



WHO Target Product Profile for Lassa virus Vaccine

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Purpose of the document

Selected disease areas are identified as WHO priorities for product development. In the case of Lassa virus, 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 recommendations 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

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¹ http://www.who.int/csr/research-and-development/list_of_pathogens/en/

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, the Netherlands, Sweden, the US and the UK. [2,3]

It is estimated that there are between 100,000 to 300,000 infections in West Africa per year and 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 may 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 rodents, inhalation of aerosolized infectious rodent secretions). Human-to-human transmission occurs during close contact and exchange of body fluids (e.g. saliva, urine, nasal secretions, semen).[7] Nosocomial transmission has been documented during LF outbreaks.[8] In the absence of proper nursing barriers and infection prevention and control, healthcare workers (HCW) caring for LF patients are at substantial risk. [2,9]

In the development of a Lassa virus 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 virus is endemic.² 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 is the result of an extensive consultation process with key stakeholders in the public and animal health, scientific, funding and manufacturer communities. It is intended

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.

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. The TPP also includes considerations which highlight technical challenges to vaccine development and limits to scientific and epidemiological understanding which is important for subsequent vaccine implementation.

Considerations:

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 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 are biased due to limited availability of testing capacity. [10,11]

Need for improved diagnostics. 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]

There is a need for more information on kinetics of Lassa virus detection in blood and non-blood samples to correctly identify all infected patients in different stages of the disease. This information will be important in the development of better diagnostic tests for Lassa virus detection in various intended use settings.

Correlate of protection. 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.

Mathematical modelling. Estimating the potential impact of Lassa virus vaccines with different efficacy profiles and administered in the different vaccination strategies is a priority to help refine desired characteristics. Possible changes in the virus and independent non-virus factors (i.e., community density and interconnectivity, movement and spread to a major city, etc.) which would result in a larger outbreak should be considered and vaccine platforms with a surge capacity for rapid scalability of vaccine production would be ideal. Mathematical modelling may be useful in simulating these scenarios.

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

1 I. Target Product Profile

2 Non-emergency settings: Preventive use

Vaccine characteristic	Preferred	Critical or Minimal
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	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 relevant

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 in patients less than 1 year old have been reported in published literature.

⁵ Studies have shown that infection during pregnancy causes high fetal mortality and increased fatalities in pregnant women.

⁶ Other auditory and vestibular side effects include tinnitus, vertigo and dizziness. Neuropsychiatric symptoms reported include depression, psychosis, dementia, etc.

		<p>animal model together with clinical immunogenicity may be considered⁷⁸</p> <p>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</p>
Dose regimen	Single-dose regimen preferred without requirement for a booster	<p>Primary series: No more than 3 doses, and with preference for short interval between doses</p> <p>Homologous schedules preferred over heterologous prime-boost</p> <p>Booster doses: No more frequent than every 3 years</p>
Durability of protection	<p>Confers long-lasting protection of 5 years or more following the primary series and can be maintained by booster doses</p> <p>Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases</p>	<p>Confers protection of at least 3 years after primary series and can be maintained by booster doses</p> <p>Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases</p>
Route of Administration	<p>Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for WHO PQ or needle-free delivery</p> <p>Oral or non-parenteral route desirable</p>	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for WHO PQ
Coverage	Coverage against Lassa virus lineages I to IV ⁹	
Product Stability and Storage	Shelf life of at least 5 years at 2-8°C	Shelf life of at least 12 months at -20°C and 6 months at 2-8°C

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 model.

⁹ Supporting data that demonstrates cross reactive immune responses from vaccines and supplemented by pre-clinical data.

	<p>Additional data on thermostability at higher temperatures</p> <p>The need for a preservative is determined and any issues are addressed</p> <p>Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container</p> <p>Vaccines that are not damaged by freezing temperatures (<0°C) are preferred</p> <p>Vaccines that can be delivered via the Controlled Temperature Chain are preferred¹⁰</p>	<p>The need for a preservative is determined and any issues are addressed</p> <p>Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container</p>
Co-administration with other vaccines	The vaccines can be co-administered with other vaccines licensed ¹¹ 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	The vaccine will be given as a stand-alone product not co-administered with other vaccines
Presentation	<p>Vaccine is provided as a liquid product in mono-dose or multi-dose presentations with a maximal dosage volume of 0.5 mL</p> <p>Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.</p>	<p>Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose presentations with a maximal dose volume of 1.0 mL</p> <p>Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy</p> <p>Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent</p>

¹⁰ 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.

Registration and Prequalification	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 agencies ¹²
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¹² <http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf>

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 prequalification procedure is described in detail in the document Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO TRS 978) available here: <http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf>

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)

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 has 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.

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