# 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

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    - Control conditions and ensure adequate exposure
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- 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

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- *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?

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2. Are the animals being vaccinated (adequately)?

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   **Vaccine effectiveness**

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- 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

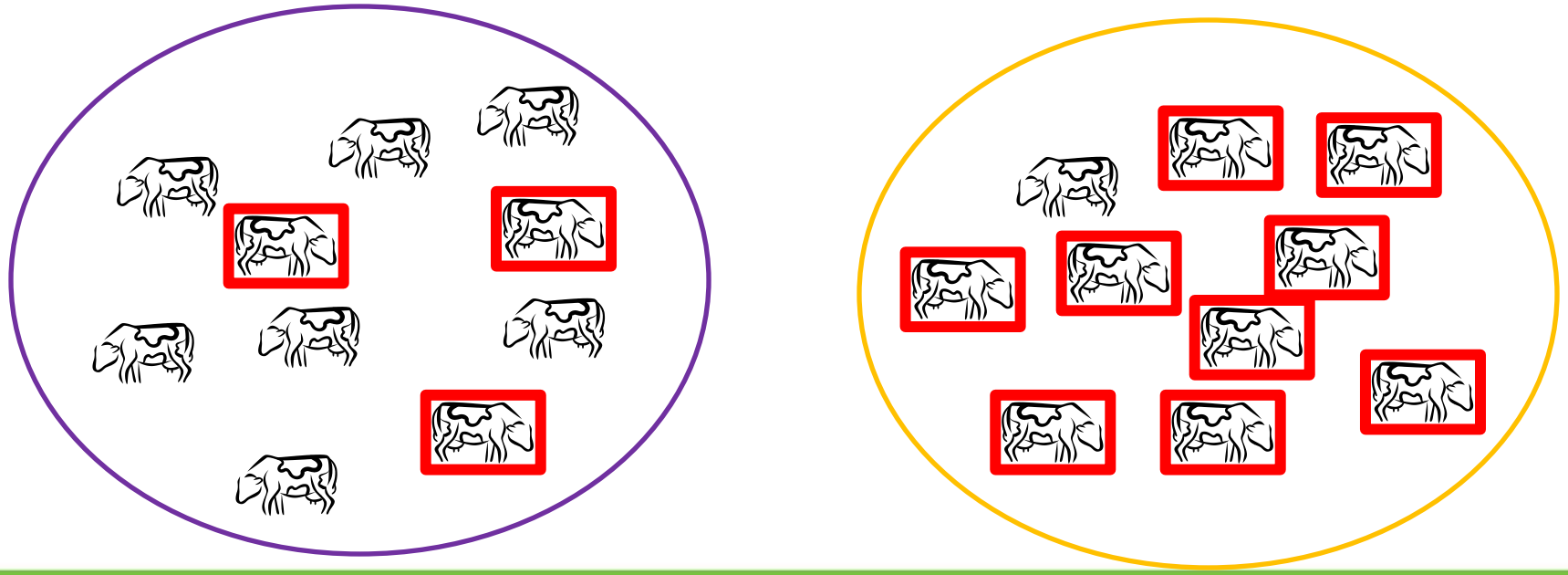
- What is the bigger problem in your country?
  - Vaccine coverage
  - Vaccine effectiveness
  - Both
  - Don’t know

# Vaccine effectiveness

After an outbreak:

**Compare incidence in vaccinated and unvaccinated**

**Vaccinated** *versus* **Unvaccinated**



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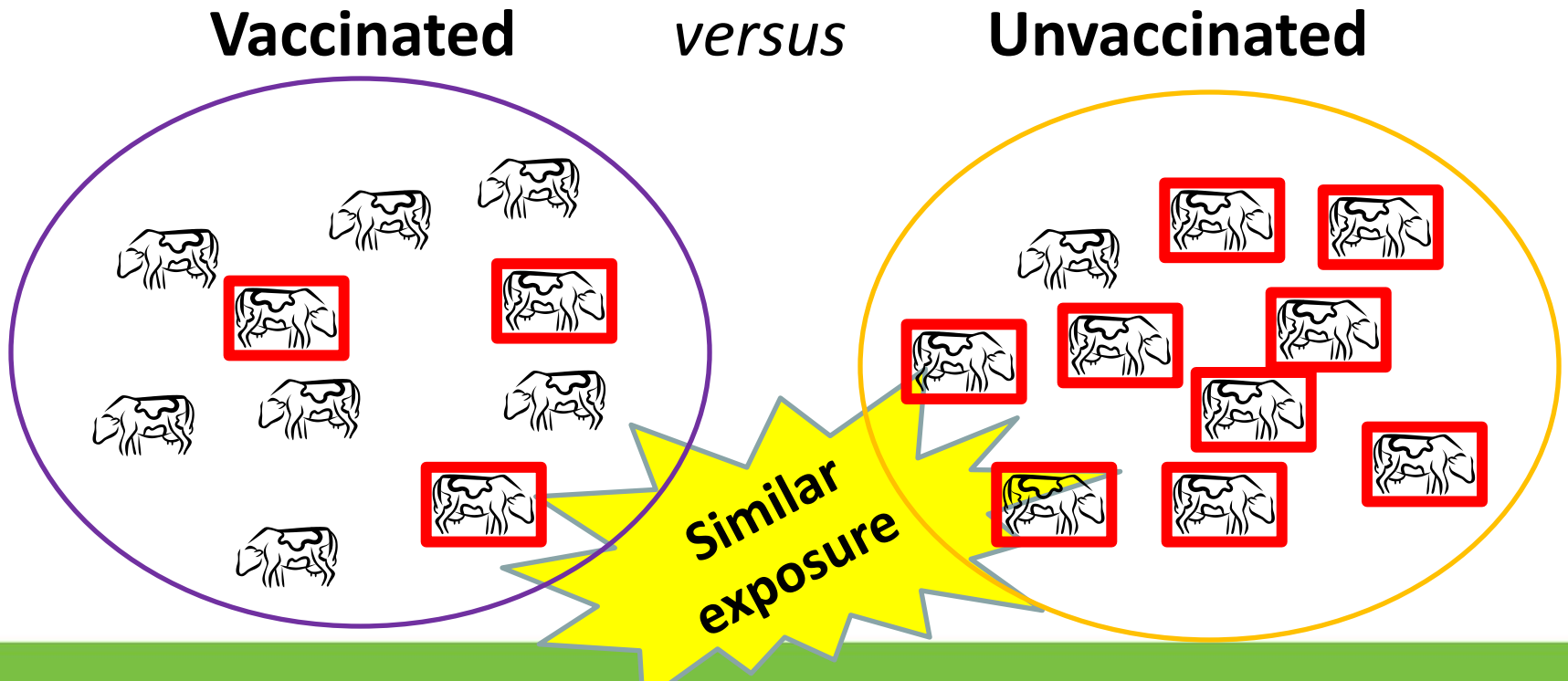


# Vaccine effectiveness

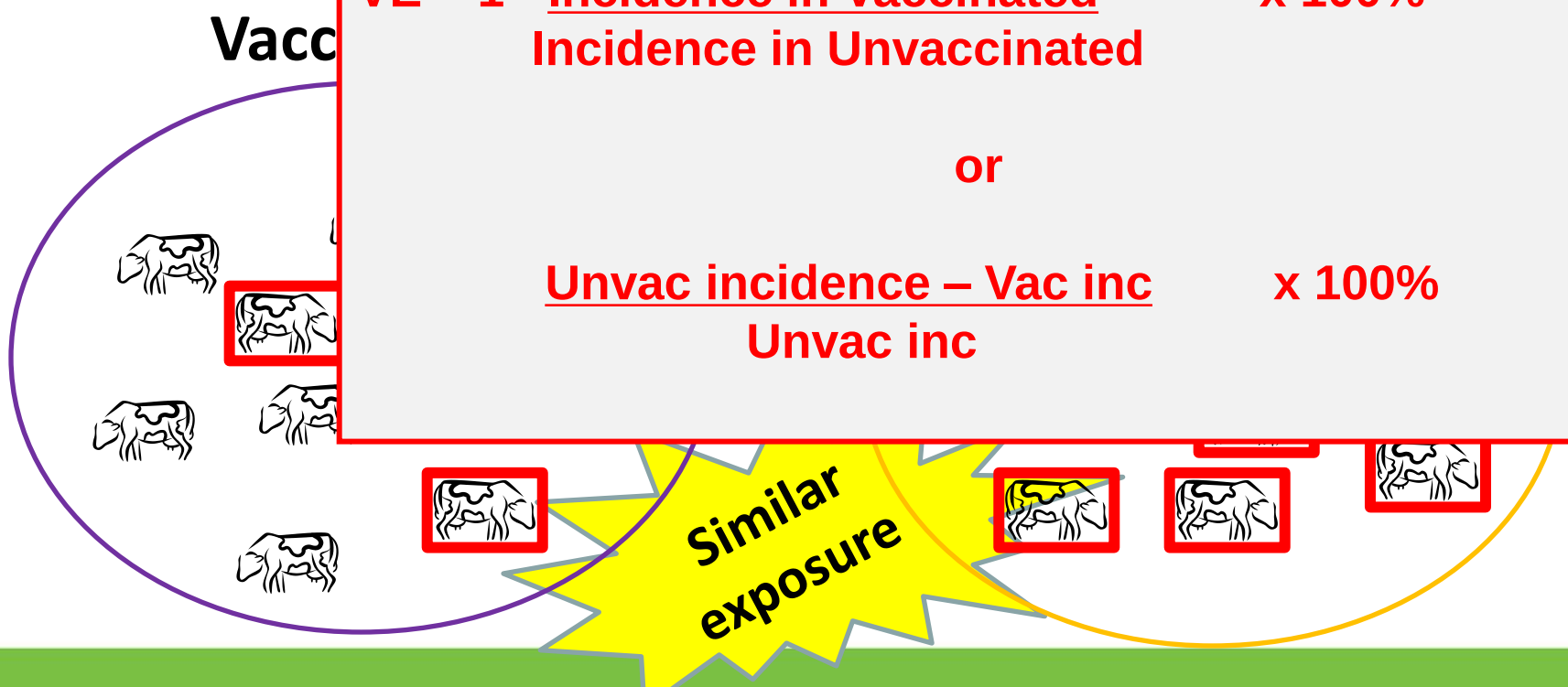
After an outbreak:

**Compare incidence in vaccinated and unvaccinated**

**VE = 1- Incidence in Vaccinated / Incidence in Unvaccinated x 100%**

**or**

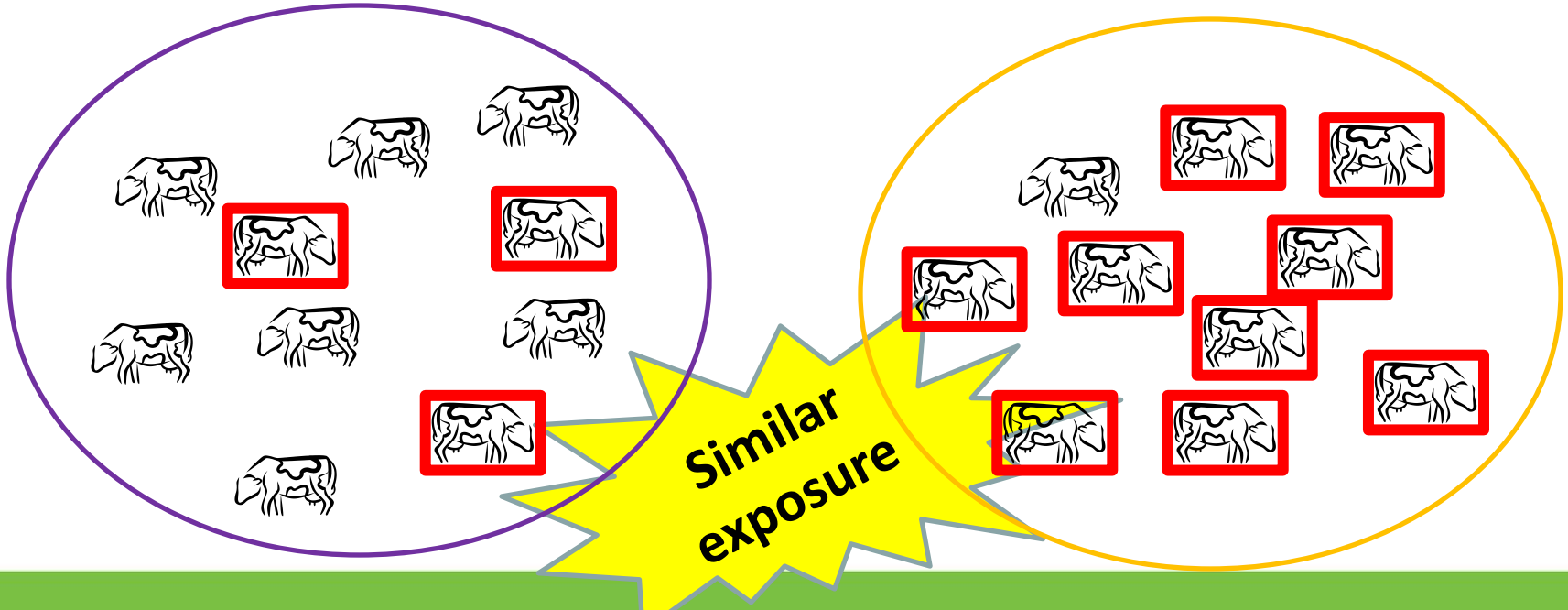
**Unvac incidence – Vac inc / Unvac inc x 100%**



# Vaccine effectiveness

**Vaccine efficacy -> under controlled trial**

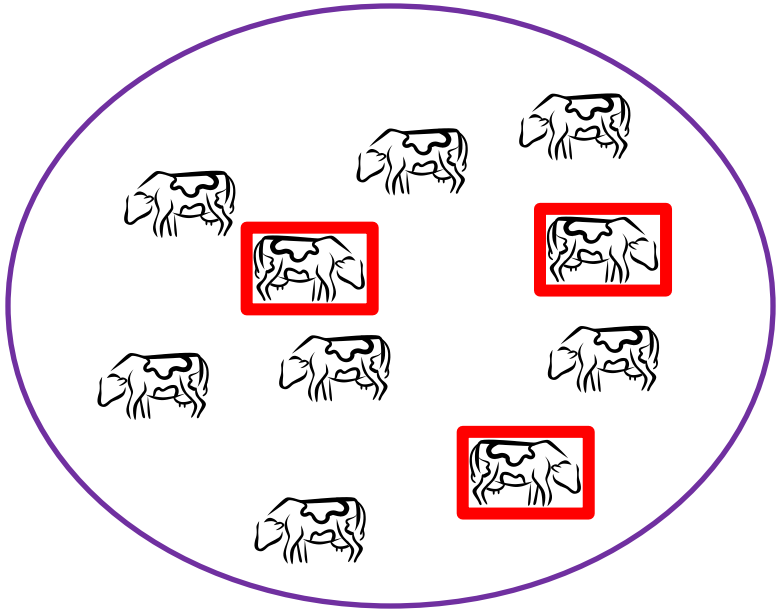
**Vaccine effectiveness - > observational study**
**(field study – program conditions)**

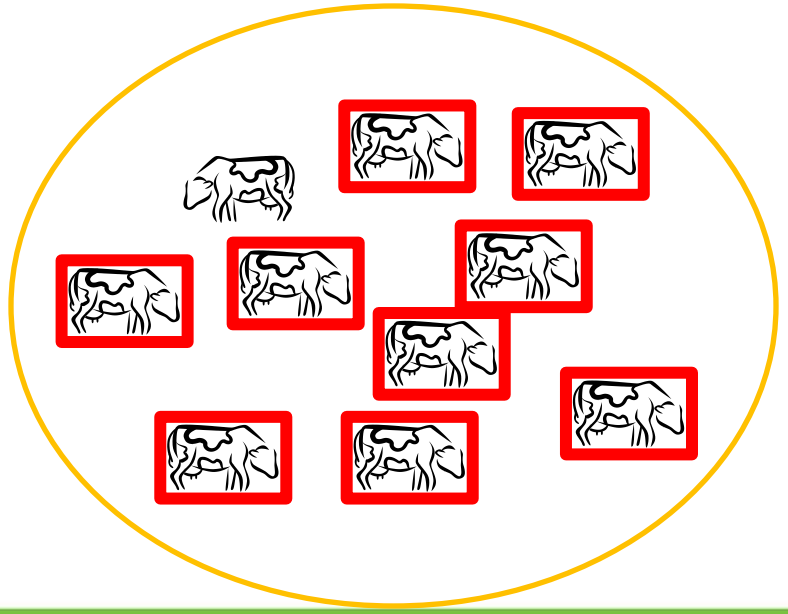


# Vaccine effectiveness

**What is VE in this example:**

**Vaccinated** *versus* **Unvaccinated**

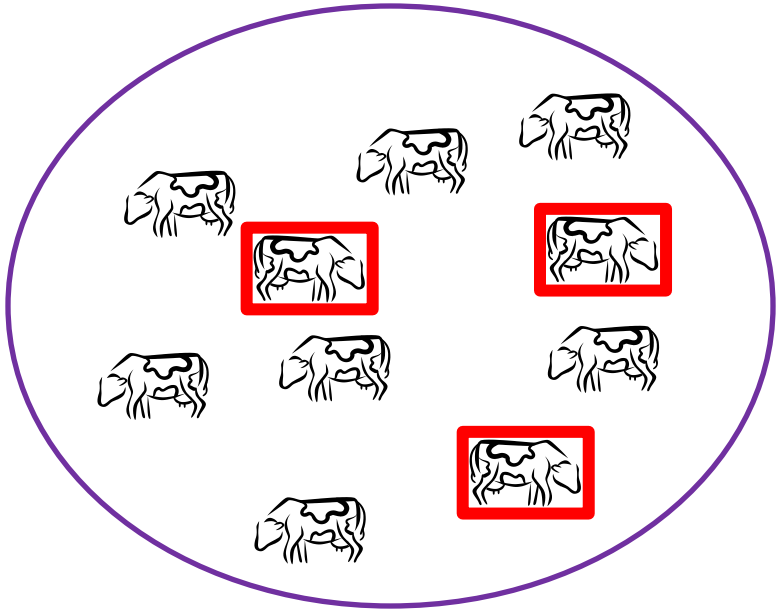


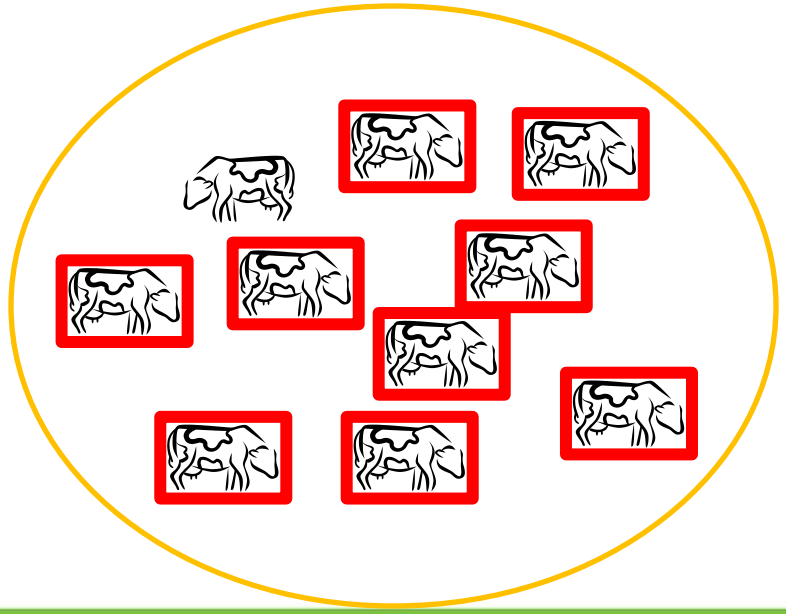


# Vaccine effectiveness

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

**Vaccinated** *versus* **Unvaccinated**

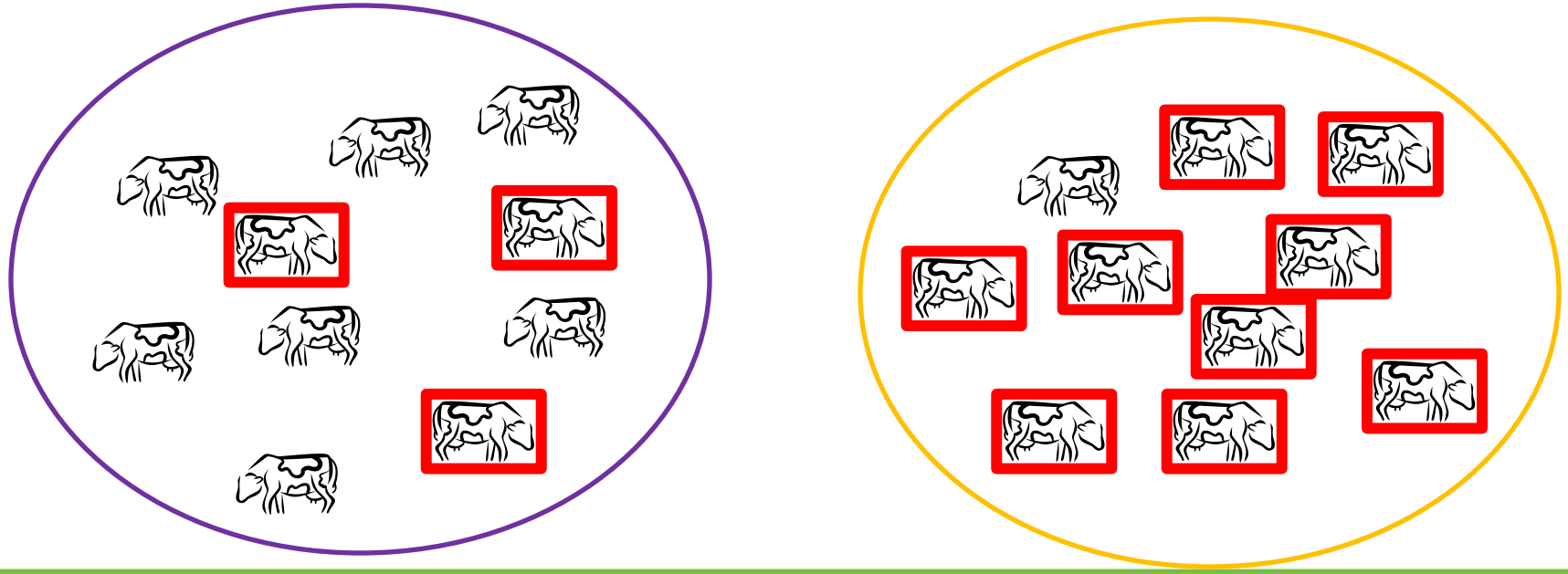




# Vaccine effectiveness

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

**Vaccinated** *versus* **Unvaccinated**



# Vaccine effectiveness

**What is VE in this example:**
**Vaccinated incidence = 3/10 = 30%**
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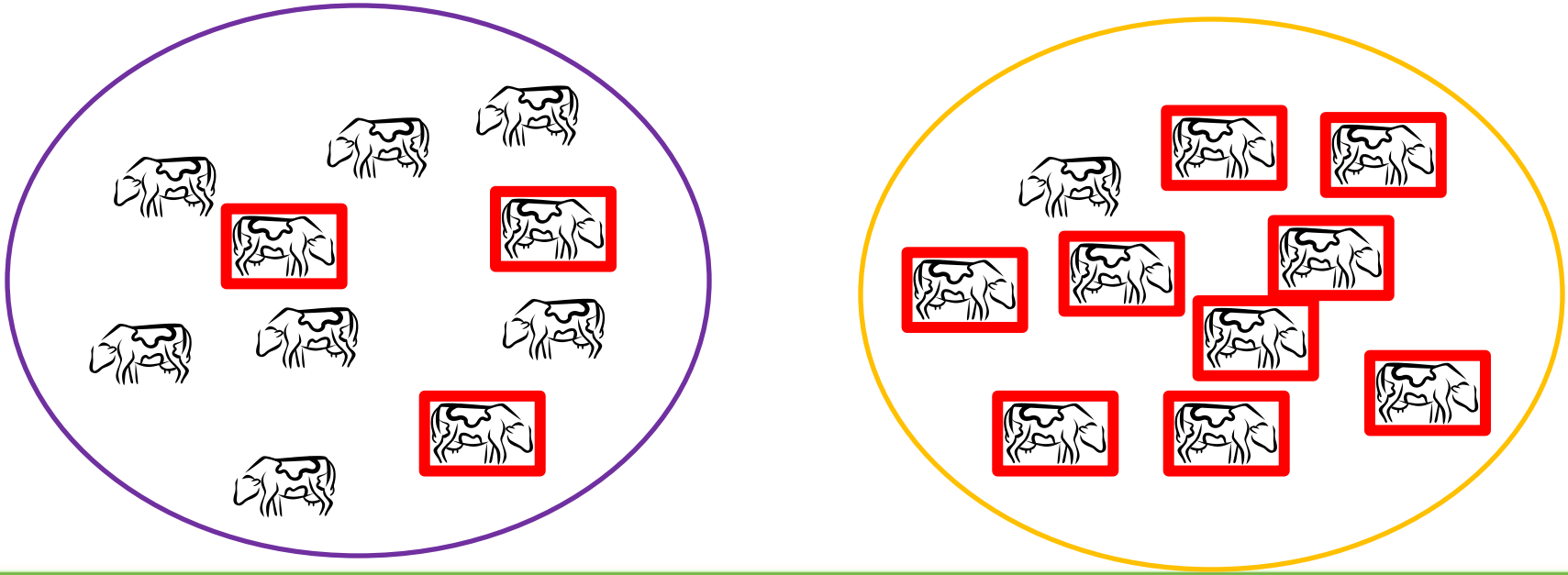
**VE = $\frac{90-30}{90}$ = 0.666 = 66.6%**

**Vaccinated** *versus* **Unvaccinated**



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**or**

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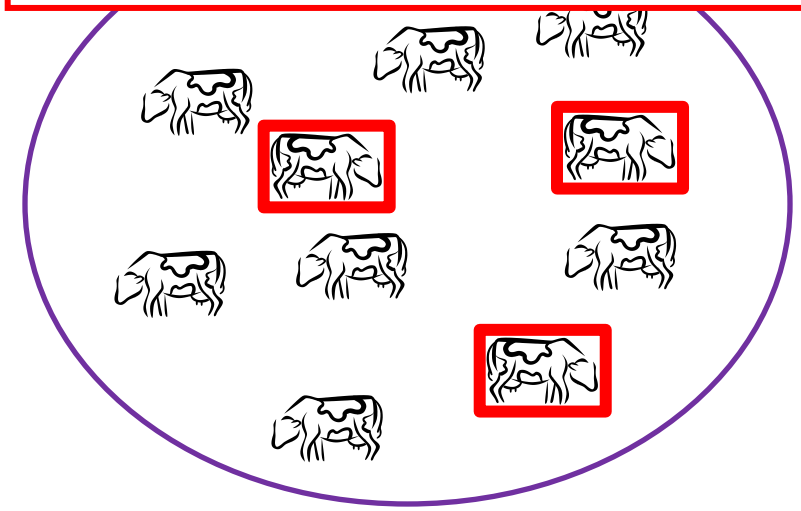

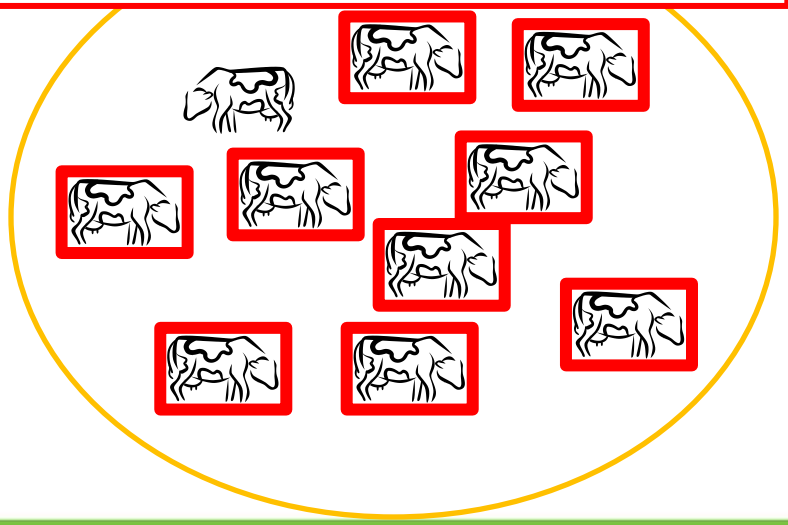

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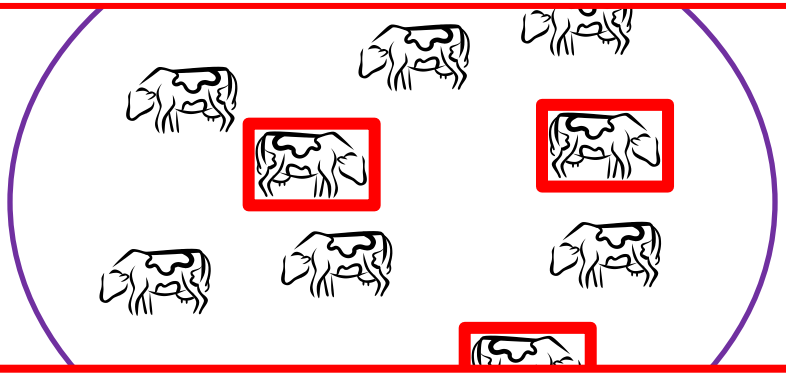

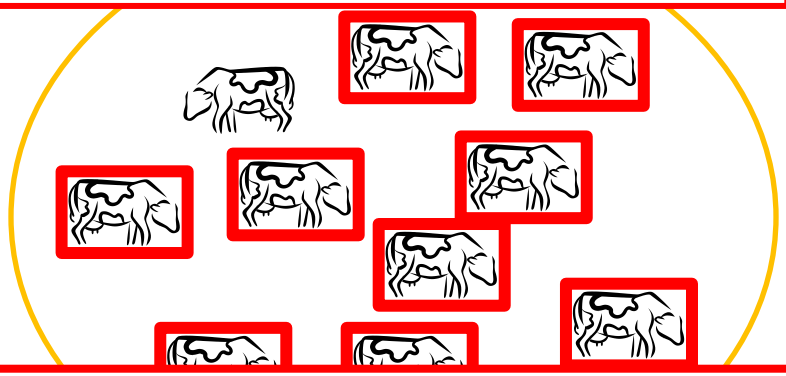

**VE 100% = complete protection with 0% incidence in vaccinated**

**VE 0% = no protection – same incidence in vaccinated & unvaccinated**

# Question

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%

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

# 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

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**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?

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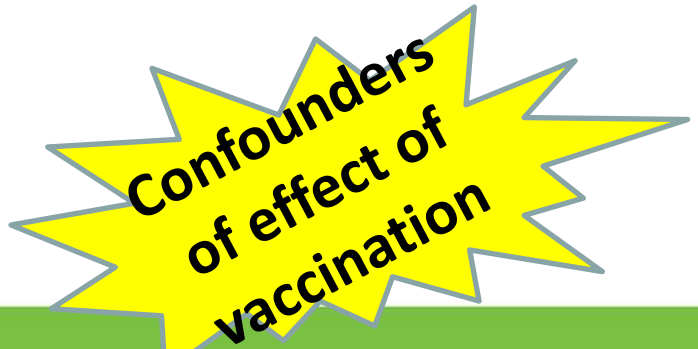

# But FMD risk is affected by other factors that affect susceptibility and exposure

- Age
  - Assess different age groups separately
  - Exclude <7 months – maternal immunity
- Prior infection
  - Exclude village or exclude old cattle if outbreak a few years a go
- 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

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- Number of times prev… vacc…
  - Assess separately accor…
  - Limitation… doses – closer…
- 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:

| Age | Vaccinated | Unvaccinated | VE |
|---|---|---|---|
| 7-12 months | 15% | 60% | 75% |
| 13-24 months | 25% | 85% | 71% |
| >24 months | 5% | 25% | 80% |
| **Overall** | **20%** | **80%** | **75%** |

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

# Example 2

Incidence risk by age:

| Age | Vaccinated | Unvaccinated | VE |
|---|---|---|---|
| 7-12 months | 20% | 30% | 33% |
| 13-24 months | 25% | 100% | 75% |
| >24 months | 10% | 25% | 60% |
| **Overall** | **15%** | **90%** | **83%** |

**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 Programmed spreadsheet or stats software**

**– regression modelling [adjust for many factors at same time]**

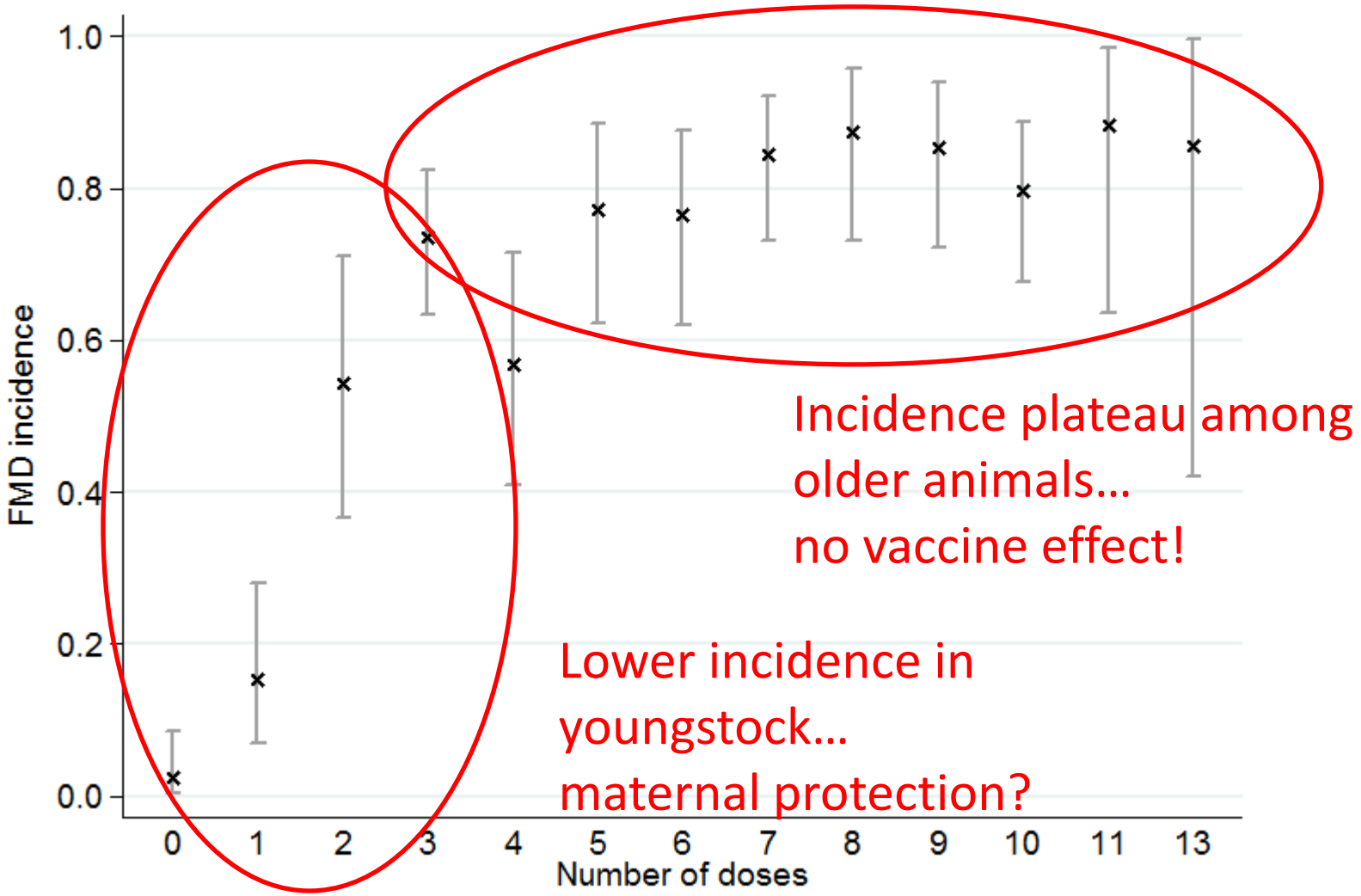
***Remember p values and confidence intervals!***

# Simplest of all

- What if no unvaccinated animals?
- Just looking at incidence by number of doses is useful

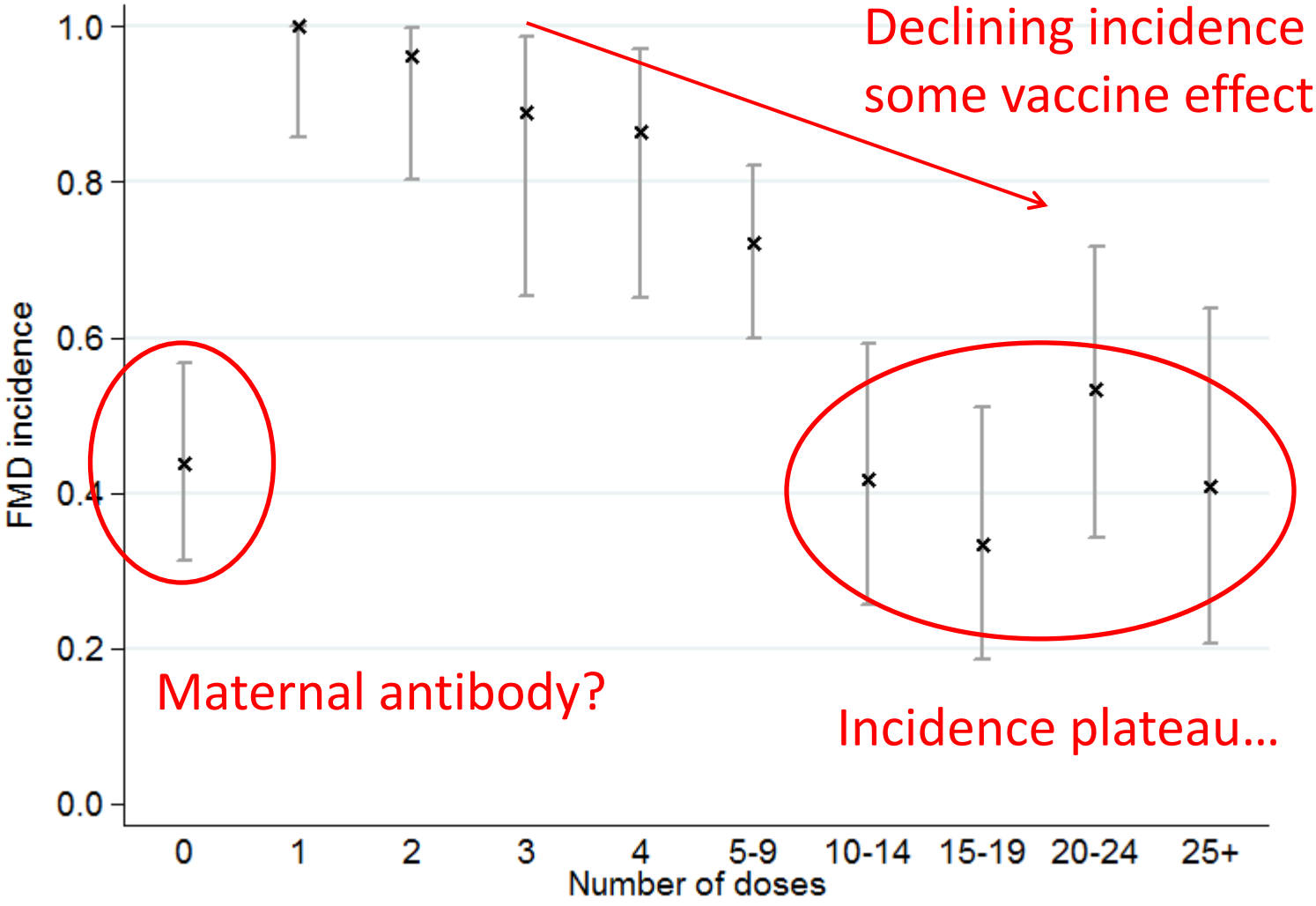
# Farm 1 – Vaccine – Lyons, Kenya

"**Incidence risk**" versus "**Number of lifetime doses**"



# Farm 2 – Vaccine – Lyons, Kenya

"**Incidence risk**" versus "**Number of lifetime doses**"

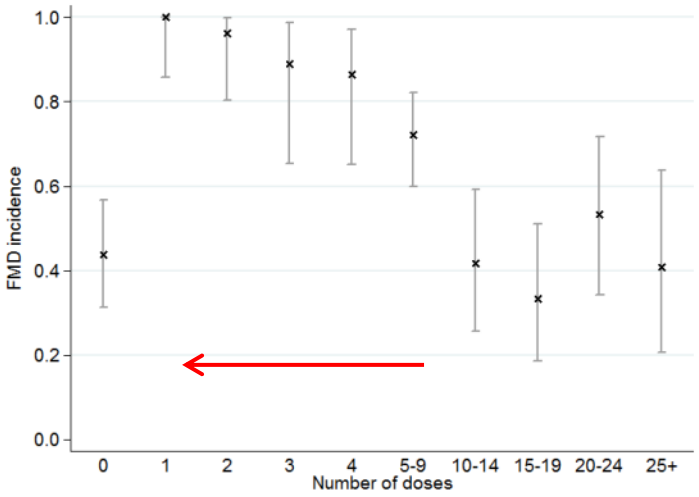


# Possible reasons for incidence pattern on Farm 2

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


**Knight-Jones T.J., Bulut A.N., Gubbins S., Stark K.D., Pfeiffer D.U., Sumption K.J., Paton D.J. 2014 Retrospective evaluation of foot-and-mouth disease vaccine effectiveness in Turkey. Vaccine (32), 1848-1855.**

# 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

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

**Need to adjust for other confounding factors – age, husbandry, etc…**

# Asia-1: Multivariable model

| Risk factor | | Vaccine effectiveness [95% CI] |
|---|---|---|
| Recently Vaccinated | **Sindh-08** | **69% [50% to 81%]** |
| | **Shamir** | **-36% [-137% to 22%]** |
| | | Rate Ratio |
| 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 |

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**63% [ 29% to 81%] protection against infection**

# Results

**Several investigations for one vaccine preferable**

| Vaccine | Inve | ed | | |
|---|---|---|---|---|
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**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**

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**

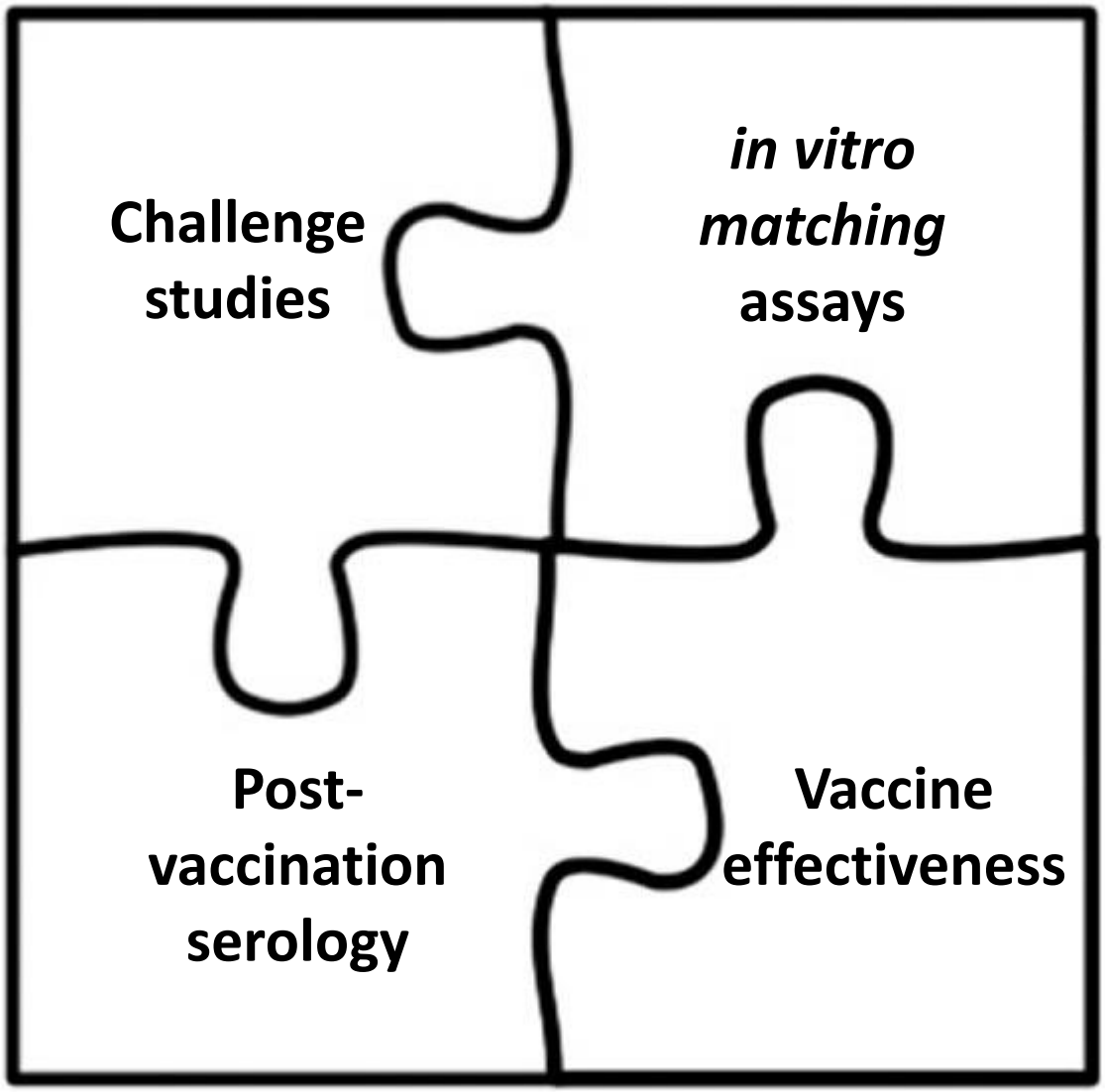
# Conclusions

- ***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




***Other…***

# Key References

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

Knight-Jones T.J.D., Bulut A.N., Gubbins S., Stark K.D., Pfeiffer D.U., Sumption K.J., Paton D.J. 2014 Retrospective evaluation of foot-and-mouth disease vaccine effectiveness in Turkey. *Vaccine* **32**(16), 1848-1855 doi: 10.1016/j.vaccine.2014.01.071

Knight-Jones T.J.D., Edmond K., Gubbins S., Paton D.J., 2014 Veterinary and human vaccine evaluation methods. *Proc R Soc B* **281**(1784) 20132839 doi: 10.1098/rspb.2013.2839

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Vaccine evaluation on large-scale dairy farms using routine prophylactic schedules for FMD
Lyons, N.A., Knight-Jones, T.K.D., Bartels, C., Dulu, T.D., Stärk K.D.C., Sumption, K.J., Fine, P.E.M.
**EuFMD Open Session 2014 online**
https://eufmd.rvc.ac.uk/mod/page/view.php?id=1388

Lyons NA, Stärk KD, van Maanen C, Thomas SL, Chepkwony EC, Sangula AK, Dulu TD, Fine PEM Epidemiological analysis of an outbreak of foot-and-mouth disease (serotype SAT2) on a large dairy farm in Kenya using regular vaccination. Acta Trop. 2014 Oct 24. pii: S0001-706X(14)00302-7
doi: 10.1016/j.actatropica.2014.09.010

Lyons, N.A., Knight-Jones, T.K.D., Bartels, C., Dulu, T.D., Stärk K.D.C., Sumption, K.J., Fine, P.E.M.
Vaccine evaluation on large-scale dairy farms using routine prophylactic schedules for FMD
**EuFMD Open Session 2014 online** https://eufmd.rvc.ac.uk/mod/page/view.php?id=1388

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

Farm name_____ _____ Village: _____ Date completed / / 20__ Prior Household FMD outbreak / 20__ Number of cattle _____

Number of small ruminants:_____ Date of first case: / / 20__ Date last case recovered: / / 20__ GPS: North_____ East_____

**Sampled animals – Examine & sample cattle < 2years** **Mark "X" when not sure.**

| | Ear tag | Age *Y=years M=months* | Sex (M/F) | Group | Breed | Date of last FMD vaccination *(Aut/Spring) O=never* | Lifetime number of doses | FMD in recent outbreak *Y=yes N=no* | Farmer: FMD signs *H=hoof O= oral T=Teat* | Days stopped eating | Number of days down | Clinical Exam: FMD signs **S=severe N=No* | Sampled *Y=Yes N=No* |
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*Severe Mouth lesions: Combined diameter >50% bredth 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!