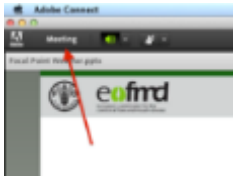
Progressive Control Practitioners' Network

Apparent vaccine failure

Welcome! We will begin at 13.00 CET

Before the webinar begins, you can check that your sound is working by selecting 'Meeting' and 'Audio Setup Wizard' and following the on-screen instructions. You don't need to set up a microphone.



If you have any problems, please use the TECHNICAL SUPPORT BOX to ask for our help. You can also say hello to your fellow participants using the CHAT BOX.

PCPractitioner Network











Month 01 – Feb 2017 What good are NSP sero-surveys for?		Month 02 – April 2017 Is outbreak investigation more than taking samples?
	Month 03 – Sept 2017 How to assess the socio-economic impact of FMD?	
Month 04 – Nov 2017 How to identify risk hotspots?		Month 05 – March 2018 What is a structured approach to investigating apparent vaccine failure?
	Month 06 – May 2018 *Stakeholders?*	

What can you expect this month on apparent vaccine failure ?

Three scenarios

on FMD outbreaks in FMD vaccinated livestock populations:

- Vaccine failure or
- Failure to vaccinate

Emperical experts

- Eyal Klement
- Bishnu Adhikari
- You?

Knowledge Bank and Job Aids

- Uploaded publications
- Schemes for investigation

Where to start and what not to forget?

Webinars and presentations

Two webinars and three presentations with invited experts on real-life situations of investigating apparent vaccine failure .

Real-life situations

What is your approach to investigate the role of vaccine and vaccination in these FMD outbreaks in vaccination livestock populations?

Discussion forum

- Your feedback on the scenarios
- Your questions on the presentations
- Your considerations on the publications and studies

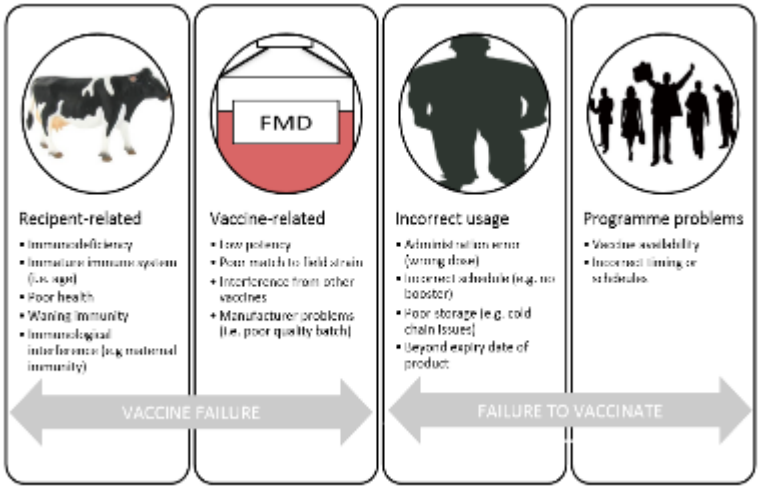
A new tool/job-aid/

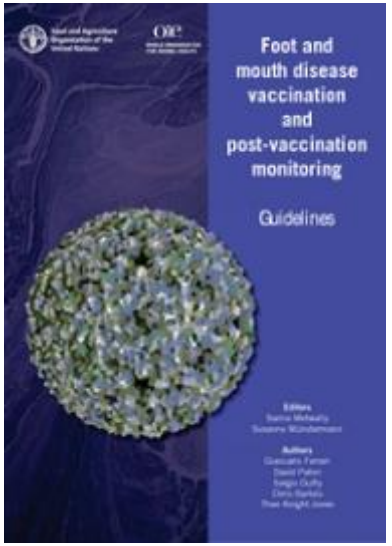
A structured approach to investigation developed based on your feedback

When	What	What about
From 22 February onwards	Uploaded scenarios	• Introduction by Laure Weber-Vintzel, co-chair of the FAO/OIE FMD Working Group • Three scenarios of apparent vaccine failure • FAO/OIE Guidelines on Post-vaccination monitoring
8 March 13.00 CET	Webinar	Introduction – outline of month 1. What is apparent vaccine failure? 2. Different categories of apparent vaccine failure 3. Suggested approach to investigation of apparent vaccine failure
From 15 March onwards	Experiences by Practitioners	Pre-recorded presentations made available 1. Report of FMD outbreak after vaccination in Asia 2. Outbreak on large dairy and beef-fattening farm (publication in Vaccine 2012) 3. … open slot for a Practitioner interested to present on an investigation into apparent vaccine failure
22 March 11.00 CET	Webinar	Discussing a systematic approach • Summarizing the discussions and inquiries of this month • Key issues on apparent vaccine failure • A systematic approach to investigating apparent vaccine failure defined

We hope that at the end of this month you are able to:

1. Explain different categories for apparent vaccine failure
2. Make use of the FAO/OIE post-vaccination monitoring (PVM) guidelines to support investigations
3. Practice a systematic approach to investigate reported vaccine failure, using a decision tree model
4. Adapt this decision-tree model to your local situation





Today's webinar

- What is apparent vaccine failure?
  - Are we discussing the same thing
  - What are the underlying assumptions
- Structured approach to investigate apparent vaccine failure
  - Draft outline – Nick Lyons
  - For discussion (suggestions, changes, elaboration or simplification)
  - Continued discussion between today and second webinar on 22 March

- YOUR INPUT IS NEEDED:
  Please keep a record of your questions, inquiries, points for discussion while the presentation is ongoing. Towards the end, we will address these

Apparent vaccine failure

Clinical FMD in vaccinated livestock populations

Underlying assumptions:

1. The clinical signs are caused by FMD
2. The animals with clinical signs have been vaccinated against FMD such that it was expected they were protected

Have you been involved in investigating FMD outbreaks with apparent vaccine failure ?

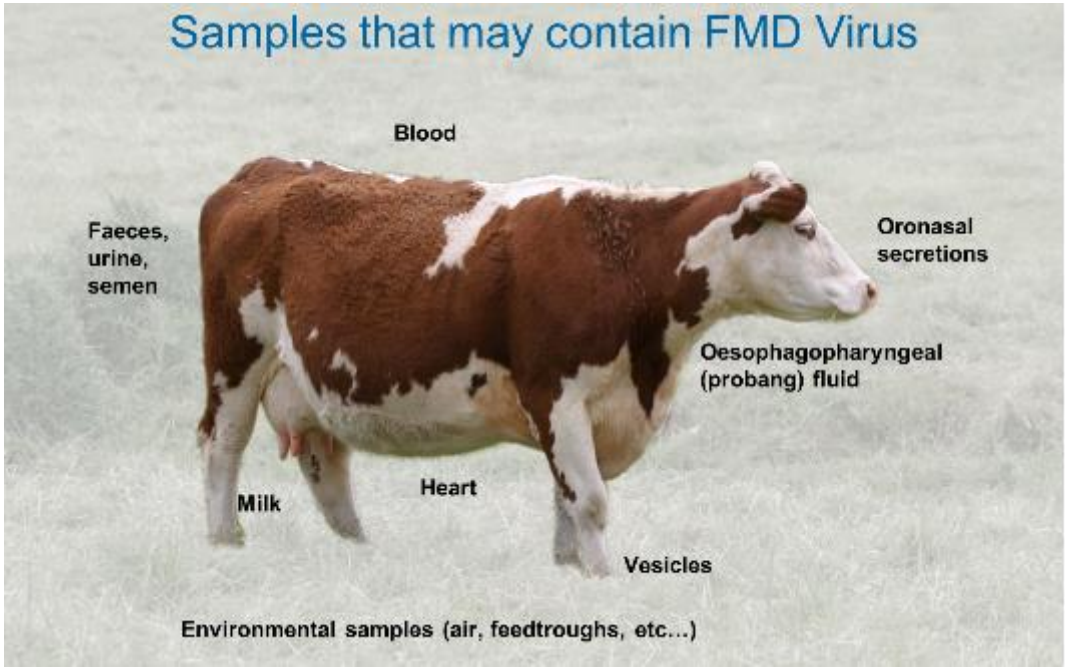
1. No
2. Yes

Confirmation of suspected FMD

Detection of FMD virus (antigen)

1. Epithelium, vesicle fluid, blood, saliva, oro-pharyngeal fluid, heart muscle
2. Positive test to Ag-ELISA, PCR, VNT, virus isolation

Make sure to have sufficient sampling materials to allow for a positive test if FMD virus is present

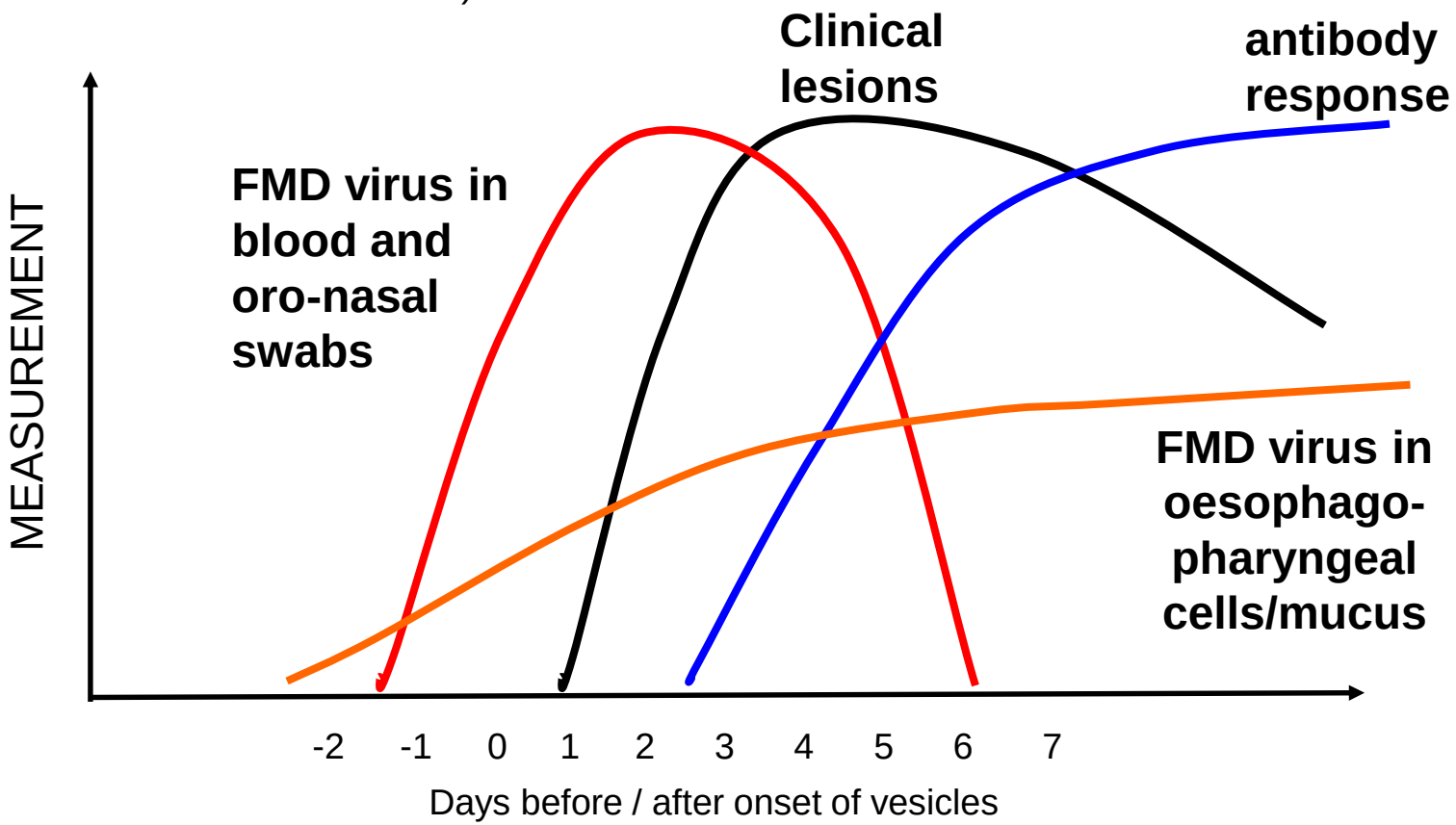


Diagnostic windows

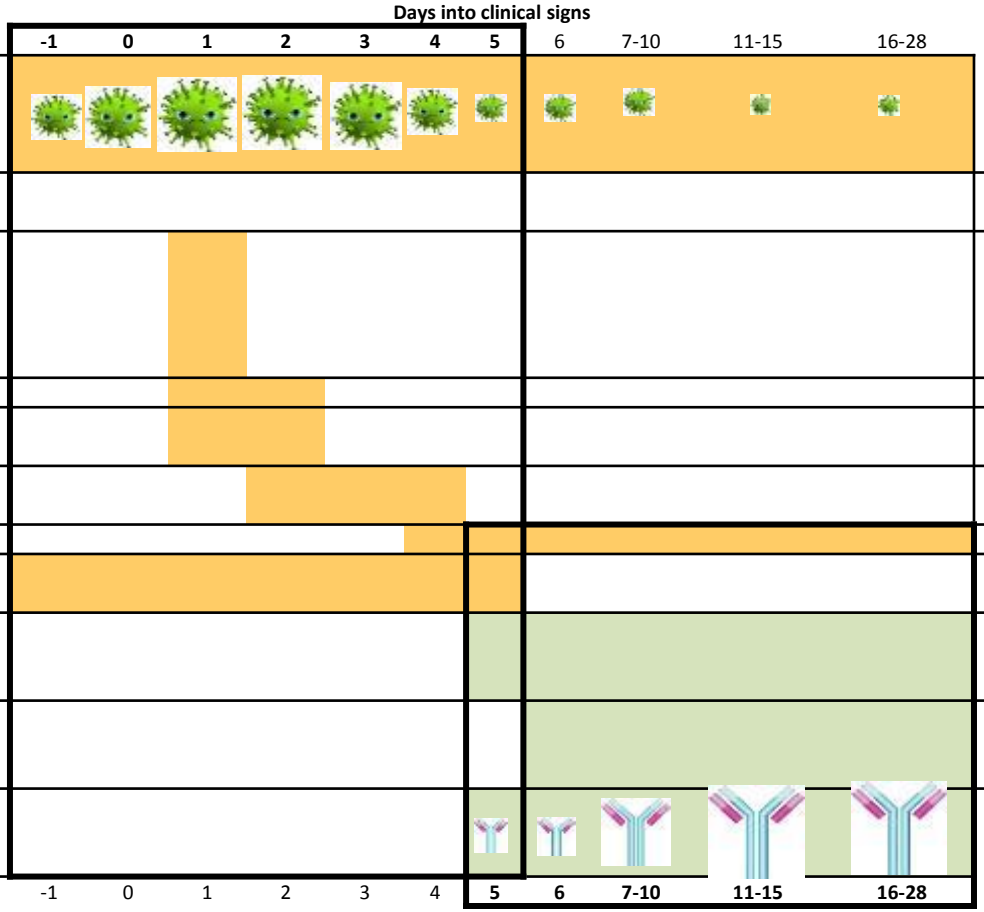
❷ Active surveillance for infected animals (including pre-clinical cases)

❶ Rapid confirmation of clinical signs

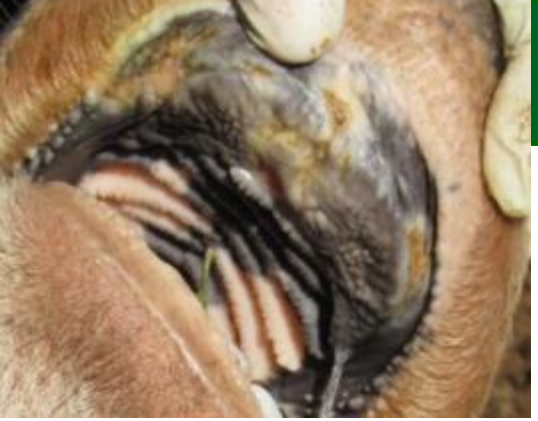
❸ sero-surveillence for FMDV exposed animals



Schedule of samples taking by days into clinical signs



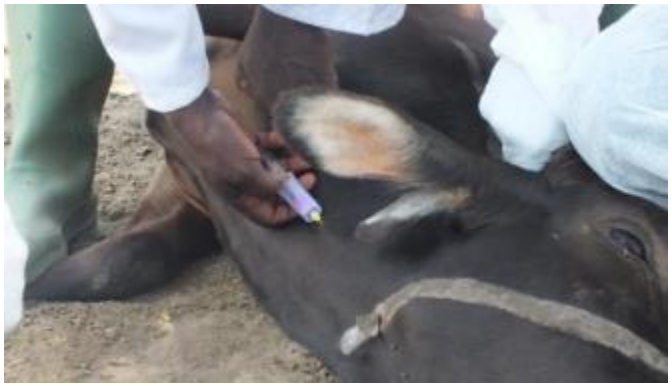
		FMD virus confirmation	Isolation, serotyping, genotyping	
Specimen	**location**	**Min number**	**Consideration**	
Vesicle fluid	Vesicles in mouth, on interdigital	3	When sampling, minimum number per • Species • age groups (< 12 months, >=12 months) • barns, houses or locations • production systems (dairy, beef)	
Epithelium	Mouth	3		
	Interdigital	3		
Swab	Rubbing lesions	5		
Mucus	Probang	3		
Whole blood	Jugular or tail vein	5		
Serum	Jugular or tail vein	10	NSP antibodies eg post-infection monitoring*	
Serum	Jugular or tail vein	10	SP antibodies eg post-vaccination monitoring*	
		FMD infection		



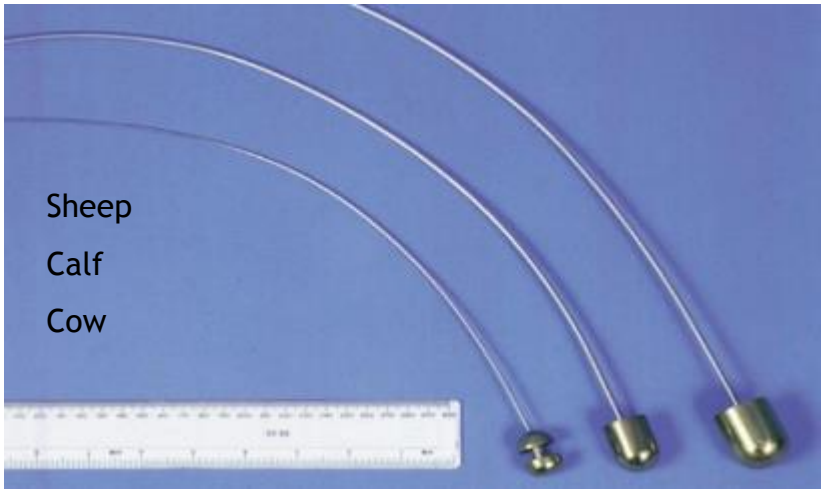
Cases With No or Old Vesicular Lesions

Select animals with suspicious clinical signs or epidemiological links (healed lesions, lameness, fever, depression, milk drop, location)

Clotted blood (for detection of antibodies) and clotted or EDTA blood especially from pyrexic animals (for detection of virus).



Oropharyngeal (probang) samples to look for pre/post clinical virus.



Why to take blood samples?

Do you think blood samples testing positive for NSP antibodies can confirm a suspected ongoing FMD outbreak?

1. No
2. Yes
3. No, unless …

Why to take blood samples?

Always collect, whether or not vesicles present

- Detection of virus in viraemic animals (Clotted or EDTA anticoagulated blood).
- Detection of antibodies in recovering/immune animals (Clotted blood)

However;

- NSP-Ab may be detectable for multiple years after natural infection
- Detection of antibodies cannot act as a confirmatory test for presence of FMD virus, or cause for clinical signs during current investigation unless …

NSP antibodies

If one wants to make use of NSP-Ab presence to confirm FMD virus in current outbreak, consider

1. Sufficient number of samples: minimum of 10 samples per category
2. Young age-category: 6 – 12 months
3. Different FMD groups: with and without clinical signs (different barns, households, locations)

NSP antibodies

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1. Sufficient number of samples: minimum of 10 samples per category
2. Young age-category: 6 – 12 months
3. Different FMD groups: with and without clinical signs (different barns, households, locations)

Example to illustrate

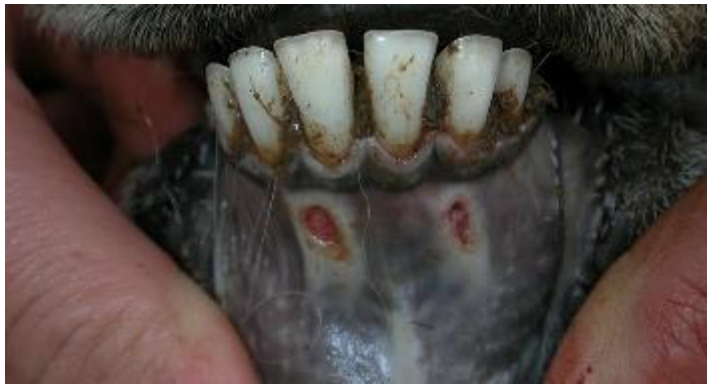
Comparison between different categories (with and without clinical signs) and presence of NSP-Ab

	Clinical FMD	No clinical FMD	Total
Presence of NSP-Ab	8	2	10
No presence of NSP-Ab	2	8	10
Total	10	10	20

There is a statistical significant association between clinical FMD and presence of NSP-Ab (chi-square, P-value = 0.01)

Differential diagnosis to FMD

What are differential diagnosis for FMD in your country situation?



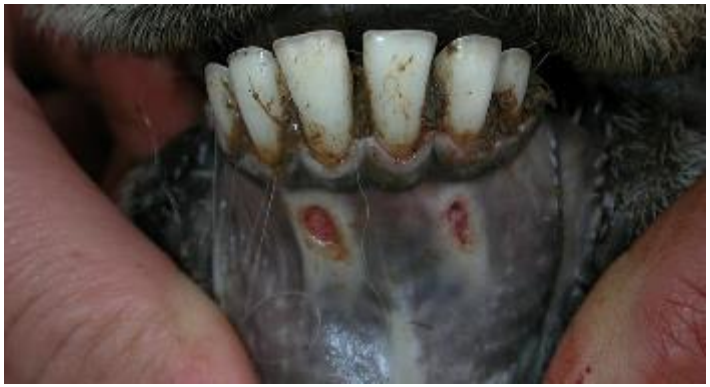
Differential diagnosis to FMD

Trauma and irritants

Foot rot/"scald" (sheep)

Various viral diseases

- Swine vesicular disease (pigs)
- Vesicular stomatitis
- Mucosal disease
- Bovine papular stomatitis,
- ORF
- Malignant catarrhal fever
- Infectious bovine rhinotracheitis
- Possibly marine calicivirus, i.e. vesivirus (vesicular exanthema of swine)
- Senecavirus A (Seneca Valley Virus)

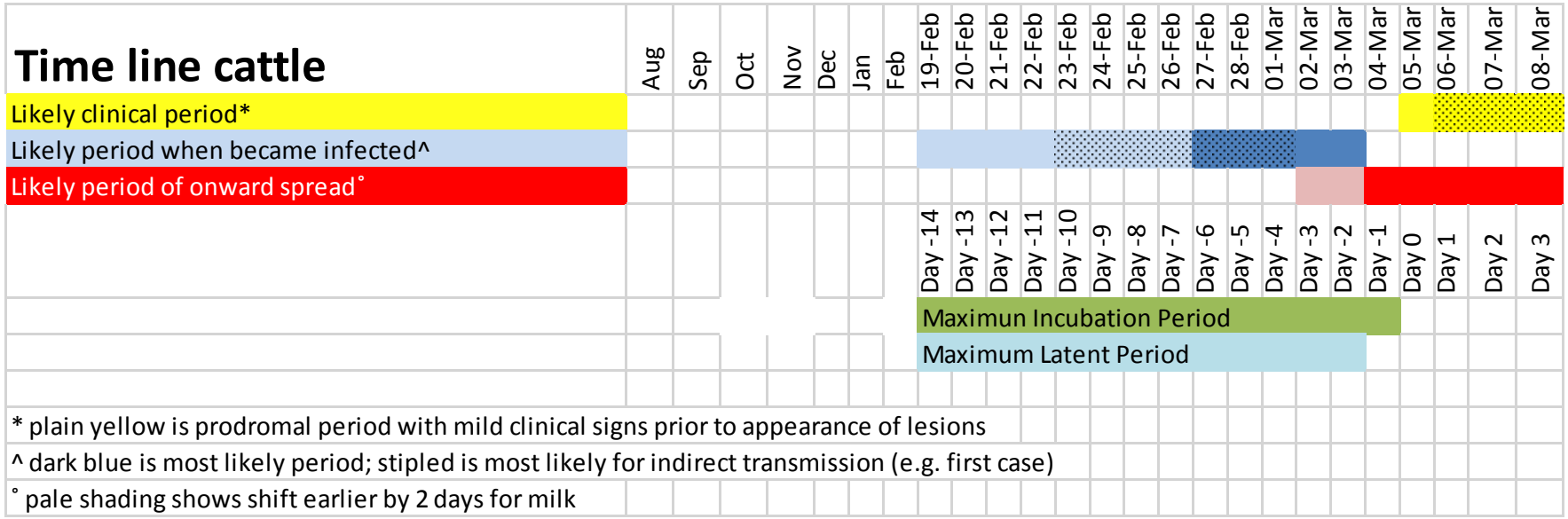


Were animals vaccinated against FMD?

- With livestock owners, double check if animals were vaccinated
  - Was/were animal(s) around when vaccination took place
  - Was person questioned today, present at that time?
  - When was the last (and the second last) vaccination?
  - Against what disease were animals vaccinated?
  - Who vaccinated the animals?
  - Does livestock owner keep any records on vaccination?
- With vaccinator or responsible official
  - What are dates of last and previous vaccination campaigns against what infections?
  - What FMD vaccine was used?
  - What circumstances (cold chain, dose, biosecurity)
  - How are vaccinations recorded (by species, by owner, by date)?

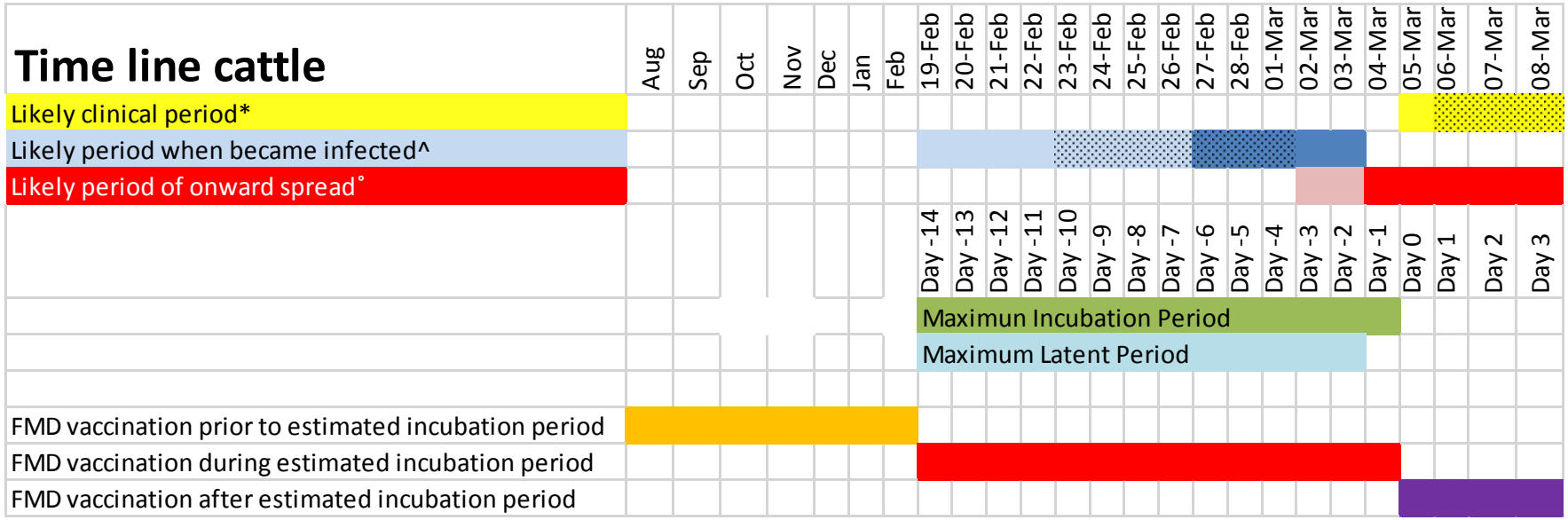
Combining information

Time line of FMD



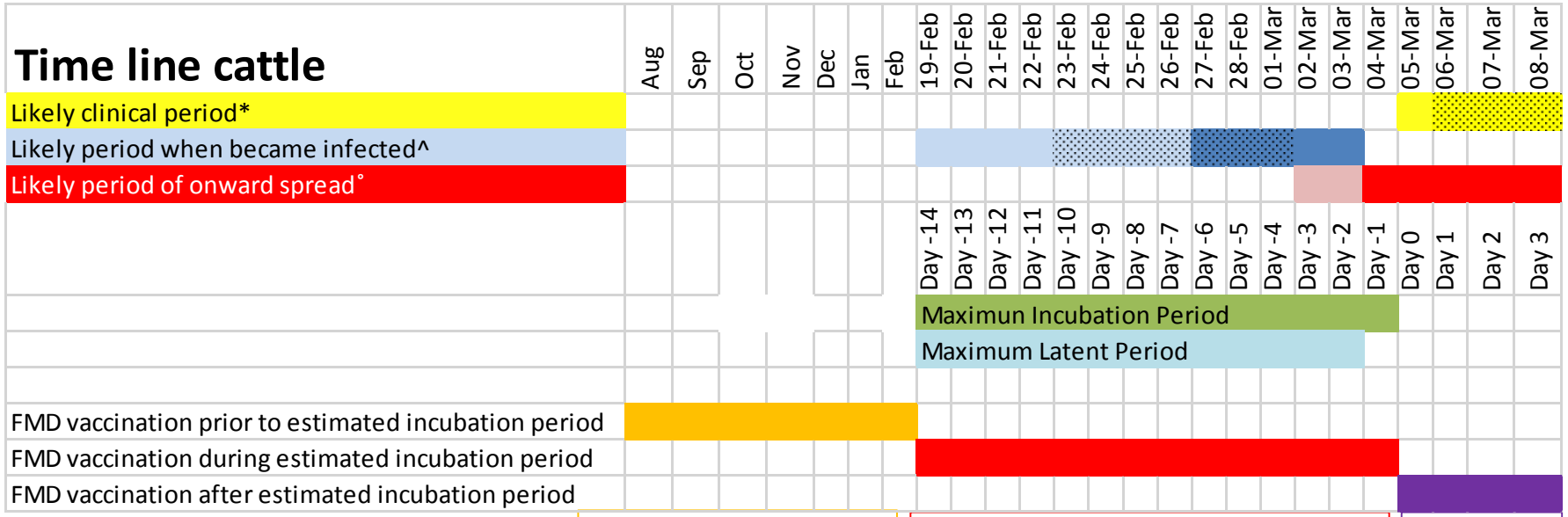
Combining information

Merge date of vaccination with time line of FMD



Combining information

Considerations



Preliminary conclusions and further actions

Vaccine and vaccination have apparently not induced sufficient protection against FMD infection. Further investigation needed into animal groups being vaccinated, vaccine quality, vaccine performance, application and program

Vaccine and vaccination have a direct relation to incubation period, thus may be one of the reasons for clinical FMD (breach in biosecurity) while there may not have been sufficient time to induce protection

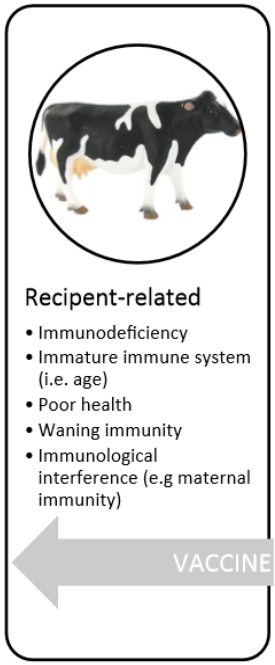
Vaccine and vaccination took place too late to be related to current clinical FMD

Structured approach to investigate apparent vaccine failure

Nick Lyons

Epidemiologist at The Pirbright Institute &
EuFMD Pillar III manager

Categories of apparent vaccine failure

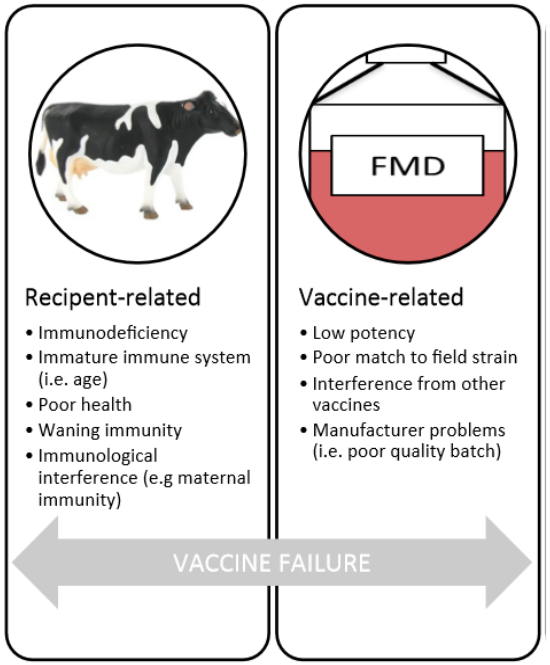


Recipient related

Individual case(s)
Clinical examination

Lyons et al, 2016

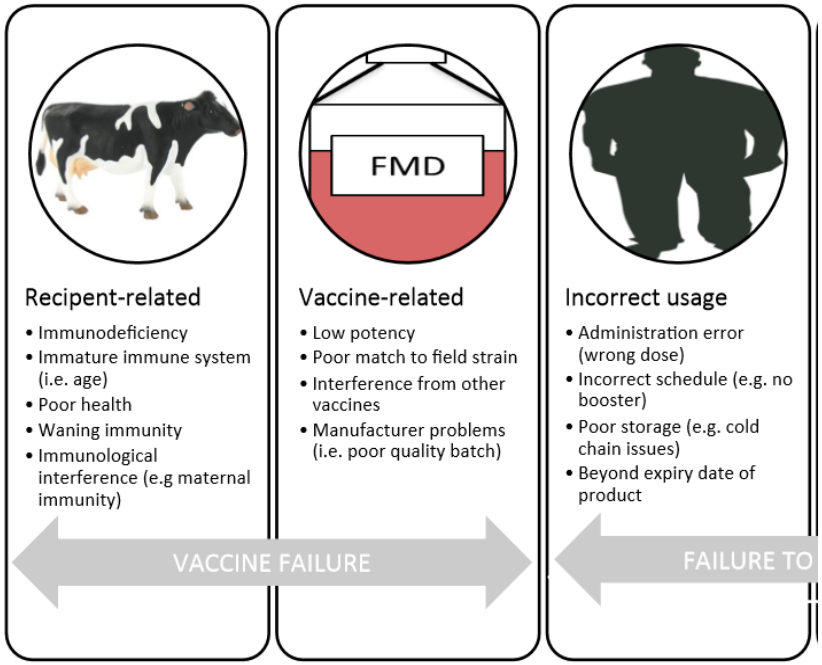
Categories of apparent vaccine failure



Vaccine related

Lyons et al, 2016

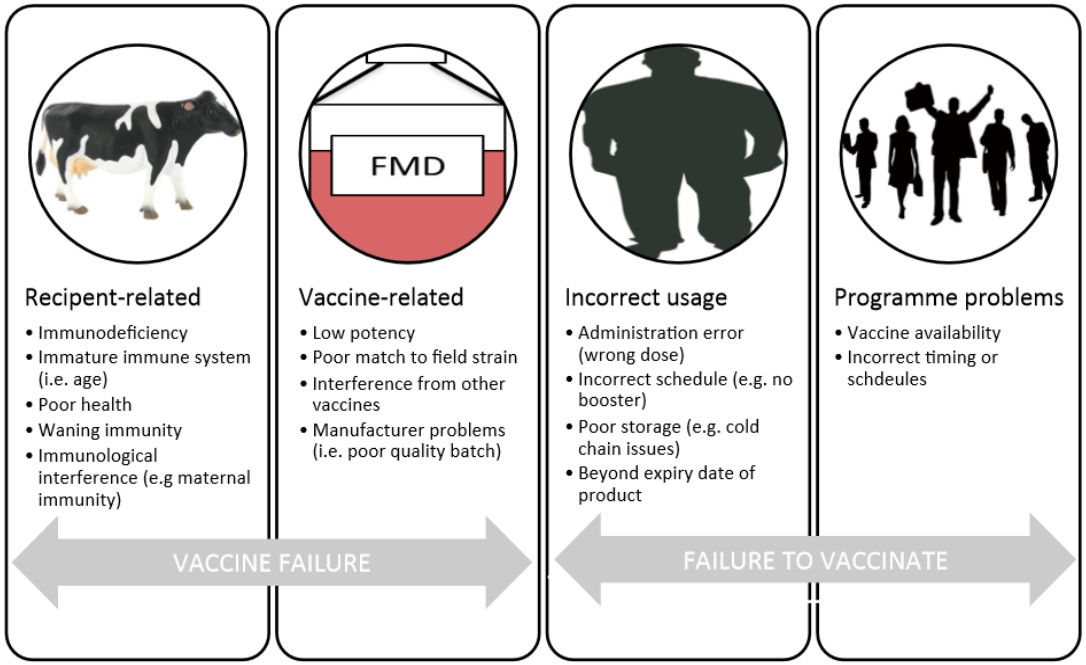
Apparent vaccine failure



Incorrect use of vaccine

Lyons et al, 2016

Categories of apparent vaccine failure



Programme related

Lyons et al, 2016

Reasons for Vaccination Failure

- You have just seen the theoretical reasons why vaccines may “fail”
- The purpose of this presentation is to propose an approach to investigating these apparent failures in an endemic FMD context

- Questions to consider today:
    - *Should I investigate?*
    - *How should I investigate?*
    - *Is there a problem?*

Has vaccination “failed”?

- *Just because you see disease in a vaccinated population, it doesn’t necessarily mean the vaccine or vaccination policy is failing or underperforming – but it should be investigated in a systematic way in case it is!*

Prelude to investigation

FMD cases have occurred in a vaccinated population:

1. Has FMD been confirmed?

Prelude to investigation

FMD cases have occurred in a vaccinated population:

1. Has FMD been confirmed? **YES**

Prelude to investigation

FMD cases have occurred in a vaccinated population:

1. Has FMD been confirmed? **YES**
2. Is the serotype known?

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Prelude to investigation

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3. When did vaccination occur relative to onset of clinical signs?
   a) Were animals incubating while vaccinated?
   b) Were animals exposed too soon after vaccination?
   c) Has the expected duration of immunity waned?

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   a) Were animals incubating while vaccinated? **NO**
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4. What livestock setting did it occur in?
   a) Individual farm (s) using routine vaccination
   b) Village setting with varied vaccination

Livestock setting

- ***Individual farm***
  - Typically think of larger-scale farms
  - Animals are often routinely vaccinated
  - Records may be present
  - Vaccine effectiveness study less likely to be possible

- ***Village setting***
  - Different farms present, maybe with different vaccine histories
  - Records less likely to be present
  - Lends itself to a vaccine effectiveness study

Vaccine effectiveness

- Relative reduction in disease incidence ascribed to vaccination

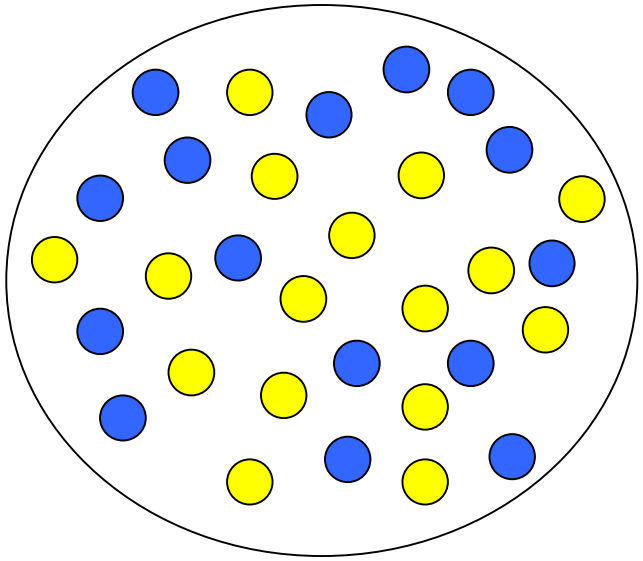
$$\textbf{\textit{Vaccine effectiveness} = 1 - } \frac{\textbf{\textit{incidence in vaccinated}}}{\textbf{\textit{incidence in unvaccinated}}}$$

- Measured using *field derived data* from vaccination under programme conditions
- Allocation of vaccine is not random! Therefore the *risk of exposure must be adjusted* for so it is equal in vaccinated and unvaccinated groups – failure to do so will lead to ***bias***

Halloran et al, 1997

Vaccine effectiveness

- Think of a village setting with smallholder farmers…

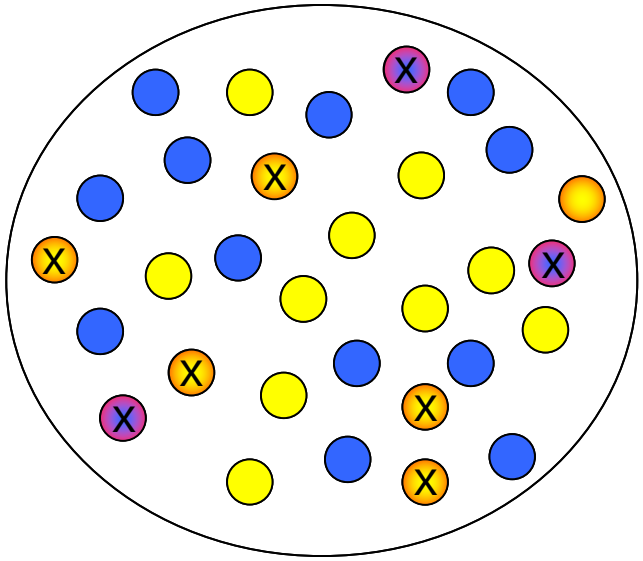


Vaccinated

Non-vaccinated

Vaccine effectiveness

- Think of a village setting with smallholder farmers…



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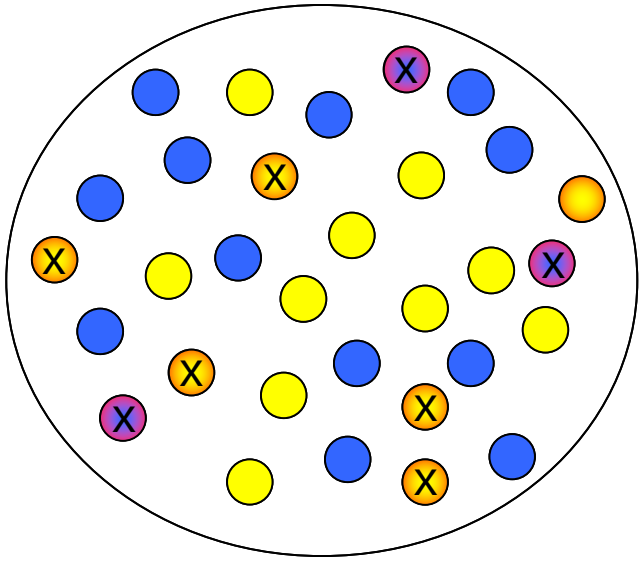


Incidence in unvaccinated = 30/75 = 0.4

Incidence in vaccinated = 15/60 = 0.25

Vaccine effectiveness = $1 - \frac{0.25}{0.4} = 38\%$

Vaccinated

Non-vaccinated

- This is a cohort study that can be performed after an outbreak has occurred
- Collect data from individual farms on the numbers of animals with disease by vaccination status
- Also data on potential confounders…

Confounders

- The risk of exposure may be different in animals that have been vaccinated compared to those that haven't
- For example:
  1. If farmers vaccinated, they may undertake more risky behaviour thinking their animals are protected
  2. If farmers vaccinated, they may be more wary of disease and do other measures that reduce their risk

QUESTION:
Can you think of some potential confounders in your country that should be measured when doing a vaccine effectiveness study?

Potential confounders for vaccine effectiveness studies

- Any risk factor for exposure!
  - Shared grazing
  - Shared water
  - Use of communal dip
  - Access of visitors
  - Use of livestock workers
  - Visiting markets
  - Visiting abattoirs
  - etc etc etc

Vaccine effectiveness

- Why is Vaccine Effectiveness important?
  - Based on “real-life setting”, not artificial experiments
  - Reflects programme performance and impact so has important implications for ***policy***
- Should not just be about investigating failure, it is also about opportunities to ***benchmark*** performance
  - Data can objectively show a programme is performing as expected which gives confidence in the vaccination policy
  - Knight-Jones et al “*After adjustment for confounding, the TUR 11 vaccine provided moderate protection against both clinical disease VE = 69% [95% CI: 50%–81%]*”

Vaccine effectiveness

- What criteria are necessary for estimating vaccine effectiveness?

  As well as the questions before

  1. Is the vaccine coverage >80%?
  2. Is the estimated disease incidence <10%

  Other considerations:

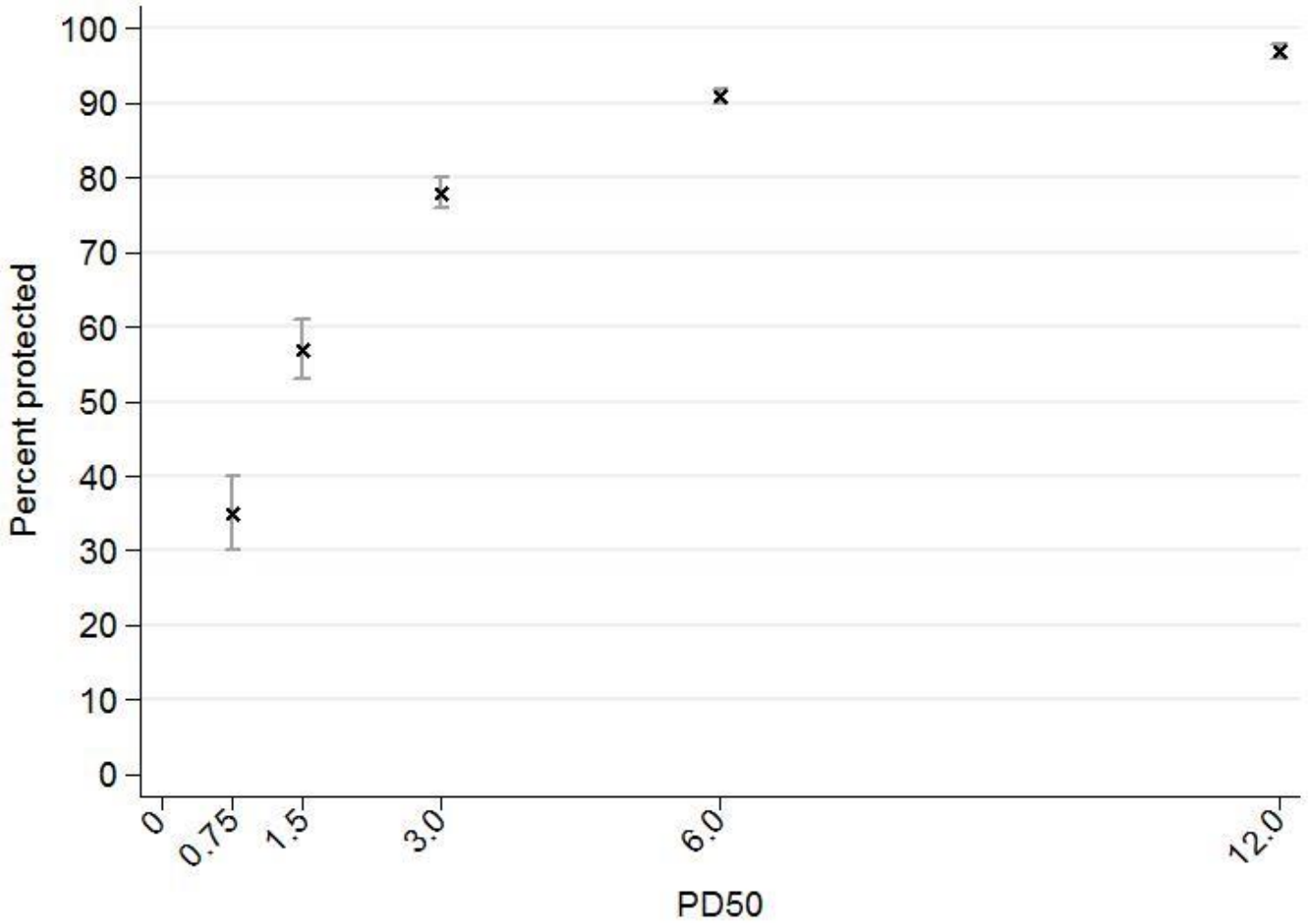
  3. Do you know which vaccine was used?
  4. Are there any vaccination records? If not, should there be?

Individual farms

- Due to use of routine vaccination, typically comparison groups to estimate effectiveness are not present

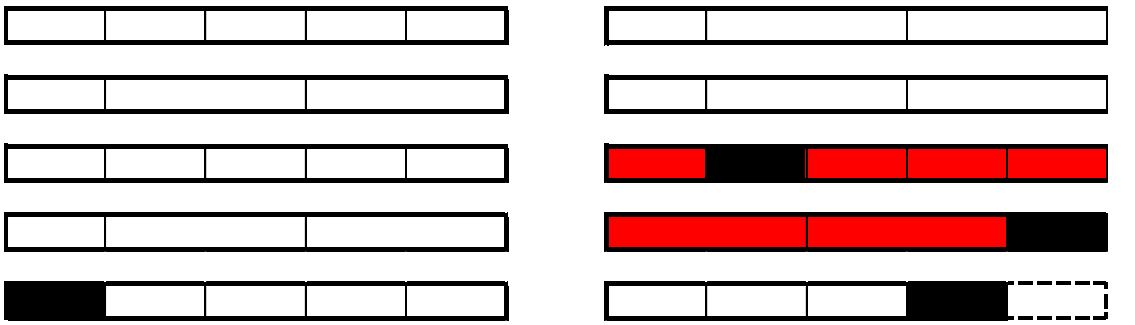
- To decide if there is a problem, first it is important to look at the overall incidence in exposed groups – but what level of incidence is “acceptable”

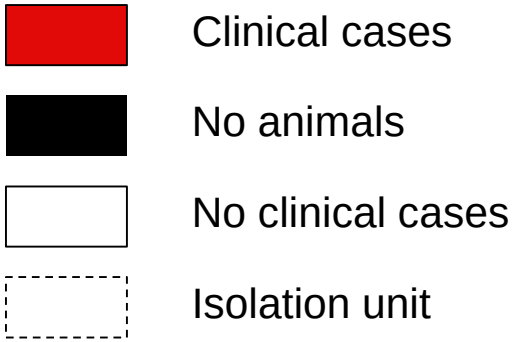
Expected incidence in vaccinated animals



Vianna Filho et al, 1993

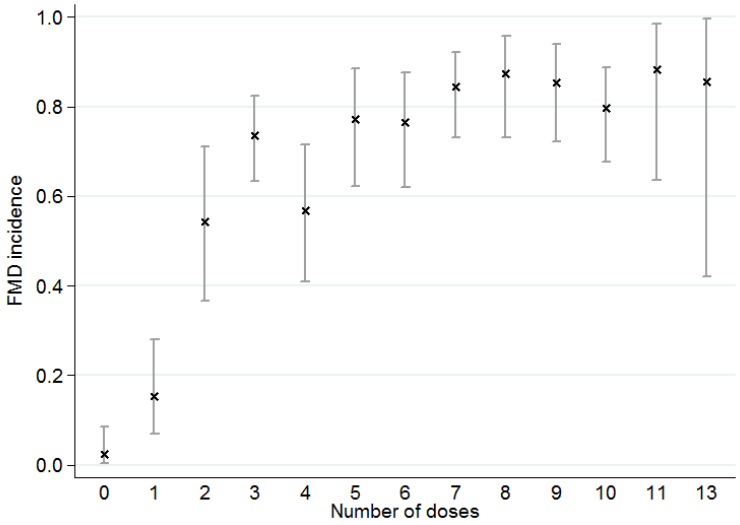
Focus on incidence in exposed groups





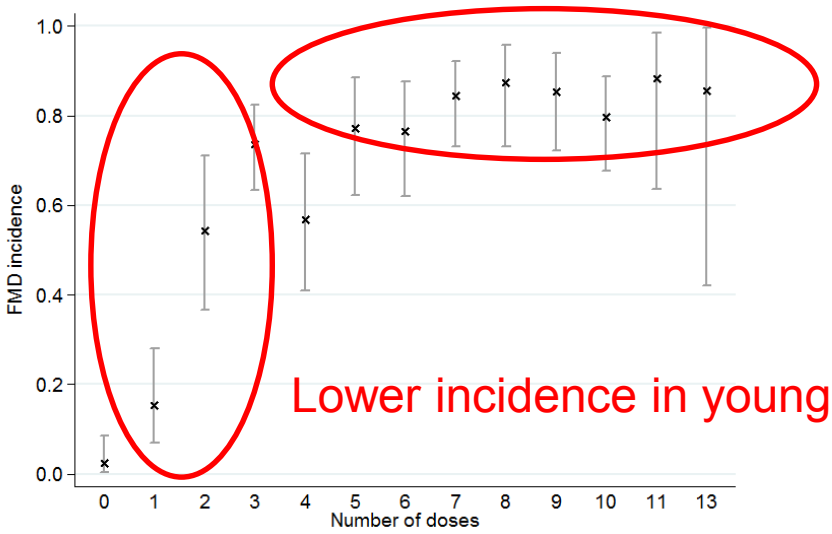
	FARM NUMBER				
	1	2		3	4
	Adults	Adults	Youngstock	Youngstock	Adults
Overall farm incidence risk (%)	107/3,800 2.8%	144/20,750 0.7%	947/14,800 6.4%	50/4,030 1.2%	882/23,200 3.8%
% groups affected	10/24 (41.7)	12/82 (15.0)	64/218 (29.4)	6/50 (12.0)	34/99 (34%)
Group level incidence risk % (95% CI)	4.7 (0-9.7)	2.6 (0.05-4.6)	20.1 (14.3-25.9)	9.9 (4.2-15.7)	9.7 (7.0-12.5)

Lyons et al, 2017



Incidence and age

Lyons et al, 2015

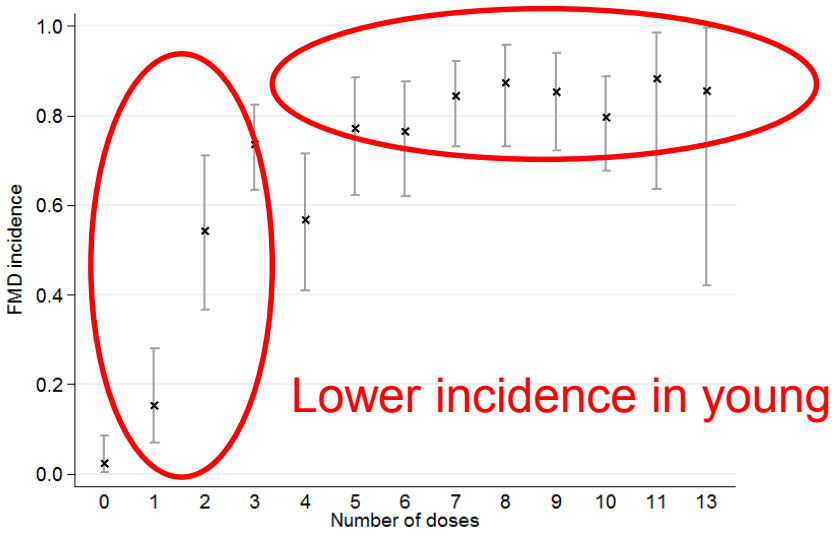


Incidence plateau among older animals…

Lower incidence in youngstock…

Incidence and age

Lyons et al, 2015



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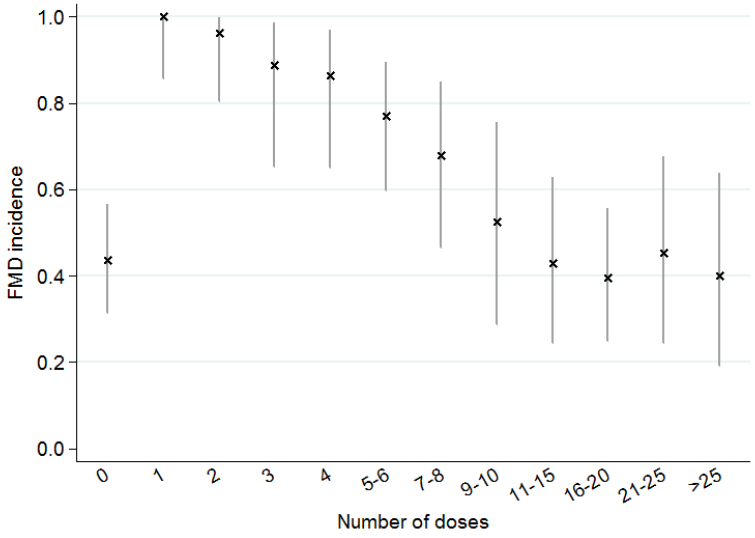
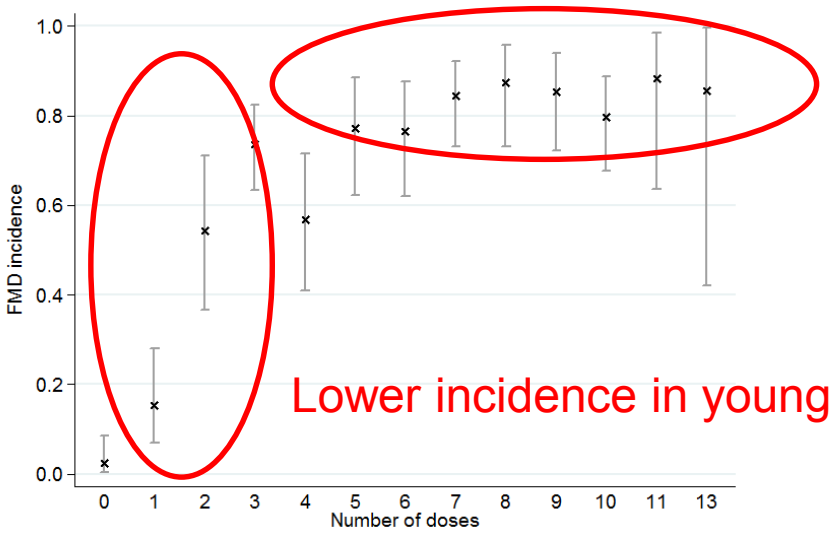


Lyons et al, 2015



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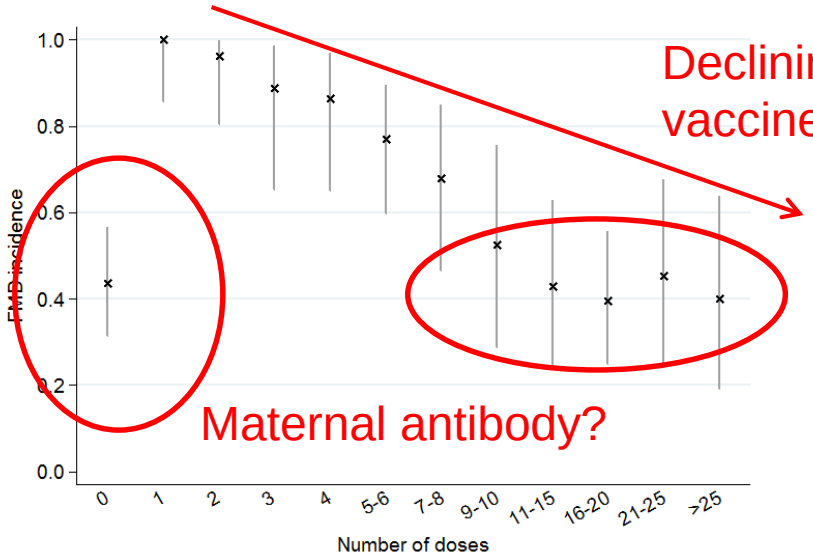
Lower incidence in youngstock…

Incidence and age



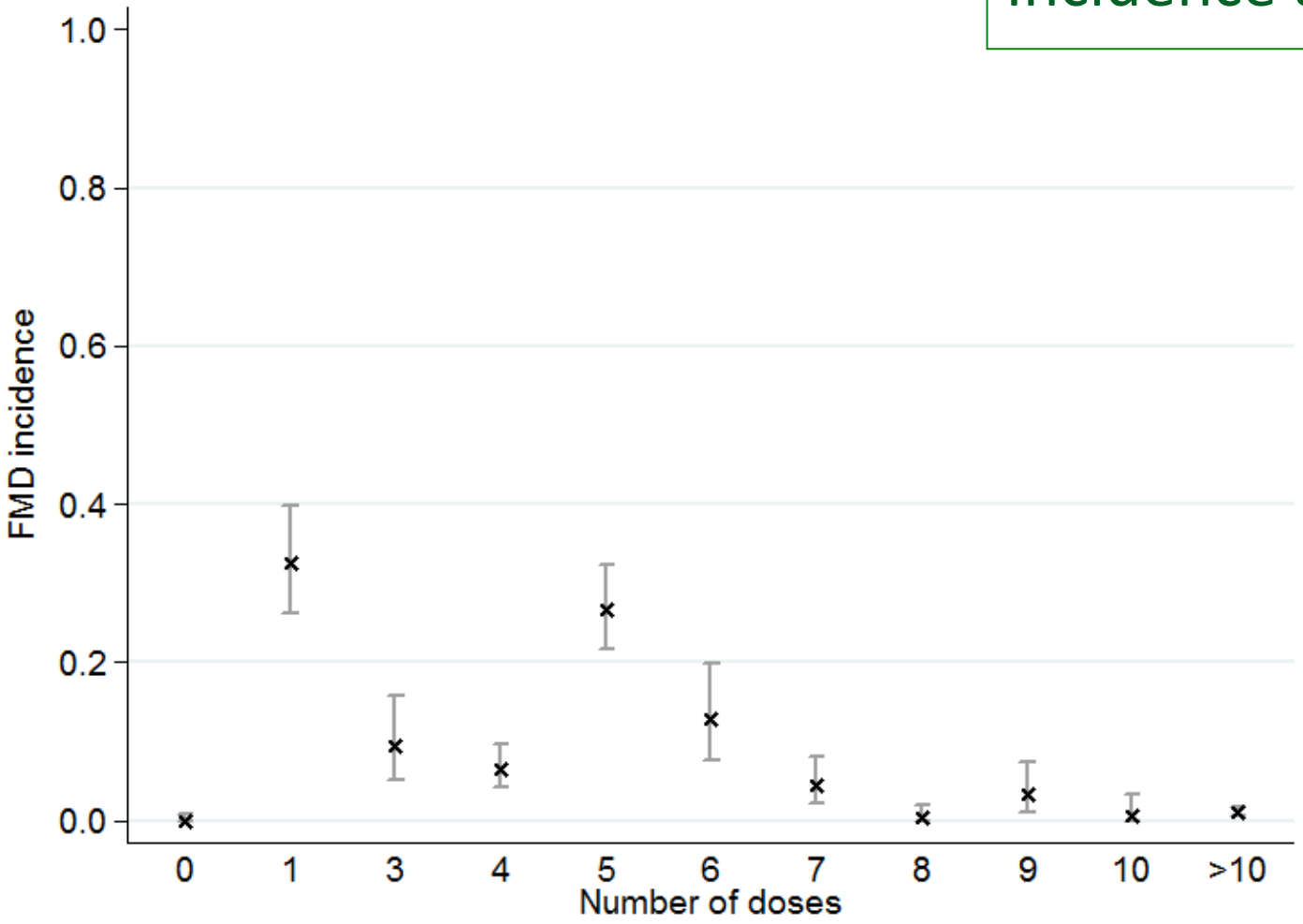
Declining incidence implies some vaccine effectiveness

Incidence plateau…

Maternal antibody?

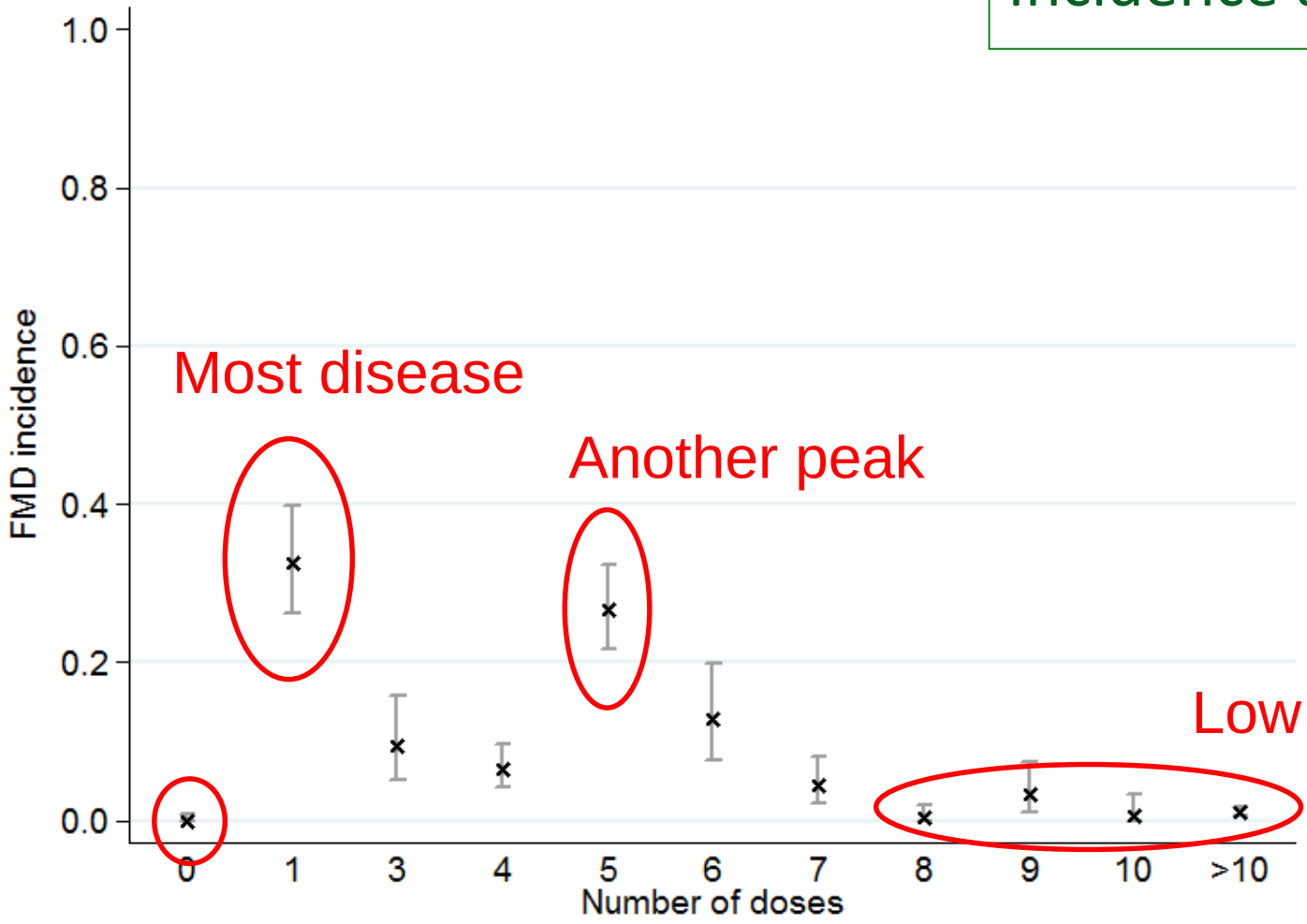
Lyons et al, 2015

Incidence and age



Vaccine Matching
0.23
0.17
0.19
0.28

Incidence and age



Vaccine Matching
0.23
0.17
0.19
0.28

Maternal antibody?

Is there a problem with vaccination?

- **Vaccine effectiveness**
  - Knight-Jones et al, 2014
    - 3xPD_{50} vaccine, well matched, VE = 69% [95% CI: 50%–81%]
  - Elnekave et al, 2013
    - 6xPD_{50} vaccine, r_1=0.37, “High effectiveness” at two weeks
- **Disease incidence**
  - Vianna Filho et al, 1993
    - Potency tests, challenge 21dpv after a single dose
    - 3xPD_{50}, perfect match, incidence = 20%
    - 6xPD_{50}, perfect match, incidence = 10%
  - Lyons et al, 2017
    - 6xPD_{50}, r_1≈0.25, incidence = 10-20% in heavily vaccinated herd

✓ ***Start investigating and create your own benchmarks***

Summary

- ✓ Just because there are cases in a vaccinated population, this does not necessary mean there is a failure in policy
- ✓ ***Data must be collected and analysed*** to provide evidence supporting effectiveness of programme
- ✓ ***Vaccine effectiveness*** studies can provide such evidence
- ✓ ***Disease incidence*** on affected farms, particularly if stratified by age, can be a useful indicator of effectiveness
- ✓ ***Benchmarks*** are needed to indicate if there is a problem

Questions

Now over to the **Progressive Control Practitioners**:

- What do you think about the suggested approaches? Are these possible? Are you doing these already? Would you do/are you doing this differently?
- How many outbreaks in vaccinated populations should be investigated in a year? All of them? A few?
- What benchmarks would you use for defining suboptimal performance?
- If vaccine performance is below your target, what are your next steps?
- What additional measures are required to permit regular evaluation of vaccination performance?

Discussion

- What do you think about the suggested approaches? Are these possible? Are you doing these already? Would you do/are you doing this differently?
- Please write these down in the text box. We may not be able to discuss all.
- However, we will address the issues raised in the previous slide in the discussion forum on the PCPNetwork page

Second webinar – 22 March 2018

- Structured approach to investigate apparent vaccine failure
  - Reviewed approach – Nick Lyons
  - Zooming in on specific steps in this approach
    - Confirmation of FMD
    - Evaluation of livestock being vaccinated
    - Issues of definition to ‘vaccine failure’
    - …
  - How helpful is this structured approach to you?

What more is there?

- Today: quiz on this webinar
- 15 March: upload of 2 video recordings on investigation of apparent vaccine failure
  - Dr Eyal Klement – Israel, Feedlot and dairy farm
  - Dr Bishnu Adhikari – Nepal, Dairy farm
  - You?
    To further discuss a specific investigation and to share this in this PCPNetwork

References

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- **Halloran**, M. E., C. J. Struchiner, and I. M. Longini. **1997**. Study Designs for Evaluating Different Efficacy and Effectiveness Aspects of Vaccines. Am. J. Epidemiol. 146:789–803
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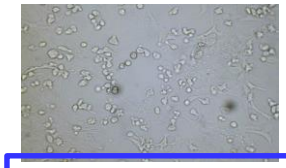
- **Lyons**, N. A., Y. S. Lyoo, D. P. King, and D. J. Paton. **2016**. Challenges of Generating and Maintaining Protective Vaccine-Induced Immune Responses for Foot-and-Mouth Disease Virus in Pigs. Front. Vet. Sci. 3:1–12 Available at http://journal.frontiersin.org/article/10.3389/fvets.2016.00102/full.
- **Lyons**, N. A., A. B. Ludi, G. Wilsden, P. Hamblin, I. A. Qasim, S. Gubbins, and D. P. King. **2017**. Evaluation of a polyvalent foot-and-mouth disease virus vaccine containing A Saudi-95 against field challenge on large-scale dairy farms in Saudi Arabia with the emerging A/ASIA/G-VII viral lineage. Vaccine 35:6850–6857.
- **Vianna Filho**, Y. L., V. Astudillo, I. Gomes, G. Fernández, C. E. Rozas, J. a Ravison, and A. Alonso. **1993**. Potency control of foot-and-mouth disease vaccine in cattle. Comparison of the 50% protective dose and the protection against generalization. Vaccine 11:1424–8

Your questions?

Thank you for your attention!

Principal lab assays for FMD Virus detection and characterisation

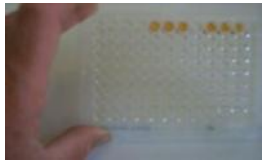


Virus isolation

1-4 days

All sample types

Enough to confirm a first case

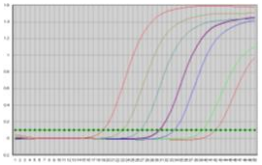


Ag ELISA

~5 hours

Identifies serotype

Only tissues or vesicular fluid



rRT-PCR

<5 hours

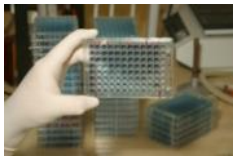
All sample types
Method can be automated

Genome sequencing

~24 hours

Identifies strain

After pre-amplification by VI/RT-PCR



Vaccine matching

>4 days after Virus Isolation

Serological comparison between virus and vaccines

1

10

100

Time to report result (hrs)

Other Samples

Other diagnostic sample options - collect if specific justification

- Oral/nasal swabs
  - Virus persists longer here than in blood (e.g. 4-5 day old lesions)
  - Detection of virus by RT-PCR or VI
- Oropharyngeal fluid (probang)
  - >1 month virus persistence in ~50% infected ruminants (carriers).
  - Low levels of virus detected by RT-PCR or VI
- Cardiac muscle in myocarditis cases
  - Rich source of virus
  - Detection by all tests – RT-PCR, Ag ELISA, VI
- Milk
  - Variable amount of virus or antibody
  - Detection by RT-PCR and by serology.
- Air or environmental samples
  - Low levels of often inactivated virus
  - Detection by RT-PCR.