Field use of FMD vaccines and challenges for FMD control

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FMD vaccines – in the field

- FMD vaccines are used extensively in livestock disease control (and represent a great cost)

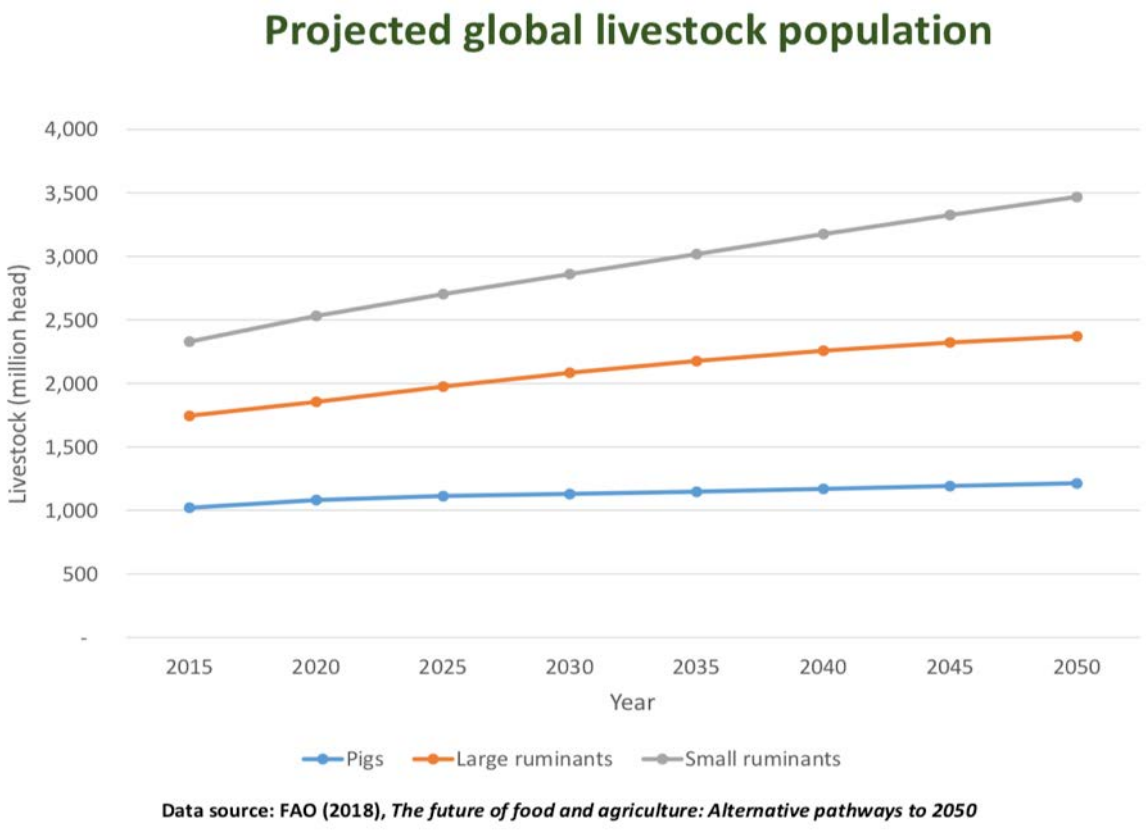
Annual FMD vaccine use by region*

	2011[a]		2017[b]	
Region	Doses (millions)	%	Doses (millions)	%
China	1600	68.1	1614[c]	67.8
India	150	6.4	21[d]	0.9
Rest of Asia	50	2.1	95	4.0
Africa	15	0.6	21	0.9
Middle East	20	0.9	71	3.0
Europe and Turkey	15	0.6	38	1.6
South America	500	21.3	520	21.8
Total	2350	100.0	2380	100.0

[a] Hammond, 2011; Knight-Jones and Rushton, 2013
[b] Mean annual use from 2015-2017 unless otherwise stated (OIE WAHIS, 2018)
[c] SEACFMD, 2018
[d] Reported annual use for 2015 (OIE WAHIS, 2015)
* Work ongoing to validate current estimates

FMD vaccines – in the field

- Yet it is inevitable that importance of FMD will increase and vaccine demand will grow as livestock populations increase



Data source: FAO (2018), *The future of food and agriculture: Alternative pathways to 2050*

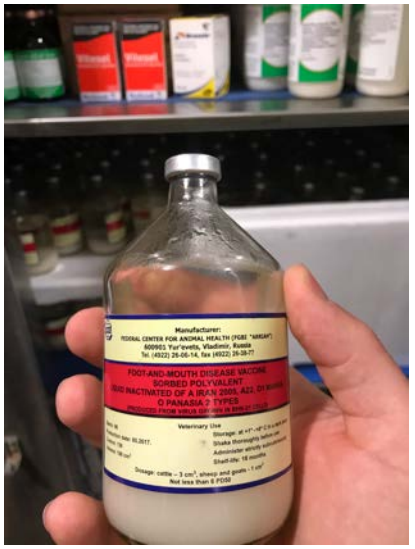
Field use of FMD vaccines

In relation to **endemic** settings, this presentation will focus on:

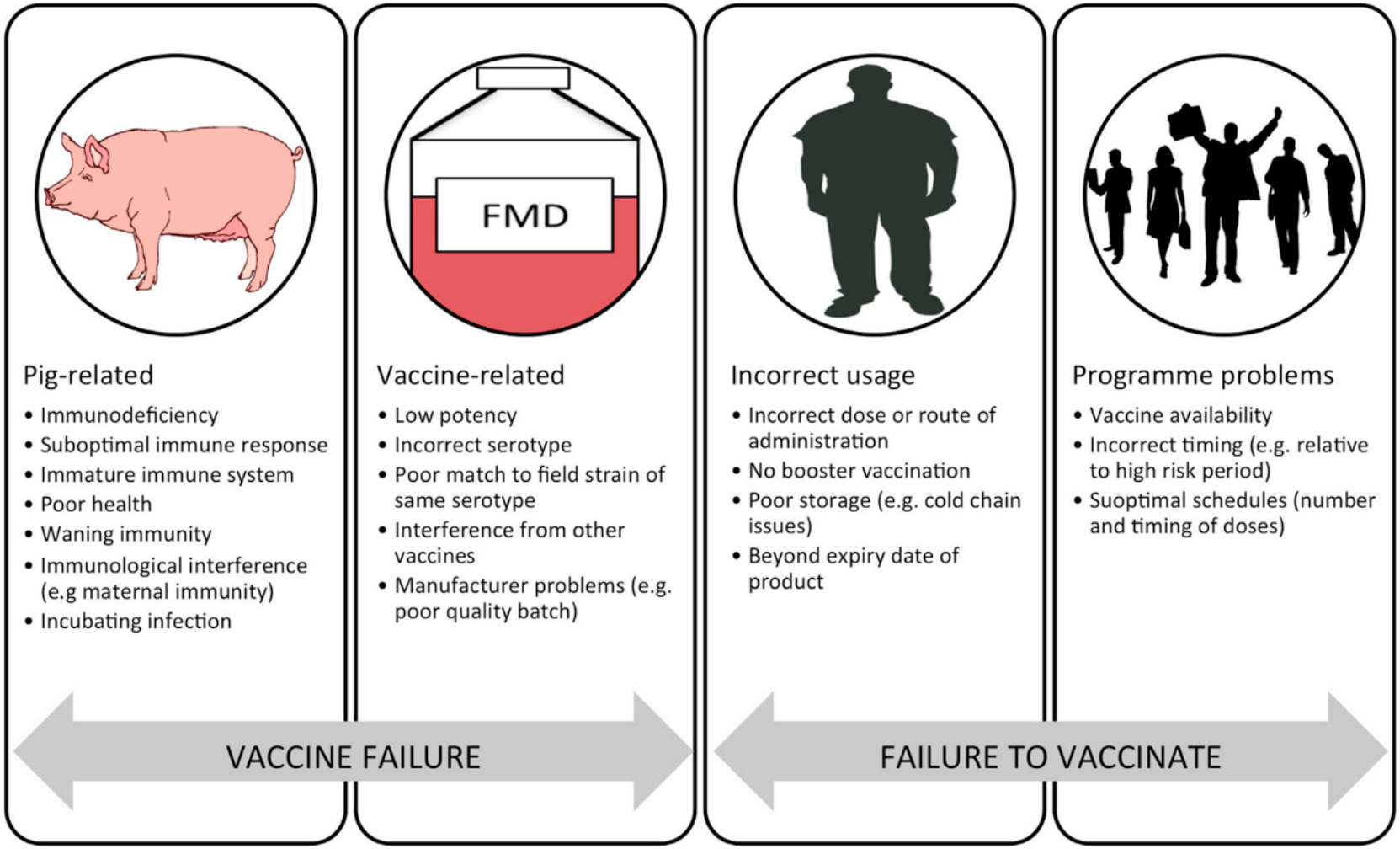
1. Current **challenges** on using FMD vaccines in the field (focus on strategy)
2. Making the case for **evaluating** their use in **field conditions**

Challenges with FMD vaccines

- Current FMD vaccines have numerous well-known limitations including:
    - Short duration of action and need for repeated doses
    - Cold chain requirements (capsid stability)
    - Differences between field and vaccine strains (“Vaccine match”)



Reasons for vaccine “failure”



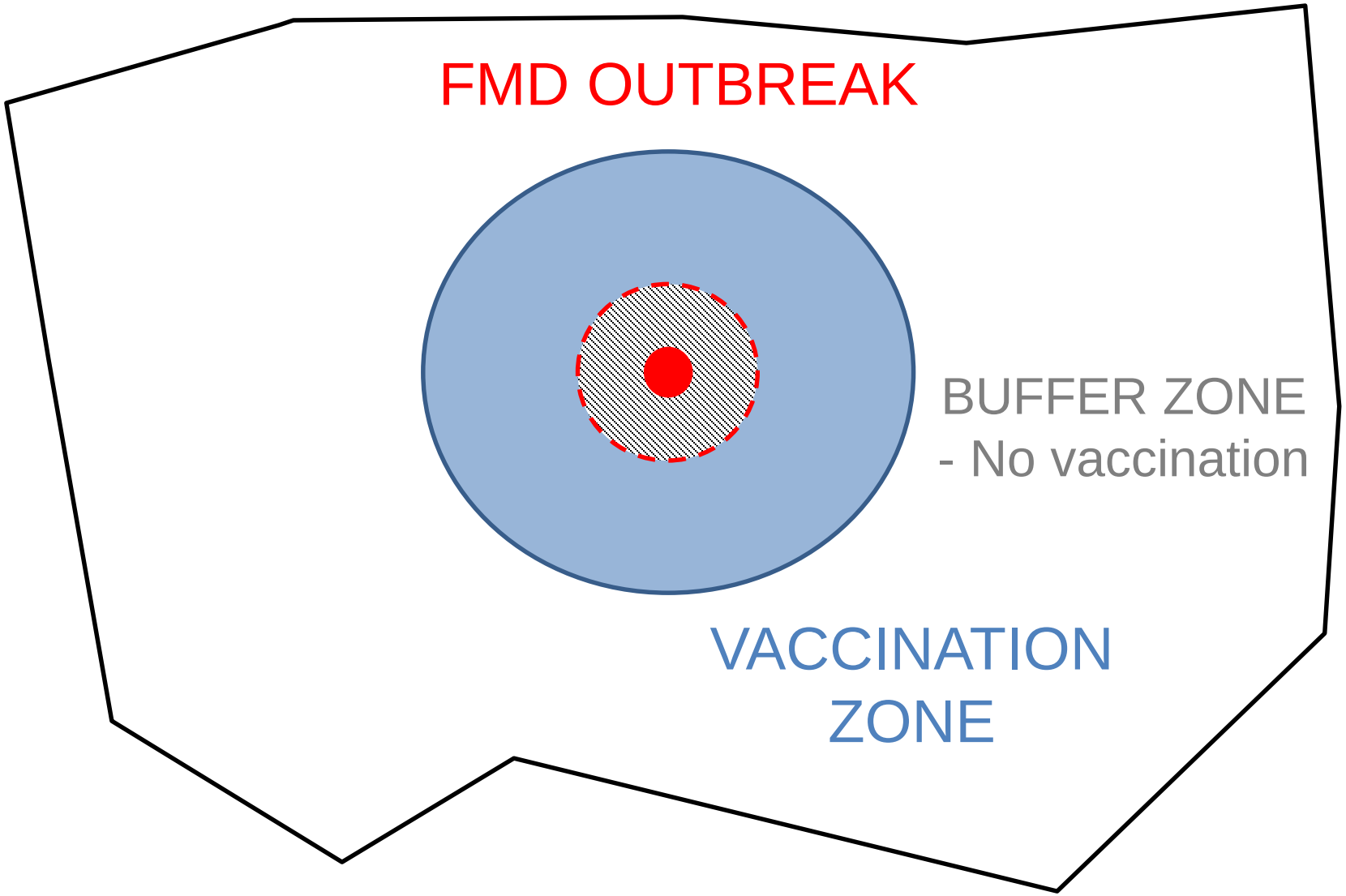
Lyons et al (2016) – adapted from Heininger et al (2012)

Vaccination strategies

Mass vaccination

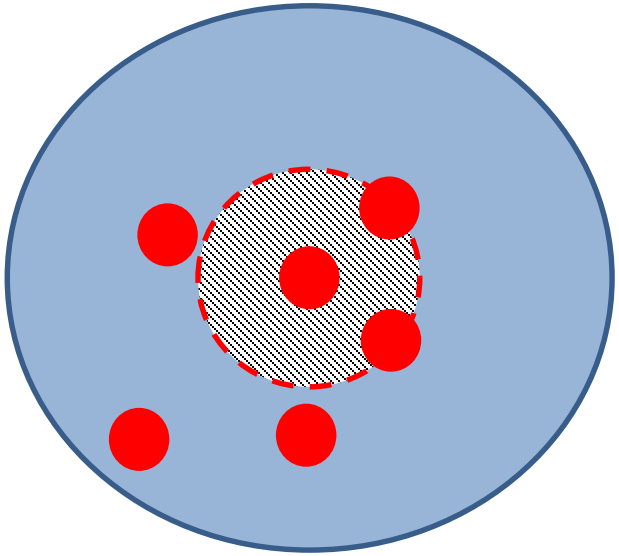
- Gold standard for FMD control?
- Very expensive!
  - Large amount of resources
  - Long term commitment - Programme may need to be continued for several years (decades)
  - Difficultly getting high coverage (80%??)
- Unlikely to be a sustainable approach if resources are limited
- Reliance on this approach holds countries back from PCP progression

Reactive (“Ring”) vaccination



Problems – Reactive (“Ring”) vaccination

1. Evaluation!!
2. Low coverage
3. Questionable vaccine quality
4. Lack of active surveillance and possible spread if infection
5. No movement controls
6. Not implemented quick enough
    - Uganda 7.5 weeks from report to vaccination (Muleme et al 2012)



SURVEILLANCE!!

Reactive vaccination should also be seen as a high resource intervention!

Reactive (“Ring”) vaccination

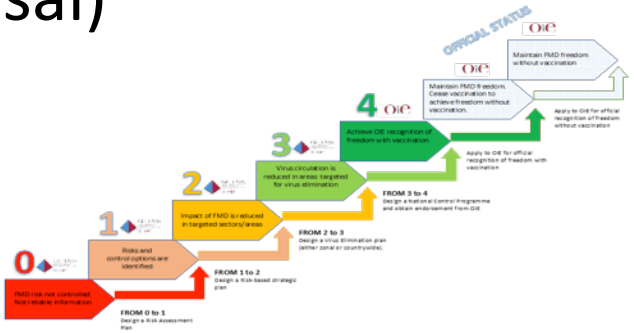
Commonly undertaken in endemic conditions because:

1. **Belief** – that the policy is effective
2. **Availability** - low - either not enough vaccine, or too expensive to use routinely; possibly related to farmer access if government controlled)
3. **Appearance** - Need for veterinary services to be seen to be “doing something” – media often reports vaccination is being done
4. **Influence** – from FMD free countries - seen as the right thing to do

Risk-based vaccination

- Risk-based or “targeted” vaccination
- Certain animals may be at a higher risk of disease or infection (e.g. management, age, breed, location)
- In some systems the disease may have a greater impact (e.g. dairy cows)
- Focussing on risk is likely to be more ***efficient*** and ***cost-effective*** way of using limited resources (for example the quantity of vaccine at your disposal)

Progressive Control Pathway for Foot-and-Mouth Disease (PCP-FMD)



Whatever the strategy, **vaccines** and **vaccination** must be **evaluated**.....

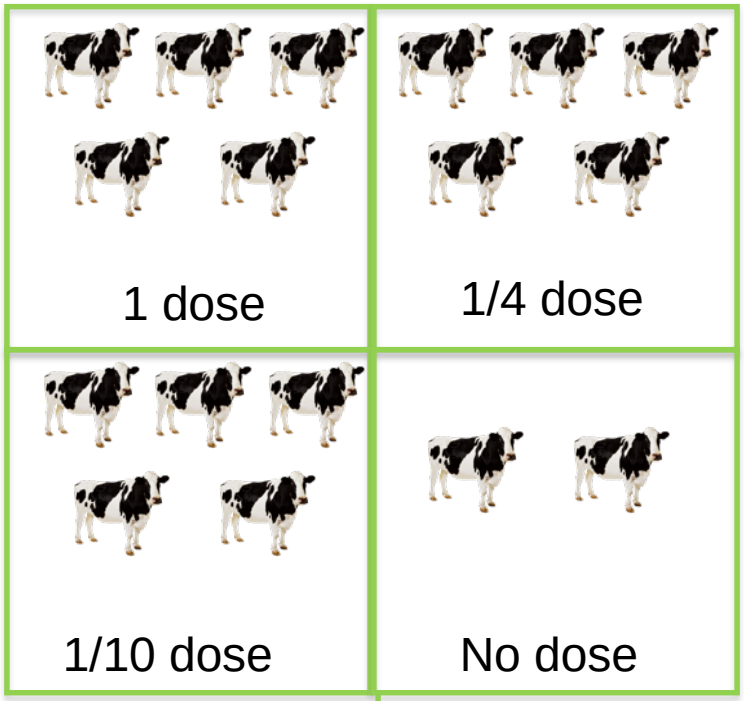
….how are FMD vaccines usually evaluated?

Conventional evaluation

- There are numerous ways FMD vaccines are typically evaluated:
  1. “Potency tests”
  2. Vaccine matching
  3. Immunogenicity studies
- These have their merits particularly in vaccine quality assessments

Potency tests

- Artificially challenge small groups of vaccinated and non-vaccinated animals and observe clinical outcomes
- OIE/European Pharmacopoeia approved methods
- PD_{50}
  - Vaccine dose that protects 50% of recipients
  - “High potency” = >6.0PD_{50}
  - “Standard potency” = 3PD_{50}
- Protection against Podal Generalization (PPG)



PD_{50} = Vaccine dose that protects 50% of recipients

Good things about “potency” tests

1. Tests are standardised
2. Lots of experience
3. Provide useful information that can indicate likely efficacy

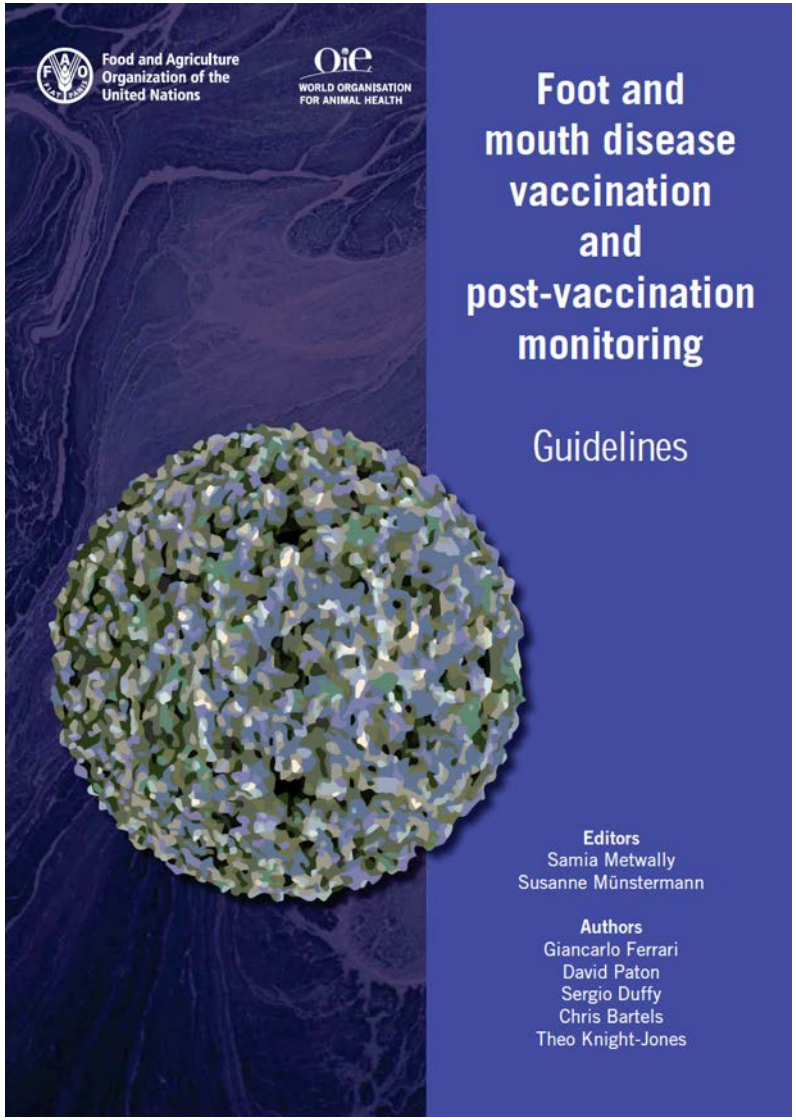
Problems with “potency” tests

1. Route of challenge is artificial (in the tongue)
2. Usually only considers a single dose of vaccine
3. Challenge is homologous (same virus as in vaccine)
4. Small sample size and inprecise (Goris et al, 2007)
5. No guidance on breeds to be used (and age >6m)
6. In around 20% of PD_{50} tests, the results are unreliable because the dose-response curve is flat (Vianna Filho et al, 1993)

Why do field evaluations?

- Overcomes some of the limitations of challenge studies (but field studies also have limitations!)
- Vaccines may be high quality and well matched but still not work in field conditions
- Vaccine may work well, but how “effective” and what is the “impact” of a vaccination *policy*

Post-Vaccination Monitoring guidelines



- FAO/OIE Post-Vaccination Monitoring (PVM) guidelines
- http://www.fao.org/3/a-i5975e.pdf

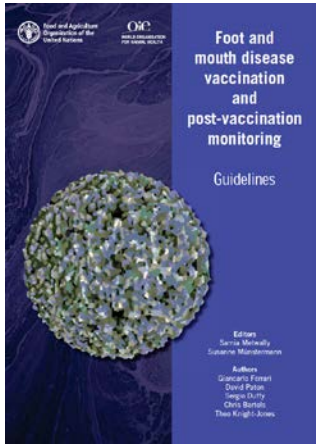
Immunogenicity studies

Very useful for the following:

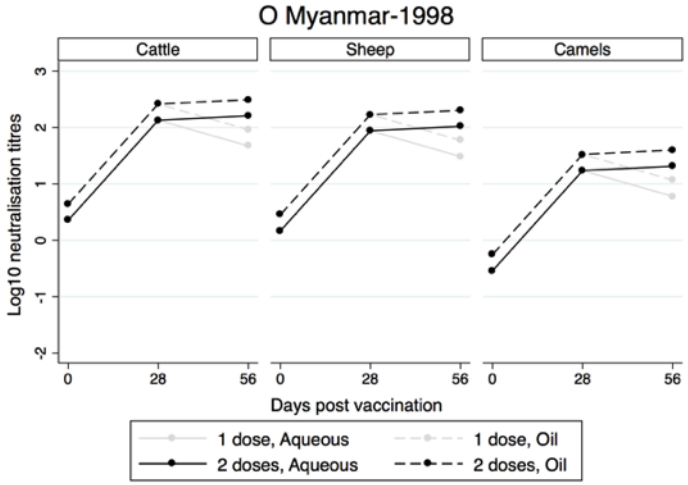
- Assessing the quality of batches or purchased vaccine
  - "**Batch potency tests**" - used for batch release using immunological correlates of protection from results of potency tests
  - "**Critical buyers**" – small-scale immunogenicity studies
- Optimizing schedules to particular circumstances

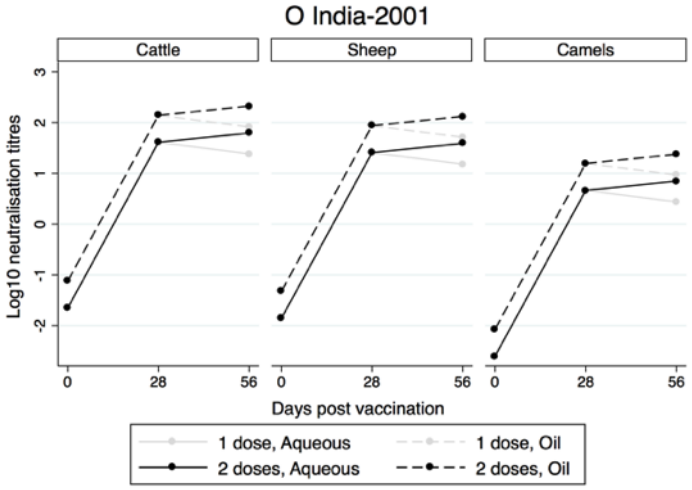
Other uses of serological assessments:

- Quantifying population-level immunity
- Addressing research questions

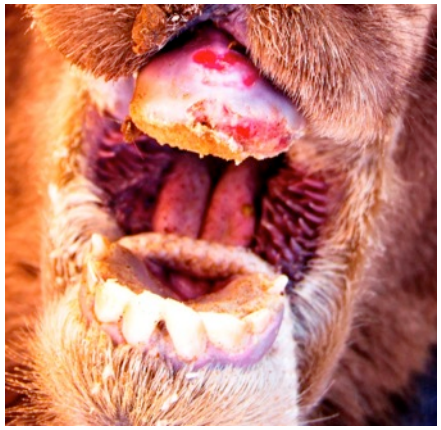


Immunogenicity studies in the field



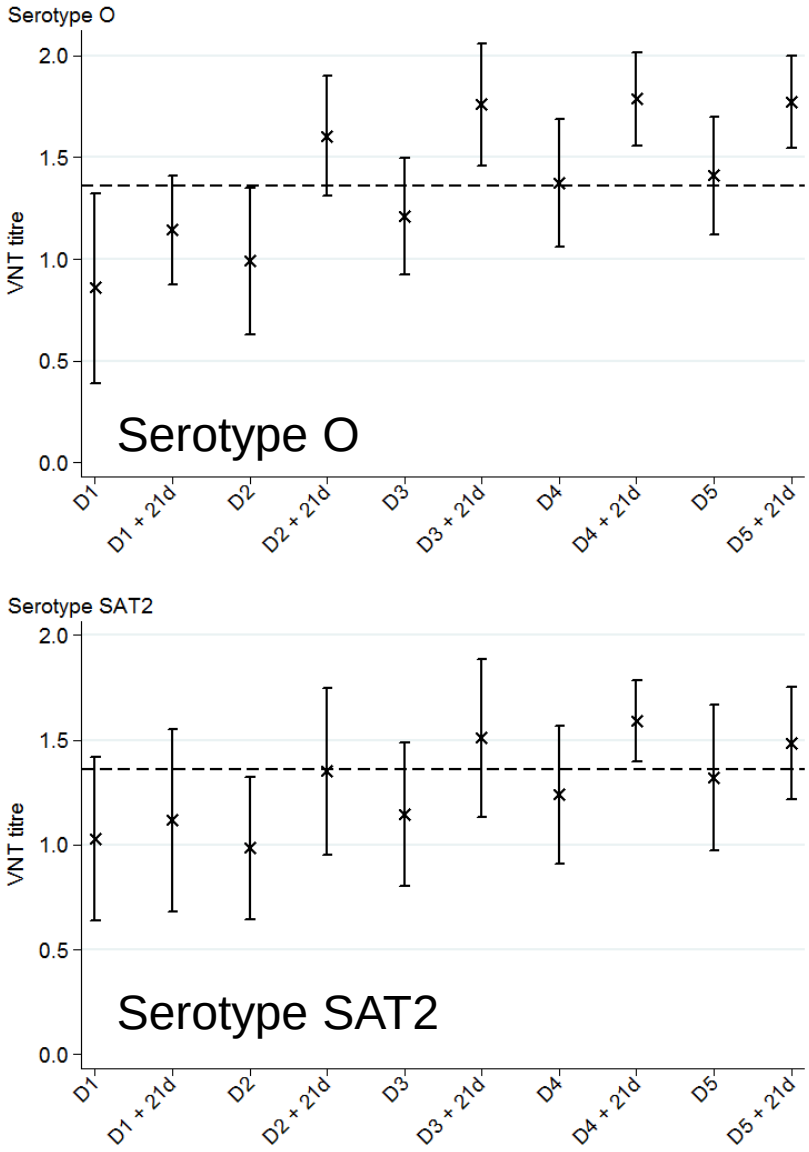


Ulziibat et al, 2018



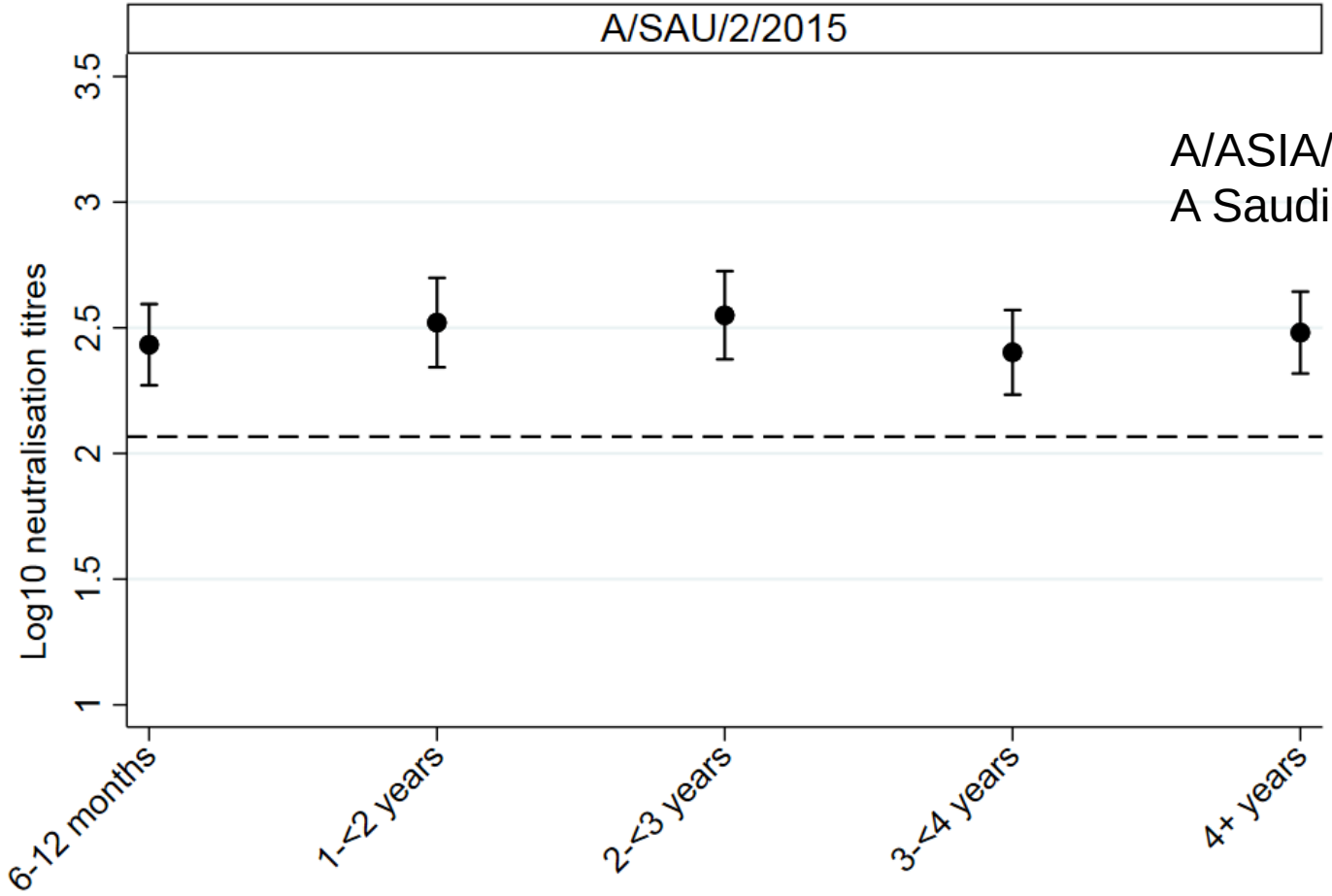
Bactrian Camels - Mongolia

Immunogenicity studies - large-scale farms



- Serum sampling at each vaccination (and 21 days after each dose)
- Useful for evaluating schedules

Immunogenicity studies - large-scale farms



A/ASIA/G-VII lineage
A Saudi-95 vaccine strain

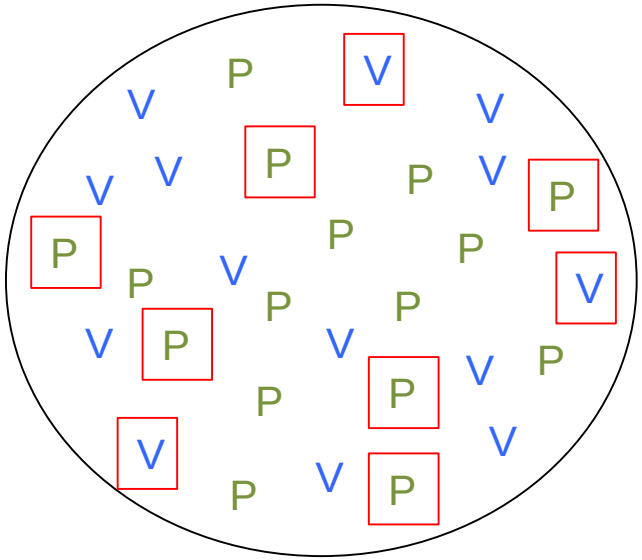
- Screen for likely heterologous “protection”

Human vaccine evaluation trials

Trial Phase	Study population (number of participants)	Outcomes assessed	Veterinary equivalent
Phase 1	Small number (10-100)	**Safety**, sometimes immunogenicity with different doses and schedules	Equivalent studies performed
Phase II	More than phase I (100-500)	Immunogenicity and safety (greater precision)	
Phase III	RCT in population of interest (1000-100,000)	Vaccine efficacy	Extensive challenge studies with limited field trials
Phase IV Post-licensure	Observational studies	Vaccine effectiveness and safety in field	Rarely performed. Post-vaccination sero-conversion studies are more common

Adapted from Knight-Jones et al (2014) Veterinary and human vaccine evaluation methods

Vaccine efficacy



Vaccinated Placebo

Vaccine efficacy = 1 – Incidence in vaccinated
Incidence in unvaccinated

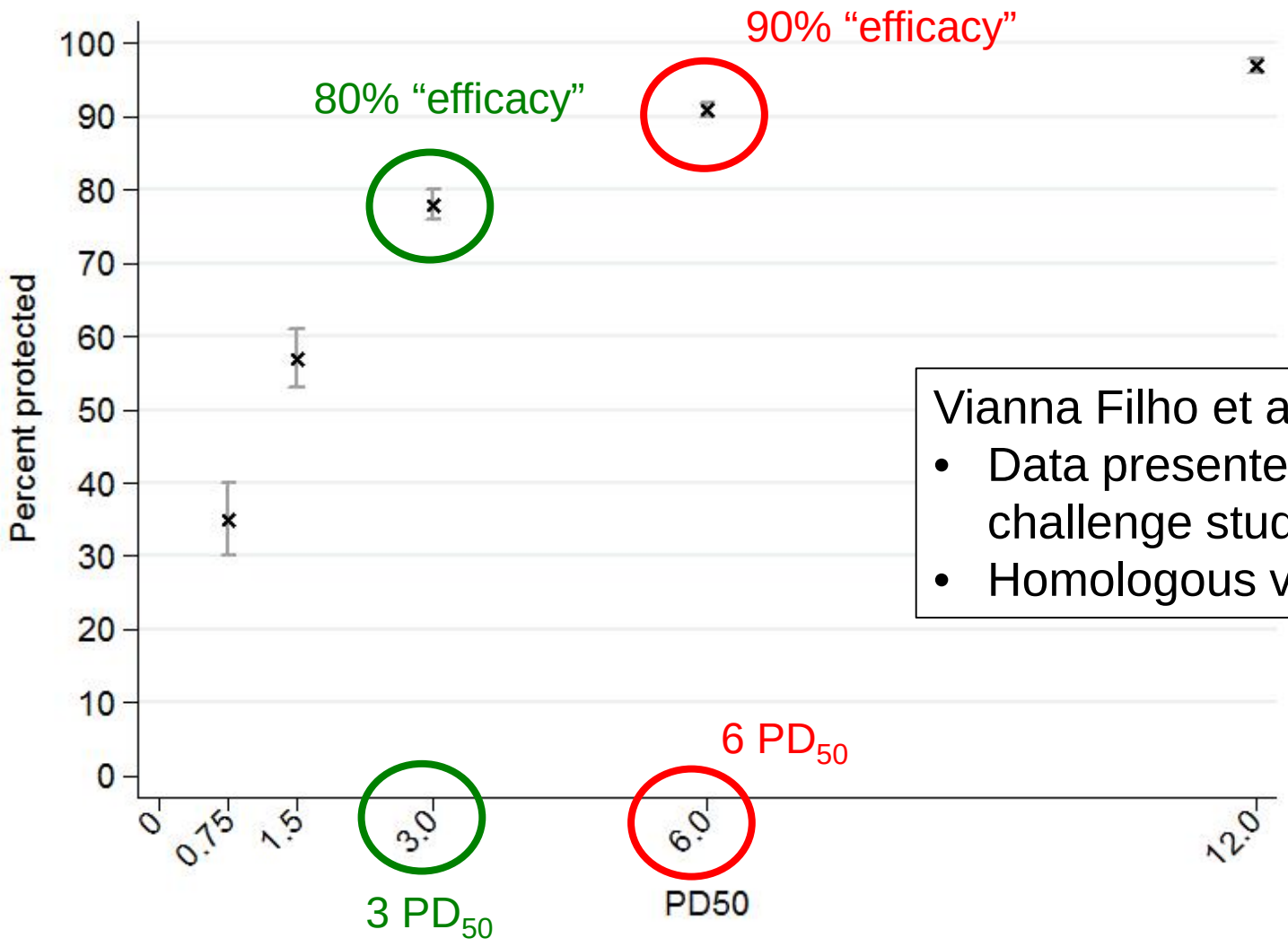
Incidence in placebo = 6/15 = 0.4

Incidence in vaccinated = 3/15 = 0.2

Vaccine efficacy = $1 - \frac{0.2}{0.4} = 50\%$

- Standard definitions are important
- For livestock vaccines, efficacy is vaguely defined (for example immunogenicity studies)

Vaccine efficacy



Vianna Filho et al (1993)

- Data presented from challenge studies
- Homologous virus

“Efficacy” because controls are not used in an epidemiological sense

RCTs in veterinary medicine

IBR vaccine efficacy (VE)

Outcome: abortion

Compared field and challenge studies

Overall VE
60% (95%CI -32-74)
Challenge VE
82% (95%CI 73-88)
Field VE
36% (95%CI 18-49)

Preventive Veterinary Medicine 138 (2017) 1–8

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Prevention of abortion in cattle following vaccination against bovine herpesvirus 1: A meta-analysis

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Infectious bovine rhinotracheitis virus
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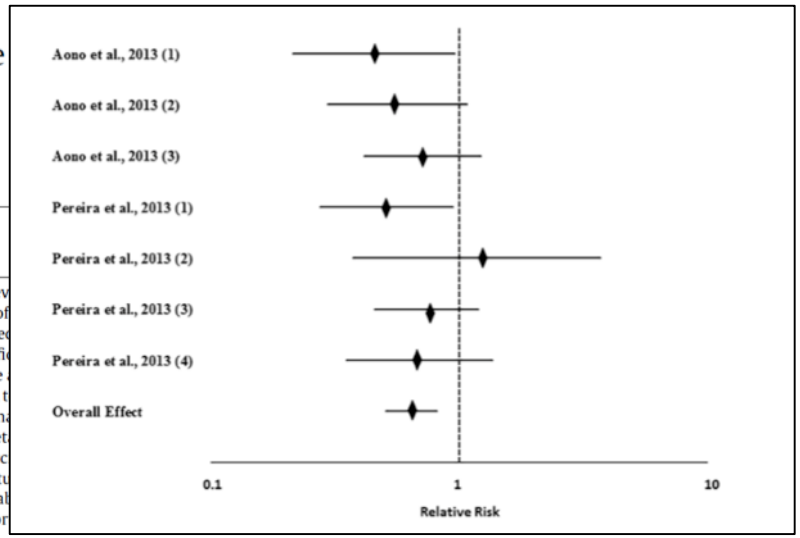
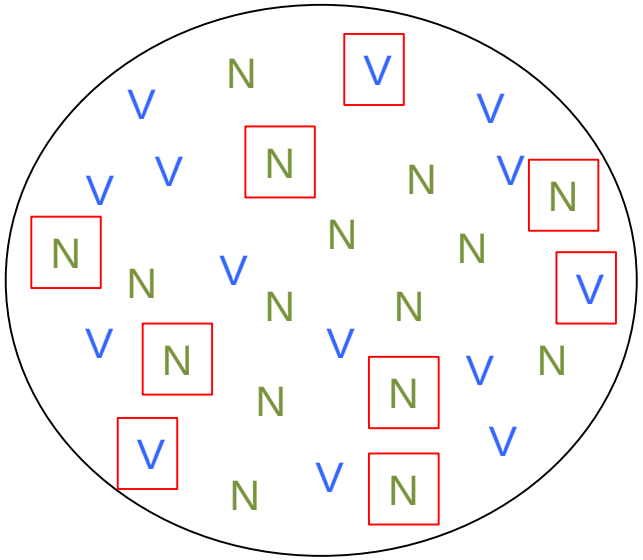
Research synthesis

ABSTRACT

Bovine herpesvirus 1 is ubiquitous in cattle populations and is the cause of sev
including respiratory disease, genital disease, and late-term abortions. Control of
of the world is achieved primarily through vaccination with either inactivate
vaccines. The purpose of this meta-analysis was to determine the cumulative effi
tion to prevent abortion in pregnant cattle. Germane articles for inclusion in the
through four online scientific databases and the examination of three review and t
reference lists. A total of 15 studies in 10 manuscripts involving over 7500 anima
meta-analysis. Risk ratio effect sizes were used in random effects, weighted met
impact of vaccination. Subgroup analyses were performed based on type of vacc
and the type of disease challenge, experimentally induced compared to field stu
abortion risk in vaccinated cattle was demonstrated. The greatest decrease in al
studies with intentional viral challenge although vaccination also decreased abor



Vaccine Effectiveness



Vaccinated Non-vaccinated

Vaccine effectiveness = 1 – Incidence in vaccinated
Incidence in unvaccinat

Incidence in non-vaccinated = 6/15 = 0.4

Incidence in vaccinated = 3/15 = 0.2

$$\text{Vaccine effectiveness} = 1 - \frac{0.2}{0.4} = 50\%$$

- Vaccine is allocated under **programme conditions**
- Important to adjust for exposure risk/confounders in the analysis
- Few examples in veterinary literature
- Low effectiveness prompts further investigations into policy (e.g. vaccine choice, review of cold chain management)

Vaccine Effectiveness

Knight-Jones et al (2014) – FMD in Turkey (Asia-1, Sindh-08)

3 outbreaks
Well matched vaccine (TUR11, r1>0.8)
63% (95%CI 29 to 81) for **infection**
69% (95%CI 50 to 81) for **disease**
83% (95%CI 67to -92% for **severe disease**

3 PD_{50} vaccine

1 outbreaks
Poorly matched vaccine (Shamir, r1 0.13-0.27)
-36% (95%CI -137 to 22) for **disease**

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Retrospective evaluation of foot-and-mouth disease vaccine effectiveness in Turkey

T.J.D. Knight-Jones[a,b,*], A.N. Bulut[c], S. Gubbins[a], K.D.C. Stärk[b], D.U. Pfeiffer[b], K.J. Sumption[d], D.J. Paton[a]

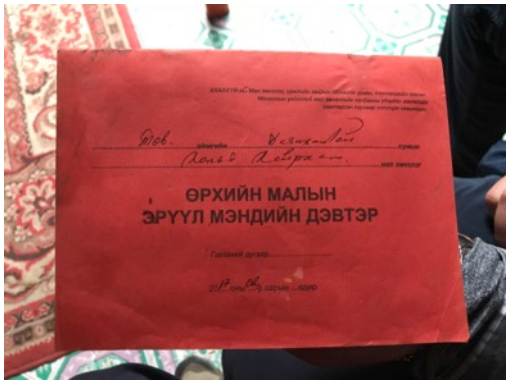
[a] The Pirbright Institute, Pirbright, United Kingdom
[b] The Royal Veterinary College (VEEPH), University of London, United Kingdom
[c] The Şap Institute, Ankara, Turkey
[d] The European Commission for the Control of FMD, FAO, Rome, Italy

Efficacy vs **Effectiveness**

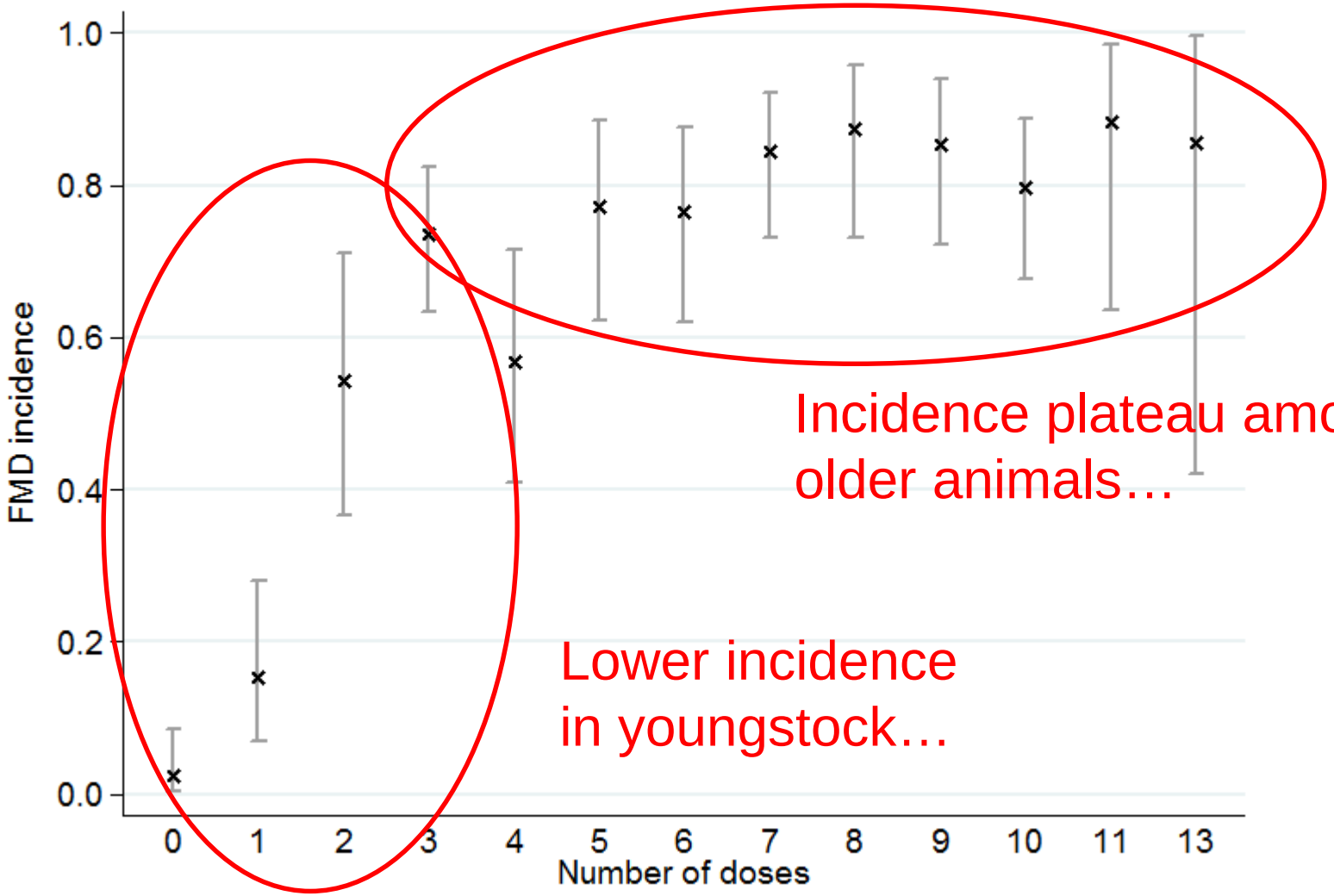
Efficacy	**Effectiveness**
Assumes equal exposure in groups (randomisation)	Vaccination not random, so need to **ADJUST for exposure**
Determined by clinical trials	Done using observational studies
Represents the performance under ideal conditions	Represents the performance under programme conditions
Done in field – so reflects field levels/routes of exposure	

High vaccine coverage

- On large-farms (and herders) often ALL animals are vaccinated so no appropriate comparison groups to estimate the effectiveness
- However, individual farms often have very good records on disease and impact may be high so it is important to investigate, but a different approach is needed



“**Incidence risk**” versus “**Age/Number of lifetime doses**”



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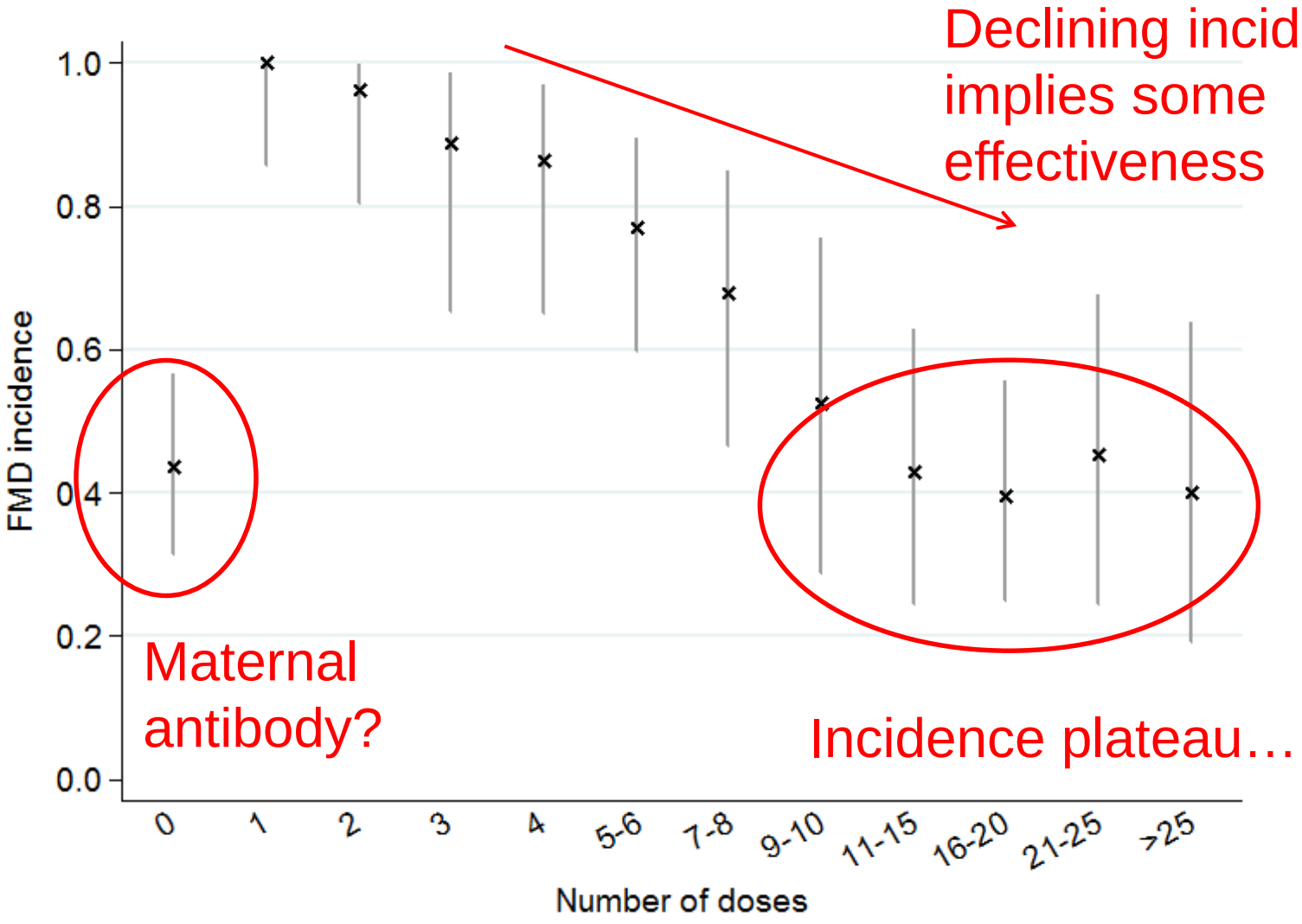

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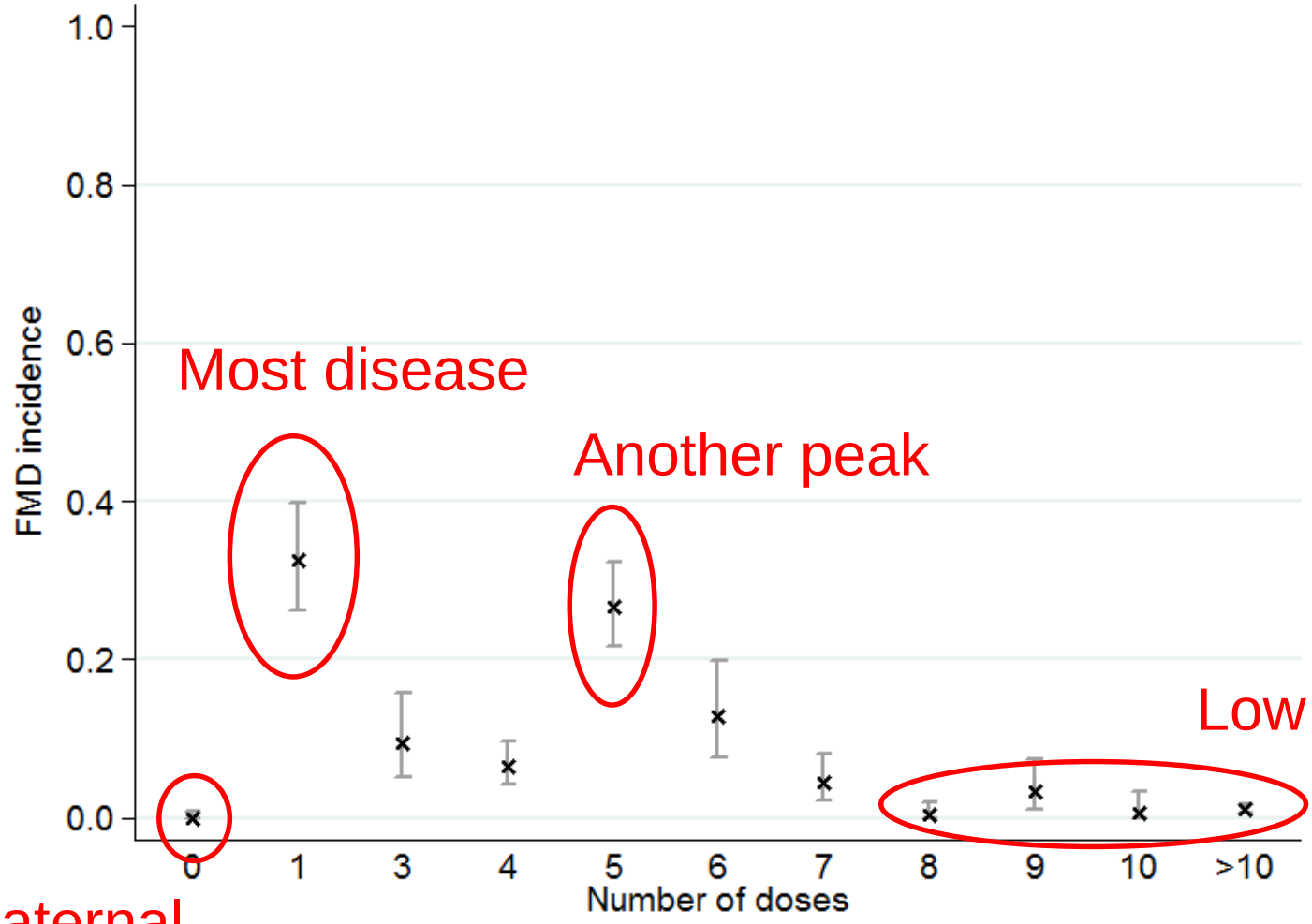

Vaccine Matching
0.23
0.17
0.19
0.28

Maternal antibody?

Conclusion

- Numerous challenges with FMD vaccines and the strategies employed
- Vaccine availability and “security” is a key issue for successful vaccination programmes
- Rigorous, repeatable field based methods (efficacy, effectiveness and immunogenicity) should be used to complement conventional activities
- Vaccine effectiveness has strong implications for policy

BBSRC bioscience for the future

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