Is my vaccination programme working?

Vaccine effectiveness: measuring vaccine protection in the field

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FAO-EU-EuFMD webinar for West-Eurasian veterinary services
15 January 2015
Contents of presentation

- Overview of traditional vaccine protection evaluation methods
- How to assess vaccine protection during an outbreak
- Overview of other vaccine effectiveness study designs
• Evaluation of FMD vaccines traditionally based on:

1. Challenge studies

2. Serological evaluation
   – Vaccine matching tests
   – Post vaccination SP antibody response – peak response and over
• Evaluation of FMD vaccines traditionally based on:

1. Challenge studies
   • Control conditions and ensure adequate exposure
   • Small numbers and may not represent natural challenge

2. Serological evaluation
   – Vaccine matching tests
     – Post vaccination SP antibody response – peak response and over
Evaluation of FMD vaccines traditionally based on:

1. Challenge studies
   - Control conditions and ensure adequate exposure
   - Small numbers and may not represent natural challenge

2. Serological evaluation
   - Vaccine matching tests
     - Useful but imprecise test
   - Post vaccination SP antibody response – peak response and over entire intervaccination interval
     - Useful but what field virus are you concerned about and how does this relate to the test and vaccine antigen
     - Have you correlated your antibody response with protection against the virus of concern in a challenge study
Field study

Batch variability
Cold chain
Shelf life
Variable animal response
Match with field virus

Field protection: protection that counts

Time since last vaccinated
Number of doses in lifetime
Level/duration of virus exposure
Vaccine effectiveness

• The percentage reduction in incidence in vaccinated compared to unvaccinated individuals under field conditions
Vaccine effectiveness

• The percentage reduction in incidence in vaccinated compared to unvaccinated individuals under field conditions

• **Incidence risk**
  – [percentage or proportion affected during defined period] – e.g. 0.01 or 1%

• **Incidence rate**
  – [number affected/sum of time at risk for all individuals] – 0.2 cases/animal–year at risk
Concerned about outbreaks in vaccinated population

- Failure to vaccinate or a vaccine failure?
Concerned about outbreaks in vaccinated population

- Failure to vaccinate or a vaccine failure?

1. Are vaccinated animals protected from FMD?

2. Are the animals being vaccinated (adequately)?
Concerned about outbreaks in vaccinated population

- Failure to vaccinate or a vaccine failure?

1. Are vaccinated animals protected from FMD?
   **Vaccine effectiveness**

2. Are the animals being vaccinated (adequately)?
Concerned about outbreaks in vaccinated population

• Failure to vaccinate or a vaccine failure?

1. Are vaccinated animals protected from FMD?
   **Vaccine effectiveness**

2. Are the animals being vaccinated (adequately)?
   **Vaccine coverage**
Vaccine failure or failure to vaccinate

• What is the bigger problem in your country?
  – Vaccine coverage
  – Vaccine effectiveness
  – Both
  – Don’t know
Vaccine effectiveness

After an outbreak:

Compare incidence in vaccinated and unvaccinated
Vaccine effectiveness

After an outbreak:

Compare incidence in vaccinated and unvaccinated
Vaccine effectiveness

After an outbreak:

Compare incidence in vaccinated and unvaccinated

VE = 1 - \frac{\text{Incidence in Vaccinated}}{\text{Incidence in Unvaccinated}} \times 100\%

or

\frac{\text{Unvac incidence} - \text{Vac inc}}{\text{Unvac inc}} \times 100\%

Similar exposure
Vaccine effectiveness

Vaccine efficacy -> under controlled trial

Vaccine effectiveness - -> observational study (field study – program conditions)
Vaccine effectiveness

After an outbreak:
Compare incidence in vaccinated and unvaccinated

Vaccinated versus Unvaccinated

What is VE in this example:

Vaccinated incidence = 3/10 = 30%
Unvaccinated incidence = 9/10 = 90%

VE = 90 - 30 = 66.6%
Vaccine effectiveness

What is VE in this example:
Vaccinated incidence = 3/10 = 30%

Vaccinated \textit{versus} Unvaccinated

\[
\text{VE} = \frac{90 - 30}{90} = 66.6\%
\]
Vaccine effectiveness

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What is VE in this example:
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VE = \frac{90-30}{90} = 0.6666 = 66.6\%
Vaccine effectiveness

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VE = \frac{90-30}{90} = 0.666 = 66.6% 

or

VE = 1 - \frac{30}{90} = 0.666 = 66.6%
Vaccine effectiveness

What is VE in this example:
Vaccinated incidence = 3/10 = 30%
Unvaccinated incidence = 9/10 = 90%

VE = \frac{90-30}{90} = 0.666 = 66.6%
or
VE = 1 - \frac{30}{90} = 0.666 = 66.6%

VE 100% = complete protection with 0% incidence in vaccinated
VE 0% = no protection – same incidence in vaccinated & unvaccinated
At an outbreak
80% of unvaccinated cattle had clinical FMD
20% of vaccinated cattle had clinical FMD

What is vaccine effectiveness?

a) 75%  b) 60%  c) 25% d) 40%

VE = \frac{Unvac\ inc - Vac\ inc}{Unvac\ inc} \times 100\%
Question

At an outbreak
80% of unvaccinated cattle had clinical FMD
20% of vaccinated cattle had clinical FMD

Protection against clinical disease
Protection against infection (NSP if purified vaccine!)
or infectiousness

a) 75%  b) 60%  c) 25%  d) 40%

VE = \frac{\text{Unvac incidence} - \text{Vac inc}}{\text{Unvac inc}} \times 100\%
Pathogen exposure

- What if only farmers whose animals have a high risk [of exposure to FMD virus] vaccinate their animals? e.g. dealers, use common grazing???

- Will vaccine effectiveness increase or decrease?
Pathogen exposure

• What if only farmers whose animals have a high risk [of exposure to FMD virus] vaccinate their animals? e.g. dealers, use common grazing???

• Will vaccine effectiveness increase or decrease?

This bias will decrease VE – vaccine may protect but vaccinated animals have a greater virus challenge than unvaccinated – unfair comparison
But **FMD** risk is affected by other factors that affect susceptibility and exposure

- Age
- Prior infection
- Number of times previously vaccinated
- Level of exposure [common or private grazing]
- Herd size?
But **FMD** risk is affected by other factors that affect susceptibility and exposure

- Age
- Prior infection
- Number of times previously vaccinated
- Level of exposure [common or private grazing]
- Herd size?

Confounders of effect of vaccination
But FMD risk is affected by other factors that affect susceptibility and exposure

- **Age**
  - Assess different age groups separately
  - Exclude <7 months – maternal immunity

- **Prior infection**
  - Exclude village or exclude old cattle if outbreak a few years ago

- **Number of times previously vaccinated**
  - Assess separately according to number of doses
  - Limitation - May not be able to adjust for both age & number of doses – closely correlated?

- **Level of exposure [common or private grazing]**

- **Herd size?**
But **FMD** risk is affected by other factors that affect susceptibility and exposure

- **Age**
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- **Number of times previously vaccinated**
  - Assess separately according to number of doses
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- **Level of exposure**
- **Herd size**

**Ideally** - vaccinated and unvaccinated are similar in terms of confounders – in reality differences will exist that must be adjusted for through design and during analysis
Example 1

Incidence risk by age:

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12 months</td>
<td>15%</td>
<td>60%</td>
<td>75%</td>
</tr>
<tr>
<td>13-24 months</td>
<td>25%</td>
<td>85%</td>
<td>71%</td>
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<tr>
<td>&gt;24 months</td>
<td>5%</td>
<td>25%</td>
<td>80%</td>
</tr>
<tr>
<td>Overall</td>
<td>20%</td>
<td>80%</td>
<td>75%</td>
</tr>
</tbody>
</table>

In this example age makes little difference to VE
So report crude VE unadjusted for age (75%)
Example 2

Incidence risk by age:

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12 months</td>
<td>20%</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>13-24 months</td>
<td>25%</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>10%</td>
<td>25%</td>
<td>60%</td>
</tr>
<tr>
<td>Overall</td>
<td>15%</td>
<td>90%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Can still have unacceptable incidence in vaccinated even when good VE
Example 2

More complex analysis sometimes needed

- get weighted average using Mantel-Haenszel methods
  [www.winepi.net](http://www.winepi.net) Programmed spreadsheet or stats software

- regression modelling [adjust for many factors at same time]

  *Remember p values and confidence intervals!*
Simplest of all

- What if no unvaccinated animals?
- Just looking at incidence by number of doses is useful
Incidence plateau among older animals... no vaccine effect!

Lower incidence in youngstock... maternal protection?
Farm 2 – Vaccine – Lyons, Kenya

“Incidence risk” versus “Number of lifetime doses”

Declining incidence implies some vaccine effectiveness

Maternal antibody? Incidence plateau...
Possible reasons for incidence pattern on Farm 2

40% incidence in multiply vaccinated clearly reveals a problem....

- Potency?
- Match?
- Cold chain?

Suboptimal schedules as well?

Can have multiple reasons for poor VE!
Retrospective effectiveness – studies
Turkey 2011/12

• Four VILLAGE outbreak investigations: Asia-1

Sampling - Retrospective cohort

- Find outbreak of the right strain where the vaccine has been used

- Timing: At or near the end of an outbreak

  - Time since vaccination is important
    - [too soon or too long after vaccination]
Sampling - Retrospective cohort

1. **Within a village – at end of outbreak:**
   1. *Select all or sample of affected households*
      
      [households with cases or NSP positive - known virus exposure]
   2. *Random or evenly spaced in village*
   3. *Sample several villages affected by outbreak [need at least 200-400 animals]*
   4. *Need vaccinated and unvaccinated animals for comparison*

2. **Within a household:**
   1. *Collect details of all cattle >5 months [may exclude more during analysis]*

3. **For each selected animal**
   1. *Ask owner about vaccination and FMD history*
      
      – *cross-ref with written records*
   2. *Examine for clinical signs*
   3. *Assess infection history by serology (<30 months)***
## Results

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Investigation</th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
<th>Unadjusted Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shamir</td>
<td>1 - Ardahan</td>
<td>19/47 (40%)</td>
<td>188/249 (76%)</td>
<td>-87% ( -140% to -40%)</td>
</tr>
<tr>
<td>Sindh08</td>
<td>2 - Afyon-1</td>
<td>64/127 (50%)</td>
<td>14/91 (15%)</td>
<td>73% (51% to 85%)</td>
</tr>
<tr>
<td></td>
<td>3 – Denizli</td>
<td>55/68 (81%)</td>
<td>134/337 (40%)</td>
<td>51% (41% to 59%)</td>
</tr>
<tr>
<td></td>
<td>4 - Afyon-2</td>
<td>71/124 (57%)</td>
<td>69/187 (37%)</td>
<td>36% (18% to 49%)</td>
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</tbody>
</table>

Need to adjust for other confounding factors – age, husbandry, etc…
### Asia-1: Multivariable model

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Vaccine effectiveness [95% CI]</th>
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<tr>
<td>Recently Vaccinated</td>
<td>Sindh-08 69% [50% to 81%]</td>
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<tr>
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<td>Shamir -36% [-137% to 22%]</td>
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<tr>
<td>Rate Ratio</td>
<td></td>
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<tr>
<td>Avoid common grazing</td>
<td>0.2 [0.1-0.36]</td>
</tr>
<tr>
<td>Age: Every month &gt;15 months</td>
<td>0.98 [0.977-0.99]</td>
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<td>Herd size &gt;30</td>
<td>0.25 [0.1 – 0.5]</td>
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<td>Random intercept: Village/Owner</td>
<td>St dev of intercept = 6 / 1.4</td>
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63% [29% to 81%] protection against infection

- Avoid common grazing: 0.2 [0.1-0.36]
- Age: Every month >15 months: 0.98 [0.977-0.99]
- Herd size >30: 0.25 [0.1 – 0.5]
- Random intercept: Village/Owner: St dev of intercept = 6 / 1.4
### Results

#### Vaccine Investigation

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Several investigations for one vaccine preferable

But: Incidence in vaccinated alone can be informative

Poor vaccine match: $r_1$-value < 0.3

Unvaccinated animals much younger - protected by maternal immunity – confounded VE

Few unvaccinated animals

Wide confidence intervals

www.pirbright.ac.uk
1. Protection from Asia-1 field strain by standard potency Asia-1 Shamir vaccine was not detected in this outbreak

2. Reasonable protection from Asia-1 field strain by Asia-1 Sindh08 [TUR 11] vaccine
Conclusions

- **Vaccine effectiveness:**

  “Give it a go!”

- Retrospective outbreak investigation is quick and simple
- Useful answers
- Gets you into the field
  - Learn things that nobody reports to HQ
FMD vaccine evaluation

- Challenge studies
- Post-vaccination serology
- in vitro matching assays
- Vaccine effectiveness

Other...
Key References

Knight-Jones T.J.D. Vaccine effectiveness guide with VE calculator – from author or EuFMD or FAO-PVM?


Vaccine evaluation on large-scale dairy farms using routine prophylactic schedules for FMD


Theo Knight-Jones Thesis Field evaluation of foot-and-mouth disease vaccination in Turkey (RVC/LSHTM) will upload to https://www.researchgate.net/profile/Theodore_Knight-Jones/contributions
FMD vaccine evaluation

What post vaccination monitoring do you do?

• Vaccine effectiveness
• Batch serology under controlled conditions
• Post-vaccination serology in the field
• Vaccine matching tests
• Challenge studies
• Evaluation of different dosing regimes
• Vaccine coverage
• Other?
VE designs

• Retrospective outbreak investigation
  – Rely on farmer & vet recollection and records
  – Are outbreaks non-representative cases of vaccine failure?

• Prospective
  – can create own vaccine groups and see what happens
  – Cohort, randomised trial
  – But what if no cases?
  – & prospective needs much more resources
    • Money & expertise & time

• If free zone monitor post-vaccination serology
<table>
<thead>
<tr>
<th>Ear tag</th>
<th>Age (Y=years, M=months)</th>
<th>Sex (M/F)</th>
<th>Group</th>
<th>Breed</th>
<th>Date of last FMD vaccination (Auw/Spring)</th>
<th>Lifetime number of doses</th>
<th>FMD in recent outbreak (Y=yes, N=no)</th>
<th>Farmer's vaccination status (H=hoof, O=oral, T=Teat)</th>
<th>Days stopped eating</th>
<th>Number of days down</th>
<th>Clinical Exam (S=severe, N=No)</th>
<th>Sampled (Y=Yes, N=No)</th>
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</table>

*Severe Mouth lesions: Combined diameter >50% breadth of tongue*

Version x
- Include animals that died during outbreak [Mark with D]

Consent - I agree that this data can be used for this vaccine effectiveness study: ______________
Any questions?
Thank you for your attention!