Rift Valley Fever Vaccine(s) - Trial Designs Considerations

This preliminary version has been developed to support deliberations throughout the consultation process. It should not be construed as reflecting the preferences or positions of the organizing committee, but rather serves as a structural tool designed to guide and enhance the quality of deliberations

DESIGN	Method	Advantages	Challenges
Individually RANDOMIZED Controlled Trials (iRCT)	Participants are individually randomized to receive either the vaccine or control (placebo or another vaccine)	High internal validity. Direct measurement of vaccine clinical efficacy (VE). Best when incidence is predictable and sample size is feasible. Includes immunogenicity and safety assessment. Amenable to multi-outbreak approach, if necessary	Unpredictable outbreaks can lead to prolonged enrollment and low event rates. May require large sample sizes if background risk is low or heterogeneous. Immunogenicity and safety data could be also informative if not enough clinical endpoints
	Clinical efficacy - YES		
	Immunogenicity - YES		
	Safety - YES		
Cluster RANDOMIZED Controlled Trials (cRCT)	Communities, villages, or groups are randomized as clusters to vaccine or control arms. Villages or well-defined communities in hyperendemic or recently affected zones. Enrollment commences in clusters only when real-time climatic/livestock surveillance thresholds are surpassed (rainfall, animal deaths, vector indices).	Clusters stratified by historical RVF risk and ecological zone. Captures both direct and indirect (herd) vaccine effects. Useful for operational convenience and reducing contamination.	Larger sample size requirements due to design effect. Risk of baseline imbalance between clusters (e.g., differences in animal exposures, animal vaccination, mosquito eradication, human exposures, etc.). Statistical analysis complexity, especially with temporal clustering.
	Clinical efficacy - YES		
	Immunogenicity - YES		
	Safety - YES		

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RANDOMIZED Ring Vaccination Trial (cRCT)	Define "rings" of contacts around incident human or animal RVF cases; rings are randomized to immediate or delayed vaccination. Modelled after successful Ebola vaccine trial designs.	In the event of confirmed human or livestock index cases, initiate rapid ring randomization for contacts. Allows more efficient capture of events in focal outbreaks. Prioritizes high-risk contacts, increasing event rates. Responsive to emergent cases in new areas this it is efficient in outbreak settings with focal clusters.	Requires rapid case identification and contact tracing. Assumes clustering of risk, which may not always hold for RVF.
	Clinical efficacy - YES		
	Immunogenicity - YES		
	Safety - YES		
Adaptive and Responsive RANDOMIZED Designs – Randomization during deployment	Enroll/enumerate subjects or clusters based on real-time surveillance triggers (e.g., climate data thresholds, livestock mortality signals), with flexible randomization or crossover schemes.	Targets enrollment to periods/ locations of highest risk. Allows rapid collection of a large amount of data. Can combine deployment of candidate vaccine with randomization Deployment occurs and is done by routine vaccination teams. No special data collection processes are required	The enumeration of individuals or groups of individuals to randomize needs to occurr before randomization. The time interval between those vaccinated early and late must be large enough to allow for analyses and accumulation of endpoints. Requires independent assessment of endpoints
	Clinical efficacy - YES		
	Immunogenicity - NO		
	Safety - YES		
NON RANDOMIZED **Immunobridging OR Animal rule approach (if**	**ANIMAL RULE** Relies on well-characterized animal models to demonstrate protection, making it feasible for pathogens where natural human infection is rare or unpredictable.	Does not need to be conducted during outbreaks (and usually less risky when not conducted during outbreaks)	Requires validated animal models that closely mimic human disease and immune response, which may not

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Correlate of Protection)	Needs standardized and validated assays	Enables vaccine approval when human efficacy trials are impractical, such as for diseases with sporadic outbreaks. Normally infeasibility of human trials is required. Can facilitate rapid development and deployment of countermeasures in outbreaks, in line with public health emergency preparedness goals. Particularly useful for high-consequence zoonotic diseases, including RVF, where large human clinical trials are not possible	always exist or be fully predictive for RVF. Regulatory acceptance hinges on demonstrating that animal surrogate endpoints can reliably predict human benefit, which is challenging for emerging diseases with limited human data. Human dose selection and immunogenicity still require supporting data, often necessitating bridging studies or modeling, increasing complexity and uncertainty. Potential species differences in immune response may lead to uncertainty about efficacy or safety in humans Regulatory agencies may demand additional safety or real-world effectiveness data.
	IMMUNOBRIDGING Uses immune response data (like antibody titers or neutralizing antibodies) from previously validated vaccines or populations to infer effectiveness in new settings.	Does not need to be conducted during outbreaks (and usually less risky when not conducted during outbreaks) Enables extrapolation across age groups, populations, or even related vaccines, provided immunological correlates of protection are robust	Requires validated immune correlates of protection, which may be lacking or uncertain for RVF, especially in naïve populations or novel vaccines. Non-inferiority designs may mask subtle differences in immune protection that are clinically significant, especially for complex diseases like RVF. Extrapolation can be limited if the immune response varies due to host

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		Can allow regulatory approval for new vaccine formulations, regimens, or target groups without conducting new efficacy trials, when immune markers of protection are established. Immunobridging is feasible if immunological correlates of protection are well established (e.g., neutralizing antibody titers), but RVF lacks exhaustive human clinical data, limiting confidence in extrapolation	factors, vaccine composition, or epidemiology. Regulatory agencies may demand additional safety or real-world effectiveness data.
	Clinical efficacy - NO		
	Immunogenicity - YES		
	Safety - YES		