Human vaccine trial designs to evaluate RVF vaccines

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World Health Organization
RVF– Potential areas for VTs
Unknown (sporadic) number of cases per year

Source: https://www.cdc.gov/vhf/rvf/outbreaks/distribution-map.html
RVF Outbreak in Kenya

FIGURE 3. Number of reported Rift Valley fever cases (n = 330), by date of illness onset — Kenya November 2006–January 2007*

*As of January 25, 2007, for cases with known date of onset.

Source: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5604a3.htm
Age distribution of cases

FIGURE 1. Number of reported Rift Valley fever cases (n = 230), by sex and age group — Kenya, November 2006–January 2007*

*As of January 14, 2007.
Vaccine trials for public health emergencies: WHO R&D Blueprint


RVF fever – basic facts for vaccine trial design

- Incubation period: 3-6 days
- Infection period: 7 days
- Pathogenicity: Asymptomatic or mild infections common
- Retinitis: 1% – 10% of symptomatic patients may have permanent vision loss
- Other serious conditions
- Miscarriage rate may be high
- CFR: Low, < 2%
RVF fever – basic facts for vaccine trial design

Transmission:
• Exposure to animals, mainly live-stock, especially sheep
  • Direct exposure to animal parts and fluids
  • Mosquitos (animal to animal)
  • No human to human transmission
• No known human-to-human transmission
RVF – target product profile scenarios

Emergency setting (Reactive/Outbreak use):
Protection of at-risk persons in the area of an ongoing outbreak of RVF.
RVF – target vaccine population

Options:
Healthy at-risk adults, excluding pregnant and lactating women, immunodeficient people
(or include some of the above depending on the vaccine and other factors)
May be important to include pregnant women
RVF – vaccine trial design

• A responsive, randomized, double-blind, placebo-controlled, efficacy trial

• Responsive in clusters with transmission
  • At risk populations: Farmers, butchers, others that handle animal products
  • Where outbreaks occur in animals
RVF – important considerations

Screening at baseline
Bleed all of the trial participants before vaccination to determine baseline seropositivity

Could contribute to design an immune correlate of risk or surrogate of protection, with this design, if the vaccine works.
RVF – endpoint considerations

Primary endpoint
Laboratory-confirmed RVF clinical illness

Secondary endpoints
• Infection
• Stratified analyses on prior immune measures
• Severe disease and death
• Immunological correlates of risk and surrogates of protection, i.e., surrogates for vaccine efficacy
Statistical analysis

The primary analysis will be the estimated vaccine efficacy against confirmed RVF illness: 

\[ \bar{VE} = 1 - \frac{\hat{\lambda}_1}{\hat{\lambda}_0} \]

- \( \hat{\lambda}_1 \) = estimated hazard of illness for individuals who receive vaccine.
- \( \hat{\lambda}_0 \) = estimated hazard of illness for individuals who receive placebo.

One-sided hypothesis test for the primary outcome:

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

Secondary analyses using same setup

Statistical method: Cluster-stratified, Cox proportional hazards model, with appropriate \( \alpha \) – spending for interim analyses
Testing more than one vaccine

• We can test $m$ vaccines against a single placebo arm, using Bonferroni or a more complex correction for $\alpha$
• e.g., two vaccines would be randomized in a 1,1,1 pattern with two hypothesis tests, each at $\alpha = 0.025$
Individual randomization within sites

Multiple sites/outbreaks

1

2

..........................

n

Sites  Enrolled participants within sites

VE = 1 - \( \frac{\lambda_1}{\lambda_0} \), combined across the n sites as stratification or regression
Sample Size for Primary Outcome With One Vaccine

90% power, 2:1 vaccine to placebo, $\alpha = 0.05$ one-sided, VE = 0.3 lower bound, 20% loss-to-follow-up

<table>
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<th>Cumulative attack rate in placebo arm</th>
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Data monitoring strategy

Interim analyses to assess efficacy or futility can be timed to occur at the end of each season (or after reaching a targeted # of events, e.g. 50%)

Study data would not be released unless the trial was stopped, for efficacy, futility, or reaching its targeted number of endpoints

Probably several years to complete trial
“Master protocol” approach

The protocol should be generalizable to other West African countries where RVF is endemic

Where outbreaks in other countries occur, the trial structure should allow new sites in affected areas to be added

Researchers and national representatives from affected countries should be engaged early on

A clear and transparent mechanism for achieving consensus regarding elements of the protocol is required (e.g. managing data, sharing samples, mediating disagreements)