Rift Valley Fever

Strategy for RVF vaccination

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Layout

• Impact of RVF
• RVF control & importance of vaccination
• RVF vaccines quick overview: current & those in the pipeline
• Vaccination strategies & options
• GALVmed contribution to improved vaccination strategies
Rift Valley Fever and its impact

• Localised in Africa, spread to the Middle East in 2000. Considered a big threat to other regions including Europe. Included in the list of potential biological warfare agents.

• 2007 outbreak in Kenya & Tanzania: more than 300 human fatalities, thousands of mortality in livestock. Destroyed meat industry.

• Kenya: cost of livestock outbreak (animal productivity, government spending): US$ 54m. In Garissa region, 89% of the households reported that RVF had affected their herds, 18.5% reported a case of human RVF in their own household, 20-60% loss of work productivity reported in surviving cases

PUBLIC HEALTH IMPACT

• Egypt 1997: 200000 human cases, 600 reported fatalities
• Mauritania 1987: over 300 fatalities
• Sudan 2007-2008: 738 human cases, 230 deaths
• South Africa 2010: 242 lab-confirmed human cases with 26 deaths
• Mauritania 2010: 63 human cases, 13 deaths
RVF control

• Epidemics result from the synergy of at least three factors which can vary considerably:
  – (i) the presence and circulation of the phlebovirus by *mosquito vectors*;
  – (ii) the number of mosquito breeding sites and hatching frequency, two parameters which are both highly dependent on *environmental conditions*, particularly rainfall events; and
  – (iii) the *distribution of domestic animal hosts*, essentially ruminants (goats, sheep and cattle), vulnerable to increased vector/host contacts at night.

• Vector control difficult to implement
• Complicating factors: Cyclical nature of the disease; variable inter epizootic periods;
• Use of sentinel animals highly dependent on good diagnostic methods (not always available)

• *Essentially reliant on surveillance & vaccination*
RVF vaccines & vaccination
RVF vaccines

• 2 types of vaccines currently used
  – Live attenuated based on Smithburn strain: South Africa & Kenya
  – Live attenuated based of Clone 13: South Africa
  – Inactivated: South Africa & Egypt

• Several initiatives for new vaccines

• Vaccination not practiced in some enzootic regions
RVF distribution and Vaccination

http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/rvffmap.htm

Yearly or regular  Outbreak-associated
# RVF situations and control approaches

<table>
<thead>
<tr>
<th>RVF Situation</th>
<th>Examples of countries</th>
<th>Current Control strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic with regular outbreaks</td>
<td>Kenya, Tanzania, Egypt, Senegal, Mali</td>
<td>Vaccination at sign of outbreak</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Egypt: continuous vaccination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No vaccination</td>
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<tr>
<td>Endemic with sporadic/re-occurring outbreaks</td>
<td>South Africa, Saudi Arabia</td>
<td>Continuous/yearly vaccination</td>
</tr>
<tr>
<td>Free high risk</td>
<td>Middle East, North Africa</td>
<td>(Active) surveillance</td>
</tr>
<tr>
<td>Free low risk</td>
<td>Europe, Americas</td>
<td>Surveillance, talks of vaccine banks</td>
</tr>
</tbody>
</table>

Currently no vaccination in West Africa
- Senegal & Mali (continuous serological evidence); Mauritania (recent outbreaks)
- No vaccination due to concerns about vaccine safety

Limited continuous vaccination of livestock in Africa:
- Cost of yearly vaccination
- Safety concerns: difficulties to determine physiological stages of pregnant animals
- Irregularity of outbreaks (years without signs of outbreak)
- Policy aspects: vaccination not always covered by government
Ideal RVF vaccine (Product profile)...

**Generic characteristics**

- **Safety**
  - Safe to produce
  - Safe to all physiological stages of animals
  - No residual virulence
  - No risk of introduction into the environment (shedding, persistence in animals etc.)
  - No risk of spread to human or other species

- **Efficacy**
  - Protection of all susceptible species
  - Quick onset of protective immunity, including in young animals
  - Long lasting immunity
  - STOP TRANSMISSION: prevent amplification of RVFV in ruminants

- **Vaccination**
  - Cost effective for producers and users
  - Single vaccination
  - Ease of application
  - Suitable for stockpiling (vaccine or antigen bank) and quick availability

**Endemic regions**

- Continuous vaccination: yearly vaccination of susceptible livestock
  - Need to know how many vaccinations may be required to build a life long immunity

- **Efficacy**
  - Solid protective immunity after 1 vaccination

**Free regions**

- Quick onset of protective immunity
- Protective in young animals and possibly newborn naïve animals
- Sterilizing immunity
- DIVA
# RVF traditional Vaccines

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>STRAIN</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| **Inactivated** (OBP, VSVRI) | Pathogenic field strain | • Safe in pregnant animals  
• Can be used in outbreak  
• Short term immunity  
• Multiple vaccinations required  
• Risk of handling virulent strain during production  
• Colostral immunity present but poor  
• Sheep better protected than cattle  
• 100 x more antigen required than for live attenuated  
• Longer production lead time |                                                                                                     |
| **Live Attenuated** (OBP, KEVEVA) | Smithburn               | • Highly immunogenic  
• Single dose  
• Good immunity (within 21 days)  
• Effective and easy production  
• Safer production  
• Large batches: >4m doses  
• Potential residual virulence  
• Teratogenic for foetus  
• Potential risk of reversion to virulence  
• Not advisable for use in outbreaks  
• Theoretical possibility of transmission by mosquitoes (?) |                                                                                                     |
## New vaccines & Candidates evaluated in Target animals

<table>
<thead>
<tr>
<th>VACCINE</th>
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<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| Live attenuated                      | MP12                    | ● Effective and good protective immunity  
● Easy and safe to produce  
● Better safety than Smithburn in most species and age groups | ● Teratogenic for foetus  
● Abortion in early pregnancy  
● Not available commercially |
| Avirulent natural mutant             | Clone 13                | ● Good protective immunity in sheep & cattle  
● Safe in pregnant animals  
● Safe in outbreak  
● Produced as standard freeze-dried live vaccine  
● More than 19 million doses used  
● Safe, effective and easy to produce  
● Possible DIVA (NSs ELISA?)  
● Registered & used extensively in South Africa | ● Only registered to date in South Africa & Namibia  
● Large scale field data in other regions needed  
● No evidence of DIVA to date |
| Recombinant Lumpy skin virus expressing RVF | LSD Neethling strain expressing RVF glycoproteins | ● Dual vaccine  
● Safe in all animals  
● DIVA  
● Long shelf life (LSD)  
● More thermo-tolerant than others  
● Efficacy shown in animal trials | ● Only proof of concept to date  
● Currently grown in primary cells  
● Possible GMO regulation challenge (?) |
RVFV Clone 13 deletion

RNA segments
- Large (L)
- Medium (M)
- Small (S)

Proteins
- Nucleocapsid protein (N)
- Viral RNA polymerase (L)
- Glycoprotein G₁
- Glycoprotein G₂
- NSm 14 & 78 KDa

100 nm
### Candidates evaluated in target animals (contd.)

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>STRAIN</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| Recombinant-multiple deletion virus | ● Reverse genetic generating RVF virus with double deletions in NSs & NSm  
  *Bird et al., 2008*            | ● Less prone to reassortment  
  ● Live vaccine  
  ● DIVA: negative marker  
  ● Easy and safe to produce | ● No published proof of concept in target animals |

![RNA segments and Proteins diagram](Image)

**RNA segments**
- Large (L)
- Medium (M)
- Small (S)

**Proteins**
- Nucleocapsid protein (N)
- Viral RNA polymerase (L)
- Glycoprotein G1
- Glycoprotein G2

![100 nm scale](Image)
<table>
<thead>
<tr>
<th>VACCINE</th>
<th>STRAIN</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avirulent (lab generated) reassortant</td>
<td>R566: deletion in the M and S segments</td>
<td>• Safer due to deletions in all 3 segments, may never reassort</td>
<td>• Never tested in target animals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Protection in mice</td>
<td>• More stringent regulatory requirements for registration (?)</td>
</tr>
<tr>
<td>Virus-vectored RVF vaccines</td>
<td>Canarypox-expressing RVF proteins</td>
<td>• DIVA: Positive &amp; Negative marker</td>
<td>• No registered vaccine yet available</td>
</tr>
<tr>
<td></td>
<td>Heterologous virus expressing GP</td>
<td>• Live vaccine</td>
<td>• No large scale field data yet available, although extensive analytical data generated</td>
</tr>
<tr>
<td></td>
<td>(Kortekaas et al., 2010)</td>
<td>• Replication deficient</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multivalent: suitable where annual vaccination is a challenge</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Potential for improved thermostability</td>
<td></td>
</tr>
<tr>
<td>Virus like particle (VLP)</td>
<td>VLP made of envelop proteins (GP)</td>
<td>• Potentially very safe</td>
<td>• No proof of concept in target animals</td>
</tr>
<tr>
<td></td>
<td>Naslund et al., 2009</td>
<td>• Immunity similar to live vaccine, but no replication</td>
<td>• Large scale production might be a challenge</td>
</tr>
<tr>
<td>DNA</td>
<td>DNA priming + inact. Vaccine Lorenzo et al., 2009</td>
<td>• DIVA</td>
<td>• Only incomplete protection demonstrated in mice</td>
</tr>
<tr>
<td></td>
<td>cDNA encoding GP Lagerqvist et al., 2009</td>
<td>• Potentially long lasting immunity</td>
<td>• Production challenges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ability to enhance and modulate induced immunity</td>
<td>• Regulatory challenges (use in food animals)</td>
</tr>
</tbody>
</table>
Vaccination strategies to be considered

- **Endemic regions**
  - Yearly vaccination
  - Multivalent or combination vaccine, consisting of RVF antigen & antigen of a vaccine likely to be used regularly
    - RVF+LSD; RVF+ s/g pox; RVF + CBPP
  - Thermostability
  - Use of sentinel animals: need for good diagnostics capability & effective
  - Emergency preparedness: Strategic reserve: Vaccine or antigen bank

- **Possible suitable candidates:**
  - Multivalents including a safe deleted RVFV vaccine

- **Free regions/ Preventing epidemics**
  - Elimination of possible source of re-infection
  - Use of non-replicating antigen vaccine
  - Early and rapid onset of immunity, even in young animals

- **DIVA**
  - Positive marker: export of animals from endemic countries
  - Negative marker: for detecting infection

- **Possible suitable candidates:**
  - Replication deficient, deleted, marker vaccine

Suitable vaccination strategies more critical than improved vaccines
GALVmed RVF interventions
GALVmed - GLOBAL ALLIANCE LIVESTOCK VETERINARY MEDICINES

• An Animal health Product development & access Partnership organisation
• A not-for-profit Public-Private Partnership – registered charity
• Sponsored by the UK Department for International Development (DFID), and with projects funded by BMGF, DFID and EC.
• **Pro-poor focus:** working with key partners to make a **sustainable** difference in access to animal health products for poor livestock keepers
## GALVmed RVF interventions

### What are we trying to achieve?

<table>
<thead>
<tr>
<th>MA 6 - Rift Valley Fever</th>
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<tbody>
<tr>
<td><strong>A</strong></td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<table>
<thead>
<tr>
<th><strong>B</strong></th>
<th>Monovalent emergency vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Field evaluation selected candidate</td>
</tr>
<tr>
<td>5</td>
<td>Facilitate registration</td>
</tr>
<tr>
<td>6</td>
<td>Support mechanisms for vaccine stockpiling at African level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>C</strong></th>
<th>Pen side diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Validate test according OIE procedures</td>
</tr>
<tr>
<td>8</td>
<td>Select manufacturing partners</td>
</tr>
<tr>
<td>9</td>
<td>Select distributing partners</td>
</tr>
<tr>
<td>10</td>
<td>Assay validation in one country</td>
</tr>
<tr>
<td>11</td>
<td>Start assay dissemination and distribution</td>
</tr>
</tbody>
</table>
Rift Valley Fever – Key achievements

Multivalent vaccine (RVF-LSD)
- Focus on Combination RVF C13- LSD (OBP - Registration trials): - PoC obtained. Registration trials ongoing

Monovalent vaccine (RVF C13)
- Field trials to facilitate registration in Kenya and Senegal
- Strategic reserve (vaccine bank)

Penside test:
- Prototype produced & under evaluation
  - Market studies ongoing
  - RVF access strategy
RVF: Lab trial in Senegal

To date: no vaccination due to safety concern with Smithburn & limited efficacy of inactivated RVF vaccine

- Lab trial for safety, including pregnant animals, 42 goats and ewes.

- No differences for mean rectal temperatures, no clinical signs, and no injection site reactions. No evidence of transmission (control animals did not seroconvert).
RVF: Field trial in Senegal

- Conducted in 3 sites with 267 sheep & goats.
- Animals were vaccinated in September 2011. So far, no adverse effect seen, good seroconversion.
- Animals were followed until October 2012 (last blood sampling). Samples being currently analysed.

Results to be used to facilitate registration in Senegal & hopefully other countries
RVF Clone 13 trial in Kenya

- In collaboration with CDC-Kenya, Vet services & OBP
- Field trial for registration
- 404 cattle, sheep and goats included in 3 separate sites, vaccinated in August 2011.
- (Please refer to poster)
## Progress up to date

<table>
<thead>
<tr>
<th>Type</th>
<th>Products</th>
<th>Diseases</th>
<th>Progress on 5 September 2012</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exploratory</td>
</tr>
<tr>
<td>Vaccines</td>
<td>RVF Clone 13</td>
<td>RVF</td>
<td></td>
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<tr>
<td></td>
<td>Combination RVF-LSD</td>
<td>RVF, LSD, SP, GP</td>
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<tr>
<td></td>
<td>Recombinant RVF-LSD</td>
<td>RVF, LSD, SP, GP</td>
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<tr>
<td>Diagnosis</td>
<td>RVF penside</td>
<td>RVF</td>
<td></td>
</tr>
</tbody>
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Availability strategy

Strategic reserve (Vaccine bank)

- Vaccine bank managed by vaccine manufacturer (EC-FMD vaccine bank model)

- Target Southern & Eastern Africa initially
  - SADC, EAC, COMESA, PANVAC, AU-IBAR partnership
  - Possibility of partnerships beyond Africa

- Stockpiling of frozen pre-lyophilization (stabilized bulk) vaccine antigen or bottled vaccine?

- Technical feasibility of the RVF Clone 13 strategic reserve
  - R&D activities identified
  - Size determination: risk mapping
  - Infrastructure of the bank
  - Policy aspects & countries participations
Thank you!