Simple, large-scale, multi-country individually randomized placebo-controlled trial

STRAWMAN VERSION

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 discussions

STUDY TITLE	**CORE protocol: Randomized Rift Valley Fever (RVF) vaccine trial in humans in multiple sites**
STUDY OBJECTIVE(S)	To estimate the vaccine efficacy in humans
STUDY DESIGN	Humans randomized to a single vaccine chosen for evaluation or control (in a 1:1 ratio) within study sites
POPULATION	Humans at elevated risk of RVF infection Livestock handlers, abattoir workers, herders, and others with frequent animal contact are recognized as the most affected population and are a high-priority sampling group. The Senegal epidemic is notably affecting young people (ages 15–30) and males, making them a key consideration for the trial's target population.
INTERVENTION	One or more experimental vaccines
COMPARATOR	Placebo (or active comparator)
RANDOMIZATION	Individual randomization to vaccine or placebo Allocation ratio 1:1
PRIMARY OUTCOME	Vaccine efficacy in humans for preventing laboratory-confirmed RFV disease (using a combination of RT-PCR testing and IgM testing for case confirmation)

SECONDARY OUTCOMES	**Vaccine efficacy in preventing severe disease -** Assessment of mild to severe cases and stratified analysis by disease severity Severe disease can be defined as requiring hospitalization, progression to organ failure/complications, or death. - For hospitalized patients, the CFR can be high in some places so would need to see what proportion of cases are being hospitalized. Can also measure viral clearance kinetics in a subgroup (this could help provide more information to plan for therapeutic trial).
	Vaccine safety - evaluate the safety and tolerability of the RVF vaccine candidate in healthy adult volunteers, including assessment of solicited local and systemic adverse events for 7 days post-vaccination, unsolicited adverse events for 28 days, and serious adverse events throughout the study duration
	Immunogenicity data - Immunological Endpoints o Neutralizing Antibody Responses: Geometric mean antibody titers (GMT) measured by focus reduction neutralization test (FRNT80) at multiple timepoints (Days 0, 7, 14, 28, 84, 112, 365, and 18 months) o IgG Antibody Responses: Geometric mean antibody titers for IgG antibodies against RVFV glycoproteins (Gn/Gc) measured by ELISA o Cellular Immune Responses: IFN-γ responses to RVFV Gn and Gc glycoproteins measured by ELISpot assay (Spot Forming Units per 10^6 PBMCs) Multi-functional T cell responses measured by flow cytometry Infection Rate: Detection of RVFV infection regardless of clinical symptoms, requiring DIVA (Differentiating Infected from Vaccinated Animals) testing
	Duration of Immunity: Assessment of antibody persistence and durability of immune responses, particularly in prime-boost vaccination regimens
EXPLORATORY OUTCOMES	**Immunological Correlates of Risk**: Identification of immune markers that correlate with protection or increased susceptibility to RVFV infection
	Surrogate Markers of Protection: Development of immunological surrogates that can predict vaccine efficacy without requiring clinical endpoints
	Minimal Protective Titer: Determination of the minimum neutralizing antibody titer required for protection (studies suggest titers ≥1:5-1:20 may be protective)

	Baseline Seropositivity Impact: Assessment of how prior RVFV exposure affects vaccine safety and efficacy
	Pregnancy Safety: Safety evaluation in pregnant women, particularly important given spontaneous abortion risks associated with both natural RVFV infection and some veterinary vaccines
	One Health Approach: In outbreak settings, evaluation of combined human and animal vaccination strategies on human disease prevention
FOLLOW-UP	To be determined; probably one year. Study may continue for longer if sufficient number of endpoints are not obtained.
STATISTICAL ANALYSIS	Planned statistical tests: Survival models will be used to estimate vaccine efficacy and effectiveness Primary analysis: Simple Cox model and Kaplan-Meier curves Safety data: Simple comparisons using t-tests or small sample equivalents Study power: Study will continue (potentially across outbreaks) until sufficient data are obtained to perform efficacy analysis. After 20 cases, a 20% lower bound on efficacy would be met with a point estimate of 70%, and a vaccine with true efficacy of 85% would have ~80% power to meet a 20% lower bound. Interim analysis: Any interim analysis will use group sequential analysis with O'Brien-Fleming stopping rules.
ETHICAL CONSIDERATIONS	**Informed consent process.** There will be informed consent before participants are vaccinated with vaccine or placebo **Ethics committee approval.** There will be full approval from the various ethics committees involved
SAFETY MONITORING (e.g., Data Safety Monitoring Board).	Trial oversight will be provided by a single Steering Committee (SC) and a single data monitoring committee (DMC). Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data. The role of the DMC will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues. Once one or more vaccines meet specified success criteria, new efficacy/lack of benefit criteria will be introduced.