R&D Blueprint for action to prevent epidemics

Considerations for trial design of CCHF vaccines (Phase 2b/Phase 3)

Ira Longini, and the
Blueprint Working Group on Clinical Trial Design
World Health Organization
CCHF—Potential areas for VTs
30 countries in Africa, the Balkans, the Middle East and Asian
Estimated 10,000 – 15,000 cases per year

Source: https://www.cdc.gov/vhf/crimean-congo/outbreaks/distribution-map.html
### Some past outbreaks

<table>
<thead>
<tr>
<th>Location</th>
<th>Years</th>
<th>Number of cases*</th>
<th>Case fatality rate (%)</th>
<th>Occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Southeast Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crimea</td>
<td>1944–45¹</td>
<td>200</td>
<td>10</td>
<td>Military members</td>
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<tr>
<td>Astrakhan</td>
<td>1953–63¹</td>
<td>104</td>
<td>17</td>
<td>Agricultural workers</td>
</tr>
<tr>
<td>Rostov</td>
<td>1963–69⁴</td>
<td>323</td>
<td>15</td>
<td>Agricultural workers</td>
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<tr>
<td>Bulgaria</td>
<td>1953–74²</td>
<td>1105</td>
<td>17</td>
<td>Agricultural workers, health-care workers</td>
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<td></td>
<td>1975–96¹⁶</td>
<td>279</td>
<td>11</td>
<td>Agricultural workers</td>
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<tr>
<td></td>
<td>1997–03¹⁶</td>
<td>138</td>
<td>21</td>
<td>Agricultural workers</td>
</tr>
<tr>
<td>Albania</td>
<td>2001¹⁷</td>
<td>7</td>
<td>0</td>
<td>Agricultural workers, health-care workers</td>
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<tr>
<td>Kosovo</td>
<td>2001¹⁸</td>
<td>18</td>
<td>33</td>
<td>Agricultural workers</td>
</tr>
<tr>
<td>Turkey</td>
<td>2002–05⁹</td>
<td>500</td>
<td>5</td>
<td>Agricultural workers</td>
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<tr>
<td><strong>Asia</strong></td>
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<td></td>
</tr>
<tr>
<td>China</td>
<td>1965–94¹⁹</td>
<td>260</td>
<td>21</td>
<td>Agricultural workers</td>
</tr>
<tr>
<td></td>
<td>1997¹⁰</td>
<td>26</td>
<td>24</td>
<td>Agricultural workers</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>1948–68¹</td>
<td>75</td>
<td>50</td>
<td>Agricultural workers</td>
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<tr>
<td>Tajikistan</td>
<td>1943–70¹</td>
<td>97</td>
<td>23</td>
<td>Agricultural and laboratory workers</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1976²⁰</td>
<td>14</td>
<td>29</td>
<td>Shepherd, health-care workers</td>
</tr>
</tbody>
</table>

Cases of CCHF in Turkey from 2002 to 2015

Source: https://www.sciencedirect.com/science/article/pii/S0166354215300401
Vaccine trials for public health emergencies: WHO R&D Blueprint


CCHF fever – basic facts for vaccine trial design

Incubation period: Tick bite, 1-3 days
Exposure to infected bodily fluids, 5-6 days

Pathogenicity: Around 10% of infectious will have symptoms

CFR: ≈ 15 - 30%, death occurring in 2nd week of illness

Transmission:
• Tick bites or through contact with infected animal blood or tissues during and immediately after slaughter. The majority of cases have occurred in people involved in the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians.
• Human-to-human transmission can occur resulting from close contact with the blood, secretions, organs or other bodily fluids of infected persons.
  • Hospital-acquired infections can also occur due to improper sterilization of medical equipment, reuse of needles and contamination of medical supplies.
CCHF – target product profile scenarios

Emergency setting (Reactive/Outbreak use):
Protection of at-risk persons in the area of an ongoing outbreak of CCHF fever.

Non-emergency setting (Preventive Use):
Populations living in areas where CCHF fever is endemic.
CCHF – target vaccine population

Options:
Healthy adults and children, excluding pregnant and lactating women, immunodeficient people, small children
(or include some of the above depending on the vaccine and other factors)
CCHF – vaccine trial design

A prospective, randomized, double-blind, placebo-controlled, efficacy trial

Individual randomization in geographic clusters in areas mapped to have transmission, mixture of

- Pre-selected, pre-vaccinated clusters of highest risk
- Closely monitored high-risk clusters with responsive vax
- Responsive addition of clusters with transmission
CCHF – 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 protection, with this design, if the vaccine works.
CCHF – endpoint considerations

Primary endpoint
Laboratory-confirmed CCHF clinical illness

Secondary endpoints
• Infection
• Stratified analyses on prior immune measures
• 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 CCHF illness: $\hat{VE} = 1 - \frac{\hat{\lambda}_1}{\hat{\lambda}_0}$

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

One-sided hypothesis test for the primary outcome:

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

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

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>
<thead>
<tr>
<th>VE</th>
<th>Average required total # of events</th>
<th>Cumulative attack rate in placebo arm</th>
<th>Cumulative attack rate in vaccination arm</th>
<th>Sample size in placebo arm</th>
<th>Sample size in vaccination arm</th>
<th>Total sample size</th>
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</thead>
<tbody>
<tr>
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<td>360</td>
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<td>0.25%</td>
<td>44292</td>
<td>88583</td>
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<td>0.50%</td>
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<td>9667</td>
<td>19333</td>
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<td>90%</td>
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<td>3875</td>
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<td>2%</td>
<td>0.20%</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
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</tbody>
</table>
The case of CCHF vaccine trials

Emergency setting (Reactive/Outbreak Use)
• It may be possible to accumulate enough data to assess VE in a single year, but more than one year will probably be needed

Non-emergency setting (Preventive Use)
• It will probably involve several years and a variety of locations to accumulate enough cases to assess VE
• We could combine data from the preventive and reactive trials to get an answer sooner
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
“Master protocol” approach*

Where outbreaks 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).

Statistical considerations

“Standard” sequential monitoring plan based on information fraction

- Number of participants in vaccine trial

Pre-specified analyses or flexibly timed to occur when outbreaks end
Thank you