WHO Target Product Profiles for Lassa virus Vaccine

April 2017

Purpose of the document

Selected disease areas are identified as WHO priorities for product development. In the case of Lassa fever, target product profile development followed prioritization of Lassa fever as part of the WHO R&D Blueprint for Action to Prevent Epidemics¹. The target audience includes vaccine scientists, product developers, manufacturers and funding agencies.

All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply. The criteria below lay out some of the considerations that will be relevant in WHO’s case-by-case assessments of Lassa virus vaccines in the future.

None of the characteristics in the tables below dominates over any other. For certain vaccine characteristics, footnotes are added to provide the rationale and assumptions made. Therefore should a vaccine’s profile be sufficiently superior to the critical characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Vaccines which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO’s processes.

A generic description of WHO’s Vaccine Prequalification process can be found at the end of this document.

Acknowledgement

WHO gratefully acknowledges the many individuals and institutions that provided comments to the draft at the public consultation stage.

Background

Lassa fever (LF) is an acute viral haemorrhagic illness caused by Lassa virus (LASV), first identified in 1969 in Nigeria. [1] It is endemic in Benin, Guinea, Liberia, Mali, Sierra Leone, and Nigeria with peaks in incidence closely related to seasonal patterns. There have also been reports of imported cases in Germany, Netherlands, Sweden, US and UK. [2,3]

It is estimated that there are between 100,000 to 300,000 infections in West Africa per year and causes approximately 5,000 deaths. [4] Around 80% of infected individuals are asymptomatic or have mild symptoms while 20% progress to disease. Case fatality rate is estimated to be around 15% among those who develop severe disease, however in 2016, the mortality rate was reported to be above 50%. [2] Pregnant women with LF have a high mortality rate especially in the third trimester. [5] Recovered LF patients experience hearing loss as well as other neurologic side effects.[2,6]

LASV is primarily transmitted through close rodent and human interaction (i.e., eating rodent contaminated food, physical contact with infectious rodent, inhalation of aerosolized infectious rodent secretions). Human to human transmission occurs during close contact and exchange of body fluids (saliva, urine, nasal secretions, semen).[7] Nosocomial transmission has been documented during LF outbreaks [8] In the absence of proper nursing barrier and infection prevention and control, healthcare workers caring for LF patients are at substantial risk. [2,9]

In the development of a Lassa fever vaccine target product profile, two scenarios were considered:

1. Non-emergency setting (Preventive Use): The vaccine is intended for protection of populations living in areas where Lassa fever virus is endemic. [2] Health care workers (HCW) at particularly high risk of LF due to their profession (i.e., HCW in endemic areas, laboratory personnel, deployed international HCWs) would also benefit from a preventive use vaccine.

2. Emergency setting (Reactive/Outbreak use): The 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. A reactive use vaccine will be very useful if a large outbreak occurs, potentially in a new/unexpected setting, with extensive human-to-human transmission.

WHO considers that the highest priority for development between the two profiles is for preventive use and this TPP is focused on that scenario. The rationale is based on the current epidemiology of LF and towards addressing the burden of LF in endemic countries. It is possible that some vaccine products may address both scenarios such as a vaccine predominantly targeting preventive use, with features allowing use for outbreak control (i.e., some protection after the first dose with more durable protection after the second dose). Such a product would be ideal and have a practical advantage including simplification of stockpiling.

The final version of this TPP will be the result of an extensive consultation process with key stakeholders in the public and animal health, scientific, funding and manufacturer communities. It is

2 While better epidemiological data is being generated, one possible strategy is vaccination where LF is hyper endemic and where clusters of cases are reported annually,
intended that the final versions will guide and prioritize the development of vaccines. As new
scientific evidence is generated, this TPP may require further review and revision.

Considerations:

Need for improved diagnostics – implications for implementation and assessment of vaccine efficacy

The vaccine strategy envisioned in this TPP relies on better and standardized diagnostic tests for
LASV as well as enhanced surveillance capacity in endemic countries. There is a need for a more
accurate estimate of the incidence, seroprevalence and geographic distribution of LFV. The true
incidence of LF is unknown. The estimated incidence of 100,000 to 300,000 and 5,000 deaths per
year were extrapolated from a prospective study in Sierra Leone in the 1980's [4] and are likely out-
dated. Likewise, mapping the distribution of LF would need further work. Previous estimates are
limited by varying degrees of confidence in diagnostic tests that have been used (i.e., degree of
specificity for LASV identification) and biased due to limited availability of testing capacity. [10,11]

Vaccine efficacy studies evaluating prevention of LF disease will require a reliable diagnostic test for
LASV. Analysis of the four LASV lineages has shown genetic heterogeneity, with up to 27% and 15%
sequence diversity at the nucleotide and amino acid levels, respectively. [12] A fifth LASV lineage has
been proposed. [13–15] This needs to be taken into consideration in the choice of primers specific to
the LASV strains in circulation for a particular region. Development of diagnostic assays capable of
detection of all LASV lineages will be ideal. Another important consideration is that the diagnostic
target site be different to the vaccine target site, in order to differentiate natural infection versus
transient vaccine related viraemia in patients presenting with Lassa-like fever. Current LASV nucleic
acid test detection by RT-PCR targets the S or L segment. [12,16]

Measuring clinical and pre-clinical immunogenicity will require validated and standardized assays.

Based on animal studies, both neutralizing antibodies and cell-mediated immunity appear to have a
role in preventing LASV infection. However, immune markers demonstrating vaccine effectiveness
appear to be different across vaccine platforms. [17–21] These studies indicate that LASV specific
antibody; neutralizing antibodies and markers of cell-mediated immunity will need to be tested.

Social science research to understand the affected community’s attitudes and preferences towards
vaccination in general as well as key vaccine characteristics will be important for the success of the
vaccine strategy implementation. Early community engagement will also be useful as vaccine
products and clinical studies are being developed.
### I. Target Product Profile

#### Non-emergency settings: Preventive use

<table>
<thead>
<tr>
<th>Vaccine characteristic</th>
<th>Preferred</th>
<th>Critical or Minimal</th>
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</table>
| Indication for use     | For active immunization of persons considered potentially at risk based on specific risk factors to protect against LF disease.  
                        | Risk groups will include certain communities in endemic areas, health care workers (HCWs)\(^3\). |  |
| Target population      | All age groups\(^4\).  
                        | Suitable for administration to pregnant women\(^5\). |  
                        | Healthy adults and children, excluding pregnant and lactating women. |
| Safety/Reactogenicity  | Safety and reactogenicity at least comparable to WHO-recommended routine vaccines, providing a highly favourable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination, including in individuals with compromised immune function.  
                        | No neurological complications associated with LF, including sensorineural deafness and neuropsychiatric side effects\(^6\). |  
                        | Safety and reactogenicity whereby vaccine benefit clearly outweighs safety risks.  
                        | Safety profile demonstrated primarily mild, transient health effects and rare serious AEs related to vaccination. |
| Measures of Efficacy   | At least 90% efficacy in preventing infection or disease  
                        | If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during |  
                        | At least 70% efficacy in preventing infection or disease  
                        | If demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a standardized and |

\(^3\) HCWs at particularly high risk of LF due to their profession (i.e., HCW in endemic areas, laboratory personnel, deployed international HCWs).

\(^4\) Cases less than 1 year old have been reported in published literature.

\(^5\) Studies have shown that infection during pregnancy causes high fetal mortality and increase fatalities in pregnant women.

\(^6\) Other auditory and vestibular side effects include tinnitus, vertigo and dizziness. Neuropsychiatric symptoms reported include depression, psychosis, dementia, etc.
<table>
<thead>
<tr>
<th>Dose regimen</th>
<th>Single-dose regimen preferred without requirement for a booster.</th>
<th>Primary series: No more than 3 doses, and with preference for short interval between doses. Booster doses: No more frequent than every 3 years or at time of new outbreak.</th>
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<tbody>
<tr>
<td>Durability of protection</td>
<td>Confers long-lasting protection of 5 years or more following the primary series and can be maintained by booster doses. Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.</td>
<td>Confers protection of at least 3 years after primary series and can be maintained by booster doses. Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. Oral or non-parenteral route desirable.</td>
<td>Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ.</td>
</tr>
<tr>
<td>Coverage</td>
<td>Coverage against Lassa virus lineages I to IV.</td>
<td>Coverage against lineage of Lassa virus relevant to the geographical setting.</td>
</tr>
<tr>
<td>Product Stability and Storage</td>
<td>Shelf life of at least 5 years at 2-8°C.</td>
<td>Shelf life of at least 12 months at -20°C and 3 months at 2-8°C.</td>
</tr>
</tbody>
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7 These considerations should be discussed between manufacturers and regulators early in the development process.
8 An attempt should be made to identify correlates of protection in an appropriate pre-clinical mode.
9 Supporting data that demonstrates cross reactive immune responses from vaccines and supplemented by pre-clinical data.
<table>
<thead>
<tr>
<th>Additional data on thermostability at higher temperatures. The need for a preservative is determined and any issues are addressed. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container. Vaccines that are not damaged by freezing temperatures (&lt;0°C) are preferred. Vaccines that can be delivered via the Controlled Temperature Chain are preferred.</th>
<th>The need for a preservative is determined and any issues are addressed. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration with other vaccines</td>
<td>The vaccines can be co-administered with other vaccines licensed for the same age and population groups without clinically significant impact on immunogenicity or safety of the Lassa virus vaccine or the co-administered vaccines.</td>
</tr>
<tr>
<td>Presentation</td>
<td>Vaccine is provided as a liquid product in mono-dose or multi-dose (10-20) presentations with a maximal dosage volume of 0.5 mL. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO’s multi-dose vial policy.</td>
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10 [http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf](http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf)

11 Co-administration with e.g., inactivated influenza, Tdap, HPV, YF, depending on recommended in-country immunization schedule indicated for target population.
<table>
<thead>
<tr>
<th>Registration and Prequalification</th>
<th>Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies¹²</th>
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Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.

II. Considerations on Programmatic suitability

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, the vaccine alliance, require WHO Prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Licensure by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.


The WHO PQ process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification. ([http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf](http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf))

Considerations of Programmatic Suitability for Prequalification

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO’s preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. In addition, introduction of new vaccines that have higher volume, cold chain capacity or disposal demands have had a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.
Reference:


