	
			Epidemiological studies		Clinical trials (CT)		n=Important/yes; N=11		n=Important/yes; N=11	
			Average	Median	Average	Median	n	n/N (%)	n	n/N (%)
Fever		Fever threshold	1,45	1	1,20	1	5	45%	7	64%
		Fever duration	1,30	1	1,22	1	5	45%	8	73%
Rule out		Malaria, Typhoid	1,44	1	1,50	1	2	18%	6	55%
		No response to 2d anti-malarials or antibiotics	1,30	1	1,33	1	3	27%	7	64%
		Local inflammation	1,91	2	2,20	3	2	18%	4	36%
Symptoms	General	Malaise	1,64	1	1,44	1	4	36%	6	55%
		Headache	1,55	1	1,67	2	5	45%	7	64%
		Myalgia	1,50	1,5	1,38	1	4	36%	6	55%
		Profuse weakness	1,82	2	1,67	1	8	73%	3	27%
		Arthralgia	1,88	2	1,88	2	5	45%	6	55%
		Tinnitus	1,75	1,5	1,88	2	5	45%	5	45%
	Cardio Vascular	Retrosternal pain	1,70	1	1,57	1	4	36%	5	45%
		Facial swelling	1,73	2	1,56	1	7	64%	5	45%
		Persistent Hypotension	2,30	2,5	1,71	1	7	64%	3	27%
	Respiratory	Sore throat	1,45	1	1,33	1	6	55%	5	45%
		Cough	1,82	2	1,56	1	4	36%	5	45%
	Gastro Intestinal	Nausea	2,00	2	2,00	2	3	27%	5	45%
		Vomiting	1,91	2	1,67	1	6	55%	5	45%
		Diarrhea	2,09	2	1,78	2	5	45%	5	45%
		Abdominal pain	1,70	1,5	1,75	1,5	6	55%	4	36%
	Genital	Abnormal vaginal bleeding	1,56	1	1,38	1	7	64%	3	27%
	Ocular	Conjunctivitis	1,70	1,5	1,63	1,5	2	18%	4	36%
	Dermatological	Rashes	2,50	3	2,38	2,5	1	9%	3	27%
Complications	Neurological	Encephalopathy	1,67	1	1,38	1	9	82%	3	27%
		Hearing loss	1,50	1	1,50	1	4	36%	4	36%
	Cardio Vascular	Shock	1,60	1	1,50	1	8	73%	3	27%
		Bleeding (B*)	1,20	1	1,43	1	9	82%	3	27%

Renal	Acute kidney injury	1,56	1	1,57	1	9	82%	3	27%
Pregnancy related	Spontaneous abortion	1,70	1,5	1,50	1	9	82%	2	18%
	Fetal death	1,67	1	1,25	1	9	82%	2	18%
	Post-partum hemorrhage	1,80	2	1,25	1	6	55%	3	27%
	Sepsis	1,56	1	1,25	1	7	64%	4	36%
Exposure	Travel endemic area last 21d + contact rodents	1,55	1	1,57	1	1	9%	5	45%
	Living in endemic area	1,91	2	2,17	2	1	9%	5	45%
	Contact excreta or urine rodents	1,36	1	1,57	1	1	9%	6	55%
	Contact Lassa case last 21d (L)	1,18	1	1,29	1	1	9%	5	45%
Biochemistry	Proteinuria	1,50	1	1,33	1	5	45%	2	18%
	Leukopenia (<4000/L)	2,00	2	1,71	2	4	36%	1	9%
Death	Death	2,00	2	1,67	2	4	36%	4	36%