An R&D Blueprint for action to prevent epidemics

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

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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
31 Oct – Nov 1, 2019 | Blueprint Meeting: CCHF
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>
</tr>
<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>
</tr>
<tr>
<td>Bulgaria</td>
<td>1953–74²</td>
<td>1105</td>
<td>17</td>
<td>Agricultural workers, health-care workers</td>
</tr>
<tr>
<td></td>
<td>1975–96¹⁶</td>
<td>279</td>
<td>11</td>
<td>Agricultural workers</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>1965–94²⁹</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>
</tr>
<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>1976¹⁰</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
CCHF fever – basic facts for therapeutic 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 2\textsuperscript{nd} 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 therapeutics

• There are no licensed therapeutics for CCHF
• Ribavirin is used ‘off-label’
• Various dosing regimens
• Expensive (>USD1000)
• Difficult to source
• Efficacy of ribavirin?
Trial Design: Primary considerations

• **Design:** A multicenter, individually-randomized, two-arm, placebo-controlled trial comparing ribavirin plus optimized standard of care (oSOC) versus oSOC with placebo for the reduction of mortality in hospitalized patients with laboratory-confirmed CCHF

• **Primary objective:** To evaluate whether intravenous ribavirin improves survival in patients with confirmed CCHF compared to placebo

• **Primary endpoint:** 28-day after randomisation
Trial Design: Secondary considerations

- **Secondary objectives:**
  - To evaluate the safety of intravenous ribavirin in patients with confirmed CCHF compared to placebo.
  - To evaluate whether intravenous ribavirin reduces viral load in patients with confirmed CCHF compared to placebo.
Secondary endpoints

• Frequency of serious adverse events [Time frame: 28 days after randomisation]
• Time to undetectable viral load by PCR [Time frame: right censored by day of death or discharge]
• Area under the curve (AUC) viral load [Time frame: right censored by day of death or discharge]
## Crude sample size estimates

<table>
<thead>
<tr>
<th>oSOC + placebo CFR</th>
<th>Ribavirin efficacy</th>
<th>Rib + oSOC CFR</th>
<th>Sample size (cases) per arm</th>
<th>Total sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>30%</td>
<td>0.070</td>
<td>1,356</td>
<td>2,712</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.050</td>
<td>435</td>
<td>870</td>
</tr>
<tr>
<td>0.15</td>
<td>30%</td>
<td>0.105</td>
<td>864</td>
<td>1,724</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.075</td>
<td>278</td>
<td>556</td>
</tr>
<tr>
<td>0.20</td>
<td>30%</td>
<td>0.140</td>
<td>615</td>
<td>1,230</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.100</td>
<td>199</td>
<td>398</td>
</tr>
<tr>
<td>0.25</td>
<td>30%</td>
<td>0.175</td>
<td>464</td>
<td>928</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.125</td>
<td>150</td>
<td>300</td>
</tr>
</tbody>
</table>
RANDOMIZATION

Eligible cases to be individually randomized using block randomization with randomly varying block lengths

Randomization will be stratified by site

Sites added over outbreaks and countries

To balance treatment allocation between sites and reduce confounding by inter-site heterogeneity in CFR.
“Master protocol” approach*

Where outbreaks, 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 therapeutic trial

Pre-specified analyses or flexibly timed to occur when outbreaks end
Interim and secondary analyses under the master protocol

Annual blinded interim and post outbreak analysis by DSMB for efficacy and futility.

A planned sample size review at interim analysis based on blinded, aggregated CFR across both groups.

Interim analyses will inflate sample size (5-10%)

Secondary stratified analysis of CFR by:

- Time from symptom onset to treatment (perhaps binary ≤ 6 vs > 6 days)
- Baseline CT value
- AST/SGOT < 150 vs. ≥150
Maintaining confidentiality

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

Discussion