Overview of CCHF vaccine candidates

Inactivated virus vaccines
Nucleic acid ...
Subunit ...
Reverse genetics VLP...
Plant expressed ...
Virus vectored ...
Other approaches...
CCHF Virus

- Make up
  - GPC > GP spike
  - N terminal more variable
  - Complicated processing GPC
  - Mature G N G C - structure not defined
  - V difficult to express / manipulate

N Protein
- Important role in RNP
- Dominant
- Conserved

Vectored vaccines that have successfully reported protection used viral NP as target antigen

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Vaccine construct</th>
<th>Protection effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola virus</td>
<td>Venezuelan equine encephalitis virus replicons</td>
<td>Protection in C57BL/6 mice</td>
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<tr>
<td></td>
<td>Cytomegalovirus</td>
<td>Protection in mice</td>
</tr>
<tr>
<td>Hantavirus</td>
<td>Recombinant vaccinia virus</td>
<td>Partial protection in Mongolian gerbils</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>DNA prime and recombinant adenovirus boost</td>
<td>Protection in mice</td>
</tr>
<tr>
<td></td>
<td>Recombinant adenovirus</td>
<td>Protection in mice</td>
</tr>
<tr>
<td>Lassa virus</td>
<td>Recombinant vaccinia virus</td>
<td>Protection in guinea pigs</td>
</tr>
<tr>
<td>Measles</td>
<td>Recombinant vaccinia virus</td>
<td>Protection from encephalitis in rats</td>
</tr>
<tr>
<td>Pichinde virus</td>
<td>Recombinant vaccinia virus</td>
<td>Delayed mortality in Syrian hamsters</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>Raccoon poxvirus</td>
<td>Protection in mice against lethal challenge</td>
</tr>
<tr>
<td>Rift Valley fever</td>
<td>DNA vaccine</td>
<td>Partial protection of mice against lethal challenge</td>
</tr>
</tbody>
</table>

M-ORF GPC

NP
Inactivated virus vaccines

❖ Soviet / Bulgarian vaccine

- Virus* amplified in brains of suckling mice
- CHCl₃ / Heat (58°C) inactivation
- Al(OH)₃ adsorption
- Licenced in Bulgaria since 1974

➢ No trail / efficacy data
➢ Claims of reduced CCHF incidence since its use in Bulgaria
➢ Retrospective studies showed induced immunity
➢ No efficacy data

* Different viruses have been used
Inactivated virus vaccines

❖ Turkish cell culture approach
  o CHCl₃ / Heat (58°C) inactivation
  o Al(OH)₃ adsorption

➢ Induction of VNT antibodies
➢ Efficacy / protection data in mouse model (80%)
DNA vaccines

❖ Complete M segment ORF
  o Gene gun delivery IM induced immunity

➢ Induction of antibodies inc VNT
➢ Protection data (80%)

❖ Multiple plasmid approach NP + G_N + G_C
  o ID delivery of 3 doses [Ub tagged proteins]

➢ Induction of cell mediated, antibody responses (inc VNT)
➢ 100% protection in mouse model

❖ NP DNA vaccine 100% protection NHPs
mRNA vaccines

❖ Naked mRNA
  o Injected delivery IM – (S segment)
  ➢ Booster dose resulting in 100% protection
  ➢ ... many advantages

❖ Self amplifying mRNA
  o e.g. Alphavirus replicons
  ➢ ..virus packaging
Transcriptionally competent - VLP

- Self assembled VLPs (native conformation) non-infectious
  - ID delivery of 3 doses
  - Induction of cell mediated, antibody responses (inc VNT)
  - 40% protection in mouse model

- CCHFV replicon vaccine
  - Single round of replication
Plant expressed vaccines

❖ Rec – tobacco expressing $G_N$ and $G_C$
  o Stable transgenic tobacco plants fed to mice
  o Similar glycosylation patterns to humans
  o High expression

➢ Induced immunity (IgA & IgG)
➢ No efficacy work
Subunit vaccines

- **Baculovirus expressed** $G_N G_C$ **tagged protein**
  - Truncated ectodomains purified
  - IP vaccination

- Induction of antibodies
- Protection data (0%) in mouse challenge model (STAT-1)
Viral vectors

❖ MVA – GP (complete M segment ORF)
  o Prime / boost ID administration

➢ Induction of antibodies & T cell responses
➢ Protection data (100%) in mouse challenge model
➢ No sterilizing immunity
  ➢ GMP manufacture & Phase 1 clinical train [Innovate UK & BBSRC]

❖ MVA – NP (complete S segment ORF)
  o Prime / boost ID administration

➢ Induction of cell mediated, antibody responses
➢ 0% protection in mouse model
Viral vectors

❖ Adenovirus (AdHu5) – GPC (complete M segment ORF)
  o IM administration $10^{10}$ (particle counts)
  ➢ Induction of antibodies & T cell responses
  ➢ Protection data (0%) in mouse challenge model (STAT-1)

❖ Adenovirus (AdHu5) – N ORF
  o IM / IN administration
  ➢ Induction of cell mediated, antibody responses
  ➢ ~80% vaccine efficacy

❖ Adenovirus ChAd – NP (complete S segment ORF)
  o IM administration
  ➢ Induction of antibody responses
  ➢ 100% protection.
Viral vectors

- VSV – CCHFV- GPC (complete M segment ORF)
  - Replication competent recombinants
  - 100% protection mouse model
Additional research

• Correlates of protection not clearly defined
  – vaccines need to demonstrate protection in lethal dose animal models before protective efficacy can be established.

• NHP models of disease
  – vaccine approval under the Animal Rule devised by the Food and Drug Administration (FDA) in the USA for demonstration of efficacy in place of human clinical trials

➢ CEPI funding..?
Future approaches

❖ Strain choice
  • Initial approaches based on lab strain IbAr10200
    o Some evidence of cross protection...

❖ Alternative vaccine approaches
  • Tick vaccines...
    Cement & midgut antigen (Bm86) partially protective
    *Rhipicephalus* sp... TickGARD
    *Hyalomma* sp ...
    • Ferritin & tropomyosin identified as candidates
    • Vaccination of calves led to >60% reduction in tick infestation
Phase I Clinical Trial  \text{MVA}^{\text{GP}} \text{ vaccine}

Phase 1a “open label, multi-centre, human, dose escalation” CCHF vaccine trial

- Safety in healthy volunteers of using a prime boost regime
- Assess the humoral and cellular immunogenicity, and ex-vivo efficacy of MVA-GP when administered to healthy volunteers

- **Trial period 15 months**
- **24 volunteers**

**Group 1**
- Subgroup 1A: 4 volunteers; 1 dose of MVA-GP \text{LOW} intramuscularly
- Subgroup 1B: 4 volunteers; 1 dose of MVA-GP \text{MEDIUM} intramuscularly
- Subgroup 1C: 4 volunteers; 1 dose of MVA-GP \text{HIGH} intramuscularly

**Group 2**
- 12 volunteers; 2 doses of MVA-GP at the most well tolerated and immunogenic dose from Group 1
## Product profile for a human CCHF vaccine

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Induction of humoral and cellular responses</td>
<td>Only vaccine approaches which induce both arms of the adaptive immune system have demonstrated protection against CCHFV challenge. So far...</td>
</tr>
<tr>
<td>Authentic expression of gene product</td>
<td>The antigen exposed to the immune system needs to be identical to the target virus to optimise linear and non-linear epitope recognition.</td>
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<tr>
<td>Acceptable ‘Costs of Goods’ profile</td>
<td>Cost will be a key factor in uptake by authorities in endemic regions where healthcare finances are limited.</td>
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<tr>
<td>Manufacturing capability</td>
<td>Ease of production and in sufficient quantities for immunisation of at risk groups in endemic regions.</td>
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<tr>
<td>Thermostable</td>
<td>Thermostabile vaccine would reduce logistics and extra costs associated with maintaining a cold chain.</td>
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<tr>
<td>Safety profile</td>
<td>A vaccine based on technologies with existing safety data is more likely to be successful in clinical trials and faster to license.</td>
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<tr>
<td>Few doses required</td>
<td>Vaccine uptake will be increased if multiple boosters are not required.</td>
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</table>
Chronology of events during a CCHFV outbreak

- Domestic animal epizootic
- Human outbreak
- Wildlife

Number of Cases vs TIME (days)
Outbreak response & control

Anticipate New Trends & Forecasting

Rapid Response

Early Detection

Control Benefits to animals

Control Benefit to Humans

1. Preparedness / surveillance
2. Alert
3. Control
4. Recovery

Domestic animal epizootic
Human outbreak
Wildlife

Number of Cases

Control Benefits to animals

Vector Control

Outbreak response & control