Proposed CORE protocol : Randomized Rift Valley Fever (RVF) vaccine trial in humans in multiple sites

Ira Longini
University of Florida
Consultant to WHO R&D Blueprint

World Health Organization

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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

OUTCOMES

PRIMARY OUTCOME:

Vaccine efficacy in humans for preventing laboratory-confirmed RFV disease

SECONDARY OUTCOME(S):

Vaccine safety

Immunogenicity data - Immunological Endpoints

Vaccine efficacy in preventing severe disease

Duration of Immunity

EXPLORATORY OUTCOMES

Immunological Correlates of Risk

Surrogate Markers of Protection

Minimal Protective Titer

Duration of Immunity

Baseline Seropositivity Impact: Assessment of how prior RVFV exposure affects vaccine safety and efficacy

Pregnancy Safety

One Health Approach: In outbreak settings, evaluation of combined human and animal vaccination strategies on human disease prevention

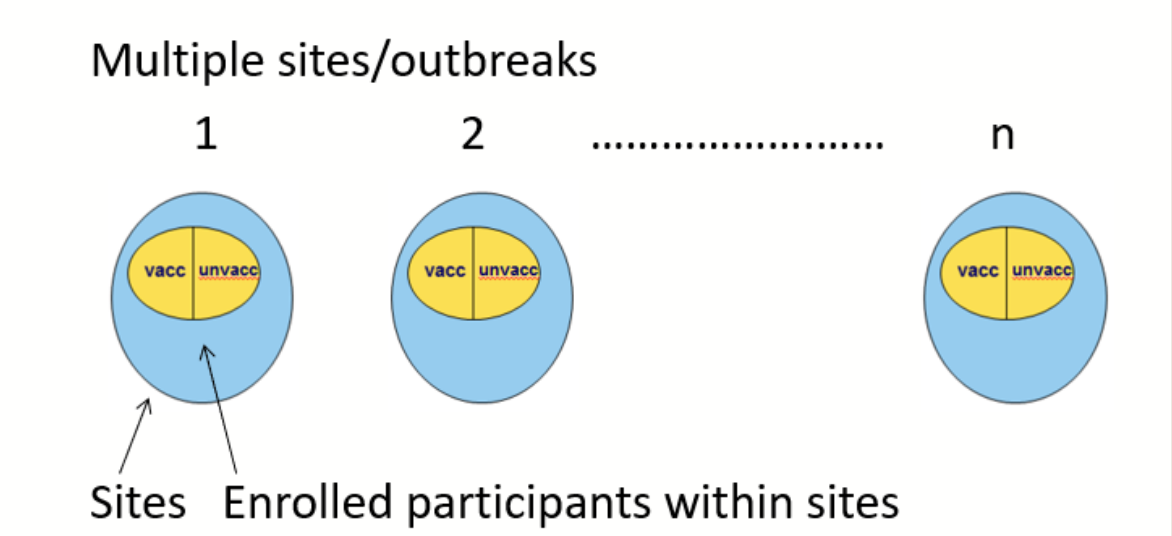
EXPLORATORY OUTCOMES

Pregnancy Safety

FOLLOW-UP

To be determined; probably one year. Study may continue for longer if sufficient number of endpoints are not obtained.

Multiple sites where outbreaks are occurring or at high risk of outbreaks



VE = 1 - $\frac{\lambda_1}{\lambda_0}$, combined across the n sites.

Statistical analysis

The primary analysis will be the estimated vaccine efficacy against confirmed RVF illness: $\widehat{\mathrm{VE}} = 1 - \widehat{\lambda_1}/\widehat{\lambda_0}$

- $\widehat{\lambda_1} =$ estimated hazard of illness for individuals who receive vaccine.
- $\widehat{\lambda_0} =$ estimated hazard of illness for individuals who receive placebo.

One-sided hypothesis test for the primary outcome:

- H_0: $\mathrm{VE} \leq 0.3$ versus H_a: $\mathrm{VE} > 0.3$. In addition, a lower 95% confidence bound will be calculated for $\widehat{VE}$

Secondary analyses using same setup

Statistical method: Cox proportional hazards model with stratification
Appropriate α – spending for interim analyses (Obrien-Fleming)

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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

- 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.

Thank you

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STUDY POWER

Trial 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.