Target Product Profiles for Rift Valley Fever Virus Vaccines

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Powering research to prevent epidemics

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Purpose of the document

Because of its potential to cause a public health emergency and the absence of an efficacious vaccine, Rift Valley Fever (RVF) is a WHO priority disease for which accelerated vaccine research and development is urgently required[1]. As part of the WHO R&D Blueprint for Action to Prevent Epidemics, these Target Product Profiles (TPPs) for Rift Valley Fever Virus Vaccines (hereinafter the 'TPP Guideline') aim to provide early technical guidance for development of a vaccine to protect human public health interests. TPPs are provided for human vaccines for reactive use in outbreak settings with rapid onset of immunity and for long term protection of persons at high ongoing risk. With respect to the TPP for a veterinary vaccine, characteristics have been set to limit an RVF outbreak in the animal population and to preclude virus transmission from the animal reservoir to humans. The extent of the veterinary TPP has been limited to ruminants for this preliminary draft, however the fact that RVF can infect various animal species both within livestock and wild animals will be addressed in a later version.

This TPP Guideline is meant for private and public parties that are professionally involved in the development and eventual production of a vaccine against RVF and to facilitate the most expeditious development of vaccine candidates against RVF. This TPP guideline should be used and interpreted applying necessary awareness of its limitations, since much is still unknown about RVF virus life cycle, pathology and the role of the various arms of the adaptive immune response in protective immunity[2].

Future assessment by WHO of forthcoming RVF vaccines will consider the targets for each of the characteristics as indicated in the tables underneath. Two targets, i.e. 'minimally acceptable' and 'optimal' have been assigned for the vaccine attributes according to the current understanding of what a future RVF vaccine may look like.

- **Minimally Acceptable Target**: This case represents the "shall meet" requirements necessary for effective acceptance of the RVF vaccine. Vaccines which fail to meet minimally acceptable targets are unlikely to achieve favorable outcomes from WHO's processes.

- **Optimal Target**: This case represents the "should aim for" guidelines. They represent a potential scenario that would be a significant improvement over the minimally acceptable targets and may provide options for a future RVF vaccine to excel in terms of product characteristics.

In addition, all the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will apply. A generic description of WHO's Vaccine Prequalification process can be found at the end of this document.

Acknowledgement

[*to be added*]

I. Background

The causative agent of Rift Valley Fever is the *Rift Valley fever phlebovirus* (RVFV). The virus is a mosquito-borne, human and veterinary pathogen, associated with multiple outbreaks in countries of Africa and the Middle East[2,3]. There are a few commercially available veterinary vaccines, and some clinical experience with classical inactivated and attenuated human vaccines. RVFV remains a threat to public health and a WHO expert consultation determined that there is an urgent need for accelerated R&D for RVFV, given its potential to cause a public health emergency and in the absence of efficacious medical countermeasures[4].

RVF disease.

In humans the virus generally causes uncomplicated disease with headaches and body aches followed by fever that may last 3-5 days[5]. Severe systemic disease occurs in a small number of cases[6] which may become apparent with symptoms of ocular disease (retinitis), meningo-encephalitis[2], or hemorrhagic fever including liver failure and hemorrhagic manifestations[5]. This hepatic/hemorrhagic form of RVF is highly lethal[5]. In addition, recently an association was found between RVFV infection and miscarriage in pregnant women[7].

Among livestock animals, RVFV outbreaks are characterized by widespread abortion and lethality[2]. In pregnant ruminants, infection with RVFV causes abortions, fetal malformation and subclinical to fatal febrile illness. Newborn lambs often succumb due to acute hepatitis[6].

Transmission.

Infections of humans result from transmission by infected mosquitoes or through contact with infected blood, milk or tissue such as aborted materials[2,8]. Persons at risk for infection are generally in direct contact with wildlife or livestock, such as animal handlers, butchers and veterinarians. Direct human-to-human transmission has not been demonstrated and there have been only few examples of vertical transmission in humans[9].

For transmission, infected mosquitoes and wild animals are the main reservoir. Flood water mosquitoes may vertically transmit the virus to their eggs which may survive for years during dry periods. Outbreaks generally occur in periods of heavy rainfall, resulting in hatching of eggs and larger numbers of infected mosquitoes. The disease can spread through livestock movement or mosquitoes' dispersal. During such outbreaks multiple other genera of mosquitoes become infected that may horizontally transmit the virus to other animals and to humans.

Virology.

RVFV belongs to the genus *Phlebovirus* of the family *Phenuiviridae* in the order of *Bunyavirales*. RVFV has a tripartite, negative-stranded, segmented RNA genome, named small (S), medium (M) and large (L) segments. The S-segment, however, functions as an ambi-sense RNA, which encodes the *N* gene in the negative sense and *NSs* gene in the positive sense. Due to the segmented nature of the RVFV genome, reassortment between strains of RVFV is possible[8]. Specifically, reassortment in a man who was co-infected with a wild-type strain and a live-attenuated vaccine strain has been reported[10]. The M segment encodes the viral envelope proteins Gn and Gc which form heterodimers on the surface of virion[11]. Gn plays a role in receptor binding and Gc serves as a class II fusion protein. Viral attachment starts with the interaction of Gn/Gc and DC-SIGN[12]. Alternatively, the virus can bind to heparansulfate for entry[13]. Following attachment, the virion is internalized by dynamin-dependent caveolae-mediated endocytosis[12]. RVFV entry is completed following Gc mediated fusion of the viral envelope to the cell membrane[12].

Immune responses.

Innate immune response. In animal models, IFN-α responses have been associated with protection against RVFV[14,15]. The NSs protein is a major virulence factor which mediates viral evasion. A NSs-deficient RVFV strain induces an abundant production of type-I interferon in mice and cannot establish viremia[11].The mechanisms by which NSs suppresses innate immunity have been studied in detail[11].

In humans, much is unknown about protection although i) the induction of a type-I interferon response has been shown to contribute to protection against lethal RVFV infection; and ii) it is hypothesized that fatal RVFV infection is associated with dysregulation of inflammatory cytokines and chemokines (Algaissi, Landscape analysis).

Humoral immune response. From animal models it is known that neutralizing antibodies are sufficient to protect from virulent RVFV challenge[11]. RVFV surface glycoproteins (Gn/Gc) represent the major targets for such neutralizing antibodies[16].

Cellular immune response. Studies in mouse models showed that immune control of RVFV infection requires CD4+ T lymphocytes. CD4+ T cells were also shown essential for mounting robust IgG and neutralizing antibody responses (Algaissi, Landscape analysis).

This document describes the preferred and minimally acceptable profiles for three vaccines:

1. A human vaccine for reactive/emergency use intended to prevent RVFV disease in vaccinated individuals. Its use may be in populations experiencing an outbreak, and in populations geographically close to an outbreak.
2. A human vaccine for long term protection of persons at high ongoing risk of RVFV infection such as those handling animal tissues during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or involved with the disposal of carcasses or fetuses. High risk occupational groups include herders, farmers, slaughterhouse workers and veterinarians.
3. An animal vaccine – for prevention of transmission of RVFV among ruminants and from ruminants to humans.

Ideally, a single vaccine might be used for both 1 and 2 above.

These Target Product Profiles (TPPs) were developed through a consultation process with key stakeholders in human and animal health, scientific, funding and manufacturing communities. It is intended that they will guide and prioritize the development of vaccines. As new scientific evidence is generated, these TPPs may require further review and revision.

Considerations:

Need for active surveillance. RVF human disease is generally immediately preceded by an epidemic in animals but often RVFV outbreaks are recognized only after human cases have been diagnosed[17]. There is a need for active surveillance, so that very rapidly, at onset of a new epidemic, all measures can be taken to prevent further spread of the virus (including ideally vaccination of all reservoir species). This may rely on any or all of the following actions: i) effective early detection of cases in animals by active surveillance of livestock (including monitoring of sentinel herds) and monitoring of sudden increase in abortions in endemic areas through clinical and serological investigation[9,18,19] (M. Denis, manuscript); ii) applying early warning systems based on satellite remote sensing data (as used for predicting RVF outbreaks in Kenya in the past)[16,20].

Correlates of protection. Studies of vaccine immunogenicity and efficacy in suitable animal models will be needed. To this end, testing the vaccine in various animal models may be necessary to give insight into the potential protective effect of the vaccine and to study immune responses. Extrapolating animal data to humans needs careful consideration since regulation of immune responses in humans may vary significantly from animal models.

Neutralizing antibody responses have been associated with protection in several animal models and may be explored as parameters for determining immunity in humans[11,21,22,23,24]. As other arms of the immune response were found to have a role in mounting protective immunity, it is advised to characterize the immune response after vaccination including a profile of the cellular immune response.

Mathematical modelling. Modelling of the transmission dynamics of RVF and the potential impact of vaccines is a priority to further refine desired vaccine characteristics. Specifically, vaccine developers are encouraged to test efficacy profiles and immunization strategies in silico. Modelling of both animal and human vaccination will only have value should more experimental data emerge on the mechanisms of disease transmission[25].

Veterinary vaccines / One health. Human epidemics of RVFV are often preceded by outbreaks in farmed animals. Hence, an animal vaccination strategy may be the best way to prevent human outbreaks. Livestock and specifically ruminants are highly susceptible to RVFV infection and vaccination of susceptible animals may effectively break the virus transmission cycle leading to human infections. Furthermore, animal disease cause significant economic losses and hardships in the areas affected, and so protective animal vaccine would also benefit the community regardless human transmission. Thereto an integrated approach under One Health of professionals working in animal and human sector is a useful model for the prevention and control of RVF. Essential in the veterinary field is the development of an affordable vaccine that is safe, including in pregnant animals, does not need a cold chain, allows its use during epidemics

(e.g. needle-free delivery device), induces a rapid immune response, and is compliant with DIVA (differentiating naturally infected from vaccinated animals).

II. Target Product Profiles

II.A. Veterinary vaccine

Ruminants vaccine: Develop and license a vaccine suitable for administration to ruminants to disrupt the RVFV transmission cycle and to prevent infection of humans resulting from handling of animal materials, both to be administered prophylactically and during outbreaks. Manufacturing procedures should conform to OIE technical standards for manufacturing and quality control of veterinary vaccines as outlined in the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*[30].

Vaccine characteristic	Optimal Target	Minimally Acceptable Target
Indication for use	To significantly reduce RVFV infections in ruminants to reduce transmission of RVFV to humans resulting from handling of ruminant materials and to disrupt the RVFV transmission cycle.	
Target population	All domestic ruminants in RVF -prone areas, i.e. sheep, cattle, goats, and dromedary camels.	
Safety/Reactogenicity	Live attenuated virus vaccines are not to be used for vaccination of potentially viraemic animals during an outbreak of RVFV, given their potential to reassort with wild type virus. Must be safe for administration to ruminants when administered according to label recommendations; must not cause abortion or teratogenesis in pregnant animals and must not be vertically transmitted to the fetus. Live attenuated vaccines in any form must be sufficiently weakened not to cause reversion to virulence or creation of reassortments transmissible via mosquitoes.	
	Safety and reactogenicity whereby vaccine has minimal and transient apparent local and systemic adverse events related to vaccination with a low to negligible rate of moderate to serious adverse events related to vaccination. Safety profile to the consumer demonstrated (e.g. milk, meat products)	Safety and reactogenicity whereby vaccine benefit clearly outweighs safety risks. Safety profile demonstrated primarily mild, transient local or systemic health effects and only very rare serious adverse events related to vaccination. Safety profile to the consumer demonstrated (e.g. milk, meat products).

	Safety profile for non-target species likely to be in contact with vaccinated animals.	
	No prolonged shedding of vaccine virus.	
Efficacy	At least 90% protection against viremia and death upon challenge infection. Pregnant animals protected against abortion and teratogenesis. Colostrum of vaccinated ewes confers protection of newborn lambs via passive immunity. DIVA compliant.	At least 70% protection against viremia and death upon challenge infection. Pregnant animals protected against abortion and teratogenesis. DIVA compliant vaccine is preferred.
Dose regimen	Single dose primary series.	Up to 2 vaccine doses, preference for short interval between doses and with some protection after first dose. Booster doses: Not more frequent than annually.
	Vaccination regime compatible with programs for other vaccines to be administered concurrently.	
Duration of protection	At least 3 years.	At least 1 year after last vaccination.
Route of Administration	Needle free delivery desirable. Spray for mucosal delivery (intranasal).	Injectable (IM, SC).
Coverage	Protective against any RVFV strain likely to cause infection[8,10].	Protective against any RVFV strain likely to cause infection[8,10].
Product Stability and Storage	Shelf life of 5 years at 2-8°C. Clear label statement to specify storage conditions and expiration date.	Shelf life of at least 12 months at -20°C, and at least 6 months stability at 2-8 °C. Clear label statement to specify storage conditions and expiration date.

	Thermotolerance. Specific thermotolerance claims should be supported by data from time–temperature studies undertaken under the relevant storage or transport conditions.Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.	
Co-administration with other vaccines	Vaccine may be administered alone, co-administered with other vaccines, or blended into a multi-component vaccine. Data to support co-administration with other vaccines licensed for ruminants of the same age groups without significant impact on immunogenicity or safety of the RVFV vaccine or the co-administered vaccines.	The vaccine will be given as a stand-alone product, not co-administered with other vaccines.
Presentation	Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose (e.g., 10-20 dose) presentations with a maximal dosage volume of 2.0 mL. Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent. Vaccine should be formulated, managed and discarded in compliance with biomedical waste disposal standards.	

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II.B. Human vaccines

Develop and license single dose RVFV vaccine suitable for reactive use in outbreak settings with rapid onset of immunity.

Vaccine characteristic	Optimal Target	Minimally Acceptable Target
Indication for use	For active immunization of at-risk persons in an ongoing outbreak for the prevention of Rift Valley Fever; to be used in conjunction with other control measures to curtail or end an outbreak.	
Target population	People living in the area of the outbreak, including pregnant women. Those having contact with infected animals or tissues from infected animals, including consuming milk and handling raw meat products.	People living in the area of the outbreak. Those having contact with infected animals or tissues from infected animals, including consuming milk and handling raw meat products.
Safety/Reactogenicity	Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; with mild, transient adverse events related to vaccination. No live attenuated virus vaccine to be used unless reassorting is excluded.	Safety and reactogenicity whereby vaccine benefits clearly outweigh safety risks. Usage of an attenuated live vaccine that may allow reassortment is not indicated in an outbreak setting. No live attenuated virus vaccine to be used unless reassorting is excluded.
Efficacy	At least 90% efficacy in preventing laboratory confirmed disease[a].	At least 70% efficacy in preventing laboratory confirmed disease[a].

	Rapid onset of immunity (preferably less than 2 weeks). It is advised to broadly characterize the immune response after vaccination including profiles of the humoral and cellular immune response.	Rapid onset of immunity (less than 3 weeks).
Dose regimen	Single-dose regimen highly preferred.	No more than 2 doses, preference for short interval (less than 3 weeks) between doses and with some protection after first dose.
Durability of protection	Confers protection for at least 1 year. Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.	Confers protection for 6 months.
Route of Administration	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery[b].	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ[b].
Coverage	Protective against all RVFV lineages against any RVFV strain likely to cause infection[8,10].	Protective against all RVFV lineages against any RVFV strain likely to cause infection[8,10]. A heterologous vaccine could be considered if partial protection is demonstrated.
Product Stability and Storage	Shelf life of 5 years at 2-8°C. Additional data on thermostability at higher temperatures.	Shelf life of at least 12 months at -20°C, and demonstration of at least 1-month stability at 2-8°C.

	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.	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.
Co-administration with other vaccines	The vaccine can be co-administered with other type of vaccine without affecting safety and protective efficacy of either vaccine.	The vaccine will be given as a stand-alone product not co-administered with other vaccines.
Presentation	Vaccine is provided as a liquid product in mono-dose or multi- dose 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[26].	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. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy[26]. Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.
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.[20] Please refer to the considerations for Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the event that RVFV is declared a public health emergency of international concern[27].	

[a] confirmed case defined as the detection of live RVFV, RNA, or IgM against-RVF[10].

[b] when developing a vaccine for ID administration, measures should be taken to prevent any erroneous administration through a non-authorized route (e.g. IM/SC for an ID vaccine).

163 *2.* Develop and license vaccine for long term protection of persons at high ongoing risk

Vaccine characteristic	Optimal Target	Minimally Acceptable Target
Indication for use	For active immunization of persons considered at-risk including those working with potentially infected animals (herders, farmers, slaughterhouse workers, and veterinarians).	
Target population	Persons at high ongoing risk of RVFV infection such as those handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or involved with the disposal of carcasses or fetuses. High risk occupational groups include herders, farmers, slaughterhouse workers and veterinarians. Suitable for vaccinating pregnant women.	Persons at high ongoing risk of RVFV infection such as those handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or involved with the disposal of carcasses or fetuses. High risk occupational groups include herders, farmers, slaughterhouse workers and veterinarians.
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.	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.
Efficacy	At least 90% efficacy in preventing laboratory confirmed disease[a]. It is advised to broadly characterize the immune response after vaccination including profiles of the humoral and cellular immune responses.	At least 70% efficacy in preventing laboratory confirmed disease[a].

Dose regimen	Single-dose regimen preferred.	Primary series: no more than 2, with preference for short interval between doses.
Durability of protection	Confers long-lasting protection of 5 years or more which can be maintained by booster doses.	Confers protection of at least 3 years which can be maintained by booster doses.
Route of Administration	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery[b].	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ[b].
Coverage	Protective against all RVFV lineages A-O[8,10].	Protective against against any RVFV strain likely to cause infection[8,10].
Product Stability and Storage	Shelf life of 5 years at 2-8°C. 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 (<0°C) are preferred. Vaccines that can be delivered via the Controlled Temperature Chain are preferred[28].	Shelf life of at least 12 months at -20°C and 6 months at 2-8°C. 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.

Co-administration with other vaccines	The vaccine 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 RVFV vaccine or the co-administered vaccines.	The vaccine will be given as a stand-alone product not co-administered with other vaccines.
Presentation	Vaccine is provided as a liquid product in mono-dose or multi- dose 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[26].	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. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy[26]. Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.
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[29].	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[29].

[a] confirmed case defined as the detection of live RVFV, RNA, or IgM against-RVF[10].

[b] when developing a vaccine for ID administration, measures should be taken to prevent any erroneous administration through a non-authorized route (e.g. incorrect IM/SC administration of an ID vaccine).

III. Considerations on Programmatic suitability

IV.A. Vaccine for veterinary use

Manufacturing and production of animal vaccines should meet the minimum standard requirements recommended by the World Organisation for Animal Health (OIE)30, and conform to the specific regulatory requirements of the competent authority for the country where the vaccine is manufactured or used.

IV.B. Vaccine for human use

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 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.

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