FMD vaccine efficacy: attributes of higher potency vaccines and more recent findings

GFRA Meeting
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Control of FMD by Vaccination

Depends on the epidemiological situation and disease control policy of country.

For EU Countries, FMD is exotic and incursion more often than not results in a non-vaccination, stamping out measures.

However, vaccination has been used in emergency situations and many countries rely on National or International Strategic FMD vaccine/antigen reserves.
Strategic Antigen Reserve

- Concentrated inactivated antigen held over liquid $N_2$
- Can be formulated to choice of adjuvant
- Potency (PD$_{50}$) 6 or more (for rapid protection and greater cross-reactivity)
- 500,000 doses can be ready within 4 days

- Some vaccine strains have held or hold a EU-compliant marketing authorisation
- Negotiations in progress for a ‘virtual, global antigen bank network’
European Pharmacopoeia
FMD potency method

**QUANTITATIVE**

FMD Virus Challenge
21 days post.vacc

**PROTECTED**
(absence of clinical signs on feet)

50% protective dose

3 groups of 5 cattle
each group vaccinated with a specific dose volume e.g. 1/1, 1/4, 1/16

3 PD_{50} minimum requirement

6 PD_{50} or more for strategic reserves
Reducing animal experimentation in foot-and-mouth disease vaccine potency tests

Richard Reeve, Sarah Cox, Eliana Smitsaart, Claudia Perez Beascochea, Bernd Haas, Eduardo Maradei, Daniel T. Haydon, Paul Barnett

*Vaccine*, Volume 29, 33, 26 July 2011, Pages 5467-5473,

Statistics associated with the current EP PD$_{50}$ test (logistic regression or probit analysis) are inappropriate

That the OIE test statistics (Spearman–Kärber) is much better since it assumes the correct dose–response relationship

Identified a considerably better live animal challenge test approach –
two groups of 7 animals, one inoculated with a third of a dose of vaccine, and the other with a sixth of a dose –
for determining whether the PD50 is above 3 or 6, and is comparable to the OIE tests at determining both PD$_{50}$ and % PPG.

This test could also provide further savings in live animal usage in exchange for small reductions in sensitivity and specificity.

*Ideally we need to go over to a serological based approach.*
Some key findings with higher potency FMD vaccines

1. Rate of protection against clinical signs following aerosol challenge in three main targets - within 4 days

2. Interval between vaccination and challenge as well as antigen payload/potency important to inhibiting local virus replication

3. Duration of immunity and protection following single immunisation - 6 months in sheep and cattle and at least 7 months in pigs
Further vaccine longevity trials in Cattle using $>$6PD$_{50}$ FMD vaccines

Asia1 Shamir

O1 Manisa

- Computational model and serology indicates protection at 6 months and a boost unnecessary.
- Not all cattle protected at 10 months post vaccination (11/19) - boost may be necessary prior to this time point.
- No increased benefit of 5 x fold Ag payload in terms of antibody responses or numbers protected.
Some key findings with higher potency FMD vaccines

4. Can protect against serologically unrelated heterologous strains

- A serotype (Brehm et al 2008)
- O serotype (Nagendrakumar et al 2011)
- Asia1 serotype (Shamir vs Turkey 49/11 - Yanmin Li)
Higher potency vaccines that protect against serologically unrelated strains

Questions

the whole serological approach used

Portfolio of vaccine strains required in a ‘bank’
### Efficacy against transmission

Quantified FMDV transmission parameter $\beta$ from published experimental data to assess the effect of vaccination

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>GLM $\beta$ per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-vac and Vac sheep</td>
<td>Non-vac sheep</td>
<td>0.0066</td>
</tr>
<tr>
<td>Non-vac and Vac sheep</td>
<td>Vac sheep</td>
<td>0.0011</td>
</tr>
<tr>
<td>Non-vac pigs</td>
<td>Non-vac sheep</td>
<td>2.4</td>
</tr>
<tr>
<td>Non-vac pigs</td>
<td>Vac sheep</td>
<td>2.056 (0dpi) 0.692 (-7dpi) 0.233 (-14dpi)</td>
</tr>
<tr>
<td>Non-vac cattle</td>
<td>Vac cattle</td>
<td>0.11</td>
</tr>
<tr>
<td>Non-vac pigs</td>
<td>Vac cattle</td>
<td>13.78</td>
</tr>
<tr>
<td>Non-vac pigs</td>
<td>Vac pigs</td>
<td>27.98 (0dpi) 2.18 (-7dpi) 0.17 (-14dpi)</td>
</tr>
</tbody>
</table>

*Sheep to sheep transmission LOW regardless of vaccination*
Some areas for the future in terms of evaluating and improving vaccine efficacy

Gaps in $\beta$ parameter estimates

<table>
<thead>
<tr>
<th></th>
<th>To: non-vaccinated</th>
<th>vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>From:</td>
<td>Sheep Cattle Pigs</td>
<td>Sheep Cattle Pigs</td>
</tr>
<tr>
<td>Sheep</td>
<td>x</td>
<td>x#</td>
</tr>
<tr>
<td>Cattle</td>
<td>$x^a$</td>
<td>$x^#$</td>
</tr>
<tr>
<td>Pigs</td>
<td>$x$ $x^a$ $x^a$</td>
<td>$x^*$ $x^#$ $x^#$</td>
</tr>
</tbody>
</table>

- $x$: transmission events available in used experiments
- $a$: scarce data, therefore beta could not be determined
- *: time-effect of vaccination could be demonstrated (2nd analysis)
- #: time-effect of vaccination could not be demonstrated (2nd analysis)

Focus on inoculation approach – intradermal appears to provide scope for using much less antigen in pigs and cattle for protective immunity.