



“Efficacy trials of Lassa Vaccines: endpoints, trial design, site selection”

WHO Workshop

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1. Introduction

Lassa fever (LF) is a zoonotic disease associated with severe and potentially fatal haemorrhagic illness caused by Lassa virus (LASV). LF has been shown to be prevalent in many West African countries, such as Benin, Ghana, Guinea, Liberia, Mali, Nigeria, and Sierra Leone. Four lineages of LASV were defined, based on genetic variation. In these countries, both sporadic cases and prolonged outbreaks of the disease are observed. LF is mainly transmitted through contact with infected *Mastomys natalensis*, a widespread rodent species in West Africa, and through food and items contaminated by those rodents. The virus can also be transmitted, to a lesser extent, by person-to-person contact. LF occurs in all age groups and both sexes and is associated with a broad spectrum of clinical manifestations. Symptoms of LF are varied and non-specific, making clinical diagnosis often difficult.

LF cases occur regularly in West Africa. However, surveillance is inadequate to determine the true incidence of the disease and good epidemiological data is needed to better define the proportion of at-risk populations as well as endemic, hyper-endemic, and epidemic areas. Previous studies have indicated that about 80% of people who become infected with Lassa virus have no symptoms. 20% of infections result in severe disease, where the virus affects several organs such as the liver, spleen and kidneys. The incubation period of Lassa fever ranges from 6–21 days. The onset of the disease, when it is symptomatic, is usually gradual, starting with fever, general weakness, and malaise. After a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, and abdominal pain may follow. In severe cases facial swelling, fluid in the lung cavity, bleeding from the mouth, nose, vagina or gastrointestinal tract and low blood pressure may develop. Clinical diagnosis is often difficult, especially early in the course of the disease. LF is difficult to distinguish from other viral haemorrhagic fevers such as Ebola virus disease as well as other diseases that cause fever, including malaria, shigellosis, typhoid fever and yellow fever. Lassa virus infections can only be diagnosed definitively in the laboratory using RT-PCR, ELISA, Antigen detection tests, or by virus isolation. None of those tests are currently licensed. Early supportive care with rehydration and symptomatic treatment improves survival. Ribavirin has been widely used off-label to treat patients with LF based on the results of one clinical study performed in Sierra Leone in the 80's.

In early 2018, Nigeria has witnessed an unprecedented LF outbreak, whereby the usual annual observed LF burden has been concentrated into one trimester. From 1st January to 29th April 2018, a total of 1878 suspected cases have been reported from 21 states. Of these, 420 were confirmed positive.

The endemicity of LASV in West-Africa, the repeated occurrence of outbreaks and the recent unprecedented large LF outbreak in Nigeria have highlighted the potential for Lassa vaccines for prevention and/or reactive use. The WHO R&D Roadmap of LF identifies the following strategic goal:

“develop, evaluate, and license affordable LASV vaccines that protect against the multiple LASV lineages for preventive and reactive/outbreak use in Lassa fever endemic and at-risk areas”.

Based on that goal, a WHO Lassa vaccine Target Product Profile was in 2017 developed to provide aspirational guidance to vaccine developers, and is informed by regulatory expectations and by technological feasibility and considers both a preventive and a reactive scenario for the use of a Lassa vaccine. A preventive use vaccine is intended for protection of populations living in areas where Lassa virus is endemic. A reactive use vaccine is intended for protection of at-risk persons in the area of an ongoing outbreak for the prevention of LF as well as to interrupt chains of virus transmission and to terminate

outbreaks. The WHO mapping tool currently registers 15 Lassa candidate vaccines, developed by private or public stakeholders. None of those candidates have entered clinical trials.

On April 24, 2018, WHO convened a group of about 30 experts in epidemiology, regulatory, preclinical and clinical vaccine trials, and mathematical modelling, in a workshop on planning for Lassa vaccine efficacy trials. The workshop aimed to define generic principles on how to best design, conduct and analyse vaccine trials against LF, based on the available scientific evidence as well as on lessons learned from the public health response to LF outbreaks.

According to the R&D Blueprint processes, conclusions of the R&D Roadmap of LF and the WHO Lassa vaccine Target Product Profile were expected to help inform vaccine evaluation decisions during the workshop. Participants reviewed available evidence on Lassa epidemiology and vaccine candidates, identified and discussed methodological options to evaluate vaccines, regardless of vaccine products, and agreed on some preliminary recommendations.

It was recognised both that the preliminary recommendations are likely to evolve as new evidence is generated and also, they must be tailored to the social and cultural context of affected communities.

2. Epidemiology of Lassa, outbreak conditions, and Lassa candidate vaccines

The true burden of LF is highly uncertain.

There is a risk of zoonotic infection wherever the presence of infected *Mastomys natalensis*, or other identified infected rodents, and human population co-exist, especially in communities with poor sanitation or crowded living conditions. Human-to-human transmission can occur in nosocomial or community setting but its contribution to the total disease transmission has been observed to be relatively low (estimated 5-20%) compared to the role of rodent-to-humans transmission. Sexual transmission of LASV has also been reported.

About 80% of individuals who become infected with Lassa virus have no symptoms. 20% of infections result in severe disease. Among the few sero-surveys that have been performed in West-African countries, these suggest a significant level of seropositivity to LASV in various areas, including areas where no LF cases have been observed. Reinfection of severe LF cases has not been documented and it is unclear whether LF mild cases may be associated with a reinfection.

The magnitude of the 2018 Nigeria LF outbreak may be explained by an increase of the rodent population, an expansion in the laboratory capacity to detect LF cases, or a combination of these or other risk factors. Sequencing analysis suggested that the outbreak strain is representative of the strains that normally circulate in Nigeria.

Several knowledge gaps remain: routes of human transmission of LASV are complex, the burden attributed to a given LASV lineage, the potential role of human-to-human transmission, and the contribution of asymptomatic and mild Lassa infections to LF burden is unknown. Well-designed seroprevalence studies and enhanced surveillance, including ecological studies, in West-Africa are needed to help inform the above gaps and a thorough analysis of the 2018 Nigeria LF outbreak data must be conducted to better estimate epidemiological drivers and parameters. Also, integrated data management systems at the national level and standardization of surveillance tools and data collection across West-African countries will help improve our understanding of the LF burden.

Outbreak circumstances provide challenging conditions to the conduct of a vaccine trial.

The WHO Target Product Profile (TPP) of Lassa vaccines considers notably a scenario for the reactive use of a Lassa vaccine associated with a public health emergency. Generating evidence to support a broader use of a Lassa vaccine under that scenario may require to conduct a vaccine trial during a Lassa outbreak setting. Research has increasingly been a norm in responding to outbreaks of infectious diseases. The research response must be fully integrated in the broader control efforts and cannot be performed at the expense of the control efforts.

For instance, during the 2018 Nigeria Lassa outbreak, a series of outbreak control measures were implemented, coordinated at the national level by Emergency Operation Centre. Control measures include enhanced epidemiological surveillance, improved case management and IPC, contact tracing, risk communication and community engagement strategies. In Nigeria, there are currently three laboratory equipped with RT-PCR to detect

LASV and there are three Lassa treatment centres in the three most affected states. National authorities are also coordinating efforts towards the expansion of laboratory and case management capacity in an effort to improve access to testing and care in the affected communities and in a context where new diagnostic tools become available. The above public health response elements need to be considered in the design of a vaccine trial in the context of an outbreak. Lastly, anthropological studies are needed to assess the acceptability of a vaccine trial from affected communities in such conditions.

There is currently no licensed Lassa vaccines: there are at least 15 Lassa vaccine candidates currently identified in the pipeline and none have entered clinical trials.

The WHO TPP of Lassa vaccines considers both a preventive and a reactive scenario for the use of Lassa vaccine. The preventive use of a Lassa vaccine aims to protect the at-risk populations living in areas where LASV is endemic, and the reactive use of a Lassa vaccine aims to protect individuals in the areas of an ongoing outbreak and help interrupt chains of transmission. A reactive use vaccine will be very useful if a large outbreak occurs, potentially in an unexpected setting or location, with extensive human-to-human transmission. WHO considers that the highest priority for development between the two profiles is for preventive use given the current epidemiology. However, the TPP recognizes that an ideal product would address both scenarios, also allowing use for outbreak control. A vaccine suitable for preventive use typically requires a long-lasting protective immune response, while a vaccine suitable for reactive use typically requires a rapid ramp-up protective immunity after the first dose, especially given the very short incubation period of LF. It is recognized that a Phase 2b/3 vaccine trial may not generate all the evidence required to cover all aspects of the TPP and it is further recognized that additional studies would be required to complement the demonstration of clinical benefit that a Phase 2b/3 trial could not cover.

The current pipeline of Lassa vaccine candidates consists of over 14 candidates; however none of these have yet entered clinical trials. These candidates are based on a diversity of technologies, and includes e.g. recombinant glycoproteins, live-attenuated vaccines (e.g. ML29), viral vector-based (e.g. MVA, VSV, rabies, yellow fever), DNA vaccines approaches expressing one or several antigens representative of LASV virulence factors (e.g. GPC or NP). Several candidate vaccines have shown to be immunogenic and effective in preventing death and reducing viremia in a variety of animal models (e.g. guinea pigs, marmosets, cynomolgus macaques). There is no established correlate of protection for Lassa, although cellular responses are associated with survival in patients, but how well protective immunity in animals reflects protective immunity in humans remains to be determined. Of note, the majority of the animal challenge studies were conducted using the LASV Josiah strain, a strain that was isolated in the 70's in Sierra Leone, that is not known to circulate in recent years, and that is genetically diverse to some of the LASV strains that are currently circulating. The TPP suggests that it is expected that Lassa vaccines should cross-protect across the four lineages of LASV. However, the optimal antigen remains to be determined as well as determining the ability of vaccine candidates to generate protection across lineages causing most of the disease burden. The TPP also suggests that it is expected that Lassa vaccines should have a safety profile compatible with use populations such as children, pregnant and lactating women, and immunocompromised individuals.

Different vaccine technology platforms may be suitable for different use cases, as described in the TPP. DNA vaccines tend to have a generally acceptable safety profile in all population but would typically require several doses to confer protective immunity and would likely require a delivery device (e.g. electroporation), making it challenging for reactive use. Live-attenuated and replication-competent vector-based vaccines approaches tend to confer rapid

protection after the first dose (e.g. around 10 days post immunization) and could be suitable for reactive use, although safety profile need to be carefully assessed in humans, notably in immunocompromised and vulnerable populations. As the immunological factors responsible for potential protection have not been well identified, there is very limited data on the potential mechanism of protection in humans. Expected challenges may also pre-existing immunity to LASV or to the viral vector of the vaccine, as well as the need for prime-boost approaches to target both preventive and reactive use cases.

The demonstration of benefit based on a clinical endpoint is the optimal way to evaluate a Lassa vaccine but, if this is not feasible, other approaches may be necessary.

Licensure of vaccines generally requires the demonstration of benefit based on a clinical endpoint or based on a scientifically well-established marker of protection, using evidence generated by well-controlled clinical studies. In a context where there is no established immune marker of protection against LF, clinical trials to evaluate vaccine efficacy are preferred. However, if the demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a standardized and relevant animal model together with clinical immunogenicity may be considered sufficient to support licensure in countries where such legislation exists (e.g. FDA's animal rule). If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak to the extent possible. Assessing the feasibility of efficacy trials was also one of the aim of the workshop, and would require addressing gaps in epidemiological data on disease burden as well as exploring potential sites for future efficacy trials.

There is no well-established immunological surrogate of protection: animal models have mainly assessed the IgG and neutralizing antibodies response. Immunological assessment of LF cases and survivors also suggest that neutralizing antibodies appear relatively late after infection and that cellular immune response may be required for protection. Defining appropriate immunological surrogates of protection will rely on functional and standardized assays utilized in clinical studies on LASV patients, or by animal challenge studies. International standards, strains and reagents must be defined to allow the comparison of the immune responses elicited by different Lassa vaccines. Phase 2b/3 trials may also provide an opportunity to help define a surrogate of protection by looking at relationships between the characteristics of immunity correlated with the observed protection in trial participants.

3. Trial design and TPP use cases; reactive or preventive

The WHO draft TPP for Lassa vaccines, which has been developed in consultation with a wide range of vaccine and disease experts, was used to inform workshop participants in the rationale of defining trial design elements.

Vaccine trials should be designed to generate evidence to explore whether a vaccine can be recommended for either reactive use, preventive use or both of these scenarios; as defined in the Lassa vaccine TPP. Furthermore the TPP guides the use case for which a particular vaccine candidate is most suitable (e.g. one dose for reactive, multiple doses for preventive).

Trials designed to generate evidence on whether a preventive use of a Lassa vaccine is justified may encounter low cumulative attack rates, whereas trials designed to support a reactive use of a Lassa vaccine will face the unpredictable conditions and locations of conducting a trial in an outbreak setting. Strengthening laboratory capacity will be required to address those challenges in countries anticipated to cause significant disease burden.

Exploring a trial design for evidence on reactive use, assuming a vaccine with 70% expected efficacy against LF would require to observe 62 events on average. This corresponds to a sample size of about 15 000 trial participants¹ for cumulative attack rates representative of outbreaks conditions (about 1% in the comparator arm). Considering a trial design for preventive use, sample sizes are expected to raise to at least one level of magnitude higher.

In the light of those preliminary numbers, the question of the feasibility of trials designed for preventive use was raised, given the very low and unpredictable incidence of Lassa infections. A better understanding of LF incidence is needed to help refine sample size calculations. Lastly, it is expected that the implementation of a vaccine trial would come along and rely on a strengthened (or even active in a subset) surveillance system in order to increase primary endpoints detections. In

Based on the current dataset on disease incidence of LASV, there is uncertainty whether a trial to generate evidence on preventive use is feasible. A trial may for example extend over several seasons and locations to include the required events to enable an estimate of efficacy. Including more than one vaccine in a platform trial could potentially reduce the total number of placebo recipients compared to separate studies, however impact on time use and sample size are key for feasibility.

A reactive trial design may be more achievable than a preventive trial design; given a vaccine candidate offering rapid protection. However, it was recognized that outbreak conditions (e.g. public health measures, behavioural change ...) may significantly interfere with the conduct of a trial design. Lessons learned from outbreaks of other infectious diseases demonstrated that is nevertheless feasible to test a vaccine in outbreak conditions.

One may also imagine trials designed to generate evidence in an effort to support both a preventive and reactive use of a vaccine, or one could evaluate a vaccine in the most feasible context that may differ from the targeted intended use of the vaccine and later on verify clinical benefit in other studies.

¹ Assuming a 2:1 randomization, with a one-sided hypothesis test, a lower efficacy bound of 0.3, and 20% loss-to-follow-up.

3.1 Clinical endpoints selection (both reactive and preventive)

Laboratory-confirmed LF of any severity and severe LF illnesses should be co-primary endpoints of a Phase 2b/3 Lassa vaccine trial.

The definition of primary endpoints should also be supportive of the public health objectives outlined in the TPP for Lassa vaccines. Because the clinical spectrum of LF is extremely heterogeneous and because both severe LF cases and all LF cases concentrate the burden of LF disease, participants agreed to define two primary endpoints: laboratory-confirmed LF regardless of severity and severe LF cases. However, because it would be more difficult to detect LF mild cases (severe LF cases present typically themselves to Lassa treatment centres), active surveillance on a random subset of trial participants could be performed.

It was agreed that the definition of endpoints should be closely linked to a standardized case definition for LF confirmed cases and to the surveillance system of a given country. For instance, a LF confirmed case in Nigeria is defined as any suspected case with laboratory confirmation (positive IgM, PCR or virus isolation). The LF confirmed case definition currently does not distinguish mild and severe, but this distinction will be defined for surveillance and for the context of a vaccine trial in the near future. A new definition of suspected cases will also be developed to improve its specificity and to capture more systematically mild events in the trial. The often fragile and underfunded public health surveillance systems in the LF affected countries will require significant capacity strengthening to generate the level of diagnostic and data management quality on capturing and documenting disease events to satisfy regulatory considerations for vaccine development.

For all vaccine design approaches, except for live-attenuated vaccines, confirmation of cases by a highly sensitive and specific PCR (e.g. RT-PCR) – that targets genes that are not included in the vaccine design of interest - provides an appropriate method for case ascertainment and primary endpoint measurement in the context of a vaccine trial. Furthermore, determining the lineage of cases by sequencing is beyond routine public health surveillance in LF target countries, but is key as there are concerns of whether vaccine candidates will provide cross-protection across lineages. Viral load trends estimated by RT-PCR could also help distinguish between mild and severe LF cases.

Laboratory-confirmed LASV infection, LF-caused mortality, and potential immunological surrogates of protection should be secondary or exploratory endpoints of a Phase 2b/3 Lassa vaccine trial.

Assessing efficacy against LASV infection rely on sensitive, specific and reliable assays able to distinguish between vaccine-induced and LASV-induced immunity. RT-PCR or NP-ELISA provide a confirmatory test to make such a distinction for all vaccine design approaches, except for live-attenuated vaccines. Experimental RDT targeting the NP gene exist, but its performance needs to be established.

To assess LF-caused mortality, the history of treatment would need to be known. Here again, RT-PCR plays an important role in treatment initiation, continuation and patient discard.

In the absence of well-established surrogates of protection, Phase 2b/3 vaccine trials may provide an opportunity to help identify immunological surrogates of protection for a given vaccine design, which would reasonably likely predict clinical benefit. ELISPOT provide a reference assay for measuring cellular immunity in serum and could be performed in a subset of participants. However, ELISPOT assays needs to be developed to clearly differentiate vaccine response and natural infection response. PRNT (using LASV or

pseudotypes) provide a reference assay for measuring neutralizing antibodies in plasma and both assays could be performed in the same subset of participants, while GP-ELISA on plasma samples could be performed on all participants to monitor the IgG response and to help establish a relationship between protection and IgG levels (even though IgG levels may not necessarily cause protection, IgG levels may be associated with protection, and ELISA assays are generally more safe, precise, easier to standardize and less expensive than other assays).

Baseline blood samples are needed to be collected from trial participants to help account for prior immunity to LASV in the trial analysis for both primary and secondary endpoints. The collection of baseline blood samples is also essential to help characterize the immune response to the vaccine and help define an immunological surrogate of protection. Of note, a negative ELISA at baseline does not necessarily mean that the participant is LASV-naïve but it could be that the level of antibodies has significantly decreased. Stratified analyses according to pre-existing immunity to LASV and according to different lineages could be exploratory.

Standardized, validated assays, with agreed units of measurement will be critical to quantitate and compare protection among vaccine candidates. Lastly, tests sensitivity may be challenged by the collection and transport conditions of samples and by the nature of the sample, whether it is representative of an acute, mild or convalescent samples.

3.2 Study population and site selection (both reactive and preventive)

Healthy adults and children should be the study population of a Phase 2b/3 Lassa vaccine trial

LF affects the general population at all ages and considerations should also be given to the inclusion of pregnant and lactating women, and other special populations depending on the risk-benefit analysis on a given Lassa candidate vaccine in those populations. One should also distinguish the risk-benefit analysis on special populations for preventive and reactive scenarios. Currently, there is no safety data of any Lassa vaccines in humans. Dose-escalation Phase 1 and Phase 2 studies are needed to assess the safety profile in healthy adults and special populations, including immunocompromised people. For vaccine candidates that would be expected to have a favourable profile for pregnancy, pregnant women could be included in the trial at some stage. The intended use of a preventive Lassa vaccine is expected to cover the general population, and therefore, clinical benefit to the populations excluded from the trial, must be verified in post-licensure studies.

The need for a multi-site approach

Given the low incidence of LF, there is a risk that incomplete results from underpowered trials may be misleading to decisions-makers. A multi-site approach under a “Master Protocol” may be required to increase the chance of including groups with a high incidence of LF disease, as well as providing an opportunity to evaluate vaccine efficacy across different populations. Multiple seasons may be required to accumulate enough evidence as well. If the trial does not achieve the targeted number of events in the first season, the study must remain blinded to allow for further data collection.

Although LF occurs regularly in the same areas, it is difficult to anticipate where the next LF outbreak will occur. Planning of a Lassa vaccine trial rely on good surveillance and

epidemiological data. More research is needed to assess the true incidence of LF as well as to identify the geographical units, where enough transmission occur, to define sites. Sero-prevalence surveys and longitudinal cohorts could help inform site selection for vaccine trials. A multi-site trial requires standardization of concepts (e.g. same protocol, LF case definition), fit-for-purpose instruments (e.g. laboratory assays) used in the trial. LASV strain would also need to be sequenced to map any lineage specific protection.

3.3 Randomization and comparator (both reactive and preventive)

A double-blind placebo-controlled individually-randomized trial is the optimal design to evaluate the efficacy of one or several Lassa vaccine candidate(s).

Individual level of randomization is preferred – Individual level randomization would occur in distinct areas mapped to have LF incidence. Individual level randomization is preferred to a cluster-randomised trial design because of the patchiness of LF infection from area to area, which mitigates against a cluster-randomised design. Also, very low human-to-human transmission does not favour to learn on herd immunity from cluster randomization. A 2:1 randomization scheme could be used in order to learn more on the Lassa candidate vaccine (e.g safety profile). Careful analysis of Lassa transmission is needed to help define the size of relevant cluster or areas in which individual randomization would be performed.

Using individual randomisation, multiple vaccines could potentially be tested simultaneously within the same trial through a two-times 2:1 (vaccine 1 or 2:placebo) randomization scheme. When testing multiple vaccines, a Phase 2b screening trials would realistically likely be required given the sample size calculations of a full Phase 3 trial with multiple vaccines and would help dropping any unsuccessful vaccines.

Masking procedures: placebo is preferred - A placebo-controlled trial would be ethically acceptable. A vaccine against another disease, that the trial population would not normally receive and that does not affect the incidence of the primary and secondary endpoints, might also be considered. However, assessment of the reactogenicity of the Lassa vaccine may be hampered if the comparator vaccine is highly reactogenic (which might also compromise blinding).

3.4 Statistical Analysis

Define a statistical analysis plan *a priori* –

A statistical analysis plan should be prepared prior to the start of a trial. This should include consideration of any interim analyses, with specification of the circumstances in which the trial would be halted for overwhelming efficacy or for futility. The analysis would likely involve combining data across sites and/or outbreaks. Adaptive elements are acceptable (for example, dropping a poorly performing vaccine early, if several are being tested in the same trial), as part of a Phase 2b screening trial for instance, but all go/no go decisions need to be established in advance. Both Per-Protocol and Intention-To-Treat analysis should be performed. For the Per-Protocol analysis of a reactive design, caution should be done to the start of an analysis period, based on the incubation period and the ramp-up immunity of the vaccine.

If the trial does not achieve the targeted number of events in the first outbreak, the study remains blinded to allow for further data collection.

In the context of the proposed individually-randomized placebo-controlled trial, the primary analysis will be the estimated vaccine efficacy against confirmed LF illness (severe and regardless of severity), based on the ratio between the estimated hazard of illness for individuals who receive vaccine and those who receive placebo. Because the vaccine TPP suggests that only highly effective vaccines would be acceptable from a public health perspective, participants agreed that the primary outcome for the hypothesis test could be one-sided with a null hypothesis based on a lower efficacy boundary of 30% (i.e. the test should be formulated such that one would reject the null hypothesis that the Lassa vaccine efficacy is below 30%). Lower boundaries could be considered to lower the sample size depending on how confident a vaccine could demonstrate high efficacy. However, because it would be more difficult to detect LF mild cases, a standard two-sided hypothesis test with a lower boundary at 0% could be used for the all LF cases co-primary endpoint. The statistical significance level α could be split between 0.04 for the severe and 0.01 for all LF. Using this share, 44 LF severe LF events and 90 LF events regardless of severity would be required for a 70% efficacy vaccine under previous sample size conditions. Some other hierarchical approach could be used.

4. Establishing a transparent framework for selecting vaccines to be evaluated in Phase 2b/Phase 3 trials

It is hoped that the availability of a transparent framework to review various candidates' attributes to help inform the selection of those to be taken into clinical trials would contribute to ensure resources are utilized most efficiently, aimed at evaluating and licensing efficacious vaccines.

Given the number of candidate vaccines under development and the challenges of identifying and establishing trial sites, it was discussed that there may be merit for transparent and evidence based approach for selection of candidate vaccines for trials. Some initial considerations were discussed.

It was recognized that the decision to move forward a Lassa vaccine candidate to Phase 2b/Phase 3 should be based on how good the Lassa vaccine characteristics matches with the characteristics of the WHO vaccine TPP and how likely it is expected to demonstrate efficacy values that are close to the target measured efficacy as described in the TPP, provided an acceptable safety profile.

5. Next Steps and recommendations

A series of collaborative steps to continue to advance the discussions were outlined and agreed upon. It is anticipated that the steps will be implemented in close collaboration with the workshop participants and other experts in the community as appropriate.

- a) **Developing an annotated generic protocol for Lassa vaccine efficacy trials, based on preliminary design consensus.** The generic protocol will be developed with inputs from all participants, and it will be published on the WHO website for public consultation by Fall 2018. It is anticipated that candidate vaccine developers, affected countries regulatory authorities and LASV research communities will be included in the consultation process to provide their perspectives. Affected countries NRAs should strive to agree on a specific protocol and be encouraged to host efficacy trials ahead of time. To facilitate a rapid adaptation of a protocol, one should perform an annual review of assessing the readiness of all elements required for performing an efficacy trial, including a review of development progress status for individual vaccine candidates.
- b) **Develop a TPP for Diagnostics that include the diagnostic needs for surveillance and vaccine trials.** In addition, WHO and FIND are working on protocols for diagnostic evaluation that will be shared.
- c) **Continue efforts towards standardization and harmonization of core clinical variables and clinical case management.** A case definition of LF that account for the distinction between mild and severe LF cases will be developed.
- d) **Collate and review all existing LASV disease case and laboratory data in West Africa,** to identify data gaps and key parameters (e.g. transmission) required for efficacy trial design, to be addressed in prospective epidemiology studies prior to vaccine efficacy studies.
- e) **Support expansion of laboratory capacity in Nigeria and other affected countries to improve surveillance systems and better understand the LF burden.** Expansion of laboratory capacity is required across West-Africa to better understand the true burden of LF. Ecological studies are needed to help monitor the rodent population, help understand rodent-borne routes of transmission, and help understand the magnitude of the 2018 LF outbreak in Nigeria. Well-designed community sero-surveys are also needed to help understand the true incidence of LASV and help define geographic areas where vaccine trial could be implemented. Prospective research-oriented surveillance studies are encouraged in regions where public health surveillance is weak, but with likely disease incidence enabling vaccine efficacy trials.
- f) **Support research capacity and plan for clinical trials.** WHO and key partners will continue to promote collaboration with relevant groups, to gain knowledge on LASV transmission, and to link clinical management with research by preparing for a multi-site approach for LF vaccine evaluation in concertation with the national authorities of the affected countries, including regulatory authorities and ethics committees. WHO will also support training of healthcare workers to prepare for clinical research.

g) Establishing a transparent framework for selecting vaccines to be evaluated in Phase 2b/Phase 3 trials. There are 17 LF candidate vaccines in various stages of development and there would be benefit from establishing a framework for vaccine selection to ensure resources are utilized for development of candidates that demonstrate the highest likelihood of success.

g) Develop a geographically-explicit stochastic mathematical model of Lassa transmission. This model will be used to help develop the optimal study design for Phase 2a/3 vaccine trials and help refine sample size calculation. In addition the model will be used to help devise vaccination strategies for an efficacious Lassa vaccine.