CEPI

Workshop Report*
Launching Lassa fever epidemiology studies across West Africa

8th and 9th of October 2019

**Executive summary, summary of Day 2 only*

Meeting report prepared by

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Acronyms and abbreviations

AEFUTHA – Alex Ekwueme Federal University Teaching Hospital, Abakaliki
ALERRT – African Coalition for Epidemic Research, Response and Training
AVAREF – African Vaccine Regulatory Forum
BNITM – Bernhard Nocht Institute of Tropical medicine
BSC – biosafety cabinet
CEPI – Coalition for Epidemic Preparedness Innovations
CERMEL – Medical Research Center of Lambaréné
CFP – call for proposals
CFR – case fatality rate
CHW – community health workers
CIF – case investigation form
CITI – Collaborative Institutional Training Initiative
CM – contract manager
CNLS-TP – Conseil National de Lutte contre le VIH/SIDA, la Tuberculose, le Paludisme, les Hépatites, les Infections sexuellement transmissibles et les Epidémies
COLECT – Coalition for Lassa Epidemiology and Clinical Trials
CPP – costed project proposal
CRF – case report form
DMS – data management system
DNSP – Direction nationale de la santé publique
EC – ethics committee
EDC – electronic data capture
EDCTP – The European & Developing Countries Clinical Trials Partnership
ELISA – enzyme-linked immunosorbent assay
FAST – Faculty of Technical Sciences, University of Abomey-Calavi
FMCO – Federal Medical Centre Owo
FORS – Fondation pour la Recherche Scientifique
FP – CEPI focal point
GCP – good clinical practice
GCLP – good clinical laboratory practice
GP – glycoprotein
HDSS – health and demographic surveillance system
HFP – Haemorrhagic Fever Project
IAVI – International AIDS Vaccine Initiative
IDSR – integrated disease surveillance and response
Ig – immunoglobulin
IRCB – Institut de Recherche Clinique au Bénin
IRSP – Regional Institute of Public Health
ISTH – Irrua Specialist Teaching Hospital
LASV – Lassa virus
LFT – liver function test
LMIC – low- and middle-income country
MPH – Master of Public Health
MTA – material transfer agreement
NCDC – Nigeria Centre for Disease Control
NIBSC – National Institute for Biological Standards and Control
NLFRC – Nigeria Lassa Fever Research Consortium
NLHF – National Laboratory of Haemorrhagic Fevers
NMIMR – Noguchi Memorial Institute for Medical Research
PANDORA-ID-NET – Pan-African Network for Rapid Research, Response, Relief, and Preparedness for Infectious Diseases Epidemics
PI – principal investigator
PPE – personal protective equipment
PSC – programme steering committee
qRT-PCR – quantitative reverse transcriptase polymerase chain reaction
RDT – rapid diagnostic test
RKI – Robert Koch Institute
RRT – rapid response team
RUN – Redeemer's University Ede, Nigeria
SNHL – sensorineural hearing loss
SOP – standard operating procedure
SORMAS – Surveillance, Outbreak Response Management and Analysis System
SRS – simple random sampling
TPP – target product profile
TWG – technical working group
VHF – viral haemorrhagic fever
VHFCTulane – VHF Center Tulane University
VHFC – Viral Haemorrhagic Fever Consortium

Executive Summary

On 8th and 9th October 2019, the Coalition for Epidemic Preparedness Innovations (CEPI) organised a workshop on "Launching Lassa fever epidemiology studies across West Africa", with the following objectives:

- Allow the technical working groups (TWGs) and Programme Steering Committee (PSC) to meet face to face, thereby ensuring cohesiveness of the group and open communications before launch of the CEPI-funded Lassa fever epidemiology study
- Review study launch plans and resolve issues that may impede study progress
- Share best practices, experiences, and insights
- Review critical attributes of the study protocol and TWG documents/deliverables

The workshop was held at Noguchi Memorial Institute for Medical Research (NMIMR) in Accra, Ghana.

Gunnstein Norheim, CEPI, opened the workshop and explained the meeting objective: preparing for the launch of Lassa fever epidemiology studies across five West-African countries, with the intention of investigating the incidence as well as seroprevalence of Lassa fever. The studies aim to generate new knowledge about Lassa fever, and to inform future clinical vaccine trials.

Jakob Cramer, CEPI, explained how the epi studies fit into the overall clinical development plan for a Lassa vaccine. In the context of data needs to assess the feasibility of Phase IIb/III clinical trials, he listed the objectives of the epi studies:

1) gaining knowledge of incidence/prevalence in subgroups;
2) assessing risk factors for infection and disease;
3) observing the clinical course and outcomes of disease;
4) assessing the frequency of co-infection with malaria parasites; and
5) capacity building in conducting clinical trials in endemic areas.

Chikwe Ihekweazu, CEO of the Nigeria Centre for Disease Control, placed the epi studies in a public health context. He stated that many unknowns remain about Lassa fever, as well as many challenges including a lack of standardised care, of trained personnel, and of capacity in diagnostics, as well as huge logistics challenges to maintain a supply of samples and reagents. Against this backdrop, he cited the significant import of the Lassa epidemiology studies, which will:

1) Inform the design of a clinical Phase IIb/III randomised, placebo-controlled trial, hopefully bringing us closer to a Lassa fever vaccine;
2) help identify sites suitable for the conduct of clinical trials, so that the next time around we can hit the ground running;
3) enable the strengthening of sites and investigators, and build their capacity to conduct and manage clinical field trials in the future; and
4) facilitate decisions regarding vaccination strategies.

Vasee Moorthy, head of R&D Blueprint at WHO, reviewed some of the key evidence gaps that were discussed at a September meeting on Lassa vaccine development progress arranged by WHO in Senegal:

1) Whether exposure to Lassa results in lifelong immunity;
2) Need for serology and disease incidence studies to be conducted in endemic areas to characterise risk factors, co-infections, and disease;
3) Understand whether reinfections really occur;
4) Need to address the critical question of lineage-specificity of immunity;
5) Understand the spectrum of disease, i.e., the extent of undiagnosed, mild, and asymptomatic infection

Dr Moorthy stated that the epidemiology studies offer a major opportunity to build capacity, even for Phase IIb/III studies in the countries involved. It marks the beginning of country engagement in end-to-end product development for an important endemic disease in Africa, with the possibility of vaccine manufacturing in Europe or North America. He underscored the need for linking scientific knowledge and public health as well as regulatory and ethical considerations with clinical development, and advocated for thoughtful collaboration between partners in West Africa and high-income countries.

Each of the five study countries then presented on their specific projects, giving a background of Lassa fever in their context, existing and planned research, treatment and public health efforts, and progress toward execution of the Lassa epi study. Presenters included study coordinators and principal investigators from each site. Across all countries, priority activities centered on reaching final contract agreements and preparing the necessary documents for ethics review submission (protocol, case report forms, informed consent/assent forms, etc.).

CEPI staff provided an overview of financial and project management best practices, sharing information on processes for funds disbursement and activity reporting, and reviewing a framework for project management and communications to be coordinated both locally within country consortia as well as centrally with oversight by CEPI.

Each of the Technical Working Groups for the project met during breakout sessions held in the afternoon of the 8th and morning of the 9th. (The Programme Steering Committee held a closed launch meeting in parallel.) The Field Implementation TWG discussed key considerations around finalising the core protocol and other documents necessary for ethical review. The Laboratory TWG reviewed the study flow diagram, sampling procedures, and discussed the steps needed to develop and finalise the necessary protocols and guidelines for laboratory activities. The Data Management & Statistical Analysis TWG focused on identifying requirements for a common data management platform and identified steps and timelines to development, testing, deployment and use. The Capacity Strengthening TWG reviewed a list of trainings envisioned for the study, soliciting feedback and consensus on the format and priority of trainings to be conducted. The Communications and Community Engagement TWG discussed priorities for ensuring robust local engagement, including a stakeholder analysis, use of existing community health workers, and developing tools for rapid communications to subjects as well as local, regional, and national stakeholders.

Peter Smith with the London School of Hygiene and Tropical Medicine offered insights on the collaborative execution of field trials such as the Lassa epi studies, offering as a reference the book *Field trials of health interventions – A toolbox*. He shared information about the INDEPTH Network as an example of existing resources for standardised tools for surveillance activities.

Dr Smith further shared that CEPI and EDCTP have decided to partner on a joint call for proposals (CFP) for phase II/III clinical trials of LASV vaccine candidates, with a call budget of € 40 million and a deadline for applications of April 7, 2020. The scope of the call is to prepare and conduct one or more large-scale clinical trial(s) with the potential to achieve proof-of-concept and/or demonstration of efficacy for candidate vaccines against LASV.

Professor Abraham Annan, director of the Noguchi Memorial Research Institute hosting the workshop, offered a welcome to participants and underscored the importance of the workgroup's mission to global health security. He shared his enthusiasm for future engagements with the Lassa project participants in supporting preparedness for, and prevention of, infectious diseases in the region.

Nicole Lurie (CEPI) and Tom Verstraeten (P-95) chaired a final open discussion segment. During this segment, participants discussed clinical care procedures and support for management of identified Lassa cases, policies for sharing of study data between CEPI and country partners, EDCTP application guidance, and next steps for resolving questions concerning the core protocol and other documents raised during the TWG and other discussions.

Jakob Cramer closed with a few remarks on launch timeline and next steps, including final study protocol refinements and other needs for ethical review. The meeting was then adjourned and participants thanked for their attendance and valuable contributions.

Day 2

Meetings of TWGs (Concurrent breakout sessions)

- TWG 1 – Field Implementation
- TWG 2 – Laboratory Analysis
- TWG 3 – Data Management and Statistical Analysis
- TWG 4 – Capacity Strengthening
- TWG 5 – Communications and Community Engagement

Please refer to the progress updates provided below.

Progress updates: TWGs

TWG 1 – Field Implementation (Akpéyédjé Yannelle Dossou)

Before study launch, the objectives of the Field Implementation TWG are:

1) Revise core protocols based on input from the other TWGs;
2) facilitate implementation of core protocols, with adaptations to the individual study sites;
3) develop site-specific implementation plans for achieving the primary and secondary objectives of the study;
4) provide support in obtaining ethical approvals;
5) develop/harmonise consent forms to be used across the study sites;
6) establish study manual incorporating key standard operating procedures (SOPs);
7) review and adopt SOPs developed by the other TWGs;
8) develop and maintain project management tools.

After study launch, the Field Implementation TWG is responsible for:

1) Identifying key field implementation bottlenecks and proposing solutions, based on periodic implementation reports from the study sites;
2) Developing timely reports on the field implementation status and challenges, for the study operations headquarters.

The Field Implementation TWG has had two telephone conferences so far and is now meeting face to face for the first time. The TWG has documented and summarised the process of obtaining ethical approval in each of the participating countries, and has drafted an informed consent form, as well as a case report form (CRF) and a study questionnaire/procedure (in review). At this meeting, several key questions were discussed:

- Should all febrile cases detected be tested for Lassa fever? What harmonised definition for fever should we use?
    1. Key considerations:
        i. A case definition for the study needs to work for children as well as adults, it needs to be somewhat specific to Lassa fever, it needs to work in the field in the context of active follow-up (co-existing with the case definition used in public health surveillance), and it needs to work in future clinical trials, to document the effect of a vaccine. It does not need to detect mild or asymptomatic cases of Lassa fever (they will be accounted for in the sero-incidence cohort);
        ii. The fever needs to have had a certain duration, to improve the chances that it is related to LASV infection. A temperature cut-off may be necessary, and one could be interested in considering other disease symptoms, as well;

iii. To ensure the ability to detect circulating virus by RT-PCR, the fever should be ongoing at the time of follow-up;

iv. The case definition needs to be easy to understand for participants, and easy to report in the active follow-up (every 2 weeks, with face-to-face follow-up every 4 weeks);

v. In many of the communities involved, up to 50 % may be infected with malaria, and possible malaria infection should be ruled out;

vi. It is important to sensitise the participants to the value of the study and make it clear that there are advantages to participating, such as free access to health care. In this way, one can rely on study participants calling in when they fall ill, which will improve the passive surveillance and ensure that temperature readings can be conducted (thermometers available at health centres only).

2. Outcome: Suggested study case definition of suspected Lassa fever case: Has had fever and at least one symptom for more than 48 hours (2 nights). All suspected cases, with active fever (verifiable at the health centre; more likely to yield positive test for circulating virus) and symptom(s), will be tested for malaria as well as for Lassa fever.

- Should a baseline blood sample be collected from all study participants upon enrolment? For now, the plan is to collect blood only from the sero-incidence cohort (a sub-cohort of n = 1,000).
    1. Key considerations:
        i. Testing all patients (n = 5,000) for immunoglobulin (Ig) G at baseline will provide more power to the baseline seroprevalence analysis, and testing after a subsequent fever episode would serve to confirm seroconversion, i.e. that the participant has indeed been infected by LASV (provided the baseline sample was Ig negative);

        ii. Knowing the participant's serostatus at baseline (IgG is more interesting than IgM in this context) allows for assessments regarding the possible preventive effect of former LASV infection;

        iii. While testing of blood samples could be postponed and only conducted on confirmed Lassa fever cases, the baseline testing of all participants does not constitute an inordinate amount of work (high-throughput ELISA for analysis), and may be easier logistically;

        iv. Testing immediately, and providing the test results to the participants in a timely and understandable manner, will strengthen community engagement and study compliance (including improved likelihood that the participant will consent to the drawing of blood);

        v. The Communications and Community Engagement TWG should be involved to sensitise communities to participate in the study, and to support the communication of results (one should avoid scaring or confusing participants by communicating results that are of no or unknown clinical relevance). A description of how the results will be used and communicated needs to be included in the submission for ethical approval;

        vi. Incentivising participants with added clinical tests or remuneration was deemed less appropriate than engaging with the communities and communicating the benefits of the study.

    2. Outcome: A blood sample will be collected from all 5,000 participants at baseline and tested for IgG. The results will be reported back to the participants in the course of follow-up.

- What should be the minimum age for participant inclusion?
    1. Key considerations:
        i. It is important to include vulnerable populations yet drawing blood from infants can be difficult:
        ii. In a Phase II/III vaccine trial, including the smallest children will not be required;
        iii. One could base the lower age in the study on the lowest age of observed Lassa fever cases;
        iv. While breastfed, children will have circulating antibodies from their mother, which would confound lab tests.
    2. Outcome: It was decided to set the minimum participant age to 2 years.
- Age distribution: should we ensure appropriate distribution at recruitment?
    1. Key considerations:
        i. It is easier to recruit adults, and to have a representative selection of participants one may have to pay extra attention to the recruitment of children and youth – for example by defining minimum thresholds for each age interval that correspond with the population overall.
        ii. Recruiting by household or at village meetings may be enough to ensure representability.
    2. Outcome: Yes.
- Participant sampling strategy: should recruitment be conducted by the household? In the current protocol, recruitment by household has been suggested.
    1. Key considerations:
        i. With recruitment by household, it is important to ensure a representative selection of households (by random selection), as some households may be more exposed to the vector than others, even within the same village;
        ii. The strategy for randomisation of households needs to consider the population density;
        iii. An alternative could be to do a simple random sampling (SRS) of for example 2 individuals per household, to include a wider selection of households;
        iv. Household sampling may be the easiest way of achieving a representative age distribution;
        v. Monitoring the age distribution while recruiting for the study will allow for adjustments in the recruiting process, if necessary.
    2. Outcome: Recruitment will be conducted by the household.
- Should we test for pregnancy? For now, every woman is pregnancy tested at baseline in the protocol.
    1) Key considerations:
        i. Pregnancy could be a risk factor for severe disease, but is unlikely to predispose to infection (baseline testing of all women is not necessary to ascertain the latter);
        ii. collecting this data at baseline is unprecise because it only shows pregnancy at the start of the trial;
        iii. we would need to decide on whom to offer the test;

iv. there may be issues of acceptability when conducting a pregnancy test at baseline;
v. identifying the at-risk population of pregnant women may be useful, but in a clinical trial one might simply decide to use this information to exclude them as participants;
vi. it is conceivable that pregnant women experience a different course (or severity level) of Lassa fever, which makes it interesting for the epidemiology study to be able to identify this group;
vii. instead of offering the pregnancy test at baseline, it could be offered to confirmed Lassa cases if study personnel consider the participant to be in childbearing age.

- Outcome: Only confirmed cases will be tested (using urine or blood test according to local standard of care).

- Remove probable case definition from study? In the current protocol, the case definition for a probable case of Lassa fever is: "Death or loss to follow-up of suspected case with no laboratory confirmation".

1. Key considerations:

i. It may be difficult to define the cause of death;
ii. for most deaths, post-mortem sampling will be difficult (this case definition could, however, potentially be used during an outbreak);
iii. all deaths among participants will be recorded, and deaths in the community will be a topic during active follow-up;
iv. deaths should be investigated in a timely manner (within 2-4 weeks), to prevent loss of information;
v. A site could still do more frequent call if they want. Suggestion to set a timeframe during which death should be investigated and not wait too long to capture the right information. Within a month or two weeks. a standardised questionnaire should be used to collect information on the cause of death;
vi. a specially trained fieldworker should administer the verbal post-mortem questionnaire;
vii. how to deal with deaths should be included in the study manual and specific procedures;
viii. community deaths are unlikely to be included in this study.

2. Outcome: The probable case definition will be removed from the study.

- How do we categorise severity?

1. Key considerations:
i. Severity categorisation should be based on lab tests as well as clinical symptoms;
ii. there is no utility in knowing the classification of a case as long as the categories have not been properly defined.;
iii. at this point we should focus on collecting the data and information, and use this to create severity classifications later;
iv. an endpoint review committee consisting of Lassa fever experts can assign "severe" or "non severe" to cases based on symptoms and signs recorded at the time of diagnosis. The three categories that are currently in the protocol should be removed.

- Outcome: Key data points to collect will be harmonised in the curated CRF, and severity categories will be assessed as an outcome of the study.

- We would suggest conducting an interim analysis. When should this occur and what key elements should it target?
    1. Key considerations:
        i. An interim analysis after the coming season would allow for testing of all study systems and procedures, as well as ensuring that the study is on track;
        ii. conducting interim analyses following each season is another option, providing details about study progress once all sites are operational;
        iii. among the participants recruited over the planned 6-month period (or until October 2020), few may have been infected in time for the first interim analysis; 4) interim analysis (or monitoring) will be conducted "behind the scenes", not disrupting recruitment;
        iv. follow-up starts, for each participant, as soon as he or she has been recruited (with the first interaction two weeks later);
        v. calling it "interim analysis" builds certain expectations, and may cause participants/personnel to wonder whether the study is about to end;
        vi. the consent form does state, among other things, that the study may be stopped at the sponsor's discretion.
    2. Outcome: An interim analysis will be conducted by the end of October 2020, to test the system. Additional means of monitoring the study at certain milestones may also be put in place.
- Should we define a maximum period for recruitment (or date at which recruitment should be interrupted)?
    1. Key considerations:
        i. It would make sense for recruitment to focus on the coming Lassa season, yet recruitment is unlikely to commence until January/February (half-way through the season);
        ii. the seasonality of Lassa fever may not be as strict as previously thought, and cases are now seen throughout the year;
        iii. ideally, recruitment should be completed before the next Lassa fever season (2020/21).
    2. Outcome: Aim to complete recruitment within 6 months of study launch, or by October 2020.
- What actions can be taken to ensure good coordination with public health response to cases of Lassa?
    1. Key considerations:
        i. During the study, one may expect to detect more than the normal number of cases;
        ii. the study has an obligation to report detected cases to the authorities, and may provide support to the public health system in the form of consumables, PPE, and medicines, as well as helping trace contacts, to compensate for the added burden;

iii. if volunteering personnel, one needs to avoid conflicts between study tasks and public health tasks, and the line of command needs to be clear;

iv. there needs to be a distinction between the scientific study and activities related to patient care (public health authorities remain responsible for the latter, but study resources may be used to fill gaps);

v. public health authorities will need to be engaged, much like the communities involved, and engagement should start well before study launch;

vi. country-specific actions may have to be considered;

vii. data sharing agreements will need to be put in place for patients transferred to public treatment facilities (like Lassa treatment centres).

2. Outcome: Intend to coordinate actively with public health authorities.

- What sampling strategy for the subset of 1,000 subjects for the serosurvey?
    1. Key considerations:
        i. One sampling strategy could be to include the 1,000 first participants enrolled in the study (who consent to blood sampling every 6 months) to the serosurvey cohort;
        ii. it may not be possible to start recruiting from all study sites at the same time, resulting in a potential recruitment bias;
        iii. age distribution could be monitored at interim;
        iv. participants will need to be spread across all sites, and selected at the discretion of the local principal investigator (PI);
        v. consent will have to be individual, and each participant will be given a study identifier;
        vi. sampling could be made in a randomised and systematic way to allow for representative data on incidence. However, this is not the main objective of the study, and study sites have already been selected among areas of known high Lassa fever prevalence.
    2. Outcome: Allocate the first 1,000 consented participants into the sero-incidence cohort, with distribution across sites (especially rural areas) and attention to age distribution (defined targets for age groups < 5 and < 18).

Key outcomes from the discussions in the Field Implementation TWG are as follows:

1) Baseline serology should be obtained at the time of recruitment of each study participant (process for inclusion in the study, and dissemination of results, to be discussed with the Community Engagement TWG);
2) minimum age of study participants is 2 years;
3) sampling by household, allowing for local adjustments based on population density;
4) active follow-up of study participants every 2 weeks;
5) suspect case defined as "ongoing fever episode of > 48 hours (or two consecutive nights) + 1 symptom";
6) definition for "probable case" to be removed from the study protocol (keeping "suspected" and "confirmed" only);
7) disease severity will be assessed based on the harmonised CRF, and included as an outcome of the study;
8) pregnancy tests to be conducted on confirmed cases only;
9) planning to perform interim analysis, and make necessary adjustments to the study accordingly;

10) aiming to recruit all 5,000 participants within the first six months of the study;
11) active coordination with public health authorities; 12) for the subset of 1,000 patients in the repeat sero-survey, measures will be taken to include sufficient numbers of patients < 5 years and < 18 years, as well as to ensure rural representation. Sampling to be stratified by site.

Next steps:

1) Final revision and adoption of harmonised protocol;
2) finalise CRF, defining key data points to capture;
3) finalise informed consent forms;
4) review and integrate outputs from other TWGs;
5) resolve issues regarding survivor follow-up and sensorineural hearing loss (SNHL) assessment.

TWG 2 – Laboratory Analysis (Dr Ephraim Ogbaini-Emovon)

The objectives of the Laboratory Analysis TWG are:

1) review clinical and laboratory capacities and limitations at the study sites, conduct quality assurance;
2) ensure uniform sample collection, handling, processing, labelling, storage, transfer, analysis, and tracking across all designated laboratories;
3) revise the core protocol taking into consideration the laboratory capacity gaps, and provide feedback to the Field Implementation TWG.

The Laboratory Analysis TWG has had about five meetings so far, including teleconference sessions before the workshop. The group's deliverables prior to study launch are:

1) final draft laboratory analysis plan [completed];
2) laboratory manual with comprehensive list of laboratory procedures [ongoing];
3) map of existing SOPs suitable for the study [completed];
4) revised and harmonised SOPs to be used in the study [to do];
5) plans for laboratory strengthening, based on the Integrated Epidemiology Project Plans, site assessment reports, and input from TWG site representatives [ongoing];
6) advisory on the transfer of samples and materials, including regulatory aspects and the preparation of material transfer agreements (MTAs) [ongoing].

After study launch, the Laboratory Analysis TWG is responsible for:

1) approving periodic reports from the designated labs and solving any challenges in a timely fashion;
2) providing timely reports on laboratory implementation status, and any challenges, to the study operations headquarters.

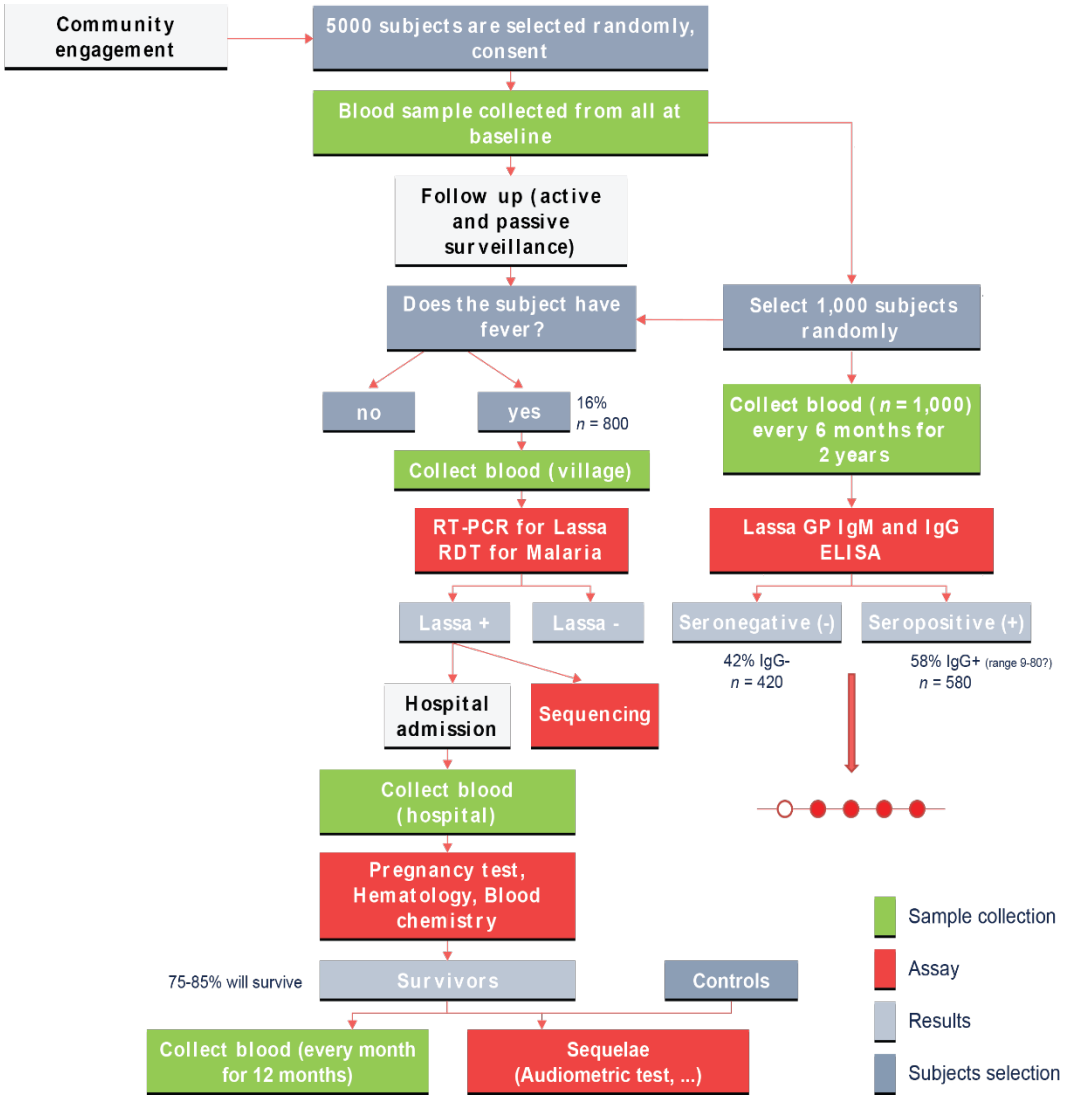

Figure 3. Study flowchart

A study flowchart was presented, detailing the laboratory analyses and the flow of participants (see Figure 3). The study has two arms, for:

1) active Lassa fever surveillance (prospective Lassa fever cohort; n = 5,000) and
2) repeated serology testing (sero-incidence cohort; n = 1,000, randomly selected from the prospective Lassa fever cohort).

In the prospective Lassa fever cohort, all participants are followed up to detect any incidence of fevers. In the sero-incidence cohort, the participants additionally undergo blood testing every 6 months to detect any circulating antibodies (IgM or IgG) specific to LASV glycoprotein (GP). Lassa fever diagnosis is confirmed by RT-PCR, upon which the participant will be admitted to hospital, to receive standard care. The LASV genotype is identified by sequencing. Lassa fever survivors are subjected to blood sampling every month for 12 months, and any sequelae (such as SNHL) are documented and compared to a control group.

Using the same analysis platform on all sites is imperative for achieving comparable results. Batch analysis of collected samples is another measure to this end. An overview of sample requirements for the study is provided in Figure 4.

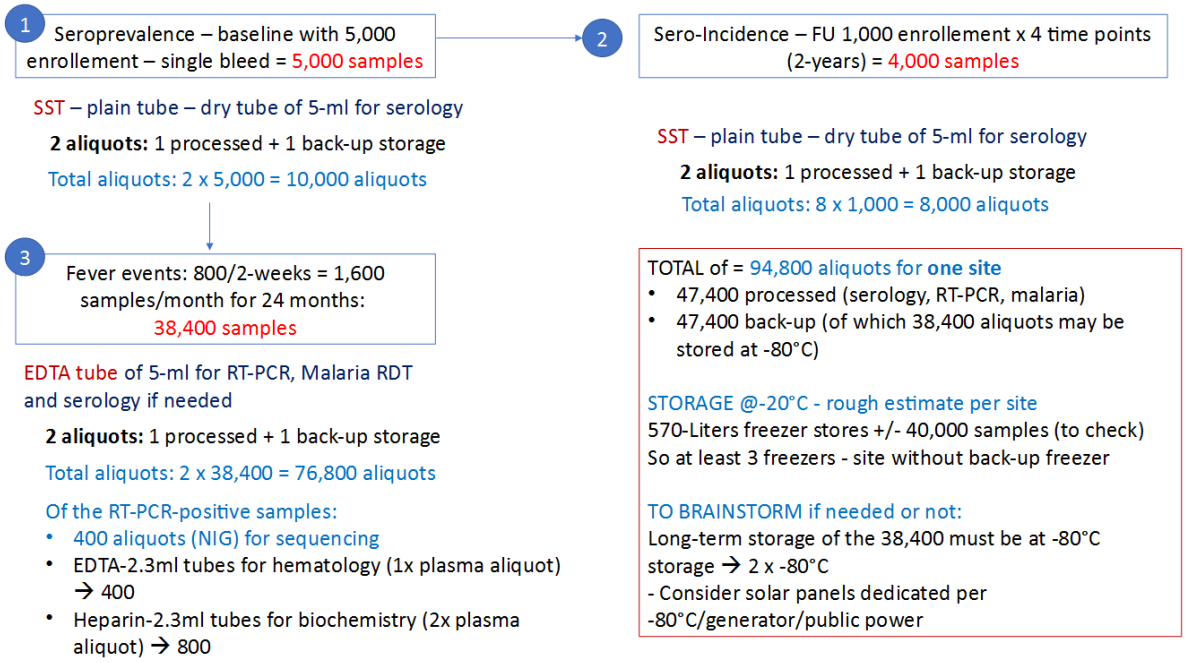

Figure 4. Sample requirements for the epidemiology study with respect to testing of 1) seroprevalence; 2) sero-incidence; and 3) fever events.

Next steps:

1) Complete draft of the laboratory manual;
2) develop harmonised SOPs;
3) develop plans for laboratory strengthening;
4) develop harmonised MTA.

The Laboratory Analysis TWG currently has the following main concerns:

1) Ensuring capacity for the 5,000 baseline samples;
2) choosing platforms for blood chemistry and haematology – will CEPI make this decision, or will the decision remain at the discretion of each study site;
3) what support may be provided for the treatment of confirmed Lassa fever cases – establishing harmonised standard of care.

Other concerns include:

1) How to manage contacts of confirmed Lassa fever cases;
2) performing malaria rapid diagnostic test (RDT) in parallel to Lassa fever RT-PCR on all febrile participants (to be conducted in biosafety cabinet, BSC);
3) should LASV IgM-positive participants of the sero-incidence cohort also receive diagnostic testing by RT-PCR, in the absence of fever?;
4) is there a second mode of analysis, with large capacity, that could be used in place of ELISA for serological sample testing, as a plan B;
5) considerations pertaining to biobanking.

TWG 3 – Data Management and Statistical Analysis (Dr. Euripide Avokpaho)

The Data Management and Statistical Analysis TWG has the following objectives:

1) review and refine specifications for, and achieve consensus on, a common electronic data capture & management (EDC/DMS) platform to serve all study sites;
2) review and refine the data management plan drafted by CEPI, enabling both site-specific and harmonised procedures;
3) review and refine the statistical analysis plan;

4) review the core protocol concerning data management procedures, allowing for country- and site-specific considerations, and suggest revisions to the Field Implementation TWG.

Prior to study launch, the deliverables of the Data Management and Statistical Analysis TWG are:

1) map of data management systems (DMSs) and CRFs used across study sites [completed];
2) final specifications for a uniform and centralised DMS [completed];
3) selection of DMS [pending];
4) final procedure for data entry from CRFs [completed];
5) data management training and supervision to ensure compliance [pending];
6) final dictionary for data variables according to CRF [pending];
7) SOPs adopted, while distinguishing between SOPs to be used uniformly and SOPs requiring local adaptations [pending];
8) data management plan incorporating the variable dictionary, referenced SOPs, and selected DMS (to be shared with the Field Implementation TWG) [pending];
9) statistical analysis plan following the primary and secondary objectives of the study [pending].

After study launch, the Data Management and Statistical Analysis TWG is responsible for:

1) conducting periodic reviews of EDC/DMS activities across all sites to flag possible issues and address them;
2) periodic reporting of results, in collaboration with the Communication TWG.

One question put to the Data Management and Statistical Analysis TWG during this workshop was whether the study objectives should also include performing pooled analyses across all participating countries. If the tools and procedures used in the study are sufficiently harmonised, this is not a significant additional effort and should therefore be pursued. However, national analyses should be completed first, and there need to be systems in place for ensuring the countries' data ownership and the ability to segregate pooled data by country. Finally, caution was advised in interpreting indicators based on pooled data, as they might be misleading and not representative of the heterogeneity encountered across countries.

Several considerations were raised by the group concerning the selection of an EDC/DMS platform:

1) a centralised system (versus decentralised) has added flexibility, for example in the ability to globally adjust protocols. On the other hand, it was argued that having servers in each country would be good for capacity building purposes;
2) local servers also provide the ability to manage data without the need for internet connection;
3) asynchronous data storage is necessary for the synchronising of offline data;
4) training needs to be provided to ensure that CHW are able to adhere to a paperless system;
5) EDC forms need to include quality checks during data entry to avoid incorrect and/or missing data;
6) the cost of providing electronic devices to all personnel involved in data collection needs to be considered;
7) paper-based data collection could serve as a fallback option, if provided for;
8) it is possible to use a hybrid system where CHW choose paper-based or electronic reporting based on individual preferences;
9) the workflow in the EDC tool should closely mimic the overall study design and flow of study activities that are described in the protocol;
10) in order to comply with GCP, the chosen EDC/DMS platform needs to include detailed audit trails, identifying individual users;
11) once the choice of EDC/DMS platform has been made, one needs to ensure proficiency in using the tool at each of the study sites at baseline;
12) Resource and training needs will be defined based on the chosen platform, and CEPI will fund the capacity building for this (countries are not expected to pay for this extra cost);
13) a review of CRF and other data collection tools, to ensure conformity with EDC/DMS requirements, will need to be coordinated with the Field Implementation TWG;

14) the EDC/DMS platform chosen needs to accommodate future clinical trials, as well as the epidemiology study. The objective of capacity building is continued, long-term development;
15) whatever system is chosen, an implementing partner should be accountable for development, implementation, and ensuring data quality. Local data managers will also play an important role in this, independent of choice of platform.

Next steps:

1) Finalise EDC/DMS platform specification, with selection of platform;
2) review data collection tools for EDC/DMS suitability;
3) develop, implement, and validate the platform;
4) conduct test field deployment;
5) train personnel in data management using the selected platform;
6) deploy live EDC/DMS platform, prepare for study launch.

TWG 4 – Capacity Strengthening (Dr. Manfred Accrombessi)

The objectives of the Capacity Strengthening TWG are:

1) define minimal requirements for the capacity needed to carry out the proposed studies;
2) develop a reasonable and feasible capacity strengthening plan per site within allocated budget per consortium;
3) revise the core protocol, taking into consideration the capacity strengthening gaps, and provide feedback to the Field Implementation TWG.

Prior to study launch, the following deliverables have been allocated to the Capacity Strengthening TWG:

1) map of resources available in each study site [completed];
2) minimal resources required (human resources, training, infrastructure, materials) to carry out the planned studies [pending];
3) prioritised list of capacity strengthening and training needs, based on site assessments and feedback from the consortia [ongoing];
4) capacity strengthening plans for each site [ongoing];
5) training materials for the study sites [pending];
6) training activities [pending].

Following the launch of the study, the Capacity Strengthening TWG will develop minimal requirements for the ability to carry out phase III clinical trials, in terms of infrastructure, human resources, and materials.

At this meeting, much attention was given to training plan revisions, resulting in a reduction in the number of trainings that are considered part of the minimal requirements for the study. Using the train-the-trainer model, harmonised courses will be held across all study sites. There is hope that CEPI may provide funding for postgraduate training and the recruitment of Master of Public Health (MPH) students. The 14 trainings currently included are:

1. Study protocol and SOPs [mandatory to all personnel, held at each study site. SOP content tailored to each group of personnel];
2. Good clinical laboratory practice (GCLP), including personal protective equipment (PPE) [mandatory to personnel involved in clinical work, sample handling, and data management. Training packages available through Collaborative Institutional Training Initiative (CITI) or IAVI];
3. Infection prevention and control (IPC) [mandatory to all personnel who has contact with study participants. Course materials available from WHO];
4. Training for health workers [orientation of CHW involved in handling suspected and confirmed Lassa fever cases, based harmonised standard of care];

5. Community engagement training [centralised training by CEPI on community methods and community engagement microplanning, for 2-3 communicators from each site];
6. Field data collection [training on tools and procedures for collecting data, including the use of global positioning devices (GPS) – provided the Data Management and Statistical Analysis TWG concurs];
7. Project management and coordination [one project management session for all study personnel, and parallel sessions covering I) stockpile management; ii) GCLP audits; iii) financial management and reporting; iv) study coordination];
8. Ethical research practice [training focusing on the protection of study participants];
9. Field team communication practices [if the Communication and Community Engagement TWG agrees, this will be a separate training];
10. Risk communication and counselling for field teams;
11. Data capture [training in electronical data capture according to CEPI's data management plan and harmonised choice of tools, to be organised in accordance with the implementation of a data management system – leaving the details with the Data Management and Statistical Analysis TWG];
12. Data monitoring [referred to the Data Management and Statistical Analysis TWG for input];
13. Statistical analysis [training covering the statistical plan; Data Management and Statistical Analysis TWG to provide input]; and
14. Statistical software training.

Next steps:

1) continue working on the training plan, focusing on training required before or at the beginning of the study;
2) assess the need for non-training capacity strengthening, including minimum requirements for personnel and infrastructure;
3) biweekly meetings with representatives from each consortium.

TWG 5 – Communications and Community Engagement (Dr. Lansana Kanneh)

Objectives of the Communications and Community Engagement TWG are:

1) develop expectations and guidance to inform the development of community engagement plans tailored to study sites;
2) develop a communication plan to be used consistently across study sites;
3) provide recommendations on communication and community engagement to the Field Implementation TWG, to inform protocol revisions.

Prior to study launch, the deliverables of the Communications and Community Engagement TWG include:

1) map of existing communication and community engagement resources in each study site [completed];
2) minimal requirements for community engagement to ensure that residents at the study site are willing to participate in the study [ongoing; harmonised community engagement plan template reviewed and adopted]. This involves
    i. building on experience and best practices, and tailoring to each study site;
    ii. describing how to engage with residents to address objections, questions, or suggestions;
    iii. specifying how to identify key stakeholders in the communities affected by the study;
    iv. exploring ways of conveying the potential risks and benefits of participating in the study (for the individual, society at large, and science);

v. ensuring participation and mutual respect of values and actions, and preparing for future clinical trials with Lassa vaccine(s).

Following study launch, the Communications and Community Engagement TWG is responsible for:

1) implementing communication plans for the PSC, including internal communication, crisis management procedures, and external communication including dissemination of results;
2) providing feedback on "lessons learned" in community engagement, to be shared across study sites.

Key considerations from the Communications and Community Engagement TWG meeting include:

1) communication and community engagement need to be a continuous process throughout the study, engaging stakeholders to participate actively through the use of a set of predefined goals;
2) a thorough stakeholder analysis is of utmost importance to understand stakeholder needs, expectations, and limitations;
3) already existing CHW should be used, if possible, since this almost always guarantees a smooth community engagement process;
4) community advisory boards (CABs) consisting of key community stakeholders should be established early, for transparency and clear communication between the study sites and the local community (they may also be useful in managing crises);
5) timely feedback of lab results to study participants is important, as participants expect to know their results before the next blood draw;
6) ensuring involvement of survivors in the CABs can strengthen community engagement;
7) the clinical care provided to confirmed Lassa fever cases should be standardised and clearly communicated;
8) the communication and community engagement strategy should be evaluated periodically to ensure that the community really is engaged.

Next steps:

1) develop country-specific communication plans;
2) finalise the publication policy with input from the Field Implementation TWG;
3) after study launch, establish PSC communication plan and provide continuous support to the study sites.